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TAILORING MEROPENEM TREATMENT FOR CRITICALLY ILL PATIENTS WITH HOSPITAL-ACQUIRED OR VENTILATOR-ASSOCIATED PNEUMONIA: A PERSONALIZED PK/PD APPROACH

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critically ill
PK/PD
bacteria
antibiotics
biomarkers
pneumonia
patients
clearance
CL
Vd
C-RP
IC50
VAP
HAP
TDM
Css/MIC
pharmacokinetics
pharmacodynamics
modeling
meropenem
treatment
efficacy
MIC
eGFR
variability
Gram-negative
C-reactive protein
volume
individualization
optimization

Abstract

Critically ill patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) pose a formidable challenge in clinical management due to the profound alterations in their pharmacokinetics (PK) resulting from their underlying pathophysiological conditions. This leads to substantial inter- and intra-patient variability in drug exposure.

HAP and VAP are frequently caused by Gram-negative pathogens, for which meropenem is recognized as an effective treatment option by guidelines. The efficacy of antibiotics hinges on their pharmacological properties, namely, their PK and pharmacodynamics (PD). Specifically, for meropenem, the PK/PD efficacy target is a drug concentration (C_{ss}) to minimum inhibitory concentration (MIC) ratio (C_{ss}/MIC) greater than 4 for the entire duration of therapy.

This thesis aims to investigate strategies for optimizing meropenem PK and PD in critically ill patients with HAP/VAP.

To enhance meropenem PK optimization in critically ill patients, I evaluated the performance of various methods for estimating renal function, which is crucial for dosing adjustments. These methods included the measurement of creatinine clearance (mCL_{CR}) and its estimation using CKD-EPI, Cockcroft-Gault (CG), and MDRD equations. Linear regressions were used to calculate the dose predicted by each method based on the actual mero-penem clearance.

For PD optimization of meropenem in patients with HAP/VAP, I developed a PK/PD model to quantify the relationship between meropenem concentrations and changes in C-reactive protein (C-RP), an inflammation biomarker. Then, I simulated C-RP fate for different C_{ss}/MIC scenarios.

In the first project involving 46 patients, 133 meropenem concentrations were analyzed. The CKD-EPI formula consistently overestimated mCL_{CR} up to 90 mL/min, after which it underestimated it. CG and MDRD formula consistently overestimated mCL_{CR} across the entire range of glomerular filtration rates (GFR).
Consequently, in critically ill patients, dose adjustments for 24-hour continuous infusion of meropenem should be based on mCL_{CR}. The use of equations for GFR estimation may result in significant under- or overestimation of meropenem dosages.

In the second project with 64 patients, 211 meropenem steady-state concentrations and 415 C-RP measurements, I successfully built a PK/PD model. Simulations demonstrated that higher C_{ss}/MIC ratios were associated with greater and more rapid reductions in C-RP from baseline. Specifically, C_{ss}/MIC ratios of 4-8 was associated with more than a 55 % decrease in C-RP at day 4, which could be used to evaluate the effectiveness of meropenem in empirical treatments.

This research endeavors to personalize the treatment of critically ill patients with HAP/VAP who are being treated with meropenem. It is essential to optimize both PK and PD aspects of therapy. In this pursuit, the measurement of creatinine clearance (mCL_{CR}) is essential, and empirical estimation formulas should not be relied upon. Regarding the PD, our findings demonstrate that C-RP serves as a biomarker reflecting meropenem's efficacy (as indicated by C_{ss}/MIC ratio) and can be used in clinical practice, particularly during empiric treatments, to assess whether the PK/PD efficacy target has been achieved. This comprehensive approach holds promise for enhancing the clinical management of critically ill patients with HAP/VAP and advancing the field of antibiotic therapy optimization.

Riassunto

I pazienti critici con polmonite nosocomiale (HAP) e polmonite associata alla ventilazione meccanica (VAP) costituiscono una sfida formidabile nella gestione clinica a causa delle profonde alterazioni nella loro farmacocinetica (PK), dovute alle loro condizioni fisiopatologiche. Ciò porta a una significativa variabilità inter- e intra-paziente nell'esposizione ai farmaci.

HAP e VAP sono frequentemente causate da patogeni Gram-negativi, per i quali il meropenem è un'opzione di trattamento secondo le linee guida. L'efficacia degli antibiotici dipende dalle loro proprietà farmacologiche, quindi, dalla loro PK e dalla loro farmacodinamica (PD). In particolare, per il meropenem, l'obiettivo di efficacia PK/PD è un rapporto tra concentrazione del farmaco (C_{ss}) e concentrazione minima inibente (MIC) (C_{ss}/MIC) superiore a quattro per l'intera durata della terapia.

Questa tesi mira a investigare strategie per ottimizzare la PK e la PD del meropenem nei pazienti critici con HAP/VAP.

Per migliorare l'ottimizzazione della PK del meropenem nei pazienti critici, ho valutato le prestazioni di vari metodi per stimare la funzione renale, cruciale per gli aggiustamenti posologici del meropenem. Questi metodi includevano la misurazione della clearance della creatinina (mCL_{CR}) e la sua stima utilizzando le equazioni CKD-EPI, Cockcroft-Gault (CG) e MDRD. Delle regressioni lineari sono state utilizzate per calcolare la dose prevista da ciascun metodo basata sulla clearance effettiva del meropenem.

Per l'ottimizzazione della PD del meropenem nei pazienti con HAP/VAP, ho sviluppato un modello PK/PD per quantificare la relazione tra le concentrazioni di meropenem e l'andamento della proteina C-reattiva (C-RP), un biomarcatore dell'infiammazione. Successivamente, ho simulato l'andamento della C-RP per diversi scenari di C_{ss}/MIC.

Nel primo progetto coinvolgente 46 pazienti e 133 concentrazioni di meropenem, abbiamo mostrato che la formula CKD-EPI sovrastima la mCL_{CR} fino a 90 mL/min, dopodiché la sottostima. Le formule CG e MDRD sovrastimano la mCL_{CR} su tutto il range del tasso di filtrazione glomerulare (GFR). Di conseguenza, nei pazienti critici, gli aggiustamenti posologici per l'infusione continua di meropenem dovrebbero essere basati sulla mCL_{CR}. L'uso di equazioni per la stima del GFR può portare a significative sottostime o sovrastime delle dosi di meropenem, che è dannoso per il paziente.

Nel secondo progetto con 64 pazienti, 211 concentrazioni di meropenem e 415 misurazioni di C-RP, ho costruito con successo un modello PK/PD per cui le simulazioni hanno dimostrato che rapporti C_{ss}/MIC più elevati erano associati a riduzioni maggiori e più rapide della C-RP rispetto ai valori iniziali. In particolare, i rapporti C_{ss}/MIC di 4-8 erano associati a una diminuzione superiore al 55 % della C-RP al giorno 4. Questo valore e la descrizione dell'andamento della C-RP nel tempo potrebbero essere utilizzati per valutare l'efficacia del meropenem nei trattamenti empirici.

Questa ricerca si impegna a personalizzare il trattamento dei pazienti critici con HAP/VAP trattati con mero-penem. È essenziale ottimizzare sia gli aspetti della PK che della PD della terapia. In questa ricerca, abbiamo mostrato che la misurazione della clearance della creatinina (mCL_{CR}) è essenziale, e non si dovrebbe utilizzare formule di stima empiriche. Per quanto riguarda la PD, i nostri risultati dimostrano che la C-RP è un biomarcatore che riflette l'efficacia del meropenem. Può essere utilizzata nella pratica clinica, in particolare per valutare se l'obiettivo PK/PD del meropenem è stato raggiunto nei trattamenti empirici. Questo approccio completo offre prospettive promettenti per migliorare la gestione clinica dei pazienti critici con HAP/VAP e per far avanzare il campo dell'ottimizzazione della terapia antibiotica.

Résumé

Les patients critiques atteints de pneumonie nosocomiale (HAP) et de pneumonie associée à la ventilation mécanique (VAP) représentent un défi considérable en matière de prise en charge clinique en raison de leurs conditions pathophysiologiques qui résultent des altérations profondes de leur pharmacocinétique (PK). Cela engendre une grande variabilité inter- et intra-patients dans l'exposition aux antibiotiques.

La HAP et la VAP sont fréquemment causées par des agents pathogènes à Gram négatif, pour lesquels le méropénème est une option de traitement selon les directives européennes et américaines. L'efficacité des antibiotiques repose sur leurs propriétés pharmacologiques, à savoir leur PK et leur pharmacodynamie (PD). Plus précisément, pour le méropénème, la cible d'efficacité PK/PD est un rapport entre la concentration plasmatique du médicament (C_{ss}) et la concentration minimale inhibitrice du pathogène (CMI) (C_{ss}/CMI) supérieur à 4 pendant toute la durée du traitement.

Cette thèse vise à étudier différentes stratégies pour optimiser la PK et la PD du méropénème chez les patients critiques atteints de HAP/VAP.

Pour optimiser la PK du méropénème chez les patients critiques, j'ai évalué les performances de différentes méthodes d'estimation de la fonction rénale, essentielle pour les ajustements posologiques du méropénème. Ces méthodes comprenaient la mesure de la clairance de la créatinine (mCL_{CR}) et son estimation à l'aide des équations CKD-EPI, Cockcroft-Gault (CG) et MDRD. Des régressions linéaires ont été utilisées pour calculer la dose prédite par chaque méthode en fonction de la clairance réelle du méropénème.

Pour l'optimisation de la PD du méropénème chez les patients atteints de HAP/VAP, j'ai construit un modèle PK/PD permettant de quantifier la relation entre les concentrations de méropénème et les variations de la protéine C-réactive (C-RP), un biomarqueur de l'inflammation. J'ai ensuite simulé la cinétique de la C-RP pour différentes valeurs de C_{ss}/MIC.

Dans la première étude, menée sur 46 patients et 133 concentrations de méropénème, la formule CKD-EPI surestimait de manière constante la mCL_{CR} jusqu'à 90 mL/min, après quoi elle la sous-estimait. Les formules CG et MDRD surestimaient de manière constante la mCL_{CR} sur l'ensemble de la plage des taux de filtration glomérulaire (GFR). Par conséquent, chez le patient critique, les ajustements posologiques du méropénème devraient être basés sur la CL_{CR} mesurée. L'utilisation d'équations pour l'estimation du GFR peut entraîner une sous- ou une surestimation significative des doses de méropénème, ce qui peut avoir des conséquences préjudiciables pour le patient. Par conséquent, il est impératif de mesurer la créatinine dans les urines et de ne pas recourir à des formules mathématiques pour estimer la fonction rénale.

Dans le second projet, incluant 64 patients, 211 concentrations de méropénème et 415 prélèvements de C-RP, j'ai construit avec succès un modèle PK/PD. Les simulations ont montré que des rapports C_{ss}/CMI plus élevés étaient associés à des réductions plus importantes et plus rapides de la C-RP par rapport aux valeurs de base. Plus précisément, les rapports C_{ss}/CMI compris entre 4 et 8 étaient associés à une diminution de plus de 55 % de la C-RP au jour 4, ce qui pourrait être utilisé pour évaluer l'efficacité du méropénème.

Cette recherche vise à personnaliser le traitement des patients critiques atteints de HAP/VAP traités par méro-pénème. Il est essentiel d'optimiser à la fois la PK et la PD du médicament. Pour optimiser la PK, la mesure de la clairance de la créatinine (mCL_{CR}) dans les urines est essentielle, et les formules d'estimation empiriques ne devraient pas être utilisées. En ce qui concerne la PD, nos résultats montrent que la C-RP peut être utilisée en clinique, notamment pour évaluer si la cible PK/PD a été atteinte et si la dose de méropénème administrée est adéquate pour la guérison du patient. Cette approche globale offre des perspectives prometteuses pour améliorer la prise en charge clinique des patients critiques atteints de HAP/VAP et pour faire progresser le domaine de l'optimisation de la thérapie antibiotique.

Contents

Abbreviations

AIC	Akaike information criterion
AMR	Antimicrobial resistance
ANOVA	Analysis of variance
AUC	Area under the curve
BIC	Bayesian information criterion
BL/BLI	β-lactam / β-lactamase inhibitor
BLI	β-lactamase inhibitor
BSI	Blood stream infection
BSV	Between-subject variability
C_{max}	Maximal concentration of a drug
C_{min}	Minimal concentration of a drug
C_{ss}	Steady-state concentration of a drug
CAP	Community-acquired pneumonia
CART	Classification and regression tree
CG	Cockcroft-Gault
CI	Continuous infusion
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CL_M, CL_{MER}	Meropenem clearance
CL_{CR}	Creatinine clearance
CLSI	Clinical and Laboratory Standards Institute
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRE	Carbapenem-resistant Enterobacterales
DDI	Drug-drug interactions
DNA	Deoxyribonucleic acid
DTR	Difficult-to-treat resistance
DV	Dependent variable, the observed concentrations
E_{max}	Maximum effect of a drug

EC_{50}	Concentration required to produce half of the maximum effect
ECPA	Expert clinical pharmacological advice
eGFR	Estimated glomerular filtration rate
$eGFR_{CG}$	eGFR calculated using CG formula
$eGFR_{CKDEPI}$	eGFR calculated using CKD-EPI formula
$eGFR_{MDRD}$	eGFR calculated using MDRD formula
EMA	European Medicines Agency
ESBL	Extended-spectrum β-lactamases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EV	Extra-venous administration
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HAP	Hospitalized acquired pneumonia
HCAP	Healthcare associated pneumonia
IAI	Intra-abdominal infection
IC_{50}	Half-maximal inhibitory concentration
ICU	Intensive care units
II	Intermittent infusion
IIV	Intra-individual variability
IPRED	Individual predicted concentrations
IQR	Interquartile range
IRCSS	Istituto di ricovero e cura a carattere scientifico
IV	Intravenous
IWRES	Individual weighted residuals
k_{in}	Production constant rate
k_{out}	Elimination constant rate
KDIGO	Kidney Disease: Improving Global Outcomes
KPC	*Klebsiella pneumoniae* carbapenemase-producing bacteria
LD	Loading dose

MBL	Metallo-β-lactamases
mCL_{CR}	Measured creatinine clearance
MD	Maintenance dose
MDR	Multi-drug resistance
MDRD	Modification of Diet in Renal Disease
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
OF	Objective function
OFV	Objective function value
PCT	Procalcitonin
PD	Pharmacodynamics
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/pharmacodynamics
popPK	Population pharmacokinetics
R^2	Squared coefficient of regression
RNA	Ribonucleic acid
RR	Risk ratio
RRT	Renal replacement therapy
RSE	Relative standard error
RUV	Residual unexplained variability
SAEM	Stochastic approximation expectation-maximization algorithm
$t_{1/2}$	Half-life
V_D	Volume of distribution
VAP	Ventilator-associated pneumonia
VPC	Visual predictive check
WHO	World Health Organization

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Chapter I

Research context: challenges of antibiotic therapy in critically ill patients with hospital-acquired and ventilator-associated pneumonia

I.1 Hospital-acquired and ventilator-associated pneumonia

I.1.1 Definition of hospital-acquired and ventilator-associated pneumonia

Pneumonia (from the Greek $\pi\nu\epsilon\upsilon\mu\omega\nu$, pneumôn, "lung") is an acute infection of the pulmonary parenchyma caused by a wide variety of microorganisms, including bacteria, viruses, fungi or parasites [1]. The lung parenchyma refers to alveolar tissue with respiratory bronchioles, alveolar ducts, blood vessels and terminal bronchioles (Figure I.1). Pneumonia is categorized into distinct categories:

- Community-acquired pneumonia (CAP): pneumonia acquired outside of the hospital setting or within the first 48-72 h of hospital admission,
- **Hospital-acquired pneumonia (HAP)**: pneumonia contracted by a patient at least 48-72 h after being admitted to the hospital,
- **Ventilator-associated pneumonia (VAP)**: subcategory of HAP that occurs in patients receiving mechanical ventilation for at least 48-72h and
- Health care–associated pneumonia (HCAP): pneumonia acquired in lower-acuity health care settings [1–4].

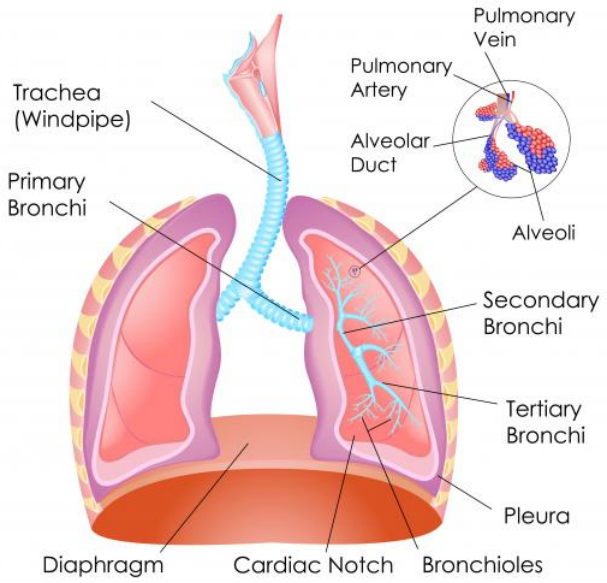


Figure I.1: Anatomy of the lungs.

I.1.2 Epidemiology and etiology of hospital-acquired pneumonia and ventilator-associated pneumonia in critically ill patients

According to the World Health Organization (WHO), acute respiratory infections were the leading cause of morbidity and mortality from infectious disease in the world in 2020 [5]. Almost 4 million people die from acute respiratory infections each year, with 98 % of these deaths due to lower respiratory tract infections such as pneumonia [5]. Fifty-six percent of the infections in ICU are hospitalized-acquired which barely varies between geographic regions (55.3 % in Western Europe, 49.6 % in North America, 51.8 % in Australasia, 64.8 % in Africa, 66.8 % in Easter Europe, 52.6 % in Asia/Middle East and 58.6 % in Central/South Africa) and gross national income (55.5 % in upper, 57.4 % in upper-middle and 50.5 % in lower-middle and lower gross national income) [5].

HAP and VAP are the second most common hospitalized-acquired infection in the world, affecting 0.5 to 1.7 % of hospitalized patients [6]. In intensive care units (ICU), one fifth of critically ill patients is likely to acquire a HAP. According to the EU-VAP/CAP study, a prospective observational study conducted among 1,089 patients with pneumonia from 27 ICU in 9 European countries, 20.57 % of the patients (827 patients) had a HAP and 42.70 a VAP (n = 465) [3]. HAP and VAP were the most common infection in ICU [7] and were directly related to death in 19.6 % of the patients [3]. HAP and VAP are also a frequent lethal complication of hospitalization and contributed for 43.9 % of the deaths in critically ill patients [3].

HAP and VAP are mainly caused by bacteria and viruses, and more rarely by fungi or parasites. In a retrospective multicenter cohort study conducted in 13 Korean tertiary or university-affiliated hospitals in 2019, bacteria were the most frequent pathogens, accounting for 86.3 % of the pathogen identification [8].

Bacteria can be classified considering different properties. The most common is based on Gram stain, developed in 1882 by Hans Christian Gram, which characterizes bacteria based on the structural characteristics of their cell walls. The thick layers of peptidoglycan (long sugar polymer) in the ”Gram-positive” cell wall stain purple, while the thin ”Gram-negative” cell wall appears pink [9]. Gram-negative bacteria, or by simplification Gram-negatives, are protected from external attack by an outer membrane, unlike Gram-positive (Figure I.2). Gram-negatives are also the most frequent isolated pathogens in hospital-acquired infections (77.9 % of the ICU patients) whereas Gram-positives were isolated in 31.3 % of the critically ill patients [10].

At this point, it is important to note that patients may be infected by several different pathogens (bacteria, viruses, fungi, parasites), varied species of bacteria or even different families of bacteria; this is known as polymicrobial infection.

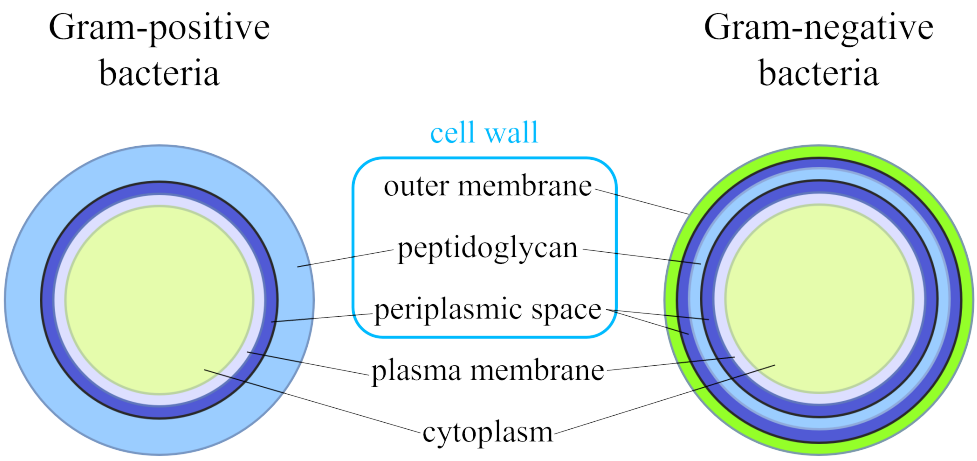


Figure I.2: Structure of Gram-positive and Gram-negative bacteria.

The bacteria most frequently responsible for HAP and VAP are *Pseudomonas aeruginosa* (23.0 %), *Klebsiella pneumoniae* (22.6 %), *Acinetobacter* species (16.6 %), and *Escherichia coli* (12.0 %), for Gram-negatives and Methicillin-sensitive *Staphylococcus aureus* (MSSA) (6.5 %) and Methicillin-resistant *Staphylococcus aureus* (MRSA) (4.0 %) for Gram-positives [10–12].

I.1.3 Physiopathology of hospital-acquired pneumonia in critically ill patients

Lung is not a sterile environment but has its own flora; the "lung microbiome", composed notably by *Prevotella*, *Veillonella*, *Streptococcus*, *Fusobacterium*, and *Hemophilus* species. The lung microbiome is a dynamic community, with a constant equilibrium among species and in an interaction with lung immunity [13]. In pneumonia, this balance is upset and a species of bacteria, whether or not from the microbiome, multiplies. Bacteria outside of the lung microbiome typically enter the lower respiratory tract through aspiration from oral cavity or nose. This happens in healthy conditions during sleep. Progression to pneumonia is rare but some conditions such as host immune system or virulence of bacteria can lead to pneumonia [1] . Another feasible way of colonization is via blood stream: when achieving the lungs, bacteria can invade spaces between cells and alveoli. For intubated patients, the endotracheal tube is a direct route of entry for bacteria to the lower respiratory tract (e.g., VAP) [13].

The risk of acquiring HAP or VAP increases with patient age and the presence of comorbidities (such chronic respiratory diseases, cardiovascular and renal diseases, epilepsy, dementia, stroke) or lifestyle-related factors (smoking, alcohol, chronic malnutrition, and poor dental hygiene). Other factors (structural lung disease, recent antibiotic or corticosteroid use) favor Gram-negative infections [1].

I.1.4 Treatment of hospital-acquired pneumonia and ventilator-associated pneumonia in critically ill patients

To treat bacterial infections, antibiotics are employed. The term ”antibiotic” is derived from the Greek words ”$\alpha\nu\tau\iota$” (anti), meaning ”against,” and ”$\beta\iota o\varsigma$” (bios), meaning ”life”. A comprehensive study conducted across 1,150 medical centers spanning 88 countries involved 15,302 patients, of whom 53.6 % [8, 14] were confirmed to have bacterial infections [10]. Among these infected patients, 34.2 % received treatment with carbapenems, and 31.36 % with penicillins, two significant classes of antibiotics. Remarkably, antibiotics were also administered to 39.2 % of patients who did not have confirmed infections. In the subsequent section I.2, we will delve deeper into the pharmacological properties and classes of antibiotics. However, it is worth noting at this point that antibiotics play a pervasive role in healthcare settings worldwide.

The initial treatment of HAP and VAP is determined by various patient factors: patients clinical and pathological conditions (such as sepsis), the length of stay before infection, recent history of intravenous antibiotic use within 90 days, the causative pathogen, previous infections over the past 90 days, and local antibiotic-resistance data, including the prevalence of *Staphylococcus aureus* in the hospital [2].

In the scenario of empirical treatment, where the specific causative pathogen is not yet known, as opposed to targeted treatment when the pathogen is identified, European guidelines advise the use of combination therapy that includes:

- a Gram-positive antibiotic with MRSA activity (e.g., glycopeptides or oxazolidinones) and

- one or two Gram-negative antibiotics with an activity against *Pseudomonas* species (antipseudomonal activity), one β-lactam–based agent (penicillins, cephalosporins, carbapenems or monobactams) and/or one non-β-lactam–based agent (fluoroquino - lones, aminoglycosides or polymyxins), depending on the risk factor for antimicrobial resistance [2].

In case of HAP, recommended initial empiric antibiotic therapy for HAP includes:

- a Gram-negative antibiotic for patients with no elevated risk of mortality and no factors increasing the likelihood of MRSA,
- a Gram-negative antibiotic plus linezolid or vancomycin in patients with no elevated risk of mortality but with factors increasing the likelihood of MRSA and
- two Gram-negative antibiotics plus linezolid or vancomycin in patients with high risk of mortality and with factors increasing the likelihood of MRSA [2].

These guidelines were published in 2017 for the European guidelines [2] and 2016 for the American guidelines [15]. In recent years, new therapeutic options have emerged to address multi-drug resistant (MDR) pathogens in HAP/VAP.
In 2022, updated guidelines were developed to tackle these difficult-to-treat pathogens [16–18]. Several novel antibiotics have been introduced for targeting MDR pathogens [13, 19, 20]:

- Ampicillin-sulbactam: a combination agent containing an existing β-lactam antibiotic (ampicillin) with β-lactamase inhibitor (BLI) (sulbactam)
- Cefiderocol: a siderophore cephalosporin that binds to iron and enters the bacterial cell, active against a wide range of carbapenem resistant pathogens including Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii.
- Ceftazidime-avibactam: a combination of a third-generation cephalosporin with a non-β-lactam and β-lactamase inhibitor, approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for HAP/VAP

- Ceftolozane-tazobactam: a combination of a cephalosporin and BLI, approved by the FDA and EMA for HAP/VAP.
- Imipenem-relebactam: a combination agent containing an existing β-lactam antibiotic (imipenem) with non-β-lactam β-lactamase inhibitor (relebactam).
- Meropenem-vaborbactam: a combination agent containing an existing β-lactam antibiotic (meropenem) with a non-β-lactamase inhibitor (vaborbactam), not approved for VAP, but with an advantage for clinical recovery when compared with the best available therapy in a trial that included mechanically ventilated patients with carbapenem resistant Enterobacteriaceae [20, 21].

Updated European and American guidelines for MDR pathogens, including these novels antimicrobials are summarized in Table I.1. Guidelines typically recommend a course of antibiotic therapy lasting 7 to 10 days, although this duration may vary based on factors such as the specific pathogens involved, the patient's clinical response, and the presence of complicating factors [2, 3].

Once culture results become available, and if the patient's clinical condition remains stable, healthcare providers may consider de-escalating the antibiotic regimen. This involves switching to narrower-spectrum antibiotics to mitigate the risk of antibiotic resistance [2, 3].

Table I.1: European and American recommendations on the treatment of severe difficult-to-treat Gram-negative infections according to resistance phenotypes [16–19].

Resistance phenotypes	European guidelines	American guidelines
Carbapenem-resistant *Enterobacterales* (CRE)	Meropenem-vaborbactam or ceftazidime-avibactam for severe infections if active *in vitro* Ceftazidime-avibactam plus aztreonam or cefiderocol for severe infections caused by metallo-β-lactamase-producing CRE	Meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-relebactam for non-urinary infections caused by Klebsiella pneumoniae-producing carbapenemase Ceftazidime-avibactam as first-line therapy for OXA-48 infections Ceftazidime-avibactam plus aztreonam or cefiderocol for CRE infections
Pseudomonas aeruginosa with difficult-to-treat resistance	Ceftolozane-tazobactam as first-line therapy if active in vitro	Cefftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam as first-line therapy for non-urinary infections caused by difficult-to-treat resistance *Pseudomonas aeruginosa*
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)	Ampicillin-sulbactam as first-line therapy if active *in vitro* Recommendation against cefiderocol for the treatment of severe CRAB infections Combination agent options include tigecycline or polymyxin B if active *in vitro*	Ampicillin-sulbactam as first-line therapy if active *in vitro*, in combination therapy in case of severe infections Cefiderocol in combination therapy for refractory infections to other antibiotics Combination agent options include minocycline, tigecycline, or polymyxin B if active *in vitro*

I.2 Pharmacological properties of antibiotics

The term pharmacology comes from two Greek words: $\phi\alpha\rho\mu\alpha\kappa\omicron\nu$ (pharmacon), ”poison, drug”, and $\lambda\omicron\gamma\omicron\varsigma$ (logos), ”discourse, doctrine, knowledge”. It has been defined as “the science of developing and applying mathematical and statistical methods to characterize, understand, and predict a drug’s pharmacokinetic and pharmacodynamic behavior” [22] Pharmacology is a bridging discipline, as the field includes pharmaceutical sciences, clinical pharmacology, medicine, computational science, programming, and statistics [23]. Pharmacology is divided into two disciplines: pharmacokinetics (PK) and pharmacodynamics (PD). The PK describes the fate of the drug in the organism whereas the PD describes its mechanisms of action and its pharmacological effects. Simply put, PK studies how the body handles the drug, and PD how the drug affects the body [24].

I.2.1 Mode of actions of antibiotics

According to their properties, antibiotics can either inhibit bacteria growth (they are called bacteriostatic antibiotics) or kill bacteria (bactericidal antibiotics). It exists different families of antibiotics, depending on their chemical structure and mechanism of action. They may target the cell wall, the cytoplasmic membrane, the protein synthesis, the nucleic acid synthesis or the folate synthesis of the bacteria [25]. The Figure I.3 illustrates these different mechanisms of action.

Antibiotics targeting bacterial cell wall such as β-lactams or glycopeptides are bactericidal: by inhibiting the synthesis of peptidoglycan or peptidoglycan cross-linkage which are essential for bacterial survival, they kill bacteria.

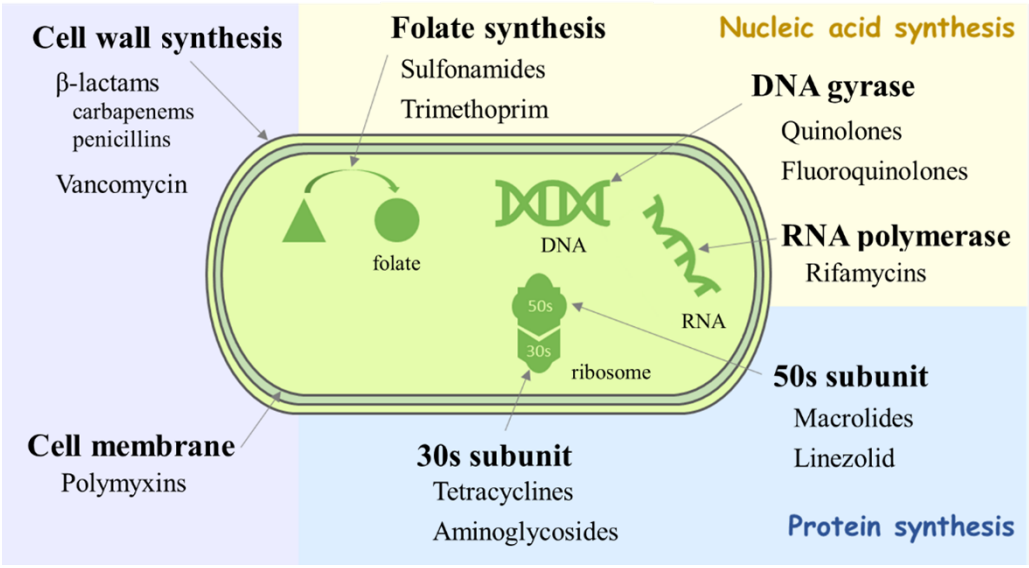


Figure I.3: Mechanisms of action of antibiotics.

The cell membrane is attacked by polymyxins, causing cell permeability, cytoplasm leakage and eventually bacteria death.

To growth and reproduce, bacteria need to replicate their deoxyribonucleic acid (DNA), transcript it into ribonucleic acid (RNA) thanks to folic acid, and make protein using ribosomes (macromolecular machines performing protein synthesis, made up of two subunits: 50s and 30s). Some bacteriostatic antibiotics like sulfonamide and trimethoprim block folic acid synthesis. Quinolones and fluoroquinolones block the action of the DNA gyrase, an enzyme involved in DNA replication. Rifamycins target RNA polymerase, an enzyme essential for RNA transcription. They are bactericidal. Protein synthesis in bacteria can be prevented by antibiotics, which block ribosomes. Macrolides and linezolid act on 50s subunit of ribosomes while tetracycline and aminoglycosides act on 30s subunit. They can be bactericidal or bacteriostatic.

Antibiotics used nowadays in clinics are most often derived from natural compounds, such as actinomycetes or other bacteria, and fungi (Figure I.4) [26]. They were isolated from organisms competing with bacteria in their natural environment. Microbes are among the oldest organisms and have been existing for billions of years. They thus have developed mechanisms to defend themselves against aggressions from other species, and to attack the others, in a constant state of equilibrium [27]. Bacteria can adapt themselves to these attacks, and therefore to antibiotics action. It is known as **antimicrobial resistance** (AMR).

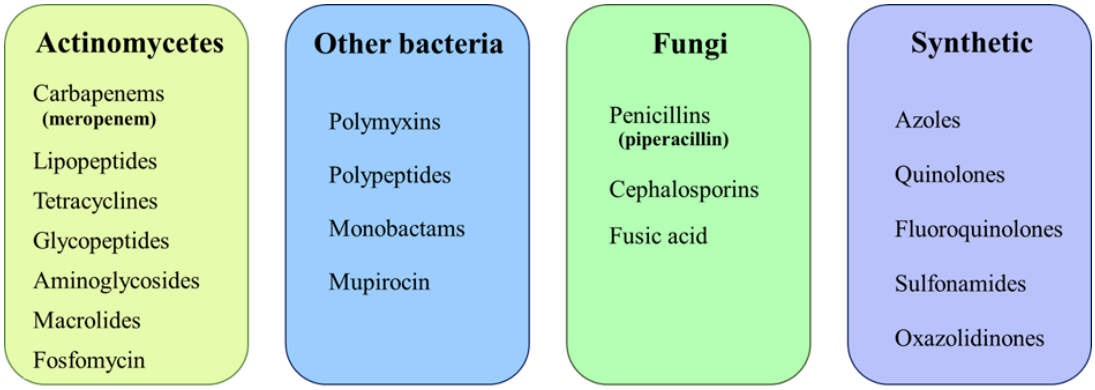


Figure I.4: Origin of most common classes of antibiotics.

I.2.2 Bacterial resistance to antibiotics

Mechanisms of resistance

Bacteria have developed resistance mechanisms to survive in their natural environment, becoming increasingly adept over time. They create resistance genes as a defense against antibiotics and can even share these genes with subsequent generations (vertical transfer) and across distinct species (horizontal transfer) (Figure I.5). Vertical gene transfer is the transmission of genetic material from one generation of bacteria to the next within the same lineage, typically through reproduction. It does not involve gene exchange between different species. One the other hand, horizontal gene transfer refers to the transfer of genetic material between different bacteria of the same generation. This can occur through processes like conjugation (direct exchange of DNA between bacteria via a structure called pilus), transformation (absorption of DNA by bacteria from the surrounding environment), and transduction (bacteriophages can transfer genes by infecting different bacteria cells), allowing bacteria to exchange genes and traits. Horizontal and vertical gene transfers are combined, especially within confined environments such as infection sites [28].

We might wonder how bacteria acquire resistant gene. They undergo mutations due to selective pressure; some of these mutations confer resistant properties to them. They survive and transfer these new abilities through both horizontal and vertical gene transfers. These mutations regard modifications of the antibiotics target or the inactivation of antibiotics. Some bacteria show resistance by efflux mechanism (bacteria expel antibiotics before they have time to work), while others show altered permeability or bypass of the metabolic pathway [25]. The different mechanisms of AMR are illustrated in Figure I.6.

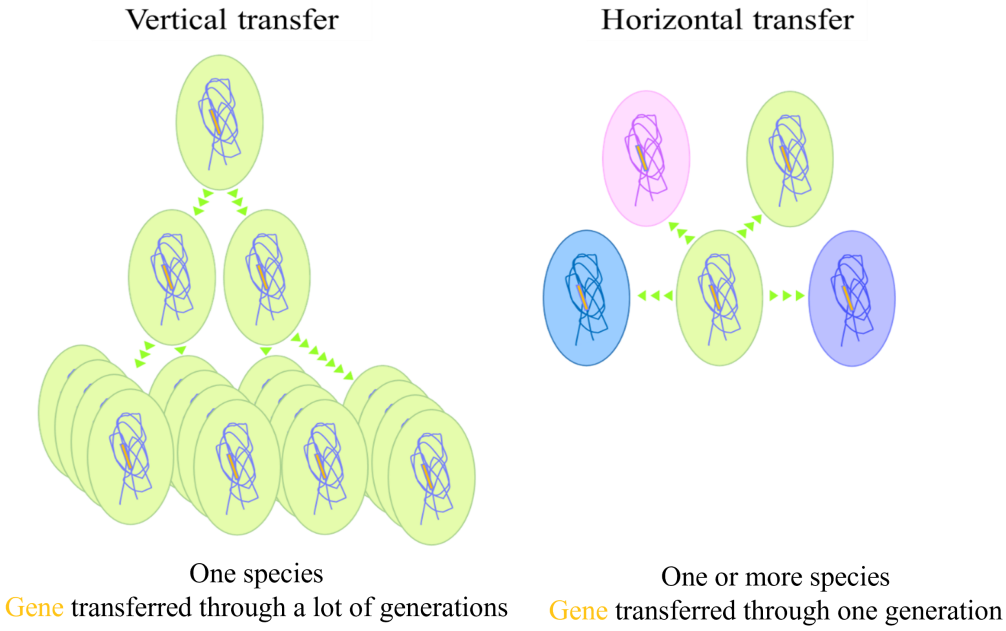


Figure I.5: Horizontal and vertical gene transfer. **Vertical gene transfer** is the transmission of genetic material from one generation of bacteria to the next, typically through reproduction. This process leads to the inheritance of genetic information from parent to offspring. **Horizontal gene transfer**, on the other hand, refers to the transfer of genetic material between different bacteria of the same generation. This can involve the same bacterial species or different bacterial species, allowing for the exchange of genes and traits.

Consequences in clinics

Multidrug-Resistant (MDR) bacteria are bacteria that have developed resistance to multiple classes of antibiotics. This phenomenon makes the treatment of bacterial infections increasingly challenging in clinical settings. Drug resistance can spread rapidly, limiting effective treatment options and increasing the risk of severe and potentially life-threatening infections. This burden poses a major and worsening clinical challenge, as their prevalence continues to rise, resulting in significant mortality [29].

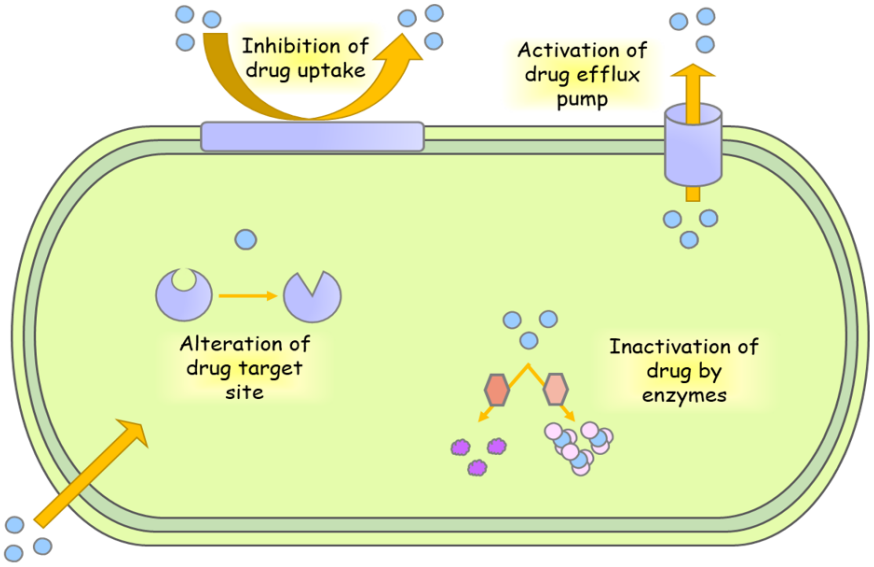


Figure I.6: Mechanisms of antibiotic resistance.

In both the EPIC-III survey and the EUROBACT-2 study focusing on infections in ICU, Gram-negative bacterial infections constituted a majority, comprising over 60 % of the reported cases [10, 30]. Furthermore, more than 24 % of these bacterial strains were classified as difficult-to-treat resistance (DTR) [10, 30]. This classification denotes an intermediate or resistant phenotype to all first-line agents within the carbapenem, β-lactam, and fluoroquinolone categories.

In the context VAP, it has been observed that Gram-negative bacteria exhibiting MDR profiles are prevalent in up to half of the reported cases [2, 3, 10]. Within the DTR Gram-negatives, several species stand out, including DTR Enterobacterales, DTR *Pseudomonas aeruginosa* and DTR *Acinetobacter baumannii* [31]. Within Enterobacterales strains, the primary mechanism of antibiotic resistance often revolves around the production of Class A carbapenemases (e.g., KPC) and Class D carbapenemases (e.g., OXA-type) [32]. Additionally, Class B carbapenemases, including metallo-β-lactamases (MBL), contribute significantly to the development of resistance. DTR *Pseudomonas aeruginosa* exhibits a range of resistance mechanisms, encompassing the upregulation of efflux pumps, the loss or reduction of outer membrane porins (OprD), increased production of AmpC enzymes, and mutations affecting penicillin-binding proteins [33, 34]. Similarly, DTR *Acinetobacter baumannii* employs various mechanisms to resist multiple antibiotics, including efflux pumps and alterations in antibiotic binding sites, along with the expression of carbapenemases. The predominant class of carbapenemases in this context is Class D, including variants such as OXA-23-like, OXA-24/40-like, and OXA 58-like [31].

Antibiotic resistance poses a significant global concern in the context of HAP and VAP, especially because of its association with prolonged length of hospital stay and higher mortality rates [2, 3, 31]. The continual rise of MDR microorganisms has created a situation where many of the currently available antibiotics are steadily losing their effectiveness [35, 36]. As a result, drug-resistant infections have become a leading cause of death worldwide [35]. This predicament is compounded by the troubling shortage of new antimicrobial agents currently in the developmental pipeline [37].

Antibiotic stewardship, research into new therapies, and robust infection control measures are essential components of the strategy to address this growing healthcare concern. This thesis centers on the optimization of antibiotic stewardship, with a particular emphasis on enhancing the pharmacological properties of antibiotics, namely the PK and the PD. The following section I.2.3 will provide an explanation of PK, highlight its major parameters, and outline methods for modeling drug PK.

I.2.3 Notions of pharmacokinetics

PK studies the effect of the organism on a drug, here, on antibiotics. Its goal is to predict drug concentrations along treatment in the blood and possibly in the organs. For this purpose, it is important to understand how a molecule is absorbed in the body, distributed throughout it, metabolized, and eliminated.

Absorption, Distribution, Metabolism and Elimination (ADME)

We can see the fate of the antibiotics in the body as a journey. It seems obvious that to be effective, a drug must reach its target, in our case, the bacteria causing pneumonia. The first stage of the antibiotic's journey is therefore to reach the general bloodstream from its administration site; it is the **absorption** [38].

By definition, if the antibiotic is administered intravenously, there is no absorption (being injected directly into the general bloodstream). For extra-vascular routes of administration (as opposed to intra-vascular), such as oral, subcutaneous or aerosol administrations, the antibiotic will have to pass through the body's natural barriers protecting us from toxic elements (like gastric acidity, the intestinal barrier, and the liver in the case of an oral route) before reaching the general bloodstream. One parameter of interest is linked to absorption and can be directly measured: the maximum concentration of the antibiotic in the general bloodstream, known as C_{max} (Figure I.7).

Once in the systemic bloodstream, the antibiotic can reach its target following the bloodstream. The **distribution** phase characterizes this passage of drugs from the bloodstream to other tissues and organs and vice-versa. Drugs can then exert their therapeutic effect in the body sites where they are intended to act (e.g., lungs in pneumonia, central nervous system in meningitis or encephalitis, abdomen in intra-abdominal infections… [39–41]) but can also cause undesirable or even toxic effects in other sites, such as daptomycin which causes skeletal muscle toxicity [38]. It should be noted that drug molecules can only diffuse from plasma to tissues and from tissues to plasma when they are in unbound, i.e., not bound to plasma proteins such as albumin.

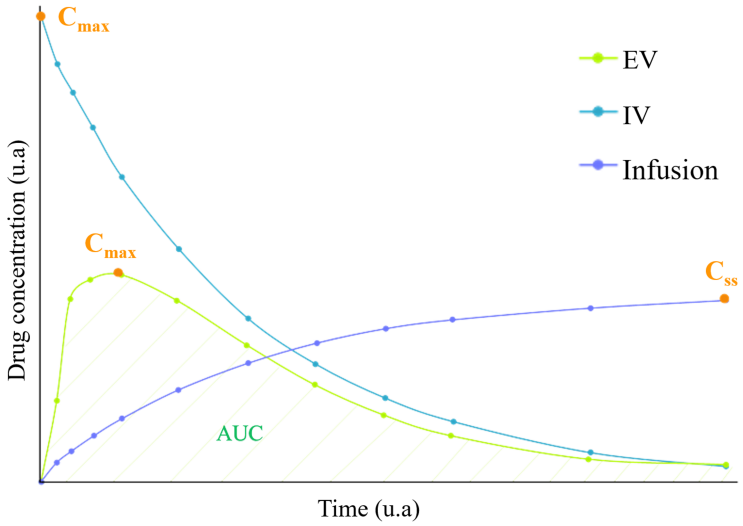


Figure I.7: PK parameters derived from the drug concentration versus time profile. Antibiotic concentration-time curve showing the maximum concentration (C_{max}) (in orange, one for each curve) and the exposure (area under the curve or AUC) (in green, shown only for the green curve but can be calculated for the three curves) following an intravenous (IV, in blue), an extra-vascular (EV, in green) and a continuous infusion (in purple) administration. Note that with a continuous infusion, concentrations reach a plateau when the rate of elimination of the drug is equal to the rate of infusion. This state of equilibrium is called steady-state and the resulting concentrations are called C_{ss} (steady-state concentrations). To reach this plateau more quickly, it is possible to administer an IV dose of the drug, known as the loading dose (LD), to immediately reach the steady state.

A fundamental PK parameter characterizing the drug distribution is the volume of distribution (V_D). The V_D represents the theoretical volume used to quantify the distribution of a drug between plasma and the rest of the body. It is defined as the volume required to accommodate the total quantity of an administered drug while maintaining the same concentration observed in the blood plasma, thereby illustrating the significance of drug distribution within tissues [38]. This relationship can be expressed mathematically as shown in Equation I.1. Consequently, drugs with high V_D values are extensively distributed throughout the body, while those with low V_D values exhibit limited distribution [38, 42, 43]. In other words, a drug that remains primarily within the plasma would have an extremely low V_D (approximately 3 L for a 70 kg man). Conversely, if all a drug's molecules left the plasma to distribute to other tissues, the V_D would be infinite (Figure I.8). The highest known V_D is the quinacrine's one (50,000 L) [38].

$$V_D = \frac{total \quad amount \quad of \quad drug \quad in \quad the \quad body \quad (dose)}{drug \quad plasma \quad or \quad blood \quad concentration} \tag{I.1}$$

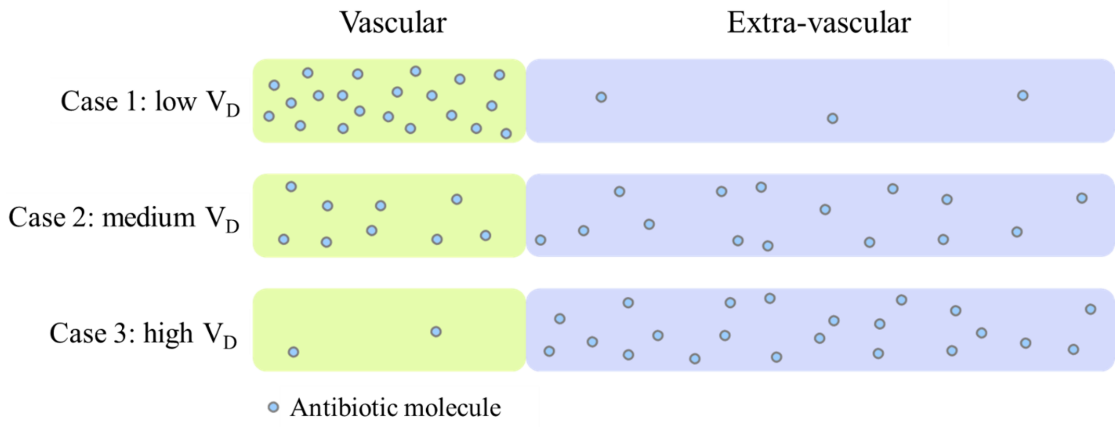


Figure I.8: Concept of volume of distribution (V_D). A low V_D indicates a (very) low capacity for tissue diffusion of the drug, due to a too high molecular weight (macromolecules are too large to diffuse) or to strong binding to plasma proteins (small molecules bound to proteins become too large to diffuse). In these cases, V_D do not exceed 10 L. Intermediate V_D are found for small molecules (< 500 Da) that diffuse easily into the extracellular water space (such as aminoglycosides, with a V_D around 15 L) or extra- and intracellular molecules (V_D similar to the total volume of water in the body, i.e., 45 L). High V_D indicate that the drug diffuses easily into peripheral tissues, and even a high capacity to bind in these tissues.

The human body, through its remarkable evolutionary adaptations, possesses the capacity to recognize and eliminate xenobiotics—substances foreign to a living organism. Consequently, drugs, being perceived as foreign entities, trigger various mechanisms aimed at their removal from the body. One such elimination pathway is metabolism.

The **metabolism** entails enzymatic reactions that alter the drug's structure, resulting in the creation of one or more derivative compounds referred to as metabolites. The primary objectives of this phase include the deactivation of the drug, reduction of its potential toxicity, and the conversion of the drug into a water-soluble form, facilitating its elimination through either bile or urine. Many classes of drugs, including fluoroquinolones, macrolides, oxazolidinones, rifamycins, and azoles, undergo this metabolic transformation. Alternatively, another pathway for drug excretion involves renal elimination.

Renal elimination pertains to the expulsion of the drug in its unaltered form, i.e., without undergoing metabolic changes, through the urine. This excretion pathway primarily applies to small, water-soluble molecules, including the majority of β-lactams, glycopeptides, and aminoglycosides. The body's overall capacity to eliminate a molecule is characterized by the **clearance** (CL). Clearance is defined as the volume of plasma from which a substance, such as an antibiotic, is entirely removed within a specific unit of time [24, 38].

Clearance is another fundamental PK parameter; serving as a measure of the rate at which a substance undergoes elimination from the body. Clearance can be specified for each organ involved in drug excretion, encompassing hepatic clearance, renal clearance, intestinal clearance, pulmonary clearance, and others. The total clearance is derived by summing these individual clearances. In the context of most drugs, only hepatic and renal clearance are of significant consideration, with the contributions of other organs being negligible. For drugs primarily excreted via the urinary route, renal clearance is often sufficient for approximating the total clearance, as observed in the case of β-lactams, for instance [24, 38]. In the scenario of intravenous (IV) administration, clearance can be quantified as the ratio between the administered dose and the area under the concentration-time curve **AUC**, as represented by Equation I.2. AUC corresponds to the integral of drug concentration over time (Figure I.7). It provides insights into both the extent of drug exposure and the rate at which it is cleared from the body. In cases of repeated administration, the overall AUC (from the first dose onward) or AUC over a specific period (such as between the penultimate and last doses) can be derived.

$$CL = \frac{Dose}{AUC} \tag{I.2}$$

The minimum concentration, often referred to as the residual concentration or trough concentration (C_{min}) is another parameter of interest in PK. It represents the lowest concentration of a drug present in the bloodstream, specifically the concentration just before the administration of a new dose. C_{min} also serves as an indicator of the body's capacity to eliminate a substance.

Assessing the ability to eliminate a substance is of utmost importance in clinical practice. If a drug's elimination capability is exceedingly low, patients may be at risk of toxicity. Conversely, if it is excessively high, there is a potential for therapeutic failure. In most cases, the precise measurement of drug clearance is not readily available, primarily due to practical and economic constraints. As a result, clinicians often rely on surrogate markers to determine appropriate drug dosing regimens.

For drugs that are primarily eliminated through the kidneys, such as β-lactams, considering renal function is essential when adjusting dosage regimens to ensure safe and effective treatment [44].

Renal clearance, glomerular filtration rate and creatinine clearance

The kidney plays a key role in the elimination of a wide variety of xenobiotics [45]. Each kidney is made up of around 1.2 million nephrons [46]. The nephron is the kidney's structural and functional unit responsible for urine formation [24, 38, 45, 46]. The kidney consists of Bowman's capsule, the proximal convoluted tubule, the Henle's loop, the distal convoluted tubule and the collecting duct (Figure I.9) [24, 38, 45, 46]. The kidney is highly vascularized, with 2 main capillary networks: the first forms the glomerulus, housed in Bowman's capsule, and the second surrounds the tubular capillaries [47]. Urine is formed from plasma in three stages: glomerular filtration, tubular reabsorption, and tubular secretion.

Small water-soluble molecules, such as water, sugar, ions and certain antibiotics like meropenem, are filtered through Bowman's capsule (which acts like a molecular sieve) and pass from the blood capillaries to the nephron; this is the glomerular filtration [24, 38, 45–48]. The indicator of the capacity of kidney to filtrate plasma is the **glomerular filtration rate** (GFR), the rate at which plasma is filtered through Bowman's capsule [49, 50].

The ultrafiltrate or primary urine formed after glomerular filtration undergoes changes in its chemical composition, in the proximal convoluted tubule, the loop of Henle and the distal convoluted tubule, where certain molecules can be reabsorbed from the nephron into the blood: this is tubular reabsorption. In this way, glucose, 99 % of water and some ions are reabsorbed. Other molecules can be secreted directly from the peritubular capillaries. This is known as tubular secretion. The final urine accumulates in the bladder via the collecting duct [24, 38, 45–48]. In a more mathematical way [48]:

$$Drug\,CL = [\,glomerular\;\; filtration + tubular\,secretion\,] - tubular\,reabsorption \tag{I.3}$$

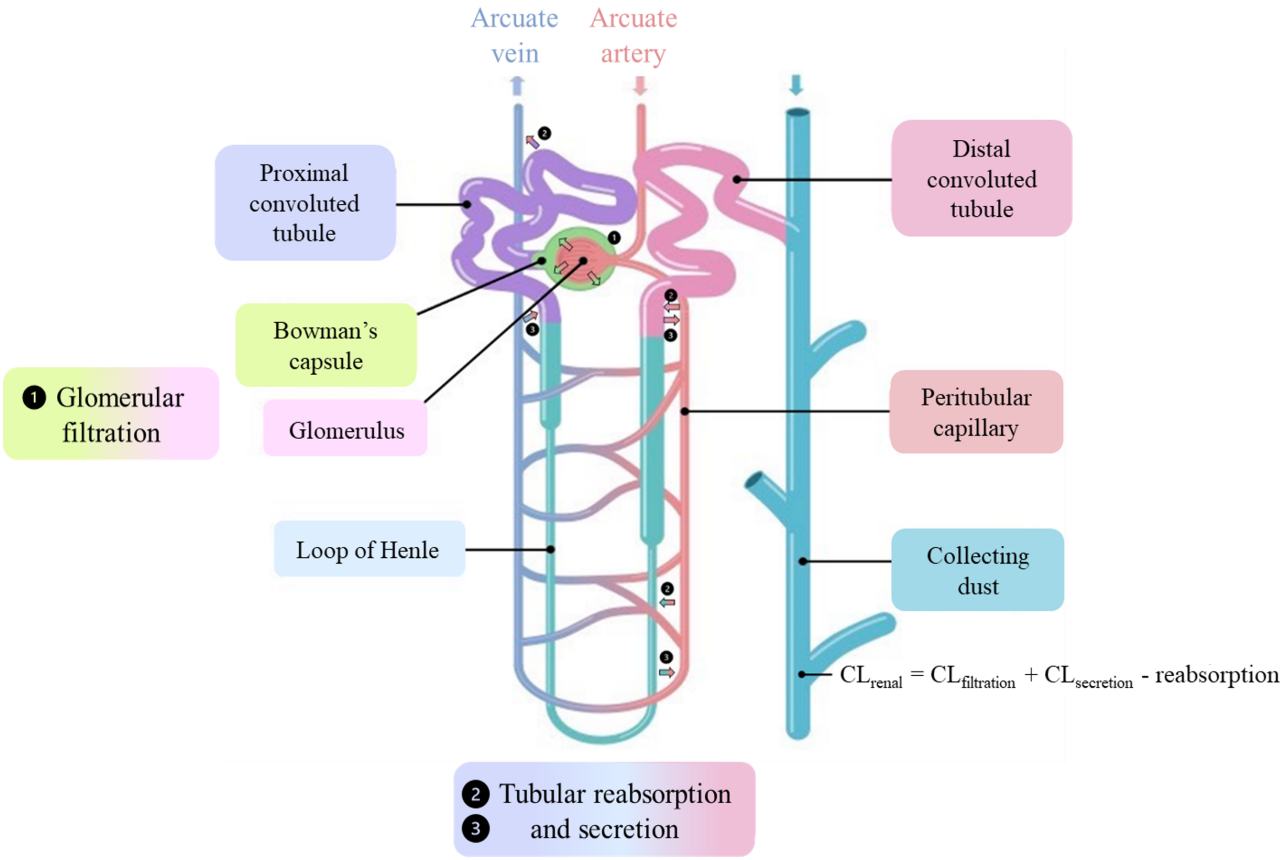


Figure I.9: Schematic representation of the functional unit of the kidney, the nephron. Renal clearance (CL_{renal}) is a composite of three distinct phenomena: glomerular filtration ($CL_{filtration}$), tubular reabsorption and tubular secretion ($CL_{secretion}$). Adapted from [51].

Ideally, the renal clearance of a drug should be determined by collecting the patient's urine and measuring its urinary concentration. However, this is impractical in routine clinical practice, time-consuming and expensive. Although renal function is not limited to the glomerular filtration process, the GFR is considered the best indicator of renal function in clinics [49, 50]. GFR The direct measurement of GFR is not feasible; however, it can be evaluated through the measurement of clearance of some markers. These markers employed to assess GFR can either be endogenous, originating within the organism, or exogenous, introduced from external sources. It is crucial that these markers are non-metabolized (e.g., undergo renal elimination exclusively), are produced or administered at a constant rate, and are subject to filtration without involving secretion or reabsorption processes. In the realm of GFR assessment, the gold standard is the measurement of inulin clearance [49, 52]. However, this procedure is intricate and costly, making it impractical for routine clinical use [50]. Theses inconveniences have encouraged the use of endogenous markers.

The most commonly employed endogenous marker for GFR assessment is creatinine [24, 38, 49, 50, 53]. Creatinine results from the breakdown of creatine phosphate in muscle tissue. It is produced by the body at a constant rate [49, 54, 55], which is contingent upon an individual's muscle mass. Importantly, creatinine undergoes complete renal elimination without reabsorption or secretion [54]. Therefore, creatinine clearance (CL_{CR}) serves as clinical parameter for evaluating kidney function, and it can be determined through measurement or estimation.

The measurement of CL_{CR} (referred to as mCL_{CR} for measured CL_{CR}) necessitates the collection of urine over a 24-hour period. Creatinine clearance is then calculated using Equation I.4 [49, 54]. In contrast, the estimation of CL_{CR} provides a more convenient means of approximating GFR without requiring urine collection [49, 50]. It relies on the measurement of plasma creatinine levels and different formulas have been developed for this purpose:

- The Cockcroft & Gault or CG formula (*named after its creators*) is based on sex, age and weight [56];
- The Modification of Diet in Renal Disease or MDRD formula (*name of the study that identified it*) is based sex, ethnicity and age [57],
- The Chronic Kidney Disease Epidemiology collaboration or CKD-EPI formula (*name of the study that identified it*) is based on sex, ethnicity and age [58].

$$mCL_{CR} = \frac{U_{CR} \times U_{Volume}}{S_{CR} \times T} \tag{I.4}$$

where U_{CR} is the urinary creatinine concentration (mg/dL), U_{Volume} is the urinary volume (mL), S_{CR} is the serum creatinine concentration (mg/dL), and T is the 24-h collection time.

The KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines defined the distinct stages of renal function according to GFR (Table I.2).

Table I.2: Classification of renal function according to GFR ranges.

GFR ranges (mL/min/1.73 m²)	Description of renal function
≥ 90	Normal or high
60-89	Mildly decreased
45-59	Mildly to moderately decreased
30-44	Moderately to severely decreased
15-29	Severely decreased
< 15	Kidney failure

Mathematical modelling

In order to predict anti-infective concentrations over time, all the different PK processes (absorption, distribution, metabolism, and elimination) need to be translated into mathematical language. The prevailing method frequently employed is the utilization of ”compartmental” models. These models employ systems of differential equations to delineate the concentrations of a drug in the distinct compartments of the model as they evolve over time [23].

In PK, a compartment is a virtual distribution space in which the drug is instantaneously distributed homogeneously, then eliminated or exchanged with other compartments, following identical kinetics at all points and over time in the compartment. Sometimes, the drug does not distribute homogeneously in the whole body (accumulation in some tissues for example) and more than one compartment is needed to describe the drug PK. The different compartments (usually, 1 to 3) represent the whole body [23, 24, 38].

PK compartments are based on several assumptions and conditions; the first is that concentrations are always homogeneous within the compartment. The second is that exchange rates between compartments are of order one, and that rate constants and volumes are constant over time. Compartments are said to be mamillary; meaning that all transfers take place from the central compartment, including those entering and leaving the body (Figure I.10).

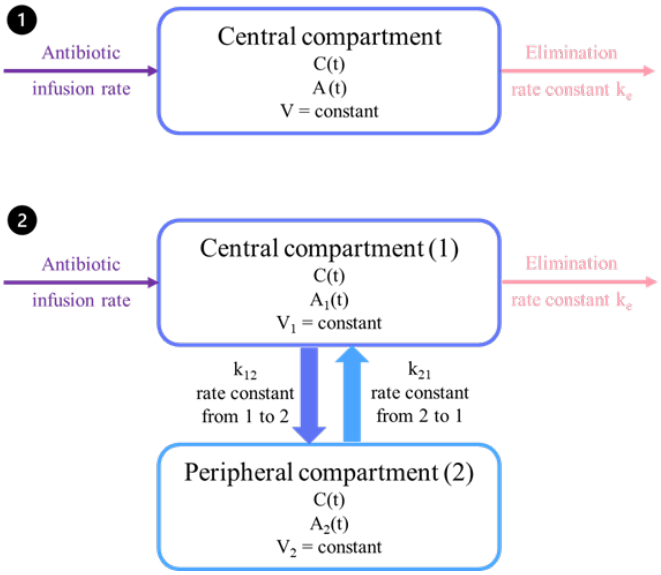


Figure I.10: Schematic representation of a 1 (upper panel) and 2-compartment (lower panel) pharmacokinetic model.(t) is the drug concentration over time in plasma and $A_x(t)$, the drug amount over time in compartment x. From [38].

The PK describes the relationship between drug dosing and the drug concentration-time profile in the body. The drug concentration change over time (C(t)) can in the simplest case be approximated to decline from an initial concentration (C_0) with time (t) by an exponential function (Equation I.5). In this case, the elimination rate (k_e, in /time unit) at any given time point is proportional to the concentration remaining in the system. Equation I.5 represents a one compartment model with intravenous (IV) administration. As is commonly done [2, 13, 15, 44], antibiotics are routinely administered intravenously to critically ill patients at our hospital. Therefore, we will not delve into models describing extra venous administration.

$$C(t) = C_0 \times e^{-k_e \times t} \tag{I.5}$$

Once the PK parameters have been estimated, it is possible to predict drug concentrations in an individual with the model. In order to do the same at the level of a population of individuals, it will be necessary to add to these models the notions of individual variability and residual error. This is what we call the population approach, developed in the next section I.2.3.

Population approach

The population approach in PK modeling is a method used to estimate the PK parameters of an entire population, rather than just an individual. The population approach involves the use of PK modeling techniques to analyze data collected from a group of individuals, and then make predictions about the PK of individuals in the population based on statistical modeling. The concept of population pharmacokinetics (popPK) was first proposed by Sheiner and Beal in the 1970s [59].

The aim of popPK is to define the mean PK parameters and their dispersion (variance) in a group of patients, to estimate the inter-individual or even intra-individual variability of PK parameters, and to quantify the relationships that exist between a patient's physiological state and his PK properties. Therapy can thus be individually optimized.

There are three important components of popPK models: the structural model, the statistic models, and the covariate models.

The structural model describes the general evolution of drug concentration over time using the mathematical equations explained in the previous section I.2.3 (e.g., 1 or 2 compartments, type of administration…). The obtained PK parameters, such as CL and V_D, are average population parameters or typical population parameters. They represent a hypothetical patient representative of the population being studied.

The statistical model describes variability around the structural model and the distribution of individual PK parameters. There are two main sources of variability in population PK: between-subject variability (BSV) or inter individual variability (IIV), which is the variance of a parameter across individuals; and residual variability, which refers to the unexplained variability that remains after accounting for other sources of variability. This residual variability takes into consideration factors such as imprecision in time sampling and drug concentration determination. It also acknowledges the inherent limitations of attempting to precisely describe a complex phenomenon using a "simplified" mathematical formula.

The individuals of the studied population do not have the same PK parameter values (each patient, for example, has his or her own CL and V_D values). Individual PK parameters are random variables whose distribution can be estimated. A statistical model must therefore be chosen to describe the distribution of individual parameters as a function of the typical population parameter. For most parameters, a lognormal distribution is assumed, as they must be positive (CL and V_D values cannot be negative, for example) and often right skewed. Therefore, the individual parameter of the i^{th} patient (P_i) can be calculated using the value of the mean population parameter (P_{pop}) and the deviation from the median of the parameter i^{th} patient (η_i) as:

$$P_i = P_{pop} \times e^{\eta_i} \tag{I.6}$$

Taken across all evaluated individuals, the individual η values are assumed to be normally distributed with a mean of zero and variance ω^2. That is the hypothesis assumed in Monolix, the software used to build the PK and PD models in this thesis.

The residual unexplained variability (RUV) arises from multiple sources, including assay variability, errors in sample time collection, and model misspecification. It describes the deviation between the concentrations predicted by the model (IPRED for individual predicted concentrations) and those actually observed (DV for dependent variable or obs for observations). It is noted ϵ. There are several possible models for describing RUV: additive (Equation I.7), uncertainty is independent of concentration levels), proportional (Equation I.8), uncertainty is proportional to the concentration levels) or combined (Equation I.9), among others.

$$DV = IPRED + \epsilon \tag{I.7}$$

$$DV = IPRED + \epsilon \times IPRED \tag{I.8}$$

$$DV = IPRED + \epsilon_1 \times IPRED + \epsilon_2 \tag{I.9}$$

Apart from estimating dose-concentration-time profiles of each patient and quantifying inter-individual variability, the population approach enables the search for factors that can explain part of the variability. These factors may include age, gender, body weight, renal function, and other medical conditions that may affect drug PK (Figure I.11). These several factors are known as covariates and partly explain variations in PK parameters between individuals or, sometimes, even within the same individual during treatment. Covariates models account for the effect of covariates. As an example, creatinine clearance (CL_{CR}) is often a significant covariate for CL of renally excreted drugs, and incorporation of a relationship between this covariate and CL will likely reduce the inter-individual variability. CL_{CR} can thereby provide guidance in the individualization and choice of dose so that patients with a low CL_{CR} receive a lower dose in accordance with their reduced capacity to eliminate the drug [23].

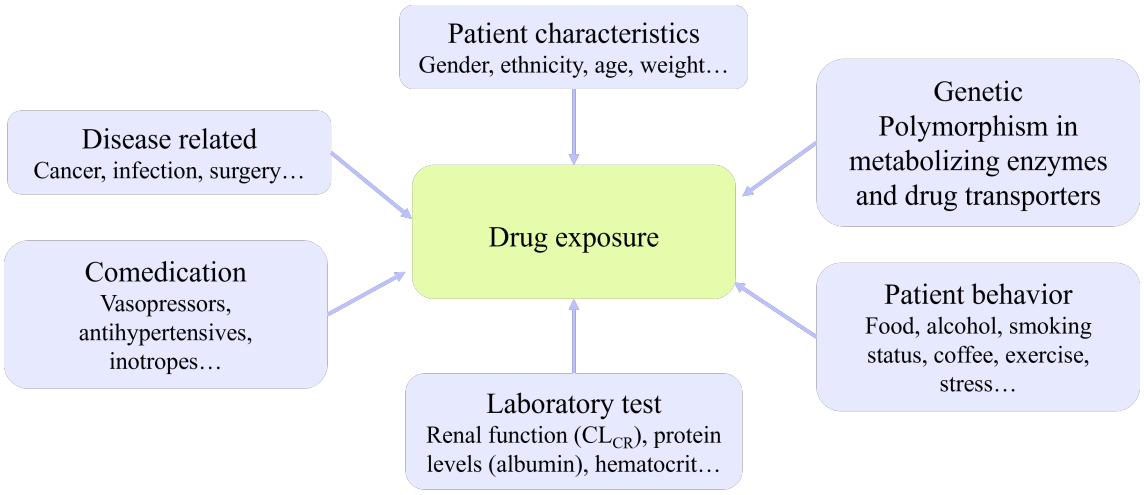


Figure I.11: Factors explaining inter-individual variability and affecting drug exposure. From (59).

From a statistical point of view, popPK modeling refers to non linear mixed effects modeling because it combines two diverse types of models: non-linear models and mixed effects models. Non-linear models are used to describe relationships between concentrations and parameters (which varies with time, dose, age, and other factors). Mixed effects models, on the other hand, refer to the fact that popPK models incorporate fixed effects, which are parameters that are constant across subjects, and random effects, which are parameters that vary across subjects.

Several algorithms can be used to estimate the popPK parameters, like the SAEM algorithm in Monolix (stochastic approximation expectation-maximization algorithm). They are iterative meaning that they use repeated cycles of model estimation, assessment, and refinement to improve the ability of a model to accurately describe the PK behavior of a study population. Algorithm are based on a likelihood function, calculated to judge the performance of the estimates, and maximized to improve model performance. As estimation cycles progress, this likelihood function is optimized to stabilize and stop the algorithm; it is the convergence.

Different models can be compared with each other's using the objective function (OF), calculated according to Equation I.10. Two models can be confronted by comparing their OF value (OFV). The difference between the two OFV follows a χ^2 (chi-squared) distribution with 1 degree of freedom (if the number of parameters is identical), with a threshold value $\Delta \geq 3.84$ for rejection of the null hypothesis at a first-species risk of 5% ($p < 0.05$). So, if the model 2 has an OFV 3.84 smaller than the OFV of the model 1, model 2 is preferable. To take into account the complexity of the model and with a view to parsimony, so-called penalty criteria can be used, such as the Akaike information criterion (AIC) or the Bayesian information criterion (BIC), which can be calculated using the equations I.11 and I.12, respectively.

$$OFV = -2 \times ln(likelihood) \tag{I.10}$$

$$AIC = -2 \times ln(likelihood) + 2 \times k \tag{I.11}$$

$$BIC = -2 \times ln(likelihood) + n \times k \tag{I.12}$$

where k is the number of parameters to be estimated in the model and n, the number of observations.

Other conventional criteria are used to choose between different models and to validate the model. Parameter accuracy is assessed using the relative standard error (RSE), a measure of a statistical estimate's reliability (lower the RSE is, more accurate is the parameter estimation). Linear regression between population or individual model-predicted concentrations and observed concentrations highlights potential bias in estimation. The model's predictive capability is assessed using a virtual population whose characteristics are randomly selected based on the model, and whose simulated observations are compared with actual observations. The latter must be homogeneously distributed in relation to the simulations. This representation is called a VPC for visual predictive check. Finally, the bootstrap, a patient resampling technique, is used to check the robustness of the model and the accuracy of the estimated parameters [23, 38].

Once validity has been established, the model can be used for extrapolation. The Monte Carlo method is generally used to run simulations, generating random values of parameters and covariates according to their own distribution law to produce many PK profiles (thousands). One of the most common and useful application of simulations is to investigate different dosage regimens in different patient groups (renal impairment, elderly, obese…).

I.2.4 Notions of pharmacodynamic modeling

To describe the dose-response relationship of antibiotics, once the PK has been determined, the PD needs to be characterized. PD modeling is used to describe and quantify the relationship between the concentration of a drug and its biological effect. The time course of effects can be directly or indirectly related to plasma drug concentration.

Direct effect models describe the relationship between plasma drug concentration and immediate pharmacological effects. These models assume that the drug directly binds to its target (e.g., useful when the target is in the plasma) and produce a response that is proportional to the plasma drug concentration. The simplest form of direct effect models is the E_{max} model (Equation I.13), which assumes a maximum effect (E_{max}) that can be achieved for a drug and a concentration required to produce half of the maximum effect (EC_{50}). The E_{max} model can be graphically represented by a sigmoid curve that shows the relationship between drug concentration and response. The E_{max} model was modified in sigmoidal E_{max} (according to Equation I.14) to consider the fact that multiple drug molecules can interact with one target, leading to a sigmoidal dose-response curve.

$$E(t) = \frac{E_{max} \times C_p(t)}{EC_{50} + C_p(t)} \tag{I.13}$$

$$E(t) = \frac{E_{max} \times C_p(t)^{\gamma}}{EC_{50}^{\gamma} + C_p(t)^{\gamma}} \tag{I.14}$$

where E(t) is the drug effect over time, E_{max} is the maximum effect, EC_{50} is the drug concentration that produces 50 % of the maximum effect, $C_p(t)$ is the plasma drug concentration over time, and γ is the sigmoidicity coefficient or Hill number which represents the steepness of the drug effect-concentration curve.

Direct effect models are useful for drugs that act rapidly and have a direct and reversible effect on their targets. However, they may not be suitable for drugs with complex pharmacological effects or drugs that act through indirect mechanisms. Direct effect models also may not account for the time course of drug action, as they assume an immediate effect that is independent of drug concentration changes over time.

Effect compartment models describe the temporal relationship between drug concentration and effect. These models assume that the drug has a rapid distribution phase, followed by a slower elimination phase, and that the drug's effect is delayed and sustained compared to its plasma concentration. The delayed response is due to the time required for the drug to reach its target site in the body and to produce a pharmacodynamic effect. This delayed response can be modeled by introducing an effect compartment that represents the time delay between drug concentration in the plasma and drug concentration at the target site. The relationship between the concentration of the drug in the effect compartment and the effect is described using the following equations, using E_{max} (Equation I.15) or sigmoidal E_{max} (Equation I.16) models:

$$E(t) = \frac{E_{max} \times C_e(t)}{EC_{50} + C_e(t)} \tag{I.15}$$

$$E(t) = \frac{E_{max} \times C_e(t)^{\gamma}}{EC_{50}^{\gamma} + C_e(t)^{\gamma}} \tag{I.16}$$

where E(t) is the drug effect over time, E_{max} is the maximum effect, EC_{50} is the drug concentration that produces 50 % of the maximum effect, $C_e(t)$ is the drug concentration over time in the effect compartment, and γ is the sigmoidicity coefficient or Hill number which represents the steepness of the drug effect-concentration curve, similarly to the direct effect models (see Equations I.13 and I.14).

Effect compartment models are particularly useful for drugs with slow onset and prolonged duration of action, such as anesthetics and sedatives. They can also account for factors that affect drug distribution and elimination, such as tissue binding and metabolism. But these models are insufficient when a surrogate is used to reflect response to a drug (e.g., inflammation markers to reflect antibiotic treatment, called biomarkers) or when adding an effect compartment is not enough to model drug response.

Turnover models describe the relationship between drug concentration and the rate of biomarkers production or elimination. These models assume that the drug acts by modulating the turnover rate of the biomarker, usually a protein (enzyme, receptor…). Basically, the drug can enhance or inhibit the production or the degradation of the biomarker, leading to 4 different scenarios (Figure I.12). The equations used to describe these scenarios are similar to the ones describing E_{max} model (Equations I.15 and I.16).

$$I(t) = 1 - \frac{I_{max} \times C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}} \tag{I.17}$$

$$S(t) = 1 + \frac{I_{max} \times C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}} \tag{I.18}$$

where I(t) and S(t) represent the inhibition and simulation function, I_{max} and S_{max} the maximum inhibition and simulation at the effect site (S_{max} should be > 0 and 0 < I_{max} <1), IC_{50} and SC_{50} the drug concentration producing 50 % of the maximum inhibition or simulation achieved at the effect site, respectively, C_P the drug plasma concentration and γ is the sigmoidicity coefficient (can be set at 1 if no sigmoidicity is needed).

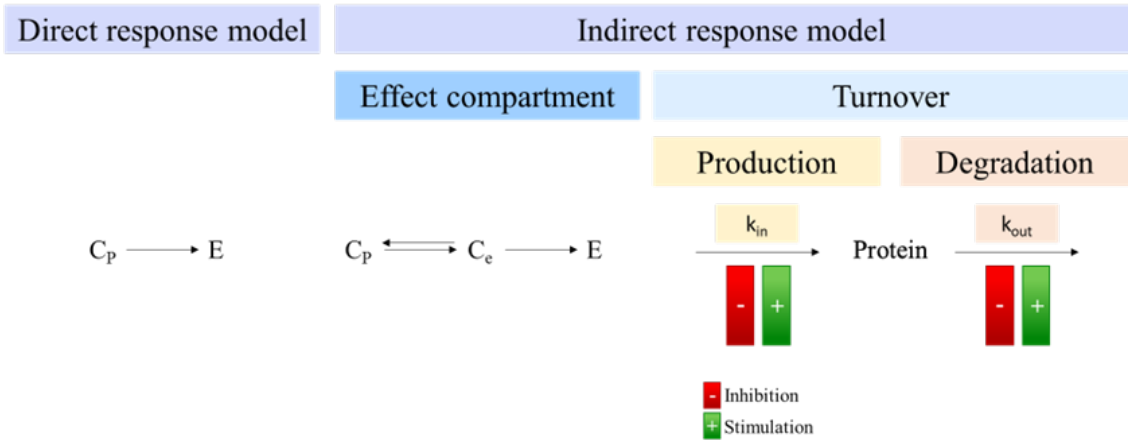


Figure I.12: Diverse ways of considering drug-effect relationship. In the direct response model, the hypothesis is that the effect (E) is directly linked to the drug plasma concentration (C_p). Most of the time, a delayed response is observed because a drug must reach its target to induce an effect, or because the effect is observed only after a cascade of events triggered by the drug. In the first case, drug-effect relationship can be modelled by adding a virtual compartment (effect compartment C_e) to represent the delayed response due to drug distribution to its target site. In the second case, the drug can eventually lead to simulation or inhibition to a protein production (described by a production rate k_{in}) or inhibition (described by a degradation rate k_{out}).

I.2.5 Pharmacokinetic/pharmacodynamic relationships of antibiotics

The PK/PD of antibiotics is distinct from other drugs because their target is not human cells but organisms from distinct species, and an ideal antibiotic would not directly affect the patient or cause side effects. Regarding antibiotics, the PD definition ”how the drug affects the bacteria” would thus be more appropriate than ”how the drug affects the body” [23].

PK is the study of how drug concentrations change over time after administration, and PD is the study of the relationship between a pharmacological effect and drug concentrations. PK/PD is the combination of these two sciences that ultimately enables to be monitor the effect of the drug as a function of time (Figure I.13).

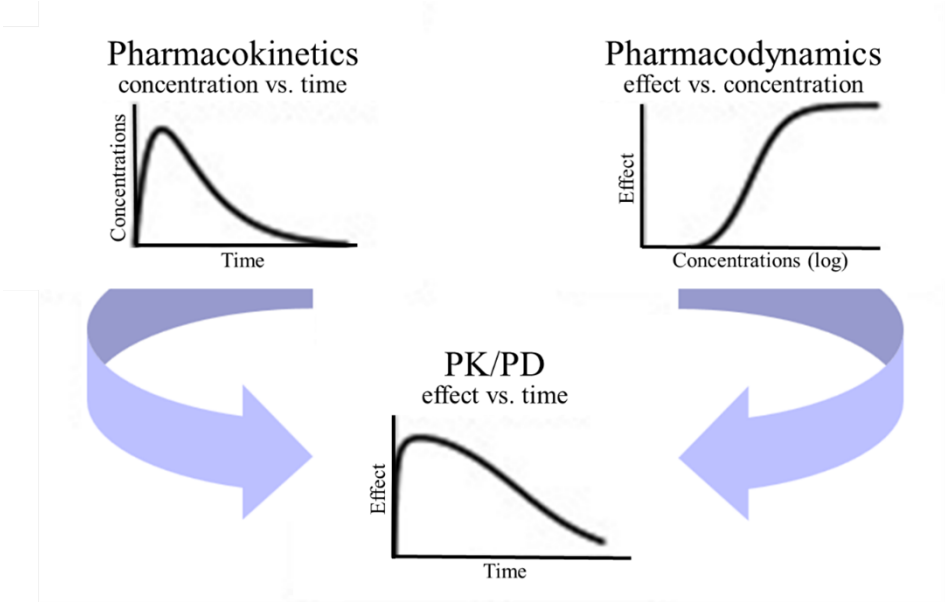


Figure I.13: Schematic representation of PK/PD relationship, integrating the PK (drug concentrations versus time, top, left panel) and the PD (drug effect versus its concentrations, top, right panel), allowing for the description of the complete effect profile over time. From [60].
PD, pharmacodynamics; PK, pharmacokinetics.

PK/PD indexes of antibiotic efficacy

Ideally, to measure the effect of antibiotics, bacteria would be counted. Since it is obviously impossible to measure bacterial load in patients, we use a surrogate. To determine the overall sensitivity of a bacterial population to a given antibiotic, the minimum inhibitory concentration (MIC) is used. It represents the lowest concentration associated with inhibition of bacterial growth. It is determined in microbiology laboratory, *in vitro*, under standardized conditions [61]. It is the PD criterion considering the specific sensitivity of a bacterial strain and can be associated to three traditional PK indices to predict antimicrobial activity for different antibiotic classes (Figure I.14):

- The ratio of the maximum plasma drug concentration to MIC ($f_{C_{max}/MIC}$) is used for the so called "concentration-dependent antibiotics" such as some aminoglycosides (gentamicin, tobramycin, amikacin), some fluoroquinolones and polymixins [61–66].

- The percentage of time that the unbound drug concentration exceeds the MIC over a 24-h period ($\%f_{T>MIC}$) is the PK/PD index for the so called "time dependent" antibiotics, such as penicillins (piperacillin), carbapenems (meropenem), tetracyclines, macrolides and cephalosporines (cefepime, cefazoline, ceftazidime) [61–66]. It should be noted that, in practical terms, the measurement of a residual concentration before a new antibiotic administration shows whether 100 % of the therapeutic interval has been effectively covered.

- The ratio of the area under the drug concentration–time curve to MIC ($f_{AUC/MIC}$) is used for antibiotics with both time and concentration dependencies, such as fosfomycin, daptomycin, levofloxacin, vancomycin, colistin, linezolid, ciprofloxacin and tigecyclines [61–66].

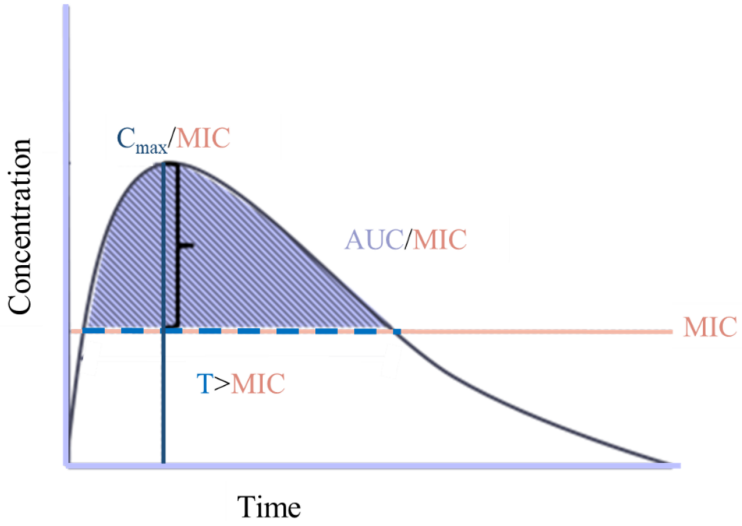


Figure I.14: Traditional PK/PD indexes used in antibiotic therapy. The ratio of the maximum antibiotic concentration (C_{max}) to the MIC (minimum inhibitory concentration), the time during which the antibiotic concentration is above the MIC and the area under the curve (AUC) above the MIC define the PK/PD indices. The PK parameters are shown in blue and the PD parameter in salmon. From [67].

The MIC value is currently the best available parameter to reflect the effectiveness of an antibiotic against pathogens. It is used as the criterion for determining a given pathogen's category of sensitivity or resistance to a given antibiotic [63]. The determined MIC value must be compared with MIC clinical breakpoints to assess whether the strain is susceptible or resistant to the antibiotic. Clinical breakpoint is the actual concentration of any antibiotic which defines if the given isolate is sensitive or resistant to this antibiotic (MIC < breakpoint: sensitive strain, MIC > breakpoint: resistant strain). This reference is given by the European EUCAST (European Committee on Antimicrobial Susceptibility Testing) [68] and the American CLSI (Clinical and Laboratory Standards Institute) [69]. In Europe, EUCAST updates breakpoint each year, the first of January, and has introduced three categories since the first of January 2019 [70]:

- Susceptible (S): there is a high likelihood of therapeutic success using a standard dosing regimen of the agent,
- Susceptible (I, for intermediate): there is a high likelihood of therapeutic success using an increased dosing regimen, (even if this category is subject to debate [71])

- Resistant (R): there is a high likelihood of therapeutic failure even when there is increased exposure.

The comparison MIC to clinical breakpoint is used for antibiotic selection in targeted therapy (between two potentially effective antibiotics, the one with the highest clinical breakpoint/MIC ration is chosen).

In empiric treatment (at the beginning of therapy, or when isolates or their MIC are unknown), clinicians consider clinical breakpoint as a surrogate of MIC to determine PK/PD index [72]. Clinical breakpoint MIC represents a worst-case scenario regarding bacterial susceptibility that needs to be considered when patients are treated empirically.

Therapeutic window

The therapeutic window (or therapeutic margin) of a drug refers to the range of drug concentrations that causes the desired therapeutic effect without causing significant toxicity or adverse effects. In other words, it represents the range of drug dosages that can be administered safely and effectively to a patient. The therapeutic margin is an essential concept in pharmacology as it determines the likelihood of a drug being an effective treatment option for a specific condition. Under dosing or over dosing the patient would lead to therapeutic failure, due to insufficient drug concentrations or to toxicity, respectively (Figure I.15).

The slope for therapeutic effects is steep within therapeutic range and then plateaued. At the same time, toxicity may increase accordingly to the drug level in a flat way (Figure I.16). The therapeutic window of a given drug represents the range of concentrations between those that are ineffective and those that are toxic. The narrower this range, the more complex the handling of the drug. Since the aim of antibiotics is to inhibit or kill living organisms, patients may experience toxicity when the target of antibiotic action is similar in bacteria and humans.

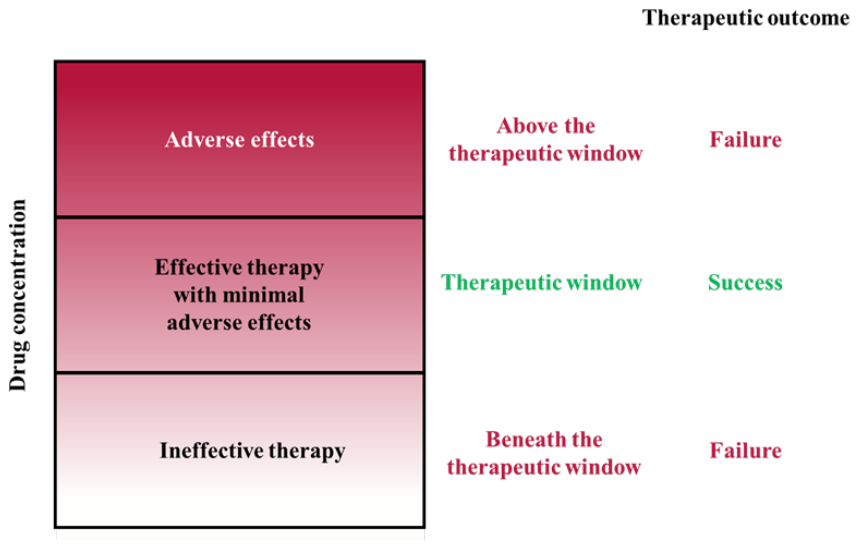


Figure I.15: Schematic diagram of the therapeutic window of a drug The therapeutic window of a drug lies between two regions of concentrations associated with therapeutic failure. The therapeutic failure in the lower region is principally caused by the absence of adequate efficacy and in the upper region, by the inability to have adequate efficacy without unacceptable adverse response. From [24].

Toxicities

A drug with narrow therapeutic window means that a slight increase in his drug concentration can cause significant harm to the patient, which makes it more challenging to find the optimal dose that has a prominent level of efficacy in treating the bacterial infection without causing significant toxicity. Antibiotics can be highly toxic, for kidneys notably.

Aminoglycosides such as amikacin, gentamycin, tobramycin, neomycin, and streptomycin are associated with renal and auditory toxicity linked to exposure (AUC) [74–77].

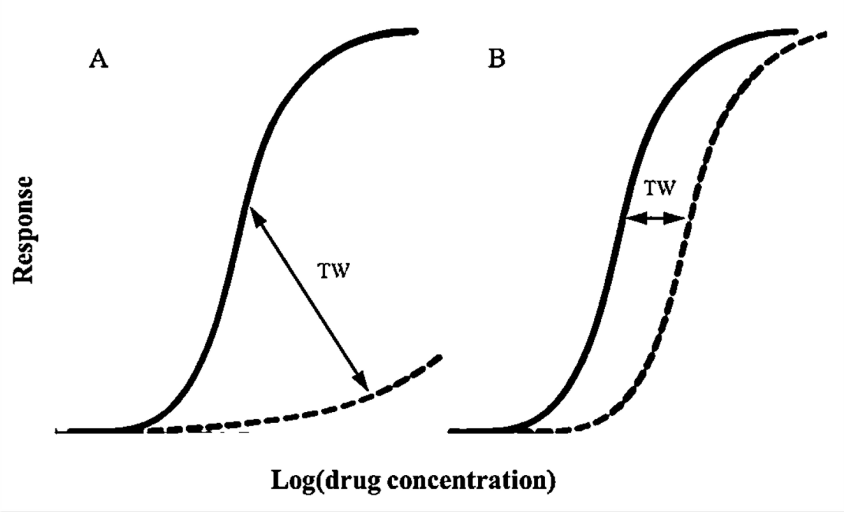


Figure I.16: Concentration–response relationship for wide (A) and narrow (B) therapeutic window (TW) (solid line = efficacy curve and dotted line = toxicity curve). From [73].

Glycopeptides, and particularly vancomycin, can cause nephrotoxicity [78–81], and the incidence of vancomycin-associated acute kidney injury (AKI) is as high as 43 % [81]. A meta-analysis including 53 studies demonstrated that vancomycin-related factors (treatment duration and serum trough levels) significantly increased the risks of vancomycin-associated AKI [80]. Colistin adverse effects include nephrotoxicity as well [82, 83], but also pulmonary toxicity [84]. Linezolid has multiple adverse effects, including serotonin syndrome [85], thrombocytopenia [86], peripheral neuropathy, reduced visual acuity, and anemia [87], while daptomycin may induce myopathies [88] eosinophilic pneumonia [88] and pulmonary toxicity [89].

High β-lactam serum levels are to be related to neurotoxicity [90–92], hematological adverse events, hepatotoxicity, allergy, nephrotoxicity, and *Clostridium difficile* infections [90, 92, 93]. A retrospective study conducted in 199 septic patients treated with meropenem, piperacillin/ tazobactam, ceftazidime or cefepime found that worsening neurological status was associated with increased trough concentrations normalized to the clinical breakpoint of *Pseudomonas aeruginosa* and occurred in approximately half of the ICU patients treated with piperacillin/tazobactam and approximately two-thirds of the ICU patients treated with meropenem [94]. Another retrospective study in patients treated with piperacillin or meropenem showed that neurotoxicity was associated with higher trough concentrations ($C_{min} > 361.4$ mg/L for piperacillin and $C_{min} > 64.2$ mg/L for meropenem) [95]. Conversely, researchers who conducted a retrospective study among 93 critically ill patients receiving either conventional or higher-than-conventional doses of meropenem or piperacillin/tazobactam concluded that there were no significant between group differences in rates of various toxicities, although mean daily doses were more than 40 % higher in the high-dose groups [96]. Meropenem and piperacillin are thus pretty safe to use, the therapeutic window being large (threshold of C_{min} being high). Their convulsive activity is 6 and 9 times lower than that of penicillin G, for meropenem and piperacillin respectively, in contrast to cefazolin and cefepime, which have a convulsive activity 1.6 and 2.94 times higher than penicillin G, respectively [92]. Cefepime and cefazolin have a lower neurotoxicity threshold and cefepime is associated with encephalopathy [92].

To conclude, PK and PD are key components in modern drug development. Once PK and PKPD are characterized, the concentration leading to the desired effect and limited side effects can be identified, and the dosing regimen that will result in the target concentration range can be computed [23]. But critically ill patients are a very heterogeneous population, and many factors affect their PK. This PK variability obviously affects their exposure to antibiotics.

I.3 Challenges in antibiotic therapy: pharmacokinetic alterations in critically ill patients

Critical patients are patients with serious and potentially life-threatening conditions requiring hospitalization in intensive care units (ICU). These conditions may include multiple organ dysfunction, trauma, severe infection, burns, stroke, heart or respiratory failure, or complex surgery. Critical patients often require complex and varied drug treatments. However, their pathological conditions can alter the PK of the drugs they receive, leading to difficulties in managing their treatment, as well as a possible alteration in the efficacy of antibiotics. In this section I.3.1, we will discuss some of the causes of alterations in the PK of drugs.

I.3.1 Alterations in absorption processes

Many factors might alter antibiotics absorption. Shock leads to a reduction in blood flow and motility, resulting in delayed gastric emptying and diminished absorption that cannot be restored by using of vasopressors (or antihypotensive agents, tend to raise low blood pressure). Alternatively, during shock or use of vasopressors skin perfusion will be reduced thereby decreasing absorption of subcutaneously administered drugs. Shock and use of vasopressors reduce skin perfusion and thus, absorption of antibiotics administered subcutaneously. Absorption of oral antibiotics in the small intestine is modified in case of intestinal infections, coeliac disease, inflammatory bowel disease or gastrectomy. Surgery or intestinal infection can lead to increased intestinal motility and to a reduction in the absorption. In case of liver injury, the absorption of oral antibiotics can be enhanced, with a risk of toxicity [43, 44, 97, 98]. To avoid any variability in antibiotic absorption in critically ill patients, antibiotics are administered intravenously (IV bolus, intermittent or continuous infusion).

I.3.2 Alterations in distribution processes

Critical illness and a plethora of associated interventions affect the distribution of antibiotics. This includes sepsis (a life-threatening organ dysfunction caused by a dysregulated host response to infection), shock, burn injury, pancreatitis (inflammation of the pancreas), or alterations in plasma protein binding.

Sepsis induces vasodilation (an increasing of vascular permeability), causing the capillary leak syndrome, formation of edema, and thus, contributes to an augmented V_D. The V_D is also increased when using mechanical ventilation, extra-corporal circuits (e.g., cardiopulmonary bypass or plasma exchange), fluid resuscitation (fluid and electrolytes administration to maintain organ perfusion and substrate delivery), intravenous fluid therapy, use of vasopressors and inotropes (drugs affecting the contraction of heart muscle), parenteral nutrition, post-surgical drainage, advanced liver disease, ascites (abnormal build-up of fluid in the abdomen), mediastinitis (infection of mediastinum), pleural effusion (accumulation of excessive fluid around the lungs), and burn injury [43, 44, 97, 99, 100]. The clinical importance of an increased V_D is particularly relevant for hydrophilic antibiotics with low V_D such as β-lactams, aminoglycosides, and glycopeptides. Indeed, these antibiotics are more distributed in the peripheral tissues conducting to antibiotic inefficacy [43, 44, 97, 99, 100]. To do not compromise clinical outcomes, an increased dosage of the loading dose is required.

Finally, protein binding playing an important role in drug distribution, since only the unbound fraction of a drug is pharmacodynamically active, the hypoalbuminemia (low level of blood albumin concentrations) occurring in more than 40 % [101, 102] of patients admitted to ICU may result in a greater unbound drug proportion and thus an increased V_D of hydrophilic antibiotics.

I.3.3 Alterations in metabolism processes

Drug metabolism occurring predominantly in the liver, hepatic dysfunction leads to alterations in metabolism. Critically ill patients may develop hepatic dysfunction due to inflammation, ischemia, or drug-induced liver injury [43, 44, 97, 99, 100]. This can affect the metabolism of antibiotics that are primarily metabolized by the liver, such as macrolides and tetracyclines, leading to higher drug concentrations and potential toxicity. The ability of the liver to clear drugs is proportionate to blood flow and/or the hepatic extraction ratio of the drug, driven by enzymes [24, 38]. Critical illness affects thus metabolic activity throughout alterations in plasma protein concentration, hepatic enzymatic activity, and blood flow.

Additionally, many drugs used in critically ill patients may either induce or inhibit the activity of the enzymes, associated with reduction or enhancement of drug-metabolizing activities [43, 44].

Drug-drug interactions (DDI) can alter the PK of hepatically metabolized antibiotic, as many molecules of different drugs compete for liver enzymes, leading to higher blood concentrations of some drugs and potential toxicities [43, 97, 100, 103].

I.3.4 Alterations in kidney elimination processes

Finally, the elimination process can be disturbed during critical illness as renal clearance can be either enhanced or impaired.

Multiple factors can cause enhancement in renal clearance: burn, early sepsis, use of hemodynamically active drugs (aiming at improving hemodynamics and renal blood flow), hematological malignancies, leading to augmented renal clearance (ARC) [97, 98].

Reduced capacities of kidneys elimination can be due to several mechanisms such as renal failure (after trauma, multiple organ failure, extensive burns, cardiogenic or hypovolemic shock), renal replacement therapies (RTT) (dialysis, hemofiltration, and hemodiafiltration), muscle wastage, long-term bedridden, chronic kidney disease (CKD) or acute kidney disease (AKI) [43, 44, 97–100]. AKI occurs in about half of adult critically ill patients admitted to the ICU and significantly affects clinical outcomes [41]. DDI can occur for β-lactams co administered with other drugs such as probenecid, salicylate and methotrexate, which competitively inhibit antibiotic kidney elimination, causing accumulation in the body [99].

In this section, we explained that pathophysiological conditions of critically ill patients are major sources major sources of inter- and intra-individual PK variability (Figure I.17. This variability complicates the optimization of antibiotic treatment, particularly through changes in the V_D.

Many factors can modify the PK of antibiotics. The clinical state of a patient changes rapidly in critical care, and these changes may even evolve on a daily basis within an individual [10, 27–32]. The two main PK parameters, V_D and CL, can be highly modified in critically ill patients [104]. For example, it has been shown that V_D could vary by more than 4 fold among critically ill patients (meropenem V_D was 15.7 L in septic patients and 69.5 L in polytraumatized patients) [104]. V_D and CL were also significantly different among critically ill patients treated with meropenem, doripenem, cefepime, ceftazidime and ceftriaxone [104].

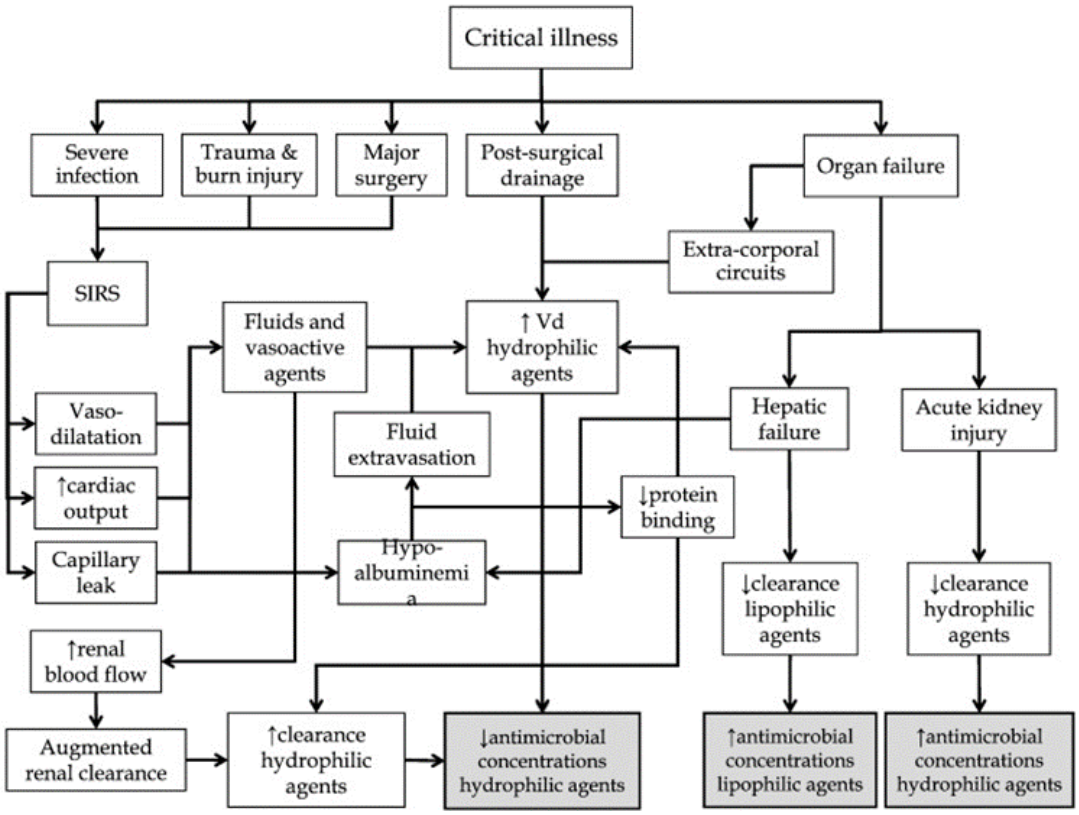


Figure I.17: Antibiotic pharmacokinetics in critically ill patients' response to treatment is influenced by multiple factors, leading to variability. From [43].

This variability can be source of antibiotic under- and overdosage. It has been shown that, for the same antibiotic dosage, it is possible to obtain sub-therapeutic plasma concentrations which are correlated with a reduced probability of clinical cure, and conversely, overdoses which are correlated with increased risk of toxicity [33]. Solutions have thus been developed to overcome the variability in critically ill patients and improve antibiotic efficacy. This is discussed in the next section I.4.

I.4 Existing solutions to ensure the effectiveness of antibiotic therapy: individualizing critically ill patients' treatment

There are different tools to optimize antibiotic treatment in critically ill patients. The first one is to adjust the dosing regimen to ensure the efficiency PK/PD target is met (as discussed previously; time/MIC, C_{min}/MIC, or AUC/MIC). Therapeutic drug monitoring (TDM) allows to assess patients' blood drug levels to ensure that they are within the therapeutic window. If not, the dosage regimen can be adjusted accordingly. Finally, clinicians rely on biomarkers (a molecule, usually a protein which reflects patients' state, and in case of antibiotics, inflammation's state) trends to evaluate whether the antibiotic is effective or not.

I.4.1 Optimization of antibiotic therapy

The first way of ensuring the effectiveness of any antibiotic is to optimize its dosage regimen, in terms of mode of administration, interval between administrations and dose. In the case of β-lactams, time dependent antibiotics, studies in ICUs have demonstrated that continuous infusion (CI) (over 24 h) of β-lactam antibiotics leads to improved outcomes compared to intermittent (0.5-1 h) or prolonged (3-4 h) infusions without increased adverse events [105–111].

In a meta-analysis of 632 critically ill patients with severe sepsis from three randomized trials, the rates of hospital mortality was reduced in the CI group compared to the intermittent infusion (II) group (19.6 % versus 26.3 % ($p = 0.045$)), and the clinical cure rate was significantly increased (55.4 % versus 46.3 % ($p = 0.021$)) [107].

In a meta-analysis of 1,191 critically ill patients treated by CI or II meropenem for sepsis, the mortality risk was reduced by 34 % in the CI group (risk ratio (RR) = 0.66, p = 0.03), a significant higher clinical cure rate (RR = 1.15, p = 0.026), and significant lower length of ICU stay (RR = -1.40, p = 0.005), hospital length of stay (RR = 1.87, p < 0.01), and emergence of resistance (RR = -16.23, p = 0.02) [108].

In a two-center randomized controlled trial of CI versus II dosing of β-lactams, conducted among 140 critically ill participants with severe sepsis, patients treated with CI administration had higher clinical cure rates (56 versus 34 %, p = 0.011), higher PK/PD target attainment rates of 100 % $f_{T>MIC}$ on day 1 (97 versus 70 %, p < 0.001) and on day 3 (97 versus 68 %, p < 0.001) than patients treated with II administration [110]. Similarly, in critically ill patients with respiratory infections, clinical cure rates were significantly higher in patients treated with CI meropenem (89 patients, 90.47 versus 59.57 % for CI and II, respectively), ceftazidime (121 patients, 89.3 versus 52.3 % for CI and II, respectively), and piperacillin (83 patients) [109]. β-lactams are thus preferably administered in continuous infusion in ICUs.

It has also been shown that targeting steady state concentrations over MIC ratio of at least 4 (C_{ss}/MIC > 4) maximizes β-lactam efficacy and reduces the risk of developing resistance [106, 111–117]. In a study led in 44 critically ill patients with documented Gram-negative bacterial infections and treated with CI-meropenem, authors used a classification and regression tree (CART) and identified a cut-off value of 4.63 as valuable predictor of favorable clinical cure (77.1 % of the patients with a C_{ss}/MIC ratio equals or above 4.63 were cured and 0 % of the patients with a ratio below this threshold were cured, p = 0.01) [112].

Similarly, in a study of 116 critically ill patients treated with CI β-lactams (52 treated with meropenem, 45 with piperacillin and 19 with ceftazidime), a significant higher microbiological failure and/or resistance development was observed in patients with C_{ss}/MIC ≤ 5 compared to those with C_{ss}/MIC > 5 (21/30 versus 5/86, p < 0.001).

Comparable results were also found in 43 critically ill COVID-19 patients with Gram-negative superinfections treated with CI meropenem, where the microbiological failure rate was significantly lower in patients with a C_{ss}/MIC > 4 compared to those with a C_{ss}/MIC < 4 (33.3 % versus 75.0 %; p = 0.01). A review compiling data of 64 articles (24 for meropenem, 21 for piperacillin, 10 for cefepime, and 9 for ceftazidime), proposed to use the target of 100 % $f_{T>4MIC}$, as this would allow for maximal bacterial killing, protect against bacterial regrowth, and ensure positive clinical outcome [105]. Considering that critically ill patients are severely vulnerable to suboptimal dosing and represent a source of selection of (multi)resistance to antibiotics, guidelines recommend to maintain β-lactam concentrations at least 4 times higher than the MIC during 100 % of the dosing interval (100 % $f_{T>4MIC}$) as PK/PD target of efficacy [2, 106].

Regarding vancomycin, the target for therapeutic effectiveness is a daily AUC/MIC > 400 [91, 114]. TDM is usually based on trough concentrations, targeting a C_{min} of 15-20 mg/L vancomycin [114]. However, it has been shown that even in patients with trough levels below 10-15 mg/L vancomycin, the AUC was still within the therapeutic range, and that AUC guided-vancomycin dosing was associated with decreased nephrotoxicity [118]. Nephrotoxic risks could be reduced by maintaining trough concentrations below 15 mg/L [119]. Updated guidelines recommend that daily AUC values (assuming a MIC of 1 mg/L) should be maintained between 400 and 600 mg.h/L to maximize efficacy and minimize the likelihood of nephrotoxicity [120].

The therapeutic target commonly associated with optimal antimicrobial activity of aminoglycosides (e.g., amikacin, gentamicin) is a C_{max}/MIC ratio of 8-10 [74, 114], but an AUC/MIC ratio of 80 110 may provide optimal outcomes in critically ill patients [121]. Using the breakpoints of *Pseudomonas aeruginosa* as defined by the EUCAST [68], guidelines recommend targeting an amikacin C_{max} of 60-80 mg/L and a gentamicin C_{max} of 30-40 mg/L for empirical therapy, which correspond to a C_{max}/MIC ratio between 8 and 10 [74].

Measuring plasmatic concentrations of antibiotics showed that a variable proportion of critically ill patients achieved the PK/PD target of efficacy. Table I.3 shows the percentage of critically ill patients who attained the PK/PD of efficacy for different antibiotics. In a large study led in 384 critically ill patients treated with β-lactams, only 35.0 % of the patients achieved the PK/PD target of 100 % $f_{T>4MIC}$. It is thus necessary to ensure that antibiotic concentrations are sufficiently high for each patient, which is the topic of the next section I.4.2.

I.4.2 Importance of TDM to guide antibiotic therapy

The inherent variability in antibiotic PK within and among critically ill patients presents a substantial challenge, as it can lead to suboptimal dosing. Such suboptimal dosing poses a significant risk, potentially resulting in unfavorable clinical outcomes or selection of antibiotic-resistant bacteria. Consequently, the evaluation of patient treatment should prioritize drug concentrations rather than simply administered doses. To achieve this, therapeutic drug monitoring (TDM) emerges as a crucial tool for optimizing antibiotic dosing in critically ill patients.

Table I.3: Attainment of PK/PD targets in critically ill patients.

Antibiotic [reference]	Class of antibiotics	No. of patients	Daily dose	PK/PD target	Achievement rate (%)
Amoxicillin [122]	β-lactam	71	6.0 g (3.5-6.0)	100 % $f_{T>4MIC}$	11.3
Ampicillin [122]	β-lactam	18	12.0 g (8.3-12.0)	100 % $f_{T>4MIC}$	22.2
Amikacin [123]	aminoglyc.	47	30 mg/kg	C_{max} > 60 mg/L	76.6
Amikacin [124]	aminoglyc.	66	22.6 mg/kg (± 6.9)	C_{max} > 60 mg/L	24.2
Cefazolin [122]	β-lactam	14	3.0 g (3.0-4.0)	100 % $f_{T>4MIC}$	14.3
Cefepime [122]	β-lactam	14	6.0 g (5.0-6.0)	100 % $f_{T>4MIC}$	71.4
Ceftriaxone [122]	β-lactam	33	2.0 g (2.0-4.0)	100 % $f_{T>4MIC}$	87.9
Doripenem [122]	β-lactam	13	1.75 g (1.50-3.0)	100 % $f_{T>4MIC}$	30.8
Gentamycin [123]	aminoglyc.	16	8 mg/kg	C_{max} > 30 mg/L	6.3
Gentamycin [124]	aminoglyc.	24	6.6 mg/kg (± 2.3)	C_{max} > 30 mg/L	4.2
Meropenem [122]	β-lactam	89	3.0 g (3.0-4.0)	100 % $f_{T>4MIC}$	41.6
Meropenem [103]	β-lactam	25	6.0 g	100 % $f_{T>4MIC}$	88.0
Piperacillin [122]	β-lactam	109	12.0 g (12.0-16.0)	100 % $f_{T>4MIC}$	30.3
Piperacillin [103]	β-lactam	36	12.0 g	100 % $f_{T>4MIC}$	$11.1/61.0^{a}$
Vancomycin [125]	glycopep.	42	27 mg/kg (± 13)	AUC/MIC > 400	71.0
				$C_{min} \geq 15$ mg/L	57.0

aminoglyc., aminoglycoside; AUC, daily area under the curve (over 24 h); glycopep., glycopeptide.
[a]Depending on the species considered, 61.0 % for Enterobacteriaceae and 11.1 % for *Pseudomonas aeruginosa*.
Daily doses are given as median ± SD or median (interquartile range).

TDM affords the individualization of antibiotic dosing regimens based on the substantial PK variability exhibited by critically ill patients. Through the quantification of antibiotic levels in plasma or other relevant body fluids, clinicians can effectively gauge antibiotic exposure levels and subsequently tailor dosages to achieve the desired PK/PD target, optimizing therapeutic efficiency while mitigating the risk of toxicity (Figure I.18).

Historically, TDM was initially introduced in the late 1960s, primarily as a means to minimize the toxicity associated with drugs possessing narrow therapeutic indices. Specifically regarding antimicrobial agents, aminoglycosides were among the first to undergo dose adjustments guided by TDM [91]. In recent decades, the utilization of TDM has gained traction in the context of antimicrobial drug dosing. Indeed, an international survey, lead among clinicians in 9 ICUs in Europe, USA and Australia performing β-lactam TDM, indicated that piperacillin and meropenem were the most commonly monitored β-lactams (100 % of units), followed by ceftazidime (78 %), ceftriaxone (43 %), and cefazolin (43 %) [126].

TDM approach proves particularly pertinent in the ICU setting, characterized by the high degree of variability frequently encountered. Notably, some recent studies have also indicated that TDM can serve to minimize the risk of antibiotic-related toxicities [92, 127]. A recent systematic review including 11 studies and 1,463 critically ill patients concluded that TDM-guided dose adaptation was associated with greater target attainment (85 % higher), improved clinical (17 % higher) and microbiological cure (14 % higher), and a 21 % reduction in risk of treatment failure compared to control group [128]. Similarly, another recent meta-analysis, including 10 randomized controlled trials and 1,241 participants showed that individualized antimicrobial dose optimization was associated with significantly higher target attainment rates and a decrease in treatment failure and risk of nephrotoxicity [98].

In a recent retrospective study, the first year of implementation of an expert clinical pharmacological advice (ECPA) program based on TDM results was evaluated for its impact on tailoring therapy involving 18 different antimicrobial agents across a tertiary university hospital setting. Out of the 1,010 critically ill patients included in the study, the clinical pharmacology unit recommended dosage adjustments in 62.9 % of the initial requests. These adjustments aimed to either achieve the PK/PD target for efficacy (requiring increased dosages) or reduce the risk of potential toxicities (necessitating decreased dosages) [129].

In summary, rational TDM represents a paradigm shift in the management of antibiotic therapy for critically ill patients. Its ability to detect PK variations, facilitate precise dose adjustments, and foster PK/PD target attainment while simultaneously curbing the risks of toxicities has ushered in a new era of personalized medicine (Figure I.19). As we navigate the complex landscape of infectious diseases and the formidable challenge of antimicrobial resistance (AMR), TDM stands resolute as a cornerstone of evidence-based antibiotic management, offering renewed hope for the future of patient care.

I.4.3 Use of biomarkers to guide antibiotic therapy

Monitoring the response to antibiotic therapy is another critical aspect of optimization. Since we cannot directly measure the number of bacteria in a person, clinicians rely on biomarkers—molecules that reflect biological processes, in our case, the response to antibiotics. In clinical routine, C-reactive protein (C-RP) and procalcitonin (PCT) are biomarkers extensively used for infection diagnosis and management [14, 130–134].

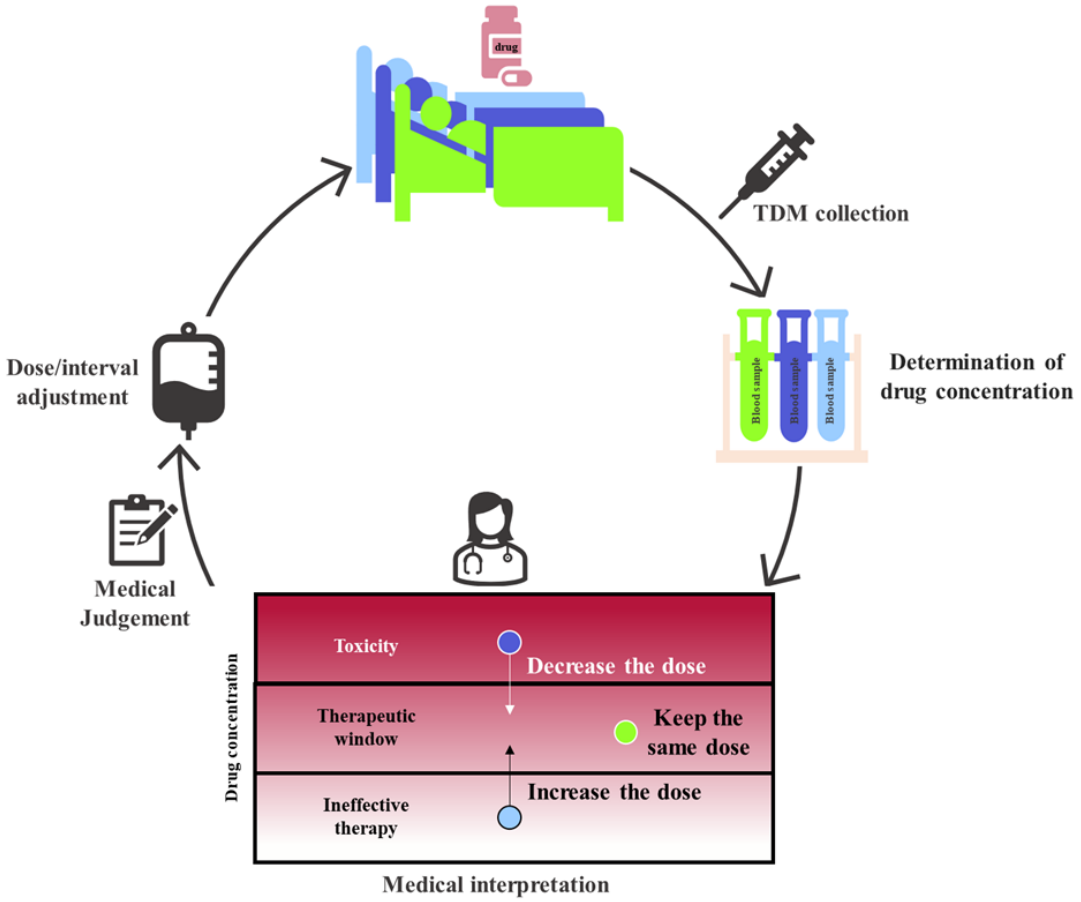


Figure I.18: Concept of therapeutic drug monitoring (TDM). The drug concentrations measured in plasma are transmitted to clinicians for interpretation and for dosage regimen adjustment (change the dose in case of continuous infusion administration and change the dose and/or the schedule in case of other administration) to optimize patient's treatment. Note that this is a simplification of the process, clinicians also consider sources of variability (such as renal function for drugs which are renally eliminated) to take decisions. From [24].

Biomarkers can be used to discriminate between infections due to Gram-negative, Gram-positive pathogens and fungi. A study conducted on 1,949 samples from patients suspected of having bloodstream infections revealed striking differences in the median PCT levels among the pathogens. In cases of Gram-negative bacteremia, the median PCT value was notably elevated at 13.8 ng/mL (with an interquartile range (IQR) of 3.4–44.1), whereas in Gram-positive infections, it measured substantially lower at 2.1 ng/mL (with an IQR of 0.6–7.6). Fungal infections exhibited even lower median PCT levels, averaging at 0.5 ng/mL (with an IQR of 0.4–1). This discrepancy in PCT levels was statistically significant ($p < 0.0001$) [135].

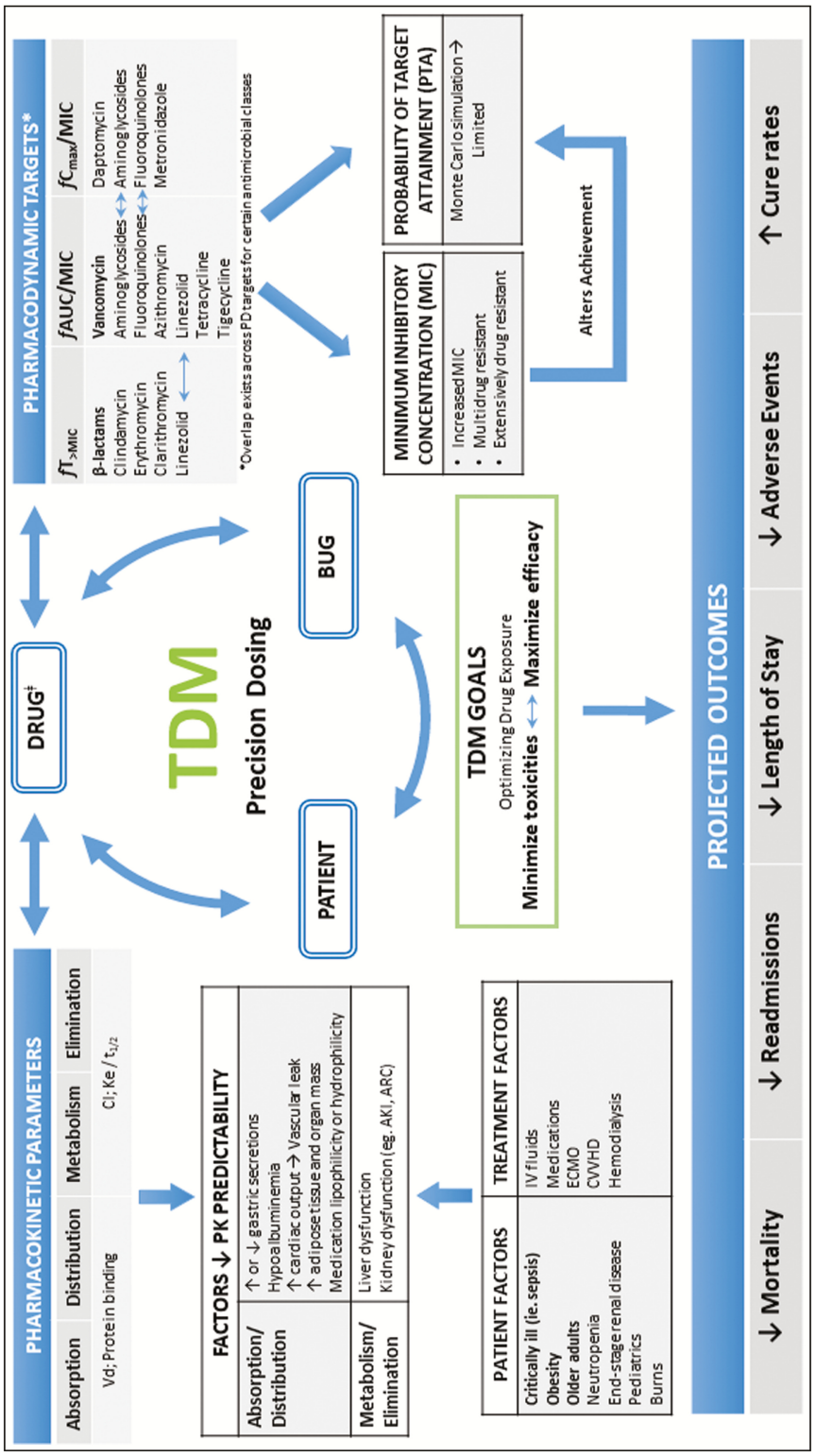


Figure I.19: TDM conceptual model implementation in clinics. AKI indicates acute kidney injury; ARC, augmented renal clearance; Cl, clearance; CVVHD, continuous venovenous hemodialysis; ECMO, extracorporeal membrane oxygenation; $fT_{>MIC}$, free unbound drug concentration time above minimum inhibitory concentration (MIC); fAUC/MIC, ratio of free unbound drug concentration area under the curve to MIC; fC_{max}/MIC, ratio of free peak plasma concentration to MIC; Ke, elimination rate constant; IV, intravenous; PK, pharmacokinetics; $t_{1/2}$, half-life; Vd, volume of distribution. From (91).

Furthermore, another study proposed a practical algorithm based on PCT levels for guiding empirical antibiotic therapy decisions. According to this algorithm, when PCT levels surpass the threshold of 2 ng/mL, it suggests considering the possibility of Gram-negative bacteria as the etiological agents of the infection [136].

Several studies have explored the use of biomarkers to guide the early discontinuation of antibiotic treatment, and these investigations have yielded promising results [137–144]. In a randomized clinical trial, patients with uncomplicated Gram-negative bacteremia who received antibiotic treatment guided by C-RP levels exhibited 30-day rates of clinical failure that were equivalent to those who followed a standard 14-day antibiotic regimen. The C-RP-guided group experienced fewer instances of treatment failure at all time points, and the median duration of antibiotic therapy for this group was notably shorter (7 days) [139]. Similarly, in a randomized, open-label, controlled clinical trial involving 130 critically ill patients, those who received guidance based on C-RP levels had a median antibiotic treatment duration of 6 days, compared to 7 days in the control group [140].

These findings underscore the potential of C-RP guidance to streamline antibiotic treatment. PCT has also been investigated in this context. A multicenter, prospective, parallel-group, open-label trial conducted in 621 critically ill patients assessed the initiation or discontinuation of antibiotics based on predefined PCT concentration thresholds. In the PCT-guided group ($n = 307$), mortality rates at both days 28 and 60 were noninferior to those in the control group ($n = 314$) following current guidelines. Additionally, patients in the PCT-guided group had significantly more days without antibiotics, with an absolute difference of 2.7 days ($p < 0.0001$) [144]. Moreover, meta-analyses conducted elsewhere have consistently shown reductions in the duration of antimicrobial therapy in critically ill populations with infections when PCT-guided treatment is implemented [145, 146].

These findings collectively suggest that biomarker-guided approaches, involving C-RP and PCT, hold promise for optimizing antibiotic treatment duration in critically ill individuals.

Biomarkers might also serve as valuable indicators of the effectiveness of antibiotic therapy [133, 147–153]. In a prospective, multicenter, observational study involving 37 patients with microbiologically documented VAP, C-RP levels and C-RP ratio to baseline at days 4 and 5 were significantly different between patients who survived and those who did not [147]. Similar results were observed in a prospective study of 129 cancer patients with healthcare-associated pneumonia: C-RP levels and C-RP ratio to baseline were significantly higher in non-survivors by day 4 [148]. A 13-year retrospective study focusing on critically ill patients showed that elevated C-RP values were associated with increased risk of organ failure and 72-hour mortality [149].

Additionally, a meta-analysis was conducted to assess the accuracy of PCT in predicting mortality in pneumonia patients. This analysis encompassed 9 studies involving 608 critically ill patients with CAP or VAP. The results indicated that elevated PCT levels were linked to a heightened risk of mortality ($p = 0.046$, RR 4.18, 95 % CI: 3.19–5.48) and that the prognostic performance was similar between patients with VAP or CAP [150].

Further supporting these findings, a prospective observational study conducted in a medical intensive care unit within a university hospital demonstrated comparable results. Multivariate logistic regression analysis involving 63 critically ill patients with VAP showed a strong correlation between PCT levels on days 1, 3, and 7 (e.g., at sampling days) and patient outcomes ($p < 0.002$, $p < 0.0001$, and $p < 0.0001$, respectively) [151]. Likewise, a multinational observational study involving 157 critically ill patients with HAP, VAP, or CAP suggested that PCT could serve as a prognostic marker for both morbidity and mortality [152]. These findings collectively emphasize the potential of biomarkers, particularly C-RP and PCT, in predicting clinical outcomes in critically ill patients with pneumonia.

Biomarkers might also predict PK changes and target-site concentrations (e.g., in lungs for pneumonia, in the urinary tract for urinary tract infections, in the central nervous system for meningitis…). However, there is currently a lack of clinical evidence, standardization, and defined thresholds for these biomarkers [154].

In summary, biomarkers are a promising tool to further individualize treatment. They have been shown to be useful for diagnostic, for early-stop treatment and for predicting the outcome. Nevertheless, data are lacking on the relationships between antibiotics PK and biomarkers kinetics.

I.4.4 Conclusion

In conclusion, the optimization of antibiotic therapy in critically ill patients necessitates a meticulous and tailored strategy. Our exploration unveiled the formidable challenges posed by HAP and VAP, delving into their epidemiology, physiopathology, and treatment intricacies. Subsequently, our scrutiny extended to the pharmacological properties of antibiotics, shedding light on their potential modes of action, the possible mechanisms of resistance they may exhibit, and the intricate realm of PK alterations in critically ill patients. It is imperative to underscore that these alterations in PK introduce a challenging variability, arduous to master, and capable of leading to the failure of antibiotic therapy.

Moreover, integrating biomarkers such as C-RP emerges as a pivotal aspect of individualizing treatment, considering PK alterations. These biomarkers serve as invaluable tools, reflecting the patients' immune response and providing clinicians with a nuanced understanding to gauge the efficacy of antibiotic therapy. Incorporating these biomarkers into the outlined comprehensive strategy not only adds an additional layer of precision but also empowers clinicians to monitor and adjust antibiotic regimens dynamically, addressing the intricacies introduced by PK alterations.

To reinforce this holistic approach, the chapter underscores the significance of early initiation, judicious antibiotic selection, **personalized dosing**, and fostering multidisciplinary collaboration. Implementation of these strategies not only enhances patient outcomes and prevents antibiotic resistance but also aligns with the goal of promoting rational antibiotic use in critically ill patients. This comprehensive guide positions healthcare providers to navigate the intricate landscape of antibiotic therapy judiciously, ensuring a tailored approach that caters to the unique needs of critically ill individuals, thereby contributing significantly to elevated standards of patient care.

Building upon this foundation, the chapter emphasized solutions to enhance antibiotic effectiveness, highlighting the importance of early initiation, proper selection, **personalized dosing**, and multidisciplinary collaboration. By implementing these strategies, clinicians can improve outcomes, prevent antibiotic resistance, and promote rational antibiotic use in critically ill patients. This comprehensive guide positions healthcare providers to navigate the complexities of antibiotic therapy judiciously, ensuring a tailored approach that meets the unique needs of critically ill individuals, ultimately contributing to improved patient care.

Chapter II

This PhD thesis: aims and outline of the project

In the preceding section, the first chapter (section I.3), we delved into the myriad challenges faced in the realm of antimicrobial therapy when it comes to critically ill patients. These challenges are primarily rooted in the substantial inter-patient variability in antibiotic response, stemming from alterations in various PK processes. Consequently, there is a compelling need to tailor antimicrobial therapy to the unique characteristics of each critically ill patient.

The discipline of antimicrobial pharmacology revolves around the intricate interplay of PK and PD. To achieve the goal of personalized antimicrobial therapy, it becomes imperative to individualize both the PK and PD aspects. The overarching objective of this thesis centers on the investigation of strategies for optimizing both the PK and PD of antibiotics, with a particular focus on β-lactams. This antibiotic class holds paramount importance as it is the most frequently administered in intensive care units [155–159], and within this class, we zero in on meropenem, an antimicrobial of frequent use [129, 159–162]. Within the scope of this thesis, we present two primary projects: the optimization of PK, discussed in chapter 3, and the optimization of PD, explored in chapter 4, both focusing on meropenem.

The third chapter of this research project sets out to optimize the PK of meropenem in critically ill patients. This is accomplished through a comprehensive exploration of the impact of various methods for estimating renal function on the dosage adjustment of meropenem. The kidneys play a pivotal role in the elimination of many antibiotics, including meropenem. Therefore, accurate assessment of renal function is essential to ensure that the drug is administered at the appropriate dose, thereby optimizing its effectiveness while minimizing the risk of toxicity.

Moving on to the fourth chapter, our focus shifts to the PD optimization of meropenem. In this section, we investigate the utility of C-RP as a biomarker that reflects the antibiotic's efficacy. Monitoring the response of critically ill patients to meropenem treatment is a complex endeavor, and C-RP emerges as a promising indicator of the drug's impact on the infection. In this chapter, we seek to enhance our understanding of C-RP fate during meropenem treatment.

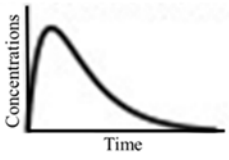
In conclusion, the fifth chapter encapsulates the findings and insights garnered throughout this research endeavor. It offers a comprehensive summary of the optimization strategies explored for meropenem therapy in critically ill patients, emphasizing the importance of tailoring treatment to individual patient profiles. Additionally, this chapter provides a glimpse into future perspectives and potential avenues for further research in this critical area of antimicrobial therapy.

Eventually, this thesis serves as a contribution to the ongoing quest for improved antimicrobial therapy in the complex and challenging context of critical care.

BACKGROUND

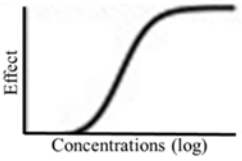
Components of drug pharmacology

Pharmacokinetics (PK)
concentration vs. time



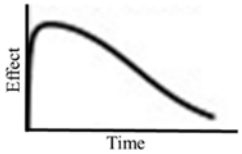
Dose → Concentration

Pharmacodynamics (PD)
effect vs. concentration



Concentration → Effect

PK/PD
effect vs. time



Dose → Effect

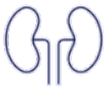
THIS PhD THESIS

Tailoring meropenem treatment for critically ill patients: a personalized approach

PK optimization

Meropenem is renaly excreted

→ Meropenem dose adjustment is based on renal function



Kidney function not directly measurable so use of surrogates:

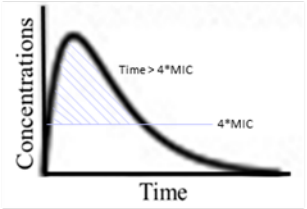
- Measured creatinine clearance (best but time- and resource-consuming)
- Empiric formula (easy but might be not accurate)

→ Are empirical formulas as reliable as measured creatinine clearance in calculating the daily dose of meropenem?

PD optimization

C-reactive protein (C-RP) is a biomarker of inflammation.

Meropenem PK/PD target of efficacy is: C_{ss}/MIC during the whole treatment duration



→ Could a quantitative relationship be established between C-RP trends and meropenem C_{ss}/MIC ?

Figure II.1: Illustration of the project aims.
C_{ss}, meropenem steady-state concentration; MIC, minimum inhibitory concentration.

Chapter III

Optimizing meropenem pharmacokinetics to individualize meropenem treatment in critically ill patients

III.1 Abstract

Assessment of glomerular filtration rate (GFR) is necessary for dose adjustments of β-lactam that are excreted by the kidneys, such as meropenem. The aim of this study was to compare the daily dose of 24 h-continuous infusion (CI) meropenem when GFR was calculated by means of measured creatinine clearance (mCL_{CR}) or estimated by the CKD-EPI ($eGFR_{CKDEPI}$), Cockcroft–Gault ($eGFR_{CG}$), and MDRD ($eGFR_{MDRD}$) equations. Adult critically ill patients who underwent therapeutic drug monitoring (TDM) for the assessment of 24 h-CI meropenem steady state concentration (C_{ss}) and for whom a 24 h urine collection was performed were retrospectively enrolled. Meropenem clearance (CL_M) was regressed against mCL_{CR}, and meropenem daily dose was calculated based on the equation infusion rate = daily dose/$eGFR_{MDRD}$. $eGFR_{CKDEPI}$, $eGFR_{CG}$, and $eGFR_{MDRD}$ were regressed against mCL_{CR} in order to estimate $eGFR_{MDRD}$. Forty-six patients who provided 133 meropenem C_{ss} were included. $eGFR_{CKDEPI}$ overestimated mCL_{CR} up to 90 mL/min, then mCL_{CR} was underestimated. $eGFR_{CG}$ and $eGFR_{MDRD}$ overestimated mCL_{CR} across the entire range of GFR. In critically ill patients, dose adjustments of 24 h-CI meropenem should be based on mCL_{CR}. Equations for estimation of GFR may lead to gross under/overestimates of meropenem dosages. TDM may be highly beneficial, especially for critically ill patients with augmented renal clearance.

III.2 Introduction

III.2.1 Rationale of studying meropenem

Multidrug-resistant (MDR) Gram-negative pathogens are the leading cause of severe infections in critically ill patients [10]. Despite available treatments, the in-hospital mortality rate for patients with suspected or proven infections is as high as 30 % [10]. Among the most important causes of antimicrobial treatment failure and worse clinical outcome in critically ill patients are the high level of antimicrobial resistance, the high inter-individual pharmacokinetic variability, and the frequent immunocompromised state [44, 97].

Current Italian and European guidelines recommend the novel β-lactams/ β-lacta - mase inhibitors as first-line agents for the treatment of severe infections caused by carba - penemase-producing Gram-negative pathogens [16, 163]. However, meropenem still remains a valuable option in the context of extended-spectrum β-lactamases (ESBLs)-pro - ducing Enterobacterales [164, 165], as well as for susceptible strains of *Pseudomonas aeruginosa* or *Acinetobacter baumannii* [164, 166].

III.2.2 PK/PD target of efficacy of meropenem

Meropenem has time-dependent bactericidal activity, and its efficacy is related to the duration of time the serum concentration is above the minimum inhibitory concentration (MIC) of the micro-organism (time above MIC) for at least 40 % of the dosing interval [112, 167]. However, in critically ill patients and/or immunocompromised subjects, more aggressive PD targets of efficacy up to 100 % t > 4-8 × MIC are currently advocated for maximizing efficacy [112] and preventing the development of resistance [113]. The attainment of such higher PD targets may be facilitated by the use of 24 h-continuous infusion (CI) administration [108, 168].

III.2.3 Assessing glomerular filtration rate

Considering that meropenem is mainly excreted as an unmodified drug by the renal route, the calculation of the daily dose that is necessary for attaining the PD efficacy target should be based on patient's glomerular filtration rate (GFR) [169–171]. GFR is one of the measures of kidney function; it describes the flow rate of fluid filtered through the kidney [172]. It cannot be measured directly. Alternatively, in clinical settings, an endogenous filtration marker, creatinine, found in serum and urine, is commonly used to assess GFR. Creatinine clearance (CL_{CR}) is the volume of blood plasma cleared of creatinine per unit time. It can be measured in urines or estimated from serum concentration [172].

Measured creatinine clearance (mCL_{CR}) should be approached as the best surrogate of GFR, but this could be time- and resource-consuming. That is why GFR is frequently estimated nowadays by means of validated mathematical formulas, such as the Cockcroft–Gault (CG), the chronic kidney disease epidemiology collaboration (CKD-EPI), and the modification of diet in renal disease (MDRD) equations. However, such formulas were not assessed and validated specifically in the critical care setting, so that estimated GFR (eGFR) based on them could deviate consistently from mCL_{CR}, thus, leading to drug underdosing or overdosing.

III.2.4 Objectives

The aim of this study was to evaluate whether eGFR based on CG, CKD-EPI, and MDRD equations could be as reliable as mCL_{CR} in calculating the daily dose of 24 h-CI meropenem for properly treating nosocomial infections in a cohort of critically ill patients.

III.3 Material and methods

III.3.1 Patients' enrollment

This retrospective monocentric study was conducted among critically ill patients admitted to the post-transplant Intensive Care Unit of the IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy, in the period December 2020–January 2022. All of the included patients received 24 h-CI of meropenem and underwent real-time therapeutic drug monitoring (TDM) for optimizing empirical or targeted treatment of Gram-negative infections.

The following demographic and clinical data were collected from each patient's medical record: age, gender, weight, height, serum creatinine, type, and site of infection. Patients undergoing renal replacement therapy were excluded.

III.3.2 Meropenem administration

Meropenem therapy was started with a loading dose of 2 g over 2 h and continued with a maintenance dose initially based on the patient's renal function (ranging from 1 g q6h over 6 h to 0.25 g q6h over 6 h) and subsequently optimized by means of TDM coupled with expert clinical pharmacological advice (ECPA). Stability of 24 h-CI meropenem was granted by reconstitution of the aqueous solution every 6-8 h with infusion over 6-8 h [173].

TDM of meropenem was performed within 48-72 h from the starting treatment and then reassessed every 48–72 h. Peripheral venous blood samples were centrifugated, and plasma was then separated. Meropenem plasma concentrations were analyzed by means of a liquid chromatography-tandem mass spectrometry (LC–MS/MS) commercially available method (Chromsystems Instruments & Chemicals GmbH, Munich, Germany), with a lower limit of detection of 0.3 mg/L. The desired pharmacodynamic target of meropenem efficacy was set at a steady state concentration (C_{ss}) to MIC (C_{ss}/MIC) ratio of 4–8 [170].

III.3.3 Assessment of glomerular filtration rate

At each TDM assessment, mCL_{CR} (mL/min) was performed and calculated as follows:

$$mCL_{CR} = \frac{U_{CR} \times U_{Volume}}{S_{CR} \times T} \tag{III.1}$$

where U_{CR} is the urinary creatinine concentration (mg/dL), U_{Volume} is the urinary volume (mL), S_{CR} is the serum creatinine concentration (mg/dL), and T is the 24 h collection time (equal to 1'440 min).

Creatinine was measured both in serum and urine by enzymatic assay.

Patients with mCL_{CR} < 30 mL/min/1.73 m² were defined as having an episode of acute kidney injury (AKI), whereas those with $mCL_{CR} \geq$ 130 mL/min/1.73 m² were defined as having an episode of augmented renal clearance (ARC). Instead, eGFR was assessed by means of three different formulas: the Cockcroft and Gault formula ($eGFR_{CG}$) [56], the CKD-EPI formula ($eGFR_{CKDEPI}$) [57], and the MDRD formula ($eGFR_{MDRD}$) [58].

III.3.4 Estimation of meropenem daily dose

A multistep approach was used to assess whether the eGFR calculated by means of the aforementioned formulas could be considered as reliable as the mCL_{CR} for properly calculating the daily meropenem dosages needed for optimal treatment for the critically ill patients.

First, meropenem total clearance (CL_M) was calculated in each single patient by means of the following equation:

$$CL_M = \frac{IR}{C_{ss}} \tag{III.2}$$

where CL_M is the meropenem clearance (L/h), IR is the hourly meropenem infusion rate (mg/h), and C_{ss} is the meropenem steady-state plasma concentration (mg/L).

Second, linear regression between CL_M and mCL_{CR} was performed.

Third, the meropenem daily dosing regimen was estimated by means of the mCL_{CR}. For doing so, CL_M was expressed as a function of mCL_{CR} by means of Equations III.3 and III.4.

$$meropenem \quad IR = CL_M \times C_{ss} \tag{III.3}$$

$$CL_M = a + b \times mCL_{CR} \tag{III.4}$$

where a and b are the intercept and slope, respectively.

In this way, the daily meropenem infusion rate ($meropenem \quad daily \quad IR-mCL_{CR}$), was calculated as following in mg/24 h:

$$meropenem \quad daily \quad IR - mCL_{CR} = [a + b \times mCL_{CR}] \times C_{ss} \times 24 \qquad \text{(III.5)}$$

Subsequently, linear regressions between mCL_{CR} and each of the eGFR, namely $eGFR_{CKDEPI}$, $eGFR_{CG}$, and $eGFR_{MDRD}$, were assessed. The resulting linear regression equations were used for estimating the meropenem daily dosing regimens based on each of the eGFR formulas (one each for $eGFR_{CKDEPI}$, $eGFR_{CG}$, and $eGFR_{MDRD}$).

Accordingly:

$$IR - eGFR_{CKDEPI} = [c + d \times mCL_{CR}] \times C_{ss} \times 24 \qquad \text{(III.6)}$$

$$IR - eGFR_{CG} = [e + f \times mCL_{CR}] \times C_{ss} \times 24 \qquad \text{(III.7)}$$

$$IR - eGFR_{MDRD} = [g + h \times mCL_{CR}] \times C_{ss} \times 24 \qquad \text{(III.8)}$$

The squared coefficient of regression (R^2) was used to evaluate the performance of each regression. A one-way analysis of variance (ANOVA) was used to assess differences between measured and estimated renal function and between the meropenem daily dose based on mCL_{CR} versus eGFR.

All statistical analysis and plotting were performed using R (version 4.0.3).

III.4 Results

III.4.1 Patients' enrollment

A total of 46 patients (76.1% males, 35/46) were included in this analysis and contributed 133 meropenem C_{ss}. Patient's demographic and clinical characteristics are reported in Table III.1. Median (IQR) age, weight, and serum creatinine were 58.5 (54.0 –67.0) years, 70.0 (60.0–80.0) kg, and 0.7 (0.4–1.2) mg/dL, respectively. Overall, hospital-acquired pneumonia and intra-abdominal infections accounted for the majority of indications for meropenem treatment (60.8 %, 28/46 patients). Overall, median GFR was significantly different when using mCL_{CR} compared to $eGFR_{CKDEPI}$, $eGFR_{CG}$, and $eGFR_{MDRD}$ (74.7 mL/min vs. 103.1 mL/min/1.73 m² vs. 112.6 mL/min/1.73 m² vs. 108.5 mL/min/1.73 m², $p < 0.001$). No difference was observed in the median eGFR values obtained by means of the three empiric formulas. AKI was observed in 28.3 % (13/46) of the subjects, and 26.1 % of patients (12/46) had at least an episode of ARC.

III.4.2 Comparison of performances of formulas to estimate GFR

Linear regression between CL_M vs. mCL_{CR} is shown in figure III.1. Linear regressions between $eGFR_{CKDEPI}$ vs. mCL_{CR}, $eGFR_{CG}$ vs. mCL_{CR}, and $eGFR_{MDRD}$ vs. mCL_{CR} are shown in Figure III.2. Bland-Altman plots for assessing the agreement between mCL_{CR} vs. $eGFR_{CKDEPI}$, mCL_{CR} vs. $eGFR_{CG}$, and mCL_{CR} vs. $eGFR_{MDRD}$ are presented in Figure III.3. $eGFR_{CG}$ showed a better correlation with mCL_{CR} ($R^2 = 0.78$), compared to those of $eGFR_{CKDEPI}$ vs. mCL_{CR} and $eGFR_{MDRD}$ vs. mCL_{CR} ($R^2 = 0.62$ and 0.63, respectively). Both $eGFR_{CG}$ and $eGFR_{MDRD}$ overestimated mCL_{CR} across all ranges of renal function, while $eGFR_{CKDEPI}$ overestimated mCL_{CR} up to 90 mL/min, then underestimated it.

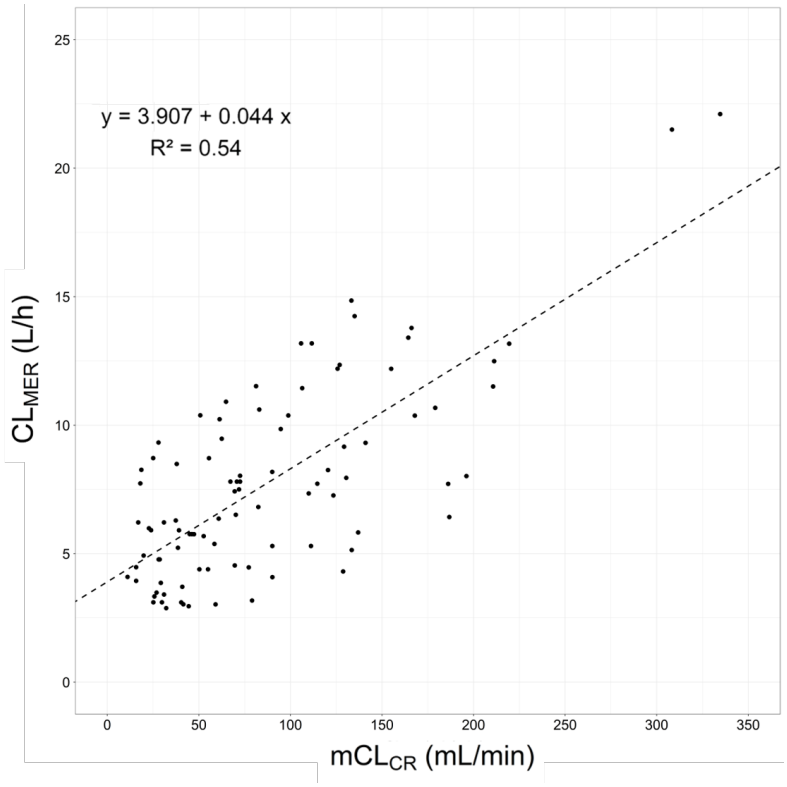


Figure III.1: Linear regression between meropenem clearance (CL_{MER}) vs. measured creatinine clearance (mCL_{CR}). The dashed line represents the line of regression.

III.4.3 Estimation of meropenem daily dose

The daily dose of 24 h-CI meropenem needed to attain a PK/PD target of Css/MIC of 4–8 considering the EUCAST clinical breakpoint of meropenem against Enterobacterales and Pseudomonas aeruginosa (namely, Css of 8 or 16 mg/L) based on IR-$eGFR_{CKDEPI}$, IR $eGFR_{CG}$, and IR-$eGFR_{MDRD}$ are depicted in Figure III.4 and Figure III.5, respectively.

Meropenem daily dosages based on eGFR equations were consistently different from those based on mCL_{CR}. When GFR was calculated by means of $eGFR_{CG}$ or $eGFR_{MDRD}$, higher than necessary doses were estimated due to an overestimation of mCL_{CR}. Similarly, this occurs when using $eGFR_{CKDEPI}$ in patients with mCL_{CR} < 90 mL/min. Table III.2 reports the median difference in meropenem daily dose when using $eGFR_{CKDEPI}$, $eGFR_{CG}$, and $eGFR_{MDRD}$ with respect to mCL_{CR}.

III.5 Discussion

This is the first study that assessed the performances of commonly empirical formulas for eGFR estimation in determining meropenem dosages that are optimal for the empirical treatment of Gram-negative infections in critically ill patients.

For hydrophilic antibiotics that are eliminated mainly unmodified by the renal route, such as meropenem, a high correlation between creatinine clearance and drug clearance was described in different patient populations [170, 174]. The existence of such a relationship is of utmost importance for clinicians, as it allows them to adjust drug dosage based on the degree of a patient's renal function [170]. In our patients, mCL_{CR} was linearly associated with CL_M, but it could account for no more than 54 % of the variability of meropenem elimination. This is plausible, considering that meropenem is also eliminated by tubular secretion [175] and that normal physiology is greatly modified in critically ill patients so that the PK of antibiotics predominantly cleared by the renal route may be highly variable. Consistent with our observation is that reported by a recent prospective study conducted among 25 critically ill patients with sepsis who were treated with 3 h-extended infusion meropenem every 8 h [25]. The correlation between CL_M and mCL_{CR} was even lower than ours, the R^2 ranging 0.23–0.30 according to the time of the PK assessment after starting therapy.

Different studies assessed the performances of eGFR equations compared to mCL_{CR} across different ranges of GFR, and almost all showed important flaws when using such mathematical equations for renal function estimation in critically ill patients [176–178].

A recent retrospective study conducted on 237 critically ill patients in Arabia with a mean mCL_{CR} of 102.7 ± 65.4 mL/min showed that $eGFR_{CKDEPI}$, $eGFR_{CG}$, and $eGFR_{MDRD}$ had an accuracy as low as 12.7–30 % in estimating mCL_{CR} within ± 10 %, and that both $eGFR_{CG}$ and $eGFR_{MDRD}$, but not $eGFR_{CKDEPI}$, were significantly biased. Moreover, that study confirmed an overestimation of all equations in patients with AKI and in patients with ARC, an overestimation of $eGFR_{CG}$, and an underestimation of $eGFR_{CKDEPI}$ [179]. GFR-estimating equations showed poor performances both in patients with AKI and ARC. In the former scenario, eGFR formulas performed poorly when compared to mCL_{CR}, with a bias ranging from 7.4 to 11.6 mL/min [180]. On the contrary, in the context of ARC, eGFR equations have been shown to generally underestimate mCL_{CR} [181] We can confirm this finding for $eGFR_{CKDEPI}$, but we observed an overestimation, especially for the $eGFR_{MDRD}$ in our cohort. In this regard, it should be noted that the MDRD equation was validated only for patients with impaired or modestly impaired renal function (eGFR < 60 mL/min/1.73 m²), and its use should not be extended to patients of higher classes of renal function.

Collectively, these data clearly indicate that in critically ill patients, renal function should be measured rather than estimated, especially for those experiencing ARC [181]. For drugs that are eliminated mainly by the kidneys, the implications of a proper assessment of renal function are of utmost importance for drug dosing.

From our findings, it emerges that in critically ill patients, estimation of meropenem dosages should be based on mCL_{CR}. The use of empirical formulas should be discouraged, as it may lead to an underestimation of the daily maintenance dose with the consequent substantial risk of meropenem underexposure if $eGFR_{CKDEPI}$ is used, or to an overestimation of the drug dose if $eGFR_{CG}$ or $eGFR_{MDRD}$ are used.

However, it is worth noting that nowadays the optimal administration of β-lactams in critically ill patients should be supported by TDM, and results should be interpreted by clinical pharmacologists with experience in antimicrobial and infectious diseases. In a recent experience of antimicrobial TDM in critically ill patients, we reported the need for a dose increase based on TDM for meropenem in 13.5 % of cases and a dose decrease for piperacillin-tazobactam in 44 % of patients [182].

In critically ill patients the attainment of an aggressive PD target of efficacy for β-lactams has been shown effective both for achieving a positive clinical outcome from the infectious episode and for preventing the development of resistance. Specifically, a recent retrospective study conducted among 74 critically ill patients who received 24 h-CI meropenem for the treatment of different infections between December 2020 and July 2021 showed that achieving a C_{ss}/MIC $\geq$ 4.63 was associated with a clinical cure [112].

Another retrospective study conducted among 116 critically ill patients who received CI meropenem, piperacillin, or ceftazidime for the treatment of documented Gram-negative infections showed that targeting a C_{ss}/MIC ratio > 5 for these β-lactams could prevent microbiological failure and/or resistance development [113].

We are aware of the presence of some limitations in this study. First, our data were retrospectively collected, and this only allowed us to get sparse pharmacological and laboratory data. Second, the sample size was quite limited due to the need for both meropenem plasma concentrations and mCL_{CR}. Third, we applied the empirical formulas to all ranges of renal function, which may be inaccurate in some circumstances. A strength of our analysis was that the continuous infusion mode of administration gave us the opportunity to exactly calculate CL_M in each patient and to associate this pharmacokinetic variable to different estimates of renal function.

III.6 Conclusions

In conclusion, we showed all the eGFR equations are not adequate for calculating the doses of 24 h-CI meropenem that are needed to attain optimal PK/PD targets of efficacy in critically ill patients. Clinicians should rely on mCL_{CR} and TDM for optimizing the 24 h-CI meropenem dose in empiric therapy against susceptible Gram-negative pathogens in the critically ill population. This study outlines the importance of optimizing the pharmacokinetics of β-lactams in critically ill patients.

Table III.1: Demographic and clinical characteristics of the population (n = 46).

Variable	Median or Count	IQR Range or %
Age (years)	58.5	54–67
Gender (male/female)	35/11	76.1/24.9
Body weight (kg)	70.0	60.0–80.0
BMI (kg/m2)	24.2	21.7–26.8
Assessment of renal function		
Serum creatinine	0.7	0.4–1.2
mCL_{CR} (mL/min)	74.7	40.5–129.3
$eGFR_{CKDEPI}$ (mL/min/1.73 m²)	103.1	62.6–126.7
$eGFR_{CG}$ (mL/min/1.73 m²)	112.6	61.7–185.2
$eGFR_{MDRD}$ (mL/min/1.73 m²)	108.5	58.9–207.0
Patients with AKI	13	28.3
Patients with ARC	12	26.1
Reason for meropenem		
IAI	18	39.1
HAP	10	21.7
Sepsis/septic shock	9	19.6
BSI	6	13.1
Others	3	6.5
Meropenem treatment		
Dose (g q24h by CI)	2.0	2.0–4.0
Treatment duration (days)	12.0	8.0–19.0
C_{ss} (mg/L)	13.4	9.4–19.5
Clearance (L/h)	7.8	5.3–11.6

ARC, augmented renal clearance (defined as $mCL_{CR} \geq 130$ mL/min); AKI, acute kidney injury (defined as $mCL_{CR} < 30$ mL/min); BMI, body mass index; BSI, bloodstream infection; C_{ss}, meropenem steady-state concentration; $eGFR_{CG}$ estimated glomerular filtration rate calculated by means of the Cockcroft–Gault formula; $eGFR_{CKDEPI}$ estimated glomerular filtration rate calculated by means of the CKD-EPI formula; $eGFR_{MDRD}$ estimated glomerular filtration rate calculated by means of the MDRD formula; HAP, hospital acquired pneumonia; IAI, intra-abdominal infections; mCL_{CR}, measured creatinine clearance.
Data are presented as median (IQR) for continuous variables and as a number (%) for categorical variables.

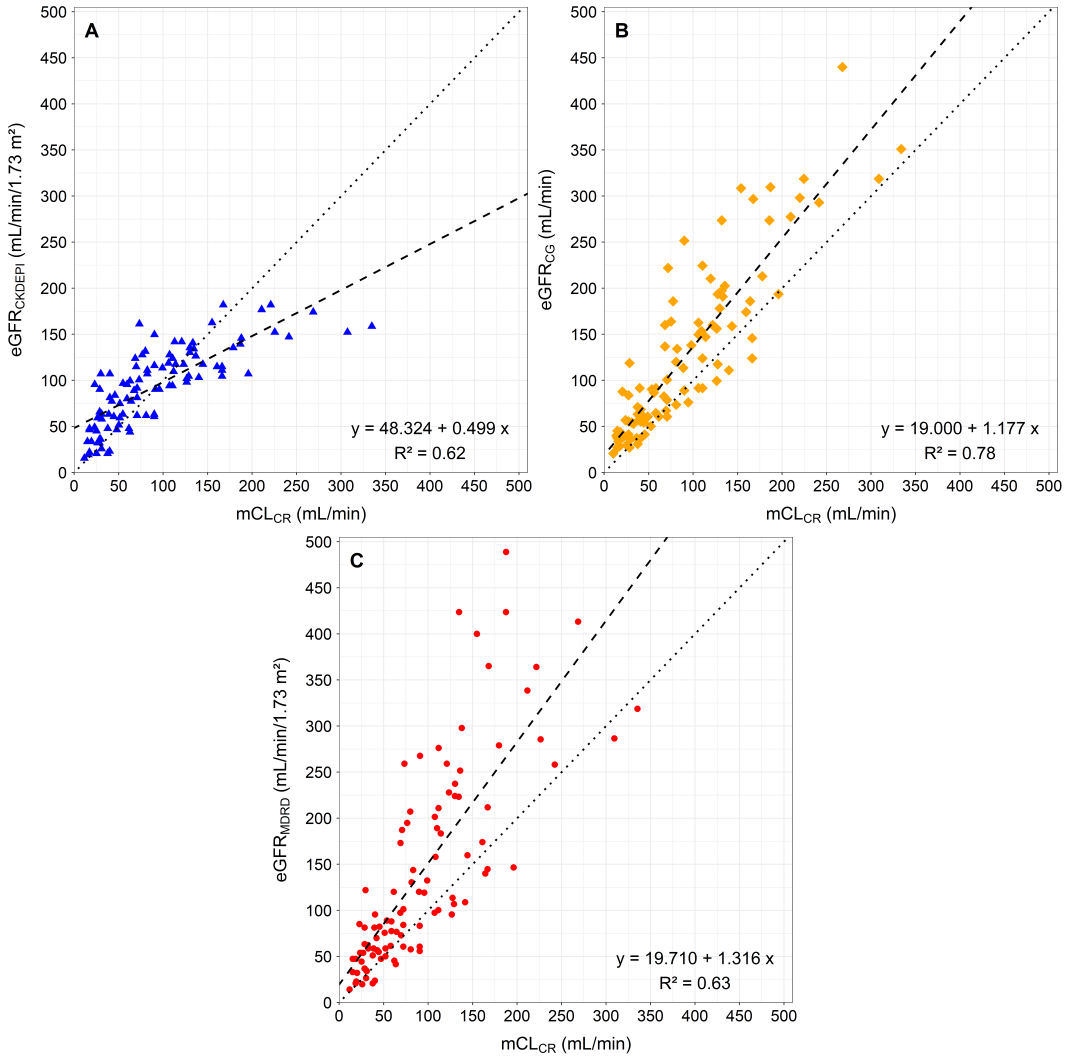


Figure III.2: Linear regressions between (A) estimated glomerular filtration rate (eGFR) calculated by means of the CKD-EPI formula ($eGFR_{CKDEPI}$) vs. measured creatinine clearance (mCL_{CR}), (B) eGFR estimated by means of the Cockcroft–Gault formula ($eGFR_{CG}$) vs. mCL_{CR} and (C) eGFR estimated by means of the MDRD formula ($eGFR_{MDRD}$) vs. mCL_{CR}. The dashed lines represent the line of regression. The dotted lines are the identity lines.

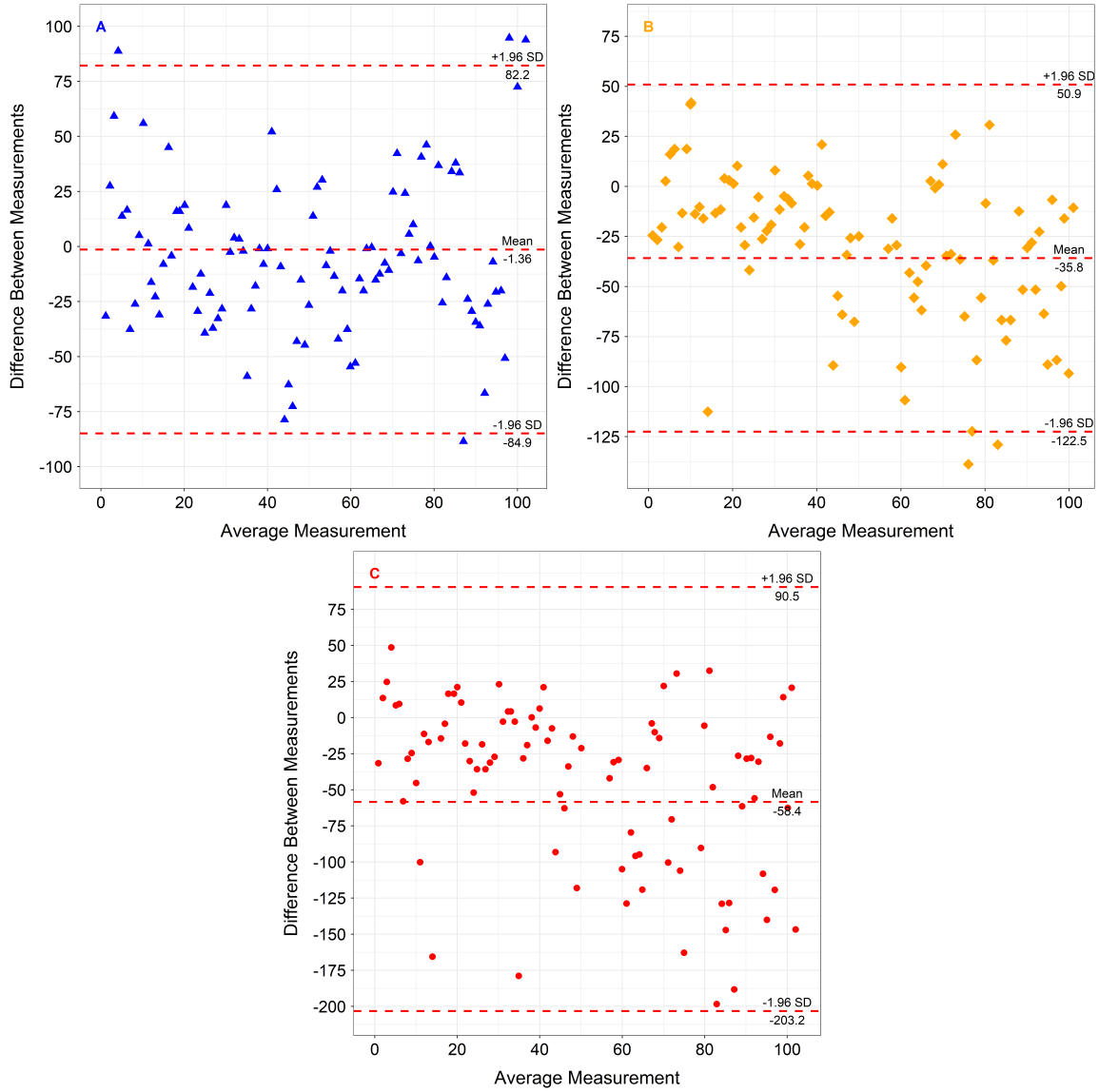


Figure III.3: Bland–Altman plots for assessing the agreement between measured creatinine clearance (mCL_{CR}) vs. (A) estimated glomerular filtration rate (eGFR) calculated by means of the CKD-EPI formula ($eGFR_{CKDEPI}$), (B) eGFR estimated by means of the Cockcroft–Gault formula ($eGFR_{CG}$), and (C) eGFR estimated by means of the MDRD formula ($eGFR_{MDRD}$). The red dashed lines represent the average difference and the 95% C.I. for the average difference.

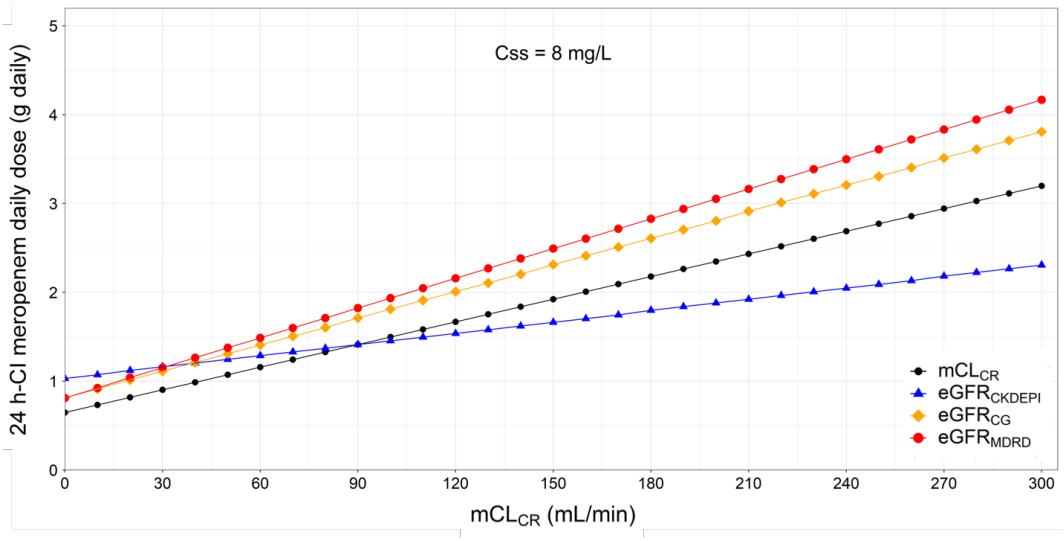


Figure III.4: 24 h-CI meropenem daily dose necessary to achieve the targeted C_{ss} of 8 mg/L by using $eGFR_{CKDEPI}$, $eGFR_{CG}$, or $eGFR_{MDRD}$ compared to mCL_{CR}.

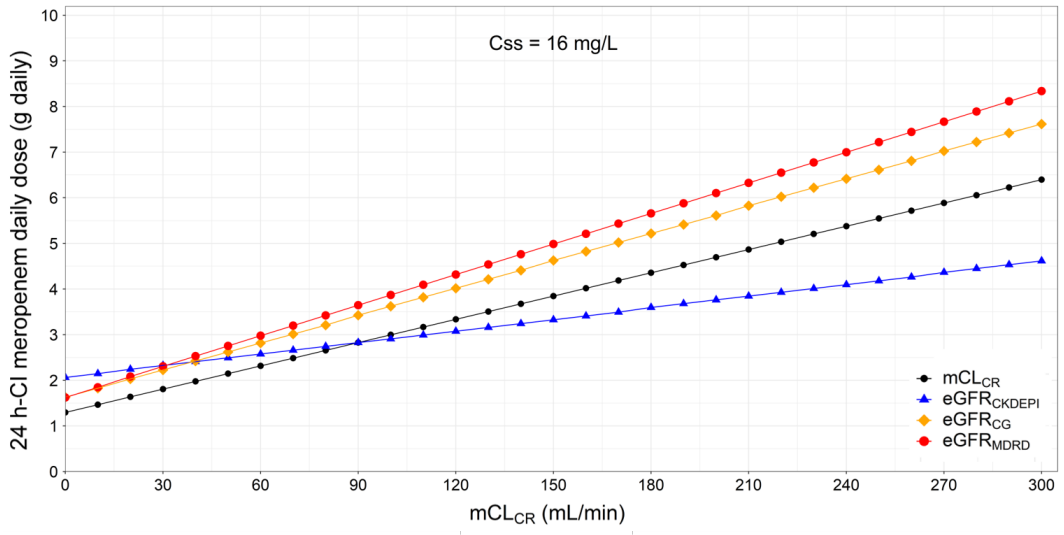


Figure III.5: 24 h-CI meropenem daily dose necessary to achieve the targeted C_{ss} of 16 mg/L by using $eGFR_{CKDEPI}$, $eGFR_{CG}$, or $eGFR_{MDRD}$ compared to mCL_{CR}.

Table III.2: Differences in meropenem dose amount (in g/daily by CI) when using eGFR formulas compared to mCL_{CR}, for targeting C_{ss} at 8 and 16 mg/L.

mCL_{CR}	C_{ss} = 8 mg/L			C_{ss} = 16 mg/L		
	$eGFR_{CKDEPI}$	$eGFR_{CG}$	$eGFR_{MDRD}$	$eGFR_{CKDEPI}$	$eGFR_{CG}$	$eGFR_{MDRD}$
10	0.34	0.18	0.19	0.68	0.36	0.38
30	0.26	0.21	0.25	0.52	0.42	0.50
60	0.13	0.25	0.33	0.26	0.50	0.66
90	0.00	0.30	0.41	0.00	0.60	0.82
120	−0.13	0.34	0.49	−0.26	0.68	0.97
150	−0.26	0.39	0.57	−0.52	0.78	1.14
180	−0.38	0.43	0.65	−0.76	0.86	1.30
210	−0.51	0.48	0.73	−1.02	0.96	1.46
240	−0.64	0.52	0.81	−1.28	1.04	1.62
270	−0.76	0.57	0.89	−1.52	1.14	1.78
300	−0.89	0.61	0.97	−1.78	1.22	1.94

Chapter IV

Use of C-RP as a biomarker to optimize the PD

IV.1 Abstract

In critically ill patients with hospital-acquired pneumonia (HAP) and ventilator-asso - ciated pneumonia (VAP), the antibiotic treatment failure due to insufficient efficacy is an important clinical challenge, especially with the global rise of antibiotic resistance. Strategies to individualize treatment are therefore needed. C-reactive protein (C-RP) dynamic models could help for predicting patients' response to antimicrobial therapy. We investigated the relationship between meropenem exposure and C-RP dynamics in critically ill adults with HAP/VAP.

Critically ill patients treated by continuous infusion (CI) meropenem with HAP/VAP were included between December 2020 and August 2023 at the IRCCS Azienda Ospeda - liero-Universitaria di Bologna, Italy. Non-linear effects modelling was performed to estimate the pharmacokinetic (PK) parameters. Then, a turnover response model to characterize C-RP trend was applied. Finally, Monte Carlo simulations were used in to simulate C-RP course considering different meropenem dosing regimens and all covariates included in the final PK/pharmacodynamic (PD) model.

Sixty-four patients were enrolled and 211 meropenem steady-state concentrations were retrieved. A one-compar-tment model with first order elimination and eGFR as covariate on meropenem clearance adequately fitted the PK data. Mean meropenem population clearance was 7.32 L/h.

The PD analysis included 415 C-RP measurements in 47 patients who received either meropenem monotherapy (n = 24) or in combination with a Gram-positive antimicrobial in the absence of documented Gram-positive infection (n = 23). The PD was described with an indirect turnover model with full inhibition of C-RP production. MIC and concomitant therapy with a Gram-positive antimicrobial were the only covariates on IC_{50}. The C-RP elimination rate was 0.012 h^{-1} and IC_{50} was 1.90 for an MIC of 2 mg/L in patients receiving meropenem monotherapy. C-RP reduction was simulated for different meropenem concentration (C_{ss})/MIC ranges (< 1, 1-4, 4-8, > 8), considering a meropenem dosage adapted to the eGFR. Higher C_{ss}/MIC values were associated with a greater and quicker C-RP relative reduction from baseline (> 55 % decrease in C_{ss}/MIC 4-8 and > 8, 35 % decrease in C_{ss}/MIC 1-4, and 10 % decrease in C_{ss}/MIC < 1 at day 4).

The first PK/PD model of CI meropenem and C-RP in critically ill patients with HAP/VAP was successfully built. C-RP reduction and MIC are important to consider when tailoring critically ill patients with HAP/VAP treated with CI-meropenem and a cut off value of 55 % of relative C-RP reduction from baseline could discriminate patients with an optimal C_{ss}/MIC in empirical treatment.

IV.2 Introduction

IV.2.1 Rationale of studying meropenem

In intensive care units (ICU), the most frequent infections are hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [183]. In particular, their prevalence ranges from 24.7 to 34 % (3,188) and the 30-day mortality risk is increased by 82 % [184].

HAP and VAP are mainly caused by Gram-negative pathogens, accounting for 77.9 % of isolated pathogens [10]. Among these, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* are the most frequent, corresponding to 23.0 %, 22.6 %, and 16.6 %, respectively [10].

Current European and Italian guidelines recommend using the new β-lactams/ β-lactamase inhibitors (BL/BLI) such as ceftazidime-avibactam and meropenem-vaborbactam as first line to treat severe infections caused by carbapenemase-producing Gram-negative pathogens [16, 163]. Nevertheless, meropenem can be used against extended-spectrum β-lactamases (ESBLs)-producing Enterobacterales, and against susceptible strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [165, 166].

IV.2.2 PK/PD target of meropenem efficacy

Meropenem exhibits a time-dependent bactericidal activity. In critically ill patients, targeting a plasma meropenem concentration at least four times the minimum inhibitory concentration (MIC) of the causative bacteria for 100 % of the dosing interval ($f_{T \geq 4MIC}$ = 100 %) maximizes meropenem efficacy [106, 112, 113]. Thus, continuous infusion (CI) associated with real-time therapeutic drug monitoring (TDM) might be the optimum to enhance meropenem efficacy in critically ill patients [106, 112, 113, 182].

IV.2.3 Rationale for studying C-RP

The response to antimicrobials treatment is monitored by biomarker trends in clinical routine [130]. There are few studies on biomarkers guided therapy for early stop treatment [138–140]. C-reactive protein (C-RP) is a biomarker used extensively for infection diagnosis and management in clinical practice [132]. It has been shown to reflect antibiotic therapy efficacy [147]. Indeed, C-RP and C-RP relative change from baseline during the first six days of antibiotic therapy was significantly decreased in survivors compared to non-survivors in VAP [147]. But there is still a knowledge gap in linking meropenem exposure to C-RP trend.

IV.2.4 Objectives

The aim of this study was to develop a population PK/PD model to quantify meropenem exposure and C-RP kinetics relationships and to simulate the trend of C-RP for different CI meropenem dosing regimens in critically ill patients with HAP/VAP.

IV.3 Material and methods

IV.3.1 Patients' enrollment

This was a monocentric, retrospective clinical study conducted among critically ill patients admitted to the ICU of the IRCCS Azienda Ospedaliero Universitaria di Bologna, in Italy, during the period December 2020 August 2023. All included patients had a HAP or a VAP treated with 24 h-CI meropenem and underwent real-time TDM.

Patients were divided into distinct groups according to their possible combination therapy. None of the patients received a combination therapy including antifungals.

This study was approved by the local ethics committee (No. 308/2021/Oss/AOUBo on 24 May 2021). Due to the retrospective nature of this investigation, informed written consent was waived.

The following demographic and clinical data were collected from each patient's medical record: age, gender, weight, height, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), type and site of infection, and microbiological isolates with the MIC for meropenem. The eGFR was estimated by means of Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) formula.

IV.3.2 Meropenem administration and TDM

At our Institution, all patients received an initial bolus of 2 g of meropenem over 2 h immediately followed by a maintenance dose (MD). MD was initially adjusted to the eGFR, according to: 1 g q6h over 6 h in patients with eGFR ≥ 60 mL/min/1.73 m² or of 0.5 g q6h over 6 h in those with eGFR < 60 mL/min/1.73 m². Stability of 24 h-CI meropenem was granted by reconstitution of the aqueous solution every 6–8 h with infusion over 6–8 h [173].

Patients underwent real-time TDM coupled with expert clinical pharmacological advice to guarantee the achievement of an optimal PD target of meropenem. This was defined as a meropenem steady-state concentration (C_{ss})-to-MIC ratio of 4–8, PK/PD target of meropenem efficacy recommended by the consensus documents [106, 112, 185].

IV.3.3 Blood sampling

Blood samples for TDM were collected to determine meropenem C_{ss} and C-RP measurements. Five mL of peripheral venous blood were centrifugated and sent to our laboratory for analysis. Concentrations were analyzed by means of a liquid chromatography-tandem mass spectrometry (LC–MS/MS) commercially available method (Chromsystems Instruments & Chemicals GmbH, Munich, Germany), with a lower limit of detection of 0.3 mg/L. Concentration determinations and expert clinical pharmacological advice were available few hours after blood sampling to adjust meropenem dosage.

IV.3.4 Outcome definition

Clinical cure and microbiological eradication were assessed by clinicians. The clinical cure was defined as the complete resolution of signs and symptoms of the infection coupled with documented microbiological eradication at the end of treatment and absence of recurrence or relapse at 30-day follow up or development of meropenem resistance. Microbiological eradication was defined as the absence of the index pathogen from the primary site of infection in at least one subsequent assessment.

IV.3.5 PK/PD modelling

The PK/PD analysis was conducted with Monolix 2023-R1. To avoid instability and biases in modeling clinical sparse data, a sequential PK/PD model was built in a two-step process as already performed [186–189]. First, a PK model was built based on the previously published pharmacokinetics model of Cojutti *et al.* [112]. Second, the median Bayesian posterior estimates of the PK parameters were considered as fixed input in the PD model. The PD model was developed and fitted to the C-RP data over time.

Population PK modeling was performed using a stochastic approximation of the standard expectation maximization (SAEM) algorithm. As meropenem was administered by CI, a one compartment with first-order elimination was selected for the model structure [112]. The volume of distribution, V_D was fixed at 20.0 L, according to Cojutti *et al.* [112].

To describe the PD, models of full or partial inhibition/activation and with or without sigmoidicity were tested on C-RP production and degradation.

Inter-individual variability (IIV) was evaluated for all PK and PD parameters, except for the V_D (fixed at 0.40 according to Cojutti *et al.* [112]). Additive, proportional, and combined error models were tested for residual variability.

In the second step, the following clinical variables were tested as covariates on each PK/PD parameter: eGFR, weight, height, age, gender, pathogen's MIC, and type of microbiological isolates (Pseudomonas vs. non-Pseudomonas species and fermenting vs. non-fermenting microorganisms). Regarding the MIC, in case of multiple microbiological isolates, the one with the highest MIC for meropenem was considered.

IV.3.6 Model evaluation

The model was evaluated considering (1) a significant decrease in the objective function value (OFV; equal to −2 log-likelihood, decrease of at least 3.84 points for 1 degree of freedom) and in Akaike information criterion (AIC), (2) the precision of parameter estimation (decrease in relative standard error (RSE)), the goodness-of-fit plots: (3) population and individual observations vs. predictions plots, and (4) residual plots (individual weighted residuals (IWRES) vs. individual predicted concentrations and vs. time), (5) graphical visual predictive checks (VPC) and (6) bootstrap. A non-parametric bootstrap resampling technique of 1'000 patients was used to evaluate the uncertainty of all PK and PD parameter estimates and the robustness of the final model. From the bootstrap empirical posterior distribution, the 95% confidence interval (2.5–97.5 percentiles) for the parameters was obtained. The bootstrap resampling was obtained using the "Rsmlx" package in R (R version 4.2.1).

IV.3.7 Monte Carlo simulations

Monte Carlo simulations using the final PK/PD model were performed with Simulix 2023-R1 and included all covariates retained significant. C-RP profiles were explored for different C_{ss}/MIC ranges. For this, 80'000 patients were simulated, and patients were divided into diverse groups, based on their C_{ss}/MIC ratio. For each group of C_{ss}/MIC ranges, median of relative C-RP reduction from baseline was calculated.

All plots were generated using the "ggplot2" package in R (R version 4.2.1).

IV.4 Results

IV.4.1 Patient Demographics

From a total of 154 patients, 64 patients were enrolled and 211 meropenem C_{ss} values were collected. Patients were excluded of the analysis because they had a concomitant therapy with antifungals (n = 82), they had less than 48 h meropenem treatment duration they were pediatric patients (n = 2) or they did not receive meropenem in CI (n = 2) (Figure IV.1).

Median (IQR) age, weight, and eGFR, were 65.5 (57.0-74.0) years, 75.00 (65.00-85.00) kg, and 70.00 (39.00-100.00) mL/min/1.73 m², respectively. Median (IQR) meropenem treatment duration, dose and C_{ss} were 9.00 (6.50-14.00) days, 2.00 (1.50-4.00) g daily by CI and 15.90 (9.75-27.60) mg/L, respectively.

Overall, 24 patients were treated with meropenem monotherapy, 23 were treated with meropenem plus an anti-Gram-positive agent, 5 were treated with meropenem plus fosfomycin with or without at least one Gram-positive antimicrobial, and 12 received meropenem plus at a Gram-positive antimicrobial with a documented infection due to a Gram-positive pathogen. The 47 patients receiving meropenem monotherapy (n = 24) or with at least one Gram-positive antimicrobial in the absence of Gram-positive isolate (n = 23) were included in the analysis for the PD model.

In this sub-population, median (IQR) C-RP at baseline and C-RP along treatment were 14.70 (7.46-26.89) mg/dL, and 11.79 (6.85-20.08) mg/dL, respectively. Among these 47 patients, 13 were infected by *Pseudomonas aeruginosa* (MIC ranging from 0.12 to 16.00 mg/L), 13 by *Klebsiella pneumoniae* (MIC ranging from 0.12 to 8.00 mg/L) and 7 by *Acinetobacter baumannii* (MIC ranging from 0.12 to 64.00 mg/L). Mean MIC for meropenem was 6.97 mg/L. Other microbiological data are summarized in Table IV.1.

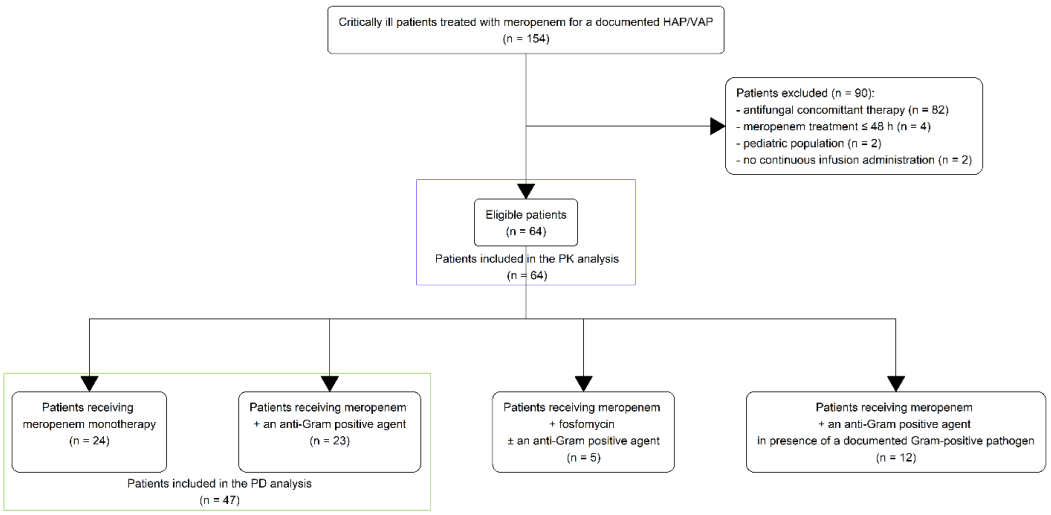


Figure IV.1: Flowchart of patients' inclusion. The PK analysis was conducted among 64 patients (in purple) and the PD analysis among 47 patients (in green).

IV.4.2 PK/PD model

The PK/PD model parameters are shown in Table IV.3. The PK analysis was lead among the 64 patients. The final PK model included eGFR as a covariate on CL_{MER}. Including eGFR as a covariate on CL_{MER} lead to a decrease in OFV of 45.73 and in AIC of 43.73. The mean population CL_{MER} was 7.32 L/h.

The PD was described in the subpopulation of 47 patients with an indirect response and full inhibition of C-RP production without sigmoidicity (Equation IV.2). The PK/PD model structure is highlighted in Figure IV.2 and the relationship between drug host and pathogens investigated in this model is described in Figure IV.3.

Table IV.1: Summary of patients' data.

Variable	Mediand or Count	IQR Range or %
Age (years)	65.5	(57.0-74.0)
Gender (M/F)	36/28	(56.25/43.75)
Height (m)	1.70	(1.68-1.75)
Weight (kg)	75.00	(65.00-85.00)
Lab measurements		
Serum creatinine (mg/dL)	0.96	(0.62-1.31)
eGFR (mL/min/1.73 m²)	70.00	(39.00-100.00)
C-RP at baseline (mg/dL)[a]	14.70	(7.46-26.89)
C-RP (mg/dL)[a]	11.79	(6.85-20.08)
Meropenem treatment		
Treatment duration (days)	9.00	(6.50-14.00)
Dose (g daily by CI)	2.00	(1.50-4.00)
C_{ss} (mg/L)	15.90	(9.75-27.60)

[a] In the 47 patients included in the PD analysis. If not specified, data from the 64 patients.
CI, continuous infusion; C-RP, C-reactive protein along treatment; C_{ss}, meropenem concentration at steady-state; eGFR, estimated glomerular filtration rate calculated with the CKD-EPI formula.
Data are presented as median (IQR) for continuous variables and as number (%) for categorical variables.

$$\frac{dC\text{-}RP}{dt} = 1 + \frac{(k_{in} \times (1 - C_{ss})}{C_{ss} + IC_{50}} - k_{out} \times C\text{-}RP \tag{IV.1}$$

$$k_{in} = C\text{-}RP_0 \times k_{out} \tag{IV.2}$$

where k_{in} is the C-RP production rate (mg/L/h) calculated according to Equation IV.2; C_{ss}, the meropenem steady-state concentration (mg/L); k_{out}, the C-RP degradation rate (h^{-1}); $C\text{-}RP_0$, the C-RP concentration at baseline (mg/L); C-RP, the C-RP concentration (mg/L); and IC_{50}, the half maximal inhibitory concentration (mg/L).

Overall, C-RP concentrations were well fitted by the PD model. In particular, PD parameters were estimated with a RSE of less than 30 %, apart from θ_3 (RSE of 53.4 %) and θ_5 (RSE of 31.9 %). Pathogen MIC was significantly associated with IC_{50}, with a decrease of 4.83 and 3.93 in OFV and AIC, respectively. The concomitant administration of a Gram-positive antimicrobial was another significant covariate on IC_{50} with a decrease of 11.83 and 9.83 in OFV and AIC, respectively. Interestingly, infections due to *Pseudomonas aeruginosa* or to fermenting pathogens were not considered different to others by this model.

IC_{50} was 1.90 mg/L considering an MIC of 2 mg/L in patients receiving meropenem monotherapy. The C-RP elimination rate was 0.012 h^{-1}.

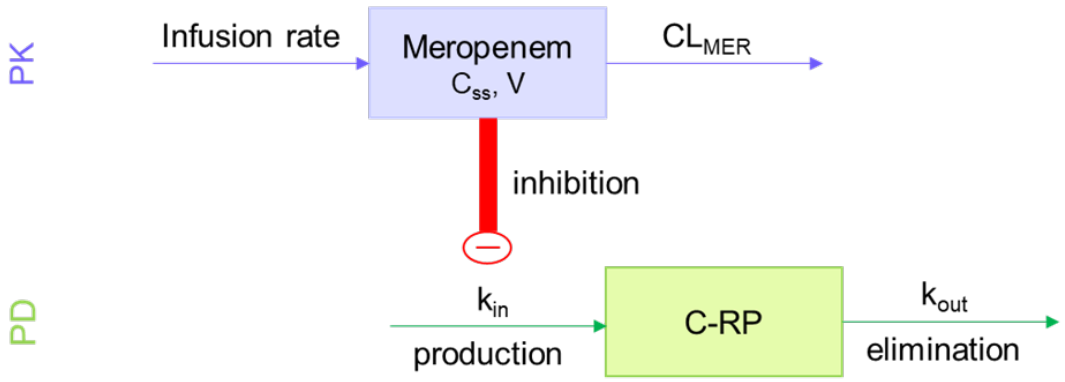


Figure IV.2: Schematic representation of the pharmacokinetic (PK) (in purple) and pharmacodynamic (PD) (in green) relationships of the model built. Increasing meropenem concentrations inhibit the production of C-RP.

IV.4.3 Model evaluation

Diagnostic plots for the PK/PD models showed a good agreement between the observed and predicted data (Figure IV.4), resulting in an R^2 of 0.72 for the PK model and 0.77 for the PD model. The individual weighed residuals vs. meropenem and C-RP concentrations did not show any trend indicative of model misspecification (Figure IV.4).

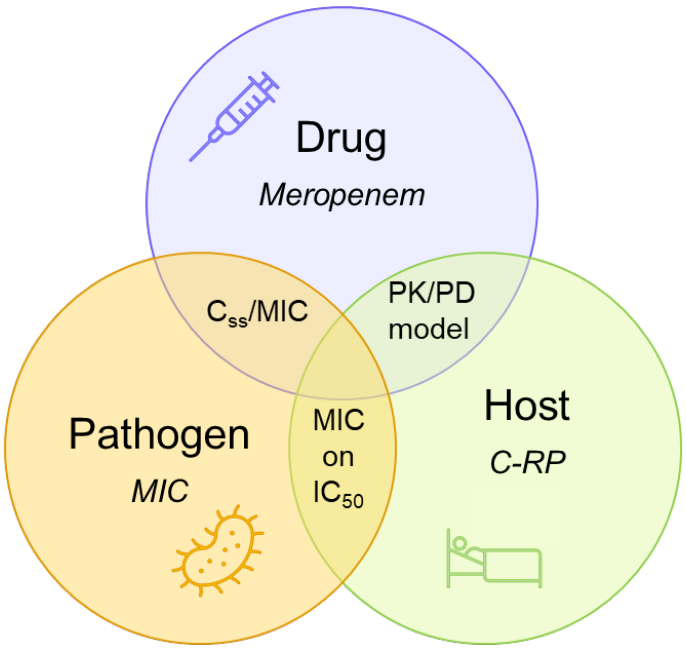


Figure IV.3: Drug-host-pathogen relationships investigated in this study.

The VPC indicated adequate goodness-of-fit and a good predictive performance of the final PD model (Figure IV.5). The VPC showed that the median of the observed C-RP was comprised within the median of the simulated prediction bands, and that the 90 % prediction interval is also consistent with the corresponding observed C-RP-based percentiles. The VPC of the PK model showed that the median of the observed meropenem concentrations was comprised within the median of the simulated prediction bands, but that the model underestimates the highest meropenem concentrations at 144 h. But VPC showed acceptable predictive performance of the PK model.

The bootstrap median and 95 % confidence interval are presented in Table IV.3.

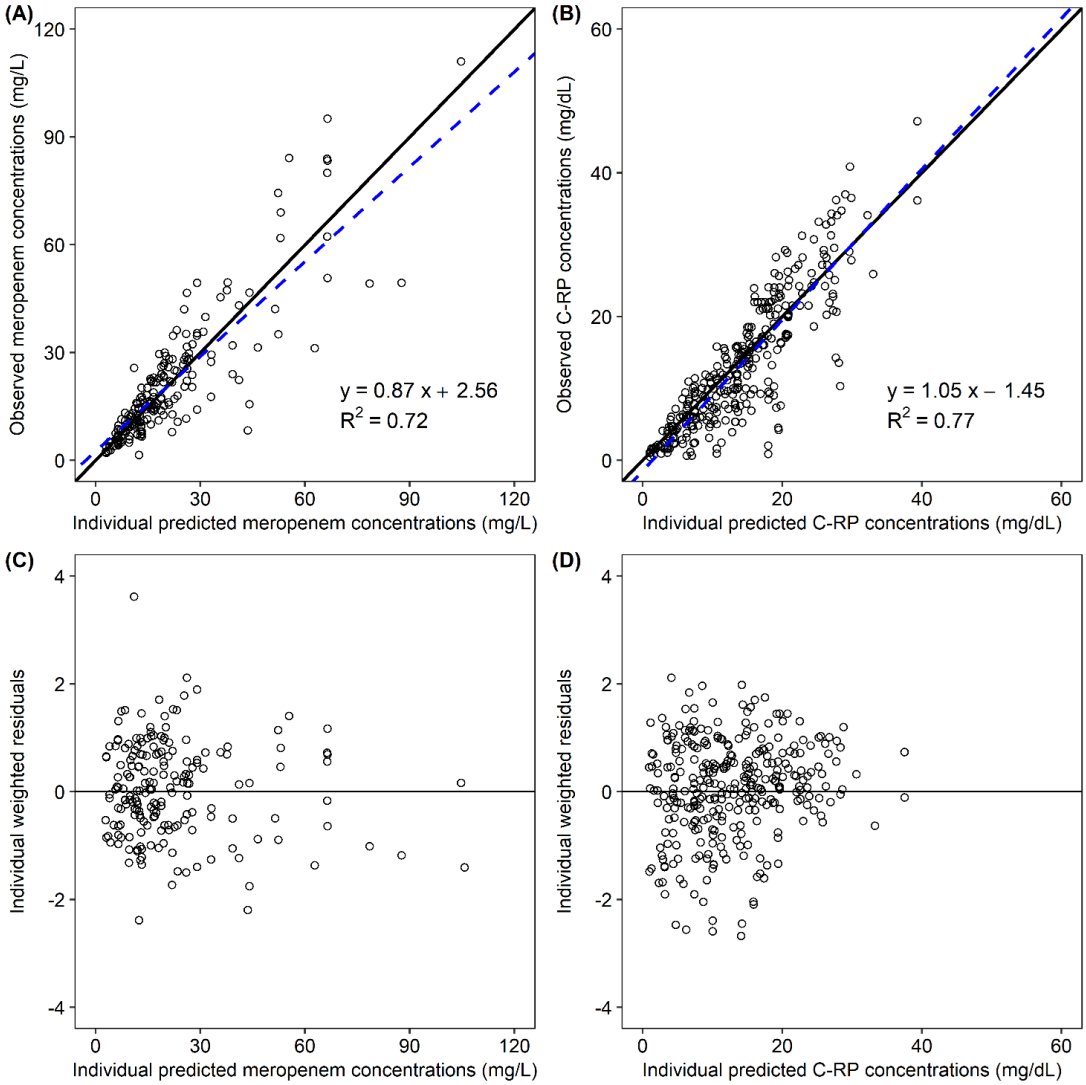


Figure IV.4: Observations-versus-individual predictions (upper panels) and individual weighted residuals (IWRES) versus individual-predicted concentrations (lower panels) for meropenem concentrations (left panels), and C-RP concentrations (right panels).

IV.4.4 Monte Carlo simulations

Simulations were conducted considering a meropenem dosage adapted to the eGFR (e.g., 0.75, 1.5, 3, 4, and 6 g daily by CI for an eGFR of 0-30, 30-60, 60-90, 90-120 and 120-150 mL/min/1.73 m², respectively) and a representative range of MIC (e.g., 0.12, 0.5, 1, 2, 4, 8, 16 and 32 mg/L). Simulated patients were classified in four groups of meropenem C_{ss}/MIC ratios: non optimal (< 1), quasi-optimal (1-4), optimal (4-8) and more than optimal (> 8) [154].

Median C-RP relative reduction from baseline for the different C_{ss}/MIC ratios are shown in Figure IV.6 for group 1 (meropenem monotherapy) and in Figure IV.7 for group 2 (meropenem + anti-Gram-positive antimicrobial). In group 1, in the optimal scenario (C_{ss}/MIC 4-8), C-RP was reduced by 40 % and 55 % after 2 and 4 days of therapy, respectively and reached 75 % reduction after 10 days of therapy. Conversely, in suboptimal conditions (C_{ss}/MIC < 1), C-RP was reduced by less than 10 % after 10 days of therapy and around 5 % reduction after 2 and 4 days of therapy. In quasi-optimal conditions (C_{ss}/MIC 1-4), C-RP was reduced by 25 %, 35 %, and 50 % after 2, 4 and 10 days of therapy, respectively. It is worth noting that high C_{ss}/MIC ratios (> 8) did not result in a greater reduction in C-RP than under optimal conditions (80 versus 75 % after 10 days of therapy). In group 2, the simulations showed similar trends with group 1 with a slower reduction (40 %, 35 %, 17 % and 2 % C-RP reduction after 10 days therapy in C_{ss}/MIC < 1, 1-4, 4-8, and > 8, respectively).

IV.5 Discussion

In this study, the CI-meropenem exposure and C-RP dynamics were described in critically ill patients with HAP/VAP using population PK/PD approach for the first time. The PK of meropenem could be satisfactorily described by a one compartment model with first order elimination with eGFR as covariate on CL_{MER}, and the PD by an indirect response model with MIC and concomitant therapy as covariates on IC_{50}. The simulations showed different C-RP trends depending on meropenem C_{ss}/MIC ranges. This is the first study to quantitatively link meropenem and C-RP relationships. This study provides the necessary tools to take the next critical steps to provide truly individualized antimicrobial therapy for critically ill patients with HAP/VAP receiving meropenem.

Meropenem concentrations were maintained in a quite narrowed range, which is in adequation with the nature of the data (TDM dose adjustment). A one-compartment model well described the data. This is in line with the findings of previous studies [112, 190–192]. The only significant covariate on CL_{MER} was eGFR. This is in agreement with previous findings [112, 191, 193–195], and with the fact that meropenem is mainly eliminated by the renal route [116]. Meropenem clearance was close to what was previously found in critically ill patients: 7.27 L/h for a median eGFR of 91.5 mL/min/1.73 m² [112], 7.34 L/h for a median eGFR of 67 mL/min [196], 7.82 L/h for a median eGFR of 59.43 mL/min [191], 7.48 L/h for a mean eGFR of 35.69 mL/min/1.73 m² [197].

The VPC showed acceptable predictive performances of the PK model and all parameters were well estimated. Some meropenem population PK models have already been published and the aim of this study was not to describe the meropenem PK but to use the meropenem PK to describe the C-RP kinetics. We thus sequentially estimated the PK and the PD, as it was previously done [186–189].

The turnover response model with full inhibition of C-RP production well described the data. To our knowledge, there is only one other study describing the C-RP kinetics using a similar indirect turnover response model with full C-RP inhibition. This study included 237 Japanese non critically patients with Gram-positive infections treated by teicoplanin for PK modeling and 181 for PD modeling [198]. Even though this model was built in a different patient population and for another antibiotic, they reported a similar IC_{50} (of 2.66 mg/L), consistent with our findings and with concentrations in clinics. Furthermore, the estimation of all principal parameters in our models is precise and plausible.

The C-RP vs. population predictions illustrated the C-RP high variability in critically ill patients. The model could describe this variability when considering patients and bacteria characteristics (e.g., C-RP vs. individual predictions). Two other PK/PD models were built using C-RP but for other antibiotics and other patients in Gram-positive infections. An open-label study of 18 English neonates linked teicoplanin concentrations and C-RP using a sigmoidal E_{max} model [199]. Another study was led among 25 non-critically ill English adults linking vancomycin concentrations and C-RP using the same sigmoidal E_{max} model [187]. None of them considered Gram-negative infections or critically ill patients. They both used AUC/EC_{50} (area under the curve representing patient's exposure to antibiotics and antibiotics concentration that produces the half-maximal C-RP inhibition ratio) as a surrogate of AUC/MIC. Our approach was similar, but we concluded that MIC was important to consider and that it was not possible to consider C_{ss}/IC_{50} only, since IC_{50} depends on MIC. This difference could be due to the to the fact that we had MIC.

MIC was a significant covariate on IC_{50}. MIC role in meropenem treatment is predominant as its PK/PD target of efficacy depends on C_{ss}/MIC ratio [2, 106, 112, 113]. Meropenem PK/PD target of efficacy have been proposed to be $f_{T>4MIC}$ = 100 % [106, 112–117]. In a study led in 44 critically ill patients with documented Gram-negative bacterial infections and treated with CI-meropenem, authors identified a cut-off value of 4.63 as valuable predictor of favorable clinical cure [112].

Similarly, in a study of 116 critically ill patients treated with CI β-lactams (52 treated with meropenem, 45 with piperacillin and 19 with ceftazidime), significant higher microbiological failure and resistance development were observed in patients with C_{ss}/MIC ≤ 5 compared to those with C_{ss}/MIC > 5.

Comparable results were found in 43 critically ill COVID-19 patients with Gram-negative superinfections treated with CI meropenem, where the microbiological failure rate was significantly lower in patients with a C_{ss}/MIC > 4 compared to those with a C_{ss}/MIC < 4.

A review compiling data of 64 articles (24 for meropenem, 21 for piperacillin, 10 for cefepime, and 9 for ceftazidime), proposed to use the target of 100 % $f_{T>4MIC}$, as this would allow for maximal bacterial killing, protect against bacterial regrowth, and ensure positive clinical outcome [105].

Predicting C-RP trends for different meropenem C_{ss}/MIC ratios is thus an asset and we discriminated C-RP in patients with non-optimal, quasi-optimal, optimal and higher then optimal meropenem PK/PD target of efficacy, similarly to a previous study [154].

In clinical practice, C-RP is commonly used to inform anti-infective therapy decisions. However, a substantial portion of this process relies on informal and intuitive practices. In our study, we established a direct connection between meropenem serum concentrations and alterations in circulating C-RP levels. Monitoring C-RP in individual patients offers a real-time assessment of their response to the drug. This approach presents distinct advantages as C-RP provides quantitative data, is readily accessible, and is widely embraced by clinicians. C-RP, alone or in combination with TDM, could lead to a better therapeutic management. Indeed, C-RP was shown to be different in survivors and non-survivors [148].

In a prospective, multicenter, observational study of 37 microbiologically documented VAP, the C-RP, and its ratio to baseline at days 4 and 5 were significantly different between patients who survived and those who did not [148].

Similar results were found in a prospective study lead among 129 cancer patients with healthcare-associated pneumonia: C-RP and C-RP ratio to baseline were significantly higher in non-survivors by day 4 [148]. Our results suggests that a relative decrease from baseline in C-RP of more than 55 % at day 4 is reflecting an optimal meropenem exposure. The Monte Carlo simulations of C-RP kinetics between different meropenem C_{ss}/MIC ratios showed a greater decrease at the beginning of therapy, period during which C-RP could discriminate survivors and non survivors, with a similar pattern to what has been described [147, 148].

C-RP-guided therapy is also associated with reduction in antibiotic treatment [139, 140, 143]. In a randomized clinical trial, 30 day rates of clinical failure among patients with uncomplicated Gram-negative bacteremia was noninferior in C-RP-guided antibiotic durations group compared to 14-day durations of antibiotic therapy [139]. The C–RP-guided group had the fewest failures at every time point, and the median antibiotic duration was 7 days [139].

Similarly, in a randomized, open-label, controlled clinical trial led in 130 critically ill patients, the median duration of antibiotic treatment was 6 days in the C-RP-guided treatment group and 7 days in the control group [140].

This appears of crucial importance when considering AMR progression worldwide. Indeed, shortening antibiotic treatment duration decreases risks of resistant organisms' emergence. Both American and European guideline recommended a 7-day course of antimicrobial therapy rather than a longer duration in HAP/VAP treatment [2, 15]. Our results described expected C-RP trends for the first 10 days of therapy.

European guidelines reported a higher mortality rate in cases caused by *Pseudomonas aeruginosa* and *Acinetobacter* spp. [2]. Interestingly, infections due to *Pseudomonas aeruginosa* or to nonfermenting bacteria were not retained different than other infections in this model. That could be due to the difference in MIC between species, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* having the highest MIC in our population.

To our knowledge, this is the first study investigating the C-RP dynamics in critically ill patients with HAP/VAP and treated by CI-meropenem.

We acknowledge some limitations to our study. Indeed, this is a retrospective design, with limited number of TDM and C-RP assessments per patient. Due to the CI administration, we had to fix the volume of distribution and the PK model showed some limitations. Conversely, the fact that this is the first description of the relationship between CI-meropenem exposure and changes in C-RP dynamics against documented Gram-negative HAP/VAP in critically ill patients and the possibility to integrate pathogens characteristics in humans remain valuable points of strength.

IV.6 Conclusions

To conclude, it was possible to describe drug, host, and pathogen characteristics in a single model. Indeed, meropenem PK and C-RP dynamics were successfully linked using routinely collected patient data in critically ill patients with Gram-negative HAP/VAP.

This study investigated the optimization of the PD of meropenem treatment using C-RP in critically ill patients with HAP/VAP. C-RP reduction could reflect meropenem C_{ss}/MIC and a cut off value of 50 % of relative C-RP reduction from baseline at day 4 could discriminate patients with an optimal C_{ss}/MIC in empirical treatment.

Monitoring C-RP and considering eGFR and MIC might be useful to optimize mero - penem treatment in adult critically ill patients with HAP/VAP treated by CI meropenem. Clinicians should expect a slower decrease in C-RP when the PK/PD target of efficacy is not attained.

Table IV.2: Summary of microbiological data (n=47).

Variable	Mediand or Count	IQR Range or %	MIC ranges (mg/L)
Reason for meropenem use			
VAP	35	(74.47)	
HAP	6	(12.77)	
VAP + BSI	5	(10.64)	
HAP + BSI	1	(2.12)	
Gram-negative isolates:			
Pseudomonas aeruginosa	13	(27.66)	0.12-16.00
Klebsiella pneumoniae	13	(27.66)	0.12-8.00
Acinetobacter baumannii	7	(14.89)	0.12-64.00
Enterobacter aerogenes	3	(6.38)	0.12
Serratia marcescens	3	(6.38)	0.12-8
Escherichia coli	2	(4.26)	0.12-2
Enterobacter cloacae	2	(4.26)	0.12-1
Proteus mirabilis	2	(4.26)	0.12
Klebsiella oxytoca	1	(2.13)	0.12
Enterobacter bugandensis	1	(2.12)	1
MIC (mg/L)	0.25	(0.12-4.00)	
Microbial eradication[a]	28	(63.63)	
Clinical outcome			
Cured	29	(61.70)	
Failed	18	(38.30)	

[a] Among the 44 patients with bronchoalveolar lavage cultures in at least one subsequent assessment.
BSI, bloodstream infection; HAP, hospital-acquired pneumonia; MIC, minimum inhibitory concentration; VAP, ventilator-associated pneumonia.
Data are presented as median (IQR) for continuous variables and as number (%) for categorical variables and as min-max value for MIC ranges.

Table IV.3: PK/PD model parameter estimates.

Parameter	Estimate (% RSE)	Bootstrap median	Bootstrap 95% confidence interval
PK model			
Population parameters			
CL_{MER} (L/h) = $\theta_1 \times \exp^{(CL_{CR} \times \theta_2)}$			
θ_1 (L/h)	2.72 (16.7)	2.73	2.32 – 3.13
θ_2	0.011 (20.0)	0.011	0.0085 - 0.014
V_D (L)	-	-	-
Inter-individual variability			
ω CL_{MER}	0.59 (10.4)	0.58	0.52 - 0.64
ω V_D	-	-	-
Residual variability			
Proportional error	0.37 (6.53)	0.36	0.33 – 0.41
PD model			
Population parameters			
$C\text{-}RP_0$ (mg/dL)	22.58 (9.55)	21.51	20.47 – 23.04
IC_{50} (mg/dL) $= \theta_3 \times \exp^{(MIC \times \theta_4)} \times \exp^{\theta_5}$ [a]			
θ_3	0.79 (53.4)	1.02	0.38 - 1.32
θ_4	0.44 (15.9)	0.31	0.24 - 0.48
θ_5	2.46 (31.9)	2.50	1.92 - 3.97
k_{out} (h^{-1})	0.012 (27.2)	0.012	0.0097 - 0.014
Inter-individual variability			
ω $C\text{-}RP_0$	0.51 (15.8)	0.48	0.39 - 0.59
ω IC_{50}	1.59 (22.5)	1.32	1.12 – 2.00
ω k_{out}	1.08 (21.6)	1.01	0.82 – 1.51
Residual variability			
Proportional error	0.35 (4.87)	0.38	0.35 - 0.44

[a] $\theta 5$ is the parameter that corrects IC_{50} in patients receiving meropenem and an anti-Gram-positive antimicrobial.
95% CI, 95% confidence interval; CL_{MER}, meropenem clearance ; $C\text{-}RP_0$, C-RP value at baseline; IC_{50}, half maximal inhibitory concentration; k_{out}, C-RP degradation rate; MIC, minimum inhibitory concentration; % RSE, percentage of relative standard error; V_D, meropenem volume of distribution; ω, standard deviation of inter-individual variability.
Proportional error was estimated using: observation = prediction × (1 + proportional error).

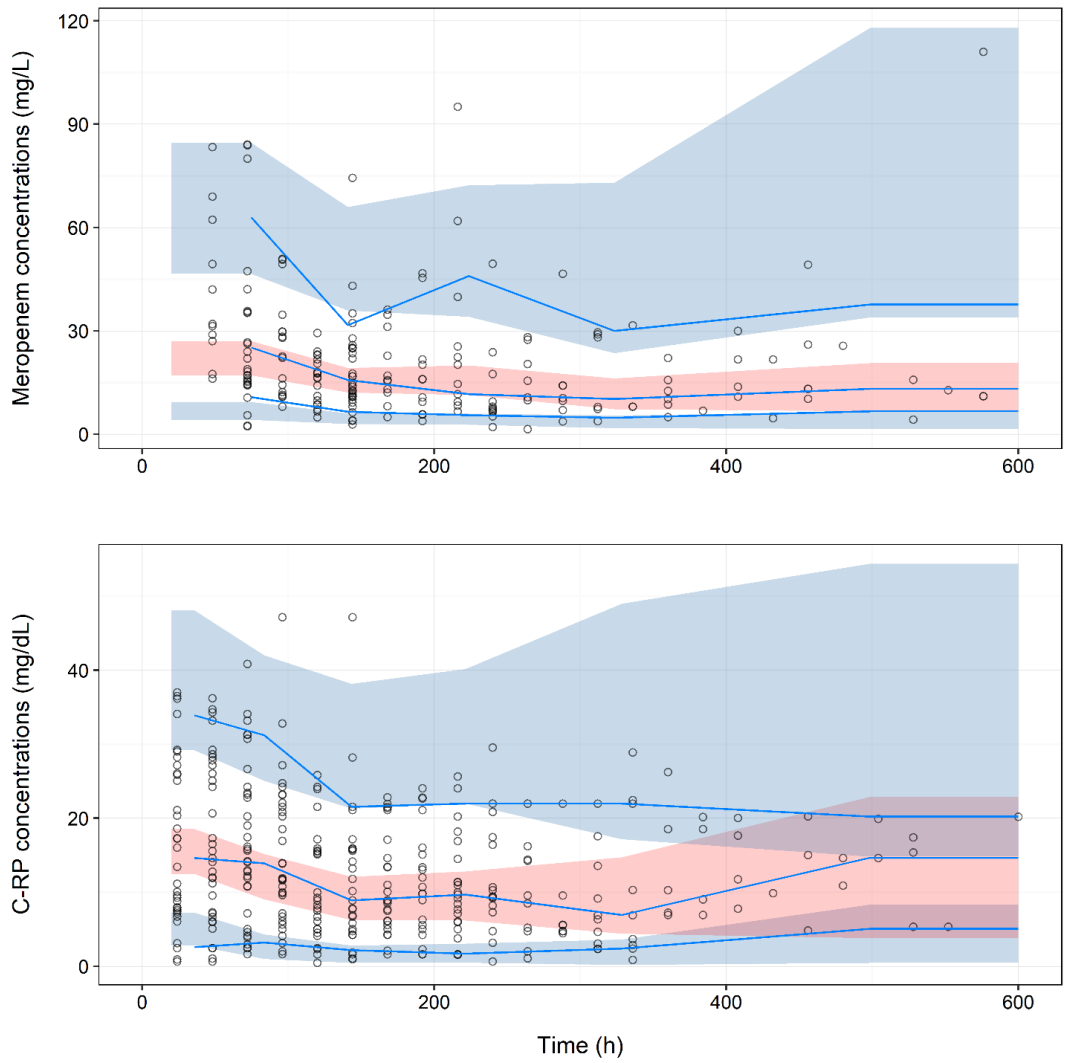


Figure IV.5: Visual predictive check (VPC) for the population pharmacokinetic (PK) model (upper panel) and the pharmacodynamic (PD) models (bottom panel). Blue lines represent the median, 10^{th}, and 90^{th} percentiles of the observed values; shaded areas are the prediction intervals for the median (red middle area) and 10^{th} and 90^{th} percentiles (light blue bottom and top areas).

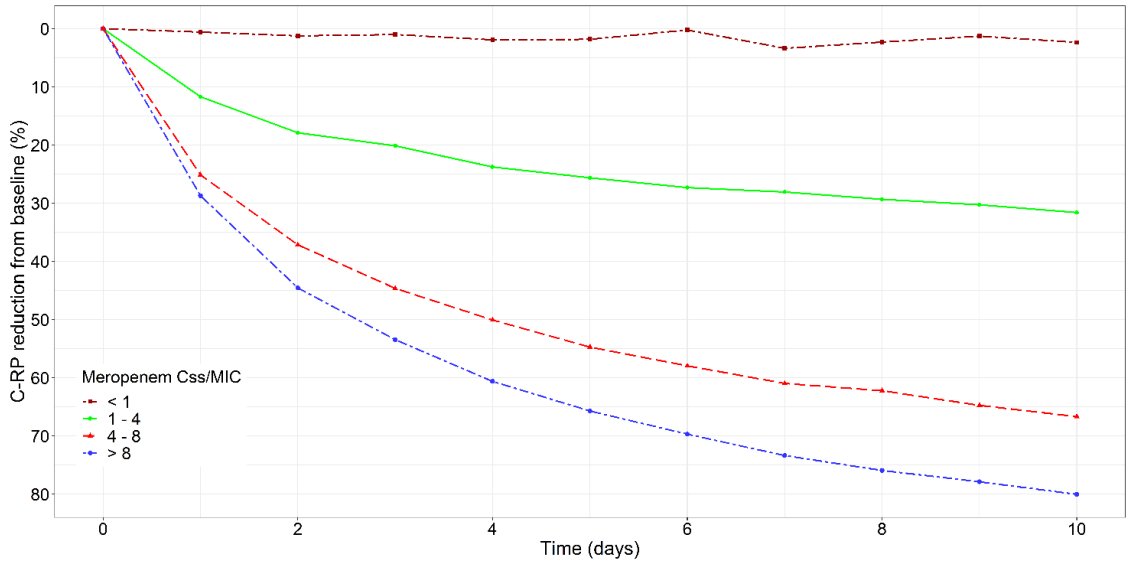


Figure IV.6: C-RP relative reduction from baseline for different PK/PD target of meropenem efficacy in Group 1 (meropenem monotherapy).

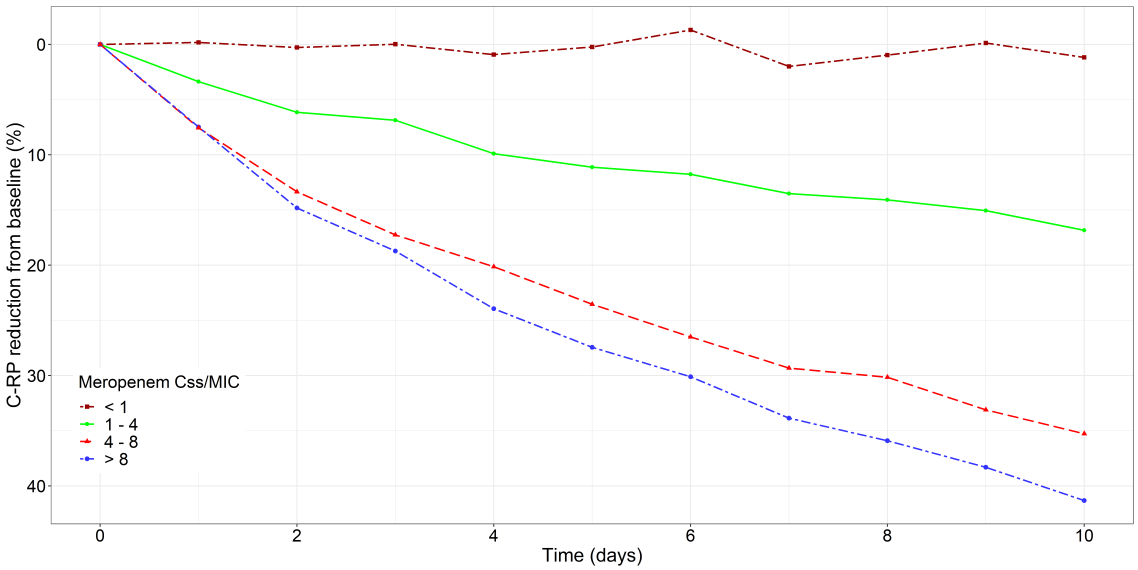


Figure IV.7: C-RP relative reduction from baseline for different PK/PD target of meropenem efficacy in Group 2 (meropenem + anti-Gram-positive antimicrobial).

Chapter V

Conclusions and future perspectives

This research focused on optimizing the treatment of critically ill patients with HAP/VAP who were receiving meropenem. These patients presenting complex challenges due to significant variations in their drug exposure caused by their underlying health conditions, to improve their therapy with meropenem, two key aspects were investigated: optimization of the PK and of the PD (FigureV.1).

In the first project, various methods for estimating renal function were evaluated to enhance meropenem PK optimization. The study revealed that the commonly used estimation formulas for estimating the GFR led to incorrect dosing recommendations. The actual measurement of creatinine clearance (mCL_{CR}) was found to be crucial for meropenem dosing adjustments in critically ill patients.

The second project aimed at optimizing meropenem PD by developing a PK/PD model that quantified the relationship between meropenem concentrations and changes in C-RP, an inflammation biomarker. Simulations demonstrated that achieving an optimal target concentration ratio (C_{ss}/MIC) was associated with higher and faster reduction in C-RP levels.

To conclude:

1. Accurate measurement of creatinine clearance is essential for optimizing meropenem dosing in critically ill patients. Relying on estimation formulas for GFR can lead to dosing errors.

2. The use of C-RP as a biomarker can aid in assessing the effectiveness of meropenem therapy, especially during empirical treatment.

Overall, this research provides valuable insights into tailoring meropenem treatment for critically ill patients with HAP/VAP, emphasizing the importance of individualized dosing based on measured renal function and the potential use of C-RP monitoring to guide therapy. This study has also made a significant contribution by delving into the intricate interplay between patients, drug, and pathogen. For the first time in the literature, our work has explored the relationships between these elements, addressing one of the six key research priorities set forth by leading organizations such as the International Society of Anti-Infective Pharmacology, and the European Society of Clinical Microbiology and Infectious Diseases [200]. Our research acknowledges the crucial gaps in traditional PK/PD approaches to antibiotic optimization and aligns with their overarching goal of personalizing antibiotic therapies. By doing so, we aimed to advance our understanding of antibiotic pharmacology and, ultimately, to enhance patient outcomes.

However, this research does not address all knowledge gaps, and there are still numerous questions awaiting investigation. This thesis can serve as a foundational work upon which to build and further explore these inquiries.

The findings from this research can serve as a foundation for the investigation of the meropenem C_{ss}/MIC ratios, C-RP trends and clinical or microbiological outcome in critically ill patients with HAP/VAP. Future perspectives could include a cut-off value of C-RP predicting the probability of clinical cure at different key time-point of the treatment.

While C-RP showed promise as a biomarker for assessing meropenem effectiveness, future studies could explore additional biomarkers or combinations thereof, such as procalcitonin. This could lead to more comprehensive monitoring tools that provide clinicians with real-time feedback on antibiotic therapy response.

The principles and methodologies applied in this research could be extended to other antibiotics with similar PK/PD properties (e.g., other β-lactams) and further investigated in other antibiotics, using the same workflow. Investigating the PK/PD relationships of different antibiotics in critically ill patients may lead to more personalized and effective treatment strategies.

As healthcare continues to move towards precision medicine, future work could involve the development of individualized dosing algorithms for meropenem based on a patient's specific clinical and pharmacological profile. This would take into account not only renal function but also other patient-specific factors.

The research could pave the way for clinical trials aimed at validating the proposed dosing strategies and biomarker monitoring in larger patient populations. These trials could provide robust evidence for the effectiveness of the approach.

Ultimately, the success of optimized antibiotic dosing strategies relies on the collaborative efforts of pharmacologists, infectious disease specialists, intensivists, and clinical pharmacists. Looking ahead, fostering these interdisciplinary collaborations represents a promising avenue for driving continuous improvements in patient care.

In summary, the future perspectives of this work encompass a wide range of possibilities, from practical clinical applications to further research endeavors aimed at refining antibiotic dosing in critically ill patients and advancing the field of infectious disease management.

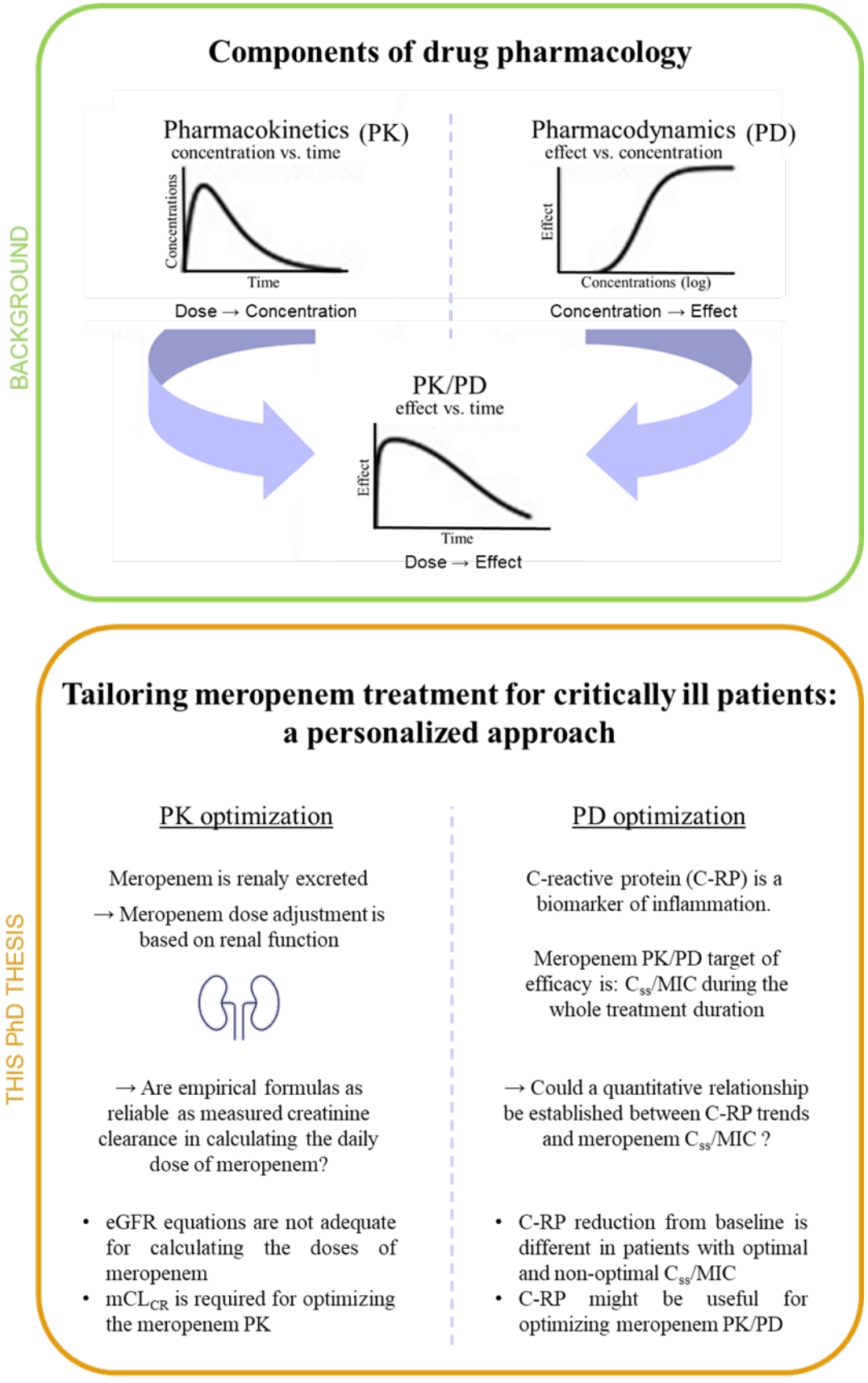


Figure V.1: Illustration of the project. C_{ss}, meropenem steady-state concentration; eGFR, estimated glomerular filtration rate; mCL_{CR}, measured creatinine clearance; MIC, minimum inhibitory concentration.

Chapter VI

Publications and communications

VI.1 Scientific publications

Troisi C, Cojutti PG, Rinaldi M, Laici C, Siniscalchi A, Viale P, Pea F. Measuring Creatinine Clearance Is the Most Accurate Way for Calculating the Proper Continuous Infusion Meropenem Dose for Empirical Treatment of Severe Gram-Negative Infections among Critically Ill Patients. Pharmaceutics. 2023 Feb 7;15(2):551. doi: 10.3390/pharmaceutics15020551. PMID: 36839872; PMCID: PMC9967919.

Sanz Codina M, Gatti M, **Troisi C**, Fornaro G, Pasquini Z, Trapani F, Zanoni A, Caramelli F, Viale P, Pea F. Relationship between Pharmacokinetic/Pharmacodynamic Target Attainment and Microbiological Outcome in Critically Ill COVID-19 Patients with Documented Gram-Negative Superinfections Treated with TDM-Guided Continuous-Infusion Meropenem. Pharmaceutics. 2022 Jul 29;14(8):1585. doi: 10.3390/pharmaceutics14081585. PMID: 36015211; PMCID: PMC9412264.

VI.2 Scientific communications

Poster presentation at the 31st European Congress of Clinical Microbiology & Infectious Diseases (ECCMID) – 2021: Troisi C, Gatti M, Liu C, Cojutti PG, Pea F. Relationship between pharmacokinetic/pharmacodynamic target attainment of meropenem and change in inflammatory biomarkers in critically ill patients: a prospective observational study.

Poster presentation at the 19^th *International congress of Therapeutic Drug Monitoring & Clinical Toxicology* – 2021: Troisi C, Gatti M, Liu C, Cojutti PG, Pea F. Is estimated glomerular filtration rate always reliable in choosing the right dose of continuous infusion meropenem for attaining appropriate exposure against Gram-negatives in critically ill patients? A pilot investigation.

Poster presentation at the 19^th *International congress of Therapeutic Drug Monitoring & Clinical Toxicology* – 2021: Liu C, Cojutti PG, Gatti M, Troisi C, Pea F. TDM-guided empirical treatment with beta-lactams in CAR-T patients with febrile neutropenia: proof of concept.

Poster presentation at the Training towards Innovative Personalized Antibiotic Therapy (TIPAT) spring meet-up – 2022: Troisi C, Gatti M, van Hasselt C, Cojutti PG, Pea F. Integrating therapeutic drug monitoring and pharmacokinetics/pharmacodynamics to predict outcomes in critically ill patients.

Poster presentation at the Population Approach Group in Europe (PAGE) – 2022: Troisi C, Cojutti PG, Bussini L, Del Turco ER, Giannella M, Pea F. Population pharmacokinetics of continuous infusion ampicillin in the treatment of enterococcal infections in adult hospitalized patients.

Poster presentation at the Uppsala Pharmacometrics summer school (UPSS) – 2022: Troisi C, Gatti M, Cojutti PG, Pea F. Population PK/PD model of continuous-infusion meropenem and C-RP in critically ill patients with HAP.

Poster presentation at the Training towards Innovative Personalized Antibiotic Therapy (TIPAT) winter school – 2023: Troisi C, Gatti M, van Hasselt C, Cojutti PG, Pea F. Integrating TDM and PK/PD to predict outcomes in hospital-acquired pneumonia.

VI.3 Other activities

VI.3.1 Scientific dissemination

- Organization of Pint of Science Bologna, "Our Body" theme: 2023.
- Chair of the student session and co-chair of the "New Approaches in PK Modelling and QSP of Biologics" session at the Group of Metabolism and Pharmacokinetics (GMP) congress: 2022/2023
- Organization of a game in an elementary school in Leiden to raise children's awareness of bacterial resistance to antibiotics: November 2022
- Chair of the student session at the DMDG/GMP/SPS joint meeting: 2022
- Co-chair of the student session at the Group of Metabolism and Pharmacokinetics (GMP) congress: 2021

VI.3.2 Other projects in which I have been involved

- Relationships between meropenem C_{ss}/MIC ratio, C-RP over time and clinical and microbiological outcomes using time-to-event modeling in critically ill patients (collaboration with Leiden university).
- External validation of published PK models of meropenem and piperacillin-tazobactam (collaboration with Leiden university).
- Predictions of the best and worst population PK models of vancomycin for model-informed precision dosing using machine learning (collaboration with InsightRX, Uppsala university, and Vienna university).
- Population PK modeling of CI-ampicillin in hospitalized patients with enterococcal infections.

Chapter VII
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