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Pharmacometrics to improve evaluation and individualisation of β-lactam/β-lactamase inhibitor combinations

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Abstract

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β-lactam/β-lactamase inhibitor (BL/BLI) combinations are essential for treating infections caused by multidrug-resistant Gram-negative bacteria, particularly in critically ill patients. However, pharmacokinetic (PK) and pharmacodynamic (PD) variability complicates dosing, potentially leading to suboptimal exposure, reduced bacterial eradication, and treatment failure. Despite widespread use, BL/BLI therapy relies largely on standard dosing approaches, with limited individualisation. This thesis explores pharmacometric strategies to better understand the complexities of BL/BLI therapy in critically ill patients by evaluating drug exposure, efficacy target attainment, and dosing strategies through real-world patient data, PKPD modelling, and simulation-based approaches.

Both simulated and patient-derived data were analysed. Population PK analysis was applied to characterise ceftazidime-avibactam (CAZ-AVI) disposition in critically ill patients with pneumonia and those undergoing continuous venovenous hemodiafiltration (CVVHDF). PK/PD indices and targets for avibactam were investigated in preclinical and clinical settings. In simulations, target attainment was evaluated for multiple BL/BLI regimens across different infection sites and renal function groups. Additionally, host response biomarkers were assessed for their potential role in treatment monitoring and individualisation.

Significant interindividual variability in CAZ-AVI PK was observed, even after accounting for renal function, suggesting additional unexplained sources of variability. Standard dosing in CVVHDF patients resulted in lower early (0-2 h) and higher later (4-8 h) concentrations compared to non-CVVHDF patients, indicating a larger volume of distribution and the need for tailored regimens. Both $fT>C_T$ and fAUC/MIC were identified as the best PK/PD indices for avibactam, depending on bacterial strain and mode of infusion, challenging the assumption of universal PK/PD indices. Simulations revealed that insufficient BLI exposure frequently limited target attainment, underscoring the need to consider both BL and BLI concentrations in dose optimisation. Analysis of immune response biomarkers revealed dynamic changes over the course of treatment, with one identified relationship between drug exposure and host response, though further clinical validation is needed.

This work demonstrates how model-based approaches can enhance BL/BLI therapy evaluation and individualisation by characterising PK variability, refining efficacy targets, and assessing dosing strategies in critically ill patients. Future research should focus on linking target attainment to clinical outcomes and integrating therapeutic drug monitoring and biomarker-guided approaches where relevant to optimise therapy.

Keywords: pharmacokinetics, pharmacodynamics, biomarkers, pharmacometrics, antibiotics, β-lactam/β-lactamase inhibitor combinations

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To the brave fools who dare to take on challenges – foolish enough to begin and stubborn enough to see it through, growing in the process.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **O'Jeanson, A.**, Nielsen, E.I., Friberg L.E. (2024) Therapeutic drug monitoring (TDM) of β-lactam/β-lactamase inhibitor (BL/BLI) drug combinations: insights from a pharmacometric simulation study. *J Antimicrob Chemother*, 80(1): 79-86.

II. **O'Jeanson, A.**, Nielsen, E.I., Athanassa Z., Ginosyan, A., Ioannidis, K., Manioudaki, S., Petsa, I., Giamarellou H., Bader, I., Skarmoutsou, E.M., Sakagianni, A., Loryan, I., Karaiskos, I., Friberg, L.E. An exploratory pharmacokinetic-pharmacodynamic (PKPD) analysis of ceftazidime-avibactam (CAZ-AVI) and various biomarkers in patients with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) caused by *Klebsiella pneumoniae*. *Manuscript*.

III. **O'Jeanson, A.**, Ioannidis, K., Nielsen E.I., Galani, L., Ginosyan, A., Paskalis, H., Loryan, I., Giamarellou, H., Friberg L.E., Karaiskos, I. (2025) Ceftazidime-avibactam (CAZ-AVI) pharmacokinetics in critically ill patients undergoing continuous venovenous hemodiafiltration (CVVHDF). *Int J Antimicrob Agents*, 65(1): 107394.

IV. **O'Jeanson, A.**, Nielsen, E.I., Friberg L.E. (2025) A model-based evaluation of the pharmacokinetics-pharmacodynamics (PKPD) of avibactam in combination with ceftazidime. *JAC Antimicrob Resist*, 7(2): dlaf036.

Additional paper not included in this thesis:

Allander, L., Vikdahl, E., Chatzopoulou, M., **O'Jeanson, A.**, Sandegren L., Lagerbäck, P., Tängdén, T. Evaluation of ceftazidime-avibactam in combination with colistin against KPC-2-producing *Klebsiella pneumoniae* with porin deficiency in static and dynamic time-kill experiments. *Submitted.*

Contents

Abbreviations

AMR	Antimicrobial Resistance
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARC	Augmented Renal Clearance
AUC	Area Under the Curve
AVI	Avibactam
BL	β-Lactam
BLI	β-Lactamase Inhibitor
CAZ	Ceftazidime
CET	Ceftolozane
CFU	Colony Forming Unit
cIAI	Complicated Intra-Abdominal Infection
CL	Clearance
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum (or peak) concentration
C_{min}	Minimum (or trough) concentration
CrCL	Creatinine clearance
CRP	C-Reactive Protein
cUTI	Complicated Urinary Tract Infection
CV	Coefficient of Variation
CVVHDF	Continuous Venovenous Hemodiafiltration
eGFR	Estimated Glomerular Filtration Rate
ELF	Epithelial Lining Fluid
EoT	End of Treatment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
fu	Fraction Unbound
ICU	Intensive Care Unit
IIV	Interindividual Variability
IMI	Imipenem
IOV	Interoccasion Variability
IV	Intravenous
HAP	Hospital-Acquired Pneumonia
MER	Meropenem
MIC	Minimum Inhibitory Concentration
MIPD	Model-Informed Precision Dosing
NaN	Not a Number

NCA	Noncompartmental Analysis
NLME	Nonlinear Mixed-Effects
OFV	Objective Function Value
PBPs	Penicillin-Binding Proteins
pcVPCs	Prediction-Corrected Visual Predictive Checks
PD	Pharmacodynamics
PIP	Piperacillin
PK	Pharmacokinetics
PopPK	Population Pharmacokinetics
PTA	Probability of Target Attainment
REL	Relebactam
RRT	Renal Replacement Therapy
RSE	Relative Standard Error
RUV	Residual Unexplained Variability
r^2	Coefficient of determination
SA	Saturation coefficient
SCTK	Static Concentration Time-Kill
SIR	Sampling Importance Resampling
SmPC	Summary of Product Characteristics
SOFA	Sequential Organ Failure Assessment
TAZ	Tazobactam
TDM	Therapeutic Drug Monitoring
TRC	Typical Renal Clearance
$t_{1/2}$	Half-life
UPLC	Ultra-Performance Liquid Chromatography
VAB	Vaborbactam
VAP	Ventilator-Associated Pneumonia
V1	Central volume of distribution
WHO	World Health Organization

1 Introduction

In 1928, Dr Alexander Fleming – a Scottish physician and microbiologist – discovered penicillin, a ground-breaking antibacterial compound produced by a mould [1]. This discovery marked a pivotal moment in medical history: for the first time, humanity had a powerful tool to control bacterial infections. With the introduction of antibiotics, once fatal diseases became treatable, marking the beginning of the modern era of medicine [2]. Over time, a wide range of antibiotics have been discovered and developed, and these agents have been classified into groups such as aminoglycosides, macrolides, cephalosporins, and β-lactams (BLs), which has become one of the most widely used classes [3,4].

This newfound control over bacteria, however, proved to be temporary. Over time, bacteria evolved mechanisms to resist the effects of antibiotics, such as enzymatic degradation, amplification of efflux pumps, and target site alterations. The emergence of antimicrobial resistance (AMR) has rendered many antibiotics ineffective, posing a significant threat to global health [2,5]. Resistant bacterial strains make infections more difficult to treat, increase the risk of disease transmission, and contribute to higher mortality rates. The scale of this issue is substantial: in 2019, AMR was responsible for 1.27 million deaths worldwide and was associated with nearly 5 million deaths [6]. Without intervention, the United Nations estimates that this number could rise to 10 million deaths annually by 2050 [7].

The fight against bacteria, in many ways, mirrors the fictional struggles depicted in the 1993 film *Jurassic Park*. In the movie, scientists successfully clone dinosaurs and create a theme park to showcase them. To maintain control, the cloned dinosaurs are engineered to be female, preventing reproduction. However, as one of the characters famously observes:

"*John, the kind of control you're attempting is […], it's not possible! Listen, if there's one thing the history of evolution has taught us, it's that life will not be contained. Life breaks free. Expands to new territories. It crashes through. Painfully, maybe even dangerously! But, huh […] Life finds a way.*"

- *Ian Malcolm*

This insight is symbolic of the relationship between humans and bacteria. Just as the dinosaurs in the park overcome the artificial barriers designed to contain them, bacteria adapt and evolve in response to antibiotics. The rise of AMR highlights this dynamic: bacterial populations subjected to selective pressure have "found a way," developing resistance and threatening the progress made in treating infections.

In response, researchers have sought new strategies to regain control over resistant bacteria. Among these, β-lactam/β-lactamase inhibitor (BL/BLI) combinations have emerged as a key approach [8–10]. While these combinations represent a critical advancement, their efficacy depends on their proper use, requiring careful consideration of pharmacokinetics (PK) and pharmacodynamics (PD) to optimise dosing and individualise therapy [8,11].

Pharmacometrics provides a framework for addressing these challenges by integrating PKPD principles with quantitative modelling. This thesis explores the application of pharmacometrics to the evaluation and individualisation of BL/BLI combinations. By investigating the interplay between the drug, the pathogen, and the host, this work aims to contribute to the development of strategies that sustain the utility of these essential therapies in the fight against AMR.

1.1 Drugs

1.1.1 β-lactam/β-lactamase inhibitor combinations

The term “β-lactam” (BL) refers to a class of antibiotics characterised by the presence of a BL ring in their chemical structure. This structural feature is shared by penicillins, cephalosporins, carbapenems, and monobactams [12]. All BL antibiotics exert their bactericidal activity by binding to penicillin-binding proteins (PBPs) in bacterial cells, thereby inhibiting cell wall biosynthesis and ultimately leading to bacterial death [13].

However, the widespread use of BL antibiotics has accelerated the emergence of bacterial resistance mechanisms, with β-lactamases being particularly significant. These enzymes hydrolyse the BL ring and inactivate the antibiotic. To counteract this, BLIs have been developed. When combined with a BL antibiotic, a BLI neutralises β-lactamases and restores the efficacy of the BL component.

The first BL/BLI combinations, such as amoxicillin-clavulanic acid, appeared in the 1980s, followed by others like ampicillin-sulbactam and piperacillin-tazobactam (PIP-TAZ). More recently, additional combinations – ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (CET-TAZ), imipenem-relebactam (IMI-REL), and meropenem-vaborbactam (MER-VAB) – have been introduced, with several new combinations in development

[9,14]. These BL/BLI are typically available as fixed-dose formulations with set ratios of BL to BLI (for example, CAZ-AVI is available in a 4:1 ratio).

Although this fixed-ratio approach simplifies clinical use, it poses a general challenge to the understanding of PKPD relationships. One example can be found in *in vitro* susceptibility testing, where standardised tests often maintain the BLI at a constant concentration while varying the BL component, which does not necessarily reflect the marketed BL-to-BLI ratio [15,16]. This discrepancy complicates the interpretation of laboratory data and its translation into real-world efficacy, as PKPD relationships may differ from those observed under fixed-ratio conditions.

1.1.2 Ceftazidime-avibactam

CAZ-AVI is a fixed-dose combination pairing a third-generation cephalosporin, CAZ, with the BLI AVI. This combination was developed to address resistance mechanisms involving β-lactamase production and has been available on the US and EU markets since 2015 under the commercial names Avycaz® and Zavicefta®, respectively [17,18].

CAZ-AVI is indicated for the treatment of severe bacterial infections, including complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and associated bacteraemia. It is administered intravenously (IV), typically at a dose of 2000 mg CAZ plus 500 mg AVI every eight hours (q8h) for 5 to 14 days, depending on the type and severity of the infection [17,18]. CAZ exerts bactericidal activity by binding to PBPs, while the main mechanism of action of AVI is the inhibition of Ambler class A, C, and D β-lactamases, preventing hydrolysis of the BL ring. AVI does not inhibit class B metallo-β-lactamases.

This broad-spectrum activity encompasses most Enterobacteriaceae, including β-lactamase-producing strains that are resistant to CAZ alone. Due to its effectiveness against multidrug-resistant organisms, CAZ-AVI is viewed as a "last-resort" type antibiotic in the therapeutic arsenal, often reserved for cases where other therapeutic options are exhausted. Its critical role in addressing resistant pathogens has led to its inclusion in the World Health Organization's (WHO) list of essential medicines [19,20].

1.1.3 The need for optimising β-lactam/β-lactamase inhibitor therapy

Although BL/BLI combinations represent a major advancement in the fight against resistant bacteria, their success relies on optimal dosing strategies that account for patient-specific factors and evolving resistant patterns. The rationale for optimising antibiotic therapy is multifaceted: achieving maximal

efficacy, preventing toxicities, minimising treatment failure, and curbing further resistance development [21]. The conventional one-size-fits-all ("flat") dosing approach often overlooks the variability in patient physiology, particularly in critically ill individuals who may exhibit altered PK [22,23].

In an attempt to address this diversity, clinicians sometimes use "covariate-based" dosing, where the regimen is adjusted according to factors such as body weight or creatinine clearance (CrCL). However, even these broad categories may not fully capture the complexity of individual patient profiles. More refined "individualised" dosing strategies aim to integrate PK and PD principles, along with patient-specific data (e.g., therapeutic drug monitoring results, biomarkers, and disease severity), to tailor therapy [24].

In the context of escalating resistance, inadequate dosing can contribute to treatment failure and further selection of resistant strains. Conversely, overly aggressive dosing may raise the risk of adverse effects, particularly in patients with compromised organ function. Hence, balancing efficacy, safety, and stewardship considerations is central to optimising BL/BLI therapy in clinical practice.

1.2 Pathogen

Understanding bacterial population dynamics is critical for evaluating antibiotic efficacy and informing treatment strategies. However, directly measuring bacterial burden over time is seldom feasible in clinical settings. Instead, treatment decisions rely on indirect markers, such as microbiological cultures and inflammatory biomarkers, which only partially capture the progression of infection and treatment response [25]. Preclinical studies provide valuable insights into drug-bacteria interactions, but their direct applicability to patient care is limited by differences in host factors between experimental models and patients [26]. This gap between preclinical findings and clinical practice highlights the need for improved methods to monitor infection dynamics and treatment effects in real time.

1.2.1 A brief introduction to bacterial resistance mechanisms

Bacteria have developed multiple mechanisms to resist BL antibiotics, the most prominent being β-lactamase production. These enzymes hydrolyse the β-lactam ring, rendering the antibiotic ineffective. β-lactamases are classified into four main Ambler classes (A, B, C, and D), each with distinct hydrolytic profiles [27]. Notably, some metallo-β-lactamases (Class B) remain unaffected by commercially available BLIs, limiting treatment options [28]. Many Gram-negative pathogens produce multiple β-lactamases, a feature particularly problematic in carbapenemase-producing organisms [27].

Beyond enzymatic degradation, additional resistance mechanisms include reduced membrane permeability – where porin modifications restrict antibiotic entry – and increased efflux activity, which actively removes the drug from the bacterial cell. Furthermore, modifications in PBPs can lower β-lactam affinity, particularly in Gram-positive bacteria [29].

BLIs counteract β-lactamases by neutralising enzymatic activity, thereby restoring the efficacy of β-lactam antibiotics. However, bacteria can respond by overproducing β-lactamases or evolving additional resistance mechanisms [30], illustrating the dynamic nature of the microbial "arms race". Understanding this interplay is essential for optimising BL/BLI therapy and ensuring sustained antimicrobial efficacy.

1.2.2 Minimum inhibitory concentration

The minimum inhibitory concentration (MIC) is the most widely employed *in vitro* measure of bacterial susceptibility. Defined as the lowest antibiotic concentration that inhibits visible growth after a fixed incubation period (typically 18 to 20 hours), the MIC is standardised by guidelines such as those from the Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). MIC testing is widely used in both research and clinical settings due to its simplicity and relatively rapid turnaround time. However, its reproducibility can be poor, particularly across laboratories and testing methods [31,32], highlighting the ongoing need for improved susceptibility testing approaches.

Beyond its utility in clinical decision-making, MIC testing is also foundational to antibiotic development and regulatory approval [33]. The PK/PD evaluation of new antibiotics is centred around MIC-based analyses, with the identification of a PK/PD index and target, and the establishment of clinical breakpoints. By determining which MIC values are treatable with standard antibiotic doses, these breakpoints directly influence treatment guidelines and antibiotic susceptibility reports. In addition, surveillance programs rely on MIC testing to monitor emerging resistance trends and inform antibiotic stewardship strategies.

Despite its ubiquity, MIC testing has inherent limitations [31,32]. By providing only a binary outcome – "growth" or "no growth" – it fails to capture the dynamics of bacterial killing over time. Moreover, when testing BL/BLI combinations, the methodology typically fixes the BLI concentration while varying the BL, which does not always reflect the clinically used ratio. This discrepancy complicates the direct translation of *in vitro* results into treatment efficacy. MIC testing also does not account for the risk of resistance emergence during treatment, which can occur even if an antibiotic initially inhibits bacterial growth [34,35].

1.2.3 Time-kill experiments

Time-kill experiments offer a dynamic alternative to MIC testing by measuring bacterial viability over time in the presence of one or more antibiotics [36]. Unlike MIC testing, which provides a single static endpoint, time-kill studies capture bacterial growth and death at multiple time points, generating a bacterial killing curve. These experiments are particularly valuable for assessing the rate and extent of bacterial killing and understanding how bacterial populations respond to antibiotics during prolonged exposure [35].

These studies can be conducted using static concentration setups – where a constant antibiotic level is maintained throughout the experiment – or dynamic concentration setups – where drug levels are modulated to mimic a desired PK profile. The dynamic approach more closely approximates *in vivo* conditions, capturing changes in drug concentration that occur in patients. In both cases, researchers typically enumerate colony-forming units (CFUs) at regular intervals to construct time-kill curves.

Time-kill experiments are particularly valuable for evaluating the effects of combination therapies like BL/BLI. They shed light on whether an antibiotic duo demonstrates synergy, antagonism, or an additive effect. Moreover, the granular data generated can reveal regrowth patterns, offering early indications of resistance emergence. Mathematical models are often used to interpret these complex data, enabling the estimation of key parameters (such as kill rates, the onset of resistance, and the time required to achieve a specific reduction in bacterial load) and providing a bridge between *in vitro* observations and clinical predictions [37,38].

1.3 Host

CAZ-AVI and other recent BL/BLI therapies are indicated for treating "severe" or "complicated" bacterial infections [18,39–42]. These terms generally describe either the severity of the pathological symptoms (potentially life-threatening or associated with significant morbidity) or the presence of complicating factors, such as immunocompromising conditions or the development of sepsis. Such factors may elevate the likelihood of unfavourable outcomes and prompt the need for specialised care in an intensive care unit (ICU). Although not all patients with severe or complicated infections require ICU admission, those who are administered BL/BLI combinations are typically critically ill and are often found in such specialised care settings.

1.3.1 Critically ill patients

Critically ill patients are characterised by severe, life-threatening conditions necessitating continuous and intensive medical care [23,43]. These

individuals often exhibit significant pathophysiological changes that substantially raise the risk of morbidity and mortality. Infections are particularly prevalent in this group and may lead to dire outcomes; sepsis and septic shock, for instance, can result in mortality rates approaching 60% [44–47].

One of the key challenges in treating infections in critically ill patients is the pronounced variability in PK and PD [23,48–52]. Factors such as altered organ function, dynamic fluid shifts, and extensive use of supportive therapies can influence a drug's absorption, distribution, metabolism, and excretion (ADME) and its ultimate effect on pathogens. This variability gives rise to significant interindividual and interoccasion differences in drug exposure and response. For example, the same drug dose to different patients – or the same dose to a patient at various time points – can result in disparate plasma concentrations and clinical outcomes (i.e., interindividual variability [IIV] and interoccasion variability [IOV], respectively) [21,53].

Multiple elements contribute to this variability, including pathophysiological changes (e.g., sepsis-induced alterations in vascular permeability), clinical interventions (e.g., fluid resuscitation or organ support therapies), drug-drug interactions, and the intrinsic properties of the drug itself. PD variability may further arise from differences in receptor sensitivity or expression levels, as well as interactions between multiple drugs. Although these complexities may necessitate individualised dosing strategies, few clinical trials focus exclusively on critically ill populations, limiting the availability of data-driven recommendations and underscoring the need for more personalised approaches to optimise antibiotic therapy.

1.3.2 Renal replacement therapy and continuous venovenous hemodiafiltration

In critically ill patients with acute or chronic renal failure, renal replacement therapy (RRT) is often employed to manage fluid and electrolyte imbalances [54,55]. While lifesaving, RRT may complicate antibiotic dosing by introducing additional variables that govern drug elimination. Achieving and maintaining therapeutic drug concentrations in these patients requires a thorough understanding of how RRT affects drug clearance.

Several factors influence drug removal during RRT. Protein binding is central: highly protein-bound drugs remain primarily unavailable for filtration or diffusion [56]. Residual renal function also plays a role, as any preserved renal clearance contributes to overall drug elimination. The specifics of the RRT modality (e.g. continuous or intermittent), the characteristics of the filter membrane, blood flow rates, ultrafiltration rates, and dialysate flow rates are critical factors [57]. RRT generally facilitates drug removal through two primary mechanisms:

- Convection, which removes solutes (including drugs) and water during ultrafiltration.
- Diffusion, in which solutes move across a semipermeable membrane down a concentration gradient.

Many RRT procedures combine both processes to varying extents. Continuous venovenous hemodiafiltration (CVVHDF) is widely used in ICUs and blends convection with diffusion for efficient solute clearance while maintaining hemodynamic stability. However, subtherapeutic concentrations may lead to treatment failure and escalate the risk of resistance, whereas excessive concentrations could precipitate toxicity. To optimise antibiotic therapy, certain parameters need to be quantified, such as:

- Saturation coefficient (SA), indicating the fraction of drug removed by filtration,
- Drug clearance across the CVVHDF membrane (CL_{CVVHDF}), and
- The contribution of CVVHDF to total drug clearance.

Understanding these elements enables a more precise calibration of dosing to meet therapeutic targets.

1.3.3 Biomarkers in infection management

Biomarkers serve as measurable indicators of biological processes, pathological states, or responses to interventions, making them invaluable tools in infection management [58]. They play a role in establishing diagnoses, monitoring disease progression, and guiding therapeutic decisions. In antibiotic therapy, biomarkers can support key clinical decisions such as initiating treatment, refining dosages, and assessing treatment response [59].

One example of a key biomarker is CrCL, which helps tailor dosing for renally excreted antibiotics. Accurately accounting for renal function is especially vital in critically ill patients, where rapid fluctuations in renal performance may necessitate frequent dose adjustments. Other biomarkers, like C-reactive protein (CRP) and procalcitonin, offer insights into inflammatory status and can assist in distinguishing bacterial infections from viral etiologies or inflammatory conditions [60–64]. Elevated CRP frequently corresponds to acute inflammatory episodes [65], whereas procalcitonin rises more specifically in bacterial infections and has been used to justify antibiotic de-escalation as levels subside [59,61]. Additionally, novel platforms capable of measuring multiple immune-related biomarkers simultaneously are emerging [66], providing potentially earlier or more precise indicators of treatment success and supporting personalised therapy decisions.

1.3.4 Therapeutic drug monitoring

TDM is a strategy aimed at ensuring a drug achieves optimal exposure – maximising efficacy while minimising toxicity. For antibiotics, this means effectively eradicating the infection while avoiding harm to the patient. In the case of BLs, which are suggested to have a time-dependent efficacy, TDM can be especially valuable [67–70]. By measuring drug levels in plasma or other biological samples, clinicians may be able to adjust doses to achieve the best possible balance between efficacy and safety.

However, TDM is not without its limitations. Each measurement provides only a single snapshot of a drug's concentration-time profile, IIV, IOV or residual unexplained variability (RUV) may still lead to suboptimal dosing decisions if additional patient-specific factors are not considered. In many clinical settings, TDM remains a reactive approach – adjusting doses only once concentrations deviate outside a predetermined interval [71]. This method does not fully exploit the dynamic nature of drug PK in critically ill individuals.

Integrative methodologies, such as model-informed precision dosing (MIPD), seek to extend TDM by incorporating patient-specific data, population pharmacokinetic (PopPK) models, and simulation-based predictions to proactively refine dosing regimens [72]. MIPD represents a pivotal advancement that can help individualise therapy, especially for high-risk or complex patients where standard dosing regimens frequently fail to achieve desired results [73].

1.4 Keys to a rational antibiotic therapy

A rational approach to antibiotic therapy is essential to maximise therapeutic efficacy, mitigate the emergence of resistance, and preserve the effectiveness of existing antibiotics for future use [74]. The success or failure of antibiotic therapy is driven by three key determinants: the antibiotic (drug), the bacterium (pathogen), and the patient (host). Given these interdependent factors, a comprehensive understanding of the drug-pathogen-host interaction is crucial for optimising treatment strategies. This ensures that therapeutic decisions consider the properties of the antibiotic, the susceptibility of the pathogen, and the clinical status of the patient. Within this framework, four interconnected elements guide the implementation of rational antibiotic therapy [75]:

1. Appropriate indication [76,77]. Antibiotics should be prescribed only when there is clear evidence of a bacterial infection. Using these agents for non-bacterial conditions, such as viral infections, can expedite resistance development and expose patients to unnecessary risks. Proper diagnostic tools, including microbiological testing and clinical

assessment, are essential to distinguish bacterial from non-bacterial etiologies.

2. Choice of an appropriate drug. Selecting an antibiotic with demonstrated efficacy against the identified or suspected pathogen is paramount. This process often involves interpreting susceptibility testing or leveraging local epidemiological data to ensure that the chosen compound effectively targets the causative organism [76]. For empirical treatments, knowledge of local resistance patterns and guidelines can guide initial therapy, which will be refined later based on specific culture results.
3. Appropriate timing of therapy. Timely initiation of antibiotic therapy is particularly crucial in life-threatening situations such as sepsis or septic shock. Multiple studies have shown that delayed treatment in these settings is associated with increased mortality [78–80]. In vulnerable populations, starting the correct antibiotic regimen early can significantly improve clinical outcomes.
4. Appropriate dosing of therapy. Achieving effective drug concentrations at the infection site is indispensable. Even if the most suitable antibiotic is selected and administered in a timely manner, suboptimal dosing may compromise therapeutic success, prolong infection, and facilitate resistance. Approaches guided by PK and PD principles, as well as individualised dosing strategies (e.g., through TDM), can help maintain drug levels that maximise bacterial killing while minimising toxicity.

By adhering to these four elements – appropriate indication, choice of drug, timing, and dosing – clinicians can orchestrate a rational antibiotic therapy. Nevertheless, the increasing prevalence of resistant organisms and the complexity of certain patient populations, such as the critically ill, underscore the need for more advanced and individualised methods. Innovations in diagnostics, TDM, and MIPD illustrate the evolution of antibiotic stewardship practices, offering more personalised solutions that account for the intricate dynamics of the drug-pathogen-host interplay.

1.5 Pharmacometrics

Pharmacometrics is a multidisciplinary field at the intersection between pharmacology, biology, medicine, statistics, and computational science [81]. It aims to quantify the time-course of drug behaviour and disease processes across individuals and settings by using mathematical models. These models incorporate PK and PD principles to elucidate how drugs are absorbed, distributed, metabolised, and excreted and how they exert their effects on the body or pathogens. In doing so, pharmacometrics provides a rigorous

framework for optimising dosing regimens, predicting therapeutic outcomes, and ultimately improving patient care.

1.5.1 Nonlinear mixed-effect modelling

Nonlinear mixed-effects (NLME) modelling, also known as population modelling, underpins most pharmacometric analyses. Often described as a "top-down" or "data-driven" approach, NLME modelling uses observed data to build empirical or mechanism-based models that describe how a drug's concentration or effect changes over time [53]. These models typically consist of three key components:

- Describing PK or PD at the population level: The model estimates "fixed effects", representing typical parameter values (e.g., clearance, volume of distribution) that are assumed to be common across the population.
- Quantifying variability at different levels: "Random effects" capture IIV, IOV, and RUV. RUV accounts for discrepancies between the observed data and model predictions that are not captured by interindividual/interoccasion factors or covariates. It encompasses measurement errors, assay imprecision, model misspecifications, and any other unmodeled sources of variation.
- Explaining variability through covariates: Covariates such as body weight, renal function (CrCL), or disease status can account for a portion of the observed variability, helping to identify patient subgroups that require different dosing strategies.

The term "nonlinear" reflects that the relationship between dependent (e.g., drug concentration) and independent (e.g., time) variables often follows complex, nonlinear relationships. By simultaneously estimating fixed effects and random effects, NLME models provide a robust framework for characterising the typical behaviour of a drug, the variability around that behaviour, and potential explanatory factors. Once established, these models can be used to simulate "what if" scenarios, enabling researchers and clinicians to predict how modifications in dosing regimens, patient characteristics, or treatment settings might influence drug concentration or responses. In clinical applications, NLME modelling supports MIPD by facilitating the selection of an appropriate first dose or adjusting subsequent doses in response to patient-specific data [82].

1.5.2 Pharmacokinetics-pharmacodynamics of antibiotics

PK describes how the body handles a drug – covering absorption, distribution, metabolism and excretion – while PD examines the relationship between drug

concentration and its therapeutic (or adverse) effects [82]. When studying antibiotics, integrating PK and PD principles is essential for designing effective dosing strategies.

Current antibiotic development often relies on dose fractionation studies and the derivation of PK/PD indices [33,83]. These indices link a PK summary metric to the MIC, which serves as a PD summary metric representing bacterial susceptibility. Three PK/PD indices are typically investigated:

- The percentage of the dosing interval during which free drug concentrations remain above the MIC (fT>MIC)
- The ratio of the peak free drug concentration to the MIC (fC$_{max}$/MIC)
- The ratio of the area under the free concentration-time curve to the MIC (fAUC/MIC)

Although the free fraction of the drug in plasma is commonly used in these evaluations, the applicability of plasma-based indices to infection sites can be limited, depending on the proportionality between plasma and tissue concentrations [35]. Additional complexity arises when evaluating BL/BLI combinations, as a distinct PK/PD index must be identified for the BLI [33]. Unlike BLs, where MIC-based indices are typically used, one of the three PK/PD indices commonly derived for BLIs is linked to a threshold concentration (C$_T$) of the BLI rather than the MIC (e.g., fT>C$_T$) [16,84]. Moreover, many of these targets are derived from 24-hour static or short-term *in vivo* models that may not fully capture regrowth, resistance selection, or interspecies differences [35,85,86]. Despite these limitations, PK/PD indices remain the most practical tool available for guiding clinical breakpoint determinations and dosing recommendations by regulatory authorities, reinforcing their central role in antibiotic therapy.

1.5.3 Modelling biomarkers

Biomarkers, which are quantifiable indicators of biological processes or therapeutic responses, hold significant promise for refining antibiotic treatment decisions [59,87]. By reflecting disease severity, the degree of inflammation, or changes in drug clearance, biomarkers can provide real-time feedback on how a patient responds to therapy. For instance, inflammatory markers such as CRP, procalcitonin, and interleukin-6 may serve as surrogate endpoints for antibiotic efficacy or as early signals of treatment failure [87–90].

Despite the potential of biomarker-driven approaches, their clinical application is still limited. Key knowledge gaps remain in understanding how biomarker dynamics relate quantitatively to drug exposure and pathogen response. As pharmacometric models become more sophisticated, integrating biomarker kinetics into antibiotic PKPD models may enable clinicians to

refine treatment strategies, identify early warning signs of therapeutic failure, and personalise therapy based on individual patient profiles.

1.5.4 Model-informed precision dosing

MIPD expands upon traditional TDM by taking what is essentially a single "snapshot" of drug concentration and transforming it into a detailed, patient-specific PK profile. For instance, in trough-based TDM, one plasma sample is often collected immediately before the next infusion. Clinicians typically make decisions based on whether this single concentration lies above or below a predefined threshold, thus preventing extreme under- or overdosing. However, this method does not fully use the information available from dosing history, patient characteristics and PK data.

MIPD addresses this limitation by integrating TDM results and dosing history with PopPK models and relevant patient covariates, such as age, weight, renal function, or comorbidities [72]. Through this integration, individual PK parameters (e.g. clearance, volume of distribution) can be estimated using maximum a posteriori Bayesian estimation, allowing a reconstruction of the entire concentration-time profile for that dosing interval. More importantly, MIPD enables clinicians to simulate subsequent dosing intervals under different hypothetical regimens. By exploring these "what if" scenarios, they can anticipate how adjustments in dose amount, dosing frequency, or infusion duration might affect future plasma concentrations.

When combined with defined PK/PD targets (e.g., X% *f*T>MIC for a BL antibiotic), MIPD allows individualised evaluation of dose adequacy. By comparing the likelihood of meeting these targets under various dosing strategies, clinicians can select the approach most likely to achieve therapeutic success while minimising the risks of toxicity or underexposure.

1.5.5 Modelling strategies for β-lactam/β-lactamase inhibitor combinations

Although the PK/PD index approach remains a core component of antibiotic development and clinical guidance, it does not fully capture the interactive dynamics between BL and BLI components. In many drug development programs, including that of AVI (used in combination with CAZ), dose selection has traditionally relied on short-term *in vitro* or animal studies and surveillance data from global resistance patterns [91,92]. These investigations frequently identify a PK/PD index for the BLI alongside the established BL index and then use preliminary PopPK models to estimate the joint PTA [33,93].

While these methods have successfully guided dosing recommendations and supported regulatory approval, their reliance on simplified endpoints (e.g., bacterial count at 24 hours) can obscure important phenomena such as

resistance emergence or immune-mediated clearance. Consequently, advanced modelling techniques, including mechanism-based PKPD models that account for bacterial subpopulations, synergy effects, and potential regrowth, are increasingly being explored [94–96]. Post-marketing studies have demonstrated the usefulness of such models for CAZ-AVI or aztreonam-AVI, highlighting how AVI potentiates the activity of its partner antibiotic against organisms like *Pseudomonas aeruginosa* and Enterobacteriaceae [97,98].

Moving forward, a more proactive and iterative integration of pharmacometric modelling during antibiotic development could refine and accelerate the process of dose optimisation.

2 Aims

General aim

The overall aim of this thesis was to develop and apply pharmacometric approaches to improve the evaluation and individualisation of β-lactam/β-lactamase inhibitor (BL/BLI) combinations in critically ill patients.

Specific aims

- To evaluate whether BLIs achieve effective concentrations at the site of infection and to explore the potential role of therapeutic drug monitoring (TDM) for BLIs in clinical practice (Paper I)
- To characterise the population pharmacokinetics (PK) of ceftazidime-avibactam (CAZ-AVI) in critically ill patients with hospital-acquired or ventilator-associated pneumonia and in patients undergoing continuous venovenous hemodiafiltration (CVVHDF) (Papers II and III)
- To investigate the time course of immune response biomarkers in critically ill patients receiving CAZ-AVI and assess their potential role in monitoring treatment response (Paper II)
- To explore PK/PD targets and dosing strategies for AVI in combination with CAZ using mechanism-based PKPD models (Paper IV)

3 Materials and methods

3.1 Data sources

Both simulated (Papers I & IV) and patient-derived (Papers II & III) data were used in this thesis to explore different aspects of BL/BLI therapy. By integrating these approaches, we developed new models, applied previously published models, and conducted simulations to explore various preclinical and clinical scenarios.

3.1.1 Virtual patients treated with β-lactam/β-lactamase inhibitor combinations (Paper I)

For the evaluation of drug exposure at the site of infection, virtual cohorts of 10,000 individuals per scenario were simulated. These individuals were assumed to be 70 kg, 170 cm, and 65 years old, with variations based on:

- Type of infection: complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and associated bacteraemia or prostatitis.
- Treatment regimen: standard-of-care dosing regimens for CAZ-AVI, ceftolozane-tazobactam (CET-TAZ), imipenem-relebactam (IMI-REL), meropenem-vaborbactam (MER-VAB), and piperacillin-tazobactam (PIP-TAZ) [18,39–42].
- Renal function: individuals were classified as having either normal renal clearance (CrCL of 80 mL/min, typical renal clearance [TRC]) or augmented renal clearance (CrCL of 200 mL/min, ARC), a phenomenon frequently observed in critically ill patients.

The simulations were based on published PopPK models [99–103] and were used to predict unbound drug concentrations at relevant infection sites (e.g., epithelial lining fluid [ELF] for lung infections, peritoneal fluid for intra-abdominal infections, and prostate tissue for prostatitis). These concentration-time profiles were then used in combination with established PK/PD targets [104–108] to assess the probability of target attainment (PTA).

3.1.2 Patients treated with ceftazidime-avibactam (Papers II & III)

Critically ill patients with HAP/VAP (Paper II). Data were collected from ten critically ill patients enrolled in the ARCADIA study at Hygeia General Hospital and Sismanogleio General Hospital (Athens, Greece). Eligible patients had HAP or VAP caused by *K. pneumoniae* and required at least seven days of CAZ-AVI therapy. Standard dosing (2000/500 mg q8h as a 2-hour intravenous infusion) was administered, with dose adjustments made for patients with CrCL < 50 mL/min [17,18].

- PK sampling: Blood samples for PK analysis were collected following an optimal design approach, using previously developed PopPK models [45] to define three sampling windows:
    - Ascending phase: 15 minutes to 1 hour after the start of infusion.
    - Descending phase: 15 minutes to 1 hour after the end of infusion.
    - Trough phase: 15-20 minutes before the next infusion.

  PK samples were collected during the first dose (4-5 samples) and on subsequent treatment days (2-3 samples every other day) until the end of treatment (EoT).
- Simultaneous drug determination of CAZ and AVI in plasma: Plasma concentrations of CAZ and AVI were quantified using ultra-performance liquid chromatography (UPLC) coupled with tandem mass spectrometry (MS/MS).
- Protein binding characterisation: The fraction unbound (fu) of CAZ and AVI in plasma was determined using equilibrium dialysis.
- Biomarker sampling: Blood was collected daily from one day before treatment initiation until the EoT to assess inflammatory markers and immune response.
- Determination of immune response biomarkers: A multiplex immunoassay (Target 96 “immune response” panel, Olink Proteomics AB, Uppsala, Sweden) was used to measure a panel of immune-related biomarkers. Additionally, CRP, procalcitonin, and lactate levels were measured as part of routine clinical assessments.

Patients undergoing CVVHDF (Paper III). Four ICU patients receiving CAZ-AVI as part of the standard of care and undergoing CVVHDF for acute kidney injury were enrolled at Hygeia General Hospital (Athens, Greece). Additional data from six patients receiving CVVHDF from a previously published study (Shields et al.) were also digitised for comparative analysis [109].

- PK sampling:
    - Venous blood samples were collected over the 8-hour dosing interval at infusion start, at hourly intervals, and just before the next dose.
    - CVVHDF circuit sampling: Three samples were simultaneously collected per dosing interval:
        - Pre-filtration blood sample (from the IV tubing to the CVVHDF machine).
        - Post-filtration blood sample (from the blood return line).
        - Ultrafiltrate sample (from the ultrafiltrate and spent dialysate container).
- Simultaneous drug determination of CAZ and AVI in plasma and ultrafiltrate: Total CAZ and AVI concentrations in plasma and CVVHDF-circuit samples were quantified using UPLC-MS/MS.
- Protein binding characterisation: Plasma protein binding of CAZ and AVI was assessed using equilibrium dialysis.

3.1.3 Bacterial response to ceftazidime-avibactam (Paper IV)

To investigate PK/PD targets for AVI in combination with CAZ, as well as to explore optimised dosing strategies, a series of virtual preclinical and clinical studies were generated using mechanism-based PKPD models. The simulations focused on understanding bacterial responses under different dose regimens and evaluating the potential for improved antibiotic dosing strategies.

Dose fractionation study in mice. A dose fractionation study was simulated in mice, where bacterial responses to CAZ-AVI were assessed under different dosing strategies. The objective was to identify the PK/PD index that best correlates with bacterial killing and to estimate the required exposure level for efficacy. PK profiles were simulated for mice receiving a fixed dose of CAZ at 240 mg/kg every 4 hours, administered as a subcutaneous bolus. This dosing regimen was designed to match the AUC exposure of standard human dosing (2000 mg every 8 hours). AVI was administered at doses ranging from 5 to 1,000 mg/kg/day, with different administration frequencies from every 2 hours to once daily, as well as continuous infusion. A total of 56 different CAZ-AVI dosing regimens were simulated. The bacterial infections were caused by six different Gram-negative pathogens: *K. pneumoniae* (NCTC13438, KP981690), *Enterobacter cloacae* (EL871203) and three *P. aeruginosa* strains (NCTC10783, 9750 and 2154). The initial bacterial inoculum in simulations was set to 6.0 $\log_{10}$ CFU/mL.

Dose fractionation study in humans. A virtual dose fractionation study was conducted in humans to translate the findings from mice to a clinical setting.

The simulated cohort consisted of adult HAP patients with a CrCL of 80 mL/min. The standard CAZ regimen of 2000 mg every 8 hours, infused over 2 hours, was used, while AVI was administered at doses ranging from 50 to 3,000 mg/day. Different administration frequencies (from every 2 hours to once daily) and infusion durations (ranging from 0.5 hours to continuous infusion) were tested. A total of 128 CAZ-AVI dosing regimens were simulated, with 1,000 virtual patients per regimen. The same six Gram-negative pathogens as in the murine study were used, with an initial inoculum of 6.0 $\log_{10}$ CFU/mL.

Dosing optimisation study in humans. A separate virtual dosing optimisation study was conducted to investigate alternative dosing regimens in a larger, more diverse patient population. The study included 50,000 simulated adult HAP patients with CrCL values ranging from 50 to 150 mL/min. The infections were caused by the same six Gram-negative pathogens as in the previous studies. The study assessed key dosing parameters, including infusion mode (short infusions vs. continuous infusion), administration frequency (dosing every 6, 8, or 12 hours), and different CAZ-to-AVI ratios (ranging from 1:1 to 8:1). Various dosing regimens were compared to determine which approaches maximised bacterial eradication while minimising the risk of resistance development.

3.2 Modelling and simulation workflow

3.2.1 Software and general approach

The modelling and simulation analyses in this thesis were performed using several specialised software tools. NONMEM (version 7.5, ICON plc, Dublin, Ireland) was used for NLME modelling, with model estimation conducted using the first-order conditional estimation method with interaction (FOCE+I). PsN (Pearl-speaks-NONMEM, version 5.3.0, Uppsala University, Uppsala, Sweden) facilitated model execution, parameter uncertainty estimation using sampling importance resampling (SIR), and model diagnostics such as prediction-corrected visual predictive checks (pcVPCs). Pirana (version 2.9.6, Certara, Radnor, Pennsylvania, USA) was used as the modelling interface to manage NONMEM runs and streamline model development.

Data analysis, graphical diagnostics, and statistical evaluations were conducted using R (version 4.2.1, R foundation for statistical computing, Vienna, Austria). The following R packages were used:

- ggplot2 for visualisation,
- dplyr and tidyverse for data manipulation,
- xpose4 for NONMEM model diagnostics,
- mrgsolve for NLME simulations,

- nls for nonlinear regression analyses,
- PopED for optimal design analysis.

Noncompartmental analysis (NCA) was carried out using PKanalix (version 2023R1, Lixoft SAS, Antony, France) to derive PK parameters such as clearance, volume of distribution, and AUC.

3.2.2 Use of published models for simulations

Previously published PopPK and PKPD models were used throughout this thesis to simulate drug concentration-time profiles and bacterial responses under various preclinical and clinical scenarios. These models were implemented in the simulation frameworks for Papers I-IV.

PopPK models describing the PK of CAZ and AVI in humans, developed by Li et al. [99], were used in all Papers (I-IV). These models had been built from pooled data collected during phase I-III clinical trials and described CAZ and AVI disposition using two-compartment structures with first-order elimination. CrCL was the primary covariate influencing drug clearance, with additional covariates such as age, weight, disease indication, and APACHE-II score to explain IIV. These models were applied in various contexts, including simulations of site-specific drug concentrations (Paper I), optimal sampling design analysis (Paper II), visual comparisons between observed and predicted PK data (Papers II & III), and as drivers of bacterial response in PKPD models (Paper IV).

In preclinical simulations, PK models developed by Sy et al. [96] were used to predict CAZ and AVI plasma concentrations in murine thigh and lung infection models (Paper IV). These models had been developed from digitised murine PK data [110] and featured a three-compartment structure consisting of two plasma compartments (central and peripheral) and one ELF compartment. No IIV terms were estimated in these models, as they were built from pooled murine data.

In Paper I, the CET-TAZ models developed by Zhang et al. [100] described two-compartment PK for both compounds, with CrCL and end-stage renal disease as key covariates on clearance. The IMI-REL models developed by Bhagunde et al. [101] followed a similar structure, with CrCL as the primary covariate influencing clearance. For MER-VAB, the models developed by Trang et al. [102] described two-compartment PK, but instead of CrCL, the estimated glomerular filtration rate (eGFR) was used as the primary covariate for clearance. For PIP-TAZ, PopPK models from separate publications were used for each compound. The model for PIP was developed by Udy et al. [103], while the TAZ model was developed by Zhang et al. [100]. Both followed a two-compartment PK structure with CrCL as the key covariate on clearance. These models were used to simulate concentration-time profiles at

the site of infection for different BL/BLI combinations and it was assessed whether they reached effective drug exposure levels.

In addition to PopPK models, previously published PKPD models describing the antibacterial effects of CAZ-AVI were included in Paper IV. Two different PKPD models were used. The first model, developed by Kristoffersson et al. [94], was based on SCTK experiments conducted against Enterobacteriaceae, including *K. pneumoniae*, *Escherichia coli*, and *E. cloacae*. This model accounted for three mechanisms of AVI: inhibition of β-lactamase activity, potentiation of the bactericidal effect of CAZ, and a possible direct antibacterial effect of AVI. The model included two bacterial subpopulations: a main susceptible population and a resistant subpopulation with reduced susceptibility to CAZ-AVI. The second model, developed by Sy et al. [95], was based on time-kill data against *P. aeruginosa*. Unlike the first model, it did not include a direct antibacterial effect of AVI and described a single homogeneous bacterial population without a resistant subpopulation.

By integrating PKPD models with preclinical PK and clinical PopPK models of CAZ-AVI in simulations, it was possible to investigate which PK/PD index best correlates with bacterial killing and explore alternative dosing strategies.

3.2.3 Model development

In Paper II, NLME modelling was employed to characterise the PK of CAZ and AVI in critically ill patients with HAP/VAP, as well as to describe the time course of immune response biomarkers during antibiotic treatment. The analysis followed a stepwise approach, beginning with single-drug PopPK models, followed by a joint PopPK analysis, and concluding with turnover models for biomarker dynamics.

Single-drug PopPK analysis. Separate PopPK models for CAZ and AVI were developed as a first step. One-, two-, and three-compartment structural models were evaluated, with IIV assumed to follow a log-normal distribution. Different RUV structures were tested, including additive, proportional, and combined error models. IOV was explored for all structural parameters.

The impact of renal function on drug clearance was investigated, considering CrCL estimated using the Cockcroft-Gault, MDRD, and CKD-EPI equations. Additional covariates, including age, weight, sex, and markers of systemic illness (e.g., SOFA score, inflammatory biomarkers), were explored using stepwise covariate modelling.

Joint PopPK analysis. After establishing separate models for CAZ and AVI, a joint PK analysis was performed to account for potential correlations between the two drugs. Their IIV terms were estimated in a variance-covariance block (OMEGA BLOCK in NONMEM). If a high correlation (>0.8) was observed, the model was simplified by sharing a common IIV term, with a fixed-effect scaling parameter applied to adjust for differences in magnitude.

Correlations in RUV were also assessed by implementing a variance-covariance block on SIGMA terms using the L2 data item in NONMEM.

Biomarker analysis. To describe the time course of immune response biomarkers during CAZ-AVI treatment, turnover dynamic models were developed. The biomarker analysis followed a structured approach:

1. Exploratory analysis: Empirical models were tested to identify increasing or decreasing trends in biomarker concentrations over time. First-order elimination or production models were used to screen for biomarkers that exhibited substantial changes over the treatment period. Biomarkers with very slow dynamics (elimination or production rate constant < 0.001 h^{-1}, equivalent to a half-life > 29 days) were excluded from further modelling, as their changes were unlikely to be informative within the timeframe of antibiotic treatment.
2. Baseline turnover modelling: Indirect response models were employed to describe biomarker baseline turnover. The general turnover model included a first-order elimination rate constant (k_{out}) and a zero-order production rate (K_{in}):

$$\frac{dC_{biomarker}}{dt} = -k_{out} \times C_{biomarker} + K_{in}$$

Where k_{out} represents the elimination rate, and K_{in} is the baseline production rate, which was initialised as:

$$K_{in} = (BASE + DIFF) \times k_{out}$$

BASE represents the expected biomarker level in a healthy state (i.e., without infection), while DIFF accounts for the deviations due to disease-related alterations. For biomarkers with increasing trends, BASE was fixed to the maximum observed biomarker level for the population; for decreasing trends, BASE was fixed to the minimum population observed level. IIV was tested for relevant parameters (e.g. kout and DIFF) in this step. IIV was tested on relevant parameters (k_{out} and DIFF).
3. Drug effect modelling: The effect of CAZ exposure on biomarker levels was tested on K_{in} or k_{out}. The drug effect was described using a linear ($\gamma=1$) or a power ($\gamma\neq1$) function:

$$k_{drug} = Slope \times C_{CAZ}^{\gamma}$$

or a basic ($\gamma=1$) or a sigmoidal ($\gamma\neq1$) Emax function:

$$k_{drug} = \frac{Emax \times C_{CAZ}^{\gamma}}{EC_{50}^{\gamma} + C_{CAZ}^{\gamma}}$$

Where Emax represents the maximal drug effect, EC_{50} is the CAZ concentration producing half of the maximum effect, and γ is the Hill coefficient controlling the steepness of the response curve.

Model evaluation. The final model selection was based on statistical criteria, biological plausibility, and predictive performance. Nested models were compared using the likelihood ratio test (ΔOFV < -3.84; $p < 0.05$ for forward inclusion, ΔOFV > 10.83; $p < 0.001$ for backward elimination). Non-nested models were assessed using the Akaike information criterion (AIC).

Model performance was evaluated through goodness-of-fit plots, shrinkage estimates, and pcVPCs. Parameter uncertainty was assessed using the covariance step in NONMEM, supplemented by SIR when necessary.

3.2.4 Pharmacokinetic-pharmacodynamic modelling and target identification

In Paper IV, PKPD modelling was used to investigate bacterial responses to CAZ-AVI and to evaluate PK/PD targets for treatment optimisation.

Exploration of PK/PD indices and targets. To quantify the relationship between AVI exposure and bacterial killing, three PK/PD indices were evaluated:

- *f*T>C_T: Percentage of time that unbound AVI concentrations remained above a threshold concentration (C_T of 1 mg/L).
- *f*AUC/$MIC_{CAZ/AVI}$: Ratio of the unbound AUC to the MIC of the CAZ-AVI combination ($MIC_{CAZ\text{-}AVI}$ determined with a fixed AVI concentration of 4 mg/L).
- *f*C_{max}/$MIC_{CAZ/AVI}$: Ratio of the unbound C_{max} to the MIC of the combination.

These indices were tested across different bacterial strains to determine which best correlated with bacterial killing at 24 hours. The correlation between each PK/PD index and bacterial killing at 24 hours was evaluated using a sigmoid Emax function:

$$E = E_0 - \frac{PD_{max} \times X^{Hill}}{EX_{50}^{Hill} + X^{Hill}}$$

Where E is the PKPD model-predicted bacterial density at 24h in $\log_{10}$ CFU/mL, E_0 is the value without drug treatment, PD_{max} is the maximum reduction in E, X is the PK/PD index value, EX_{50} is the magnitude of X needed to achieve 50% of PDmax, and Hill is the sigmoidal coefficient reflecting the steepness of the response curve. The coefficient of determination (r^2) was used to determine which PK/PD index best correlated with bacterial killing.

Simulation-based dosing optimisation. Simulations were conducted to evaluate the impact of different dosing strategies, including the infusion duration (0.5h, 2h, 4h, continuous infusion), the dosing frequency (q6h, q8h, q12h) and CAZ-to-AVI ratios (1:1 to 8:1). The PTA was assessed for each regimen with two different methods:

- Traditional PK/PD index-based PTA: Target attainment was assessed based on the proportion of simulated patients achieving predefined PK/PD targets: 50% fT>MIC for CAZ and 50% $fT>C_T$ for AVI, typically associated with a 2-log bacterial kill in preclinical studies.
- Time-kill curve-based PTA: Rather than relying on fixed PK/PD indices, bacterial density changes over time were directly simulated for each virtual patient. This allowed for a probabilistic evaluation of bacterial eradication at 24h for a given regimen. Targets for efficacy were defined as a 2-log reduction in bacterial density at 8h, 24h, and 48h post-administration.

3.2.5 Noncompartmental analysis

In Paper III, NCA was used to characterise the PK of CAZ and AVI in critically ill patients undergoing CVVHDF. The analysis focused on estimating drug exposure, clearance, and the extent of removal by the CVVHDF system.

Total plasma concentrations of CAZ and AVI were dose-normalized prior to analysis. Individual PK parameters at steady-state were estimated, including clearance, volume of distribution, half-life, C_{max}, and AUC, which was computed using the linear-up, log-down trapezoidal method.

To quantify drug removal by CVVHDF, the saturation coefficient (SA) was calculated as:

$$SA = \frac{2 \times C_{ULTRA}}{C_{PRE} + C_{POST}}$$

Where C_{ULTRA} is the drug concentration in the ultrafiltrate and spent dialysate container, C_{PRE} is the pre-filtration blood concentration, and C_{POST} is the post-filtration blood concentration.

The clearance of CAZ and AVI across the CVVHDF membrane (CL_{CVVHDF}, in L/h) was derived using the ultrafiltrate and dialysate flow rates:

$$CL_{CVVHDF} = (Q_{UF} + Q_D) \times SA$$

Where Q_{UF} is the ultrafiltrate flow rate (L/h) and Q_D is the dialysate flow rate. The contribution of CVVHDF to total drug clearance (CL_{SS}, estimated from NCA) was expressed as:

$$\left(\frac{CL_{CVVHDF}}{CL_{SS}}\right) \times 100$$

These results provided insights into the extent of CAZ and AVI removal during RRT, informing whether dosing adjustments may be necessary for patients receiving CAZ-AVI while undergoing CVVHDF.

4 Results

4.1 Pharmacokinetics of ceftazidime-avibactam

4.1.1 Pharmacokinetics of ceftazidime-avibactam in patients with HAP or VAP caused by *K. pneumoniae*

A total of 133 plasma samples were collected in ten critically ill patients, corresponding to 266 drug concentration measurements (133 for CAZ and 133 for AVI). Sampling was performed across 3-6 dosing occasions per patient during the course of treatment.

The PK of CAZ and AVI were best described by two-compartment models with first-order elimination. Both models included IIV on clearance (CL) and central volume of distribution (V1), assuming a log-normal distribution. A covariance relationship was implemented between CL and V1, improving model fit. RUV was modelled using a proportional error structure.

CrCL, estimated using the Cockcroft-Gault equation, significantly improved the model and reduced the IIV in CL, confirming that renal function was a major determinant of drug elimination.

Table 1. Parameter estimates and associated relative standard errors (RSE%) for the final joint population pharmacokinetic model for ceftazidime-avibactam.

Parameter	**Ceftazidime**	**Avibactam**
θ1: TVCL (L/h)	3.28 (13)	4.78 (13)
θ2: TVV1 (L)	7.84 (35)	7.21 (19)
θ3: TVQ (L/h)	24.4 (23)	26.9 (19)
θ4: TVV2 (L)	19.3 (21)	18.6 (23)
θ5: Linear CrCL on CL[1]	0.00803 (20)	0.00861 (16)
θ6: Scaling IIVCL[2]	-	1.14 (20)
θ7: Scaling IIVV1	-	1 FIX
IIV on CL (%)	28.5 (21)	
IIV on V1 (%)	113 (26)	
ω_{CL}-ω_{V1} correlation (%)	38.8 (24)	
RUV (proportional, %)	29.6 (23)	33.7 (21)
σ_{CAZ}-σ_{AVI} correlation (%)	84.6 (16)	

IIV associated with the typical value (TV) parameters is expressed as coefficient of variation (%), calculated according to: $\sqrt{e^{\omega^2}-1} \times 100$. [1]Coded as: CLCRCL=(1+θ_5×(CrCL-115)). [2]Coded as: $CL_{AVI} = \theta_{1,AVI} \times CLCRCL_{AVI} \times EXP(ETACL_{CAZ} \times \theta_6)$).

In the joint model, the IIV terms on CL and V1 were shared between CAZ and AVI, with a scaling factor applied to CL to adjust for magnitude differences. A variance-covariance block was implemented for RUV terms, and the L2 data item in NONMEM was used to account for correlations due to simultaneous drug measurements from the same plasma samples. Parameter estimates from the final joint PopPK model are presented in Table 1.

The final model adequately described observed CAZ and AVI plasma concentrations, with good agreement between observed and predicted values. Goodness-of-fit indicated little to no trends towards model misspecification, and pcVPCs demonstrated that the model accurately captured the median and variability of drug concentrations over time (Figure 1).

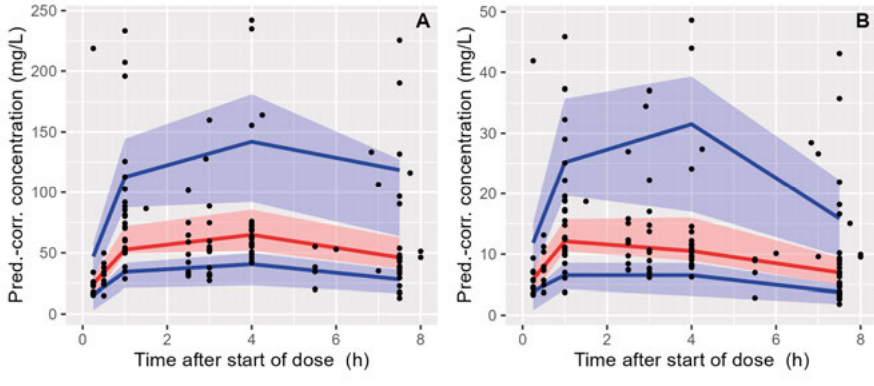

Figure 1. Prediction-corrected visual predictive checks for the final joint population pharmacokinetic model for total plasma concentrations of ceftazidime (A) and avibactam (B). Solid red lines are the 50th percentiles of observations corrected by prediction, while solid blue lines represent the 5th and 95th percentiles. Shaded areas represent the 95% confidence intervals for the simulated 5th, median and 95th percentiles of the prediction-corrected observations.

4.1.2 Pharmacokinetics of ceftazidime-avibactam in critically ill patients undergoing CVVHDF

A total of 35 plasma samples were collected from four critically ill patients. Two patients were sampled after more than one dose administration (i.e., on multiple occasions). In addition, 16 circuit samples were obtained from the CVVHDF system to evaluate drug elimination through renal replacement therapy.

NCA was performed to estimate PK parameters at steady-state: CL_{SS}, volume of distribution (V_{SS}), half-life ($t_{1/2}$), maximum and minimum plasma concentrations (C_{max}, C_{min}), and AUC for a dosing interval (AUC_{tau}). The median PK parameters for CAZ and AVI are reported in Table 2.

Table 2. PK parameters at steady-state for ceftazidime and avibactam estimated by NCA and stratified by dose group. Reported values are presented as median [90% confidence interval].

Dose group	Parameter	Ceftazidime	Avibactam
2000/500 mg q8h as 2-hour infusion[1] (n=4)	C_{max} (mg/L)	70.2 [40.1-77.2]	7.76 [4.13-8.55]
	C_{min} /mg/L)	41.0 [30.3-59.0]	3.99 [2.80-6.07]
	$t_{1/2}$ (h)	12.0 [8.05-28.1]	7.05 [4.21-30.0]
	CL_{SS} (L/h)	4.61 [4.00-7.32]	10.3 [9.29-18.6]
	V_{SS} (L)	107 [53.1-173]	177 [65.0-432]
	AUC_{tau} (mg·h/L)	440 [278-500]	48.9 [28.2-53.8]
1000/250 mg q8h as 2-hour infusion[2] (n=2)	C_{max} (mg/L)	33.9 [31.6-36.2]	3.71 [3.50-3.92]
	C_{min} /mg/L)	18.5 [15.9-21.1]	1.72 [1.65-1.80]
	$t_{1/2}$ (h)	9.04 [6.38-11.7]	5.81 [4.82-6.81]
	CL_{SS} (L/h)	4.54 [4.34-4.74]	11.0 [10.2-11.9]
	V_{SS} (L)	58.2 [37.4-79.1]	97.0 [73.6-120]
	AUC_{tau} (mg·h/L)	220 [211-230]	22.7 [21.0-24.5]

[1]Standard of care dose regimen; [2]Recommended dose regimen for adults with estimated CrCL ≤ 50 mL/min. C_{max}: Maximum plasma concentration; C_{min}: Minimum plasma concentration; $t_{1/2}$: Half-life; CL_{SS}: Clearance at steady-state; V_{SS}: Volume of distribution at steady-state; AUC_{tau}: Area under the concentration-time curve for a dosing interval.

Figure 2 illustrates the observed and simulated concentration-time profiles. In patients undergoing CVVHDF, drug concentrations exhibited flatter PK profiles, with smaller differences between peak (C_{max}) and trough (C_{min}) concentrations compared to non-CVVHDF patients. Notably, C_{min} values were substantially higher than expected based on phase III PopPK model predictions, suggesting accumulation of both CAZ and AVI in these patients.

The median SA values were 0.41 (range: 0.26–0.49) for CAZ and 0.23 (range: 0.14–0.28) for AVI, indicating that a higher proportion of CAZ was removed by the CVVHDF membrane compared to AVI.

The median CL_{CVVHDF} values were 0.87 L/h (range: 0.57–1.06) for CAZ and 0.50 L/h (range: 0.29–0.61) for AVI. The relative contribution of CVVHDF to total drug clearance was 19.8% for CAZ and 5.32% for AVI, suggesting that while CVVHDF substantially contributed to CAZ clearance, its impact on AVI elimination was more limited.

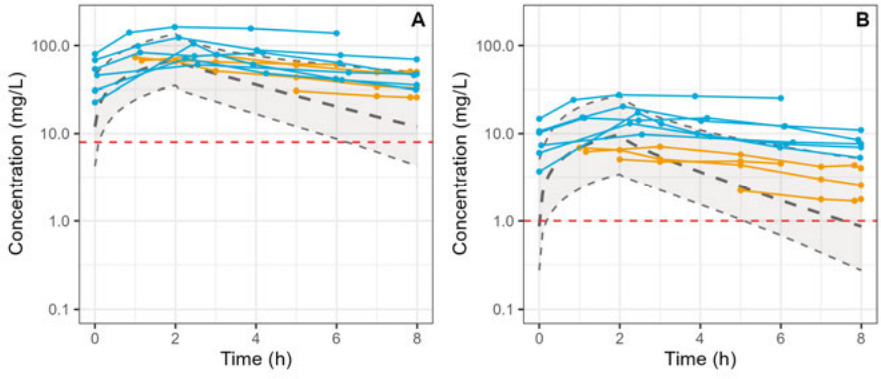

Figure 2. Visual comparison of ceftazidime (A) and avibactam (B) at doses of 2000 mg and 500 mg, respectively, administered every 8 hours as a 2-hour infusion. In orange: unbound plasma drug concentrations from patients in the current study; in blue: unbound plasma drug concentrations for the six patients from the study by Shields et al. [109]. In grey: unbound concentration-time profiles simulated for typical HAP patients receiving CAZ-AVI 2000/500 mg q8h as a 2-hour infusion, using PopPK models from Li et al. [99]. Grey dashed lines correspond to the 5th, median and 95th percentiles of simulated concentration-time profiles. Red dashed lines correspond to a $MIC_{CAZ/AVI}$ of 8 mg/L (A) and a C_T of 1 mg/L (B), respectively.

4.1.3 Protein binding of ceftazidime-avibactam in critically ill patients

A total of 74 plasma samples were analysed to determine fu for CAZ and AVI (51 from HAP/VAP patients, Paper II; 23 from CVVHDF patients, Paper III). CAZ remained almost entirely unbound in both groups, with median fu values of 1.07 (range: 0.93–1.25) in HAP/VAP patients and 1.07 (range: 0.80–1.14) in CVVHDF patients, indicating negligible plasma protein binding and minimal interindividual variability (CV: 7.55%). AVI also demonstrated low protein binding, but median fu was lower in CVVHDF patients (0.73, range: 0.55–0.92) compared to HAP/VAP patients (0.95, range: 0.80–1.24), suggesting possible alterations in protein binding dynamics due to RRT. The coefficients of variation for AVI were 10.3% in HAP/VAP patients, indicating moderate variability.

4.2 Pharmacokinetics-pharmacodynamics of β-lactam/β-lactamase inhibitor combinations

4.2.1 Target identification for avibactam in combination with ceftazidime

Dose fractionation study in mice. In mice, the most predictive PK/PD index for AVI varied by bacterial strain (Table 3). For *K. pneumoniae* (NCTC13438, KP981690) and *E. cloacae* (EL871203), the most predictive index was *f*AUC/MIC, while against *P. aeruginosa* strains (NCTC10783, 9750, 2154), *f*T>C_T (with C_T of 1 mg/L) was the most predictive index (Table 3).

At equivalent total daily AVI doses, bacterial killing was generally more pronounced against Enterobacteriaceae compared to *P. aeruginosa*. Against Enterobacteriaceae, the maximum bacterial killing was reached at AVI doses of 300 mg/kg/day, with higher doses resulting in minimal additional effect. Against *P. aeruginosa*, the best bacterial killing was observed with continuous infusion or frequent intermittent administration (q2h, q4h).

Table 3. Best fitting PK/PD index and magnitudes of avibactam metrics associated with bacteriostasis and bacterial killing (2-log kill) in simulated mouse and human dose fractionation studies.

Strain	Mouse			Human		
	Index	**Stasis**	**2-log kill**	**Index**	**Stasis**	**2-log kill**
KP981690	*f*AUC/MIC	2.19	3.27	*f*AUC/MIC	1.96	2.87
NCTC13438	*f*AUC/MIC	2.38	3.45	*f*AUC/MIC	1.99	2.91
EL871203	*f*AUC/MIC	2.28	3.35	*f*AUC/MIC	1.96	2.83
2154	*f*T>C_T[1]	43.1%	NaN[2]	*f*T>C_T[1]	NaN[3]	41.6%
NCTC10783	*f*T>C_T[1]	NaN[2]	NaN[2]	*f*AUC/MIC	6.54	12.9
9750	*f*T>C_T[1]	NaN[2]	NaN[2]	*f*AUC/MIC	4.51	22.9

By convention *f*AUC/MIC is unitless. [1]Threshold concentration (C_T) of 1 mg/L. [2]The Emax model estimated PDmax < E0, i.e. stasis or net killing was not reached. [3]The Emax model estimated E0 < 0 $\log_{10}$ CFU/mL.

Dose fractionation study in humans. In humans, the most predictive PK/PD index for AVI efficacy depended on the bacterial strain and infusion mode. Against Enterobacteriaceae strains, *f*AUC/MIC was the most predictive index in both pooled (Table 3) and mode-specific analyses. Against *P. aeruginosa* strains, the optimal PK/PD index was strain- and infusion mode-dependent:

- Pooled analysis (Table 3): *f*T>C_T was the most predictive index against *P. aeruginosa* 2154, while *f*AUC/MIC was more predictive against *P. aeruginosa* NCTC10783 and 9750.
- Mode-specific analysis: For intermittent infusions (0.5h, 2h, 4h), *f*T>C_T was the most predictive index, whereas, for continuous infusion, both *f*C_{max}/MIC and *f*AUC/MIC provided better correlations with efficacy.

For example, against *P. aeruginosa* 9750, $fT>C_T$ was most predictive across all infusion modes, while for continuous infusion, fC_{max}/MIC and *f*AUC/MIC provided similar predictive performance with comparable r^2 values.

4.2.2 Target attainment for β-lactam/β-lactamase inhibitor combinations

PTA for BL antibiotics alone. For the BL components, PTA was generally ≥90% across the recommended dosing regimens when using EUCAST PK/PD targets, except for prostatitis and HAP/VAP infections at high MIC values. In the TRC population (Figure 3), CAZ, MER, and PIP had insufficient PTA for prostatitis when $MIC_{BL/BLI}$ was 8 mg/L (PTA of 12%, 11%, and 71%, respectively). Similarly, CAZ did not reach the target at $MIC_{CAZ/AVI}$ of 8 mg/L for lung infections and cIAI.

In the ARC population, overall PTA values were lower due to increased drug clearance. For CAZ and MER, PTA was insufficient for prostate infections at $MIC_{BL/BLI} \geq 4$ mg/L. For PIP, PTA dropped below 90% even at MIC ≤ 1 mg/L in certain infections (e.g., cIAI, prostatitis).

Higher PK/PD targets, such as those proposed for severe infections and aggressive treatment strategies, further reduced PTA. For instance, in TRC patients with HAP and $MIC_{MER/VAB}$ of 2 mg/L, PTA remained >99% for standard and severe infection targets but decreased to 51% when the aggressive target (100% *f*T>MIC) was applied.

PTA for BLIs alone. For BLIs, PTA was generally lower than for the BLs, particularly for the time-dependent inhibitors AVI and TAZ. The AUC-based inhibitors REL and VAB achieved >90% PTA across all tested scenarios.

For time-dependent BLIs, PTA remained constant across all MIC values as targets were defined based on $fT>C_T$ (e.g., 50% $fT>C_T$ for CAZ-AVI, 20% $fT>C_T$ for CET-TAZ, and 40% $fT>C_T$ for PIP-TAZ). In the TRC population (Figure 3):

- AVI reached adequate PTA in bacteraemia and cUTI but remained below 90% in other infections.
- TAZ (with CET) met the suggested 20% $fT>C_T$ target for all infections.
- TAZ (with PIP) reached ≥90% PTA only in bacteraemia and HAP/VAP but failed in most other infections.

In ARC patients:

- TAZ (with CET) was just below the 90% threshold (89%) for cUTI.
- TAZ (with PIP) failed to achieve ≥90% across all infections, with values as low as 6% in prostatitis.

For AUC-driven BLIs, PTA was consistently high for REL across all infection sites and renal clearance categories. However, VAB PTA varied depending on the target. For example, in TRC patients with HAP and $MIC_{MER/VAB}$ of 2 mg/L, PTA was:

- ≥90% for EUCAST (*f*AUC/MIC ≥ 35) and severe infection (*f*AUC/MIC ≥ 50) targets
- <90% for the aggressive target (*f*AUC/MIC ≥ 65)

PTA for BL/BLI combinations. Since the PTA for BL/BLI combinations is determined by the lowest PTA between the two components, the limiting factor in most cases was the BLI. For example:

- In TRC patients (Figure 3) with HAP and $MIC_{CAZ/AVI}$ of 4 mg/L, PTA for CAZ was 98%, but PTA for AVI was 73%, resulting in an overall combination PTA of 69%.
- In ARC patients treated with CET-TAZ for cUTI ($MIC_{CET/TAZ}$ of 2 mg/L), PTA for CET was 98%, but for TAZ, it was 61%, limiting overall PTA to the same value.
- In ARC patients receiving MER-VAB for bacteraemia ($MIC_{MER/VAB}$ of 8 mg/L), PTA was >99% for MER, but VAB had only 81% PTA, limiting the combination.
- IMI-REL achieved >90% PTA across all investigated scenarios.

When the impact of fu was assessed, the conclusions on whether PTA was ≥90% or not remained unchanged in most cases. However, some exceptions were observed, such as TRC patients treated with CAZ-AVI for cUTI ($MIC_{CAZ/AVI}$ of 2 mg/L), where PTA improved with a higher assumed tissue penetration ratio value.

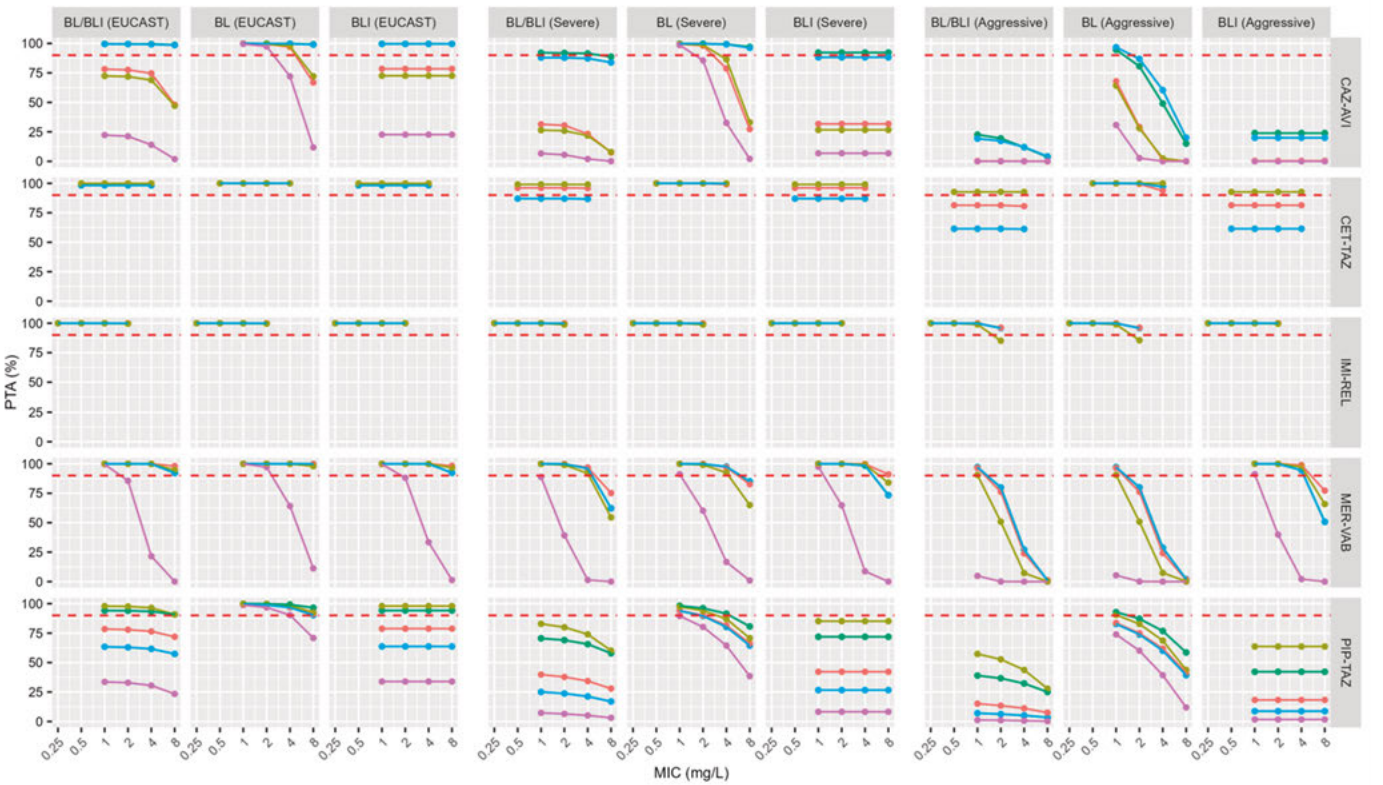

Figure 3. Probability of target attainment for ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (CET-TAZ), imipenem-relebactam (IMI-REL), meropenem-vaborbactam (MER-VAB) and piperacillin-tazobactam (PIP-TAZ) in the TRC population.

Figure 3 legend (continued). PTA results are stratified by PK/PD targets (EUCAST, Severe and Aggressive) and outputted for the BL/BLI combination as a whole, the BL drug alone and the BLI drug alone. Therapeutic indications are: complicated intra-abdominal infection (orange), hospital-acquired pneumonia and ventilator-associated pneumonia (mustard), complicated urinary tract infection (including pyelonephritis; cyan), associated bacteraemia (green), and prostatitis (purple). The red dashed line represents the 90% PTA threshold.

4.2.3 Dosing optimisation of ceftazidime-avibactam

PTA outcomes. The standard dosing regimen (2000/500 mg q8h as a 2-hour infusion) achieved satisfactory PTA (≥90%) for a 2-log bacterial kill at 24h against strains with MIC ≤ 8 mg/L. However, against *P. aeruginosa* strain 2154 (MIC 4 mg/L), PTA was suboptimal at 8h and 48h (67.3% and 78.8%, respectively). Against *P. aeruginosa* strains NCTC10783 and 9750 (MIC 16 and 32 mg/L, respectively), the standard regimen did not achieve acceptable PTA for any target.

Impact of the mode of infusion. The mode of administration had limited impact on PTA against Enterobacteriaceae, with PTA values differing by less than 3% across infusion modes. However, against *P. aeruginosa*, continuous infusion consistently outperformed intermittent infusion, improving PTA for high-MIC strains. For example, targeting a 2-log kill at 48h against *P. aeruginosa* 2154, CAZ-AVI 2000/500 mg q8h achieved PTA values of: 58.5% (0.5h-infusion), 78.8% (2h-infusion), 95.5% (4h-infusion) and 99.2% (continuous infusion).

Impact of the administration frequency. The dosing frequency had minor effects on PTA across strains with MIC ≤ 8 mg/L (differences <2%), except for *P. aeruginosa* 2154. For this strain, CAZ-AVI 1500/375 mg q6h resulted in higher PTA compared to 2000/500 mg q8h or 3000/750 mg q12h at all time points. Against *P. aeruginosa* NCTC10783 and 9750, PTA remained unsatisfactory across all administration frequencies.

Impact of CAZ-to-AVI ratio. PTA increased as the AVI proportion increased (i.e., higher doses of AVI relative to CAZ). The highest PTA values were observed at 2:1 or 1:1 ratios (e.g., 2000/1000 mg or 2000/2000 mg), suggesting that higher AVI exposure enhances bacterial killing.

Comparison of traditional PK/PD index vs. time-kill curve approach. PTA results differed between the traditional PK/PD index method (joint target of 50% $fT>MIC$ for CAZ and 50% $fT>C_T$ for AVI) and the time-kill curve-based approach. The time-kill curve approach generally resulted in lower PTA estimates, particularly against high-MIC *P. aeruginosa* strains. For example, against *P. aeruginosa* NCTC10783 (MIC 16 mg/L) with the standard regimen, PTA for 50% $fT>MIC$ and 50% $fT>C_T$ was 88.8%, while PTA for 2-log bacterial kill at 24h was only 14.9%.

4.3 Biomarkers of interest for model-informed precision dosing

In Paper II, of the 95 biomarkers evaluated, 63 biomarkers exhibited minimal time-dependent changes (elimination or production rate constant < 0.001 h^{-1}) and were excluded from further analysis. The remaining 32 biomarkers were characterised using turnover models.

Table 4. Parameter estimates and associated relative standard errors (RSE%) for the six biomarkers with the most pronounced time-course changes during ceftazidime-avibactam treatment in critically ill patients with HAP/VAP.

Biomarker	Parameter	Estimate	RSE (%)
AREG (decreasing trend)	θ1: BASE (NPX)	9.62 FIX	-
	θ2: KOUT (h-1)	0.00414	35
	θ3: DIFF (NPX)	27.2	40
	IIV on DIFF (%)	139	23
	RUV (prop.) (%)	37.6	15
CRP (decreasing trend)	θ1: BASE (mg/L)	2.37 FIX	-
	θ2: KOUT (h-1)	0.00628	11
	θ3: DIFF (mg/L)	96.1	34
	IIV on DIFF (%)	164	22
	RUV (prop.) (%)	34.7	8.1
DCBLD2 (increasing trend)	θ1: BASE (NPX)	81.3 FIX	-
	θ2: KOUT (h-1)	0.146	69
	θ3: DIFF (NPX)	-43.4	9.7
	IIV on DIFF (%)	16.9	23
	RUV (prop.) (%)	42.4	12
IL-6 (decreasing trend)	θ1: BASE (NPX)	9.29 FIX	-
	θ2: KOUT (h-1)	0.00820	17
	θ3: DIFF (NPX)	87.5	33
	IIV on DIFF (%)	104	16
	RUV (prop.) (%)	71.9	24
LAMP3 (increasing trend)	θ1: BASE (NPX)	147 FIX	-
	θ2: KOUT (h-1)	0.0234	246
	θ3: DIFF (NPX)	-79.8	17
	IIV on DIFF (%)	51.8	18
	RUV (prop.) (%)	19.7	14
TRIM21 (increasing trend)	θ1: BASE (NPX)	129 FIX	-
	θ2: KOUT (h-1)	0.00859	43
	θ3: DIFF (NPX)	-115	3.8
	IIV on DIFF (%)	10.4	31
	RUV (prop.) (%)	41.7	20

Interindividual variability (IIV) associated with the typical value (TV) parameters is expressed as coefficient of variation (%), calculated according to: $\sqrt{e^{\omega^2} - 1} \times 100\%$. Residual errors are expressed as standard deviations.

Seven biomarkers exhibited increasing trends over the course of treatment, with the largest changes observed for DCBLD2, LAMP3, and TRIM21. The

remaining 25 biomarkers showed decreasing trends, with IL-6, CRP, and AREG displaying the most pronounced declines. The half-lives estimated among biomarkers with decreasing trends ranged from 84.5 hours for IL-6 to 759 hours for BTN3A2. A summary of parameter estimates for the six biomarkers with the most pronounced changes is provided in Table 4.

Among the 12 biomarkers successfully characterised with turnover models, CRP was the only one for which a significant exposure-response relationship with CAZ plasma concentration was identified. This relationship was best described by an inhibitory effect of CAZ on CRP production, which was implemented as a linear function. No significant exposure-response relationships were detected for the remaining 11 biomarkers.

5 Discussion

5.1 The challenge of individualising β-lactam/β-lactamase inhibitor therapy

Individualising BL/BLI therapy presents significant challenges due to the high IIV in PK and PD. This variability affects drug exposure, bacterial killing, and, ultimately, treatment outcomes. In paper II, IIV in CAZ and AVI clearance was approximately 30%, while IIV in V1 reached 113%, highlighting substantial variability even after accounting for renal function. Part of this variability may be because of pathophysiological changes occurring during critical illness [111–113].

Furthermore, current standard dosing regimens, primarily developed for non-critically ill patients, do not consider that critically ill individuals and those undergoing RRT have different PK characteristics. In Paper III, CAZ-AVI PK profiles in CVVHDF patients differed from the predictions made using PopPK models developed for non-RRT patients, reinforcing the need to explore whether tailored dosing strategies could improve target attainment in this population [114,115].

The primary determinant of BL and BLI clearance is renal function, typically estimated by CrCL. Paper II confirmed CrCL as the key predictor of clearance IIV for both CAZ and AVI, supporting CrCL-based dose adjustments [17,18,99]. However, despite the role of CrCL, significant unexplained variability remained, particularly in the volume of distribution, suggesting additional unidentified factors influence drug disposition [116].

Another factor contributing to variability is plasma protein binding. In Papers II and III, CAZ was essentially unbound in both HAP/VAP and CVVHDF patients, with medians fu of 1.07 and low interindividual variability (CV < 10%). This was notably higher than the value reported in the SmPC for CAZ (fu of 0.90), which may reflect differences in study populations, as protein binding data in the SmPC is typically derived from healthy volunteers. For AVI, protein binding differed between patient groups. In Paper II, the median fu was 0.95, while in Paper III, the median fu was lower at 0.73. Despite this difference, interindividual variability within each population remained low. These differences in fu between populations may be linked to illness- and therapy-induced alterations in plasma protein content, particularly in critically ill patients with acute kidney injury [115–118].

Given these complexities, BL/BLI therapy cannot fully rely on CrCL-based dosing adjustments alone [119], particularly in critically ill patients where PK variability is pronounced. Instead, TDM and MIPD have emerged as promising strategies to individualise dosing based on measured drug concentrations. Unlike CrCL-based dosing, MIPD accounts for both known and unknown variability by integrating measured drug concentrations with patient-specific factors and detailed dosing and sampling time data. However, effective individualisation for BL/BLI therapy remains limited by the lack of well-defined efficacy or toxicity targets, particularly for BLIs [16,84].

5.2 Redefining efficacy targets for β-lactam/β-lactamase inhibitor therapy

Optimising efficacy targets for BL/BLI therapy is inherently more complex than for single-agent antibiotics due to the intricate drug-drug-bacteria interactions. Traditionally, BLIs were assumed to only protect BLs from degradation, but accumulating evidence suggests BLIs may have direct antibacterial effects, potentiate BL activity, and modulate BL PD in a species-dependent manner [15,94,95,97]. This potentiation effect, where BLIs enhance bacterial killing beyond mere β-lactamase inhibition, adds another layer of complexity. Moreover, mechanistic considerations, such as the need for BLIs to penetrate Gram-negative bacteria before inhibiting β-lactamases [30], challenge the simplistic assumption that BL and BLI PK/PD indices alone can predict efficacy.

Despite these complexities, efficacy targets for BL/BLI therapy are still primarily defined using traditional PK/PD indices [33,93], which correlate drug exposure with bacterial killing. However, Paper IV demonstrated that no single PK/PD index consistently predicted AVI efficacy across bacterial strains, species (mouse and human), and infusion modes. This inconsistency highlights a major limitation: PK/PD relationships for BLIs are highly context-dependent [85,120], making it difficult to establish universal PK/PD targets that apply across different bacterial species and clinical scenarios.

To overcome these limitations, mechanism-based PKPD models and time-kill curve approaches offer promising alternatives. Paper IV used a time-kill modelling approach that provided a more mechanistic representation of bacterial killing dynamics, capturing drug-pathogen interactions over time rather than relying on a single summary index. However, even advanced models remain incomplete – key factors such as drug penetration kinetics, β-lactamase production, and enzyme turnover rates are often not accounted for [30,121–123].

While PKPD modelling represents a major step forward, several barriers must be addressed before it can be directly used in clinical practice. More

research is needed to establish the translational capacity of preclinical time-kill models to human infection settings, and eventual standardisation will be required to ensure these models can be reliably used to guide dosing in clinical practice [124,125]. Additionally, the ability to scale PKPD relationships across different bacterial species remains a challenge. Current PKPD models also often lack consideration of host immune responses, which may influence treatment success [126]. Future research should focus on refining PKPD scaling methods for broader clinical applicability, incorporating immune response dynamics into PKPD models, and validating model-based dosing strategies in clinical studies.

5.3 Linking target attainment to clinical outcomes

An important limitation of current PKPD-based dose optimisation strategies is the assumption that achieving PK/PD targets directly translates into improved clinical outcomes [127,128]. While PTA can serve as a useful surrogate for antimicrobial efficacy or the avoidance of toxicity, its relationship with clinical cure, microbiological eradication, or the absence of adverse events requires further establishment [127,129–132]. In this thesis, PTA calculations were performed in Papers I and IV to evaluate the likelihood of achieving efficacy targets across different dosing regimens and patient populations. However, these analyses were not linked to actual clinical or microbiological outcomes, reflecting a broader gap in the field.

Future research should focus on systematically validating the relationship between target attainment and clinically meaningful endpoints, such as clinical cure, survival, microbiological eradication, recurrence rates, resistance development, and the occurrence of adverse events. Such efforts will require large-scale clinical studies incorporating real-world data from patients [132], where pathophysiological changes and polypharmacy may further influence exposure-response-outcome relationships [133]. By establishing these links, PKPD targets can be refined to support more individualised, outcome-driven therapy.

5.4 Alternative dosing strategies for β-lactam/β-lactamase inhibitor therapy

Given the limitations of standard dosing, alternative dosing strategies should be explored to improve therapeutic outcomes in cases where target attainment is insufficient. Paper IV investigated several modifications to CAZ-AVI therapy, including increasing AVI doses relative to CAZ, prolonged and continuous infusion, and increased dosing frequency.

A key finding was that increasing AVI exposure significantly improved PTA, particularly against *P. aeruginosa*. Lowering the CAZ:AVI ratio from 4:1 to 2:1 or 1:1 (by increasing the amount of AVI) enhanced bacterial killing, reinforcing the notion that BLI exposure may be the limiting factor in BL/BLI therapy. However, formulation constraints prevent dose modification, as CAZ-AVI is only available as a fixed-dose combination [17,18]. These findings support future consideration of alternative formulations that allow for more flexible dosing strategies.

Another strategy explored in Paper IV was the use of continuous infusion instead of intermittent infusion [134]. This approach aimed to prolong drug exposure, ensuring sustained concentrations – as CAZ (and AVI) have been suggested to be time-dependent drugs. The results showed that continuous infusion significantly improved PTA against *P. aeruginosa*, but with little added benefit against Enterobacteriaceae. For example, at a $MIC_{CAZ/AVI}$ of 4 mg/L, PTA for a 2-log kill at 48 hours increased from 59% (0.5h infusion) to 99% (continuous infusion), demonstrating a clear advantage of prolonged drug exposure for treating infections caused by *P. aeruginosa*. This suggests that continuous infusion may be a viable empirical treatment strategy when the causative pathogen is unknown, as it provides a more forgiving exposure profile and reduces the risk of underdosing. However, implementing continuous infusion in clinical settings comes with practical challenges. One concern is drug stability in the infusion bag [135], as prolonged infusion durations may lead to degradation of CAZ-AVI over time. Additionally, continuous infusion limits patient mobility and requires dedicated IV lines and pumps, which may not always be practical in settings with limited resources. As an alternative, prolonged infusion (e.g., 4h infusions instead of 0.5h or 2h) could provide a balance between optimising drug exposure and maintaining practical feasibility.

Increasing dosing frequency (e.g., q6h instead of q8h) was another approach tested in Paper IV, but this strategy had a limited impact on PTA compared to modifying the AVI dose or infusion mode. While more frequent dosing slightly improved PTA at higher MIC values, the effect was minor relative to the benefits seen with a continuous infusion or higher AVI exposure. Furthermore, more frequent dosing poses practical and clinical challenges, including an increased burden on nursing staff, greater logistical constraints, and a higher risk of drug accumulation and toxicity. Unlike extended or continuous infusion, which primarily modifies the time profile of drug exposure, more frequent dosing increases total daily drug exposure, which can exacerbate toxicity risks – especially in patients with fluctuating renal function. Given these limitations, this approach does not appear to be the most effective strategy for optimising CAZ-AVI therapy, particularly in critically ill patients with unpredictable renal clearance.

Ultimately, the findings from Paper IV suggest that while higher AVI doses and continuous infusion are promising approaches for optimising CAZ-AVI efficacy, practical and regulatory constraints limit their immediate clinical

application. Until alternative formulations or infusion strategies become more widely feasible, TDM and MIPD offer the most viable pathway for individualising therapy in real-world settings, although clear guidelines and widely validated software tools remain limited as these approaches continue to evolve. Future research should focus on evaluating MIPD strategies and exploring alternative formulations of BLs and BLIs to provide greater dosing flexibility.

5.5 The role of model-informed precision dosing and biomarkers

Given the high PK variability in critically ill patients, MIPD offers a proactive, real-time strategy for optimising BL/BLI therapy. Paper II demonstrated that CrCL alone does not fully predict drug clearance, highlighting the need for TDM-informed, patient-specific dose adjustments. However, Paper I revealed that BLI exposure often determines PTA for the combination, suggesting that BLI TDM should be implemented alongside BL monitoring.

Additionally, Paper II explored biomarkers as potential adjuncts for MIPD, showing that CRP turnover was linked to CAZ exposure. However, while biomarker-guided therapy holds promise, challenges remain, including high IIV in biomarker responses, confounding factors affecting biomarker dynamics, and limited clinical validation of biomarker-based dosing adjustments [58,59,136]. Future research should focus on integrating biomarker data into real-time PKPD models to potentially refine dose optimisation strategies.

A key strength of this thesis was the joint PK modelling approach used in Paper II, which accounted for shared variability in clearance and volume of distribution between CAZ and AVI. This framework is particularly relevant for MIPD, as it enables more precise individualised dosing recommendations by considering the interdependence of BL and BLI exposure. Incorporating joint models into real-world MIPD applications could allow for more accurate predictions of BL/BLI exposure rather than treating the two drugs as independent entities [137,138]. However, several barriers must be overcome before joint models can be widely implemented in clinical practice. PopPK models require external validation using external PK datasets to ensure their predictive accuracy across diverse patient populations [73,139]. Another limitation is the absence of well-established PK/PD targets for BL/BLI combinations, which hinders the development of optimised dosing strategies. Without clearly established therapeutic endpoints, it remains challenging to determine which drug exposures should be targeted to maximise efficacy and minimise toxicity.

5.6 Towards a holistic approach: Integrating host, pathogen, and drug factors

The future of BL/BLI therapy (and antibiotic therapy in general) lies in a holistic approach that integrates host, pathogen, and drug interactions. Rather than focusing solely on drug exposure, precision antimicrobial therapy must consider host-specific factors such as immune response, disease severity, and organ function, pathogen-specific PKPD relationships including β-lactamase expression [140,141] and MIC variability, and dynamic treatment adaptations such as MIPD, TDM, and alternative dosing [126].

Achieving this shift requires collaborative efforts between researchers, clinicians, and regulatory bodies to develop scalable, adaptable, and personalised dosing strategies. By advancing precision dosing, PKPD modelling, and biomarker integration, it is possible to outmanoeuvre bacterial resistance and ensure that BL/BLI therapy remains effective even as pathogens continue to evolve.

6 Conclusions

This thesis explored pharmacometric approaches for the evaluation and individualisation of BL/BLI therapy to optimise antimicrobial treatment in critically ill patients. By integrating PopPK, PKPD modelling, biomarker analysis, and dose-exposure simulations, this work advances our understanding of key factors influencing BL/BLI efficacy and highlights strategies for precision dosing.

A major finding of this thesis was the critical role of BLIs in combination therapy. In Paper I, it was demonstrated that BLIs often fail to achieve adequate target site exposures, particularly in challenging infection sites such as the lung, abdomen, and prostate. These findings challenge the conventional focus on BL concentrations alone, as suboptimal BLI exposure may significantly limit overall treatment success. Additionally, Paper IV showed that the efficacy of BL/BLI combinations depends on both components achieving adequate exposure, reinforcing the need to consider BLI concentrations in dose optimisation strategies. Findings from Paper I and Paper IV support the argument that BLIs should be monitored alongside BLs to refine dosing recommendations, particularly in critically ill patients with altered PK.

This thesis also provided key insights into factors influencing individual BL/BLI drug disposition. Paper II confirmed that CrCL is a major determinant of CAZ-AVI clearance, supporting its role as the primary covariate for dose adjustments. However, unexplained variability in drug disposition remained, indicating that additional, yet unidentified, factors contribute to PK variability. Paper III extended this analysis to critically ill patients undergoing CVVHDF, demonstrating that these patients exhibited PK profiles that differed from non-RRT populations, with lower early and higher later concentrations within the dosing interval. These findings highlight the need for further evaluation of how RRT and altered physiology impact BL/BLI PK in critically ill patients.

The dynamic interplay between BLs, BLIs, and bacterial pathogens further complicates dose optimisation. In Paper IV, it was shown that the optimal PK/PD index for AVI varies by bacterial species. Against *P. aeruginosa*, lower CAZ:AVI ratios (with an increased amount of AVI) and continuous infusion were required to maximise bacterial killing, highlighting the need for pathogen-specific dosing considerations. Furthermore, Paper IV revealed significant discrepancies between preclinical (mouse) and clinical (human)

models in terms of PK/PD indices predictive of efficacy, raising concerns about the direct translation of preclinical dosing strategies to patient care. These findings reinforce the importance of mechanism-based PKPD modelling to refine bacterial species-dependent PK/PD targets and improve the accuracy of dose selection.

This thesis also laid the groundwork for a more structured dose-individualisation framework. Papers I-IV collectively support a shift away from a "one-size-fits-all" approach towards more personalised dosing regimens that integrate BL and BLI concentrations, patient-specific characteristics (e.g., renal function, concurrent interventions), infection site, bacterial susceptibility (MIC), and immune response dynamics. In Paper II, a preliminary association was observed between drug exposure and CRP turnover, suggesting that host-response biomarkers could complement PK data when assessing treatment response; however, further validation is needed to determine the robustness and clinical relevance of these relationships. Additionally, the joint PK modelling approach used in Paper II, by accounting for shared variability between CAZ and AVI, provides a more comprehensive representation of BL/BLI PK. This type of joint modelling could support individualised dosing in future MIPD applications, although the direct benefit for dosing precision was not specifically evaluated in this thesis. Paper IV further highlighted the importance of personalised strategies by demonstrating that adjusting AVI exposure or using continuous infusion improved PTA in infections caused by *P. aeruginosa*.

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