Clinical pharmacology of antimicrobials: towards optimized treatment of infectious diseases in hospitalized patients

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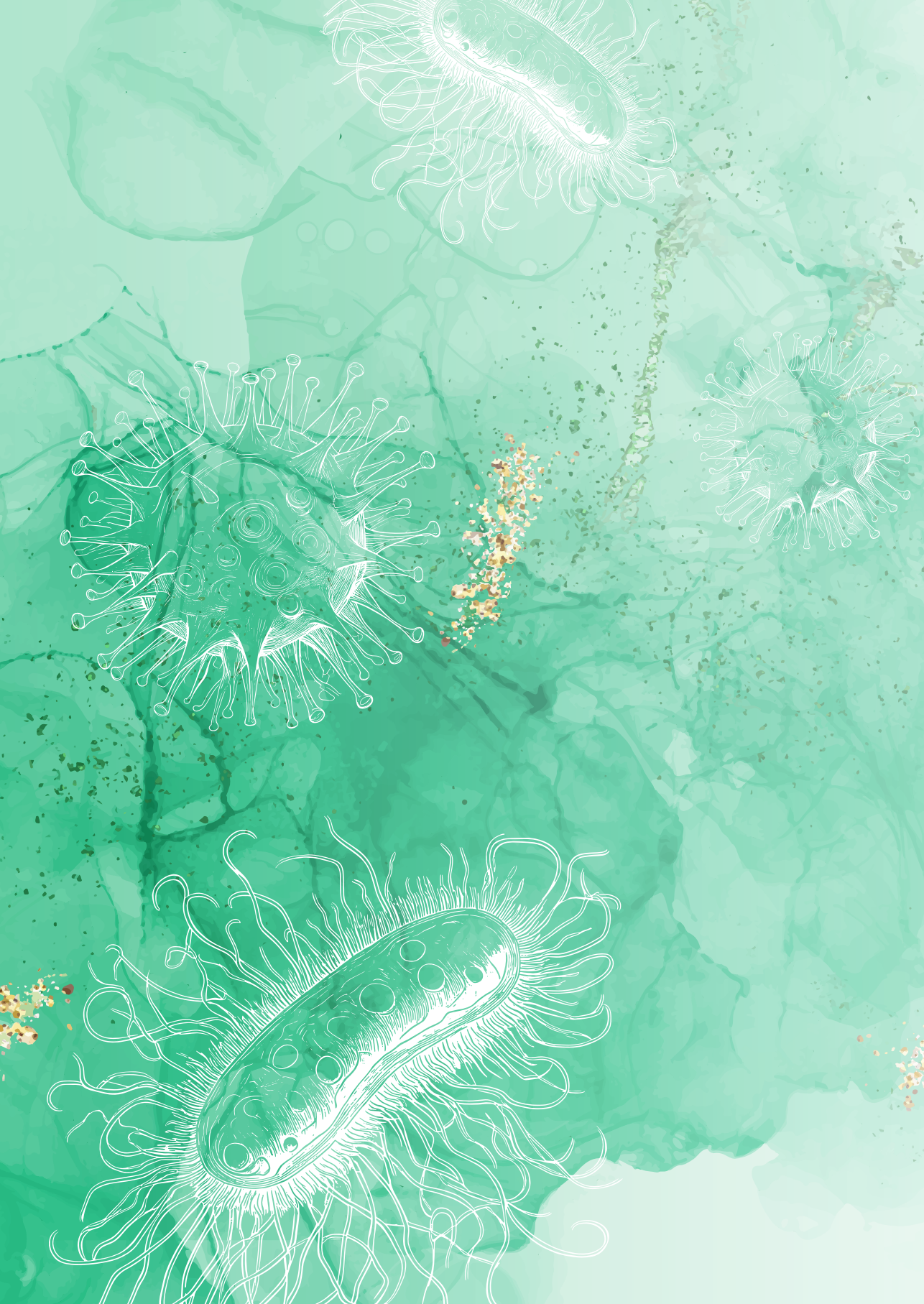

General introduction

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GENERAL INTRODUCTION

Approximately 13.7 million deaths in 2019 were caused by bacterial infectious diseases, and as of November 2023, more than 6 million people have died as a result of Coronavirus Disease 2019 (COVID-19).[1,2] Infectious diseases remain a health concern and will continue to pose major challenges for society in the future. The emergence of new infections and the development of resistance against currently used antimicrobials pose significant challenges for public health.

Emerging infectious diseases, such as HIV in the 1980s and COVID-19 in 2019, have resulted in significant impact on society. COVID-19 has had devastating global consequences, leading to widespread morbidity and mortality, as well as disruption of the economy and social systems. To combat and control emerging infectious diseases, rapid development of treatment and preventative measures is essential.

Antimicrobial resistance reduces the effectiveness of current treatments and raises the risk of untreatable infections. The causes of antimicrobial resistance include the overuse and misuse of antimicrobials in human and animal health.[3] The development of resistance often outpaces the registration of new therapies for multi-drug resistant pathogens. Without action, the United Nations has predicted that by 2050, approximately 10 million people per year could die from infections caused by multidrug-resistant pathogens.[4] To prevent further development of antimicrobial resistance, there is a need for the optimal use of currently available antimicrobials.

CHALLENGES IN TREATING INFECTIOUS DISEASES

The introduction of penicillin and sulfonamides in the 1940s was a milestone in the treatment of bacterial infectious diseases. Previously incurable infectious diseases became treatable, marking the start of the golden age of antibiotics.[5] However, clinicians continued to face challenges in the optimal use of these antimicrobials.[6] One of the main concerns has been determining the dosing regimen to maximize treatment effectiveness while minimizing the incidence of adverse events. Strategies for selecting the optimal antibiotic dosing remain relevant today, especially with the emergence of bacterial resistance and the lack of new antimicrobial therapies.[7] Therefore, it is crucial to optimize the use of the current antibiotic arsenal to ensure effective treatment for infectious diseases.

OPTIMIZING THE USE OF ANTIMICROBIALS

The appropriate use of antimicrobial agents requires an understanding of the characteristics of the drug, the host factors, and the pathogen, all of which influences the selection of the antimicrobial and the dosage regimen. Figure 1 illustrates the interactions between the patient, pathogen, and antimicrobial treatment.

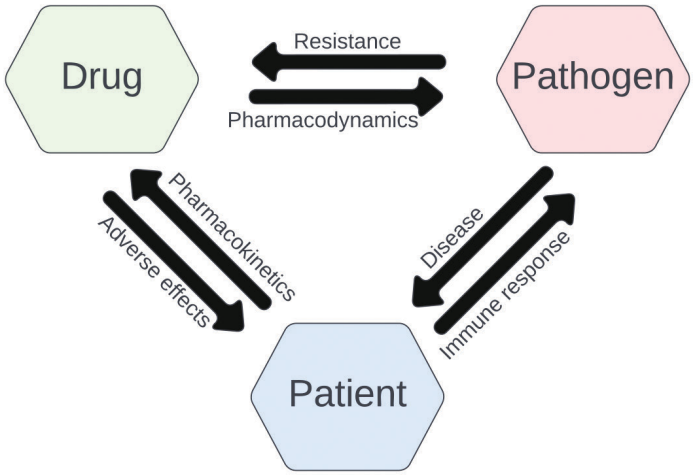

Figure 1: The factors and interplay that are relevant for the pharmacological treatment of infectious diseases

Two important factors for determining the optimal use of antimicrobials from a pharmacological perspective are the pharmacokinetics and pharmacodynamics of antimicrobials. Pharmacokinetics describes how the body processes a drug after administration, while pharmacodynamics describes how the drug affects the drug target. In the case of an infectious disease, pharmacodynamics also involves how the drug affects the pathogen.

THE PHARMACOKINETICS OF ANTIMICROBIALS

The pharmacokinetics of an antimicrobial can be described using the following processes: absorption, distribution, metabolism, and excretion (ADME). These factors determine how antimicrobials cross biological barriers, transport to and from tissues, undergo chemical transformations, and eventually exit the body. The absorption phase describes the entry into the bloodstream, and it is influenced by characteristics such as solubility and route of administration. Distribution involves the spread of antimicrobials throughout bodily tissues, including the infection site. Metabolism describes the enzymatic changes that drugs undergo. It is primarily a process to prepare drugs for elimination, but it can also affect their pharmacological effect or cause side effects. Lastly, excretion involves the removal of antibiotics and their metabolites from the body, primarily through renal elimination in the kidneys or biliary excretion.

THE PHARMACODYNAMICS OF ANTIMICROBIALS

The study of pharmacodynamics of antimicrobials focuses on the relationship between the concentration of the antimicrobial and its antibacterial or antiviral effect, but also the relation between the antimicrobial and the host.

The most commonly used parameter to describe the exposure required to produce a pharmacodynamic effect of antibiotics is the minimal inhibitory concentration (MIC).[8] This is the concentration of antibiotic required to cause an antimicrobial effect in vitro. In clinical practice, this variable is used to determine the susceptibility of a pathogen to an antibiotic. In antiviral therapy, the inhibitory concentration 50 (IC50) or sometimes effective concentration 50 (EC50) is used to describe the concentration required for 50% of the maximum antiviral effect.[9]

Both are in-vitro measurements and therefore cannot be directly translated into clinical dosing regimens. When translating this to the clinic, tissue penetration into the infection site,[10] percentage of protein binding (as only the unbound fraction exerts an antimicrobial effect),[11] and post antibiotic effect (the time an effect persists after the antimicrobial concentration drops below the MIC) are all important factors to consider.[12] Combining these factors with the IC50 or MIC can be used to determine the theoretical optimal exposure. This can be translated into dosing regimens that should result into the desired pharmacodynamic effect. In infectious disease treatment this is often aimed at cure but could also be suppression of the infection.

In addition to the impact on the pathogens, another important consideration is the effect of the antimicrobial on the host. The main goal of antimicrobial therapy is eradication of the causal pathogen(s), other effects on the human body are unwanted and should be considered adverse effects.[13] Some of these adverse effects are concentration dependent and can be mitigated by establishing a toxicity threshold concentration toxicity and adjusting dosing regimens accordingly.[14]

COMBINING PHARMACOKINETICS WITH PHARMACODYNAMICS (PK/PD)

To determine the optimal dosing regimen, a combination of pharmacokinetics and pharmacodynamics is needed. To achieve this, three different PK/PD indices are used to describe the relationship between the pharmacokinetics and pharmacodynamics of antimicrobials. These principles have often been established in preclinical studies and then translated to clinical practice.[15] The three PK/PD indices are visualized in figure 2.

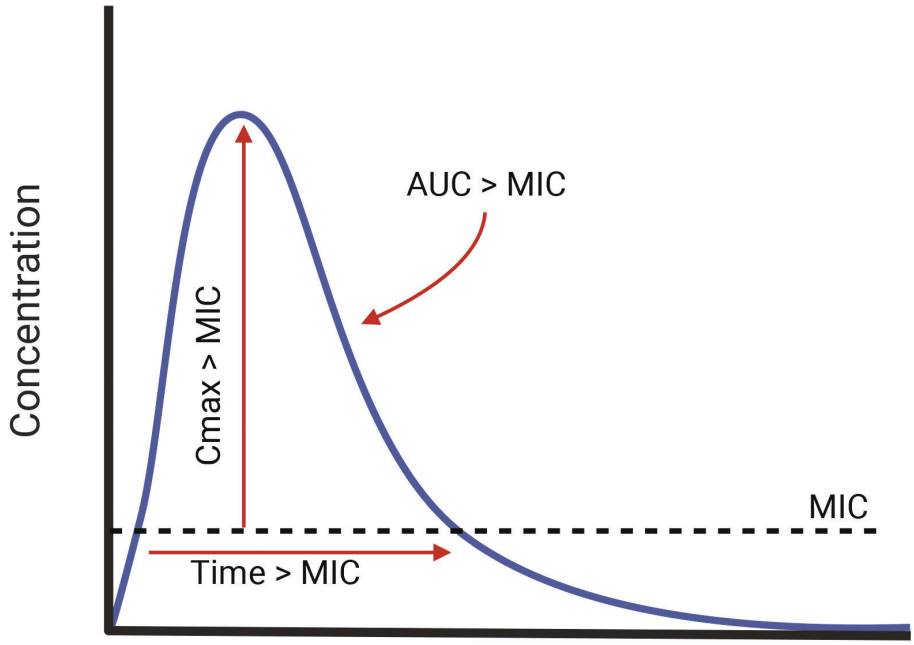

Figure 2 : The combination of pharmacokinetics and pharmacodynamics of antimicrobials

The first PK/PD index is the fraction of time above the MIC (fT>MIC). The antimicrobial effect is determined by the duration the antimicrobial concentration remains above the MIC. Concentrations much higher than the MIC are not more effective.[15] Optimizing the therapy of antimicrobials that work via fT>MIC can be achieved by increasing the dosing frequency. A class of antibiotics that works via fT>MIC are the beta-lactam antibiotics.[16] To maximize the fT>MIC, Beta-lactam antibiotics are often administered frequently (up to six times a day for amoxicillin and flucloxacillin) or through continuous infusion. The optimal fT>MIC required to cure an infection with beta-lactam antibiotics varies depending on the characteristics of the pathogen, patient characteristics, and disease severity. For example, in the case of beta-lactam antibiotics, the target varies between 40% fT>MIC and 100% fT>6xMIC.[17]

The second PK/PD parameter is Cmax>MIC, which means that these antimicrobials are more effective when the ratio between the maximum concentration (Cmax) and the MIC increases. Prolonged exposure is not advantageous. The dosage regimens for these antimicrobials are often high-dose with extended intervals.[15] For years, the effectiveness of aminoglycosides has been thought to be best described by Cmax>MIC. However, it has been found that AUC>MIC is more practical to predict their antibacterial effect in clinical practice.[18]

The third mechanism is the AUC>MIC. For antimicrobials that work via AUC>MIC, the total exposure is the most relevant parameter.[15] A class of antibiotics that works via AUC>MIC are the glycopeptides. Vancomycin can be administered through continuous infusion or intermittent administrations with comparable clinical effectiveness.[19] The choice for a dosing regimen for antimicrobials that work via AUC>MIC is frequently based on practical considerations.

These PK/PD indices are preferably combined with a PK/toxicity ratio. However, for most antimicrobials, the association between pharmacokinetics and toxicity is unclear, and dosing regimens are based on the PK/PD association.[20] An example of an antimicrobial with a known PK/toxicity association is tobramycin. Tobramycin toxicity occurs when serum concentrations remain above 1 mg/L for prolonged periods of time.[21] Since the effectiveness is determined by AUC>MIC or Cmax>MIC, once daily dosing can avoid toxicity while maintaining effectiveness. In clinical studies, once daily dosing was found to be as effective as multiple daily dosing but less toxic. [22]

SPECIAL PATIENT POPULATIONS

One of the factors that affect drug treatment is the patient's characteristics (see Figure 1). These characteristics may modify the pharmacokinetics and pharmacodynamic response to antimicrobials. Knowledge gaps exist in the optimal treatment for patients with unusual characteristics.[23] This is partially due to the methods used for registering new pharmaceuticals. Once a promising drug is identified based on findings from animal studies, phase I studies examine its safety profile within a small cohort of healthy volunteers. The goal of such a study is to determine an appropriate dosing regimen for further studies. Subsequent steps involve phase II and III trials that establish the drug's effectiveness and tolerability in patient populations, primarily via randomized controlled trials (RCTs). Upon successful completion of these trials, regulatory agencies may grant market access, enabling the drug to be introduced to the market.

However, certain populations are often underrepresented in these trials.[24] This can be caused by several reasons, including ethical considerations (children, pregnant women), safety concerns (critically ill patients), or limited patient numbers (immunocompromised, rare genetic variations). The best treatment regimen for these patients is often not known, leading to uncertainties about dosing regimens, clinical effectiveness, and risk of toxicity.

PHARMACOKINETICS IN SPECIAL PATIENT POPULATIONS

Pharmacokinetic assessment in specific subgroups is important when these patients have unique characteristics or conditions that affect the pharmacokinetics and, thereby exposure to antimicrobials. Some of these characteristics are definitive, such as genetic alterations in patients with cystic fibrosis or ultra-rapid metabolizing cytochrome P enzymes. On the other hand, some characteristics are related to disease and result in temporary changes to the pharmacokinetics. ICU patients may have an increased clearance and volume of distribution of antimicrobials.[25] This is caused by systemic inflammation which can lead to hyper dynamic effects on the cardiovascular system, resulting in augmented renal clearance.[26] The clearance of antimicrobials in ICU patients can also be lower due to organ failure resulting in reduced clearance.[25] Neonates are another example of patients with altered pharmacokinetics, as their bodies undergo rapid changes due to maturation.[27] This affects both the volume of distribution and the clearance of antimicrobials. Careful evaluation of the pharmacokinetics in special patient populations is needed to optimize dosing regimens and effectively treat infectious diseases.

PHARMACODYNAMICS IN SPECIAL PATIENT POPULATIONS

Patients with special characteristics that lead to alternative pharmacodynamic responses may require a modification of treatment. An example of a population with alternative responses to antimicrobials is immunocompromised patients. In these patients, the antimicrobial effect is more crucial for treatment success, as the host response to infection is impaired.[28] Other examples are travelers or patients with cystic fibrosis.[29,30] Because of differences in resistance profiles of pathogens across different regions and in patients who have undergone multiple courses of prior antimicrobial treatment, alternative antimicrobials or dosing regimens might be necessary to treat infections.

COVID-19 AND REMDESIVIR

The COVID-19 pandemic emerged in late 2019 and has posed a significant challenge for the medical community. In the absence of proven effective antiviral therapies, several existing drugs were repurposed and tested for their effectiveness against COVID-19. However, most of these drugs failed to demonstrate clinical effectiveness (e.g. chloroquine, ivermectin, metformin, and fluvoxamine).[31] These drugs showed antiviral effects against SARS-CoV-2 in vitro

but not in vivo, possibly due to either inability to tolerate the required doses or altered tissue distribution, resulting in insufficient antimicrobial concentrations at the infection site. Even for the drugs that have shown effectiveness, there is still uncertainty about the optimal dose (tocilizumab) and duration of treatment (remdesivir).[32] Thus, optimizing drug use is as crucial for improving the management of emerging infectious diseases such as COVID-19 as it is for currently available antibiotics.

The first antiviral therapy to receive conditional market authorization for COVID-19 was remdesivir in 2020. Due to the urgency of the COVID-19 pandemic, this treatment was registered without a thorough evaluation of its pharmacology in special populations. The registered dosing regimen was determined using pharmacokinetic data from healthy individuals. There was no data about the pharmacokinetics in COVID-19 patients or other special populations. There was limited information available regarding target concentrations that would lead to the optimal antiviral response and which patient populations might benefit most from the use of remdesivir. Studying the pharmacokinetics and pharmacodynamics in special populations could help optimize both the dosing regimens and the use of remdesivir for COVID-19 treatment.

POPULATION PHARMACOKINETIC MODELING

There are several methods for studying the pharmacokinetics of antimicrobials. Currently the most commonly used method for establishing dosing regimens is population pharmacokinetic modeling. Population pharmacokinetic modelling aims to describe the concentration-time curve of a drug in a well-defined patient population. This method can be used to explore the variation between patients (inter-individual variation) and the variation within a patient (intra-individual variation). Furthermore, patient characteristics can be tested within the model to explore whether these characteristics account for differences in pharmacokinetics among patients. To study population pharmacokinetics, the most used technique is non-linear mixed effects modeling (NONMEM).[33]

A common goal in developing a population pharmacokinetic model is to determine the optimal dosing regimen for a specific population. Pharmacodynamic data, such as the MIC and toxicity threshold, are necessary to establish the optimal antimicrobial exposure range by combining the relationship between concentrations and antimicrobial effect. With this information, the population pharmacokinetic model can be used to simulate different dosing regimens and explore their influence on antimicrobial exposure. One technique to achieve this is through Monte Carlo simulation which relies on random sampling to estimate the probability of an outcome.[34] In PK/PD modeling, this outcome often is target concentration attainment, and the Monte Carlo simulation therefore results in a probability of target attainment (PTA). This method can be used to determine which dosing regimen will result in the highest PTA.

This thesis focuses on optimizing antimicrobial treatment in special patient populations using the principles and methods outlined in the preceding paragraphs. We aimed to 1) optimize the dosing regimens in patients with altered pharmacokinetics and 2) investigate the pharmacodynamic response to antimicrobials 3) explore which patients are at risk of alternative response to antimicrobials. This was accomplished through clinical studies that described the effects of antibiotics in various special patient populations and the use of the antiviral drug remdesivir in COVID-19 patients.

Part one consists of four studies that describe the pharmacokinetics of antimicrobials and aims to optimize dosing regimens. **Chapter 2** describes the pharmacokinetics of trimethoprim-sulfamethoxazole in hospitalized patients. This chapter presents the optimization of current dosing information and dose

adjustments for patients with reduced renal function and who are undergoing continuous venovenous hemodialysis. **Chapter 3** focuses on optimizing the use of ceftriaxone in ICU patients. A comparison is made between intermittent and continuous infusion of ceftriaxone in ICU patients. **Chapter 4** focuses on the use of beta-lactam antibiotics in neonates. The study compares the PTA for intermittent, prolonged, and continuous infusion of beta-lactam antibiotics. **Chapter 5** discusses the population pharmacokinetics of remdesivir in hospitalized patients with COVID-19.

Part two of this thesis focuses on the pharmacodynamics of antimicrobials in hospitalized patients and the selection of patient populations with different responses to antimicrobial treatment. In **Chapter 6**, the study examines the impact of flucloxacillin on the occurrence of hypokalemia. The incidence and risk factors for the development of hypokalemia are described. **Chapter 7** describes the extent of a drug-drug interaction between flucloxacillin and posaconazole. **Chapter 8** describes a case of a patient with COVID-19 who experienced drug induced liver injury likely due to intravenous remdesivir therapy. We also propose a hypothesis for drug-drug interactions with P-glycoprotein inhibitors. In **Chapter 9,** we present the findings of a multi-center cohort study that examined the impact of remdesivir on rapid clinical improvement in hospitalized COVID-19 patients.

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