Quantitative pharmacological modelling for optimizing treatment of sepsis

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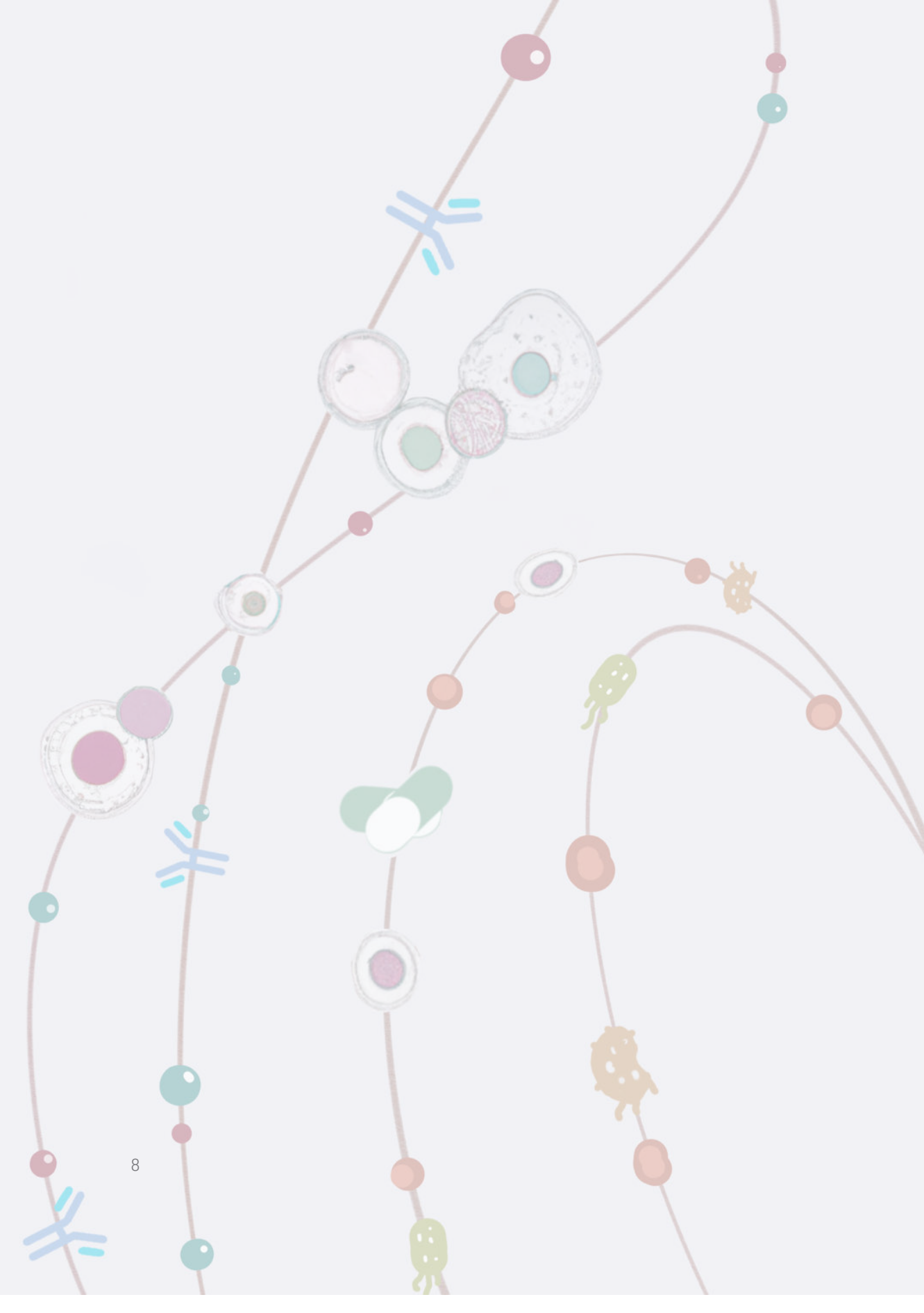
Section I

General introduction and outline



Chapter 1

General introduction and outline

1.1 Sepsis: health impact and causes

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. The most common cause of sepsis are bacterial infections[2][3][4], although sepsis can also be caused by other viral and fungal pathogens[5]. Sepsis is a complex syndrome of physiological, pathological, and biochemical abnormalities associated with a high morbidity and mortality. The health impact of sepsis is substantial, with sepsis-related deaths representing around 20% of all global deaths were reported[6]. The burden of sepsis-associated mortality is particularly high in low- and middle-income countries[7]. As such, there exists an urgent unmet medical need to further improve the treatment of sepsis, through optimization of current treatment strategies and the discovery of novel therapeutics.

1.1.1 Antimicrobial treatment of sepsis

Antimicrobial agents remain a key element of sepsis treatment. Effective and timely antimicrobial therapy of sepsis is essential to improve treatment outcomes [8]. Antibiotic treatment should ideally be started within 1 hour of diagnosis of severe sepsis or septic shock[9]. Because the causal pathogen in patients with sepsis symptoms is often unknown, empirical antibiotic treatment is typically used, which typically covers a combination of antibiotic to cover a broad range of likely pathogens is commonly used[10]. Importantly, the efficacy of antibiotics is increasingly threatened by the emergence of antimicrobial resistance (AMR)[11], whilst the discovery of novel antibiotics has not been sufficient[12].

To ensure and maintain efficacious treatment of sepsis-associated infections and prevent further emergence of AMR, it is essential to implement strategies that rationally optimize antibiotic treatment which includes careful consideration of the combinations used as well as the dosing regimens applied[13]. Establishing antibiotic dosing schedules that achieve sufficient antibiotic exposure are particularly challenging in patients with sepsis as these patients frequently show larger inter-individual variability in drug exposure. This variability may in part be explained by the effect of the inflammatory response on various physiological and biochemical processes in the body, which affect the pharmacokinetics[14]. For

example, inflammation can affect activity of hepatic drug-metabolizing enzymes [15][16] or kidney function[17], altering the rate of drug clearance. Quantitative understanding of the effect of inflammation on pharmacokinetic parameters could therefore help in the optimization of antimicrobial dosing regimens during sepsis.

1.1.2 Characterizing the inflammatory response of sepsis

Given the damaging effects of the systems inflammatory response in sepsis, targeting this response may be one important strategy to further optimize treatment of sepsis. Indeed, therapeutic modulation of the inflammatory response in sepsis has been extensively studied[18], including both non-selective strategies aimed to suppress overall inflammation (such as using corticosteroids) and targeted strategies that focus on specific mediators of the inflammatory response using novel agents [18]. Clinical trials which have aimed to modulate the host inflammatory responses in sepsis have however shown limited success[19].

Knowledge integration

One potential reason for the failure of many clinical studies in septic patients targeting the host response may be the complexity of underlying immune system interactions in sepsis[20], and the fact that targeting one single mediator may not be sufficient to alter the disease trajectory. Although the underlying mechanism of acute innate immune response in sepsis has been extensively studied, our biological understanding has not let to any paradigm shift in treatments[18]. Arguably, this may be due to the highly isolated nature in which of various cellular and biochemical processes and their interactions associated with inflammation and sepsis have been studied. Integrating knowledge of the acute inflammatory response in sepsis could be an important step towards enabling the rational design of treatment strategies.

Translational gaps

Translational gaps between preclinical and clinical models of systemic inflammation may also contribute to the challenge of developing novel therapeutics against the inflammatory response in sepsis. Numerous examples have been described where animal models for sepsis or systemic inflammation did

not translate to patients, i.e., failed to predict the (lack of) clinical efficacy[21]. Accounting for differences between animal models and humans, not only in terms of physiology but also with regards to the response to experimental models for inflammation may be essential for successful translation[22]. Specifically, enhancing our understanding of quantitative differences in the dynamics of the inflammatory response between preclinical animal models and patients may therefore help to address this translational gap. In this context, human healthy volunteer endotoxemia models are of relevance as an intermediate step between animal models and patients, and ultimately to better understand inter-species differences in the inflammatory response.

Biomarkers in sepsis

The heterogeneous character of the underlying pathophysiology of sepsis is another challenge limiting the development and optimization of treatment strategies[23]. For example, it has been found that some investigational therapies have only shown benefit in a subset of patients with a high severity of illness[19], but have minimal or harmful effects in patients that are less severely ill. Discovery of biomarkers may therefore be important to help understand and predict heterogeneity in treatment response in patients, in order to ultimately guide treatment decision making or design of clinical studies[24][25].

Biomarkers can also be used to study and predict the time course of disease progression and treatment response, i.e., to inform how to adapt and optimize treatment with antibiotics or other therapies in individual patients. However, the quantitative interpretation of biomarkers in patients, i.e., in relation to treatment outcomes represents another unsolved challenge. Directly studying such relationships facilitating the clinical interpretation of biomarker dynamics in patients is challenging due to the large underlying variation in such patients, e.g., because of differences in infection site and pathogen, comorbidities, and treatments received. More controlled studies and models to investigate the quantitative dynamics of inflammatory biomarkers are therefore needed. Human healthy volunteer endotoxemia models allow the induction of an inflammatory response in a controlled setting[26], and may be highly relevant to further support

quantitatively characterization of inflammatory biomarkers in humans, as intermediate step towards patients.

1.1.3 Quantitative pharmacological modelling approaches

To address the challenges in knowledge integration, translation, and dose optimization for treatment of sepsis, several quantitative pharmacological modeling approaches are of relevance, including population pharmacokinetic (PK) and pharmacodynamic (PD) modelling, and mechanism-based approaches such as physiologically based pharmacokinetic (PBPK) modelling, and quantitative systems pharmacology (QSP) modelling.

PK models aim to characterize the drug concentration-time profile in relation to dose, whereas PD models characterize the dynamics of drug effect in relation to drug concentrations[27]. In conjunction, PK/PD models can describe and predict the time course of drug effects associated with specific dosing schedules and can be used to subsequently optimize dosing schedules. Because clinical data is often associated with different types of variability, PK/PD models are commonly applied to quantify the variability, i.e., between individuals, associated with specific PK/PD parameters using population modeling approaches, or nonlinear mixed effect modeling[28]. Population PK models are commonly used to optimize antimicrobial treatment strategies, in order to ensure sufficient drug exposure is achieved in relation to the pathogen susceptibility, typically quantified by the pathogen minimum inhibitory concentration (MIC). Population PK-PD models are also relevant to characterize biomarker dynamics associated with inflammation [25].

PBPK modelling strategies incorporate the mechanistic basis underlying key PK parameters, e.g., clearance and volume of distribution. PBPK models commonly consist of compartments corresponding to the different organs or tissues − in contrast to empirical population PK models[29], even though minimal PBPK approaches are also commonly applied[30]. Importantly, PBPK-based approaches enable the use of drug-specific properties obtained in *in vitro* assays. Combined with often already established biological system (i.e., organism) specific parameters, predictions of expected PK profiles can be obtained[29]. Due to the

physiological basis of PBPK strategies, these models are also well suited to study the effects of disease conditions such as inflammation and sepsis on expected PK of antimicrobials or other drugs used in septic patients.

QSP models can capture relevant biological complexity of biological systems associated with disease conditions, and the effect of therapeutic modulation of the biological system or disease. These models can be developed at the molecular, cellular, and tissue level, in relation to relevant functional endpoints of translational or clinical relevance. As such QSP models could be used derive predictions related to optimal drug targets or drug treatment strategies[30][31]. The use of QSP models for complex conditions such as sepsis is thus of particular interest, even though so far, such approaches have not yet been extensively applied for this indication.

1.2 Scope and outline of thesis

In this thesis we have demonstrated how different quantitative pharmacological modeling methods can be used to contribute to drug development and treatment optimization strategies of sepsis, structured according to the following sections:

Section I: General introduction and outline

This section outlines key challenges for treatment of sepsis, highlighting the need for optimization of current antimicrobial treatments, but also the opportunities for developing treatments and biomarkers that target and describe the immune response in sepsis. Finally, we discuss how quantitative pharmacological models can help to address some of these challenges and opportunities.

Section II: Antimicrobial treatments

In Section II we discuss strategies to optimize current antimicrobial treatments for sepsis, with specific focus on the AMR in neonates, and the alteration of drug exposure in acute inflammation which is accompanied with sepsis. In **Chapter 2**, we evaluated the relationship and expected efficacy of multiple antimicrobial treatments, pathogen characteristics and treatment outcomes in neonatal sepsis in low-income and middle-income countries by using population PK/PD modelling strategies. In **Chapter 3**, we study the effects of inflammation on drug exposure

and PK during inflammation using a physiologically based modelling workflow, to explain inter-individual variability in drug exposure as commonly observed in septic patients.

Section III: Inflammation and biomarkers

In Section III we focus on the characterization of the immune response during early sepsis and acute inflammation to support drug development strategies in sepsis. In **Chapter 4**, we integrated prior biological knowledge on Toll-like receptor 4 (TLR4)-mediated inflammation in relation to key clinical endpoints using QSP modelling techniques. The model was used to evaluate the expected impact of several mono- and combined treatment strategies and their impact on clinical endpoints. In **Chapter 5**, we characterized the dynamics and inter-individual variability of multiple inflammatory biomarkers in a healthy volunteer endotoxemia challenge model using population PK/PD modelling, which may be of relevance to aid in the translation between preclinical and healthy volunteer endotoxemia studies.

Section IV: General discussion and summary

In **Chapter 6** we provide a general summary and discussion of the results described this thesis and discuss the future prospects for optimization of drug therapies for sepsis, and the utility of quantitative pharmacological modelling approaches to support this goal.

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