Quantitative pharmacological modelling for optimizing treatment of sepsis

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Section IV

General discussion and summary

Chapter 6

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General discussion, perspectives and conclusion

Sepsis is associated with a high morbidity and mortality and a strong societal impact[1]. In this context, the increasing emergence of antimicrobial resistance (AMR) complicates effective antimicrobial treatments of sepsis[2]. In addition, knowledge gaps in our understanding of the host immune response during sepsis limit the discovery of novel biomarkers and drug targets against sepsis. The challenges in optimal treatment strategies and drug development of sepsis are further introduced in **Chapter 1**. To address these challenges, in this thesis, we applied quantitative pharmacological modeling approaches to evaluate current dose regimens or pharmacokinetic variability for dose optimization of antimicrobial therapies in sepsis (**Section II**), and, to enhance understanding of the pathological dynamics of sepsis in order to identify promising biomarkers and therapeutic targets in sepsis drug development (**Section III**).

6.1 Optimization of antimicrobial treatments for sepsis

Administration of broad-spectrum antibiotics is the primary treatment of sepsis since bacterial infections cause most cases of sepsis[3]. However, the effectiveness of antibiotics will be reduced due to persistence in trends of AMR which is mainly a consequence of suboptimal use of antibiotics[2]. To this end, optimization of current treatment strategies with antibiotics is essential for enhancing treatment outcomes in sepsis and to preserve the efficacy of antibiotics on the long term[3].

Neonatal sepsis in low- and middle-income countries

In **Chapter 2**, we evaluated the efficacy and outcomes for different empirical antibiotic combination treatments of neonatal sepsis in an international multi-center study in low-income and middle-income countries (LMICs)[4][5], where 99% of global neonatal mortality occurs, with an observed all-cause mortality of 0.83 per 1000 neonate-days[4]. In this study, we evaluated the treatment outcomes in relation to (combination) antibiotic used and dosing schedules, pathogen characteristics in terms of minimum inhibitory concentration (MIC) data, alongside several other factors. By using an integrative model-based population pharmacokinetic (PK) modeling strategy we were able to generate predictions of expected treatment efficacy, which we compared with observed outcomes. Our

analysis indicates that the current first line recommended treatment of ampicillin-gentamicin[6] should be avoided for treating neonatal sepsis in LMICs due to high resistance frequency and insufficient pharmacokinetic-pharmacodynamic (PKPD) probability of target attainment (PTA).The antibiotic combination of ceftazidime-amikacin is an potential alternative treatment due to a higher PTA and lower level of resistance. In addition, mono-antibiotic treatments such as with meropenem can be considered, but may suffer from accessibility and affordability issues in LMICs.

The execution of an international multi-center observation study as described in this chapter is highly challenging due to the logistics of collecting samples and data related to patients, pathogens and treatments received. Consequently, treatment outcomes were not always obtainable due to lost to follow-up, which complicated the comparison of our simulations to the actual observed survival end point. In addition, several other covariates important for generating individualized PK predictions such as neonatal bodyweight and creatine were not available and were estimated from gestational and postnatal age. Moreover, patient-specific deviations from the site-specific dosing schedules in individual patients were not available. In our analysis we used sensitivity analyses to assess the implications of assumptions made related to covariate imputation and dosing strategies, which were found to be limited given the overall much larger variation observed in this patient population. Nonetheless, in follow-up studies it would be important to focus on the collection of deviated dosing strategies, PK blood samples, and various other clinically relevant covariates.

The applied PKPD modeling strategy allowed for integration of patient-specific covariates, pathogen-specific antibiotic susceptibility data (e.g., MIC), and dosing schedule data. This integration is of relevance to evaluate current antibiotic dose regimens. In addition, PKPD strategy can help to evaluate expected efficacy of new, untested treatments, and, to support further dose individualization strategies to enhance target achievement in individual patients[7]. For such individualized treatments, initial empiric dosing strategies can be adapted after obtaining information related to the pathogen susceptibility and/or PK to further improve outcomes and reduce the risk for AMR. However, importantly in particular in LMICs, the use of such drug treatment individualization strategies, such as based on therapeutic drug monitoring (TDM) combined with Bayesian

forecasting, is limited by available infrastructure in these countries. For LMICs, it is important to define antibiotic treatment strategies which are not too extensively relying on such additional technological infrastructure. At the same time, TDM strategies relying on dried blood spot sampling (DBS) may be an alternative approach[8] as DBS can be more easily implemented and it is already readily used in many LMICs as part of other infectious diseases such as HIV[9].

Effects on acute inflammation on pharmacokinetics

The pharmacokinetics, and ultimately the efficacy, of antibiotic treatments as well as other medications, may be affected by the acute inflammatory state associated with sepsis. Various clinical studies have reported increased yet poorly predictable inter-individual variation in patients with sepsis, which is likely associated with (variation) in the inflammatory state[10][11]. In **Chapter 3**, we studied the impact of inflammation on drug exposure for different drug types by focusing on the inflammation induced changes on clearance derived from renal glomerular filtration rate (GFR) and hepatic cytochrome P450 3A4 (CYP3A4) metabolism, using a physiologically based pharmacokinetic (PBPK) modelling approach. Our results suggest that the impact of inflammation on drug exposure varied between drug extraction ratio (ER) categories, protein binding properties, and elimination pathways (i.e., GFR or CYP3A4 activity). For drugs that are cleared through CYP3A4-mediated hepatic metabolism, drug exposure increases with the increases in severity of inflammation, whilst for predominantly renally cleared drugs, the impact is expected to be of the opposite effect. These predictions are qualitatively in line with previous reported clinical data, where the plasma levels of CYP3A4-cleared drugs like clindamycin have been observed to increase whilst the drug exposure of renal cleared drugs like gentamicin decreases in patients with inflammation[12][13]. Finally, we found that regarding the level of plasma protein binding for different drugs, the inflammation effects are reduced for drugs with larger unbound fraction especially for high ER drugs.

Our analysis demonstrated the utility of PBPK modelling workflow to quantitatively evaluate how inflammation affect drug exposure by accounting for some of the drug- and system-specific properties, in line with the application of PBPK strategies in other disease areas and patient populations[14]. Importantly,

the use of a PBPK modeling approach enabled the integration of experimental data, prior knowledge of drug- and patient-specific properties. Unlike a clinical study setting, the PBPK modeling approach allows us to specifically study the effect of specific physiological factors on drug exposure. However, our analysis considered hypothetical drugs for only two important drug elimination pathways. Ultimately, we need to understand if and how treatment strategies can be optimized in patients for specific drugs. To this end, important knowledge gaps related to the effects of inflammation on PK remain to be incorporated in the modeling framework. Specifically, expansion of the PBPK model with data on other important drug metabolizing enzymes could represent an important next step. Furthermore, expanding the model with additional effects of inflammation such as on organ blood flows or dynamic changes in plasma protein levels can be considered[15][16]. However, such data is only scarcely available and often was generated using different techniques. Generating comprehensive in vitro and in vivo datasets which systematically characterize the effects on biochemical and physiological functions related to PK are thus required. Based on such data and associated model predictions we can evaluate for which drugs dose adjustments in patients with sepsis are of relevance. Another step is further characterizing the relation between biomarkers for the extent of (acute) inflammation and PK. Selected studies have already identified relationships between biomarkers such as C-reactive protein can contribute to the prediction of clearance[10][11]. Mechanistic PBPK models may help to further elucidate this relationship.

6.2 Characterizing of inflammation and biomarkers in sepsis

Sepsis is characterized by a dysregulated host immune response which leads to organ tissue damage and/or organ failure[17]. A large number of clinical trials has aimed to therapeutically modulate the host inflammatory responses in sepsis but so far with limited success[18]. Translational gaps and integration of data between preclinical experiments and patients, and a lack of appropriate biomarkers may contribute to the negative outcomes of these historical clinical studies. In this context, quantitative pharmacological modeling approaches may help to address some of the current translational gaps.

Mediators and cellular interactions associated with the acute inflammatory response in sepsis haven been extensively studied in experiments, leading to a detailed qualitative understanding of various key mechanisms. There has however been a lack of systematic integration of this knowledge, which limits the successful translation of treatment strategies to patients. In **Chapter 4**, we applied a systems modeling approach based on Boolean networks[19] to integrate and synthesize prior data and knowledge related to key regulatory relationships of immune components associated with early sepsis pathogenesis, with a focus on Toll-like receptor 4 (TLR4)-mediated pathway. Our analysis enabled identification of several potential therapeutic targets, predicted to modulate key clinically relevant endpoints associated with sepsis, such as a combination strategy of simultaneously blocking interferon γ and interleukin 10. Even though the developed model includes key biological processes previously identified as important inflammatory mechanisms associated with TLR4-activation in early sepsis, further expansion of the model is pertinent, i.e., to expand the model at the level of pathways and/or gene expression[20], to enable studies which investigate inter-patient heterogeneity in sepsis. In our view, the use of systems-based modeling approaches such as described in this chapter is of great value to guide translational drug development strategies targeting the host response in sepsis.

From a methodological perspective, our analysis demonstrates how quantitative systems pharmacology (QSP)-type modeling strategies such as Boolean networks can be used to study complex biological interactions such as in sepsis. Boolean network models are constructed based on logic relationships and do not require full kinetic information which is required for more commonly used ordinary differential equation-based models[21]. This enables the use of a much wider range of qualitative literature data typically reported in experiments. In recent years, Boolean models have also been increasingly used in the field of quantitative pharmacology also in other therapeutic areas[22][23], highlighting their utility. Still, limitations remain, in particular because of the challenges in incorporating different time scales and the dichotomic nature of predicted outcomes.

Healthy volunteer endotoxemia models for studying inflammation

Studies of the inflammatory response in patients with sepsis is highly complex due the large variation induced by various processes and the differences in the disease state of patients. Controlled models in humans to study inflammatory responses are thus of great relevance to guide drug development in sepsis and to further characterize inflammatory biomarkers which may inform treatment strategies. In **Chapter 5** we quantitatively characterized the dynamics and inter-individual variability of multiple inflammatory biomarkers, including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), and C-reactive protein (CRP), in healthy volunteer endotoxemia model. In this challenge model, lipopolysaccharide (LPS), an immune system triggering component of the bacterial cell wall of Gram-negative bacteria, is administered to healthy volunteers, inducing an inflammatory response. So far, no quantitative models in healthy volunteers have been described. In our model-based analysis we characterized the relationship between LPS exposure and the dynamics of TNF-α, IL-6 and IL-8 production. We moreover identified a relationship between IL-6 and CRP production rate, indicating the potential relevance of IL-6 as biomarker to predict the disease severity and contribute to biomarker-guided strategies for treatment optimization, addressing some of the limitations of CRP with a much delayed response[24].

The current model was based on only the very early, acute, response to a single dose of LPS in healthy volunteers. As such, lessons learned regarding the kinetics of inflammatory biomarkers cannot be directly scaled to patients. For example, tolerance in the response against LPS can develop[25], which may be of relevance to further bridge understanding towards septic patients[26]. In this context, human LPS studies which study repeated or continued administration of LPS could help to quantitatively characterize the biomarker response on an extended time scale. In addition, exploring wider dose ranges of LPS can help to further unravel production, degradation and tolerance phases of acute inflammation associated with LPS induced TLR4 activation.

6.3 Future perspectives

Rational optimization and individualization of antibiotic treatment strategies is essential to reduce treatment failure in sepsis and to help reduce the risk for AMR development. Currently, the adjustment of antibiotic dose regimens in sepsis patients is mainly based on TDM strategies[27] and antibiotic susceptibility testing in case pathogens are identified. Although these relevant and important strategies fail to consider the host immune response into account. As discussed also in this thesis, the interpretation of biomarkers for the immune- or inflammatory response in sepsis is complex. We have demonstrated how quantitative modeling strategies can help bridge current knowledge gaps. Ultimately quantitative modeling approaches which consider patient-specific and dynamic measurement on the drug PK, pathogen, and host immune response could play an important role to uncover the relationships between drug exposure, disease (pathogen) load, and clinical outcomes, and could ultimately support the design of optimized treatment strategies. In routine patient care, often, only incomplete data is available, yet clinical decisions regarding treatment must be made. This was also observed in our analysis in **Chapter 2** in neonatal sepsis patients. In this chapter, we demonstrated how quantitative models based on previously established data could help address these situations of incomplete knowledge. Similarly, we expect that further development of quantitative *mechanism-based* models can provide guidance to support future clinical decision making in the clinical reality of incomplete knowledge.

Therapeutic strategies modulating the host inflammatory response could represent another strategy to enhance survival of patients with sepsis, even though many previous strategies have not been successful[28]. Based on the work described in this thesis we expect that systematic model-based integration of disease mechanisms is of great importance to address the current challenges in sepsis drug development. To this end, a practical challenge lies in the scattered availability of such mechanistic data, often requiring manual extraction from publications, thus limiting the efficient development of quantitative models. This illustrates the need for further implementation of FAIR (findable, accessible, interoperable, and reusable) data practices in biomedical research[29]. A second challenge is the need for predictive translational models in sepsis. The developed

models for human LPS challenges may offer a starting point to explore possibilities for scaling of model predictions between preclinical animal LPS studies[30][31] and humans, thereby overcoming the current translational challenges in the predictive value preclinical endotoxemia models[32].

The use of quantitative modeling approaches to inform drug development and for treatment optimization in patients has rapidly developed[33]. In this thesis, we applied a variety of modelling approaches to address questions around treatment strategies for sepsis, including empirical approaches such as population PK/PD modelling, and mechanism-based approaches like PBPK and QSP modelling. Differences in standard related to software technologies and modeling languages tools currently prohibit efficient integration of these methods, which could ultimately help to further enhance the predictive value of these modeling approaches. Even though initial efforts in this area have been made[34], further work remains to be done. Finally, developments in machine learning (ML) and artificial intelligence (AI) approaches are rapidly expanding, also in the field of sepsis[35]. Strategies which further enable the integration of ML/AI approaches in quantitative pharmacological models, in particular for sepsis, are of interest.

6.4 Conclusion

Optimization of current treatment strategies and the discovery of novel therapeutics of sepsis are crucial importance to improve the clinical outcome in patients with sepsis, which is a complex life-threatening syndrome and a heavy worldwide health burden. In this thesis, we applied different quantitative pharmacological modeling methods to contribute to improve the treatment of sepsis, including investigating potential alternatives for current antibiotic treatments with high rate of resistance, finding out the alteration of drug exposure in inflammation accompanied with sepsis, integrating the inflammatory relationships underlying sepsis to potential therapeutic targets and biomarkers, and charactering the biomarker dynamics in acute inflammation. This work will enable and inform the optimization of drug therapies of sepsis.

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