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Improving management of infectious diseases at the emergency department: from risk prediction to treatment strategies

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Chapter 1

General introduction

GENERAL INTRODUCTION

Infectious diseases remain a leading cause of morbidity, mortality and associated healthcare utilization.¹ This burden is increasing, due to various factors such as population growth, aging populations, climate change and increasing antimicrobial resistance.^{2,3} Emergency departments (EDs) play an essential role in the recognition and management of infections. Patients present with a broad spectrum of symptoms, ranging from a simple cough caused by a self-limiting respiratory tract infection, to life-threatening septic shock requiring rapid intensive care treatment.⁴ Unfortunately, although in some patients symptoms are evident, many symptoms are relatively unspecific and recognizing those with a high risk of a severe disease course is challenging.

Three important steps in the management of infectious diseases are ordering the right diagnostic tests, assessing the risk of complications and deciding on appropriate treatment. By ordering the right tests, one aims to make an accurate diagnosis and prognosis, which is essential to decide on targeted treatment. However, there are downsides to exposing more patients than needed to testing and treatment. For instance, false-positive blood cultures are associated with increased length of stay, increased exposure to broad-spectrum antibiotics, increased costs and even mortality.⁵⁻⁷ Risk stratification can help in deciding on site of care and intensity of monitoring or treatment. The subsequent treatment strategy is aimed at the presumed causative pathogen, ideally with the most precise effect possible. Overtreatment with antibiotics can lead to unnecessary hospital admissions, therapy-related adverse events, and antimicrobial resistance.⁸ Therefore, clinical decision-making often involves balancing the risks of doing too little against the risks of doing too much.

Finding this balance can improve individual patient outcomes, but can also play a role in addressing broader healthcare challenges. Many countries face increasing pressure on their healthcare systems, driven by rising demand and shortages of resources such as personnel and materials.^{9,10} Identifying those patients who actually benefit from diagnostic testing and more intense treatment strategies may help cope with these problems by reducing workload and reducing hospital admissions and associated costs. Furthermore, overuse of diagnostic tests and exposure to unnecessary antibiotics drive antimicrobial resistance.^{3,11,12} Antimicrobial resistance is a serious health threat, and was associated with 36% of global infection-related deaths in 2019.¹² This number is expected to increase substantially by 2050 if left unaddressed.¹² With this in mind, antimicrobial stewardship programs have been widely implemented over the last decades to optimize antibiotic use.⁸ More recently, the contribution of false-positive tests to antimicrobial resistance has initiated a call

for 'diagnostic stewardship'. This initiative aims to order the right test, at the right moment for the right patient.¹¹

OVERALL AIM

This motivates the aim of this thesis: to identify and evaluate strategies to optimize the management of infectious diseases in adult ED patients, with the objective of ensuring that diagnostic testing and treatment are provided to patients who require them, while minimizing unnecessary interventions. We consider three different aspects relevant for management of infections: diagnostics, risk stratification and treatment. This thesis focuses on two common and clinically important infectious diseases: bacteremia and community-acquired pneumonia.



Figure 1. Outline of this thesis with overall and specific aims.

OUTLINE OF THESIS AND SPECIFIC AIMS

The first part of this thesis focuses on improving the *diagnostic* process of bacteremia, aiming to safely reduce blood cultures in patients with suspected community-acquired bacteremia. This could improve patient outcomes by preventing negative consequences of false-positive blood cultures, while decreasing costs and resources utilization.

Chapter 2 presents a systematic review and meta-analysis of the diagnostic accuracy of the biomarker procalcitonin (PCT) for bacteremia.¹³ Procalcitonin is a biomarker often used to differentiate between a viral versus a bacterial infection.¹³ Under normal conditions, PCT is produced in negligible amounts by thyroid C-cells. In case of a bacterial infection, levels rise rapidly in response to pro-inflammatory

cytokines and bacterial toxins. Importantly, viral infections suppress PCT production through interferon- γ .¹⁴ This makes it a relatively specific marker for bacterial infections, in contrast to commonly used biomarkers such as C-reactive protein or white blood cell count. We investigate whether low values of PCT can help rule out bacteremia, and hence reduce unnecessary blood cultures.

Chapter 3 and **Chapter 4** show the development and validation of a diagnostic prediction model estimating the risk of bacteremia.^{15,16} When trying to identify which patients benefit from testing or treatment, one approach is to use predictive modeling. Prediction models are divided in *diagnostic* and *prognostic* models (**Table 1**).¹⁷ Diagnostic models aim to estimate the probability that an individual patient currently has a specific condition. This information can be used to support decisions about further testing or treatment. For the context of infectious diseases, the Shapiro score is an example of a diagnostic model.¹⁸ This model estimates whether the patient has a high or low risk of bacteremia, before blood culture results are available. However, this score has not found its way to clinical practice. We hypothesize that this complex model is too labor-intensive for busy EDs, while simpler models lack diagnostic accuracy.¹⁹ Therefore, we aimed to develop and validate an easy-to-use model for bacteremia with high diagnostic accuracy. **Chapter 3** describes the development and validation of multiple prediction models that combine PCT with or without C-reactive protein and clinical characteristics.¹⁴ Based on lessons learned, we set out to update the most promising models and perform another external validation in Ann Arbor, United States.¹⁵ This is described in **Chapter 4**.

The second part of this thesis focuses on evaluation of clinical outcomes in a broad emergency department population with suspected infection, while exploring and evaluating *prognostic* models to identify patients at risk for a severe disease. This aims to improve risk-stratification to guide management strategies.

In **Chapter 5** we try to improve our understanding about misdiagnosis of infection, and whether this impacts clinical outcomes.²⁰ In addition, a prognostic prediction model for misdiagnosis was developed. As mentioned, prediction models are divided in *diagnostic* and *prognostic* models. Prognostic models aim to estimate the risk of a future clinical outcome, such as ICU admission or mortality (**Table 1**).¹⁷ This risk stratification can help to guide management strategies. **Chapter 6** and **Chapter 7** focus on patients with respiratory tract infections. First, **Chapter 6** answers the question whether the Pneumonia Severity Index (PSI) or the CURB-65 score, two of the most used prognostic prediction models for community-acquired pneumonia (CAP), are associated with better clinical outcomes in the Dutch population.²¹⁻²³ These models estimate the risk of 30-day mortality in CAP patients. The Dutch national guideline for CAP advises to use one of these models to decide on treatment

strategy.²⁴ Second, in **Chapter 7** we explore clinical outcomes and prognostic factors for a severe disease course in patients with COVID-19.²⁵

Table 1. Differences between diagnostic and prognostic prediction models.

	Diagnostic model	Prognostic model
Goal	Estimate current risk of having a specific disease	Estimate future risk of a clinical outcome
Example in this thesis	Shapiro score ¹⁸	PSI score ²² , CURB-65 ²³
Application	Support whether further testing or immediate treatment is needed	Guide decisions regarding level of care and treatment intensity

Finally, *the third part* of this thesis takes a different approach to improving the management of infectious diseases. Instead of identifying individual patients that benefit from specific interventions, the aim is to explore whether antibiotic *treatment* can be safely simplified from intravenous to oral treatment. This could prevent unnecessary exposure to broad-spectrum antibiotics and potentially reduce hospital admissions.

In **Chapter 8** we evaluate clinical outcomes for patients with moderate-to-severe CAP for those treated with oral antibiotics versus those treated intravenously.²⁶

Chapter 9 is an opinion paper written for Dutch clinicians, explaining the context and rationale, advocating for a more prominent role of oral antibiotic therapy in a broader range of infectious diseases.²⁷ Finally, this thesis concludes with a general discussion, reflecting on the main findings, challenges, implications for clinical practice and directions for future research.

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