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

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Chapter 10

General discussion

GENERAL DISCUSSION

The overall aim of this thesis was to identify and evaluate strategies to improve the management of infectious diseases in adult ED patients. Diagnostic testing and treatment should be provided to patients who require them, while minimizing unnecessary interventions. This chapter first states the key findings of this thesis, followed by a more detailed discussion of all chapters, including future directions and broader considerations. This is done according to the three main parts: diagnostics, risk stratification and treatment.

KEY FINDINGS

- We developed multiple prediction models to improve the diagnostic process of bacteremia, aiming to safely reduce the number of blood cultures in patients suspected of community-acquired bacteremia at the ED. Our most promising model was able to save around 30% of blood cultures, while missing 1-5% of true bacteremia cases. We showed that especially procalcitonin was strongly predictive for true bacteremia across multiple large international cohorts.
- The second part of this thesis focused on risk prediction. First, we showed that misdiagnosis occurs in 1 in 9 patients suspected of infection at the ED and is associated with more exposure to broad-spectrum antibiotics but not with other severe outcomes. We identified risk factors for misdiagnosis, of which a positive urinary dip stick without any symptoms relatable to a urinary tract infection was most remarkable. Second, we compared the two most commonly used prediction models to guide treatment decisions for community-acquired pneumonia and showed that the use of the CURB-65 was associated with reduced mortality compared to the PSI score.
- Finally, in the third part of this thesis we compared oral versus intravenous antibiotics in patients with moderate-to-severe community-acquired pneumonia (CAP) and found no differences in outcomes for both treatment strategies. This finding forms a much needed basis for conducting a randomized controlled trial on oral versus intravenous treatment of CAP.

PART I DIAGNOSTICS

In our search for improvement of diagnostics in infectious diseases we focused on the diagnostic process of bacteremia. Bacteremia, defined as the presence of bacteria in the bloodstream, is associated with substantial morbidity and mortality.[1] The current diagnostic process will typically begin in the emergency department (ED), where patients present with signs of infection, ranging from non-specific

symptoms such as fever, to severe hypotension indicative of sepsis. Clinicians assess the risk of bacteremia and, if warranted, obtain blood cultures.[2]

These blood cultures consist of two bottles that are filled with patient blood via venipuncture. These cultures are incubated in the microbiology laboratory and continuously monitored for bacterial growth. When bacteremia is present, the first signals of positivity generally appear within 24 hours.[3] Subsequent pathogen identification and susceptibility testing require additional time, resulting in a diagnostic delay of several days before final results become available.

There are multiple aspects of this process that need improvement: To minimize the risk of missing bacteremia, clinicians often obtain blood cultures liberally, yielding a low diagnostic return: only 4–11% of cultures are positive.[4-6] Meanwhile, blood cultures are costly: ranging from 96 to 423 USD per set.[7] Moreover, when a blood culture is not collected properly, skin commensals can be introduced into the culture bottles, falsely leading to a positive blood culture result: contamination. Of all blood cultures taken at the ED, 2-8% are contaminated.[4-9] It can be hard to determine whether a positive blood culture results reflects true bacteremia or contamination. Consequently, contaminated blood cultures are associated with increased length of stay, more exposure to antibiotics, higher costs, and even increased mortality.[7-9] It would therefore be of great value to find a way to identify patients with a low risk of bacteremia, in whom we can safely withhold blood cultures.

In **Chapter 2** we showed that procalcitonin (PCT) can be useful to exclude community-acquired bacteremia (CAB).[10] PCT is a biomarker that has received much interest because, unlike commonly used inflammatory markers such as C-reactive protein (CRP), it more specifically reflects bacterial rather than viral infections. This is because PCT levels rise in response to pro-inflammatory cytokines and bacterial toxins, while it is suppressed by higher levels of interferon-γ due to viral infections.[11]

We performed a systematic review and meta-analysis and found that PCT at a low threshold (0.10 ng/mL) has high sensitivity for CAB. This implies that low values can be used to rule out bacteremia, and therefore, can support withholding blood cultures. Notably, especially the studies with low risk of bias showed high sensitivity (97%, 95% CI: 92-99%). However, we observed considerable heterogeneity in study methodology: 15 of the 40 included studies either lacked a clear definition of blood culture contamination or excluded such cultures from analysis altogether. Studies applying a clear definition demonstrated higher sensitivity, which is biologically plausible since contaminated cultures do not reflect true infection and therefore typically do not induce elevated PCT levels. If these cultures are analyzed as true positives, this would falsely lead to a reduced sensitivity. This finding underlines the need for consensus on an internationally accepted definition of contaminated blood

cultures. A Delphi process could be used to establish such consensus, building on existing criteria such as those proposed by the College of American Pathologists (CAP), the Clinical and Laboratory Standards Institute (CLSI), or the approach we developed in Chapter 4.[12,13]

After two previous meta-analysis regarding diagnostic accuracy, this meta-analysis added relevant knowledge about diagnostic properties of PCT at lower thresholds.[14,15] While some might find the associated sensitivity acceptable for use in clinical practice, others might not, as it is known that a considerable number of clinicians require a sensitivity for bacteremia of 99-100%.[16] We conclude that additional studies on the diagnostic accuracy of PCT for CAB are unlikely to yield further insights. Future research should instead focus on combining PCT with clinical parameters to evaluate whether this would further improve diagnostic accuracy, and hence, clinical applicability.

This question was the starting point for **Chapter 3.** We developed multiple prediction models using combinations of PCT, the more commonly used C-reactive protein (CRP) and clinical characteristics to identify patients at low risk for CAB.[17] In the development of these models, we especially focused on parameters that would be easy to implement in electronic health records. The models were derived off a Dutch dataset of the Haga Teaching Hospital including 2111 patients, and validated in a Spanish dataset of 4436 patients. The most promising model was able to save 29% of all blood cultures while only missing 1% of bacteremic episodes. However, calibration (is the estimated risk the same as the observed risk?), was suboptimal for all models that contained PCT. Therefore, we updated the models based on both the Dutch and Spanish dataset and performed external validation in a new setting.[18] **Chapter 4** describes this validation in a large US hospital in Ann Arbor, Michigan. Using retrospectively collected data from more than 12.000 patients, we showed that the updated models had the potential to reduce blood culture testing by 30% of blood cultures, missing 5% of true bacteremia episodes, with substantially improved calibration **(Figure 1)**.

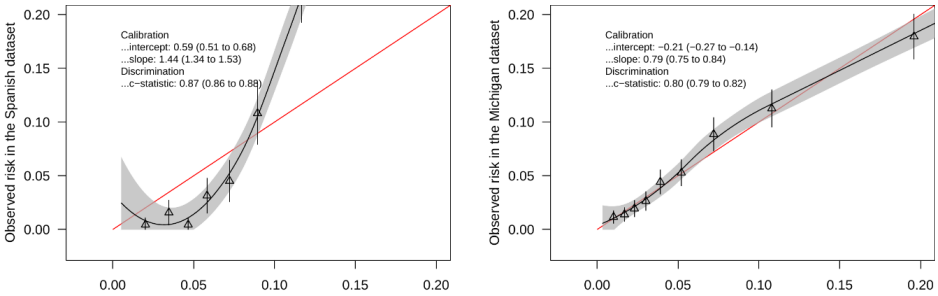

Figure 1. Calibration plots for the basic model with procalcitonin (PCT) in the Spanish data, and for the updated model in Michigan. The X-axis represents the predicted risks, the Y-axis shows the observed risks. Ideally, the calibration curve follows the red line indicating that predicted risks are in line with observed risks. We observe substantially improved calibration of the updated model.

There were multiple challenges in the development and validation of these models. First, we observed geographical variation in model performance, especially due to variation in the relation between procalcitonin and bacteremia risk. Multiple factors may have contributed to this variability.[19] When performing an external validation, it can be challenging to acquire high quality data. Local definitions might differ from the original dataset, and retrospectively collected data might have limited information. For instance, deciding which blood cultures in the Michigan dataset were contaminated was challenging as this was not automatically retrievable. We worked together with clinicians from multiple disciplines to create a step-wise approach to classify blood cultures, but as we specifically wanted to prevent misclassification of true bacteremia as contamination we erred on the side of caution in case of doubt. This might have led to an overestimation of the number of true positive blood cultures. Furthermore, differences between healthcare systems can result in differences in case-mix, and differences in patient selection by using different criteria for PCT or blood culture testing might result in different risks of bacteremia.[19] We observed a mean risk for bacteremia of 20% in the Spanish data, opposed to 9% in the Michigan data. However, we cannot exclude that there is a true difference in the relation between PCT in CAB in the Spanish population compared to the Dutch and American population. Further validation in more settings could increase our understanding of this geographical variation, although we believe this to be not essential before moving forward towards the next step.

When developing a clinical prediction model typically involved four steps: Development, validation, impact assessment and implementation (**Figure 2**).[20] Yet, most prediction models never make it to the implementation phase.[21] We addressed the first two steps in chapters 3 and 4, but an impact study is essential for successful implementation.

An impact study that prospectively evaluates clinical outcomes when using the model, could answer several relevant questions. First: how should such a model be integrated in clinical practice? Should we provide hard-stops of blood culture orders based on a low risk prediction or should it be possible for the clinician to overrule the model? If overruling the model would be possible, how would that impact the model's potential to reduce blood cultures? Second, what would happen if the models are applied to patients who currently would not be tested for bacteremia, and how can such unintended use be prevented? Finally, we expect that the risk prediction will be available for the majority of patients at the moment that antibiotic therapy is started. However, some will receive antibiotic therapy sooner, warranting a different approach. In those patients, cultures could be drawn and the decision to move forward with analysis could be made based on the final risk prediction.

Additionally, a survey among clinicians could facilitate implementation by identifying barriers and clarifying the requirements for adopting a bacteremia risk model in practice. It is especially important to understand clinicians' perspectives on the acceptable risk threshold for withholding blood cultures. While the model provides an estimated bacteremia risk for each individual patient, the decision regarding what risk is considered sufficiently low to withhold blood cultures ultimately lies with the user. We used a 5% risk threshold to report our findings, but some might only accept a 1% risk. This would miss less true bacteremia episodes, but would automatically also reduce the number of saved blood cultures.

There will be multiple challenges regarding the implementation of our bacteremia risk models. Many clinicians may be unaware of the high costs and negative consequences of contaminated blood cultures, which could limit willingness to change current practice. In addition, PCT is a biomarker that is not widely available, and costs of procalcitonin and blood cultures vary substantially around the world.[7,22,23] This complicates evaluation of cost-effectiveness. As a result, implementation may initially only be feasible in hospitals that already use PCT for patients with suspected CAB. Furthermore, in some hospitals, PCT results require multiple hours to become available, also limiting applicability. In such settings, other approaches to reduce blood cultures such as indication-based algorithms might be more feasible.[24]

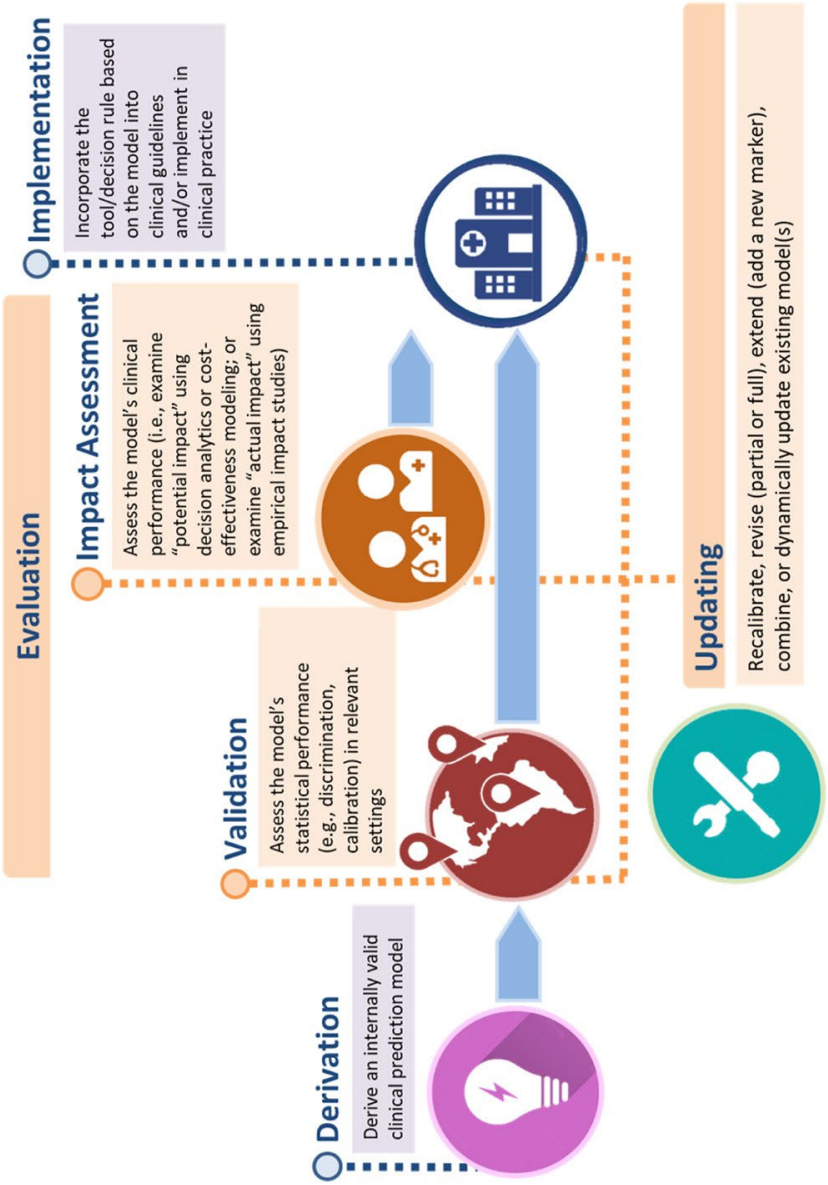

Figure 2: Steps in the development and implementation of clinical prediction models. Figure adapted from Binuya et al, 2022.[20]

In summary, we have shown that depending on the acceptable risk threshold for bacteremia, PCT alone can help to reduce blood cultures use at the ED. Moreover, our models that combine PCT with clinical characteristics offer further improved diagnostic accuracy and are promising to optimize the diagnostic process of bacteremia.

Part II Risk stratification

Pressure on healthcare systems is increasing due to rising costs, shortages in healthcare staff, and, in some settings, limited resources.[25,26] Identifying patients at high risk for severe outcomes can help prioritize care for those who need it most. Conversely, recognizing patients at low risk can prevent unnecessary exposure to treatments with potential harms. For example, while ICU admission can be life-saving, it also carries risks such as hospital-acquired infections or delirium.

This part of the thesis focused on risk stratification for poor outcomes in patients presenting to the ED with suspected infection. We approached this by identifying risk factors for adverse outcomes and by developing prognostic prediction models for a broad population of patients with suspected infection.

Because misdiagnosis in general patient populations is associated with worse outcomes, we hypothesized this might also apply to infectious diseases, particularly since treatment decisions are often guided by the most likely causal pathogens, which differ depending on the suspected site of infection.[27-29] Before our study, no data were available on misdiagnosis rates in this setting. In **Chapter 5**, we showed that one in nine ED patients with suspected infection was misdiagnosed.[30] Surprisingly, we found no association with severe outcomes such as longer length of stay, ICU admission, or mortality. A possible explanation is that these patients were more frequently treated with broad-spectrum antibiotics, possibly reflecting diagnostic uncertainty among clinicians. Nevertheless, there may be negative consequences of misdiagnosis that we could not capture in this study. A prognostic model did identify patient characteristics associated with misdiagnosis, but as the performance was only fair it will likely not directly benefit clinicians. Risk factors included older age, dementia and a positive urine dipstick without signs of a urogenital tract infection. Especially this last risk factor could be an interesting starting point for future research. Reducing uncertainty regarding urinary tract infection diagnosis might prevent unnecessary exposure to broad-spectrum antibiotics.

For community-acquired pneumonia, prognostic models are already widely used. The Dutch national guideline recommends either the PSI score or the CURB-65 for risk stratification to guide treatment and site-of-care decisions.[31-33] Both models estimate 30-day mortality risk and classify patients into different risk groups. Most

studies suggest similar prognostic performance, although some report that the PSI score is better at identifying low-risk patients.[34-37] This might explain why some clinicians prefer the PSI, while others favor the simpler and more user-friendly CURB-65.

In **Chapter 6**, we collaborated with the National Healthcare Institute to create a nationwide cohort of CAP patients using claims data.[38] We compared outcomes between hospitals using CURB-65 and those using the PSI score. Surprisingly, we found that in 50.984 patients, there was a lower mortality in 'CURB-65' hospitals. This difference might be explained because the CURB-65 is known to classify a larger proportion of patients as having 'severe pneumonia'.[37,39,40] According to the national guideline, these patients should receive broad-spectrum antibiotics such as second- or third-generation cephalosporins, whereas less severe categories are treated with narrower-spectrum regimens.[31] Therefore, some patients not classified as 'severe' by the PSI score might have been undertreated. However, given the retrospective design and limitations in claims data, residual confounding cannot be ruled out. Therefore, these findings are not sufficient to change guidelines. However, they should warrant an RCT comparing clinical outcomes according to use of CURB-65 versus the PSI score.

Finally, **Chapter 7** describes clinical and microbiological outcomes for patients with COVID-19 at the ED.[41] When the COVID-19 pandemic started, hospitals were overwhelmed by the number of patients. We aimed to identify risk factors for severe disease to help allocate scarce resources. Furthermore, since little was known about the disease course, we evaluated bacterial coinfections. We found these to be rare (1.4%) and concluded that blood cultures have limited value in this population. Both procalcitonin and the PSI score, however, proved useful for risk stratification in patients with COVID-19. While these findings are less relevant today due to changes in the patient population, driven by factors such as immunization and genetic evolution of the virus itself, they illustrate the importance of rapid data collection.[42] Because of the ongoing PredictED study during the pandemic, we were able to generate and share clinically relevant findings quickly, enabling a more informed response to a rapidly changing situation.

PART III TREATMENT

After diagnostics and risk stratification, treatment forms the next crucial step in infection management. In addition to selecting the appropriate medication to start, it is also important to decide on the route of administration. Most antibiotics will be administered either orally or intravenously (IV). In this part of the thesis, we explored the potential for oral antibiotic therapy in situations where IV antibiotics

are traditionally used. Oral treatment could reduce hospital admissions and prevent complications associated with IV administration, such as phlebitis and, more rarely, secondary infections like bacteremia or even endocarditis.

Community-acquired pneumonia (CAP) is one of the most common infectious diseases at the ED.[43-45-39] The Dutch guideline advises treatment with IV amoxicillin in moderate-to-severe pneumonia as classified by the PSI score or the CURB-65.[31-33] However, based on pharmacokinetic profiles, the local guideline of the Haga Teaching hospital differed from the national guideline with regard to this specific patient category. This local guideline advised oral amoxicillin if deemed appropriate by the treating clinician. This difference created a unique opportunity to compare clinical outcomes between oral and IV treatment in moderate-to-severe CAP, as described in **Chapter 7**.[46]

We found no differences in clinical outcomes between the groups, except for a 2.5-day longer length of stay in the IV group, explained by higher admission rates. This study is among the first to evaluate immediate oral therapy in moderate-to-severe CAP. Given the high prevalence of CAP, changing first-line therapy from IV to oral antibiotics could significantly impact healthcare utilization and costs. Our findings provide a much-needed basis to continue with a randomized controlled trial studying clinical outcomes for oral versus IV treatment in moderate-to-severe CAP. If an RCT would confirm our findings, we believe this would be sufficient to change existing guidelines.

Interestingly, while current guidelines favor IV antibiotics, the supporting evidence is limited.[31,47,48] Meanwhile, high levels of evidence are required in order to change guidelines. In the opinion article in **Chapter 8** we discussed why clinicians have come to believe that intravenous therapy is superior to oral therapy.[49] Furthermore, we explain why we believe that in deciding on route of administration, the only question should be whether an appropriate oral antibiotic can achieve adequate therapeutic concentrations at the site of infection. We describe different relevant aspects when considering oral treatment of infectious diseases. The paper outlines relevant considerations for oral antibiotic use and challenges existing assumptions, hopefully encouraging further research into oral treatment strategies for infectious diseases.

Main findings and recommendations	
Part 1: Diagnostics	
• Our bacteremia prediction model was able to save around 30% of blood cultures, while missing 1-5% of true bacteremia cases. Especially procalcitonin was highly predictive of bacteremia.	• A survey study could increase our understanding of how such models should be implemented. Impact studies are needed to facilitate successful implementation in clinical practice. • Further validation may serve as continuous monitoring of performance with potential for dynamic and local updating
Part 2: Risk stratification	
• 1 in 9 patients suspected of infection at the ED was misdiagnosed, without associated severe outcomes except for increased exposure to broad-spectrum antibiotics. Multiple risk factors for misdiagnosis were identified, such as a positive urinary dip stick without urinary symptoms	• Studies aimed at reducing uncertainty regarding urinary tract infection diagnosis might prevent unnecessary exposure to broad-spectrum antibiotics.
• In a nationwide study, the use of the CURB-65 score for treatment decisions in patients with CAP was associated with reduced mortality compared to the PSI score.	• Clinical outcomes according to the use of CURB-65 versus the PSI score should be studied in a randomized controlled trial.
Part 3: Treatment	
• We found no differences in clinical outcomes between patients with moderate-to-severe CAP treated orally or intravenously for based on the PSI score and clinical judgment.	• An RCT is warranted to compare oral versus intravenous treatment in moderate-to-severe CAP. Confirmation would justify guideline change.

Table 1. Summary of main findings and recommendations in this thesis. CAP = community-acquired pneumonia, PSI = pneumonia severity index, RCT = randomized controlled trial.

BROADER CONSIDERATIONS

Prediction models and artificial intelligence

In recent years, prediction models based on machine learning have become increasingly common. This raises the question whether machine learning approaches would provide advantages over the more 'traditional' regression models developed and evaluated in this thesis. When deciding on a modelling approach we emphasized future applicability, aiming for broadly applicable and explainable models that

would be easy to implement. It is known that machine learning has the potential to capture complex, non-linear relationships within large datasets, which may improve predictive performance compared to regression models. However, previous reviews suggest that when applied to relatively simple clinical data, the added value in predictive performance is often limited.[50,51] Indeed, a machine learning bacteremia model showed similar predictive performance to our models.[52] Furthermore, an important downside to machine learning-based models is that many function as 'black boxes', making it difficult to understand how a given prediction was generated. This lack of explainability might limit trust and willingness to use such models.[53] To address this, transparency of what predictors influence predictions is a minimum requirement. Explainable AI (XAI) has gained attention as a solution, with techniques like Shapley values increasingly being reported.[54]. Finally, we hypothesize that models that are based on predictors with a clear biological rationale for their association with the outcome are likely to be more stable across a wider range of settings.[19] Given these considerations, and our aim to develop robust and broadly applicable models based on non-complex clinical data, we chose to focus on a regression-based approach.

Aspect	Regression models	Machine learning models
Typical data	Simple, tabular data	Large datasets, possibly high-dimensional (images, free text)
Selection of predictors	Theory-based	Data-driven
Advantages	Transparent, easy to validate and apply in new settings, good explainability	Few assumptions needed, can capture complex, non-linear relationships and interactions
Disadvantages	Might underperform when true relations are complex or non-linear	Risk of overfitting, poor explainability due to 'black box' effect

Table 2. Comparison between more traditional regression models and machine learning models.

How to move forward to successful implementation?

Unlike much of contemporary medical research, this thesis does not focus on introducing additional interventions but rather asks the opposite question: what can safely be omitted? In the following section, several considerations that we believe are important for the successful implementation of this type of research are discussed.

First, it would be preferable if decisions regarding the use of prediction models to withhold tests or decide on treatment strategies, were not placed solely on individual clinicians. The potential negative consequences of such decisions are felt primarily

by the patient and their treating physician. For instance, consider a patient who is ultimately diagnosed with endocarditis after no blood cultures were obtained because of a low predicted risk of bacteremia. While our findings suggest that such cases would be rare, it is understandable that the physician involved would subsequently be hesitant to follow the model's recommendations in the future. Moreover, the benefits of reducing diagnostic testing such as lower costs and decreased resource utilization are primarily realized at the population level, leaving clinicians with little incentive to change their practice. Placing these decisions at a higher level, for instance through national expert groups such as the Dutch Working Party on Antibiotic Policy (SWAB), could help reduce such unwanted effects.

A further complication is that reasoning about risk itself is challenging. As discussed earlier, clinicians often strive to detect every single case of bacteremia, and the willingness to accept even a small risk of missing cases is low.[16] Yet this creates an illusion of certainty. For example, studies have shown that bacteremia occurs in around 10% of patients with pyelonephritis treated as outpatients, without being associated with worse outcomes.[55] Even under current practice, therefore, some cases inevitably remain undetected. Therefore, we have to acknowledge that the clinical importance of identifying bacteremia varies by condition and patient context. In this regard, we could learn from primary care, where managing diagnostic uncertainty and accepting a certain degree of risk have long been more explicitly integrated in clinical decision-making.[56]

Ultimately, a sense of collective responsibility is essential when considering the acceptance of potential increased risk, whether this is due to withholding diagnostic tests or by treating more patients with oral antibiotics. We should engage in broader discussions about what constitutes an acceptable level of risk for individual patients. Professional organizations such as the SWAB and the Dutch Internist Society could play a pivotal role by starting this dialogue and translating it into updated clinical guidelines.

CONCLUSIONS

This thesis suggests multiple improvements to the management of infectious diseases at the ED in three key areas: diagnostics, risk stratification and treatment. First, we developed prediction models that combine clinical variables with PCT. These models are promising to help avoid unnecessary blood cultures and contamination-related negative patient outcomes. Future validation and impact studies will help determine their clinical applicability. Second, we evaluated multiple tools for risk-stratification in a broad range of patients suspected of infection. This can help clinicians in deciding on site-of-care or treatment decisions in these specific

patient groups. Finally, we showed that there might be more room for oral antibiotics in the treatment of infections, potentially reducing admissions and therapy-related side-effects. Overall, this thesis represents a step forward to modern management strategies of infection by balancing safe reduction of testing and treatment without compromising safety.

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