Rational empiric antibiotic therapy in clinical practice and policy making: uncertainties, probabilities, and ethics

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Introduction and outline of the thesis

Antimicrobial resistance (AMR) occurs when pathogens adapt in ways that render the antimicrobial ineffective. Over the past decades, AMR has become one of the major threats to public health globally.[1,2] In comparison with infections caused by susceptible bacteria, those caused by multidrug-resistant bacteria are associated with higher mortality rates and prolonged hospital stay.[1,3] In Europe, the attributable mortality of AMR infections is higher than that for HIV, tuberculosis and influenza combined, and is likely to increase further in the near future.[4,5] Available studies quantifying the economic burden of AMR have methodological limitations, but the overall crude economic burden of antimicrobial resistance was estimated to be at least €1.5 billion in Europe.[6,7] AMR threatens to undermine the many advances of modern medicine. The health benefits provided by effective antimicrobials are entangled with many aspects of clinical practice, including for example oncology, with its rapidly advancing immunotherapies. A post-antibiotic era, where infectious complications of immunosuppressive therapies and other medical interventions cannot be treated effectively, would not merely impact the treatment outcome of infectious diseases, but also the practice of modern medicine in its current form.

The major driver of antimicrobial resistance is antimicrobial consumption.[8] Although hospitals account for only a minority of the total antibiotic prescriptions compared to for example the veterinary sector, the hospital setting is where most broad-spectrum antibiotics and reserve antimicrobial agents are used. Judicious use of broad-spectrum antimicrobials aims to slow the pace of emergence of resistant pathogens. At the same time, effective antimicrobial therapy is essential, potentially life-saving, in the treatment of many infections. Fostering the prudent use of antimicrobials to optimize patient outcome and preventing the misuse, are important goals of antimicrobial stewardship. Antimicrobial stewardship is the systematic effort to improve which antimicrobials are prescribed by clinicians, when and for how long. Interventions designed to improve antimicrobial prescribing in the hospital setting have been shown to confer benefits in terms of both patient outcome and reduction of unnecessary antimicrobial consumption.[9,10]

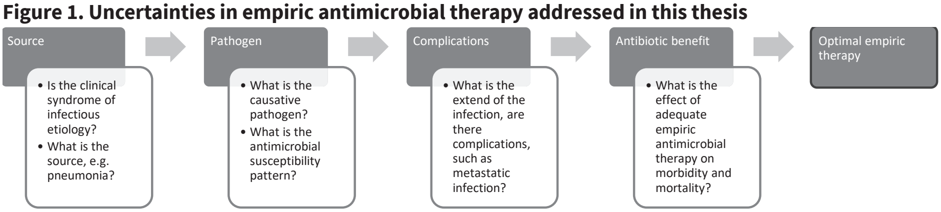
A significant proportion of the in-hospital antimicrobial consumption is used in the empiric setting, making empiric therapy an important target of stewardship interventions. Empiric antimicrobial therapy is the antimicrobial regimen that is started when the definite clinical diagnosis, causative agent and/or resistance pattern are yet unknown. This means that empiric therapy is accompanied by a varying level of uncertainty. In some cases, this uncertainty may be limited, for example in a 60-year-old patient with high fever and respiratory symptoms of acute onset, and an infiltrate on chest X-ray. In this case the clinical diagnosis is evident, the pathogen is most likely *Streptococcus pneu-*

moniae, and -in the Netherlands- the probability of penicillin resistance is negligible. On the other side of the spectrum are patients in whom clinical clues are scarce, such as patients presenting with sepsis without evidence of a source at initial evaluation. In daily clinical practice, this uncertainty about the source, pathogen and susceptibility pattern are often managed by prescribing relatively broad-spectrum antimicrobial therapy.[11] This has potential negative effects, such as toxicity and selective pressure resulting in antimicrobial resistance. Balancing the potential benefits and drawbacks of more broad-spectrum therapy is a substantial challenge, in particular when the level of uncertainty is high.

A rational approach to address these uncertainties is therefore needed to optimize patient outcome and prevent the overuse of antimicrobial agents. Decisions on empirical antimicrobial therapy should be primarily based on the clinical syndrome, e.g. pneumonia or sepsis, local epidemiology of causative pathogens, as well as on individual patient factors, such as disease severity and risk factors for an unfavourable outcome. Clinical research on how to optimally approach these issues of empiric antimicrobial therapy, and the associated residual uncertainties, has not yet sufficiently developed.

This thesis aims to address the uncertainties most relevant in daily clinical practice in empiric antimicrobial therapy (Figure 1), to determine how they affect daily decision making, and to explore how this can be translated in antimicrobial policy making and antimicrobial stewardship.

Figure 1. Uncertainties in empiric antimicrobial therapy addressed in this thesis



Uncertainties and probabilities in empiric antimicrobial therapy

The first uncertainty in the approach of a patient with fever or other symptoms that may be indicative of infection, is the *clinical diagnosis*. The clinical diagnosis has important consequences for further diagnostic and therapeutic actions. An undetermined source of infection is associated with higher mortality rates, but in many cases the diagnosis may not be apparent on the first evaluation.[12] Clinical signs of inflammation, such as fever, may be caused by a variety of syndromes, of either infectious or non-infectious origin.[13] Insight into the probability of bacterial infection, and subsequently the source of the infection is important to be able to decide on empiric therapy. Many clinical syndromes can be diagnosed or excluded within a relatively short time span, i.e. with radiographic exams to exclude pneumonia. In contrast, the diagnosis of bloodstream infection is relatively time consuming.[14] Bloodstream infections (BSI) are diagnosed with blood culture incubation systems, that measure CO2 production resulting from bacterial growth. The time needed for microbial growth to render a positive signal is known as time to positivity (TTP). In current clinical practice, BSI is considered highly unlikely if blood cultures have remained negative for three days. However, recent publications on TTP have suggested that a shorter timeframe may be justified for some pathogens.[15-18] **Chapter 2 and 3** of this thesis aim to investigate the probability of BSI when blood cultures remain negative after different time intervals. Insight into the probability of BSI at different time points, may assist the clinician in adapting the differential diagnosis and empiric antimicrobial management.

A second uncertainty, even when the source of infection has been determined, may be the *extent of the infection* and whether or not the patient has metastatic infection. A classic example is *Staphylococcus aureus* bacteraemia, in which the clinical differentiation between complicated and uncomplicated bacteraemia is notoriously difficult, but it has important consequences for dosing and duration of antimicrobial therapy. In **Chapter 4**, we developed and validated a clinical decision rule to assess the probability of complicated bacteraemia.

A third uncertainty is the *causative pathogen* and its *antimicrobial susceptibility pattern*. Although microbiological techniques have substantially improved during the past decades, it still takes several days to reliably test antimicrobial susceptibility. Antimicrobial stewardship guidelines recommend to adjust empiric therapy guidelines to the local epidemiology of pathogens. However, a framework on how to incorporate increasing resistance rates in guideline development, is not yet available. This issue is addressed in **Chapter 5**, where a method to systematically develop empiric treatment strategies - based on local microbiological and clinical data - is explored. Central in the constructed framework is the probability of a (mis)match of empiric antimicrobial therapy.

To decide whether, and to what extent, uncertainty may be tolerable during the empiric time-window, the *benefit of effective empiric therapy* needs to be considered as well.[19] What is the risk of an unfavorable outcome, if empiric therapy does not match the causative pathogen? Several observational studies have addressed the effect of a mismatch on mortality in patients with bloodstream infection and/or sepsis.[20, 21] As the selection of empiric antimicrobial therapy is influenced by many different variables, confounding by indication is a major issue in these studies.[20-22] In **Chapter 6**, the effect of a mismatch of empiric antimicrobial treatment on mortality rate in patients with BSI is estimated after applying propensity score matching (PSM) to optimally correct for confounding.[23]

Decision making in daily clinical practice and antimicrobial policy making

In Chapter 2 to 6 various uncertainties associated with empiric therapy are addressed. On a daily basis, doctors need to make decisions on antimicrobial therapy under such uncertainty.[24, 25] In order to be able to influence prescription behaviour, it is essential to understand how doctors decide on empirical antimicrobial therapy. Prescription behaviour is influenced by more than merely a rational consideration of the benefits and harm of antibiotic therapy. Hierarchic work relationships, patient expectations and juridical aspects – among others – are known to influence how healthcare professionals decide on antimicrobial therapy.[26, 27] It is likely that these factors gain weight when uncertainty increases. In **Chapter 7**, a systematic review of the cognitive determinants of prescription behaviour was conducted and a theoretical framework to understand the influence of these factors on antimicrobial decision making was constructed.

To support individual healthcare professionals in their antimicrobial decision making, guidelines for the empiric antimicrobial treatment of infectious diseases are implemented worldwide. Like individual healthcare professionals, policymakers are confronted with uncertainties and ethical dilemmas as well. Making up the balance is difficult when clinical data are lacking and future risks in terms of AMR can only be estimated.[28, 29] In addition to weighing the benefits and harms on the individual patient level, guidelines should also capture the interest of future generations. In **Chapter 8**, we developed a systematic approach to assess and weigh the available data, incorporating ethical aspects.

The results of this thesis are summarized and discussed in **Chapter 9**.

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