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

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Rational empiric antibiotic therapy in clinical practice and policy making

Uncertainties, probabilities, and ethics

Merel Mariëtte Catharina Lambregts

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Uncertainties, probabilities, and ethics

Merel Lambregts

Colophon
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Uncertainties, probabilities, and ethics

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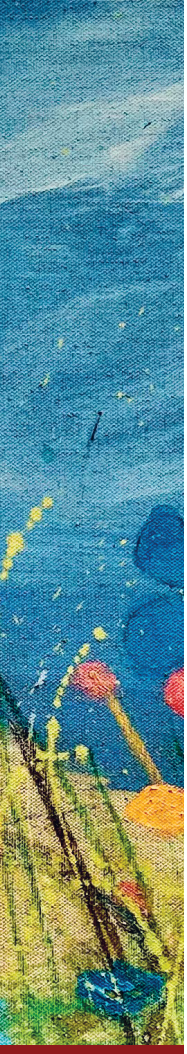

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Introduction and outline of the thesis

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]

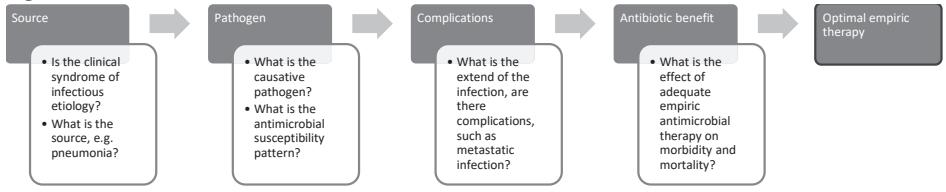
A significant proportion of the in-hospital antimicrobial consumption is used in the empiric setting, making empiric therapy an important target of stewardship interventions. Empiric antimicrobial therapy is the antimicrobial regimen that is started when the definite clinical diagnosis, causative agent 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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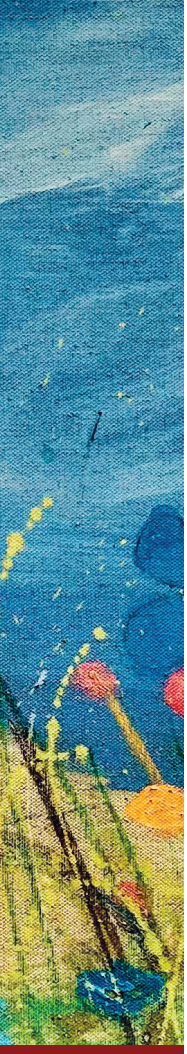
Part I

Uncertainties and probabilities in empiric antimicrobial therapy



2

Time to positivity of blood cultures supports early re-evaluation of empiric broad-spectrum antimicrobial therapy

Merel M.C. Lambregts, Alexandra T. Bernards, Martha T. van der Beek, Leo G. Visser, Mark G. J. de boer

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ABSTRACT

Background: Blood cultures are considered the gold standard to distinguish bacteraemia from non-bacteraemic systemic inflammation. In current clinical practice, bacteraemia is considered unlikely if blood cultures have been negative for 48-72 hours. Modern BC systems have reduced this time-to-positivity (TTP), questioning whether the time frame of 48-72 hrs is still valid. This study investigates the distribution of TTP, the probability of blood culture positivity after 24 hours, and identifies clinical predictors of prolonged TTP.

Methods: Adult patients with monomicrobial bacteraemia in an academic hospital were included retrospectively over a three-year period. Clinical data were retrieved from the medical records. Predictors of TTP >24 hours were determined by uni- and multivariable analyses. The residual probability of bacteraemia was estimated for the scenario of negative BCs at 24 hours after bedside collection.

Results: The cohort consisted of 801 patients, accounting for 897 episodes of bacteraemia. Mean age was 65 years (IQR 54-73), 534 (59.5%) patients were male. Median TTP was 15.7 (IQR 13.5-19.3) hours. TTP was ≤24 hours in 85.3% of episodes. Antibiotic pre-treatment (adjusted OR 1.77; 95%CI 1.14-2.74, $p<0.01$) was independently associated with prolonged TTP. The probability of bacteraemia, if BC had remained negative for 24 hours, was 1.8% (95% CI 1.46-2.14).

Conclusion: With adequate hospital logistics, the probability of positive blood cultures after 24 hours of negative cultures was low. Combined with clinical reassessment, knowledge of this low probability may contribute to prioritization of the differential diagnosis and decisions on antimicrobial therapy. As a potential antibiotic stewardship tool, this strategy warrants further prospective investigation.

INTRODUCTION

Empirical in-hospital antibiotic prescription forms a significant proportion of broad-spectrum antibiotic consumption. The in-hospital use of antibiotics is expected to increase even further due to advancing life-expectancy and an increase in the application of immunosuppressive therapies, resulting in an increasing incidence of bacterial infections.[1-3] Appropriate empirical treatment for severe bacterial infections improves survival.[1,4] However, upon presentation, the clinical diagnosis is often uncertain, and the presence of bacterial infection is not always evident. There is a broad differential diagnosis for fever, including viral infections and inflammatory states of non-infectious origin such as pancreatitis. Furthermore, thromboembolic events and severe drug reactions can mimic the symptoms of bacterial infection.[5]

Identifying patients without bacterial infection at an early time point is an important component of antimicrobial stewardship. Prolonged administration of broad-spectrum antibiotics may cause adverse events in the individual patient. Duration of antibiotic therapy is associated with toxicity, *Clostridioides difficile* infection and increased mortality rates.[6-9] Furthermore, antibiotic consumption, especially the use of broad-spectrum agents, is one of the major drivers of the increasing antimicrobial resistance worldwide.[10,11] Because of these individual and societal risks, guidelines recommend to de-escalate broad-spectrum antimicrobial treatment based on the source of infection and culture results. De-escalation of empirical therapy is defined as a reduction in number and/or narrowing of spectrum of antimicrobial agents.[12] When infection is found not to be present, the recommendation is to discontinue antimicrobial therapy.[1]

Diagnostics directed at the possible source of infection, i.e. radiographic exams and urine analysis, can be completed within hours. In contrast, differentiating bacteraemia from non-bacteraemic infection is still time consuming as reliable alternatives for conventional blood culture incubation are not yet available in clinical practice. Biomarkers for exclusion of bacteraemia lack sensitivity or have practical limitations.[13-16] Historically, the consensus is to await blood culture results for at least 48 to 72 hours, before bacteraemia is deemed unlikely.[17,18] Because of the modernisation of blood culture methods, and especially the development of continuous monitoring systems, the time to positivity (TTP) of blood cultures has been reduced substantially.[19-21]

Knowledge of the distribution of blood culture TTP is of clinical benefit in the re-evaluation of patients with a clinical syndrome consistent with infection. A low probability of bacteraemia when blood cultures have remained negative after 24 hours, may have impact on the differential diagnosis and subsequent diagnostic and therapeutic actions.

Our aim was to determine the distribution of the TTP of blood cultures in adult patients and asses the probability of bacteraemia when blood cultures have remained negative for 24 hours. In addition, we aimed to identify clinical characteristics that predict late (i.e. >24 hours) positivity.

METHODS

Setting and study participants

The retrospective cohort study was performed at the Leiden University Medical Center, a tertiary care and teaching hospital in the Netherlands.

All patients aged 18 years and older, with mono-microbial bacteraemia in 2013 and 2014 were identified. An additional 100 patients that presented in the year 2015 were randomly included, by case identification code. Patients with polymicrobial bacteraemia were excluded as the time to positivity of the individual pathogens was unknown. Furthermore the relevance of the individual pathogens to the TTP of the polymicrobial culture can not be determined.

The blood culture database of the Department of Medical Microbiology was used to identify eligible patients. Patients admitted to clinical wards, including medium and intensive care unit and cases presenting at the emergency department were eligible for inclusion. Multiple episodes of bacteraemia per patient were allowed if the antimicrobial therapy for the previous episode had been completed and clinical and microbiological cure had been achieved. All blood cultures with coagulase-negative staphylococci (CoNs) were excluded, because the likelihood that these cultures represent contamination is high. For other possible contaminants (including anaerobes) the differentiation between true bacteraemia and contamination was based on the number of positive vials and the documented assessment of the microbiologist and responsible physician.

Standard empiric therapy for sepsis of unknown origin in the study centre was a second generation cephalosporin combined with an aminoglycoside.

The study was approved by the Institutional Ethics Review Board of the Leiden University Medical Center. The requirement to obtain informed consent was waived because of the retrospective nature of the study.

Data collection

Demographic data, data about pre-existing medical conditions, clinical parameters at presentation, the most likely source of bacteraemia and the outcome data were retrieved from the electronic medical records. The classification of the source of infection was based on review of the available clinical, radiological and microbiological information. Outcome measurements included admission to the intensive care, length of hospitalisation and 30-day mortality. Microbiological data, including pathogen identification and TTP, were retrieved from the database of the Department of Medical Microbiology.

Antibiotic pre-treatment was defined as treatment with one or more antibiotic agents, administered intravenously, intramuscularly or orally, within the 24 hours preceding collection of the first blood culture. Oral antibiotics without systemic absorption, such as vancomycin, were excluded from this definition.

Blood culture handling procedures and laboratory techniques

TTP was defined as the time between collection of the blood cultures and the positive signal in the BACTEC FX continuous monitoring system (Becton Dickinson B.V., Breda). The institutional protocol is to collect both an aerobic and anaerobic vial, and to collect 8–10 ml of blood per vial.[22,23] A quality assessment in 100 individual vials showed a median blood volume of 9 ml (IQR 7–11) per vial (Supplementary files, Table S3).

The time of bedside blood culture collection was recorded in the electronic medical records, as part of the ordering procedure. Cultures were transported to the in-hospital microbiology department by dedicated hospital transportation employees. During day-hours, transportation is performed every 3 hours. Quality assessment at the beginning of the study period showed a median time from collection to placement in the incubator of 94 minutes (IQR 63–137). Outside working hours the maximum time to transportation is 5 hours.

Upon arrival at the Department of Medical Microbiology the blood cultures were directly placed in the BACTEC FX continuous monitoring system (Becton Dickinson B.V., Breda), for a minimum of seven days. The time of the positive signal was automatically recorded. During evening and night hours, blood cultures were directly placed in the BACTEC, but registration in the system was performed the following morning between 8 and 9 a.m. If the threshold for positivity was reached between placement and this registration, the culture was recorded positive at the time of registration, instead of upon positive signalling. This technical limitation leads to an overestimation of the TTP in ‘unregistered’ bottles. Therefore, median TTP was additionally calculated excluding ‘unregistered’ episodes (Supplementary files).

If multiple separate blood cultures from one patient were collected within a time frame of two hours, the shortest TTP was used for the statistical analyses.

Blood culture positivity rate

To calculate the probability of positive blood cultures when they have remained negative for 24 hours, information on the institutional blood culture positivity rate is required (see statistical analysis). To estimate the overall blood culture positivity rate, the proportion of bacteraemia was determined during two separate months, June and December 2014. During this period, all patients in whom blood cultures were obtained because of fever or (suspected) sepsis were included. True bacteraemia was defined as growth of a pathogenic bacterial species in ≥1 blood culture bottle. Definition of contamination was identical to the definition applied in the main cohort. Patients were only included for the first episode of suspected infection, subsequent episodes were excluded.

Statistical analyses

Median TTP and interquartile ranges (IQR) were determined for the complete cohort and for the most frequently isolated pathogens in patients with bacteraemia. Median TTP was additionally calculated excluding 'unregistered' episodes, because of the potential overestimation of TTP (S1 Table). Normally and non- normally distributed continuous variables were compared by Student's t test and Mann-Whitney U test, respectively. Univariate risk factor analysis was performed for short (<16 hours) and prolonged TTP (>24 hours), using Chi-square statistical tests. Results were reported as risk ratios (RR) with 95% confidence intervals (95%CI). A multivariable analysis for prolonged TTP was performed and results were reported as adjusted odds ratios (OR with 95%CI). Determinants for the multivariable analysis were selected based on <0.25 in the univariate analysis.

We applied a generalized estimating equation model to assess the potential effect of repeated measurements by inclusion of multiple episodes of bacteraemia for a proportion of patients.

The residual risk of detection of bacteraemia after 24 hours was calculated applying a previously published mathematical equation.[20] (Supplementary files, Box 1). This equation is based on the proportion of positive blood cultures in suspected sepsis and the proportion of blood cultures with prolonged TTP.

All statistical analyses were performed with the IBM SPSS Statistics, version 23.

RESULTS

Study population characteristics

After exclusion of polymicrobial and contaminated blood cultures, a total of 801 individual adult patients was included, representing 897 episodes of bacteraemia. Mean age was 65 years (IQR 54–73), 534 (59.5%) patients were male.

The majority of bacteraemia episodes (511 episodes, 57.0%) was caused by a Gram-negative pathogen, predominantly *Escherichia coli* (263/511, 51.5%). *Streptococcus spp* were the most common Gram-positive isolates (163/386, 42%). The demographic and clinical characteristics of the 897 episodes of bacteraemia are summarized in Table 1. In 450/897 (50.2%) episodes ≥2 blood culture sets were obtained within a time frame of two hours.

Table 1. Demographic and clinical characteristics among 897 episodes with bacteraemia.

Characteristic	n = 897 (100%)
Patient demographics	
Male gender	534 (59.5)
Age (years) , (median, IQR)	65 (54-73)
Medical history	
Diabetes mellitus	188 (21.0)
Corticosteroid therapy (prior 6 months)	276 (30.8)
Neutropenia	113 (12.6)
Solid organ transplantation	116 (12.9)
Solid malignancy	170 (19.0)
haematological malignancy	96 (10.7)
Dialysis (haemodialysis/peritoneal dialysis)	20 (2.2)
Clinical presentation	
Fever (temperature>38.5 °C)	538 (60.0)
Systolic blood pressure (mmHg) (median, IQR)	125 (107-142)
Pulse rate (bpm) (median, IQR)	101 (88-115)
EMV <15	173 (19.3)
PITT Bacteraemia score (median, IQR)	1 (0-2)
Quick SOFA-score (median, IQR)	1 (1-2)
Antibiotic pre-treatment	264 (29.4)
Location of presentation	
Emergency department	507 (56,5)
General ward	340 (37,9)
ICU/MCU	50 (5.6)
Hospitalization before BC (hours) (median IQR)	3.0 (0.4-136.8)

Table 1. Demographic and clinical characteristics among 897 episodes with bacteraemia. (*continued*)

Characteristic	n = 897 (100%)
Microbiological parameters	
Gram-positive bacteraemia:	386 (43.0)
Gram-negative bacteraemia	511 (57.0)
Anaerobic bacteraemia	37 (4.1)
Source of infection	
Gastro-intestinal	245 (27.3)
Respiratory	89 (9.9)
Endovascular (e.g. thrombus)	111 (12.4)
Urinary tract	232 (25.9)
Skin and soft tissue	71 (7.9)
Other	56 (6.2)
Not identified	84 (9.4)
Outcome	
ICU/MCU admission during hospitalization	180 (20.1)
Hospitalization after BC (days) (median IQR)	8.9 (3.9-19.0)
30-day mortality	134 (14.9)

Legend: BC=blood culture, ICU/MCU = intensive care unit / medium care unit, IQR= interquartile range

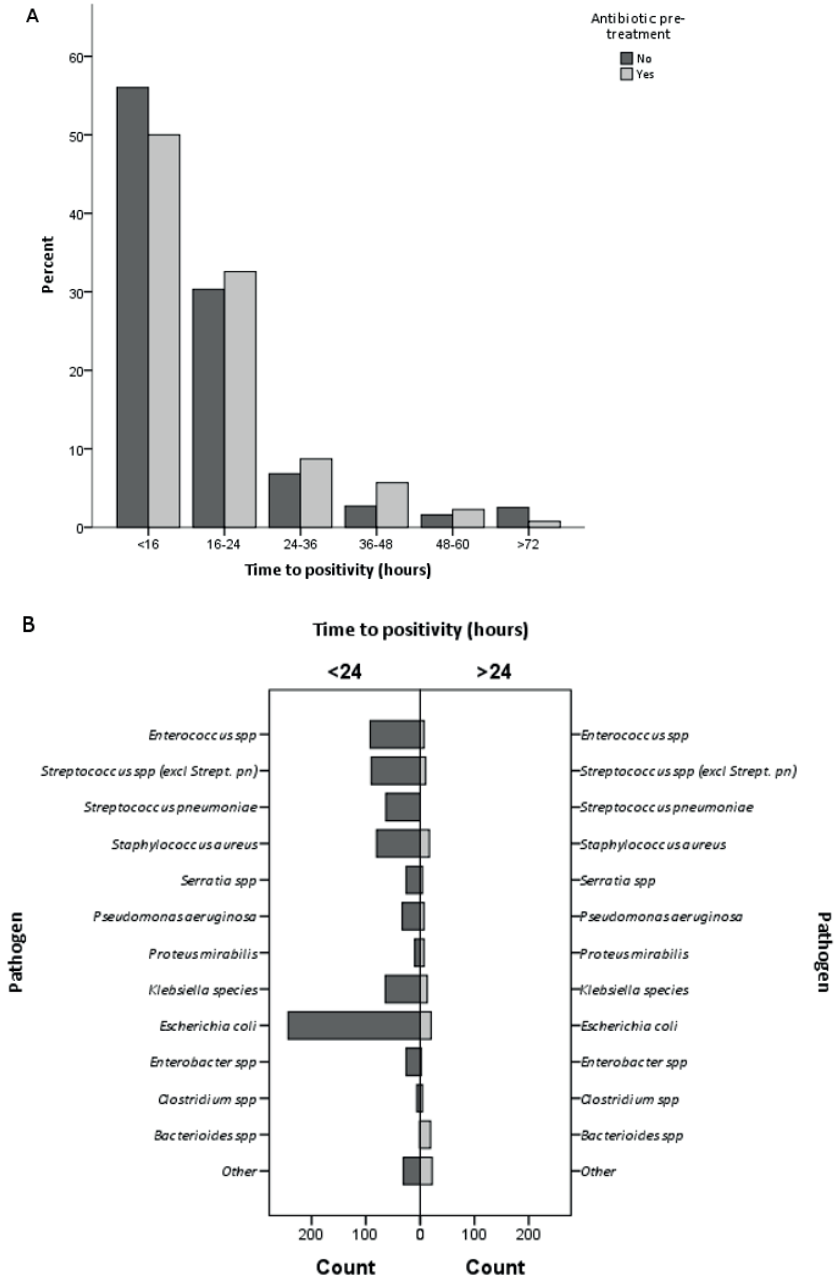
Time to positivity

The median TTP was 15.7 hours (IQR 13.5-19.3). The TTP was below 24 hours in 765 episodes (85.3%). In 34 (3.8%) episodes and 18 (2.0%) episodes TTP was longer than 48 hours and 72 hours, respectively (Fig 1).

Anaerobic bacteraemia was frequent in the prolonged TTP group, 28/132 (21.2%) episodes. After exclusion of anaerobic bacteraemia, there was no statistically significant difference in TTP between Gram-negative and Gram-positive bacteraemia (TTP 18.6 h vs 19.4 h, p = 0.48). The TTP of the most common pathogens is illustrated in Fig 2. All episodes of *Streptococcus pneumoniae* bacteraemia were diagnosed within 24 hours (median 13.4 h, IQR 11.3-15.5 h). TTP was long in bacteraemia caused by *Proteus mirabilis* (median 18.6 hr, IQR 14.8-34.9 h). All cases (n=3) of *Propionibacterium acnes* bacteraemia were diagnosed after 72 hours.

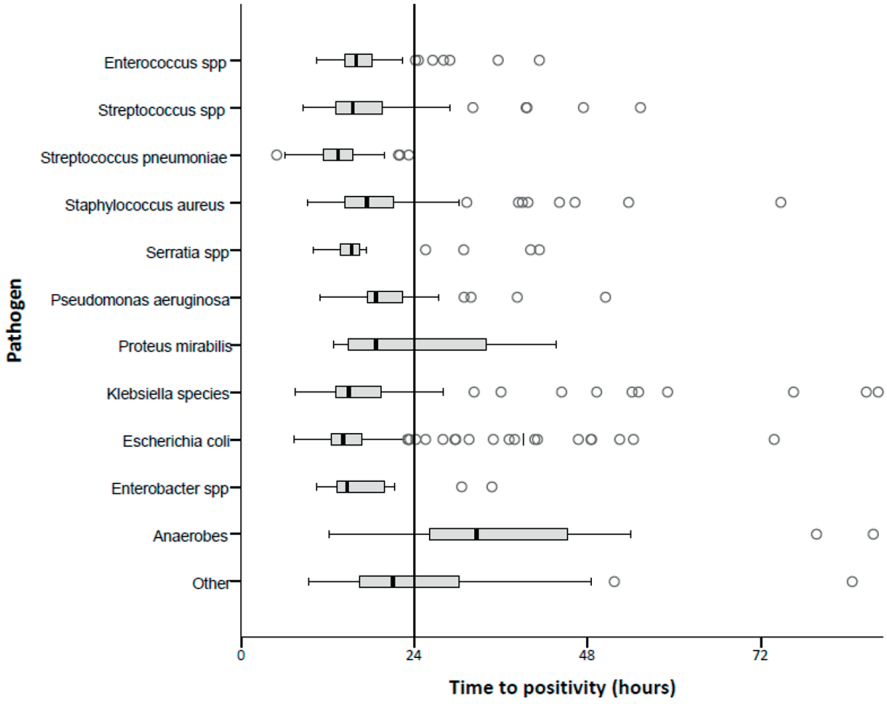
In 87 of the 132 (65.9%) episodes with prolonged TTP, the isolated pathogen was susceptible to the institutions empirical sepsis therapy (2nd generation cephalosporin and an aminoglycoside).

Fig 1. Distribution of time to blood culture positivity (TTP) in 897 episodes of bacteraemia.



Legend: Fig. 1A illustrates the distribution of TTP in patients with and without antibiotic pre-treatment at the time blood cultures were collected. Fig 1B. illustrates the distribution of TTP, short (≤24) versus prolonged (>24) TTP, according to isolated pathogen. The group 'Other' comprises *Citrobacter spp. Haemophilus spp, Listeria spp, Achromobacter spp, Acinetobacter spp, Moraxella catarrhalis, Morganella morganii, Propionibacterium acnes, Rothia mucilaginosa, Salmonella spp, Stenotrophomonas maltophilia, Lactobacillus spp, Prevotella spp, Fusobacterium spp.*

Fig 2. Pathogens and time to positivity (TTP) distributions.



Legend: The boxplot figure illustrates the distribution of TTP (median, interquartile range) for the most frequently isolated pathogens. The ends of the whiskers represent one and a half times the interquartile range.The group 'Other' comprises *Citrobacter spp. Haemophilus spp, Listeria spp, Achromobacter spp, Acinetobacter spp, Moraxella catarrhalis, Morganella morganii, Propionibacterium acnes, Rothia mucilaginosa, Salmonella spp, Stenotrophomonas maltophilia, Lactobacillus spp, Vibrio spp.*

In 108 (12.0%) episodes blood cultures were placed in the incubator 'unregistered' and reached the threshold for positivity before registration. TTP analysis excluding these episodes did not have an important effect on the results (Supplementary files, S1/2).

Predictors of short versus prolonged time to positivity

Neutropenia (RR 0.22, 95%CI 0.08-0.58, p <0.01) and corticosteroid therapy (RR 0.66, 95%CI 0.45-0.97, p=0.03) were associated with short TTP (≤24 hours) in univariate analysis (Table 2). The source of infection was not a predictor of short versus prolonged TTP. In multivariable analysis, antibiotic pre-treatment (adjusted OR 1.71 95%CI 1.11-2.65, p<0.01) was associated with prolonged TTP (> 24 hours). Neutropenia (adjusted OR 0.15 95%CI 0.05-0.43, p<0.01), was associated with short TTP. Application of a generalized estimating equations model did not detect a relevant effect of including >1 episode in a proportion of patients.

Table 2. Univariate and multivariable analysis for long time-to-positivity (>24 hours) in 897 episodes of bacteraemia.

	Univariate analysis			Multivariable analysis		
Characteristic	**RR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Patient demographics						
Male gender	0.98	0.71 - 1.35	0.91			
Age > 70 years	1.22	0.88 - 1.69	0.23	1.15	0.76-1.72	0.52
Medical history						
Immunocompetent	1.00	-	-			
Neutropenia	0.21	0.08 - 0.56	<0.01	0.15	0.05-0.43	<0.01
Corticosteroid therapy	0.64	0.44 - 0.94	0.02	0.71	0.45-1.14	0.16
Clinical presentation						
Temperature>38.5 °C	0.80	0.58 - 1.11	0.18	0.79	0.54-1.17	0.24
Systolic blood pressure <100 mmHg	1.29	0.86 - 1.94	0.23	1.09	0.65-1.80	0.73
PITT bacteraemia score≥2	0.85	0.58 - 1.25	0.41			
Quick SOFA score >1	1.10	0.69 - 1.75	0.78			
Antibiotic pre-treatment	1.23	0.92 - 1.77	0.15	1.71	1.11-2.65	0.01
Emergency department	0.77	0.56 - 1.05	0.10	0.71	0.47-1.07	0.10
Source of infection						
Gastro-intestinal	1.29	0.92 - 1.79	0.14	1.45	0.95-2.22	0.08
Respiratory tract	0.66	0.35 - 1.26	0.17	0.79	0.38-1.66	0.53
Endovascular	0.78	0.45 - 1.32	0.34			
Urinary tract	0.99	0.69 - 1.43	0.97			
Skin and soft tissue	0.95	0.52 -1.73	0.88			

Legend: CI= confidence interval. RR= relative risk. OR = adjusted odds ratio. CI = confidence interval. The PITT bacteraemia score is calculated from temperature of 35.1–36.0°C or 39.0–39.9°C (1 point), temperature of ≤35°C or ≥40°C (2 points), mental status (alert, 0 points; disoriented, 1 point; stuporous, 2 points; comatose, 4 points), hypotension (2 points), receipt of mechanical ventilation (2 points) and cardiac arrest (4 points). The Quick SOFA score is calculated from glascow coma scale <15 (1 point) , Respiratory rate ≥22 (1 point), systolic blood pressure ≤100 (1 point).

Probability of bacteraemia at T=24 hours

The two determinants in the equation of the probability of bacteraemia at T = 24 hours are the blood culture positivity rate and the proportion of blood cultures that is positive within 24 hours (S1 Box). The rate of blood culture positivity was determined during two separate months, June and December 2014. In this period 2,099 blood cultures in 778 patients were obtained because of suspected bacterial infection. In 83/778 episodes one or multiple blood cultures were positive, resulting in a positivity rate of 10.7%.

The probability of bacteraemia after 24 hours was calculated using the above estimated overall a priori risk of bacteraemia in patients with suspected infection (10.7%), and the fraction of blood cultures that were positive within 24 hours (85.3%).[20] The probability of

bacteraemia when blood cultures had remained negative after 24 hours was 1.8% (95% CI 1.46–2.14%).

DISCUSSION

We found that under the condition of adequate hospital logistics and by using modern, continuously monitoring blood culture systems, 85.3% of blood cultures is positive within 24 hours. Neutropenia was a predictor of short TTP in our study and antibiotic pre-treatment was a predictor of prolonged TTP. These predictors are in line with results from a study by Martinez *et al.*[21] Most previous studies have defined TTP as the time between incubation and positivity. To permit clinical applicability of the results, we here defined TTP as time between collection of the blood samples and blood culture positivity, taking into account the transportation and laboratory logistics during and outside office hours. As a result, median TTP in our study is longer than in most previous studies[21,24], but applicable to real-life clinical settings.

For daily practice, the proportion of blood cultures that becomes positive after different periods of elapsed time is more relevant than median TTP. Two previous studies, that included smaller numbers of patients, found similar results on TTP distribution, despite the above mentioned differences in definition.[18,25] The authors of these studies conclude that their findings support antibiotic de-escalation after 48 hours. However, to decide on the optimal timing of re-evaluation of the differential diagnosis, the more relevant question is how probable bacteraemia still is when blood cultures have remained negative at different time points. For that purpose, knowledge about the overall blood culture positivity rate, i.e. the pre-test probability, is essential. The blood culture positivity rate in our centre is 10.7%. This is in line with literature on the prevalence of bacteraemia in localised bacterial infection and systemic inflammatory response syndrome (SIRS).[26–28] By using the previously published mathematical equation (S1 Box), the probability of blood culture positivity after 24 hours is below 2 percent in our institution.[20]

This probability is centre specific, as both variables in the mathematical equation may vary between institutions. The first variable, the overall blood culture positivity rate, is dependent on the patient population and the criteria that are applied by doctors to order blood cultures. For example, a ‘culture of culturing’ will result in low blood culture positivity rates.

The second variable, the proportion of blood cultures that is positive within 24 hours, is dependent on hospital logistics. If there is an important delay in transportation of the

cultures to the laboratory or placement in the incubator, TTP according to our definition, will be longer. The mathematical equation, allows for the calculation of an institution specific probability of blood culture positivity at T = 24 hours.

With adequate hospital logistics, the overall probability of positive blood cultures at T = 24 hours is low. This knowledge is valuable for the differential diagnosis and management of patients with suspected bacterial infection. For example, in the scenario of a confirmed source of infection (e.g. pneumonia), and clinical recovery, preliminary negative blood culture results may support an early intravenous-oral switch.[29] Alternatively, when there are no signs of localised infection and blood cultures are still negative after 24 hours, bacteraemia becomes unlikely. This knowledge should prompt timely diagnostic steps into non-bacterial causes of fever that require interventions, as e.g. Influenza, thrombo-embolic events or drug-reactions. Despite low probabilities a blood culture may incidentally become positive after more than 24 hours. Furthermore, negative blood cultures do not exclude bacteraemia. Nor does the absence of positive blood cultures exclude non-bacteraemic infections. Despite this level of uncertainty, re-evaluation of empirical therapy is in place when the probability of bacterial bloodstream infection changes. Re-evaluation of clinical stability, response to empirical therapy and an update of the differential diagnosis, is essential when balancing the potential costs and benefits of de-escalating empiric therapy.

For the application of the findings to clinical practice, it is also important to emphasize that the pre-test probability of bacteraemia is variable, not only between institutions, but between patients as well.[28] For example, in the severely ill patient with septic shock, the blood culture positivity rate is higher, and TTP may be shorter, both affecting the bacteraemia probability after 24 hours.[30] In the severely ill patient without an alternative diagnosis, even a low probability of bacteraemia or non-bacteraemic bacterial infection may warrant continuation or even escalation of broad-spectrum antibiotic therapy.

To the best of our knowledge, we present the largest cohort of patients investigating the distribution of TTP. More importantly, this is the first study to approach TTP of blood cultures from a clinical perspective, providing insight into the probability of bacteraemia at the 24 hour time point. A limitation of the present study is that patients with polymicrobial bacteraemia where excluded. Based on previous research[31, 32] and on theoretical grounds, the TTP of polymicrobial episodes is comparable to monomicrobial bacteraemia, possibly even shorter. Therefore, inclusion of these episodes would at most reduce the probability of blood culture positivity at T>24 hours.

Secondly, the volume of blood collected in the vials was not recorded in the individual cases, and in a proportion of patients only 1 vial-set was collected. In daily practice TTP and the yield of blood cultures could be improved by further optimising specimen collection; specifically vial filling and number of vials.[22,23,33]

Thirdly, we were not informed about the individual vial transportation times to the microbiology laboratory. However, our institutional transport logistics and transport times are in line with current guidelines and comparable to other institutions.[34,35] Previous research has shown that transport and incubation of blood cultures outside laboratory reduces turnaround time and accelerates therapeutic interventions.[36] As blood culture collection and transportation procedures impact TTP, audit of blood culture logistics is probably a prerequisite for translation of our results to other institutions.

In conclusion, if modern blood culture systems are used in combination with adequate logistics, the probability of positivity when blood cultures are negative after 24 hours is very low. Postponing re-evaluation of the differential diagnosis, solely for the reason of pending blood culture results, is not rational at this time point. The search for alternative causes of fever can be initiated more rapidly if the probability of bacteraemia is incorporated in clinical reasoning. This may lead to better timed de-escalation, iv to oral switch and earlier hospital discharge. The safety as well as the benefits of this antibiotic stewardship opportunity should be subject of future clinical trials.

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SUPPLEMENTARY DATA

Pathogen distribution and median time to positivity excluding and including 'unregistered' episodes

In 108 (12.0%) episodes blood cultures were placed in the incubator 'unregistered' and reached the threshold for positivity before registration. TTP analysis excluding these episodes did not have an important effect on the results compared to the analysis that included all episodes.

Table S1. Pathogen distribution and median time to positivity excluding unregistered episodes.

Pathogen	Number of episodes (%)	Median TTP (hours) (IQR)
Overall	790 (100.0)	16.1 (13.3-20.0)
Gram-positive pathogen[a]:	346 (43.8)	16.3 (13.6-19.8)
Streptococcus spp	152 (19.2)	14.5 (12.4-18.5)
Strept. pneumoniae	52 (6.6)	13.4 (11.4-15.2)
Enterococcus spp.	88 (11.1)	16.5 (14.5-18.5)
Staphylococcus aureus	91 (11.5)	17.7 (14.4-21.7)
Other	15 (1.9)	26.4 (21.3-94.8)
Gram-negative pathogen[a]:	417 (52.8)	15.5 (13.1-19.3)
Escherichia coli	218 (27.6)	14.1 (12.5-17.5)
Pseudomonas aeruginosa	38 (4.8)	19.2 (17.6-22.4)
Enterobacter spp.	26 (3.3)	15.0 (12.8-20.5)
Klebsiella spp.	66 (8.4)	15.5 (13.2-20.3)
Serratia marcesens	25 (3.2)	15.7 (13.8-16.9)
Proteus mirabilis	15 (1.9)	15.8 (14.7-35.9)
Other	29 (3.7)	18.2 (15.9-24.2)
Anaerobic pathogen	27 (3.4)	32.6 (24.1-46.6)

Legend: TTP= Time to positivity, IQR= inter quartile range. [a]: aerobes only.

Table S2. Pathogen distribution and median time to positivity including unregistered episodes.

Pathogen	Number of episodes (%)	Median TTP (hours) (IQR)	Maximum TTP (hours)
Overall	897 (100)	15.3 (13.3-19.5)	303.6
Gram-positive pathogen[a]:	374 (41.7)	15.7 (13.5-19.3)	303.6
Streptococcus spp	163 (18.2)	14.5 (12.5-18.3)	55.3
Strept. pneumoniae	63 (7.0)	13.4 (11.3-15.5)	23.2
Enterococcus spp.	99 (11.0)	16.0 (14.3-18.2)	41.3
Staphylococcus aureus	96 (10.1)	17.4 (14.4-21.4)	74.8
Other	16 (1.8)	26.2 (21.1-92.2)	303.6
Gram-negative pathogen[a]:	486 (54.2)	15.0 (13.0-18.5)	162.3
Escherichia coli	263 (29.3)	14.1 (12.6-16.7)	162.3
Pseudomonas aeruginosa	40 (4.6)	18.6 (17.5-22.3)	50.5
Enterobacter spp.	28 (32.2)	14.7 (13.1-20.2)	34.7
Klebsiella spp.	77 (8.6)	15.0 (13.1-19.6)	116.1
Serratia marcesens	30 (3.3)	15.3 (13.8-16.5)	41.3
Proteus mirabilis	17 (1.9)	18.6 (14.8-34.9)	43.6
Other	31 (3.5)	18.1 (15.5-24.1)	48.6
Anaerobic pathogen	37 (4.1)	32.6 (24.1-46.6)	129.4

Legend: TTP= Time to positivity, IQR= inter quartile range. [a]: Aerobes only.

Results of the quality assessment of blood volume in blood culture vials

Vial volume was measured in 50 anaerobic vials and 50 aerobic vials. Vial volume was below 8 ml in 32/100 (32.0%) of vials and below 7 ml in 15/100 vials (15.0%).

Table S3. Results of the quality assessment of blood volume in blood culture vials.

Blood volume/vial in milliliters	Frequency (%)	Cumulative Percentage
4	3 (3.0)	3.0
5	7 (7.0)	10.0
6	5 (5.0)	15.0
7	17 (17.0)	32.0
8	15 (15.0)	47.0
9	13 (13.0)	60.0
10	5 (5.0)	65.0
11	13 (13.0)	78.0
12	5 (5.0)	83.0
13	4 (4.0)	87.0
14	4 (4.0)	91.0
15	4 (4.0)	95.0
16	3 (3.0)	98.0
17	1 (1.0)	99.0
18	1 (1.0)	100.0

Legend: Volume of blood in 100 BACTEC blood culture vials (Becton Dickinson B.V., Breda).

Residual risk of detection of bacteraemia after 24 hours

Box S1. Formula for the Estimation of probability of bacteraemia after 24 hours.

$$P = \frac{(1-TTPe) * X}{1-(TTPe * X)} * 100\%$$

P = Probability of a positive blood culture when the sets have remained negative 24 hours after bedside collection.

X = The proportion of patients with positive blood cultures among all patients in whom blood cultures are obtained for suspected bacterial infection (centre-specific).

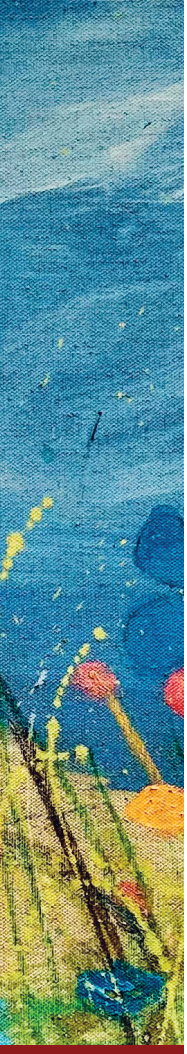
TTP_e = proportion of positive blood cultures that are positive in ≤24 hours.

Example

In the Leiden University Medical Center an estimated 10.6% of patients in whom blood cultures were obtained have true bacteremia and 85.3% (95%CI 83.0-87.6) of blood cultures is positive within 24 hours.

Then (use formula, X = 0.11 TTP_e = 0.85) If BCs are still negative after 24 hours of incubation, the probability that the culture will become positive is approximately 1.8% (95%CI 1.5-2.1).

This formula is reproduced from a publication in the European Journal of Haematology.



3

Distribution and clinical determinants of Time to positivity of blood cultures in patients with neutropenia

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ABSTRACT

Objectives: Blood cultures (BC) are essential in the evaluation of neutropenic fever. Modern BC systems have significantly reduced the time to positivity (TTP) of BC. This study explores the probability of bacteraemia when BC have remained negative for different periods of time.

Methods: All adult patients with neutropenia and bacteraemia were included (January 2012–February 2016). Predictive clinical factors for short (≤16 hours) and long (>24 hours) TTP were determined. The residual probability of bacteraemia was estimated for the scenario of negative BC 24 hours after collection.

Results: The cohort consisted of 154 patients, accounting for 190 episodes of bacteraemia. Median age 61 years, 60.5% were male. In 123 (64.7%) episodes, BC yielded a single Gram-positive microorganism and in 49 (25.8%) a Gram-negative microorganism (median TTP 16.7, 14.5 hours respectively, $p<0.01$). TTP was ≤24 hours in 91.6% of episodes. Central line associated bacteraemia was associated with long TTP. The probability of bacteraemia if BC had remained negative for 24 hours, was 1-3%.

Conclusions: The expected TTP offers guidance in the management of patients with neutropenia and suspected bacteraemia. The knowledge of negative BC can support a change in working diagnosis, and impact clinical decisions as soon as 24 hours after BC collection.

INTRODUCTION

During neutropenia, patients are at high risk to develop bacterial bloodstream infections (BSIs), which are associated with substantial morbidity and mortality.[1,2] Prompt initiation of empiric antimicrobial therapy therefore is an essential part of the treatment of neutropenic patients with fever and is universally advocated by guidelines.[3-8]

However, fever does not necessarily indicate the presence of bacterial infection. Viral and fungal infections regularly occur in this patient population. Furthermore, non-infectious origins of fever, for example paraneoplastic, transfusion-related, medicinal or thromboembolic events, can generate symptoms that clinicians usually associate with BSI. It is notoriously difficult to distinguish bacterial from non-bacterial pathology based on the first clinical assessment.

Ruling-out bacteraemia plays an important part in excluding bacterial infection. In contrast to excluding localised infection, using for example radiographic examinations, blood cultures are time-consuming. Despite tremendous efforts, there is still no reliable alternative for blood cultures when it comes to the detection of bacteraemia.[9,10] However, due to improved microbiological techniques such as continuous monitoring systems, the time to positivity (TTP) of BCs has improved markedly over the past decades. At present, the majority of BCs becomes positive within 24 hours.[11-13]

In previous studies, data on patients with neutropenia are limited. The distribution of TTP in neutropenic patients may be different from the general population. Both the immunodeficiencies and the specific microbiology in these patients may influence TTP. Knowledge of TTP is particularly relevant with respect to the differential diagnosis of (persisting) fever and may have consequences for both the diagnostic approach and rational choice and duration of empiric antimicrobial therapy. Taking into account the negative implications of broad-spectrum empiric therapy like toxicity, interactions with co-medication, and development of antimicrobial resistance, timely differentiation between bacterial and non-bacterial pathology are warranted.[14-17]

The objective of this study was to determine the distribution of the time-to-positivity (TTP) of BCs in patients with neutropenia, that is to assess after how many hours of negative BC results detection of bacteraemia becomes unlikely. In addition, we aimed to identify clinical characteristics that predict late (>24 hours) positivity of BCs in this specific patient population.

METHODS

Setting and Study population

The study was performed at the Leiden University Medical Center (LUMC), a tertiary care hospital with a dedicated haematopoietic stem cell transplantation program. During the period of study (January 1st 2012 to February 1st 2016), all consecutive patients, aged ≥18 years with neutropenia and mono- or polymicrobial bacteraemia were included. Eligible patients were identified through search of the BC database of the Department of Medical Microbiology. Neutropenia was defined as an absolute neutrophil count below 0.5 x 10^9 cells/L at the day of BC collection. Patients were eligible for inclusion if the episode of bacteraemia developed during admission as well as when presenting at the emergency or an outpatient department. Multiple episodes of bacteraemia per patient were allowed if the antimicrobial therapy for the previous episode had been completed and clinical cure had been achieved.

Coagulase-negative staphylococci (CoNS) and other common skin contaminants needed to be isolated from at least two separate BC-sets, have identical susceptibility patterns and reason for initiation of directed antimicrobial therapy, to be eligible for inclusion.

In the LUMC, standard empiric antibiotic treatment in case of suspected sepsis during neutropenia is cefuroxime plus gentamicin or vancomycin plus ceftazidime, depending on antibiotic pre-treatment.

Data collection

Clinical variables were collected from the electronic patient records, and included patient demographics, medical history and clinical variables at the time BCs were obtained. Other measured parameters included admission to the intensive care, length of hospitalisation and 30-day mortality. The classification of the source of infection was based on the documented diagnosis and review of the available clinical, radiological and microbiological information. For central line- associated bloodstream infection (CLABSI) specifically, a central line had to be in place within the 48 hours prior to BC collection. The clinical data were independently collected and classified by two of the investigators (EW and ML). In case of inconsistencies, a third investigator (MB) was involved. Detailed data about the BCs were obtained from the database of the Department of Medical Microbiology. Approval for the study was obtained from the institutional ethical re-view board.BC handling procedures and laboratory techniques

A minimum of one BC set (anaerobic and aerobic culture bottle) was collected. The time of bedside collection was automatically recorded, as an imperative part of the BC ordering

procedure, in the electronic patient file. BCs were directly transported to the Department of Medical Microbiology and placed in the BACTEC FX continuous monitoring system (Becton Dickinson B.V., Breda), which detects microbiological growth through measurement of bacterial CO_2 production and automatically records the time of BC positivity.

Definition of time to positivity.

TTP was defined as the time between BC collection and the positive BACTEC signal. If multiple separate BCs from one patient were collected within a time frame of two hours, the bottle with the shortest TTP was used for analysis.

Because of its design as a 'real-life' clinical study, laboratory closing hours had to be taken into account. When a BC was incubated after working hours (Monday to Friday after 5 p.m., Saturday/Sunday after 1.00 p.m.) technical registration in the culture system was delayed to the next morning. In bottles that reached positivity before registration, the culture was recorded positive at the time of registration, between 8 and 9 a.m., instead of upon positive signalling. This resulted in an overestimation of the TTP. In unregistered bottles that were placed after 17:00, referred to as 'evening bottles', the TTP is ≤16 hours by definition (in weekends TTP ≤20 hours).

Statistical analyses

Normally and non-normally distributed continuous variables were compared by Student-*t* test and Mann-Whitney U test, respectively. Univariate risk factor analysis for binominal variables was performed using cross tables and Fisher's exact statistical tests. Results are reported as risk ratios (RR) with 95% confidence intervals (95%CI). multivariable analysis was performed to analyse independent predictors for short (≤16 hours) and late (>24 hours) TTP. The variables for the multivariable analysis were selected based on $p < 0.20$ in the univariate analysis and plausibility.

To detect a potential effect of a repeated measurement phenomenon through inclusion of >1 episode for a proportion of the patient population, both the univariate and multivariable analyses were repeated using a generalized estimating equation model correcting for repeated measures. The median TTP was calculated by including the overestimated TTP of 'evening' and 'weekend bottles', and in an extra analysis with bottles with exact TTP data only (Supplementary files). 'Weekend bottles' were excluded from the categorical TTP analyses, as it was unknown whether TTP was ≤16 hours in these episodes.

The association between short TTP (≤16 hours) and 30-day mortality was evaluated by Kaplan-Meier analysis, using the Log-rank test.

All statistical analyses were performed with the IBM SPSS Statistics, version 23.

RESULTS

Study population characteristics

A total of 190 episodes in 154 patients were included. The median age was 61 years (IQR 47-67) and 115 (60.5%) were men. In the majority (66.8%) of patients, neutropenia was caused by the antineoplastic treatment of a haematological malignancy. Antimicrobial agents, mainly consisting of ciprofloxacin (93 episodes) and penicillin (77 episodes) prophylaxis, were used in 75.8% of patients at the time of BC collection (Table 1). Hundred and twenty-six patients (81.8%) had one episode of bacteraemia, 25 patients (16.2%) had two episodes, and three patients (1.9%) were included with three episodes. One patient had five separate episodes of bacteraemia. In 20 episodes (10.2%) BCs were placed and became positive during evening hours ('evening bottles', TTP≤16 hours) and in 8 episodes (4.2%) during a weekend ('weekend bottles', TTP≤20 hours).

In Table 2 the pathogen distribution and median TTP per micro-organism are summarized. In the majority of episodes the source of bacteraemia was chemotherapy induced mucositis or a CLABSI was diagnosed.

Time-to-positivity

Overall, the median TTP was 15.6 hours (IQR 13.6-18.9 hours). Figure 1 displays the distribution of TTP. The TTP was ≤24 hours in 91.6 % of episodes. In all episodes without antibiotic pre-treatment, the TTP was less than 24 hours. The median TTP was shorter in episodes with Gram-negative bacteraemia, as compared to episodes with Gram-positive bacteraemia (14.5 hours versus 16.7 hours respectively, p<0.01).

Short time to positivity (≤16 hours)

In the univariate analysis, presentation at the outpatient clinic or Emergency Department, being clinically moderately or severely ill and a gastro-intestinal source of infection correlated with short TTP (≤16 hours). Mono-microbial Gram-negative bacteraemia and polymicrobial bacteraemia were associated with TTP ≤16 hours (Table 3). In the multivariable analysis (Supplementary files) presentation at the outpatient clinic or first aid department (adjusted OR 3.53 95%CI 1.14-10.90, p<0.03), making a moderately or severely ill impression during physical examination (adjusted OR 2.51, 95%CI 1.19-5.32, p=0.02), a gastro-intestinal tract infection (adjusted OR 2.25 95% CI 1.09-4.65, p=0.03) and Gram-negative bacteraemia (adjusted OR 2.82 95%CI 1.07-7.45, p=0.04) were independently associated with a TTP ≤16 hours. A history of diabetes (adjusted OR 0.23 95%CI 0.07-0.74, p=0.01) was inversely correlated with a short TTP. No relevant effect of including >1 episode per patient was detected through correction by a generalized estimating equations model.

Table 1. Characteristics of bacteraemia in patients (n=154, 190 episodes) with neutropenia.

Clinical variable	n = 190 (100%)
Patient demographics	
Male gender	115 (60.5)
Age (years) , (median IQR)	61 (47-67)
Medical history	
Haematological malignancy	127 (66.8)
Solid malignancy	26 (13.7)
Stem cell transplantation	75 (39.5)
Solid transplantation	2 (1.1)
Diabetes mellitus	21 (11.1)
Prednisone use past 6 months	122 (64.2)
Clinical presentation	
Temperature>38.0 °C	155 (81.6)
Systolic blood pressure (mmHg) (median IQR)	122 (109-138)
Pulse rate (bpm) (median IQR)	106 (91-120)
Neurologic status:	
No abnormalities	122 (64.2)
Somnolent	7 (3.7)
Confused	9 (4.7)
Sedated	7 (3.7)
Clinical impression:	
Acutely or moderately ill	83 (43.7)
Not ill	63 (33.2)
Central venous catheter in situ	126 (66.7)
Antibiotic pre-treatment	144 (75.8)
Hospitalization before BC[a] (days) (median IQR)	12 (0.1-18.4)
Microbiological parameters	
Monomicrobial Gram-positive bacteraemia:	123 (64.7)
Monomicrobial Gram-negative bacteraemia	49 (25.8)
Polymicrobial bacteraemia	18 (9.5)
Source of infection	
Gastro-intestinal	67 (35.3)
Central venous catheter	56 (29.5)
Respiratory	12 (6.3)
Endovascular (e.g. thrombus)	7 (3.7)
Urinary tract	5 (2.6)
Skin and soft tissue	5 (2.6)
Other	6 (3.2)
Not identified	32 (16.8)
Outcome	
ICU/MCU[b] admission during hospitalization	48 (25.3)
Hospitalization after BC (days) (median IQR)	14 (9-25)
30-day mortality	47 (24.7)
Time between culture and death (days) (median IQR)	58 (12-193)

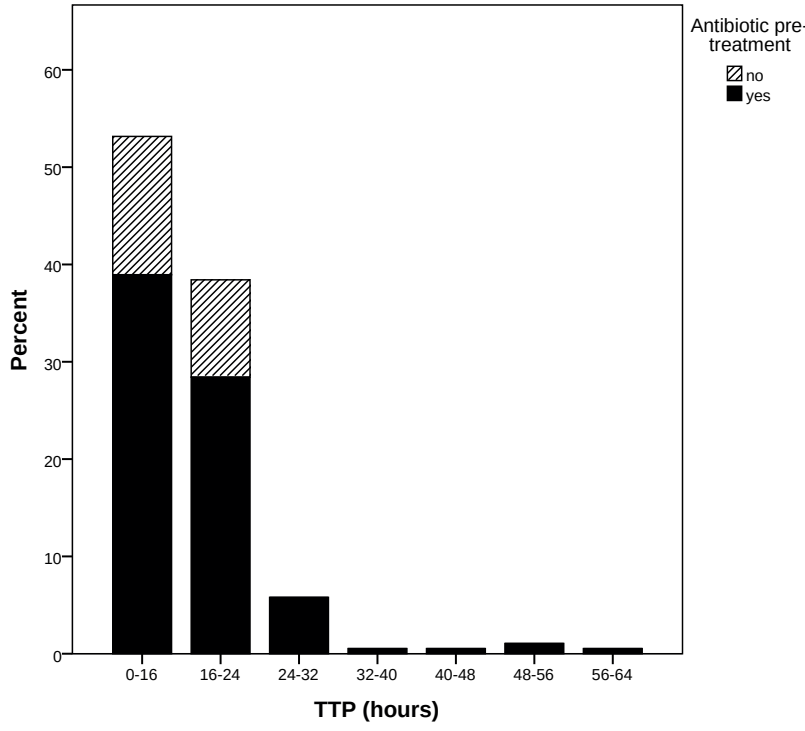
Legend: [a] BC=blood culture [b] ICU/MCU = intensive care unit / medium care unit. [c] In-hospital mortality = mortality during hospitalization episode.

Table 2. Pathogen distribution and median time to positivity(TTP) (190 episodes).

Pathogen	Number of episodes (%)	Median TTP (hours) (range)
Overall	190 (100)	15.6 (7.3-62.5)
Gram-positive:	123 (65)	16.7 (8.5-62.5)
Enterococcus spp.	57 (30)	15.5 (10.5-52.0)
Streptococcus spp.	19 (10)	15.0 (8.5-47.4)
Staphylococcus aureus	4 (2)	15.5 (13.0-19.8)
CoNS[a]	36 (19)	19.1 (12.0-31.2)
Other (including anaerobes)	7 (4)	19.3 (9.3-51.7)
Gram-negative:	49 (26)	14.5 (7.3-55.6)
Escherichia coli	24 (13)	12.5 (7.3-18.3)
Pseudomonas aeruginosa	11 (6)	17.8 (14.5-23.4)
Enterobacter spp.	5 (3)	14.4 (11.8-16.3)
Klebsiella spp.	3 (2)	13.2 (12.9-14.6)
Other (including anaerobes)	6 (3)	22.0 (13.0-55.6)
Polymicrobial	18 (9)	14.9 (8.5-22.0)

Legend: [a] CoNS = *Coagulase-negative Staphylococcus spp.*

Figure 1. Time to positivity and antibiotic pre-treatment distribution (190 episodes)



Long time to positivity (>24 hours)

Univariate analysis demonstrated that antibiotic pre-treatment, CoNS bacteraemia and CLABSI were associated with a TTP >24 hours. An acutely or moderately ill impression on physical examination was inversely correlated with long TTP (RR 0.33, 95%CI 0.11-0.99, p=0.05) (Table 3).

In the multivariable analysis, CLABSI (adjusted OR 4.66, 95%CI 1.41-15.41, p=0.01) was an independent predictor of a long TTP (Supplementary files). No relevant effect of including >1 episode per patient was detected through correction by a generalized estimating equations model.

In 16 (8.4%) episodes the TTP was above 24 hours (Table 4). The BCs in the group of patients with TTP>24 hours were mono-microbial and contained exclusively Gram-positive or anaerobic microorganisms. In 8 (50%) episodes a CLABSI with CoNS was diagnosed. No bacteraemia or sepsis attributable 30-day mortality occurred in the patients with a TTP>24 hours. There was no association between 30-day mortality and TTP<16 hours (p = 0.33)

Table 3. Univariate analysis characteristics in 182 episodes, for time to positivity (TTP) ≤16 hours and TTP>24 hours.

Characteristic	Short TTP (TTP≤16 hours)		Long TTP (TTP>24 hours)	
	RR[a] (95% CI)	P-value	RR (95% CI)	p-value[b]
Patient demographics				
Male gender	1.07 (0.81-1.39)	0.65	0.83 (0.32-2.16)	0.79
Age > 60 years	0.96 (0.74-1.25)	1.00	1.29 (0.50-3.30)	0.79
Medical history				
Haematological malignancy	0.98 (0.76-1.27)	1.00	1.06 (0.38-2.90)	1.00
Solid malignancy	1.11 (0.78-1.59)	0.66	1.60 (0.49-5.18)	0.43
Stem cell transplantation	0.99 (0.77-1.30)	1.00	0.88 (0.33-2.30)	1.00
Diabetes mellitus	0.70 (0.40-1.21)	0.16	0.54 (0.08-3.87)	1.00
Prednisone use past 6 months	0.88 (0.68-1.14)	0.35	0.53 (0.21-1.34)	0.18
Clinical presentation				
Temperature>38.0 °C	1.19 (0.80-1.75)	0.43	N.A[d]	0.08
Systolic blood pressure <100 mmHg	1.28 (0.95-1.73)	0.20	N.A.	0.13
Pulse rate >100 bpm	1.00 (0.76-1.31)	1.00	2.03 (0.68-6.13)	0.28
Neurologic symptoms	1.03 (0.65-1.64)	1.00	0.65 (0.09-4.60)	1.00
Acutely or moderately ill clinical presentation	1.65 (1.18-2.31)	<0.01	0.32 (0.11-0.99)	0.05
Central venous catheter in situ	0.74 (0.57-0.95)	0.04	3.3 (0.77-13.93)	0.10
Antibiotic pre-treatment	0.82 (0.62-1.08)	0.22	N.A.	0.03
Outpatient department	1.50 (1.18-1.91)	<0.01	0.20 (0.03-1.45)	0.08
Microbiological parameters				
Monomicrobial Gram-positive bacteraemia	0.65 (0.51-0.84)	<0.01	2.47 (0.73-8.34)	0.18
Monomicrobial CoNS[c] bacteraemia	0.34 (0.18-0.63)	<0.01	3.92 (1.58-9.75)	<0.01
Monomicrobial Gram-negative bacteraemia Anaerobic bacteraemia	1.48 (1.16-1.89)	<0.01	N.A.	<0.01
Polymicrobial bacteraemia	1.47 (1.10-1.95)	0.05	N.A.	0.37
Source of infection				
Gastro-intestinal	1.37 (1.07-1.77)	0.02	0.65 (0.17-1.92)	0.58
Central venous catheter	0.56 (0.38-0.81)	<0.01	4.95 (1.80-13.58)	<0.01
Respiratory tract	0.74 (0.37-1.46)	0.38	N.A.	0.60
Endovascular (e.g. thrombus)	0.77 (0.32-1.82)	0.70	N.A.	1.00
Urinary tract	N.A.	0.07	N.A.	1.00
Skin and soft tissue	N.A.	0.13	N.A.	1.00
Other	1.20 (0.68-2.16)	0.69	N.A.	1.00
Not identified	0.34 (0.05-2.46)	0.69	0.34 (0.05-2.46)	0.48

Legend: [a] RR = relative risk. [b] P-values were calculated using the Fishers exact test [c] CoNS = Coagulase-negative *Staphylococcus spp* test [d] N.A.: Relative risk not available as one of the cells contained a zero.

Table 4. Characteristics of episodes with a time to positivity >24 hour.

TTP (hours)	Sex, age (years)[a]	Patho-gen[b]	haematological malignancy or stem cell transplant	Solid malig-nancy	Adequate empiric treatment[c]	Source of infection	30-day mortality, cause of death
24.4	M, 65	STAPHA	yes	no	yes	CLABSI[d]	treatment withdrawal[e]
24.5	M, 65	STAPHA	yes	no	yes	CLABSI	no
24.6	M,36	ENCOFE	yes	no	yes	unknown	No
25.2	F, 73	STAPHA	yes	no	no	CLABSI	cerebral vascular infarct
26.0	F, 70	STAPHA	yes	no	no	CLABSI	no
26.1	M, 59	CLOSIN	no	no	no	gastro-intestinal	no
26.2	F, 65	ENCOFE	yes	no	yes	gastro-intestinal	no
26.4	M, 51	STAPHA	yes	no	no	CLABSI	no
26.5	F, 51	STAPEP	yes	no	no	CLABSI	fungal infection
28.5	F, 61	STAPEP	yes	no	yes	CLABSI	no
31.2	M, 32	STAPEP	yes	no	no	CLABSI	no
34.6	M, 69	FUSO	yes	no	yes	CLABSI	no
47.4	F, 69	STREOR	no	yes	yes	gastro-intestinal	treatment withdrawal
51.7	M, 27	ROMUCI	yes	no	yes	CLABSI	no
55.6	F, 50	FUSO	yes	yes	yes	gastro-intestinal	treatment withdrawal
62.5	M, 64	ENCOFA	yes	yes	no	CLABSI	treatment withdrawal

Legend: [a] M = male, F = female. [b] STAPHA = *Staphylococcus haemolyticus*, CLOSIN = *Clostridium innocuum*, ENCOFE = E*nterococcus faecium*, STAPEP = *Staphylococcus epidermidis*, FUSO = *Fusobacterium spp.*, STREOR = *Streptococcus oralis*, ROMUCI = *Rothia mucilaginosa*, ENCOFA = *Enterococcus faecalis*. [c] Adequate empirical therapy based on in vitro susceptibility testing. [d] CLABSI = central line associated bloodstream infection. [e] Treatment withdrawal = Discontinuation of treatment of the underlying disease/malignancy.

DISCUSSION

Main findings

For clinical practice, the most relevant finding of the present study is that in the vast majority (91.6%) of patients with neutropenia and bacteraemia, BC TTP is ≤24 hours, in particular in patients without antibiotic pre-treatment (100%). All patients with Gram-negative aerobic bacteraemia had positive BC results within 24 hours after venepuncture.

Moreover, from the data this study provides on TTP during neutropenia, the probability of positive cultures 24 hours after venepuncture can be estimated by using both the proportion of cultures with late positivity (8.4%) and the proportion of bacteraemia among all BCs that are obtained in suspected sepsis in this population (Box 1). The latter is highly dependent on the patient population, e.g. haematological versus oncological, and varies, based on previous reports, between 15% and 29%.[18-23] This corresponds with a general probability of approximately 1-3% of a positive BC when cultures are still negative after 24 hours.

BOX 1. Formula for calculating the probability of a positive blood culture (BC) after 24 hours of incubation.

A tool for translation to clinical practice

$$P = \frac{(1-TTPe) * X}{1-(TTPe * X)} * 100\%$$

P = Probability of a positive BC when the BC has remained negative after 24 hours of incubation.

X = The fraction of positive BCs among all BCs that are obtained in suspected sepsis in patients with neutropenia (centre-specific).

TTP_e = proportion of positive BCs that are positive in ≤24 hours = 0.92 (95% CI 0.88-0.96) For a more conservative estimation of P, the lower bound of the 95 % CI (0.88) can be chosen for TTPe.

Example

In a medical centre an estimated 20% of BCs in patients with neutropenia and fever is positive.

Then (use formula, X = 0.2 TTP_e = 0.92): If BCs are still negative after 24 hours of incubation, the probability that the culture will yet become positive is approximately 2 %.

Alternatively, using the lower bound of the 95 % CI (0.88) results in a probability of approximately 3 %.

Comparison with other studies

Only few studies have reported on TTP of BCs in patients with neutropenia, and most have focused on one specific pathogen. In these studies the correlation between TTP and clinical characteristics were only partially addressed. In the largest cohort study to date by Martinez *et al*. (n=134), TTP was 11.7 hours (IQR 9-17 hours).[11] The median TTP found in the current study was relatively longer than in previous studies.[11,12] This can be explained by the difference in the definition of TTP. In our study, TTP was measured starting from the time of BC collection at the bedside. In contrast, in most studies TTP was defined as the time between incubation and the positive signal. For interpretation and discussing the clinical consequences, the complete process should be taken into account.

We found that Gram-positive bacteraemia was relatively more common in patients with neutropenia, compared to the general patient population.[11,13] This could be explained by both the relatively high incidence of intravascular line infections in our patient population and the use of chemoprophylaxis (ciprofloxacin). This shift from Gram-negative to Gram-positive organisms in patients with neutropenia during the past few decades, due to chemo-prophylaxis, has been reported previously.[24]

Predictors for short and long TTP

The data show an association between the physicians' clinical assessment at presentation (i.e. a more or less subjective measure) and TTP, TTP being shorter when the patient was assessed to be clinically ill. This could be explained by the fact that patients with

Gram-negative bacteraemia usually are more severely ill compared to patients with bacteraemia caused by CoNS and *Enterococcus* spp., which have longer TTP. Other biological factors like circulating lipopolysaccharides (LPS) during Gram-negative BSI may contribute to this mechanism. The association was less evident for the more objective parameters, such as blood pressure and pulse rate, underlining the additive value of bedside clinical evaluation.

Strengths and limitations

A shortcoming of the present study is the unknown exact TTP in the patients with 'evening and weekend' culture bottles. The inclusion of these patients, in which the actual TTP was shorter than the registered TTP, results in an overestimation of actual TTP. A separate analysis after exclusion of these episodes showed that this barely influenced overall TTP results (Supplementary files). The adjusted definition of TTP, representing the 'practical TTP' instead of the 'microbiological TTP' used in previous studies, could be considered a limitation. However, the practical definition was chosen for reasons of applicability to daily clinical practice, as clinicians are generally not precisely informed about transportation times and details on incubator placing. Transportation and communication logistics differ between hospitals which may impair the applicability of our results to centres where BCs are not directly transported to the laboratory and placed in the incubator or positive BCs are not directly communicated to the attending physician. However, direct transportation, incubation and communication represent best practice in the field of infectious diseases and clinical microbiology.[25]

The present study has several other strengths. First, to the best of our knowledge it represents the largest cohort of patients with neutropenia, providing insight in the distribution of TTP. Secondly the design of the study enables translation to daily clinical practice. Furthermore, the collection of clinical data in addition to microbiological data provides additional insight into the distribution of TTP in subcategories of patients.

Implications for practice and future research

Knowledge on the low probability of bacteraemia after 24 hours is valuable for the management of patients with fever and neutropenia. Primarily, in the absence of a source of infection, a preliminary negative BC, should impel to (re)investigate other (non-bacterial) causes of fever.

In addition, in the scenario of a confirmed source of infection (e.g. pneumonia), preliminary negative BC results can be of value in the early de-escalation of antimicrobial therapy towards a targeted –small spectrum- treatment.

In conclusion, when using modern BC systems and adequate logistics, the probability of bacteraemia when BCs are negative after 24 hours is very low. Based on the data of the present study, there is no rationale to postpone investigations into an alternative diagnosis beyond this point in time.

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SUPPLEMENTARY DATA

Multivariable logistic regression

Table S1A. Multivariable logistic regression for short time-to-positivity (<16 hours).

Variables in the equation	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI
Moderately/acutely ill	0.92	0.38	5.78	1	0.02	2.51	1.19-5.32
Central line	0.70	0.56	1.57	1	0.21	2.04	0.67-5.96
Presentation at the outpatient department	1.26	0.58	4.79	1	0.03	3.53	1.14-10.90
Source: gastro-intestinal	0.81	0.37	4.84	1	0.03	2.25	1.09-4.65
Diabetes mellitus	-1.49	0.60	6.10	1	0.01	0.23	0.67-0.64
Systolic blood pressure <100 mmHg	.043	0.54	0.01	1	0.94	1.04	0.36-3.00
Gram-negative bacteraemia	1.04	0.50	4.37	1	0.04	2.82	1.07-7.45
Constant	-1.25	0.60	4.38	1	0.04	0.29	

Table S1B. Multivariable logistic regression for long time-to-positivity (>24 hours

Variables in the equation	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI
Gram-positive bacteraemia	0.31	0.72	0.19	1	0.67	1.36	0.33-5.57
Clinical impression: not ill	0.65	0.56	1.34	1	0.25	1.92	0.64-5.76
CLABSI[a]	1.54	0.61	6.34	1	0.01	4.66	1.41-15.41
Constant	3.58	0.66	29.70	1	0.00	0.03	

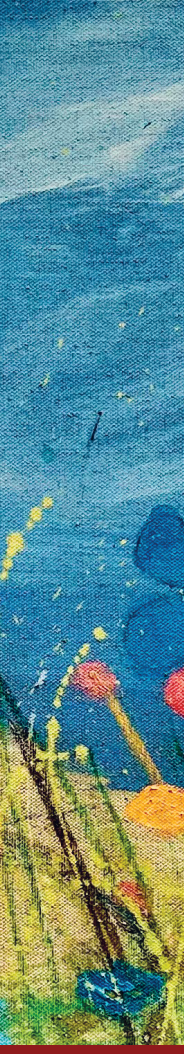
Legend: [a] CLABSI = central line associated bloodstream infection

Separate analysis of time-to-positivity (TTP) after exclusion of evening/ weekend bottles

Table S2. Pathogen distribution and median time-to-positivity (TTP) after exclusion of weekend and evening bottles

Pathogen	Number of episodes (%)	Median TTP (hours) (range)
Overall	162 (100)	15.9 (7.3-62.48)
Gram-positive:	105 (65)	16.8 (9.3-62.5)
Enterococcus spp.	45 (28)	15.5 (10.5-62.5)
Streptococcus spp.	15 (9)	14.8 (11.1-47.4)
Staphylococcus aureus	4 (2)	15.5 (13.0-19.8)
CoNS[a]	34 (21)	19.3 (12.0-31.2)
Other (including anaerobes)	7 (4)	19.3 (9.3-51.7)
Gram-negative:	42 (26)	14.5 (7.3-55.6)
Escherichia coli	18 (11)	12.1 (7.3-15.3)
Pseudomonas aeruginosa	11 (7)	17.8 (14.5-23.4)
Enterobacter spp.	4 (2)	13.8 (11.8-16.3)
Klebsiella spp.	3 (2)	13.2 (12.9-14.6)
Other (including anaerobes)	6 (4)	22.1 (13.0-55.6)
Polymicrobial	15 (9)	15.0 (10.15-22.0)

Legend: [a] CoNS = *Coagulase-negative Staphylococcus spp.*



4

Early differentiation between uncomplicated and complicated *Staphylococcus aureus* bacteraemia: potential value and limitations of a clinical risk score

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ABSTRACT

Objective: A cornerstone in the management of *Staphylococcus aureus* bacteraemia (SAB) is the differentiation between a complicated and an uncomplicated SAB course. The ability to early and accurately identify patients with - and without - complicated bacteraemia may optimize the utility of diagnostics and prevent unnecessary prolonged antibiotic therapy.

Methods: Development and validation of a prediction score in SAB using demographic, clinical, and laboratory data from 2 independent Dutch cohorts; estimating the risk of complicated disease at the time of the first positive blood culture. Models were developed using logistic regression and evaluated by c-statistics, i.e. area under the ROC-curve, and negative predictive values (NPV).

Results: The development- and validation cohorts included 150 and 183 patients respectively. The most optimal prediction model included: mean arterial pressure, signs of metastatic infection on physical examination, leucocyte count, urea level, and time to positivity of blood cultures (c-statistic 0.82, 95%CI 0.74-0.89). In the validation cohort, the prediction score performed moderately accurate, (c-statistic 0.77, 95%CI 0.69-0.84). The NPV for complicated disease for patients with a score of ≤2 was 0.83 (95%CI 0.68-0.92), with a negative likelihood ratio of 0.14 (95%CI 0.06-0.31).

Conclusion: The early SAB risk score helps to identify patients with high probability of uncomplicated SAB. However, the risk score lacked absolute discriminative power to guide decisions on the management of all patients with SAB on its own. The heterogenicity of the disease and inconsistency in definitions of complicated SAB are important challenges in the development of clinical rules to guide the management of SAB.

INTRODUCTION

Staphylococcus aureus is the second most common pathogen identified as the cause of bloodstream infection (BSI).[1] The complications of *Staphylococcus aureus* bacteraemia (SAB), such as endocarditis and metastatic infection are associated with severe morbidity and high mortality rates.[1,2]

The identification of patients with complicated SAB at an early stage is notoriously difficult, but has important implications.[3] For complicated SAB, consensus guidelines recommend higher dosages of antibiotics and prolonged duration of intravenous therapy.[4] Moreover, in this setting infectious complications often need specific additional treatment, *e.g*. surgical drainage of skin and soft tissue abscesses or valve replacement in case of endocarditis. Patients with unrecognised complications of SAB may have higher relapse rates and an increased morbidity and mortality risk.[4,5]

However, misclassification of uncomplicated bacteraemia as complicated bacteraemia may result in unnecessary diagnostic procedures, overconsumption of antibiotics and increased treatment related side effects.[6,7] Current recommendations for the duration of antibiotic therapy in SAB are based on low quality scientific evidence. Guidelines recommend prolonged therapy (4 to 6 weeks) in case of implanted prostheses; positive follow up blood cultures; persisting fever and evidence of infective endocarditis (IE) or metastatic sites.[8] It is the identification of IE and metastatic infection that is challenging in clinical practice. An echocardiogram is recommended in all patients, but adherence to this guideline is limited and the sensitivity of transthoracic echocardiography for endocarditis is low.[9,10] The likelihood of metastatic sites is traditionally assessed based on clinical and laboratory clues.[11] By these alone, asymptomatic metastatic infection may be difficult to detect. Positron emission tomography (PET) scan is valuable for the detection of metastatic foci, that were not detected by clinical examination.[12-14] However, as SAB is very common, performing a PET in all patients with SAB is time- and resource consuming.[6]

An efficient SAB-risk score to timely stratify the risk of complicated disease would therefore be of great additional value to efficiently direct additional testing. In this study, we report the development and validation of an early clinical risk score for complicated disease and illustrate the challenges of risk scores in SAB.

METHODS

Setting and study population of the development cohort

In the retrospective development cohort all consecutive adult patients (age ≥ 18 years) presenting at the Leiden University Medical Center (LUMC), the Netherlands, with SAB between January 2013 and December 2015 were eligible for inclusion. SAB was defined by ≥1 blood culture positive for *S. aureus.* Patients were excluded if: 1) *S. aureus* was detected simultaneously with other pathogens or with contaminants (polymicrobial culture), 2) The patient died within 24 hours after blood culture collection. In patients with multiple episodes of SAB only the first episode was included.

Study Definitions

Uncomplicated SAB was defined as an episode of bacteraemia with ≥1 blood culture with *Staphylococcus aureus*, without evidence of endocarditis/metastatic infection and without positive cultures after 48 hours of adequate therapy and that was treated for a maximum of two weeks and no relapse occurred and the patient survived > 72 hours after presentation.

Adequate therapy was defined as treatment with a least one effective antimicrobial agent, based on in vitro sensitivity testing of the microorganism detected in the blood culture. Relapse was defined as a positive culture of *S. aureus* from any sterile body site within 3 months after sterilisation of blood cultures. All cases that did not meet the criteria for uncomplicated SAB were considered complicated SAB. Confirmed complicated SAB was defined as *S. aureus* bacteraemia with endovascular infection (i.e. endocarditis), and/or other metastatic foci and/or positive blood cultures after 48 hours of adequate antimicrobial therapy. Infective endocarditis (IE) was defined by modified Duke's criteria. [15] Metastatic infection was defined as a radiographical examination and/or culture concordant with vertebral osteomyelitis, epidural abscess, deep tissue abscess (e.g. psoas-) septic pulmonary or cerebral emboli, arthritis or meningitis.

Data collection

In the study centre, all patients with SAB are evaluated by the infectious diseases team through bedside consultation and findings are reported in the electronic patient files. The clinical data were collected through review of the electronic medical charts by two reviewers separately. The following data were obtained: demographic characteristics, medical history, antibiotic therapy at the time of presentation, duration and type of symptoms, clinical parameters, endocarditis stigmata and signs of metastatic infection on physical examination, laboratory test results, radiography results and outcome parameters: duration of hospital admission, relapse, admission to the intensive care unit,

30 day mortality. In addition, time to positivity of blood cultures (TTP) was collected as previous studies indicated TTP to be prognostic of hematogenous spread in SAB.[5, 16, 17]

Time to positivity was defined as the time between venepuncture and the positive alert signal of the blood culture monitoring system. If multiple blood cultures were obtained within a time frame of two hours , the shortest TTP was included in the analysis. Blood samples were inoculated in both anaerobic and aerobic bottles and incubated in the BACTEC FX continuous monitoring system (Becton Dickinson B.V., Breda, The Netherlands). The time of blood culture sampling was automatically recorded. All samples were placed in the BACTEC, within one hour after arrival at the microbiology department.

Setting and study population of the validation cohort

In the validation cohort, patients with SAB were included in three Dutch hospitals. Patients were included consecutively between Jan 1st 2016 and August 1st 2017. For each of these patients the demographic variables, the variables needed for calculation of the risk score and outcome variables were collected through review of the electronic patient files. Definitions of (un)complicated SAB were identical for the development and validation cohort.

Statistical analyses

Descriptive statistics were performed in both the developmental and validation cohort. Data are presented as rates (percentages) for categorical variables and as medians (interquartile range/IQR) for continuous variables.

Risk score development

In the developmental cohort, patients with complicated SAB were compared with patients with uncomplicated SAB using Student's t-test and Mann Whitney-test for continuous variables and Fisher's exact test for nominal variables. A logistic regression model was applied with complicated SAB as the dependent (outcome) variable. All possible clinical and laboratory variables with $P<0.2$ in the univariate analysis were included in the multivariable regression analysis. Continuous variables were categorized if the model's predictive value was not negatively affected by categorization. Points for individual predictors were based on the co-efficient from the multivariable model rounded to the nearest .5 or .0. The values of the independent predictive values were summed, resulting in the early SAB risk score. These SAB risk-scores were compared to the observed proportion of patients with complicated SAB. The negative and positive predictive value of the SAB-risk score was calculated for several cut-offs. A clinically applicable cut-off was selected based on the negative predictive value (NPV), as the primary goal of the risk score is to exclude complicated SAB. The area under the receiver

operating characteristic (c-statistic, AUC-ROC) curve was reported as a measure of the discriminative value of the model.

Risk score validation

The performance of the model was tested in an independent validation cohort and the c-statistic was determined. The NPV and negative likelihood ratio (NLR) of the SAB-risk score for complicated SAB were reported. The NLR is defined as the probability that a patient with complicated SAB has a low SAB-risk score (false negative) divided by the probability that a person with uncomplicated SAB tested has a low SAB-risk score (true negative). The NLR represents how the probability of complicated disease shifts when the SAB risk score is low.

Missing data in the variables of the risk score were imputed in the validation cohort, using multiple imputation. All analyses were performed with SPSS (IBM statistics, version 25) software for Windows.

Ethical approval

Ethical approval was granted by Leiden University Medical Center institutional ethical review committee, the Haga Teaching Hospital and the Alrijne hospital.

RESULTS

A total of 150 patients were included in the development cohort. The patient characteristics are summarised in Table 1. *Borderline oxacillin resistant S. aureus* and *methicillin-resistant S. aureus* (MRSA) were both isolated in one episode. In 58 (38.7%) patients complicated bacteraemia was confirmed. Endovascular infection (endocarditis, or infected thrombi) and metastatic infection were diagnosed in 12 (8.0%) and 22 (14.7%) patients respectively. In 23 (15.3%) patients, complicated bacteraemia was not confirmed by diagnostics, but the patient was treated for complicated disease, with prolonged intravenous therapy. In the development cohort, 69 (46.0%) patients fulfilled the definition for uncomplicated SAB. Missing data fields were <2%.

Derivation of the early SAB risk-score

The univariate analyses for complicated bacteraemia in the development cohort are shown in the Supplementary files. Community acquired infection was associated with complicated SAB (OR 4.6, 95%CI 2.2-9.2, p<0.01). Urea levels ($p < 0.01$) and leukocyte count ($p < 0.01$) were associated with complicated SAB. A TTP below 16 hr was associ-

ated with complicated disease (OR 3.3, 95% CI 1.6-6.9, p<0.01). Sensitivity, specificity and predictive values for different TTP cut-offs are shown in the Supplementary files.

Table 1. Characteristics of the developmental (n=150) and validation cohort (n=183).

	Development cohort N=150	**Validation cohort** N=183
Male sex	108 (72)	113 (61.4)
Age	62 (51.0-75.3)	71 (61-81)
Comorbidities		
Neutropenia	5 (3.3)	8 (4.4)
Organ transplantation	14 (9.3)	6 (3.3)
Diabetes	35 (23.3)	52 (28.3)
Receiving dialysis	7 (4.7)	7 (3.8)
Intravascular catheter	33 (22.0)	19 (3.3)
Location		
Emergency department or out-patient clinic	93 (62.0)	137 (75.3)
General ward	57 (38)	42 (22.8)
Intensive care department	11 (7.3)	4 (2.2)
Clinical parameters		
Mean arterial pressure	88.5 (79.6-100.0)	90 (78-102)
Newly diagnosed hearth murmur	14 (9.3)	27 (14.8)
Time to positivity (hours)	18.1 (14.8-22.6)	16.3 (13.5-16.3)
Diagnosis		
Uncomplicated SAB	69 (46.0)	73 (39.9)
Complicated SAB	81 (54.0)	110 (60.1)
Confirmed complicated SAB	58 (38.7)	80 (43.7)
Endocarditis	8 (5.3)	28 (15.2)
Metastatic disease	22 (14.7)	53 (28.8)
Persistent positive blood cultures	39 (26.0)	45 (24.5)
Outcome		
Intensive care admission	36 (24.0)	30 (16.3)
30-day mortality	31 (20.7)	35 (19.1)

Legend: Values are numbers (%) for continuous variables and median ± IQR for continuous variables. Uncomplicated SAB was defined as an episode of bacteraemia with ≥1 blood culture with *Staphylococcus aureus*, without evidence of endocarditis/metastatic infection and without positive cultures after 48 hours of adequate therapy and that was treated for a maximum of two weeks and no relapse occurred and the patient survived > 72 hours after presentation. All cases that did not meet the criteria for uncomplicated SAB were considered complicated *SAB*.* Newly diagnosed diastolic hearth murmur, endocarditis stigmata and/or signs of metastatic infection on physical examination. TTP = time to positivity.

In the multivariable logistic regression analyses, independent predictive variables for complicated diseases were mean arterial pressure, signs of metastatic infection on physical examination, neutropenia, urea level, leukocyte count and time to positivity (p<

0.01). For the resulting model (Table 2), the fraction of explained variation (Nagelkerke R^2) was 0.39. The range of the constructed prediction score was 0 to 9, with a higher score indicating a higher probability of complicated SAB (Table 2). When using a cut-off of 2 points, the negative predictive value was 91.9% (78.5-97.2). The discriminative ability, c-statistic was 0.82 (95%CI 0.74-0.89).

Table 2. Independent predictive variables for development of complicated *S. aureus* bacteraemia and attributed points in the prediction score.

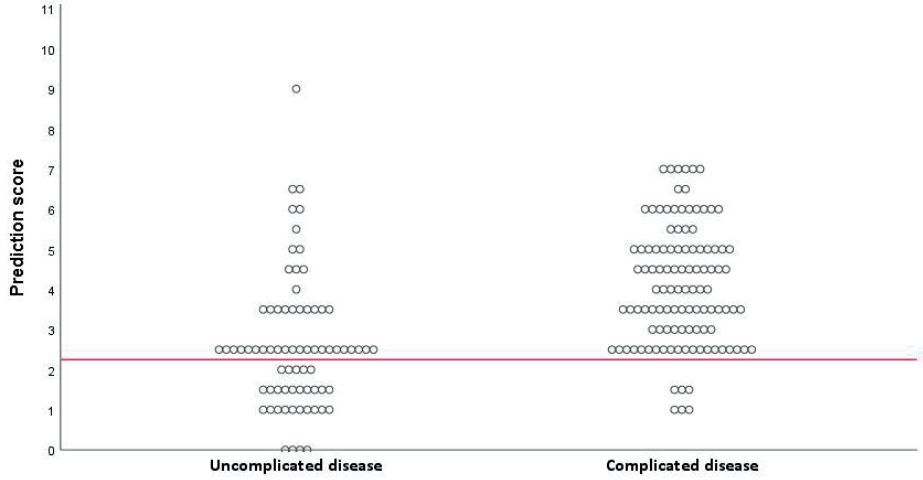
Variable	B	OR (95%CI)	p-value	Points*
Clinical parameters				
Signs of metastatic infection‡	1.4	4.2 (1.6-10.9)	<0.01	1.5
Mean arterial pressure < 90 mmHg	1.1	2.9 (1.3-6.8)	0.01	1
Laboratory parameters				
Leucocyte count > 15 x 10^9/L	1.2	3.2 (1.3-7.7)	0.01	1
Neutropenia < 0.5 10^9/L	3.1	20.4 (1.4-307.4)	0.03	3
Urea > 13 mmol/L	1.2	3.3 (1.4-7.8)	0.01	1
Time to positivity				
0-16 hours	2.3	8.7 (2.6-29.0)	<0.01	2.5
16-24 hours	1.0	2.7 (0.9-8.3)	0.09	1
>24 hours	0	-	-	0

Legend: B =regression coefficients. OR = odds ratio; * Points were attributed based on the regression co-efficient. ‡ ; signs of metastatic infection' was defined as: newly diagnosed diastolic hearth murmur, endocarditis stigmata and/or signs of metastatic infection on physical examination.

Validation of the risk-score

In the validation cohort, 183 patients were included (Table 1), 73 (39.9%) patients fulfilled the criteria for uncomplicated SAB. In 80 (43.5%) patients a complicated disease was confirmed. Missing data were <2 %. The risk scores for patients with uncomplicated SAB compared to the patients with complicated SAB (confirmed or unconfirmed) are presented in Figure 1. In patients with uncomplicated disease the median prediction score was 2.5 (IQR 1.5-3.5), for complicated disease 4 (IQR 3-5). The AUC-ROC value was 0.77 (95%CI 0.69-0.84). The performance of the SAB-risk for different cut-off values is presented in Table 3. The negative predictive value for the cut-off 2 was 0.83 (95%CI 0.68-0.92), with a negative likelihood ratio of 0.14 (95%CI 0.06-0.31).

Figure 1 Prediction scores for patients with *S. aureus* bacteraemia in the validation cohort.



Legend. Uncomplicated SAB was defined as an episode of bacteraemia with ≥1 blood culture with *Staphylococcus aureus*, without evidence of endocarditis/metastatic infection and without positive cultures after 48 hours of adequate therapy and that was treated for a maximum of two weeks and no relapse occurred and the patient survived > 72 hours after presentation. Complicated *SAB*: All cases that did not meet the criteria for uncomplicated SAB. The red line indicates the 2 points cut-off.

Table 3. Performance of the *Staphylococcus aureus* bacteraemia (SAB) risk-score-risk score, in the validation cohort (n=183).

Score	Uncomplicated disease N (%)	Complicated disease N (%)	Endocarditis N (%)	Metastatic infection N (%)
0-2	29 (82.9)	6 (17.1)	3 (8.6)	2 (5.7)
2.5-4.5	36 (35.0)	67 (65.0)	15 (12.3)	29 (28.2)
≥5	8 (17.8)	37 (82.2)	10 (23.8)	22 (48.9)

Legend: Values are the number (%) of patients with a score in the corresponding range. Complicated SAB = evidence of endocarditis/metastatic infection and/or with positive cultures after 48 hours of adequate and/or that was treated with prolonged antibiotic therapy (>2 weeks), and/or relapse occurred and/or the patient diseased <72 hours after presentation. All other cases were considered uncomplicated. Endocarditis was defined by the modified Duke criteria. Metastatic infection = radiographical examination and/or culture concordant with vertebral osteomyelitis, epidural abscess, deep tissue abscess (e.g. psoas) septic pulmonary or cerebral emboli , arthritis or meningitis.

DISCUSSION

The SAB risk-score, developed and validated in this study, facilitates to discriminate patients with low probability of complicated SAB from patients with high probability of complicated SAB, using readily available parameters. However, the rule lacked negative predictive power to accurately guide decisions on the management of patients with SAB on its own. This is exemplified by the observation that with a low-score, the probability of complicated disease was 17.1%, which is not acceptable, considering the morbidity and mortality associated with unrecognised sequelae and relapse.

A prognostic model for SAB should primarily aim to reliably exclude complicated disease, with a high negative predictive power. However, prevalence of complicated disease depends on the setting and patient population and negative predictive values are prevalence dependant. Therefore, reported NPVs may not be applicable to other settings. Unlike NPV, the negative likelihood ratio (NLR) does not vary with prevalence and is a relevant marker in SAB risk scores.

Previous clinical risk scores

Multiple attempts have been made to assess the risk of complicated SAB in the past. Table 4 provides an overview of prior published prediction rules in SAB. Most of these prediction rules focus on infective endocarditis alone, discarding other foci of metastatic infection that may be relevant for the management of the infection. Furthermore these studies are limited by low rates of TEE and therefore lack a sensitive reference

Table 4. Clinical risk scores for complications in *S. aureus* bacteraemia.

Study	N	Endpoint	NPV (95%CI)	NLR (95%CI)	External validation
Joseph 2013 [27]	306	IE (TTE or TEE)	1.00 (0.96-1.00)	0.00 *	No
Gow 2015 [28]	574	IE (Duke)	1.00 (0.99-1.00)	0.00*	No
Rasmussen 2011 [29]	244	IE	0.95 (0.90-0.98)	0.19 (0.09-0.41)	No
Palraj 2015 [30]	678	IE (Duke)	0.98 (0.95-0.99)	0.09 (0.04-0.20)	No
Buitron de la Vega 2016 [31]	398	IE (Duke)	1.00 (0.99-1.00)	0.00 *	No
Kaasch 2011 [32]	304 432	IE (Duke)	1.00 (0.94-1.00) 0.99 (0.95-1.00)	0.00* 0.08 (0.02-0.59)	Yes**
Kaasch criteria in Khatib [19]	177	IE (TEE)	0.80 (0.66-0.90)	0.72 (0.40-1.28)	-
Khatib 2013 [19]	177	IE (TOE)	0.98 (0.86-1.00)	0.20 (0.01-0.78)	No
Tubiana 2014 [9]	2091	IE (Duke)	0.99 (0.98-0.99)	-	No
Heriot 2015 [33]	532	IE (TEE)	1.00 (0.86-1.00)	0.00*	No
Showler 2015 [34]	268	IE (Duke)	0.99 (0.95-1.00)	0.05 (0.01-0.35)	No
Incani 2013 [35]	144	IE (Duke)	0.84 (0.72-0.92)	0.51 (0.30-0.88)	No
Mölkänen 2016 [36]	430	Metastatic infection	0.36 (0.30-0.44)	0.41 (0.32-0.53)	No
Gliddon 2015 [37]	259	Metastatic infection	1.00 (-)	0.00*	No
Lesens 2004 [38]	104	Metastatic infection	0.83 (0.73-0.90)	0.34 (0.19-0.62)	No
Fowler 2003 [3]	724	Complicated SAB	0.84 (-)	-	No
Lambregts (this study)	150	Complicated SAB	0.83 (0.68-0.92)	0.14 (0.06-0.31)	Yes

Legend: The negative predictive value (NPV) and negative likelihood ratio (NLR) are provided in this table as they represent the performance of the score in excluding complicated SAB/endocarditis. If a score performs well, the NPV will be high and the NLR low. IE = infective endocarditis. TTE = transthoracic echocardiography. TEE = transesophageal echocardiography. * Confidence interval calculations could not be performed because of zero events of endocarditis in the low-risk group. ** The criteria by Kaasch were applied to two separate cohorts. The risk score was later applied in the study by Khatib et al [19] to a selected population of patients assessed with TEE. ***The retrospective cohort was randomly divided into a developmental and validation cohort.

standard for endocarditis.[18] The rules that do focus on all aspects of complicated SAB most often go unvalidated. The prediction score by Fowler *et al*. was derived from a large, prospective cohort study, and proposed a comprehensive prognostic model of 4 clinical factors to estimate the likelihood of complications.[3] However, even with a score of 0, approximately 16% of patients had complicated disease. This result is comparable to the current study. The model by Fowler *et al*. was not validated externally.

Unfortunately, external validation in SAB risk scores has often been omitted. The importance of validation was illustrated with the disappointing performance of the Kaasch criteria for endocarditis in a cohort of patient assessed with TEE.[19] The diversity in patient population, reflected in the differences in prevalence of complicated SAB in the various studies stresses the need for external validation.[20-22]

Recognition of SAB in clinical practice

Despite the lack of solid validated risk scores, a recent study randomized patients to algorithm based therapy versus standard of care.[23] Therapy failure among patients that were treated for uncomplicated SAB using the algorithm was relatively high, 29.4%. High rates of relapse and therapy change due to unsatisfactory clinical response, suggest that these patients may have been misclassified using the algorithm.

Failure to identify patients with complicated SAB at an early timepoint may be explained by the heterogeneity of disease associated with SAB. Both host and pathogen virulence factors determine the clinical presentation as well as the course of the disease.[3,24] It may simply not be feasible to develop a comprehensive risk score with an acceptable negative predictive value for this clinical entity.

Another challenge in the development of clinical rules is the definition of complicated SAB and the translation of this definition to observational studies.[25] In daily practice, a relevant proportion of patients is treated with prolonged courses of antibiotic treatment based on clinical clues, without additional tests to confirm complications.[18] This 'grey zone' of patients who receive prolonged treatment without confirmed complications impairs the development and validation of risk scores.

Strengths and limitations

In this study a broad definition of complicated SAB was applied, to limit misclassification as uncomplicated bacteraemia. This may have negatively impacted NPV, as patients may have been misclassified as complicated disease.

A second limitation the study is that one of the predictors (neutropenia) was estimated imprecisely, because of the low prevalence of neutropenia in the study cohort.

An innovative feature of the current study is the use of TTP as an important element of the risk-score. TTP may vary between institutions and is dependent on hospital logistics. Despite this limitation, use of TTP is biologically plausible and promising with regard to the assessment of SAB. The association between TTP and metastatic infection has been described previously and hence was confirmed in this study.[26]

Summary and conclusions

Despite the high incidence of SAB globally, contemporary strategies for differentiating uncomplicated and complicated bacteraemia in real life clinical practice, are based upon low or moderate quality evidence. This study provides a validated risk score for discriminating patients with low and high risk of complicated SAB. More studies, incorporating both clinical and laboratory variables, with thorough work-up including nuclear imaging to define the clinical end-point, are needed to optimize the clinical rule, aiming at further improvement of the negative predictive power.[5,6]

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SUPPLEMENTARY DATA

Table S1: Univariate predictors of complicated *Staphylococcus aureus* bacteraemia (SAB) in the developmental cohort (n=150).

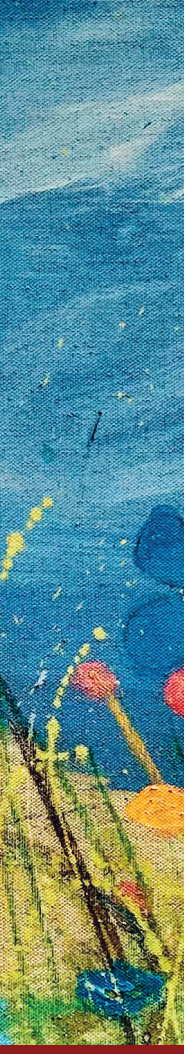
Characteristics	Uncomplicated SAB N=69	Complicated SAB N=81	p-value
Male sex	47 (68.1)	61 (75.3)	0.37
Age, mean ± SD	61.8 (17.0)	61.7 (18.7)	0.98
Medical history			
Diabetes	12 (17.4)	23 (28.4)	0.13
Malignancy	15 (21.7)	12 (14.8)	0.29
Organ transplantation	7 (10.1)	7 (8.6)	0.79
Corticosteroids	22 (31.9)	24 (39.6)	0.86
Intravascular catheter	31 (21.0)	17 (21.0)	<0.01
Length of hospital stay	2.8 (8.3)	5.6 (8.8)	0.05
Clinical parameters			
Mean arterial pressure	92.0 (14.8)	87.0 (18.6)	0.05
History of fever (in days)	0.24 (0.7)	0.67 (1.47)	<0.01
Signs of complicated disease*	10 (14.5)	29 (35.8)	<0.01
EMV<15	11 (15.9)	14 (17.3)	1.00
Laboratory parameters			
C-reactive protein	139.4 (93.5)	168.2 (118.1)	0.18
Erytrocyt sedimentation rate	65.8 (40.7)	61.3 (34.9)	0.73
Urea, mmol/L	9.7 (8.5)	13.0 (10.7)	0.01
Creatinine, mmol/L	141.3 (173.7)	140.2 (140.4)	0.646
Leukocyte count x 10^9/L	11.0 (5.1)	13.9 (7.1)	<0.01
Thrombocyte count x 10^9/L	243.4 (138.4)	214.3 (156.1)	0.84
TTP of blood cultures	61.8 (17.0)	19.0 (11.2)	<0.01

Legend. Values are numbers (%) for continuous variables and mean ± SD for continuous variables. *Uncomplicated SAB* was defined as an episode of bacteraemia with ≥1 blood culture with *Staphylococcus aureus*, without evidence of endocarditis/metastatic infection and without positive cultures after 48 hours of adequate therapy and that was treated for a maximum of two weeks and no relapse occurred and the patient survived > 72 hours after presentation. All cases that did not meet the criteria for uncomplicated SAB were considered complicated *SAB*.* Newly diagnosed diastolic hearth murmur, endocarditis stigmata and/or signs of metastatic infection on physical examination. TTP = time to positivity.

Table S2: Sensitivity, specificity, positive predictive value and negative predictive value for endocarditis/metastatic infection for different cut-offs of TTP.

	TTP-cut-off (hours)	**Sensitivity** (95%CI)	**Specificity** (95%CI)	**PPV** (95%CI)	**NPV** (95%CI)
Endocarditis	24	100 (63.1-100.0)	23.9 (17.19-31.8)	6.9 (6.3-7.5)	100.0 (*)
	20	87.5 (47.4-99.7)	65.5 (57.1-73.3)	12.5 (9.2-16.8)	97.1 (93.7-99.8)
	16	37.5 (8.5-75.5)	68.3 (60.0-75.9)	6.3 (2,6-14.4)	95.1 (91.8-97.1)
Metastatic infection	24	95.5 (77.2-99.9)	25.8 (18.5-34.3)	18.1 (16.2-20.2)	97.1 (82.6-99.6)
	20	90.9 (70.8-98.9)	37.5 (29.1-46.5)	20.0 (17.2-23.2)	96.0 (86.3-98.9)
	16	59.1 (36.4-79.3)	72.7 (64.1-80.2)	27.1 (19.2-36.8)	91.2 (86.1-94.5)

Legend. 95%CI = 95 % confidence interval. TTP = Time to positivity in hours, PPV = positive predictive value, NPV = negative predictive value Endocarditis was defined according to the Dukes criteria. Patients with antibiotic pre-treatment were excluded. Metastatic infection was defined as a radiographical examination and/or culture concordant with vertebral osteomyelitis, epidural abscess, deep tissue abscess (e.g. psoas) septic pulmonary or cerebral emboli , arthritis or meningitis. N.a. * Confidence intervals not provided because of a null value.



5

Using local clinical and microbiological data to develop an institution specific carbapenem-sparing strategy in sepsis: a nested case-control study

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ABSTRACT

Background: From a stewardship perspective it is recommended that antibiotic guidelines are adjusted to the local setting, accounting for the local epidemiology of pathogens. In many settings the prevalence of Gram-negative pathogens with resistance to empiric sepsis therapy is increasing. How and when to escalate standard sepsis therapy to a reserve antimicrobial agent, is a recurrent dilemma. The study objective was to develop decision strategies for empiric sepsis therapy based on local microbiological and clinical data, and estimate the number needed to treat with a carbapenem to avoid mismatch of empiric therapy in one patient (NNTC).

Methods: We performed a nested case control study in patients (>18 years) with Gram-negative bacteraemia in 2013-2016. Cases were defined as patients with Gram-negative bacteraemia with in vitro resistance to the combination 2nd generation cephalosporin AND aminoglycoside (C-2GC+AG). Control patients had Gram-negative bacteraemia with in vitro susceptibility to cefuroxime AND/OR gentamicin, 1:2 ratio. Univariate and multivariable analysis was performed for demographic and clinical predictors of resistance. The adequacy rates of empiric therapy and the NNTC were estimated for different strategies.

Results: The cohort consisted of 486 episodes of Gram-negative bacteraemia in 450 patients. Median age was 66 years (IQR 56-74). In vitro resistance to C-2GC+AG was present in 44 patients (8.8%). Independent predictors for resistance to empiric sepsis therapy were hematologic malignancy (adjusted OR 4.09, 95%CI 1.43-11.62, p<0.01), previously cultured drug resistant pathogen (adjusted OR 3.72. 95%CI 1.72-8.03, p<0.01) and antibiotic therapy during the preceding 2 months (adjusted OR 12.5 4.08-38.48, p<0.01)**.** With risk-based strategies, an adequacy rate of empiric therapy of 95.2% - 99.3% could be achieved. Compared to treating all patients with a carbapenem, the NNTC could be reduced by 82.8% (95%CI 78.5-87.5%) using the targeted approaches.

Conclusions: A risk-based approach in empiric sepsis therapy has the potential to better target the use of reserve antimicrobial agents aimed at multi-resistant Gram-negative pathogens. A structured evaluation of the expected antimicrobial consumption and antibiotic adequacy rates is essential to be able to weigh the costs and benefits of potential antibiotic strategies and select the most appropriate approach.

INTRODUCTION

Current guidelines on antibiotic stewardship recommend to adapt empiric therapy to local microbiological data.[1] However, specific recommendations on when and how to change the empiric treatment guidelines in response to increasing resistance rates are lacking. The empiric strategy may need to be broadened to guarantee coverage of the most common pathogens. The downside of this action is an increase in selective pressure, driving further emergence of resistance.[2] Therefore, whether or not to escalate empiric treatment guidelines in response to new resistance data is a recurrent dilemma in antibiotic policy committees all over the world.

Strategies that break the vicious circle of increasing resistance and increasing antibiotic consumption are needed.[3-5] The use of a risk-based discrimination in empiric therapy has this potential. If patients with a high probability of infection with a resistant pathogen can be identified upfront, empiric therapy can be escalated selectively.[6,7] This approach combines the two major aims of antibiotic stewardship: promoting effective antimicrobial therapy in all patients, while limiting antibiotic usage where possible.[8] Both aims are especially relevant in sepsis guidelines.[9] The importance of prompt initiation of effective empiric therapy in this patient category is well recognized.[10–14] and the antibiotic consumption associated with empiric treatment for (presumed) sepsis is substantial.[15,16]

In the Netherlands and other countries with low to moderate resistance rates, the standard treatment for sepsis of unknown origin often is a second or third generation cephalosporin (2GC or 3GC) combined with an aminoglycoside (AG).[17] The prevalence of Gram-negative pathogens that are resistant to this empiric treatment combination, due to production of extended spectrum β-lactamases (ESBL) and other mechanisms, is increasing.[18] This development warrants regular re-evaluation of empiric sepsis therapy recommendations and consideration of escalation to a carbapenem.

The study objective was to explore a practical method to design institutional strategies for empiric therapy based on local microbiological and clinical data, and to estimate the potential treatment adequacy rates and reserve antimicrobial consumption for each of these strategies.

METHODS

The study was conducted according to the approach described in Table 1. This 7-step method is illustrated using local data. The risk factors for bloodstream infection with a Gram-negative organism with reduced susceptibility to standard sepsis treatment were identified in the case-control study. The effect of different targeted empiric therapy approaches on the proportion of patients that receive adequate empiric treatment and the

Table 1. 7-step method for the development of institution specific empiric treatment guidelines.

	Description	Example
Step 1 The clinical question	Define A) the clinical syndrome for which empiric treatment is re-evaluated, B) the patient population and C) the current empiric treatment guideline.	The clinical syndrome is sepsis. The target patient population is adult patients in an academic medical center. The current empiric treatment for sepsis is C-2GC-AG.
Step 2 Susceptibility data	Determine the local prevalence of resistance to the current empiric treatment (syndrome and population specific)	Of all patients with suspected sepsis, 6.7% are diagnosed with Gram-negative bacteraemia.* Gram-negative resistance for C-2GC-AG in blood culture isolates is 8.8 %. In the study center. Methicillin resistant *Staphylococcus aureus* (MRSA) and penicillin resistant pneumococcal species are very rare in the Netherlands.
Step 3 Definition of risk factors	Identify available predictors for resistance to the current empiric treatment	Independent risk factors of resistance to empiric sepsis therapy in the study population are prior antimicrobial use and prior isolates with a DRP.
Step 4 Targeted strategies	Identify potential targeted treatment strategies	Option A: A carbapenem in patients with a DRP cultured the previous 6 months and C-2GC-AG in other patients. Option B: a carbapenem in all patients with sepsis
Step 5 Estimating benefit	Estimate the proportion of patients that would be adequately treated if empiric sepsis therapy was changed	Option A: 95.2 % of Gram-negative bloodstream infections would be treated adequately Option B: 99.8 % of Gram-negative bloodstream infections would be treated adequately
Step 6 Estimating costs	Identify the number needed to treat (NNTC)	Option A: NNTC is 42 patients. Option B: NNTC is 173 patients.
Step 7 Selection of empiric treatment strategy	Balance the cost and benefits of phase 5 and 6 to select the most appropriate strategy.	A moral deliberation with stakeholders to decide on the most appropriate antibiotic therapy for sepsis in the institution.
Implementation and evaluation	Evaluate the costs and benefits of the selected approach	Option A was selected. After implementation adequacy rates, outcome, side-effects of antimicrobials and antimicrobial consumption were evaluated.

Legend: NNTC = number of patients needed to treat with a carbapenem instead of cefuroxime/gentamicin to prevent one case of inappropriate empiric therapy, C-2GC-AG=cefuroxime combined with gentamicin , DRP = Drug resistant pathogen.
* To estimate the overall blood culture positivity rate, the proportion of bacteraemia was determined during two separate months, June and December 2014. During this period, all patients in whom blood cultures were obtained because of fever were included. In this pilot period, of all patients with suspected infection, 53/778 (6.7%) had positive blood cultures with a Gram-negative pathogen. All other data used in the example provided in column 3 are cohort data.

number of patients needed to treat with a carbapenem to avoid mismatch of empiric therapy in one patient (NNTC), were estimated applying the case control study (2013–2016) and the cohort data (2013–2014). The reporting of the results was performed in accordance with STROBE guidelines for cohort and case-control studies.[19]

Setting and patient population

The study period was defined as from January 2013 to December 2016. The Leiden University Medical Center (LUMC) is a tertiary care hospital in the Netherlands. Standard empiric sepsis therapy in the institution consisted of a second generation cephalosporin, cefuroxime, combined with gentamicin (C-2GC + AG). In 2013– 2014, all patients > 18 years of age, with monomicrobial Gram-negative bacteraemia were included (cohort 2013– 2014). Both community acquired and nosocomial episodes were eligible for inclusion. Patients were identified through search of the microbiology laboratory database.

Gram-negative bacteraemia was defined as one or more positive blood cultures with a Gram-negative micro-organism. Cases were defined as adult patients with bacteraemia with Gram-negative micro-organisms with reduced susceptibility to C-2GC + AG. Reduced susceptibility was defined as intermediate sensitivity (I) or resistance (R) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria to 2GC and AG.

Control patients were defined as patients with Gram-negative bacteraemia with a micro-organism susceptible to 2GC, AG or both. Two control patients per case patient were randomly selected from the cohort. Using the patient identification code, every third patient meeting the criteria for control was selected.

The inclusion period for the case selection was prolonged with two additional years (2013–2016) compared to the cohort (2013–2014), because of the relatively low incidence of combined 2GC and AG resistance. It was assumed that the characteristics of the control and case populations were not variable over the period of study.

Clinical data

Clinical data were collected from the electronic medical records and included demographics, co-morbidities, clinical characteristics at the time of presentation and known risk factors of antimicrobial resistance such as a history of recurrent urinary tract infections (UTI's), previous hospital stays and previous antibiotic treatment. [6,8,20-23]

Previous antibiotic treatment was defined as administration of one or more antibiotic doses during the previous 2 months. Current antibiotic use was defined as at least one

administration of antibiotics during the 24 h preceding the collection of blood specimens. For in-hospital and outpatient clinic prescriptions these data were obtained from the institutional electronic prescription system. For other prescriptions, the documented patient history, referral letters and correspondence with other health care providers were searched.

Prior known colonization or infection with a drug resistant pathogen (prior-DRP) was defined as the isolation of one of the following pathogens from any body site, including rectal swabs: vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus*, Enterobacterales with in vitro resistance to AG, second and/or third generation cephalosporins and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporins, AG or quinolones.

In clinical practice, physicians may defer from standard sepsis therapy for a variety of reasons, including a high suspicion of antimicrobial resistance. To assess current practice, the antibiotics that constituted the initial empiric therapy were extracted from the patient records. Empiric therapy was considered adequate if at least one of the antibiotics matched the in vitro susceptibility of the isolated pathogen. Multiple episodes of bacteremia per patient were allowed if the antimicrobial therapy for the previous episode had been completed and clinical and microbiological cure had been achieved.

Microbiological data

Microbiological data were retrieved from the database of the Microbiology department and included the isolated micro-organism and susceptibility patterns of the current and previous episodes. Blood cultures were incubated using the BACTEC™ blood culture system (Becton Dickinson Benelux, Erembodegem, Belgium).

Identification of isolates was performed using matrix-assisted laser desorption/ionisation-time of flight spectrometry (MALDI-TOF) using the Microflex system (Bruker, Bremen, Germany). Antimicrobial susceptibility testing was performed with the VITEK2 system and E-tests (BioMérieux, Brussels, Belgium). Extended-spectrum beta-lactamase (ESBL) production was determined by the use of the combination disc diffusion test.[23] Minimum inhibitory concentration (MIC) breakpoints for resistance and intermediate sensitivity were based on EUCAST criteria.[24]

Statistical analysis

Imputation for missing data was not applied. Categorical variables were reported as counts and percentages and continuous variables as medians with interquartile ranges (IQR).

Univariate analysis of clinical predictors of reduced susceptibility to empiric therapy was performed using the Fisher's exact test and reported as odds ratios (OR) with 95% confidence interval (95% CI). All variables that showed a trend towards an association ($P < 0.2$) were included in the logistic regression analysis. Potential targeted empiric treatment strategies were designed based on the strongest independent predictors of resistance to C-2GC + AG. The proportion of patients with bacteraemia that would receive adequate treatment with the strategy (adequacy rate) and the number of patients needed to treat with a carbapenem to avoid mismatch of therapy in one patient (NNTC) were estimated using the formula described in the Supplementary data. The data for these estimations were derived from the study cohort: The frequency of the strategies risk factor(s) (cohort 2013/ 2014), the frequency of reduced susceptibility to gentamicin/cefuroxime and to carbapenems (cohort 2013/2014), and the sensitivity of the specific risk-based strategy for the presence of resistance to cefuroxime/gentamicin (cases 2013–2016). The NNTCs of the risk-based strategies were compared to the theoretical scenario of uniform application of the local sepsis guideline and the actual clinical practice data. The NNTC was assessed for different theoretical probabilities of Gram-negative bacteraemia in patients treated empirically for presumed sepsis. All statistical analyses were performed with IBM SPSS Statistics, version 23.

RESULTS

The cohort (2013–2014) consisted of 486 episodes of Gram-negative aerobic bacteraemia in 450 patients. The final database had < 2% missing data. Median age was 66 years (IQR 56–73), in 263 (54.1%) episodes, the patient was male. In this cohort in vitro reduced susceptibility to 2GC monotherapy was present in 176 patients (36.2%), reduced susceptibility to AG in 84 patients (12.6%) and to the combination C-2GC + AG in 43 patients (8.8%). In 95/486 (19.5%) a drug resistant pathogen (DRP) was cultured previously, in 54/95 (56.8%) the prior-DRP was isolated during the preceding 6 months. A total of 144/486 (29.6%) patients were already on antibiotic therapy when they were evaluated for suspected sepsis and 257/486 patients (52.9%) had been treated with antibiotics in the preceding 2 months. Empiric therapy contained a carbapenem in 27/486 (5.6%) of patients. Of the 43/486 (8.8%) patients with in vitro resistance to C-2GC + AG, 12/43 (27.9%) received adequate empiric treatment. The 30-day mortality rate for the cohort was 59/486 (12.1%). Resistance to carbapenems was 1/486 (0.2%).

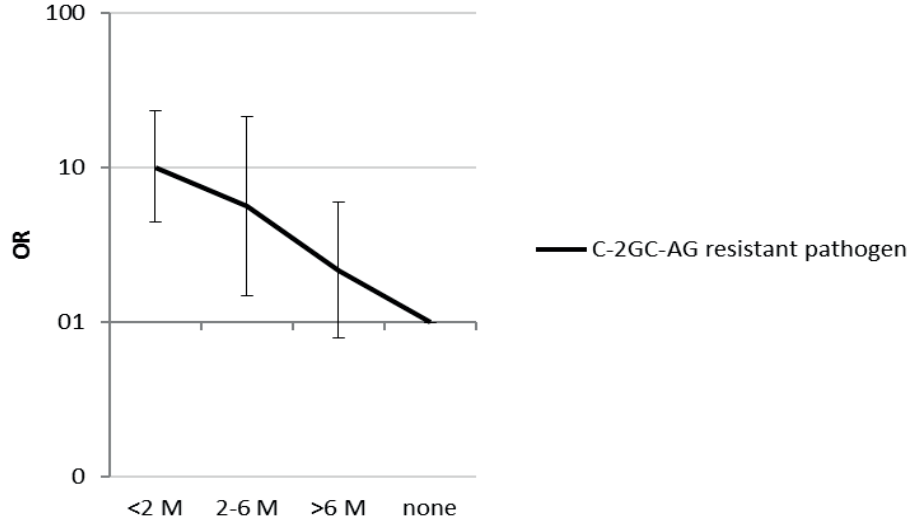
After applying the case criterion for Gram-negative bacteraemia with in vitro reduced susceptibility to cefuroxime and gentamicin, 71 patients (2013–2016) were identified as cases and 142 controls were randomly selected from the remaining patients in the

cohort. The demographic and clinical characteristics of cases and controls are shown in Table 2. The pathogen distribution is described in the Supplementary data. The causative pathogen was ESBL producing in 64.8% (46/71) and 6.3% (9/142) in cases and controls respectively ($p < 0.001$).

Risk factors for non-susceptibility to empiric therapy

The result of the univariate analyses are shown in Table 2. Patients with hematologic malignancy or neutropenia were at increased risk of a pathogen with reduced susceptibility to C-2GC + AG. Pre-treatment with antibiotics in the 2 months prior to presentation and antibiotic treatment at the day of presentation were associated with presence of reduced susceptibility to C-2GC + AG. In addition, previous admission on general wards, ICU wards and length of hospital stay were strong predictors of reduced susceptibility to standard empiric therapy. The strongest crude predictor was prior isolation of a resistant micro-organism from any site, including rectal swabs. Figure 1 depicts the odds ratio for infection with a pathogen with reduced susceptibility to C-2GC + AG, depending on the time elapsed between the DRP cultures and the current presentation with infection.

Figure 1. Odds ratio for resistance to empiric therapy related to time since the last drug resistant pathogen (DRP) was cultured



Legend. M=months. C-2GC+AG= Combination 2nd generation cephalosporin and aminoglycoside. Prior-DRP = drug resistant pathogen(s) isolated from any body site: Vancomycin resistant enterococci, multi resistant *Staphylococcus aureus*, enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacterales and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporin's, aminoglycosides or quinolones. Odds ratio for infection with cefuroxime and gentamicin resistant Gram-negative pathogen, for patients with prior-DRP isolated compared to patients without prior-DRP isolates, for different time intervals in months since the last DRP was cultured. Note that the y-axis is on a logarithmic scale.

Table 2. Demographics and clinical characteristics of cases and controls.

Characteristic	Cases n (%)	Controls n (%)	*P* Value	OR (95% CI)
Patient demographics				
Male gender	45 (63.4)	80 (56.3)	.38	1.34 (0.75-2.41)
Age >65	32 (43.7)	73 (51.4)	.31	0.77 (0.44-1.38)
Medical history				
Diabetes mellitus	19 (26.8)	50 (35.2)	.28	0.67 (0.36-1.26)
Corticosteroid therapy (prior 6 months)	32 (45.1)	47 (33.1)	.10	1.66 (0.93-2.97)
Neutropenia	14 (19.7)	9 (6.3)	.005	3.62 (1.49-8.87)
Solid organ transplantation	14 (19.7)	23 (16.2)	.57	1.27 (0.61-2.65)
Hematologic malignancy	18 (25.4)	9 (6.3)	<.001	5.01 (2.12-11.87)
Non-hematologic malignancy	12 (16.9)	33 (23.2)	.37	0.67 (0.32-1.40)
Chronic urologic disorder	13 (18.3)	33 (23.2)	.48	0.74 (0.36-1.52)
Chronic pulmonary disease	7 (9.9)	19 (13.4)	.51	0.71 (0.28-1.77)
Recurrent urinary tract infections	7 (9.9)	14 (9.9)	1.00	1.00 (0.38-2.60)
Clinical presentation				
Fever (temperature>38.5 °C)	49 (69.0)	104 (73.2)	.31	0.81 (0.43-1.53)
EMV-score <15	21 (30.6)	29 (20.4)	.23	1.57 (0.81-3.02)
Hypotension[a]	18 (25.4)	23 (16.2)	.14	1.79 (0.89-3.63)
Current antibiotic use[b]	49 (69.0)	37 (26.1)	<.001	6.32 (3.38-11.84)
Antibiotic usage preceding 2 months	67 (94.4)	67 (47.2)	<.001	18.75 (6.49-54.19)
ICU/MCU > 2 days	11 (15.5)	7 (4.9)	.02	3.54 (1.31-9.57)
ICU/MC preceding 6 months	23 (32.4)	16 (11.3)	<.001	3.77 (1.84-7.75)
Hospital stay preceding 6 months	49 (69.0)	65 (45.8)	.001	2.64 (1.45-4.82)
Hospitalization >5 days	32 (45.1)	28 (19.7)	<.001	3.34 (1.79-6.24)
Prior-DRP[c]	42 (59.2)	27 (19.0)	<.001	6.17 (3.28-11.61)
Source of infection			.06	-
Urinary tract	23 (32.4)	68 (47.9)		
Intra-abdominal tract	22 (31.0)	44 (31.0)		
Respiratory tract	3 (4.3)	9 (6.4)		
Skin/soft tissue	6 (8.6)	4 (2.8)		
Other	7 (9.9)	7 (4.9)		
Unidentified	10 (14.1)	10 (7.0)		

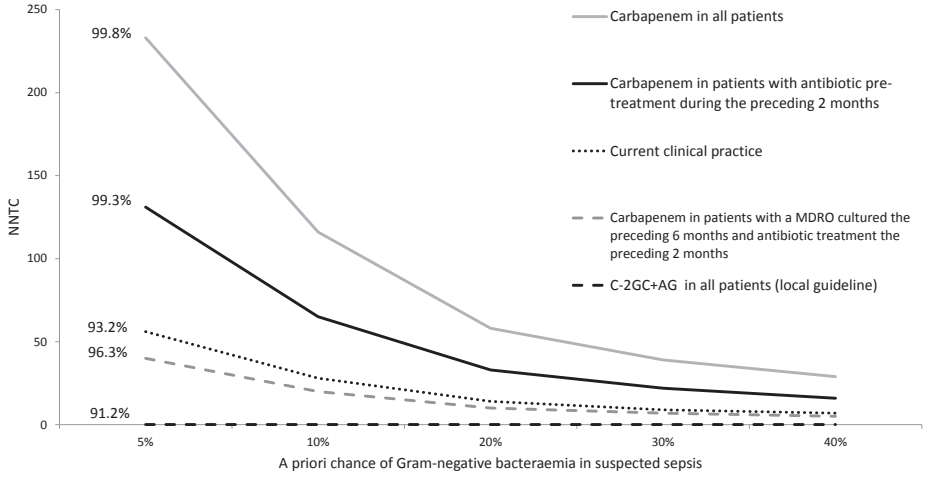
Legend. Data are presented as No. (%). P values are calculated by Fisher exact test. Abbreviations**:** OR= odds ratio, EMV-score: eye-motor-verbal score. ICU/MCU = intensive care unit / medium care unit. IQR= interquartile range. [a] Hypotension = systolic blood pressure <90 mmHg or requirement for intravenous vasopressor agents. [b] 'Current antibiotic use' = at least one administration of antibiotics during the 24 hours preceding the collection of blood specimens . [c]'Prior-DRP' = one of the following drug resistant pathogens isolated from any body site: Vancomycin resistant enterococci, multi resistant *Staphylococcus aureus*, enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacterales and/or quinolones, Pseudomonas aeruginosa with resistance to third generation cephalosporins, aminoglycosides or quinolones.

In the multivariable analysis a previous culture with a DRP (adjusted OR 3.72 95%CI 1.72–8.03, p < 0.01), antibiotic use during the preceding two months (adjusted OR 12.5, 95%CI 4.08–38.48, p < 0.01), and a hematologic malignancy (adjusted OR 4.09, 95%CI 1.43–11.62, p < 0.01) were independently associated with reduced susceptibility (Supplementary files)

Exploring the effect of risk-based sepsis guidelines: Calculated estimations

The relevant risk factors for resistance to empiric therapy derived from the multivariable analysis were used to design five different risk-based empiric sepsis treatment strategies. The calculated effect of these individual strategies on the proportion of patients with Gram-negative sepsis that would be treated adequately and the corresponding NNTC are shown in Table 3, and for a selection of strategies in Fig. 2.

Figure 2. Estimation of the effect of the different empiric strategies on effective therapy rate and consumption of carbapenems, differentiated by a priori probability of bacteraemia and compared to other strategies for selection of empiric therapy.



Legend. NNTC = number of patients needed to treat with a carbapenem instead of cefuroxime/gentamicin to avoid mismatch of empiric therapy in one patient. C-2GC+AG = 2nd generation cephalosporin/aminoglycoside combination therapy. DRP= drug resistant pathogen(s) isolated from any body site: Vancomycin resistant enterococci, multi resistant *Staphylococcus aureus*, enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacterales) and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporins, aminoglycosides or quinolones.. Current clinical practice: 2GC+AG as standard therapy, escalation to a carbapenem according to judgment of treating physician. The percentages (91.2-99.0%) indicate the proportion of patients with bacteraemia that would receive adequate treatment if the strategy was implemented. For example: if all patients were to be treated with a carbapenem, the overall rate of adequate therapy in patients with bacteraemia would be 99.0%. In case of an a priory risk of bacteraemia of 10%, the corresponding NNTC is 128 patients.

Table 3. Estimated effects of implementation of different empiric sepsis treatments on effective therapy rate and consumption of carbapenems in a population suspected of Gram-negative bacteraemia.

Treatment strategy	Sensitivity of the criterion for presence of combined resistance*	Proportion of patients with Gram-negative BSI adequately treated	Proportion of patients with Gram-negative BSI treated with carbapenem	Estimated NNTC** with carbapenem according to frequency of Gram-negative bacteraemia in suspected sepsis *A priori* probability of Gram-negative bacteraemia in suspected sepsis [a]				
				5%	10%	20%	30%	40%
1. Cefuroxime/gentamicin in all patients with sepsis	0	.912	0	-	-	-	-	-
2. Carbapenem in all patients with sepsis	1.000	.998	1.000	233	116	58	39	29
3. Only a carbapenem in patients with antibiotic pre-treatment on day of culture.	.690	.971	.296	100	50	25	17	13
3. Only a carbapenem in patients with antibiotic treatment <2 months	.943	.993	.529	130	65	33	22	16
4. Only a carbapenem in patients with a DRP[b] cultured <6 months	.465	.952	.111	55	28	14	9	7
5. Only a carbapenem in patients with a DRP cultured previously (no time restriction)	.592	.963	.195	76	38	19	13	10
7. Only a carbapenem in patients with a DRP previously and antibiotic treatment < 2 months	.549	.961	.101	42	21	11	7	5
8. Current Practice	.225	.931	.056	57	29	14	10	7

Legend [A] Frequency of Gram-negative bacteraemia as percentage of the total No. of patients with suspected sepsis in whom empiric therapy is started. [B] Drug resistant pathogen(s) (DRP) isolated from any body site: Vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus*, Enterobacterales with in vitro resistance to aminoglycosides, second and/or third generation cephalosporin's (including ESBL positive Enterobacteriaceae) and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporins, aminoglycosides or quinolones.* The sensitivity was derived from the study data (cases 2013-2016) ** NNTC = Number needed to treat with carbapenem instead of cefuroxime/gentamicin to avoid mismatch of empiric therapy for Gram-negative bacteraemia in one patient. For the calculation of the NNTC the formula in the Supplementary files was applied.

Example, strategy 5: Standard empiric treatment is cefuroxime/gentamicin, carbapenems are reserved for patients with a history of drug resistant pathogen (DRP). This results in prescription of a carbapenem in 19.5% of patients with Gram-negative bacteraemia. With this strategy, empiric treatment of patients with cefuroxime/gentamicin resistant bacteraemia is adequate in 59.2% and the overall treatment adequacy rate in Gram-negative bacteraemia is 96.3%. In the scenario of a pre-test probability of Gram-negative bacteraemia of 10%, 38 patients would be treated with a carbapenem to avoid mismatch of empiric therapy for Gram-negative bacteraemia in 1 patient.

The NNTC is to a large extent dependent on the number of patients that are empirically treated for sepsis. This number is much larger than the number of patients that are eventually diagnosed with Gram-negative bacteraemia. To account for these differences in prevalence of Gram-negative bacteraemia amongst patients that are empirically treated for presumed sepsis, the NNTC was assessed for different probabilities of Gram-negative bacteraemia. (Fig. 2, Table 3).

In the scenario of 'standard empiric carbapenem therapy in all patients', the adequacy rate of empiric therapy was 99.8%. The corresponding NNTC was 29 to 233, depending on the probability (i.e. high: 40% to low: 5%) of Gram-negative bacteraemia. Alternatively, risk-based strategies resulted in an estimated adequacy rate of 95.2–99.3%. Compared to treating all patients with a carbapenem empirically, the NNTC in the targeted approaches was a factor 2.3 to 4.6 lower, depending on the selected approach. The NNTC was lowest if a carbapenem would be reserved for patients in whom a DRP was cultured previously and antibiotic treatment had been administered in the preceding 2 months. The estimated reduction of carbapenem use was 82.8% (95%CI 78.5–87.5%). This strategy had a treatment adequacy rate of 96.1% of patients with Gram-negative bacteraemia. This is an absolute increase in adequacy rate of 4.9% compared to the local guideline and an absolute increase of 3.0% compared to clinical practice (Fig. 2, Table 3).

DISCUSSION

Using real-life clinical and microbiological data, we propose a method to develop risk-based empiric antibiotic policies and to estimate the potential costs and benefits of policy changes (Table 1).

Although there are multiple previous prediction rules for infection with resistant pathogens, the applicability of these rules to the selection of institutional empiric antimicrobial treatment is limited. The majority of prediction score studies focused on a specific pathogen or a specific mechanism of resistance, for example ESBL.[6,20,25–27] For clinical practice, it is more relevant to predict susceptibility to an empiric regimen in a predefined clinical syndrome, instead of predicting the presence of a specific mechanism of resistance. Secondly, the consequences of implementation of the prediction scores on adequacy rate and/or NNTC are frequently lacking.[6,7] Thirdly, the susceptibility of pathogens and the risk factors for resistance may vary substantially amongst institutions, making it is necessary to base empiric treatment recommendations on local epidemiology. Our 7-step method can be used to develop institutional empiric policy

for a variety of clinical syndromes, and focusses on applicability of the results in daily clinical practice.

In response to increasing resistance rates, we applied the method to improve empiric coverage of causative Gram-negative micro-organisms in sepsis, while maintaining a responsible antimicrobial policy with regard to antibiotic consumption. Our data show that in current practice, clinicians already incorporate an assessment of the risk of a resistant pathogen in decision-making, with a relatively low NNTC. The treatment adequacy rate however, can be further increased using targeted strategies, without increasing inappropriate reserve antimicrobial consumption. The NNTC was stratified according to the theoretical probability of Gram-negative bacteraemia. Previous literature on positivity rates in consecutive blood cultures, shows probabilities of Gram-negative bacteraemia below 5%.[28,29] However, the positivity rate varies substantially depending on the patient population, to up to 41% in septic shock.[28-34] As a result, the NNTC in the critically ill is considerably lower than in a low acuity population.[16,29] The strategies were based on bacteraemia. Including non-bacteraemic infections, would further decrease the NNTC. We focused on bacteraemia, as the importance of adequate empiric treatment is higher in bacteraemic, compared to non-bacteraemic episodes.

A limitation of the study is the retrospective data collection. There is potential underreporting of antibiotic pre-treatment. However, this effect is limited, given the use of electronic prescription systems. In addition, potentially important predictive factors, such as travel history, may have been missed, because of limited availability of specific information in the medical charts. Incorporating more determinants, could improve the strategies and further reduce NNTC. A second limitation is that, in our analysis of the NNTC, we assumed that the identified predictors of antimicrobial resistance are independent of the a priori risk of Gram-negative bacteraemia. On theoretical grounds, we do not expect previous antibiotic use and colonization with DRP's to have an important etiologic effect on the a priori risk of Gram-negative bacteraemia itself. Thirdly, the inclusion period for cases was prolonged compared to the initial cohort, because of the low incidence of C-2GC + AG resistance. Although the epidemiology of antimicrobial resistance is subject to change over time, it is unlikely that the prolonged inclusion period would affect risk factors associated with C-2GC + AG resistance (step 3).

The reported results on Gram-negative bacteraemia are institution specific. Differences in antimicrobial susceptibility rates, patient population and treatment guidelines between institutions may all affect treatment adequacy rates and the NNTC. However, the method that was used to determine a center-specific NNTC is applicable in every setting.

From a scientific perspective, prospective validation within the institution is preferable, before implementation is considered. However, prospective validation would hamper a timely response to the latest resistance data, resulting in a difficult process of catch-up because of changing epidemiology. Therefore, cyclic evaluation and optimization within the institution after implementation is - from a practical point of view - preferable to further improve targeted antibiotic strategies.

In step 7, the benefits of adequate therapy and the costs of the associated antimicrobial consumption need to be weighed to select the most appropriate strategy. The rate of inadequate empiric therapy that clinicians are willing to accept, varies according to the severity of the clinical syndrome. For sepsis, and especially septic shock, the optimal balance between antibiotic adequacy rate and consumption of reserve antimicrobial agents is incomparable to the setting of more benign infections, for example cystitis. How to balance these aspects is highly complex. This also involves ethics, as decisions do not merely affect patients today, but impacts future generations as well.[35] The number needed to treat with reserve antimicrobial agents contributes to this ethical discussion. This study demonstrates the feasibility of generating these numbers for the local situation.

CONCLUSIONS

The present study exemplifies a method to develop risk-based empiric antibiotic policies and estimate the effects on treatment adequacy and antimicrobial consumption. The approach has the potential to target the use of reserve antimicrobial agents and can be applied in different clinical settings to optimize empiric antibiotic therapy.

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SUPPLEMENTARY DATA

Formula for the estimation of the number needed to treat with a carbapenem

$$NNTC = \frac{\text{PropRf}}{(\text{PropRx} - \text{PropRy}) \times \text{SensRF}} \times \frac{1}{\text{Gramnegbac}}$$

NNTC= Number needed to treat with a carbapenem instead of cefuroxime/gentamicin to avoid mismatch of therapy in one patient.

PropRf = The frequency of cases with the risk factor (or risk factor combination) as a proportion of the total No. of cases in the study cohort "Gram-negative bacteraemia".
PropRχ = The frequency of cases with a pathogen that has reduced susceptibility to the combination therapy gentamicin and cefuroxime (C-2GC+AG) as a proportion of the total No. of cases in the study cohort "Gram-negative bacteraemia" .
PropRy = The frequency of cases with a pathogen with reduced susceptibility to carbapenems as a proportion of the total No. of cases in the study cohort "Gram-negative bacteraemia" .

SensitivityRF = Sensitivity of the risk factor (or risk factor combination) for combined resistance to gentamicin and cefuroxime in patients with bloodstream infection with a pathogen with reduces susceptibility to C-2GC+AG.

Gramnegbac: A priori probability of Gram-negative bacteraemia in suspected sepsis: The frequency of Gram-negative bacteraemia as a proportion of the total No. of patients with suspected sepsis in whom empiric therapy is started.

Example*:*
In the study cohort, the resistance rate to the combination cefuroxime/gentamicin was 8.8%. In this cohort, a drug resistant pathogen (DRP) was diagnosed the previous 6 months in 11.1% of cases. Of all patients with bacteraemia with a pathogen with reduced susceptibility to C-2GC+AG in 45,5% a drug resistant pathogen was isolated the preceding 6 months. In the study center 6.7 percent of patients in whom blood cultures are obtained are diagnosed with Gram-negative bacteraemia.

$$NNTC = \frac{0.111}{(0.088 - 0.002) \times 0.0.465} \times \frac{1}{0.067} = 42$$

The number needed to treat with a carbapenem instead of cefuroxime/gentamicin to treat one patient adequately = 42.

Pathogen distribution

Table S1. Isolated pathogens in cases (n=71) and controls (n=142).

	Cases n (%)	Controls n (%)	p-value*
Pathogen			.12
Escherichia coli	34 (47.9)	83 (58.5)	
Klebsiella species	13 (18.3)	25 (17.6)	
Pseudomonas aeruginosa	9 (12.7)	11 (7.7)	
Serratia marcescens	7 (9.9)	9 (6.3)	
Other Gram-negative pathogens**	8 (11.3)	14 (9.9)	

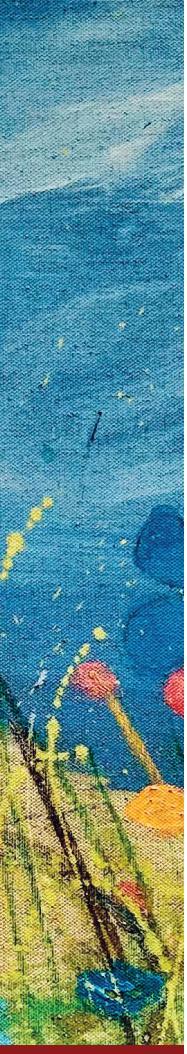
Legend: *p-value calculated by Fisher exact test. ** *Citrobacter spp*, *Enterobacter spp*, *Proteus spp*, *Morganella spp* and *Providencia spp*.

Multivariable analysis

Table S2 Multivariable analysis of predictors of infection with a pathogen with reduced susceptibility to treatment with cefuroxime and gentamicin.

	OR	95% CI	p-value
Hematologic malignancy	4.09	1.43-11.62	<0.01
Admitted to IC/MC unit ≥ 2 days	1.25	0.38-4.12	0.72
Hospital stay during the preceding 6 months	0.94	0.44-2.04	0.88
Current hospital stay ≥ 5days	1.05	0.45-2.42	0.92
Prior-DRP	3.72	1.72-8.03	<0.01
Antibiotic therapy during preceding 2 months	12.5	4.08-38.48	<0.01

Legend. Logistic regression analysis. OR = Adjusted odds ratio, 95%CI = 95% confidence interval. IC/MC = intensive care/ medium care. Prior-DRP = Drug resistant pathogen, defined as the isolation of one of the following pathogens from any body site, including rectal swabs: vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus*, Enterobacteriaceae with in vitro resistance to aminoglycosides, second and/or third generation cephalosporins and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporin's, aminoglycosides or quinolones.



Prediction tools for antimicrobial resistance in daily clinical practice: balancing optimal empiric treatment and consumption of reserve antimicrobials

Letter

The following letter was written as a reply to the study 'Development of diagnostic prediction tools for bacteraemia caused by 3rd generation cephalosporin-resistant *Enterobacteriaceae* in suspected bacterial infections' by Rottier, *et al*. In their nested case-control study, a prediction tool was developed to estimate the risk of bloodstream infection with third-generation cephalosporin-resistant Enterobacterales. In our letter we calculate the number needed to treat with a reserve antimicrobial agent that would be associated with the proposed cut-off, illustrating the method described in the first part of Chapter 5.

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With great interest, we read the recent publication by Rottier *et al*. In their nested case control study, a prediction tool was developed to estimate the risk of bloodstream infection with 3rd generation cephalosporin resistant (3GCR) Enterobacterales.[1] Such practical tools, that break the vicious circle of inappropriate use of reserve antimicrobial therapy and increasing resistance levels, are urgently needed. The scoring system provides the clinician with the probability that the patients suffers from 3GCR-E bacteraemia. The authors report a potential 40 percent reduction in consumption of carbapenems using this prediction score in community acquired infection. In view of the high incidence of presumed sepsis, the relative gain on inappropriate antibiotic consumption compared to the use of a third generation cephalosporins is promising.

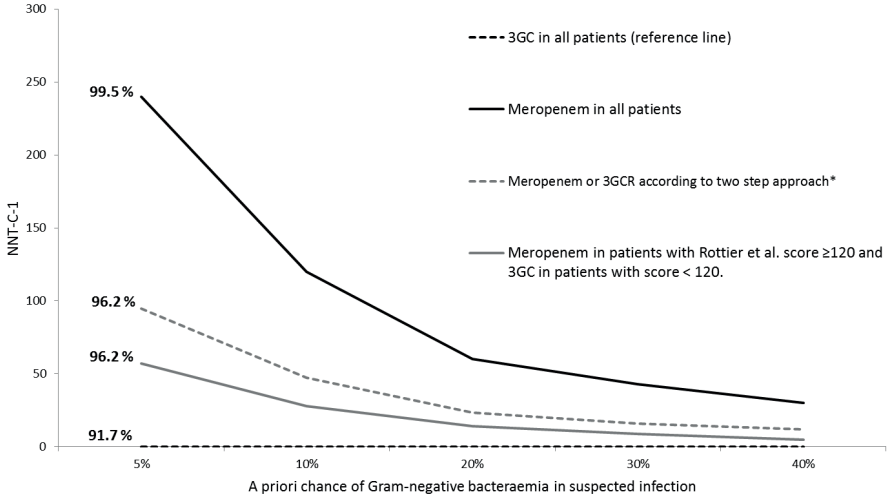
However, to quantify the absolute gain of the scoring system, calculation of the number of patients needed to treat with carbapenems to prevent one case of mismatch of empiric therapy (NNT-C-1) is highly relevant. The authors do not provide these data. Nonetheless, the NNT-C-1 is important from the perspective of the individual patient as well as from an antibiotic stewardship point of view. The prevalence of 3GCR-E-BAC was very low - 0.4% for community acquired infection - in the cohort of empirically treated patients. The proposed cut-off in the scoring system is 120 points. If the rule was to be implemented, according to Table 3, this would lead to prescription of a carbapenem in 12.8% of these patients to prevent mismatch between pathogen and antibiotic in 0.2% of patients. Compared to empiric treatment with a third generation cephalosporin in all patients, the NNT-C-1 with a carbapenem to avoid mismatch in one patient would be approximately 59 (Box 1).

Box 1 Calculation of the NNT-C-1

The prevalence of 3GCR-E bactaeremia in the study cohort was 0.4% (90/22506). The sensitivity of the prediction tool for the cutoff of 120 points was 54.3 %. Therefore 0.2% (prevalence of bactaeremia x sensitivity of the rule) of the population would be adequately treated because of administration of a carbapenem *(A*). Table 3 in the study by Rottier et al. states that, using the same cut-off, 12.8 % of patients would be prescribed a carbapenem (*B*). The NNTC-1 is 59. ($^{B}/_{A}$)

Hence, a relatively high number of patients (59 minus 1) would be prescribed a carbapenem unnecessarily. The high NNT-C-1 is the result of the relatively low *a priori* probability of Gram-negative bacteraemia in the study cohort. When deciding over empirical therapy, the probability of bacteraemia is highly relevant. In septic shock for example, the a priori chance of bacteraemia is approximately 20-30%.[2] Based on a 8.3% resistance of all Gram-negative pathogens to third generation cephalosporins.[1,3] the NNT-C-1 in septic shock would be 9-14 patients, an approximate 5-fold reduction (Figure 1). This illustrates that the reduction in NNT-C-1 that can be achieved by accounting for the *a priori* risk of bacteraemia, is much higher than the gain that can be expected by optimization of the risk score for predicting antimicrobial resistance. In addition, the potential harm of empirical mismatch in these severely ill patients is substantially more threatening than in hemodynamically stable patients. Accounting for the severity of illness in more detail is therefore important and would improve risk based antibiotic strategies.[4] Although signs of hypoperfusion are incorporated in the tool by Rottier *et al*, they are attributed only 40 out of 480 points.

Figure 1. Estimation of the effect of the Rottier et al. scoring system on effective therapy rate and consumption of carbapenems in community-acquired infection, differentiated by a priori risk of bacteraemia and compared to other strategies for selection of empiric therapy.



Legend: 3GC= 3rd generation cephalosporin. NNT-C-1 = number of patients needed to treat with a carbapenem to prevent one case of mismatch of empiric therapy. * Two step approach (current Dutch sepsis guideline) = a carbapenem in patients with cephalosporin or quinolone use during the prior 2 months or identification of 3GC resistant pathogen during the prior year. The percentages (91.7-99.5 %) indicate the proportion of patients with bacteraemia that would receive appropriate treatment if the strategy was implemented. For example: if all patients were to be treated with a carbapenem, the overall rate of appropriate therapy in patients with bacteraemia would be 99.5 percent (assuming 0.5 % carbapenem resistance). In case of an a priory chance of bacteraemia of 10 percent, the corresponding NNT-C-1 with a carbapenem is 120 patients to prevent mismatch in one patient. If the scoring system of Rottier et al. would be applied, the NNT-C-1 would be reduced to 28, for the same a priori probability of bacteraemia. This figure was based on the data provided in the publication by Rottier et al

A second aspect that influences the NNT-C-1 is the standard of care, which the risk strategy is compared to. In their study Rottier *et al*. defined standard of care as treatment with a third generation cephalosporin or a carbapenem, based on the a two-predictor model. However, in many hospitals in the Netherlands and other European countries with low to moderate resistance rates of Enterobacterales standard empiric treatment for presumed sepsis has changed since the period the study by Rottier *et al*. was conducted (2008-2010). Empiric therapy now consists of a 2nd or 3rd generation cephalosporin (or a betalactam plus betalactamase inhibitor) combined with an aminoglycoside. The addition of an aminoglycoside intends to improve effective empiric therapy rates in case of cephalosporin resistant Gram-negative pathogens, due to ESBL-production or other mechanisms of resistance.[5] Of note, susceptibility rates for cephalosporin/aminoglycoside combination therapy may be less favorable than susceptibility rates for carbapenems. Plasmids responsible for ESBL production frequently carry genes encoding resistance to aminoglycosides. Nevertheless, in many countries, the *a priori* risk for resistance to this empiric combination regimen is considerably lower than resistance to monotherapy with a 3rd generation cephalosporin.[3,5] This is relevant, as it would further increase the NNT-C-1. Since the study focusses on 3GCR-E-BAC, the research question does not fully address the clinical dilemma currently at hand. Therefore, reporting on the performance of a clinical decision rule with regard to the current standard regimen would provide better insight in the potential benefit of this clinical tool. For antibiotic stewardship reasons, empiric use of the carbapenem class should be avoided if aminoglycosides provide a good alternative. It would be helpful if the authors could provide the results of this alternative analysis of the data.

Ultimately, we look forward to data from comparative clinical studies about patient outcomes (i.e. 'hard endpoints') and the antibiotic consumption directed by this and other clinical antibiotic stewardship tools.

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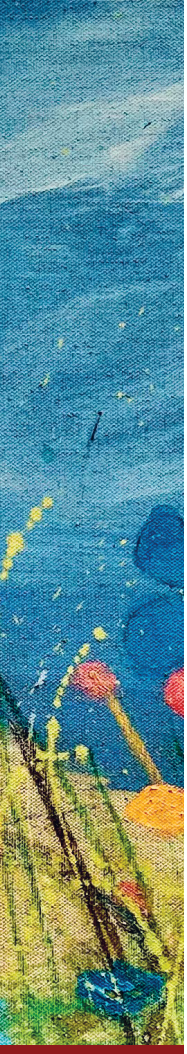

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Mortality after delay of adequate empiric antimicrobial treatment of bloodstream infection

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ABSTRACT

Background: Timely empiric antimicrobial therapy is one of the cornerstones of management of suspected bloodstream infection (BSI). However, studies about the effects of empiric therapy on mortality have reported inconsistent results. The objective was to estimate the effect of delay of appropriate empiric therapy on early mortality in patients with BSI.

Methods: Data for the propensity score matching (PSM) study were obtained from a cohort of patients with BSI. Inadequate empiric treatment was defined as *in vitro* resistance to the antimicrobial regimen administered <6 hours after blood cultures were taken. The primary outcome measure was 14-day mortality. Thirty-day mortality and median length of stay (LOS) were secondary outcomes. PSM was applied to control for confounding.

Results: Of a total of 893 included patients with BSI, 35.7% received inadequate initial empiric treatment. In the PSM cohort (n= 334), 14-day mortality was 9.6% for inadequate antibiotic treatment, compared to. 10.2% in adequate empiric treatment (p=0.85). No prolonged median LOS was observed in patients that initially received inadequate therapy (10.5 vs 10.7 days, p=0.89).

Conclusions: In this study, we found no clear effect of inadequate empirical treatment on mortality in a low-risk BSI population. The importance of early empiric therapy compared to other determinants, may be limited. This may not apply for specific subpopulations, e.g. patients with sepsis.

INTRODUCTION

Bacterial bloodstream infections (BSI) have an increasing incidence worldwide and are associated with considerable morbidity and high mortality rates.[1,2] Delay in appropriate treatment of such infections may negatively affect patient outcome. To ensure adequate treatment while awaiting blood culture results, initiation of broad spectrum antibacterial therapy is considered to be the cornerstone of medical management of BSI.[3] In an era of ever increasing antimicrobial resistance rates, a recurrent discussion occurs about whether standard empiric antibiotic treatment regimens for suspected BSI should be adjusted to a broader spectrum.[4,5] Knowledge of the effects of appropriate or inadequate initial empiric therapy on patient outcome is essential to weigh the pros and cons of upscaling empiric therapy.[6]

In previous studies inadequate empiric antimicrobial treatment was found to be associated with mortality. This association appeared to be stronger in critically ill patients or patients with a ventilator associated pneumoniae in combination with a BSI.[7,8] However, for obvious ethical reasons, studies on the effects of inadequate antibiotic therapy never applied a randomized, placebo controlled design and therefore suffer from confounding.[9-12] A meta-analysis of prospective observational studies performed by Paul *et al.* in 2010 concluded that all-cause mortality was lower in patients receiving adequate empiric antimicrobial treatment. However, the included studies were heterogeneous, had a high risk of bias and the estimated effect on mortality was highly variable.[11] Various clinical variables, e.g. the severity of sepsis and comorbidity scores, have been described to impact on the choice of empiric treatment and lead to confounding by indication.[10,11]

Propensity score matching (PSM) methodology has the potential to correct for these confounding differences in probabilities of receiving inadequate antibiotic therapy, thereby aiming to approach the outcome that would have been the result of a randomized study. The objective of this PSM study was to estimate the effect of a mismatch of at least the first administration of empiric antimicrobial treatment in patients with confirmed BSI on 14-day mortality rate in a large, longitudinal cohort study.

METHODS

Study setting and population

Data for the propensity score matching study were obtained from a large longitudinal cohort study of patients with bacteraemia[13], admitted in the Leiden University Medical Center (LUMC), a tertiary care and teaching hospital in the Netherlands. All adult patients

(≥18 years) that presented during the study period (2013-2015) with an episode of monobacterial BSI, both hospital and community acquired, were considered eligible. Patients with contaminated blood cultures were excluded. To avoid misclassification, all blood cultures with coagulase-negative staphylococci (CoNS) were considered contaminated. For other bacteria, the classification as contamination was based on the assessment of the attending medical team at the time the blood culture result was reported.

The research center has a dedicated infectious diseases consultancy team, consisting of medical microbiologists and specialists infectious diseases, which is involved in all patients with BSI, performs bedside consultations and advises on diagnostics and management. Standard empiric treatment for sepsis of unknown origin is a second generation cephalosporin, combined with gentamicin.

Data collection and microbiology methods

Data about demographic characteristics, medical history, clinical parameters, the source of infection and antimicrobial treatment were retrieved from the electronic patient files.[14] Clinical parameters were all collected at the time of presentation/blood culture collection and included hemodynamic parameters. The severity of illness was assessed by calculating the Pitt bacteraemia score (PBS) and the quick sequential organ failure assessment score (qSOFA) score.[15] If follow up in the research center was less than 30 days, the data on survival could be traced via the electronic patient file, which is linked to the Dutch Personal Records Database (BRP).

Blood culture data, including antimicrobial susceptibility patterns, were collected from the database of the Department of Medical Microbiology. In the study center, blood cultures were analyzed using the BACTEC FX continuous monitoring system (Becton Dickinson B.V., Breda). Antimicrobial susceptibility testing was performed with the VITEK2 system and E-tests (BioMérieux, Brussels, Belgium). Extended-spectrum beta-lactamase (ESBL) positivity was determined with the disc diffusion test. Minimum inhibitory concentration (MIC) breakpoints for resistance were determined according to EUCAST criteria.[16]

Study definitions

The primary outcome was 14-day all-cause mortality. Mortality at two weeks was chosen because the impact of inadequate antimicrobial therapy is potentially higher in the first weeks of follow-up.[17] The secondary endpoints were 30-day all-cause mortality and length of hospital stay after diagnosis of BSI. The day of the blood sampling that resulted in a positive blood culture was designated as day 0.

Initial empiric therapy was defined as the antibiotic treatment administered within 6 hours after blood culture collection. This antimicrobial regimen can be regarded as indicator for approximately the first 24 hours of treatment as regimens are often optimized thereafter based on culture results or clinical course of the infection. Discrimination between adequate and inadequate initial empiric antimicrobial therapy was based on the *in-vitro* susceptibility of the pathogen isolated in the blood culture. Adequate empiric treatment was defined as *in-vitro* susceptibility of the isolated pathogen to at least one of the antibiotics administered within 6 hours after drawing blood cultures. When no antibiotics were administered within 6 hours after blood culture collection, the initial empiric therapy was also regarded inadequate.

Pathogen related factors, such as virulence traits are crucial elements which may affect the clinical outcome in BSI. Based on pathogen characteristics and previous literature, pathogens were classified as low or high risk pathogens. Enterobacterales*, S.aureus, Streptococcus spp.* and *Pseudomonas aeruginosa* were defined high risk.

The BSI was considered hospital acquired if the first positive blood culture was collected after ≥ 48 hours of hospitalization. Prior colonization or infection with a multidrug resistant organism was defined as the previous isolation of one of the following pathogens from anybody site, including rectal swabs: vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus*, Enterobacterales with in vitro resistance to aminoglycosides, second and/or third generation cephalosporins and/or quinolones, *Pseudomonas aeruginosa* with resistance to third generation cephalosporins, aminoglycosides or quinolones.[5]

Statistical methods

Categorical variables were reported as numbers with percentages and compared between the treatment groups using a chi-squared or Fishers exact test. The Wilcoxon rank sum test was used for comparison of respectively the distributions and medians of continuous data that were not normally distributed. Means of normally distributed continuous variables were compared using the T-test. Odds ratio's (OR) with a 95% confidence interval (95%CI) and/or p-values were calculated as appropriate for each variable. The frequency of missing data was assessed, but missing data were not imputed.[18]

To adjust for confounding, PSM was used to compare primary and secondary outcome parameters between patient groups that did-, and those that did not-, receive adequate empiric antimicrobial treatment (see below). PSM can be used to analyse observational data concerning a specific treatment outcome by identifying which individuals have the same probability of receiving the intervention (here: inadequate antibiotic treatment for

the BSI). By assessing the outcome in relation to the intervention for patients with similar (i.e. matched) propensity scores, it is aimed to attain an estimate that approximates the outcome of a randomized study.[19]

The propensity score is the estimated probability (0-1) of receiving inadequate antimicrobial therapy based on measured confounders. Propensity scores were generated using a multivariable logistic regression model. Variables that were included in this model were defined by univariate analysis ($p<0.2$). The selected variables were associated with attribution of inadequate initial empiric treatment and/or 14-day mortality. A manual backward stepwise approach was used to remove co-linear variables. The model was evaluated by using the C-statistic. A 1:1 propensity score matching algorithm without replacement and a maximum probability distance (caliper) of 0.2 was applied. Thus, in the matched cohort a patient that did receive adequate empiric treatment was included for each patient that did not receive adequate empiric treatment, based on the propensity score. To balance baseline variables between groups of patients, calibration was performed to obtain a maximum standardized difference (SDD) of 0.10 (10%) for each covariate.

In the matched cohort, each comparison of endpoints between groups was performed by assessment of the average treatment effect in the treated population (ATT).

With the complete dataset, an analysis based on inversed probability weighting of the propensity scores (IPW) was performed as a sensitivity analysis, i.e. to assess the robustness of the results obtained by PSM. All statistical analysis were performed using STATA v.14.0 (StataCorp, College Station, TX, USA).

Ethical approval

The study was approved by the Institutional Ethics Review Board of the LUMC. The results are reported according to the STROBE statement for observational studies and a checklist of proposed guidelines for the reporting of PSM.[20] Research data were pseudonymized and securely stored, according to the General Data Protection Regulation (GDPR).

RESULTS

Cohort characteristics

Of 897 observed episodes of BSI, four episodes were excluded because data about the empiric antimicrobial treatment were missing. Less than 2% of the variable information

was missing. Of the 893 included BSI episodes, 319 (35.7%) initially received inadequate empiric treatment. The second dose usually administered after 8-12 hours, remained inadequate in 89.0% of these patients in the original and in 88.6% in the matched cohort. The remaining 574 (64.3%) patients directly received adequate empiric treatment. Overall, 14-day mortality before PSM matching was 96/893 (10.7%) and 30-day mortality was 134/893 (14.9%). Baseline characteristics were not equally distributed over the patient groups that received adequate or inadequate empiric antimicrobial treatment. The source of infection, type of pathogen, site of acquisition of the infection and physical examination were all associated with (mis)match of empiric treatment (Table 1).

Table 1. Cohort characteristics before- and after propensity score matching.

	Cohort before PS matching			**Cohort after PS matching**		
	Empiric antimicrobial treatment			Empiric antimicrobial treatment		
	adequate (N=574)	inadequate (N=319)		adequate (N=167)	inadequate (N=167)	
	N (%)	**N (%)**	**P#**	**N (%)**	**N (%)**	**P#**
Demographics						
Age, mean (range)	62.1 (18-98)	63.0 (18-92)	0.41	62.2 (20-91)	61.7 (18-92)	NS
Male	327 (57.0)	206 (64.6)	0.03	100 (59.9)	102 (61.1)	NS
Microbiology parameters						
High risk pathogen	257 (44.9)	158 (58.0)	<0.01	82 (49.1)	91 (54.5)	NS
TTP mean no. of hours (IQR)	19.0 (13-19)	21.0 (14-21)	<0.01	19.75 (13-18)	20.17 (14-21)	0.02
Gram positive pathogen	218 (38.0)	166 (52.0)	<0.001	74 (44.3)	43.1	NS
Hospital acquired infection	24.9%	141 (44.2)	<0.001	63 (37.7)	58 (34.7)	NS
Source of infection						
Urinary tract	180 (31.4)	51 (16.0)	<0.001	35 (21.0)	37 (22.2)	NS
Gastro-intestinal	436 (76.0)	212 (66.5)	0.003	113 (67.7)	115 (68.9)	NS
Pulmonary	78 (13.6)	11 (3.4)	<0.001	12 (7.2)	10 (6.0)	NS
Endovasculair	49 (8.5)	61 (19.1)	<0.001	23 (13.8)	21 (12.6)	NS
Soft Tissue	46 (8.0)	23 (7.2)	0.70	13 (7.8)	15 (9.0)	NS
Unidentified	42 (7.3)	42 (13.2)	0.006	19 (11.4)	19 (11.4)	NS
Source correctly identified at presentation	426 (74.3)	120 (38.2)	<0.001	83 (49.7)	88 (52.7)	NS
Risk factors for antimicrobial resistance						
Antibiotic Pre-treatment at presentation	152 (26.5)	111 (35.1)	0.007	61 (36.5)	58 (35.2)	NS
Antibiotic treatment in prior 2 months	246 (44.2)	188 (60.5)	<0.001	95 (56.9)	90 (53.9)	NS
Gram negative MDRO in prior 6 months	35 (6.1)	21 (6.6)	0.77	10 (6.0)	11 (6.6)	NS
Intensive care unit stay in prior 6 months	42 (7.3)	40 (12.5)	0.01	20 (12.0)	16 (9.6)	NS
Medical history						
Central intravenous catheter	90 (15.7)	79 (24.8)	0.001	34 (20.4)	33 (19.8)	NS

Table 1. Cohort characteristics before- and after propensity score matching. (*continued*)

	Cohort before PS matching			Cohort after PS matching		
	Empiric antimicrobial treatment			Empiric antimicrobial treatment		
	adequate (N=574)	inadequate (N=319)		adequate (N=167)	inadequate (N=167)	
Corticosteroïd therapy	171(29.8)	104 (32.6)	0.41	52 (31.1)	55 (32.9)	NS
Diabetes mellitus	126 (22.0)	60 (18.8)	0.30	38 (22.8)	35 (21.0)	NS
Neutropenia	80 (13.9)	33 (10.3)	0.14	28 (16.8)	25 (15.0)	NS
Stem cell transplantation	41 (7.1)	29 (9.1)	0.30	15 (9.0)	18 (10.8)	NS
Solid organ transplantation	80 (13.9)	35 (11.0)	0.21	20 (12.0)	24 (14.4)	NS
Hematologic malignancy	57 (9.9)	39 (12.2)	0.31	23 (13.8)	22 (13.2)	NS
Malignancy (non-hematological)	95 (16.6)	74 (23.3)	0.016	32 (19.2)	33 (17.5)	NS
Clinical presentation						
Temperature> 38.5 °C	380 (67.7)	157 (50.8)	<0.001	99 (59.3)	104 (62.3)	NS
Systolic bloodpressure <90mmHg	111 (19.3)	46 (14.4)	0.07	26 (15.6)	28 (16.8)	NS
Respiratory rate > 22/min	177 (30.8)	45 (14.1)	<0.001	34 (20.4)	29 (17.4)	NS
Pitt bacteraemia score, mean (IQR)	1.26 (0-2)	1.17 (0-2)	<0.003	1.09(0-1)	1.05 (0-1)	NS
qSOFA, median (IQR)	1 (0-2)	1 (0-1)	<0.001	1 (0-1)	1 (0-1)	NS

Legend High risk pathogen: Enterobacterales*, S.aureus, Streptococcus spp. or Pseudomonas.* TTP= time to blood culture positivity, defined as the time between collection of the blood cultures and the automated positive signal in the continuous monitoring system; Neutropenia: neutrophil count < 0,5 10^9/L at presentation. Corticosteroid therapy: use of corticosteroids during 6 months prior to presentation. IQR: interquartile range; MDRO: multidrug resistant organism; p: p-value; #: chi-square test or T-test or Wilcoxon ranksum test; qSOFA: quick sequential organ failure assessment score.

Source of infection and microbiology data

The most frequent isolated pathogen was *Escherichia coli* (29.3%), *Streptococcal species* (18.2%) and *Staphylococcus aureus* (11%). The most common MDROs observed were *Escherichia coli* (n=84, 28 ESBL positive), *Enterococci* (n=25) and *Klebsiella species* (n=21, 11 ESBL positive). There were no cases with MRSA infection. The most frequent sources of BSI were intra-abdominal infection (28.9%), urinary tract infection (26.1%) and intravascular infections (12.5%).

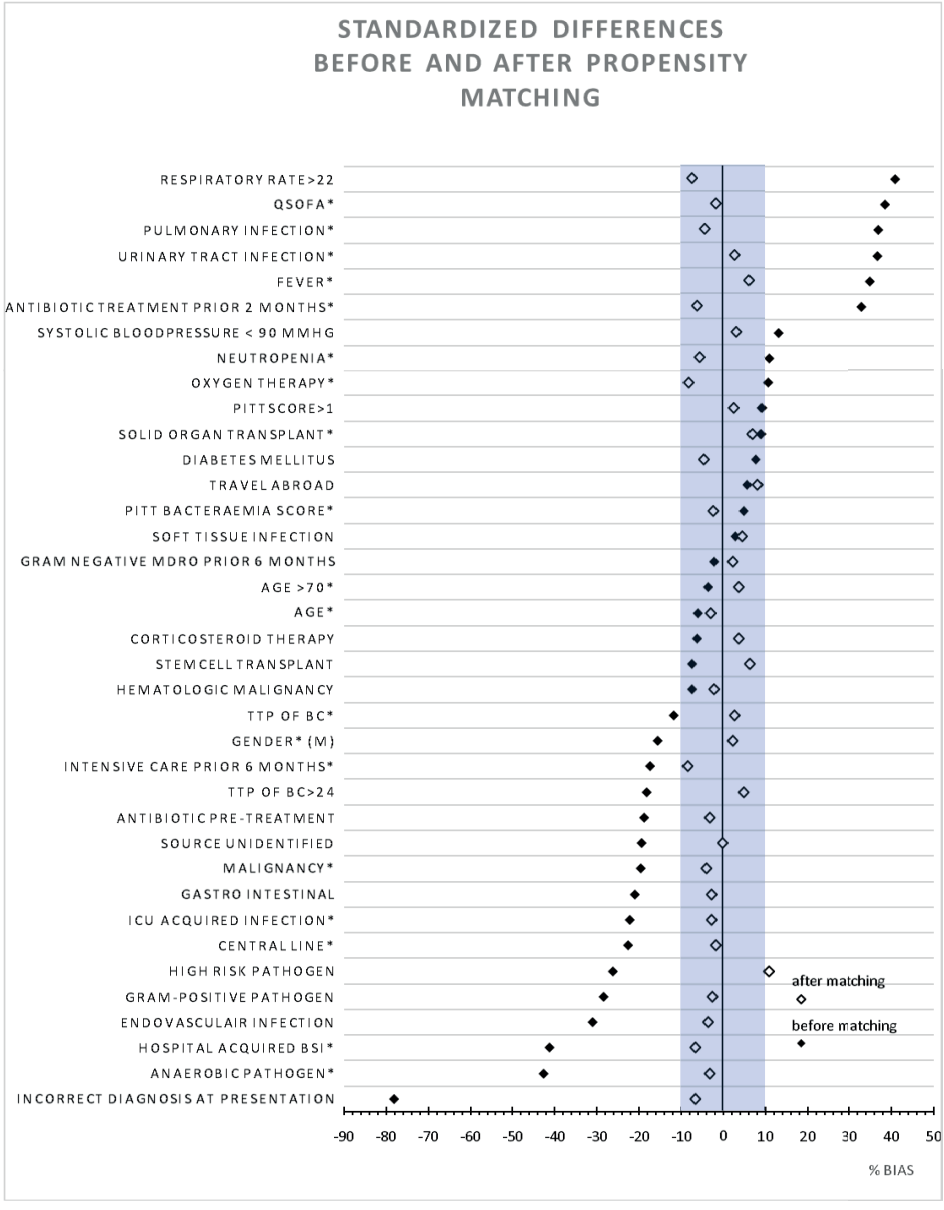
Inadequate empiric antimicrobial treatment was more frequently observed in hospital acquired BSI (49.6%) than in community acquired BSI (29.2%), OR 1.34 (95%CI 1.02-1.74, p<0.05).

Propensity score matching analysis

The logistic regression model for calculation of the propensity scores consisted of 18 variables, including demographics, microbiology parameters, disease severity scores and medical history. The C-statistic of the model was 0.83. The specific variables are

indicated with an * in Figure 1. After PSM, the matched cohort consisted of 334 patients, i.e. 167 matched patient pairs.

Figure 1. Standardized differences of study variables before- and after propensity score matching.



Legend: An * indicates that the variable was included in the propensity score model. The shaded area represents the distribution with an SDD < 10. MDRO = Multi drug resistant pathogen. TTP = Time to positivity. ICU = intensive care unit. Fever was defined as temperature >38.5 °C. Neutropenia: absolute neutrophil count <0.5 x 10^9/ml

Fourteen-day mortality in the group that received inadequate empiric treatment was 16/167 (9.6%) versus 17/167 (10.2%) in the group that directly received adequate treatment (p=0.85). No differences were observed in the secondary clinical outcomes among patients that initially received inadequate versus adequate treatment: 30-day mortality (21/167 vs. 25/167, p=0.68) and median duration of hospital stay (10.5 vs. 10.7 days, p=0.89) (Table 2). In patients with a qSOFA ≥2, 14-day mortality was 8/41 (19.5%) in the adequate treatment group, versus 10/39 (25.6%) in the inadequate treatment group (p=0.60). After stratification for setting - hospital acquired or community acquired BSI – no effect of inadequate empiric therapy om 14 day mortality was observed in either setting (p=1.00).

Table 2. Outcomes after adequate and inadequate empiric antimicrobial therapy in patients with bloodstream infection using propensity score matching.

Outcome variable	Adequate empiric regimen N (%)	Inadequate empiric regimen N (%)	Difference N(%)	OR#	95%CI	P^
14-day mortality	17/167 (10.18)	16/167 (9.58)	1 (0.60)	0.77	0.43-1.85	0.45
30-day mortality	25/167 (14.97)	21/167 (12.57)	4 (2.40)	0.78	0.42-1.47	0.45
Length of hospital stay in days*, median (IQR)	10.7 (4.6-18.2)	10.5 (4.3-20.3)		-	-	0.89

Legend: OR: Odds ratio; 95%CI: 95% confidence interval; *: Days counted after day of withdrawal of the positive blood-culture; #: ORs were adjusted for type of pathogen (high risk pathogen: Enterobacterales, *S.aureus, Streptococcus spp. or Pseudomonas spp.*) ; ^: OR and p-values were calculated by using logistic regression analyses. For comparison of the length of hospital stay a Wilcoxon ranksum test was applied.

The SDD for the variable 'BSI with a high-risk pathogen' - i.e. Enterobacterales, *S. aureus, Streptococcus* spp. or *Pseudomonas* spp - was 10.9%. For the remaining variables in the matched database, the SDD was <10%. The distribution of the cultured pathogens was listed per group (Supplementary data). A multivariable regression analysis to adjust for this slightly unbalanced determinant showed no effect of inadequate therapy.

As a sensitivity analysis, inversed probability weighting (IPW) was performed, using the variables included in the PSM model. There was no effect of inadequate initial empiric antimicrobial treatment on mortality. The average effect of inadequate empirical treatment op 14-day and 30-day mortality was -2.2%, (95%CI -6.2 – 1.8, p=0.29) and -3.4% (95%CI -8.0 - 1.3, p=0.16) respectively.

DISCUSSION

Key results

In this study, empirical inadequate empiric antibiotic treatment was not associated with increased 14-day mortality in patients with BSI after applying propensity score matching methods to correct for confounding. No statistically significant differences in length of hospital stay or 30-day mortality were observed between patient groups that did- and did not receive adequate empiric antimicrobial treatment. The low average Pitt bacteraemia and qSOFA scores show that the majority of patients were only mild to moderately ill. Hence, the interpretation of these findings would be that these patients with BSI, an initial mismatch of the antimicrobial treatment and the susceptibility of the causing pathogen may have limited consequences. Notably, in 89% of patients with an inadequate first dose of empiric antimicrobials, the second administration was also not adequate, indicating that in most patients, the duration of time without antibiotic treatment was more than 6 hours.

The results of this study are in contrast to a propensity-based study by Retamar *et al*, in which inadequate empiric treatment was associated with increased mortality.[17] Two methodological differences likely explain the contradicting results. Retamar *et al*. predominantly included patients with sepsis, including septic shock. The impact of inadequate empiric treatment is this group may be relatively high compared to the impact in patients with a lower risk for death. The low average Pitt bacteraemia score and qSOFA (Table 1) in the current study shows that the majority of patients were only mild to moderately ill. Secondly, Retamar *et al* choose a 4-fold longer time window, 24 hours, to define inadequate empiric therapy. The prolonged time without adequate antibiotic therapy and the high proportion of sepsis/septic shock most probably are multiplicative factors driving the higher mortality associated with inadequate empiric therapy.[21,22]

Other studies on the relevance of empiric antibiotic therapy also suggest that inadequate therapy leads to unfavorable outcome in BSI.[6] These studies did not apply PSM and are likely to be hampered by confounding. The complexity of the confounders that influence the adequacy of empiric treatment are illustrated in this study and stress the importance of methodology to correct for the propensity of (in)adequate treatment.[11, 23] A propensity score cannot replace a randomized control trial, but such a design is unethical in this specific condition and studies using propensity scores can be considered the next best alternative in many cases.

Propensity of inadequate empiric treatment

The adequate empiric treatment rate in this study was 64.3%. Both the adequate treatment rate and predictors for inadequate empiric therapy were comparable to previous studies investigating treatment for BSI.[24] Hospital acquired BSI, antibiotic pre-treatment and previous hospital admissions are known risk factors for antimicrobial resistance and therefore risk factors for a mismatch in empiric treatment.[25] Colonization with a MDRO was not associated with a mismatch, most likely because colonization is taken into account by the attending medical team when they select empiric therapy. Low PBS scores and low SOFA scores were both associated with an increased risk of receiving inadequate empiric antimicrobial therapy.[24] This can be due the tendency that a physicians' tolerance of a potential mismatch of empiric antibiotic therapy is probably higher in patients that are not acutely ill and lower in patients that fulfill the criteria of sepsis.

Study strengths and limitations

This study is one of the first studies that applied PSM to assess the effect of early adequate empiric antimicrobial therapy on mortality. As illustrated in this study, whether a patient receives appropriate antibiotic therapy, is subject to many variables and therefore (uncorrected) confounding is a major issue in previous studies. Propensity score analyses have been demonstrated to effectively reduce bias in baseline characteristics when assessing treatment effects.[19] However, in contrast to randomization, unobserved confounders may still be an issue in PSM. For example, in the present study, data on other management variables that may impact mortality, such as source control, were not available. However, measured variables, that were not included in the propensity score model, were well balanced after matching.

In the Netherlands the prevalence of MRSA is low. This may limit applicability of the results to settings were MRSA infections are more frequent. A second limitation is that this study focuses on 14 and 30- day mortality. Inadequate antibiotic therapy may have other relevant unfavorable (long term) effects, that were not assessed in this study.[7] Furthermore, this study does not account for suboptimal dosing of the antibiotic in the definition of adequate empiric therapy.[6]

Generalizability and implications

In the study cohort, the proportion of patients with sepsis or septic shock was relatively low. The results are therefore not applicable to selected high-risk populations. Importantly, patients present with a clinical syndrome. The exact source of infection, the yet unknown type of pathogen, the presence of sepsis/septic shock and comorbidities, may be more important determinants on the impact of inadequate antibiotics than the pres-

ence of bacteraemia. Prompt adequate antibiotic treatment remains the cornerstone of the management of patients with severe clinical infections, such as sepsis.[17,21,26]

In daily clinical practice, the threshold to prescribe broad spectrum antimicrobials is often low, and 'sepsis therapy' is frequently administered to non-septic patients suspected of BSI to avoid the risk of mismatch in empiric treatment. This study shows that the consequences of inadequate empiric therapy may currently be overestimated in a low-risk population. Therefore, in these patients, the potential beneficial effects of broad-spectrum empiric antimicrobial treatment need to be balanced with the negative effects, such as toxicity, development of AMR and *Clostridioides difficile* infections.[27-29] Unnecessarily broad empiric antibiotics may negatively impact mortality.[30] Tolerating uncertainty in the antimicrobial spectrum, as it is already part of today's medical practice, can benefit both the individual patient and the community (development of AMR).[31]

CONCLUSIONS

While it is widely adopted that prompt delivery of adequate antimicrobial treatment is of great importance in BSI, data to support this in patients that are mild to moderately ill, is limited.

The findings of this study clearly indicate that in this population with BSI, a limited delay in administration of adequate empiric antibiotic therapy was not associated with increased 14-day or 30-day mortality. From an antimicrobial stewardship perspective, not pursuing a 100% coverage of the expected causative agents of BSI, is an acceptable uncertainty in a patient without sepsis or septic shock.

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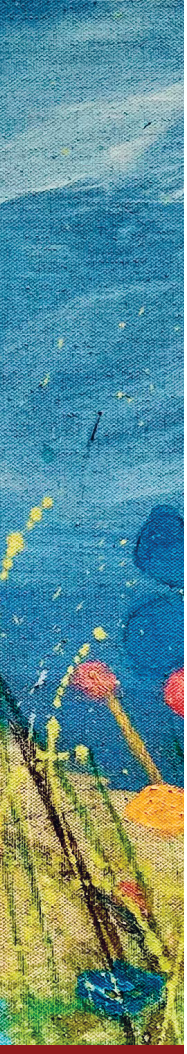
SUPPLEMENTARY DATA

Table S1. Distribution of the isolated pathogens from blood cultures per group after propensity score matching.

Species	Adequate empiric regimen N (%)	Inadequate empiric regimen N (%)
Streptococcus spp	19 (9.6)	20 (11.2)
Enterococcus spp	19 (9.6)	28 (16.8)
Staphylococcus aureus	21 (12.6)	13 (7.8)
Escherichia coli	50 (29.9)	37 (22.1)
Klebsiella spp	14 (8.4)	12 (7.2)
Pseudomonas aeruginosa	6 (3.6)	11 (6.6)
Enterobacter spp	4 (2.4)	13 (7.8)
Serratia spp	5 (3.0)	7 (4.2)
Proteus spp	5 (3.0)	1 (0.6)
Streptococcus pneumoniae	10 (6.0)	6 (3.6)
Anaerobes	7 (4.2)	6 (3.6)
Other	7 (4.2)	13 (7.8)

Part II

Decision making in daily clinical practice and antibiotic policymaking



7

Determinants of in-hospital antibiotic prescription behaviour: a systematic review and formation of a comprehensive framework

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**equal contributions*

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ABSTRACT

Background: Knowledge of determinants that influence antibiotic prescription behaviour (APB) is essential for the successful implementation of antimicrobial stewardship interventions. The theory of planned behaviour (TPB) is an established model that describes how cognitions drive human behaviour.

Objectives: The objective of this study was to identify the socio-cultural and behavioural determinants that affect APB and construct a TPB-framework of behavioural intent.

Data sources: The following online databases were searched: PubMed, Medline, Embase, Web of Science, Cochrane Library and Central.

Study eligibility criteria: Studies published between July 2010 and July 2017, in European countries, the United States, Canada, New-Zealand or Australia, were included if they identified one or more determinants of physicians' APB.

Methods: A systematic review was conducted according to the PRISMA-statement. Based on the TPB, determinants were categorised in behavioural, normative and control beliefs, thus shaping a conceptual framework of APB.

Results: Nine studies were eligible for inclusion, and identified 16 determinants. Determinants relating to fear of adverse outcome (5/9), tolerance of risk and uncertainty (5/9), hierarchy (6/9) and determinants concerning normative beliefs, particularly social team dynamics (6/9), were most frequently reported. Beliefs about antimicrobial resistance and potential negative consequences of antibiotic use were rarely mentioned.

Conclusions: Behavioural, normative and control beliefs are all relevant in APB. There is a need for quantitative studies assessing the weight of the individual determinants to be able to efficiently design and implement future stewardship interventions. The constructed framework enables a comprehensive approach towards understanding and altering APB.

INTRODUCTION

International guidelines on antimicrobial stewardship (AMS) aim to enhance the rational use of antimicrobial agents and thereby prevent their overuse.[1,2] To successfully implement stewardship strategies, it is essential to understand how physicians make decisions about prescribing antibiotics. Balancing the potential benefits and drawbacks of antibiotic prescription is a substantial challenge in daily clinical practice. Prescribing antimicrobial therapy typically involves decision making under uncertainty.[3,4] Under such uncertainty and in a complex decisional context, behavioural, social and cultural factors gain influence on decisions made with regard to antimicrobial therapy.[5,6] These determinants have been researched in a limited number of prior studies. Insight into their magnitude and relative importance in the process of managing antimicrobial therapy in the hospital setting is lacking. This knowledge is needed to design and successfully implement antimicrobial stewardship interventions that optimize antimicrobial therapy.[4,7,8] There is an urgent need to incorporate insights from behavioural and social sciences in the development of more impactful stewardship programmes.[9] However, very few studies about antimicrobial prescription behaviour (APB) enhancing interventions have focused on applying behaviour change theories.[7]

We considered the theory of planned behaviour (TPB) to be the most suitable model to better understand the cognitive determinants of APB.[10,11] This theory is social-cognitive in nature, positing that the decisions people make on whether or not to perform a certain behaviour are determined and explained by the specific ideas (cognitions) people have about the target behaviour. The theory is explained in Box 1 and visualized in Fig. 1.

Our aim was to develop a framework to explain APB by identifying its cognitive determinants. We conducted a systematic review to map the determinants that potentially affect antimicrobial prescription. The determinants identified by the systematic review were organized according to TPB to display overlap and conceptual differences.

Box 1. The Theory of Planned Behaviour

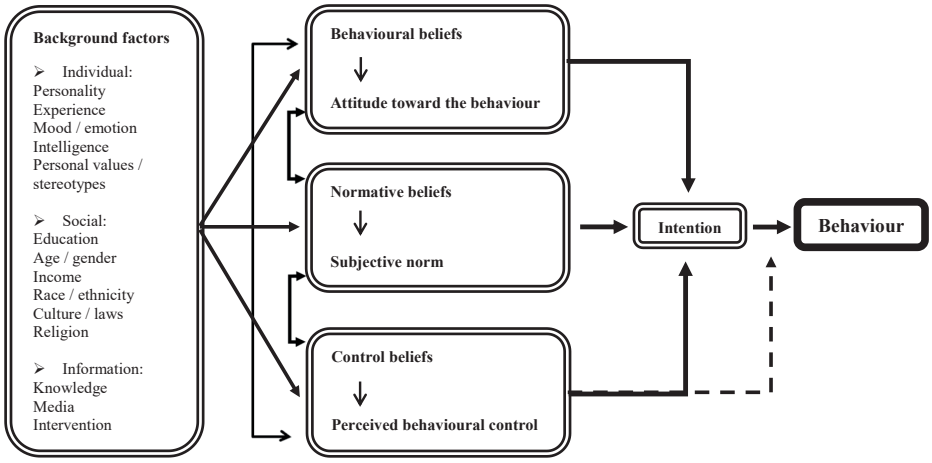
This model postulates that behaviour can be explained by three main concepts: the attitude towards the behaviour, the social norm regarding the behaviour, and the perception of control over execution of the behaviour [10,11]. Each of these concepts is based on a number of specific beliefs. Attitude, social norm and perceived behavioural control determine the intention to perform the behaviour, which is considered the best predictor of actually performing the behaviour.

Behavioural beliefs: Behavioural beliefs are the cognitions about the direct consequences of performing the behaviour - in our case the consequences of APB - for example, the risk of not providing optimal cure, or the long-term consequences for the functionality of antibiotics. A distinction can be made between beliefs pertaining to direct personal outcomes (e.g. the effect of antibiotics on survival in sepsis) and beliefs pertaining to outcomes with a moral bearing (e.g., concerning felt responsibility for the patient's health, irrespective of practical consequences. Because all beliefs constitute expectations that come with a certain degree of uncertainty, each belief is an estimate, qualified by a degree of (un)certainty. Some researchers have proposed to include the moral beliefs as a separate factor, called 'personal norm'. For the current purposes, it makes sense to include this as being part of the set of beliefs that underlie the attitude.

Normative beliefs: Normative beliefs are estimates of how the social environment of the actor will consider his/her behaviour. The relevant social environment for APB will mainly consist of colleagues, superiors, and other persons in the hospital environment. Note that explicit approval or disapproval is not required for a social norm to operate. In their latest description of the TPB Fishbein and Ajzen take also the so called descriptive norm into account: the observation what relevant others do. For APB both kinds of social norms, the explicit and the observation-based social norm, may operate on the behaviour.

Control beliefs: Control beliefs refer to the difficulty or ease of executing the behaviour. For several reasons APB may contain difficulties: for example it may be perceived difficult to get a superiors' permission to withhold antibiotic treatment or it might be difficult to explain to the patient why antibiotics are not prescribed.

Figure 1. The theory of planned behaviour.



Legend. Icek Ajzen's framework of TPB. The striped arrow represents the consideration that perceived behavioural control cannot substitute the actual behavioural control, when the perceived behavioural control is not completely accurate.

METHODS

Literature search strategy

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] To include all relevant articles, the following online databases were searched: PubMed, Medline, Embase, Web of Science, Cochrane Library and Central. The search syntaxes were formatted separately for each database. The exact search strategies and dates are listed in Supplementary data. The search output was restricted to articles published in the last 10 years (July 2007 to July 2017). The reason for this time restriction is that medical practice changes rapidly, as does society as a whole; for example, awareness of antimicrobial resistance (AMR) has improved significantly over the past decades[13,14] and antibiotic stewardship has become more prominent in daily clinical practice.[15] The intention was to focus on what currently drives doctors with regard to prescription behaviour. Reference lists of the included articles and relevant reviews were used to screen for missed articles.

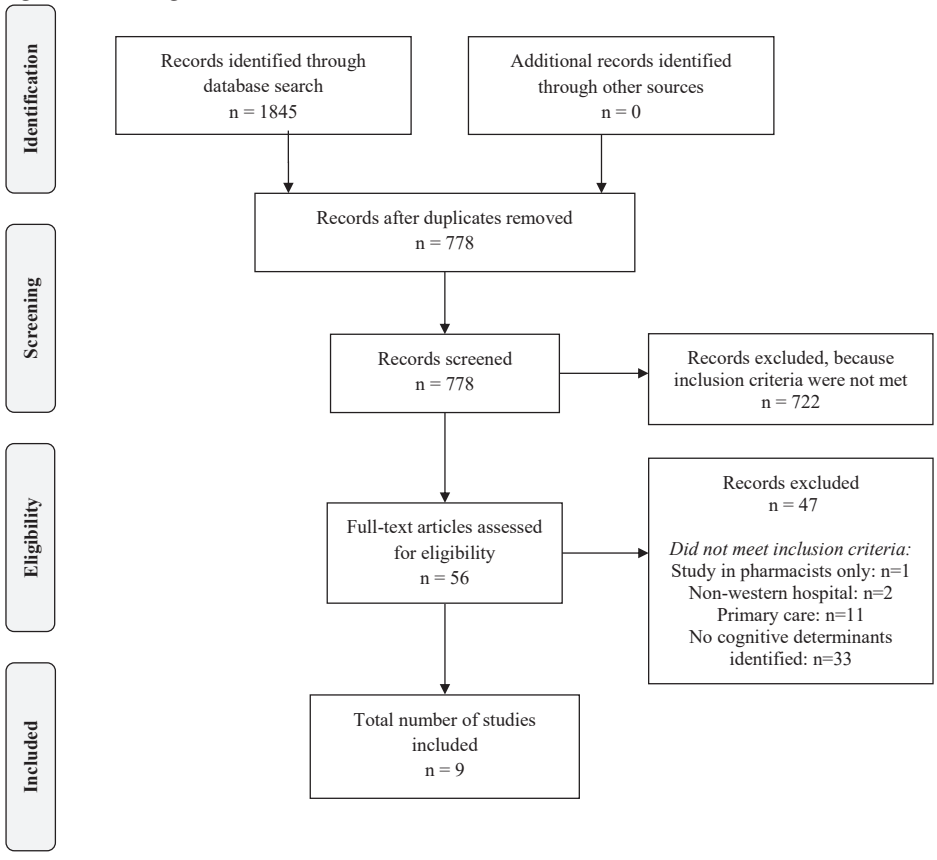
Study selection: inclusion and exclusion criteria

A study was included if it identified one or more self-reported cognitive determinants of any kind (social, personal, logistic, environmental, etc.) of antibiotic prescription behaviour of hospital physicians. Only studies performed in hospitals in European countries, the United States, Canada, New Zealand or Australia were eligible for inclusion. Studies that measured the effect of an antibiotic stewardship intervention and studies that

exclusively focused on the influence of patient-related clinical characteristics (e.g. vital parameters and suspected source of infection) were excluded, because this review is aimed at elucidating behavioural rather than biomedical determinants.

As a first step, all articles were independently screened by two individual investigators (EW and RW) based on title and abstract. Articles that were scored as relevant by at least one of these two investigators were included for the second phase that consisted of a full-text review. Articles judged to be eligible after full-text review were included for quality assessment. If doubt remained in the final phase of inclusion, a third investigator (MB) was consulted to decide on inclusion or exclusion. The result of the screening and inclusion process is displayed in the flow diagram in Figure 2. EndNote software (version X7) was used to remove duplicates and systematically complete the screening process.

Figure 2. Flow diagram (PRISMA) of the article inclusion process.



Data extraction and quality assessment

From each included study, the study design, geographical location of included hospitals, type of hospital, the number of physicians included, and the determinants of APB were extracted (Table 1). The Critical Appraisal Skills Program (CASP) 2017 scoring system for quality assessment of qualitative research was applied (Supplementary data).[16] The quality assessment was performed individually by two researchers (ML and EW) and discrepancies were discussed. If doubt remained, a third investigator (MB) was consulted.

Construction of a conceptual framework according to the theory of planned behaviour

Fishbein and Ajzen state that the TPB is sufficient to understand behaviour, such that all other influences are mediated by the concepts in the model. Personality, values and sociographic characteristics of the population may have an effect, but are extrinsic to the model and are assumed to impact behaviour through their influence on the three sets of beliefs: underlying attitude, social norm, and perceived behavioural control. For the purpose of our analysis, the first column of concept-specific beliefs is most important: the behavioural, normative, and control beliefs (Box 1).

Determinants of APB were identified from the studies and organized according to TPB principles (ML, EW). Classification and allocation of determinants within the framework were discussed within the research group (which consisted of behavioural scientists and infectious diseases specialists). Potential additional determinants that were not identified through the current systematic review, but were identified based on existing TPB literature, theoretical grounds and through discussion, were added to the model (indicated in Fig. 3 in italics)

RESULTS

Systematic review

The database search yielded 761 unique records; 56 articles were included for full-text reading, of which nine articles were selected for analysis after quality assessment.[5,6,8,17-22] The study characteristics of these nine studies are summarized in Table 1. The majority of the studies had a qualitative design, mostly based on semi-structured interviews. Parker *et al*. and Velasco *et al*. performed quantitative studies, and in the study of May *et al*. both quantitative and qualitative methods were used.[8,19,20] In all qualitative studies, between ten and 30 physicians were interviewed, based on the number of interviews needed to reach satisfaction.

Table 1. Study characteristics.

Study	Geographical location	Hospital type	Study design	Number of participants
Broom A et al. 2014 [5]	Queensland, Australia	General metropolitan hospital	Qualitative: semi-structured interview	30
Broom J et al. 2016 [22]	North-East England	1200-bed NHS[a] teaching hospital	Qualitative: semi-structured interview	20
Charani et al. 2013 [21]	West London, United Kingdom	4 hospitals of the ICHNT[b]	Qualitative: semi-structured interview	10
Cortoos et al. 2008 [17]	Belgium	Tertiary care hospital 1900-bed, university hospital	Qualitative: focus group interview	22
Livorsi et al. 2015 [6]	Indianapolis, United States of America	2 hospitals: 316-bed safety-net hospital and 209-bed tertiary-care hospital	Qualitative : semi-structured interview	30
May et al. 2014 [20]	United States of America	8 hospitals: urban tertiary care academic centres, military treatment facilities, county facility, tertiary paediatric centre	Qualitative and quantitative: Questionnaires and semi-structured interviews (non-parametric analysis of important factors and predictors)	150 /21[c]
Parker et al. 2016 [8]	South-West England	3 teaching hospitals including a tertiary referral centre, 1district general hospital	Quantitative: questionnaire (exploratory factor analysis and subsequent pairwise comparisons)	254
Schouten et al. 2007 [18]	South East of the Netherlands	3 secondary care hospitals	Qualitative: semi-structured interview	17
Velasco et al. 2011 [19]	Germany	State medical associations	Quantitative: questionnaire	3492

Legend: a. NHS = National Health Service; b. ICHNT = Imperial College Healthcare National Health Service Trust. c. 150 participants were included in the quantitative study, 21 in the qualitative study.

From the results of the included studies, 16 individual determinants of APB were identified (Table 2). Factors concerning managing risks and tolerating uncertainty were mentioned in five of nine studies. When it comes to fear of adverse outcomes, physicians primarily refer to adverse outcomes by not treating infection (5/9). Adverse effects that may accompany prescribing antibiotics, such as toxicity and *Clostridioides difficile* infection, were identified as a determinant in one study, but the influence of this on antibiotic decisions was assessed to be limited.[6]

One of the identified factors was the perceived tendency of physicians to follow the example of colleagues (3/9). The interviewed physicians referred to the influence of hospital routines and the feeling that mimicking peers is a habit. This influence works in

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions.

Determinant	Description	Example	Study	Example of potential intervention(s)
The example set by colleagues	The example of others (both peers and senior) physicians in decision making in antimicrobial prescribing	"Whatever attending you are with is the attending you learn from, and if I see them continuously not prescribe antibiotics over and over again, then I feel comfortable not prescribing antibiotics …" [6] "our behaviour is heavily influenced by what we see, and (what) people do around us" [5]	Broom et al. [5] Livorsi et al. [6] Cortoos et al. [17]	Making senior physicians aware of their role model function and training them in explicating their motivation for antibiotic therapy Enhancing young physicians' reflective assessment of their superiors' antibiotic decisions, to discern those aspects that are worth adopting [27]
Social team dynamics	Willingness to intervene in the antimicrobial decisions of peers. Preference of work relationships over questioning treatment decisions of peers	"Out of courtesy to colleagues, no criticism of the chosen antibiotic regime is made at end-of-shift meetings" [18] "The rule of non-interference with the clinical decision of others" [21] "Participants found it inherently difficult to criticize another physician's care. They did not want to 'offend' a colleague or harm a 'good collegial relationship'" [6]	Broom et al. [5] Livorsi et al. [6] Charani et al. [21] Broom et al. [22] Parker et al. [8] Schouten et al. [18]	Training medical students and physicians on giving and receiving feedback Incorporating information on the antibiotic policy (including rationale) at end-of-shift meetings Evaluating antibiotic prescription quality on the department level and acknowledging teams for improvements in quality of prescribing (team effort) [28]
Hierarchic influence	The influence of hierarchy on antimicrobial treatment decisions	"The influence of hierarchies (…..) consultants being 'unquestionable'" [22]	Broom et al. [5] Charani et al. [21] Livorsi et al. [6] Schouten et al.[18] Broom et al. [22] Parker et al. [8]	Training leadership skills (medical students and young professionals) [29] Creating projects aiming at improvement of team performance and a positive work environment
Reputational risk	The risk of being criticised for being too conservative versus for being careless	"I don't want to be criticised for being either a cowboy or too cautious. So I want to do what is recognized as the standard of care" [5]	Broom et al. [5] Livorsi et al. [6]	Promoting a positive error and safety culture [30]

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions. (*continued*)

Determinant	Description	Example	Study	Example of potential intervention(s)
Logistics	The available time to make a decision (time pressure), available resources, timing of ward rounds, timing of supervision	"Your sole purpose at 3 in the morning is to get them through till 9 in the morning" [22] "Working pressure was mentioned by both resident groups as a cause of not being able to consult guidelines" [17]	Broom et al. [5] Cortoos et al. [17] Broom et al. [22] May et al. [20] Schouten et al. [18]	Improving ward round practice: routine medication review and consideration of antimicrobial de-escalation Improving communication of microbiology results and accessibility of infectious diseases consultation
Antimicrobial resistance (AMR)	Awareness of the need to be careful with antibiotics because of resistance (population level) and ascription of responsibility concerning emerging antimicrobial resistance	"…physicians agreed that their own work has an influence on antimicrobial resistance" [19] "When it comes to individual patients I think sometimes it (resistance) is down the list I guess of considerations" [5]	Broom et al.[a 5] Livorsi et al.[a 6] Parker et al. [8] Velasco et al. [19]	Medical education about 'antibiotic awareness' [31] Facilitating monthly feedback to physicians on their own prescription characteristics (e.g. using ICT programs) Distributing posters/leaflets that enhance 'antibiotic awareness' among healthcare professionals
Benevolence	The desire to do good to patients. The (emotional) interaction between physician and patient	"Your relationship with your patient is much stronger than your relationship with the hospital inpatient population and the microbial ether that we live in …" [5]	Broom et al. [5] Livorsi et al. [6]	Addressing responsibility towards both today's patients and future patients during medical education
Guidelines	Attitude towards (local) practice guidelines/studies and beliefs on applicability of guidelines to the individual patient	"Sometimes it is difficult to use the policy because the policy will be your average sort of thing, it's not looking at someone at the top or the bottom" [21] "I am quite likely to overstep the guidelines if it was left to my devices" [21] "Both surgery groups felt that antibiotic guidelines were not adapted to their practice and that use of antibiotic guidelines in their wards could hamper efficient patient flow" [17]	Charani et al. [21] Cortoos et al. [17] Parker et al. [8] Schouten et al. [18]	Improving applicability of guidelines by adapting them to: - variants of the clinical syndrome - specific patient populations Letting prescribers participate in hospital guideline formation to improve support and adherence [17]

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions. (*continued*)

Determinant	Description	Example	Study	Example of potential intervention(s)
Professional autonomy	Feeling self-directing and independent in making decisions on antibiotic therapy	"I am a clinician and have some degree of independent practice" [21]	Charani et al. [21] Parker et al. [8]	Training and coaching of young professionals in structured antibiotic decision making [32]
Prior experiences	Prior individual cases influence future treatment decisions. A physician who has lost a patient because of too narrow antimicrobial therapy will be more likely to give broad-spectrum treatment in the future	"My anecdotal experience is that they (immunosuppressed end-stage renal population) get sick very quickly" [21]	Charani et al. [21] Velasco et al. [19]	Facilitating the availability of support groups (peers) to evaluate and discuss adverse outcome in individual cases
Clinical experience and education	Years and type of clinical experience and education	"A junior physician is more likely to prescribe broad-spectrum treatment whereas a senior physician may accept more immediate risk" [5]	Broom et al. [5] Charani et al. [21] Broom et al. [22] May et al. [20] Schouten et al. [18] Velasco et al. [19]	Training on antibiotic therapy and stewardship for medical students and young professionals [31,33]
Tolerance of uncertainty	How much risk a physician is willing to take in case of (potential) infection	"I probably tend to overtreat rather than to undertreat… fear of relapse and uncertainty that they're going to get better" [5] "just in case" [6]	Broom et al. [5] Velasco et al. [19] Livorsi et al. [6] May et al. [20] Schouten et al. [18]	Providing education on dealing with uncertainty in medical practice (in medical school and peer-to-peer groups for young professionals [3,34] Promoting rapid diagnostics to differentiate bacterial versus non-bacterial aetiology [35]
Perceived ability to communicate the decision (not to treat) to the patient	How well the provider feels to be able to communicate about the antibiotic treatment with the patient	"Sometimes the purpose in giving antibiotics sometimes is to keep the family happy" [5]	Broom et al. [5] Broom et al. [22] May et al. [20]	Training communication skills in healthcare professionals (dedicated to antibiotic therapy) [36] Improving the publics' knowledge of antibiotic therapy: antibiotic awareness campaigns [9]

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions. (*continued*)

Determinant	Description	Example	Study	Example of potential intervention(s)
Complaints/litigation	Fear of complaints or litigation	"I have seen lawsuits for delays in therapy" [6] "More than 75% of those interviewed noted the threat of patient complaints as linked to decisions about antibiotics, indicating that this is an increasingly important pressure" [22]	Livorsi et al. [6] Broom et al. [22]	Training and facilitating shared decision making [37] Executing hospital interventions to improve inpatient understanding of antibiotic therapy [38] Facilitate legal support for medical staff
Adverse outcome (1): Infection	Fear of adverse outcomes by not treating infection	"Oh, fear of relapse and uncertainty that they're going to get better" [5]	Broom et al. [5] Velasco et al. [19] Livorsi et al. [6] Broom et al. [22] Schouten et al. [18]	Providing evidence-based decision support systems for the selection of empirical therapy 39 and for safe de-escalation, e.g. for the intravenous–oral switch [40]
Adverse outcome (2): negative consequences of antibiotic treatment	Fear of adverse outcomes related to the administration of antibiotics (e.g. *Clostridium difficile* infection, renal toxicity)	"…concerns were not expressed about patients' risk for developing *Clostridium difficile* or an infection with an antibiotic resistant microorganism" [6]	Livorsi et al.[a] [6]	Incorporating the topic of side-effects of antibiotics in medical education Enabling electronic registration and review of complications of antibiotic therapy within medical teams

Legend: a: Reports limited influence.

multiple ways, as both positive (role model) behaviour and bad examples were reported to have an influence on APB.

The perceived importance of maintaining a constructive work relationship and the reluctance to intervene in a colleague's antimicrobial prescription decision were mentioned in six studies. The determinant 'hierarchic influences', meaning the extent to which behaviour is affected by advice and instructions from senior physicians, was drawn from six studies.

Awareness of the issue of AMR on the population level was identified as a factor of influence in four out of nine studies. In the study by Livorsi *et al*.[6] this awareness was attributed limited influence on APB, particularly because of low ascription of responsibility. Broom *et al*.[5] described mixed perspectives on the importance of AMR. In general, the issue of AMR on the population level was well recognized by the participants, but it was regarded as a peripheral issue in APB.

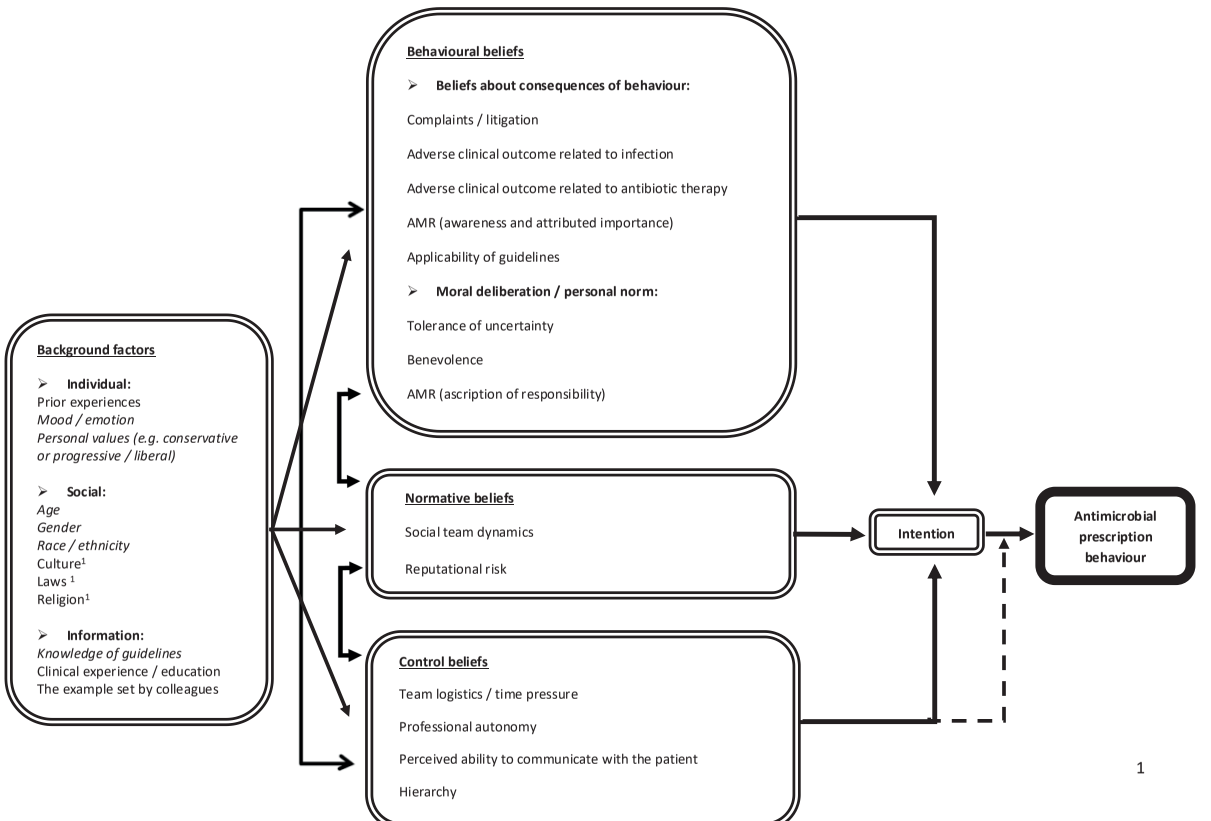
Organisation of the determinants of APB in the framework of TBP

The majority of identified determinants (13/16) were allocated to one of the three major pillars of the model (Fig. 3). The remaining three determinants were identified as background factors.

Three previous reviews focused on the subject of determinants of antibiotic prescription behaviour of physicians in Western hospitals.[4,23,24] Three additional determinants - religion, culture and law -were identified in the review performed by Hulscher *et al*.[24], and were considered relevant as background determinants in our TPB model.[24] Mood, emotion, personal values (e.g. conservative or progressive/liberal), age, gender and race/ethnicity were described as possible (background) determinants based on theoretical grounds and previous studies in fields other than APB.

Attitude towards AMR was separated into: (a) awareness and attributed importance, and (b) ascription of responsibility. For example, a physician may be well aware of the fact that antibiotic consumption drives AMR, but may not feel responsible. The first aspect (awareness) is best allocated to beliefs about the consequences of behaviour, while the second (ascription of responsibility) is best allocated to moral deliberation/personal norm. Determinants concerning the working environment and interaction with colleagues were divided into four aspects. (a) *The example set by colleagues*; the APB of other physicians, both peers and senior physicians, was considered a background factor. (b) *Social team dynamics* were classified as normative beliefs; for example, changing an antibiotic treatment that was initiated by a colleague might harm the working relation-

Figure 3. The theoretical framework of antimicrobial prescription behaviour.



Legend. The results of the systematic review were placed in the theoretical framework of antimicrobial prescription behaviour. The model is based on Icek Ajzen's framework of theory of planned behaviour (TPB). Potential additional determinants that were not identified through the current systematic review, but were identified based on existing TPB literature, theoretical grounds and discussion, were added to the model and indicated in this figure in italic type. The striped arrow represents the consideration that perceived behavioural control cannot substitute the actual behavioural control, when the perceived behavioural control is not completely realistic. AMR = attitude towards antimicrobial resistance. 1. determinant identified from the review by Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. The Lancet Infectious diseases. 2010;10(3):167-75.

ship. (c) *Hierarchy* was separated from *social team dynamics*, as it relates to beliefs on the persistence that is required to execute a desired behaviour; for example, it might be very difficult to persuade a senior physician to agree on discontinuation of antibiotics. (d) *Reputational risk* is closely related to *hierarchy* and *social team dynamics*, but was considered a separate factor as it represents primarily the beliefs on the risk of being criticized for the behaviour.

DISCUSSION

This systematic review shows that fear of an adverse outcome because of untreated infection and (lack of) tolerance of uncertainty are prominent determinants of APB. Moreover, determinants concerning the subjective norm, such as reputation, were frequently identified as being important. It is remarkable that the negative consequences of antibiotic therapy -both at the individual patient level and at the population level - were only scarcely identified by physicians as a determinant of antimicrobial treatment decisions.

One of the strengths of the TPB model is that a plurality of determinants could be summarized in a comprehensive model. It provides insight into the coherence of determinants and forms a base for further understanding of APB. This framework can be of benefit in the design and implementation of stewardship interventions, which serve the ultimate goal of improving antimicrobial prescription by influencing behavioural intent. Using this framework, relevant beliefs regarding a specific antimicrobial prescription issue or antimicrobial stewardship policy can be assessed up front. This allows for modification of stewardship interventions according to the identified determinants, which is likely to contribute to the successful implementation of those interventions.

This study provides 16 determinants that are all potential targets for which interventions can be developed. Examples of potential interventions targeting individual determinants are provided in Table 2. However, not all determinants may be influenced to the same extent. In other words, not all beliefs are equally accessible or pliable. Increasing awareness of AMR, for example, is a more realistic goal than influencing tolerance of uncertainty. To decide how to direct future stewardship interventions, it is essential to assess and consider the relative weight of the individual determinants.[25,26] For example, raising awareness of AMR has frequently been suggested by many contributors as a paramount intervention towards achieving responsible APB.[7,9] Yet the success of raising awareness vis-a-vis other interventional strategies is contingent upon several behavioural assumptions, especially upon the extent to which increased AMR awareness alters

a professional's behavioural intent. Hence, research that elucidates and subsequently validates which behavioural determinants have a substantial impact on APB contributes considerably to designing interventions that are effective, efficient and evidence-based. Empirical research, using a quantitative approach and multiple regression analysis, is mandatory to assess which of the three basic components - attitude, social norm, or perceived behavioural control - and which of the corresponding determinants have a strong influence on behaviour. Interventions could then be directed to target the most influential and thus promising component(s).

Our study has several limitations. In the included studies there were no references to TPB principles or to other established theories within the behavioural sciences. Second, it is possible that researchers' or physicians' unawareness of factors leading to (intended) behaviour may have led to underreporting or omission of relevant determinants. Hence, the content of the provided framework may not be exhaustive. Third, it should be noted that the study was aimed at affluent Western countries. The applicability of the framework to other settings (e.g. different cultural backgrounds, resources and standards with regard to medical practices) may be limited.

In conclusion, our review provides an overview of the cognitive determinants of APB. The theoretical framework of APB classifies the major determinants and provides insight into their interrelationship. This is an important step towards answering the ultimate question: what determinant(s) do we need to target to effectively impact prescription behaviour? To be able to provide answers, quantitative studies based on the TPB and focused on explicit clinical situations are warranted. In the battle against resistance, aimed at preserving adequate antibiotics for the next generation, medical expertise in conjunction with psychological insights may well be one of our most effective weapons.

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SUPPLEMENTARY DATA

Database search syntaxes

Database search was performed on 12 July 2017. In total, 778 references were screened (after duplicates were removed), in the following databases: PubMed (n=598), Medline (n=697), Embase (n=333), Web of Science (n=110), Cochrane Library (n=54), Central: (n=53).

- *Search syntax for PubMed:*

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- *Search syntax for MEDLINE:*

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OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018).yr

- *Search syntax for Embase:*

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- *Search syntax for Web of Science:*

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- *Search syntax for Cochrane Library:*

http://www.cochranelibrary.com/:

ti/ab/kw

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- ***Search syntax for CENTRAL:***

https://archie.cochrane.org/index.jsp?redirectTo=http://crso.cochrane.org/login.php&key=58c18a4283f80:

All fields

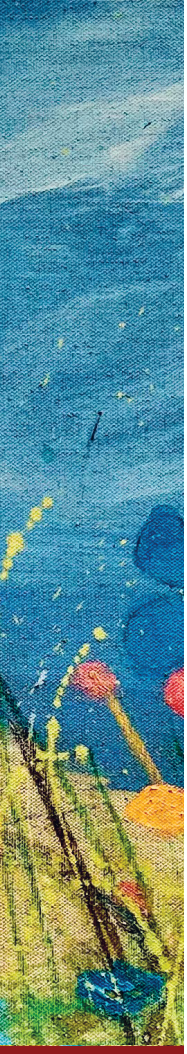
((“antimicrobial prescribing” OR “anti-microbial prescribing” OR “antimicrobials prescribing” OR “anti-microbials prescribing” OR “antibiotic prescribing” OR “anti-biotic prescribing” OR “antibiotics prescribing” OR “anti-biotics prescribing” OR “antibacterial prescribing” OR “anti-bacterial prescribing” OR “antibacterials prescribing” OR “anti-bacterials prescribing” OR ((“antibiotic use” OR “antibiotics use” OR “antibiotic usage” OR “antibiotics usage”) AND prescrib*)) AND (“determinant” OR “determinants” OR determinant* OR “factors influenc*” OR “influencing factor*” OR ((“factor” OR “factors”) AND (influenc* OR affect*mp)) OR “Culture” OR “Attitude of Health Personnel” OR “Physicians’ Practice Patterns” OR “Physicians Practice Patterns” OR “Physician Practice Patterns” OR “Physicians’ Practice Pattern” OR “Physicians Practice Pattern” OR “Physician Practice Pattern” OR “Professional Competence” OR “clinical competence” OR “Guideline Adherence”)) **AND py=(2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018)**

Quality assesment

Table S1. Quality assessment.

CASP questions	Clear statement of findings?	Qualitative methodology appropriate?	Research design appropriate?	Recruitment appropriate?	Data collection in a way that addressed the research issue?	Has the relationship between researcher and participants been adequately considered?	Have ethical issues been taken into consideration?	Data analysis sufficiently rigorous?	Clear statement of the aims of the research?
Broom A et al. 2014 [7]	+	+	+	?	+		+	+	+
Broom J et al. 2016 [20]	+	+	+	?	+	+	+	+	+
Charani et al. 2013 [19]	+	+	+	+	+	?	+	+	+
Curtoos et al. 2008 [15]	+	+	+	?	+	?	+	+	+
Livorsi et al. 2015 [8]	+	+	+	+	+	+	+	+	+
May et al. 2014 [18]	+	+	+	+	+	?	+	+	+
Parker et al. 2016 [9]	+	n.a.[1]	+	+	+	?	+	+	+
Schouten et al. 2007 [16]	+	+	+	+	+	+	+	+	+
Velasco et al. 2011 [17]	+	n.a.[1]	+	+	+	?	+	+	+

Legend. The Critical Appraisal Skills Programme (2017) scoring system for quality assessment of qualitative research was applied. 1 = This was a quantitative study, the question is not applicable. + = The study meets the requirements for this aspect of the quality assessment. - = The study does not meet the requirements for this aspect of the quality assessment. ? = Insufficient information is provided in the article to judge this criterion.



Cognitive biases in the decision-making process of antibiotic prescribing

Letter

In response to our study described in the first part of this chapter, a letter was published by Peiffer-Smadja *et al*. In their letter the authors address the importance of cognitive biases in antibiotic decision making. They argue that the theory of planned behaviour (TPB) may not be the most suitable framework to consider the common cognitive biases in antibiotic decision making. As a reply, this second part of Chapter 7 discusses how biased or inaccurate beliefs are still relevant determinants of prescription behaviour and how they fit into the TPB.

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We highly appreciate the response of Peiffer-Smadja and colleagues to our article, confirming the importance of using social sciences to understand antibiotic prescription behaviour (APB).[1,2] In their Letter, Peiffer-Smadja *et al*. advocate to supplement the proposed conceptual framework with insights from cognitive science, most notably on cognitive biases.[2]

We agree on the importance of addressing decision makers' cognitive limitations and biases, which already constitute an integral part of the theories and research in the social sciences. In our previous work we published on several of the listed cognitive limitations and biases, e.g. on the sunk cost effect, loss aversion, and omission/commission biases.[3-5]

It is important, however, to acknowledge our main study aim, to use the Theory of Planned Behaviour (TPB) as a conceptual framework to identify the beliefs and attitudes that drive APB. Notably, a biased or inaccurate belief, may still drive APB. Therefore, the biases listed by Peiffer-Smadja all fit with (and in) the framework of the TPB. The model makes no assumptions about rationality, but primarily focuses on internal consistency (e.g., does attitude follow from belief). Discussing the nature of TPB, Azjen stated: *"Whether true or false, biased or unbiased, beliefs represent the subjectively held information on which attitudes are based. Social psychology stipulated from the outset that people may hold beliefs about many objects and issues that are derived not from a logical process of reasoning but instead are biased*." [6]

Just as the authors of the TPB model embraced these insights, we underscore the importance of including and addressing people's cognitive limitations. Not as an element that should be seen as separate from the TPB framework; but as an element that may find its place in the framework. From an antibiotic stewardship perspective, all beliefs a doctor holds on antibiotics prescriptions are relevant, biased or not, as long as they influence the prescriptions they make. Again, we would like to quote Ajzen "*Although subjective and not necessarily accurate, these beliefs guide the decisions people make, and it is by examining the beliefs people hold that we can gain an understanding of decision-making in real-life situations* "[6]

Therefore, the first step is to identify the main determinants, e.g., by identifying what beliefs – valid or erroneous - doctors base their attitudes on, and by determining their relative importance. Eventually, this may provide the building blocks to subsequently base our stewardship interventions on. Nevertheless, we fully agree with Peiffer-Smadja *et al*. that in the future course of action, insights on decision heuristics and on cognitive or motivational biases are relevant and we concur with others on the call to study biases

in medical settings.[7] These insights from cognitive limitations and biases may have explanatory power as to the origin of people's beliefs and may therefore be relevant when designing specific interventions. For example, doctors may overestimate the medical risk of withholding antimicrobial therapy. In that case, correcting the misperceptions, and providing factual information may be a successful stewardship intervention.

Peiffer-Smadja *et al*. listed 17 cognitive limitations and biases; a list that we envisage could easily be enlarged to include other biases and effects as a well. Consider, for example, the disjunction effect illustrating that decision-makers often insufficiently engage in consequential reasoning when facing uncertainty.[8] Or the fact that people may display a self-serving bias in their attributions, denying responsibility for negative outcomes.[9]

However, generating a long(er) list of cognitive or motivational biases, may not be the most promising path towards a better understanding of APB. We run the risk of ending up with (again) a long list of effects and biases that lacks structure. But an organizing framework of relevant biases that provides structure might be helpful. It could be useful to distinguish between motivational and cognitive biases; or between biases affecting subjective probabilities and biases affecting the perceived severity of consequences; or between biases affecting social/normative factors and those impacting on one's perception of control over behaviour. Combined with the conceptual framework provided by the TPB this may enable us to further improve our understanding of APB and target antimicrobial stewardship interventions.

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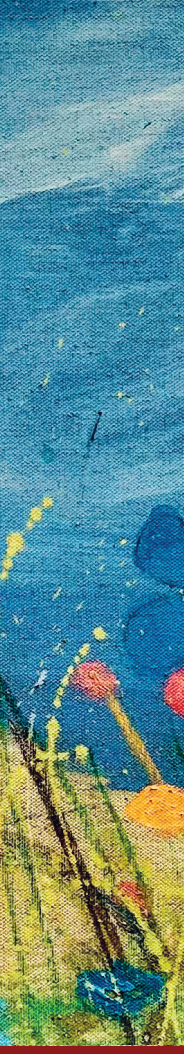

8

Antimicrobial guidelines in clinical practice: incorporating the ethical perspective

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ABSTRACT

Introduction: Guidelines on antimicrobial therapy are subject to periodic revision to anticipate on changes in the epidemiology of antimicrobial resistance and new scientific knowledge. Changing a policy to a broader spectrum has important consequences on both the individual patient level (e.g. efficacy, toxicity) and population level (e.g. emerging resistance, costs). By combining both clinical data evaluation and an ethical analysis, we aim to propose a comprehensive framework to guide antibiotic policy dilemmas.

Methods: A preliminary framework for decision making on antimicrobial policy was constructed based on existing literature and panel discussions. Antibiotic policy themes were translated into specific elements that were fitted into this framework. The adapted framework was evaluated in two moral deliberation groups. The moral deliberation sessions were analyzed using Atlas.ti statistical software, to categorize arguments and evaluate completeness of the final framework.

Results: The final framework outlines the process of data evaluation, ethical deliberation and decision making. The first phase is a factual data exploration. In the second phase, perspectives are weighed and the policy of moral preference is formulated. Judgments are made on three levels: the individual patient, the patient population and society. In the final phase, feasibility, implementation and re-evaluation are addressed.

Conclusions: The proposed framework facilitates decision making on antibiotic policy by structuring existing data, identifying knowledge gaps, explicating ethical considerations and balancing interests of the individual and current and future generations.

INTRODUCTION

Worldwide, antimicrobial therapy is the cornerstone in the management of patients with bacterial infections. Guidelines on empirical antibiotic therapy are subject to constant revision, for example in response to new scientific knowledge, advancing clinical understanding and changing epidemiology. Identifying the optimal empirical antimicrobial therapy has always been a challenge, but with the emergence of antimicrobial resistance (AMR) it is becoming an even more complex issue.

When antimicrobial resistance rates increase, the question arises whether the empirical therapy for a specific infectious disease should be adjusted to include a broader spectrum. Scientific and clinical as well as ethical arguments need to be taken into account and integrated in antimicrobial policymaking. Upscaling an antibiotic regimen may have important consequences for the individual patient in terms of effectiveness and toxicity, as well as for the population at large. Today's antimicrobial use impacts the health of both current and future societies, as antimicrobial consumption is the major driver of AMR. As a result, antibiotic effectiveness is decreasing and ultimately a post-antibiotic era with pan-resistant pathogens is lurking.[1,2] Nevertheless, there is no clearly defined antimicrobial resistance threshold, i.e. a percentage, above which a more broad spectrum treatment should be adopted in routine practice, potentially—and acceptably—at the expense of future generations.[3]

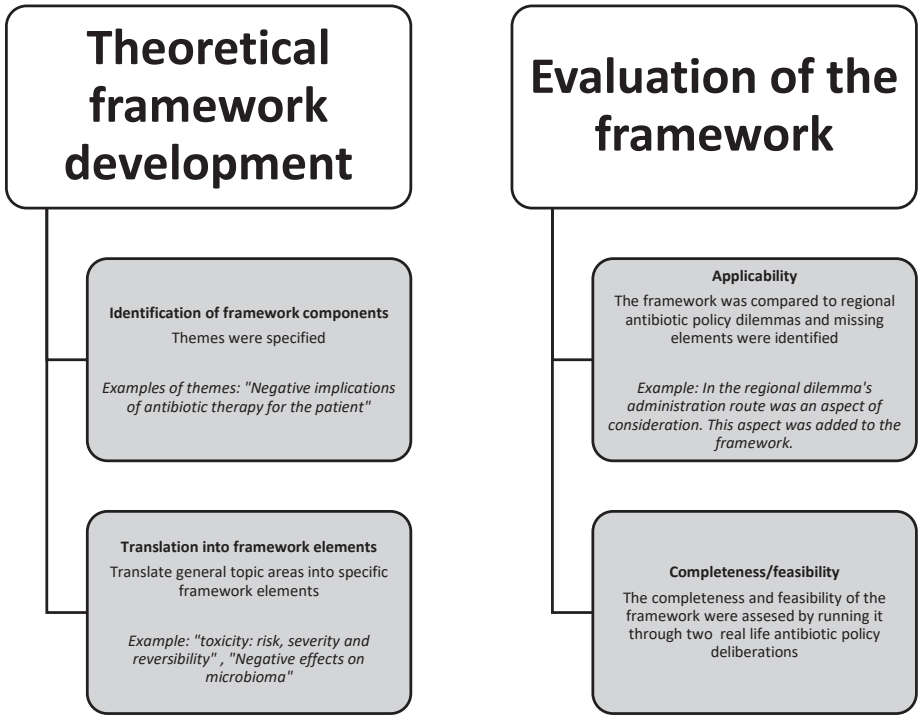
It is untenable to expect doctors to balance this trade-off during individual patient encounters, stressing the importance of guidelines for the treatment of infectious diseases. Remarkably, these guidelines rarely make explicit the ethical considerations that lie at the base of their recommendations.[4] This may be explained by the complexity and multitude of ethical issues concerned.[5] A framework to guide these complicated decisions, making the arguments explicit and facilitating ethical judgements, has not been available so far. In the literature, local microbiological resistance rates are the predominant argument for antibiotic policymaking, followed by disease severity and the attributable risk of developing future resistance.[6–10] Multiple publications on the ethical challenges related to empirical antibiotic therapy provide valuable insight into the relevant ethical principles.[11,12] However, these theoretical exercises have not yet been translated into a practical framework on how to balance benefits and harms of a proposed alteration in empirical treatment, incorporating both clinical and epidemiological data and the interests of current and future generations.

In this article we propose a method to support antibiotic policy and guideline committees when deciding on antibiotic therapy guidelines, incorporating both epidemiology and ethics.

METHODS

In this study a developmental approach was taken, with the primary aim to construct a conceptual framework that is complete and practical, whilst acknowledging different stakeholders and addressing the ethical issues related to antibiotic policy. The framework was developed and evaluated through an iterative process, outlined in Figure 1.

Figure 1. Construction of the framework.



Development of the preliminary framework

The developmental panel was formed by a pharmacist (B.H.), an internist/ infectious diseases physician (M.L.), a member of the national antibiotic policy organization (M.d.B.), a general practitioner (M.S.), a public health physician (M.P.) and two medical ethicists (B.R. and M.d.V.). General themes regarding antibiotic therapy, relevant

for any discussion over optimal empirical therapy for clinical management of patients with bacterial infections, were identified, based on available literature and experience of the panel members. Secondly, these themes were categorized and translated into specific framework elements. The importance of each element and the preferable order of elements were discussed in group discussions with the developmental panel. This resulted in a preliminary framework, consisting of three phases: data exploration, ethical deliberation and evaluation.

Evaluation and optimization of the framework

The applicability of the preliminary framework to real-life clinical practice was assessed by applying the framework to policy dilemmas in healthcare institutions. The dilemmas used for this evaluation were collected through an online survey among relevant regional stakeholders, including hospitals, primary care offices, long-term care facilities, pharmacies and municipal health services. The dilemmas were discussed in the panel group and the arguments were compared with elements of the preliminary framework. Newly identified elements were added to the framework, aiming for an optimal fit to the clinical need.

Subsequently, the completeness and feasibility of the framework was tested by applying it in two separate moral deliberation sessions: one prophylactic and one therapeutic dilemma (Box 1). To this end, a moral deliberation group was composed representing all relevant stakeholders in the context of developing antimicrobial treatment guidelines: patient, healthy individual, pharmacist, specialist medical microbiology, hospital physician, infectious disease consultant, nursing home medical specialist, general practitioner, public health specialist and hospital manager. Additional stakeholders were invited to the moral deliberation according to the type of dilemma and setting. For example, a surgeon was invited for a pre-operative prophylaxis dilemma. The moral deliberation sessions were moderated by a medical ethicist (B.R.).

The two sessions were recorded (transcript verbatim) with permission of the participants and analysed by two researchers (B.R./M.L.). The aim of the analysis was to assess the feasibility and completeness of the preliminary framework. Arguments were coded and categorized by the two researchers and inconsistencies were resolved through discussion. ATLAS.ti statistical software Version 8.4.18 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) was used to perform these analyses.[13] The conceptual framework was thereafter optimized to include all additionally identified arguments/aspects.

Box 1. Antibiotic policy cases

Therapeutic dilemma

In a local hospital the current guideline for treatment of sepsis is cefuroxime combined with gentamicin. However, a local analysis performed by the microbiology department shows that resistance to both antimicrobial agents is increasing in Gram-negative pathogens. The current resistance rate of Gram-negative pathogens in blood culture samples is 8.8%. Resistance to carbapenems is very rare. The question presented to the antibiotic policy committee was whether empiric treatment (awaiting cultures and susceptibility patterns) should be changed to a carbapenem.

Prophylactic dilemma

In a local hospital, the guideline for antibiotic prophylaxis for prosthetic joint implantation following low energetic fractures is cefazolin. Despite prophylaxis, 5-10% of patients develop a postoperative wound infection and/or prosthetic joint infection (PJI). Cultures often reveal pathogens that are not covered by the current prophylactic therapy, e.g. Gram negatives and anaerobic pathogens. The question presented to the antibiotic policy committee is whether the prophylactic therapy should be adjusted to a broader spectrum, more specifically a second generation cephalosporin combined with metronidazole, to prevent wound infection, but more importantly PJI.

RESULTS

The framework

Figure 2 (Supplementary data for the detailed version) presents the proposed framework for a deliberation on antibiotic policy. The framework outlines the process of data evaluation and decision-making in which subsequent phases can be recognized. The first phase is a factual data exploration (IA) and evaluation (IB). The second phase is an ethical deliberation in which data and perspectives are weighed and the policy of moral preference is formulated. In the final phase (III), feasibility, implementation and re-evaluation are addressed.

Preparation (not in the figure)

The deliberation session is preceded by a preparation phase, aiming to identify and involve stakeholders and retrieve the data needed for phase I of the deliberation session. Great care is taken to address the needs of those stakeholders without a medical background, notably representatives of the patient council or civilians. In anticipation of a knowledge gap that may hamper participation, all participants are provided with additional basic background information, to enable all stakeholders to actively participate in the discussion.

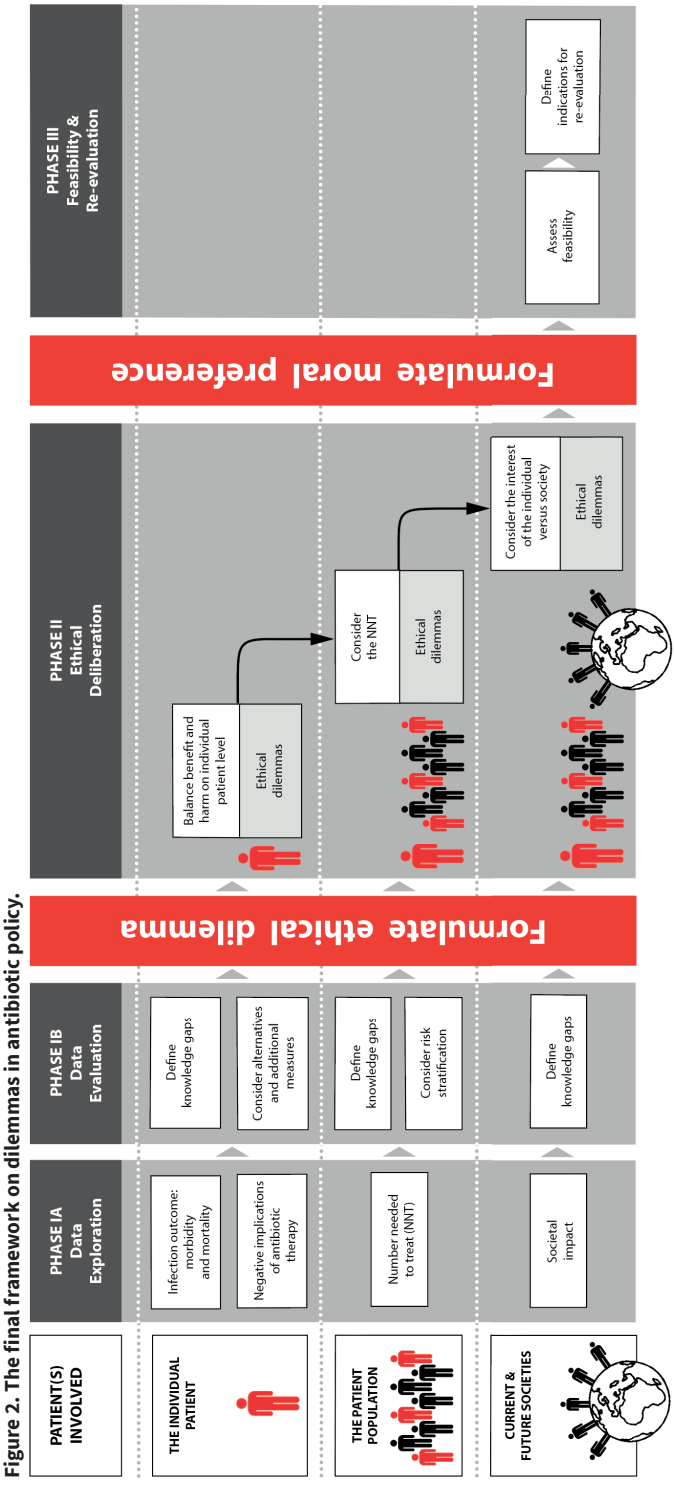


Figure 2. The final framework on dilemmas in antibiotic policy.

Phase I: data exploration (IA) and evaluation (IB)

During the first phase of the deliberation, the case is summarized and further explained. The available data from the preparation phase are reviewed and structured in four individual steps, which are described in Table 1. This includes factual information about patient population, setting and syndrome. The anticipated health gain of the proposed alternative and the number needed to treat (NNT) with antibiotics to prevent one adverse outcome are estimated. Furthermore, the harm of antibiotic policy on an individual and societal level are addressed. Finally, possibilities for mitigation are addressed: is there a less burdensome alternative, e.g. is there a possibility for risk stratification in order to minimize the negative effects on an individual and/or societal level? During this review of the available data uncertainties and knowledge gaps are identified.

After this phase, the definite moral dilemma is formulated.

Phase II: ethical deliberation

In the second phase, the data acquired in phase I are weighed on both the individual patient level and a societal level. The first question is whether the benefits of an antibiotic strategy outweigh the related risks on the individual patient level. Secondly, in case of empirical therapy, proportionality is discussed: is the NNT proportional to the anticipated benefits? Thirdly the societal burden is to be considered. The following questions need to be addressed; What are the additional costs of a specific antibiotic strategy and the associated antibiotic consumption for society? What are the additional burdens in terms of antimicrobial resistance and are these in proportion to the expected benefits for the individual patients? The ethical deliberation is finalized with a conclusion on the desirability of changing the antimicrobial policy to the proposed alternative and a proposition for a course of action.

Phase III: feasibility and future evaluation

In the last phase, the feasibility of the proposed strategy is considered and whether there are factors that may hamper implementation of the proposed course of action. Finally, the key arguments that drive the preference for one policy over another are summarized. If one of these arguments would significantly change in the future, this should prompt re-evaluation of the antimicrobial policy. For example, changing epidemiology of pathogens, or newly available therapeutic agents, may shift the balances in phase II and therefore warrant re-evaluation.

Table 1. Factual data exploration and evaluation

Factor	Description	Example*
Case summary	**Describe the patient population, the setting and the dilemma.** *Which patients will the guideline apply to. Can a subpopulation be identified?* *What is the setting?. E.g. general practice, hospital, long term care facility.*	In a local hospital the guideline for treatment of sepsis is cefuroxime combined with gentamicin. However, a local analysis of blood culture samples, shows that the resistance rates for this combination is rising in Gram-negative pathogens. The question presented is whether empiric treatment (awaiting cultures) should be changed to a carbapenem. Population: Adult patients that present at the first aid department of a Dutch hospital with suspected community acquired sepsis.
1. Infection outcome: morbidity and mortality	**Describe the most important outcome measures.** *What are the risk of the clinical syndrome in terms of morbidity and mortality. What are the non-medical detriments?*	The clinical syndrome of sepsis is diverse, with mortality ranging from 10 to 52 percent, depending on subpopulation and severity. There can be long term sequelae, including chronic kidney dysfunction and ICU acquired weakness with impact on quality of life.
2. Negative implications of antibiotic therapy	**What are the negative effects of the antibiotic treatment on the individual patient level? Consider probability and severity.** *Relevant detriments are: toxicity, allergic reactions, future infections with MDROs, impact on the microbioma. Practical disadvantages, such as dosing and route of administration and costs may also be relevant. *****	Gentamicin is oto- and nephrotoxic. It is only administered in the empiric time window, limiting toxicity. Toxicity in meropenem and cefuroxime is rare. Meropenem is more broad-spectrum, including anaerobes, and impacts the microbiome more than the cefuroxime/gentamicin combination. The risk of *Clostridium difficile* infections and candidemia is therefore higher. Antibiotic therapy selects drug-resistant pathogens/ resistance genes in the host and is accompanied by a risk of infections with multi-resistant micro-organisms in the future. The effect is greatest in the months following antibiotic therapy. All therapies are administered intravenously and are covered by health insurance.
3. Number needed to treat (NNT)	**How many patients will have to be treated with the proposed treatment to prevent the risks defined in step 2?** *To answer this question: What proportion of the patients that will receive the empirical treatment, truly has the infection? How effective is antibiotic treatment in averting morbidity and mortality in this patient population (See 1).*	Of all patients that present with sepsis, 6.7 % has positive blood cultures for a Gram-negative pathogen. Resistance to cefuroxime/gentamicin is 8.8%. 170 patients would have to be treated with carbapenem to treat one additional patient effectively. This does not account for (potentially severe) Gram-negative bacterial infections without bacteraemia, therefore, the actual NNT will be lower. Management of sepsis comprises more than antibiotic therapy only (fluid resuscitation, source control, etc). Evidence of the magnitude of the effect of adequate empiric antibiotic therapy on outcome is conflicting, but is presumed essential, especially is severe sepsis.

Table 1. Factual data exploration and evaluation (*continued*)

Factor	Description	Example*
4. Societal impact	**What are the effects of the proposed antibiotic policy for the common good?** *What is the incidence of the clinical syndrome, e.g. how many patients will be treated with the antibiotic treatment on a yearly basis. What is the associated antimicrobial consumption and what are the risks in terms of antimicrobial resistance. What are the other costs and benefits on a societal level.*	Empiric treatment is relatively short (24/48 hours). However, because of the frequency of sepsis, the associated antibiotic consumption is moderate to high. According to estimations, the incidence of sepsis is 13.000 patients/year in the Netherlands. Meropenem is a reserve antimicrobial agent, meaning it should be prescribed with caution, and reserved for strict indications. It is impossible to quantify the effect of routine administration of meropenem for sepsis on the emergence of resistance in the Netherlands. There will be an effect, and may lead to treatment difficulties for patients with Gram-negative infections in the (near) future. At the moment alternatives to meropenem are limited, but the future may bring new treatment strategies .
Alternatives and additional measures	***Are there interventions that could improve benefits or limit detriments for the individual patient and/or society?*** *For example therapeutic drug monitoring to limit toxicity and improve effectivity. Or could antibiotic policy be targeted in order to lower the NNT, both improving effectivity, but minimizing inappropriate use.*	According to local data, risk factors for a cefuroxime/gentamicin resistant pathogen are prior colonization with a multidrug resistant pathogen, and recent antibiotic therapy. Restricting carbapenem for patients with risk factors of cefuroxime/gentamicin resistance, would result in an estimated adequacy rate of 95 to 99%, depending on the strategy. Compared to treating all patients with a carbapenem empirically, the NNTC in the targeted approaches was a factor 2.3 to 4.6 lower.[30]

Legend: * To exemplify the steps, the following antibiotic policy case was used: . ** practical issues (route of administration and dosing frequency) costs for the individual patient (health insurance coverage) were added to the framework as a result of the evaluation phase. Abbreviations: NNT: number needed to treat.

Evaluation of the framework

Applicability to clinical practice

The online survey for representative ethical dilemmas resulted in a total of 24 dilemmas representing four healthcare settings (hospital *n*= 13, municipal health service *n* = 2, primary care *n*= *3*, long-term care facilities *n*= *6*). The 'cases' addressed mainly therapeutic dilemmas (18/24) and, to a lesser extent, prophylactic dilemmas (6/24). Two aspects of the dilemmas in the primary care setting were insufficiently addressed by the framework elements. The first considered practical issues (route of administration and dosing frequency). The second addressed financial costs for the individual patient (health insurance coverage). These shortcomings were resolved by adding two elements to the data exploration phase of the framework. No framework elements were removed in this phase.

Completeness and feasibility

Qualitative analyses of both moral deliberation sessions (Supplementary data, Table S1) showed that all framework elements were addressed in the deliberation sessions. No additional clinical or ethical elements were retrieved that were not yet captured in the preliminary framework.

During the data exploration phase, the limited availability of data—regarding effectiveness, detriments and future implications of a certain antibiotic treatment policy—provided a challenge in both deliberation meetings. However, an approximation of the NNT to prevent one adverse outcome, and the acknowledgement of the uncertainties that accompanied the estimations and assumptions, formed an appropriate foundation for further discussion of the dilemma in the ethical deliberation phase.

DISCUSSION

In this study, we developed a comprehensive framework for antimicrobial policymaking, that supported the integration of epidemiological data and ethical principles in antibiotic policymaking. Despite the fact that decisions on antimicrobial policy have to be taken repeatedly in various committees and healthcare institutions, little is known about the optimal approach. The fact that future generations are an important stakeholder in today's antimicrobial policy makes antibiotic guidelines unique compared with other healthcare guidelines. Remarkably, most antibiotic policy guidelines do not discuss the ethical aspects of their recommendations.[14] If these aspects are not explicitly addressed, they are unavoidably dealt with implicitly. The proposed framework aims to address the

ethical challenges explicitly and transparently. To the best of our knowledge, this is the first conceptual framework that aims to facilitate the incorporation of ethical issues in antibiotic policy decision-making.

The four principles of Beauchamp and Childress

The four principles described by Beauchamp and Childress—autonomy, beneficence, non-maleficence and justice—are generally considered as the standard structure to analyse ethical dilemmas in medicine.[15] (Supplementary data). They provide an excellent starting point for a wide spectrum of medical dilemmas, but there are limitations when it comes to the applicability to antibiotic policy. They are four individual principles that lack interconnectivity and do not provide hierarchy. A second point of criticism is that the principles are unable to cover the different levels at which judgements need to be made. This limits their application to antibiotic policy dilemmas, which are multilayered, encompassing not merely the individual patient but also groups of patients and current and future societies. The proposed framework breaks the ethical dilemma down to single layers and interconnects the ethical issues involved. The four principles of Beauchamp and Childress are still interwoven in the proposed framework, but with a different approach to the concept justice. Justice is the principle that emphasizes equality among individuals, considers whether like cases are treated similarly and is concerned with global inequalities. In antimicrobial policy specifically, the concept justice is not limited to inequalities between patients with a well-defined infectious syndrome. In the framework, the benefits and harms of antibiotic policy changes are therefore visualized for different stakeholders and in different timeframes (present and future) to provide insight in the multiple dimensions of justice.

Intergenerational justice

Antibiotic effectiveness can be considered a scarce public good that must be fairly distributed both within and across generations.[16] This raises the question whether and to what extent withholding antibiotics now—which may be beneficial—is justified in order to preserve future antibiotic effectiveness. Different theoretical frameworks have been used to address this issue.[14,17–19] According to utilitarianism, the goal should be to maximize total utility of antibiotics, regardless of place and time. Are the 'antibiotic rights' of the future unidentified patients equal to that of known patients requiring antibiotic therapy today? Uncertainty regarding the burden of AMR over time, and the development of new treatment modalities, complicates this dilemma.[20,21] Some have proposed a temporal discount rate, giving more weight to the present patient and taking into account the discovery of new therapies.[19] In both deliberation sessions, the threshold of acceptable risk of irreversible damage due to inadequate empirical coverage depended on the severity of the clinical syndrome and the estimated consequences of inadequate

therapy. Disease severity may justify broad-spectrum antimicrobial therapy in specific circumstances, regardless of the risk for future patients.[19,22]

In today's clinical practice, patients are generally not asked consent for being prescribed less than the maximum antibiotic therapy available.[19] Whether it is acceptable to curtail the autonomy of current patients in the interest of (future) societal health is a another dilemma in ethics. In both moral deliberation groups, all stakeholders, including patient and citizen representatives, agreed that autonomy of patients can—and should be—restricted when it comes to empirical antibiotic therapy, in order to prevent AMR-related harm to future patients. The fact that antibiotic effectiveness should be regarded a scarce good was the most important argument to support a suboptimal coverage and thus a risk of irreversible damage.

Applicability of the framework

The most widely adopted tool for guideline development is the GRADE methodology.[23] The strength of GRADE lies in a thorough analysis of the quality of available evidence and grading of the corresponding recommendations. However, there are specific aspects that are unique to antibiotic policymaking that are not optimally answered by GRADE, such as the variability of epidemiology of pathogens, the empirical nature of antimicrobial policymaking and the compelling interests of society.[24] Though the concept of equity has been added to the GRADE framework, this does not sufficiently cover the multi-layered dilemma of effects on patients, patient groups and current and future societies. The proposed framework is designed to match the specific aspects of antimicrobial policymaking and is therefore complementary to GRADE.

The framework may support antibiotic policymaking on a national level. In addition, it may be employed to guide translation of national guidelines to local policy. The latter aspect is important as there are significant local differences in antimicrobial resistance rates. A structured analysis enables efficient revision of the antimicrobial policy when epidemiology changes. Furthermore, it enables benchmarking of antimicrobial policy between different healthcare institutions, despite differences in local epidemiology of pathogens.

Worldwide, there are intercultural, judicial and societal factors that impact the weight attributed to different aspects in phase II. For example, the visibility of AMR, the priority directed to antibiotic stewardship, the appreciation of moral equality of current and future patients and the handling of uncertainty may all impact the outcome of a moral deliberation.[25,26] The proposed framework was not designed to result in uniform decision-making. However, its aim and strength are that it puts forward the ethical is-

sues interconnected with AMR, thereby advocating for these to be addressed instead of neglected or marginalized.

Strengths and weaknesses of the framework

An important strength of the proposed method is that all stakeholders are represented during the process. Patient participation is regarded one of the cornerstones of modern medicine. Involving patients and other individuals without medical training provides a relevant perspective.[27] This perspective goes unrevealed in the majority of antibiotic policy decisions that are being made today, even though it may be of additional importance because of the specific ethical aspects concerned.

The involvement of all stakeholders is time-consuming, which may hamper the feasibility of the proposed framework, especially for—often understaffed—local antibiotic committees. The proposed framework may be applied in a smaller committee. In that case, it should be acknowledged which perspectives were not represented.

A second challenge may be posed by incomplete data, making it impossible to calculate an accurate NNT, which is central in the proposed framework. When clinical data are lacking and future risks can only be estimated, it is difficult to make up the balance.[28] However, there is no realistic prospect of filling in all knowledge gaps in the near future and clinical dilemmas need to be dealt with now, in order to prevent escalation of the emergence and spread of antimicrobial drug resistance in the (very) near future. Even in the absence of this complete information, the systematic evaluation of the available data and being able to determine the uncertainties at hand contributes to the outcome of the process.

Conclusions

As antibiotic resistance has an impact that transcends individual patients and persists over time, dilemmas in antibiotic policy can't be solved by science alone.[29] Even the most accurate epidemiological data and trials need to be complemented with value-based judgements to solve real-life dilemmas in antibiotic policy. The proposed framework supports decision-making on antibiotic policy by concretizing the dilemma, structuring existing data, identifying relevant knowledge gaps and, importantly, integrating and explicating ethical issues in the deliberation. A structured ethical assessment, especially concerning therapeutic effectiveness for future generations, deserves a prominent place in the development of guidelines on antimicrobial therapy. Ultimately thresholds of acceptable risks need to be defined.

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SUPPLEMENTARY DATA

Qualitative analyses of moral deliberation sessions

The aim of the analysis was to assess the feasibility and completeness of the preliminary framework. Arguments were coded and categorized by the two researchers and inconsistencies were resolved through discussion. ATLAS.ti statistical software Version 8.4.18 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) was used to perform these analyses.[1]

The assessment of feasibility and completeness of the preliminary framework through identification of recurrent questions and statements in the two group discussions showed that all framework elements were addressed in the deliberation sessions. No additional clinical or ethical elements were retrieved that were not yet captured in the preliminary framework (Table S1).

On the individual patient level, the most frequently addressed framework elements regarded balancing the expected benefit and adverse effects of broader empirical treatment. Beneficence and non-maleficence were considered equally important ethical principles, as long as there is a proper balance between the (intended) benefit and the risks.[2,3] In severe sepsis, the benefit associated with appropriate treatment was considered so substantial, that toxicity may become a secondary consideration

On the population level, the NNT was a central theme in both sessions. Because of the empiric nature of the two dilemmas, a proportion of patients is exposed to an antibiotic therapy that is unnecessarily broad or from which they will not benefit at all, because their illness is not caused by a bacterial infection. At the same time, applying the standard empiric therapy, a proportion of patients is withheld potentially life-saving treatment. These aspects are reflected in the NNT, and dictated the discussion on the patient population level.

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Table S1. Summary of topics with quotes from the two moral deliberation sessions.

Phase in Framework	Topic	Quote
Patient(s) involved	The individual patient	"… What kind of patient should I think of, what kind of patient is it? If we are going to discuss this, this is important to me. Are this mainly 40 years old patients who are snatched away in in the mids of their life by the sepsis or … […]. Indeed what kind of patients, how ill are they upon admission and what are their other characteristics…?"
Phase IA	The individual patient: Infection outcome	"… In our hospital […] everyone actually just gets cefuroxime gentamicin because, even if they end up at the Intensive care unit, we are just doing fine with it…" "Based on the available microbiological data the proposed alternative treatment would target 75% of pathogens [that are not coverd by the current prophylactic therapy]"
	The individual patient: Negative implications of antibiotic therapy	"… Are there downsides on an individual level? Thus are there adverse consequences for the patient if you change the policy..?" " Well..if you have seen a few patients with refractory *Clostridium difficile* infections…"
	The patient population: Number needed to treat	"… Shouldn't we also summarize all assumptions in ms. X comment, that is with the new policy you treat 6-7 patients to prevent 1 infection…"
	Current and future societies	" There are also data that if you treat 1000 patients with a carbapenem, you could induce colonization with a resistant pathogen in 14 patients. Yes 14 out of 1000 " "Quality of care is less in patients that have to be isolated [because of colonization with a resistant pathogen]"
Phase IB	Defining knowledge gaps	"…But is all of this a problem? There is little data on that…" "..Propensity score studies have limitations ofcourse, we don't know exactly the increase in mortality as a consequence of inadequate empirc therapy."
	Consider risk stratification	"Our hospital data show that for a proportion of patients that is infected with a resistant pathogen this is predictable, risk factors being immunocompromised patients, prior hospitalization for example. You could potentially apply risk stratification…"

Table S1. Summary of topics with quotes from the two moral deliberation sessions .(*continued*)

Phase in Framework	Topic	Quote
Phase II	Balance benefit and harm on the individual patient level	" I am thinking, in many patients I know, when I do nothing, they will be fine tomorrow. In others, whatever I prescribe, he will not survive. In-between there is a large area where there is a certain benefit, we have to find the cut-off" "Not the most effective, but the best balance between advantages and disadvantages" "Based on these numbers, to treat 80 people adequately, you will induce resistance in 800 patients. […] To me that is unacceptable"
	Consider the NNT	"Patients on the ICU are given meropenem, they rarely have a resistant pathogen, but we have decided it, because we really do have our backs to the wall" "With the newly proposed prophylaxis you will have to treat 6-7 patients to prevent one post-operative infection"
	Consider the interest of the individual versus society	"… Okay, so we have patients, we have resources to help those patients. But if we take substance B the consequence might be situations such as in Tuscany or Spain […]. You also mentioned this earlieron, this aspect shouldn't we give this aspect more weight from a moral perspective than the costs or an elaboration on certain numbers..?" " Isn't it all about what risk of mortality do you want to accept in order to save the population..?" "What is the value of one life now, compared to an entire future population in which mortality will be high because of ordinary post-operative complications, that is hard to quantify"
Phase III	Assess feasibility	"… We indeed focus strongly on todays numbers and future numbers and so on, but I think that these indeed are important for feasibility and acceptance, because if you are the one who has to implement the policy, it helps enormously to know what the effect of your actions will be…"
	Define indications for re-evaluation	"We are focusing on the 8.8 % resistance rate….but in 10 years it will be 20% or 30%, it will increase with time , at a certain point, when will we have to reconsider?"

Legend: Two moral deliberation sessions were analyzed, one regarded empiric sepsis therapy, one regarded antibiotic prophylaxis for prosthetic joint implantation. Arguments were categorized using the framework elements. The questions and statements in the third columns "Quotes" are derived from these moral deliberation sessions.

The four principles of Beauchamp and Childress: ethical areas of conflict in the moral deliberation sessions

The four principles described by Beauchamp and Childress -beneficence, non-maleficence, justice and autonomy- are generally considered as the standard structure from which to analyse ethical dilemmas in medicine.[1] In this appendix we will describe these 4 individual principles, that have not been assigned an hierarchal order.

Beneficence and non-maleficence

Beneficence is the principle to act in the best interest of the patient, balancing the benefits of treatment against the risks. Non-maleficence is avoiding the causation of harm, for example toxicity. Non-maleficence is often attributed more weight, compared to beneficence; as is reflected in the Hippocratic oath: 'first do no harm'.[2] When in conflict, the risk of adverse effects of antibiotic therapy, such as toxicity and future drug resistant infections, could be regarded more important than the beneficence of adequate therapy.[3] In the moral deliberation sessions, beneficence and non-maleficence were considered equally important ethical principles, as long as there is a proper balance between the (intended) benefit and the risks. In severe clinical infectious syndromes, the benefit associated with appropriate treatment is so great, that toxicity may become a secondary consideration.[4,5] Because of the empiric nature of the dilemmas, a proportion of patients is exposed to an antibiotic therapy that is unnecessarily broad or they will not benefit from at all, because their illness is not caused by a bacterial infection. At the same time, applying the same standard empiric therapy, a proportion of patient is withheld potentially life-saving treatment. Hence, this aspect regarding the NNT and non-maleficence dictated the discussion on the individual patient level.

Justice

The concept of Justice concerns a fair distribution of health resources. Antibiotics, or more specifically antibiotic effectiveness, is a resource which can be depleted. According to 'justice' it should be fairly distributed between people. Uncertainty regarding the burden of AMR over time, and the development of new treatment modalities, complicates this dilemma.[6,7] The fact that antibiotic effectiveness should be regarded a scarce good and interests of society should also be observed, was the most important argument to support a sub-optimal coverage and thus a risk of irreversible damage for an individual patient.

Autonomy

Whether curtailing the autonomy of patients in the interest of (future) societal health is acceptable, is a recurrent dilemma in ethics. In utilitarianism, patient autonomy is neglected, as long as it does not interfere with over-all antibiotic effectiveness.[8,9] Auton-

omy is however an important aspect of principalism. In both moral deliberation groups, all stakeholders, including patients and healthy individuals, agreed that autonomy of patients can -and should be- restricted when it comes to empiric antibiotic therapy, in order to prevent AMR related harm in future patients.

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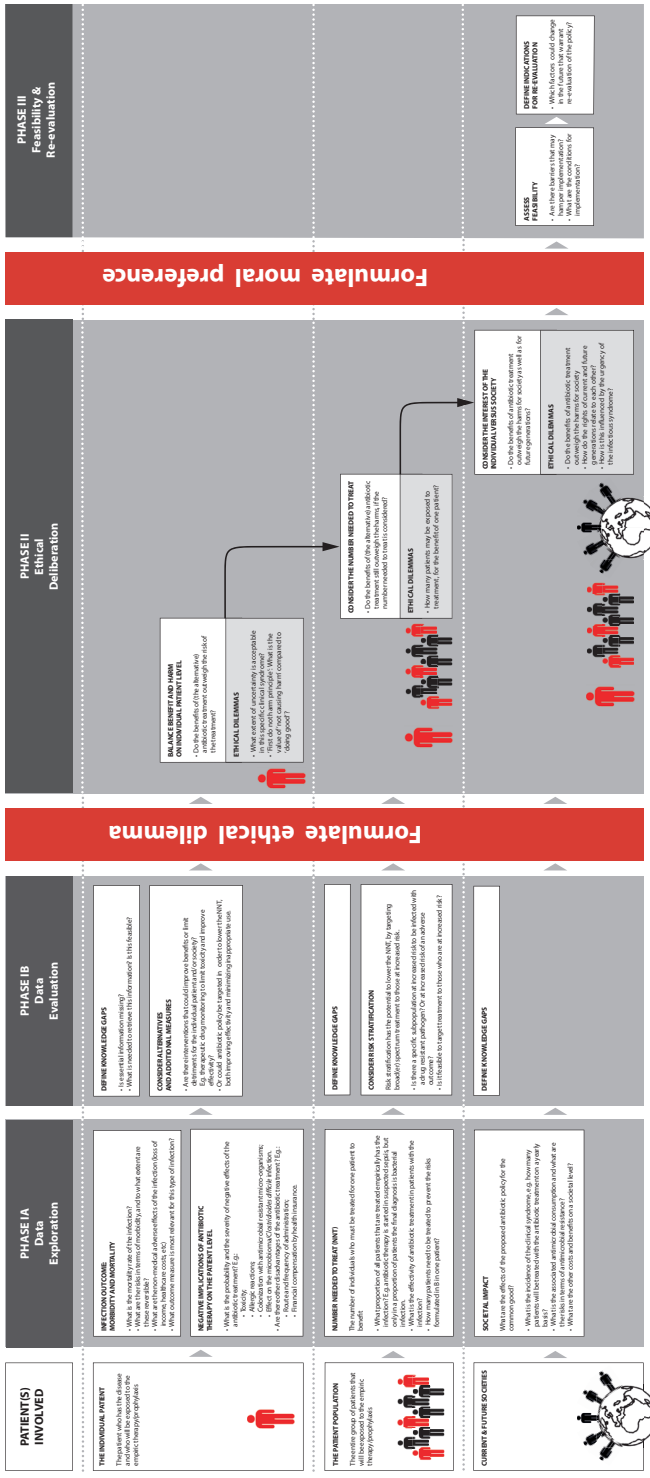
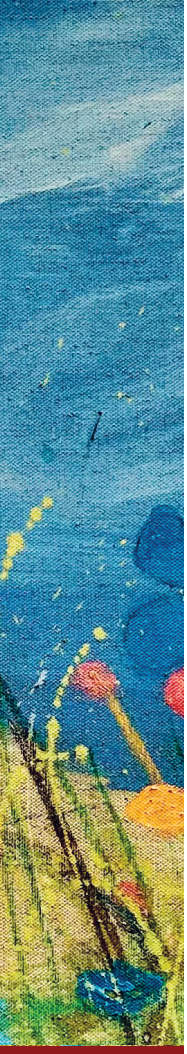
Figure S1: Detailed version of the framework on dilemmas in antibiotic policy.





Decision making in antibiotic prophylaxis: a bioethical approach

Letter

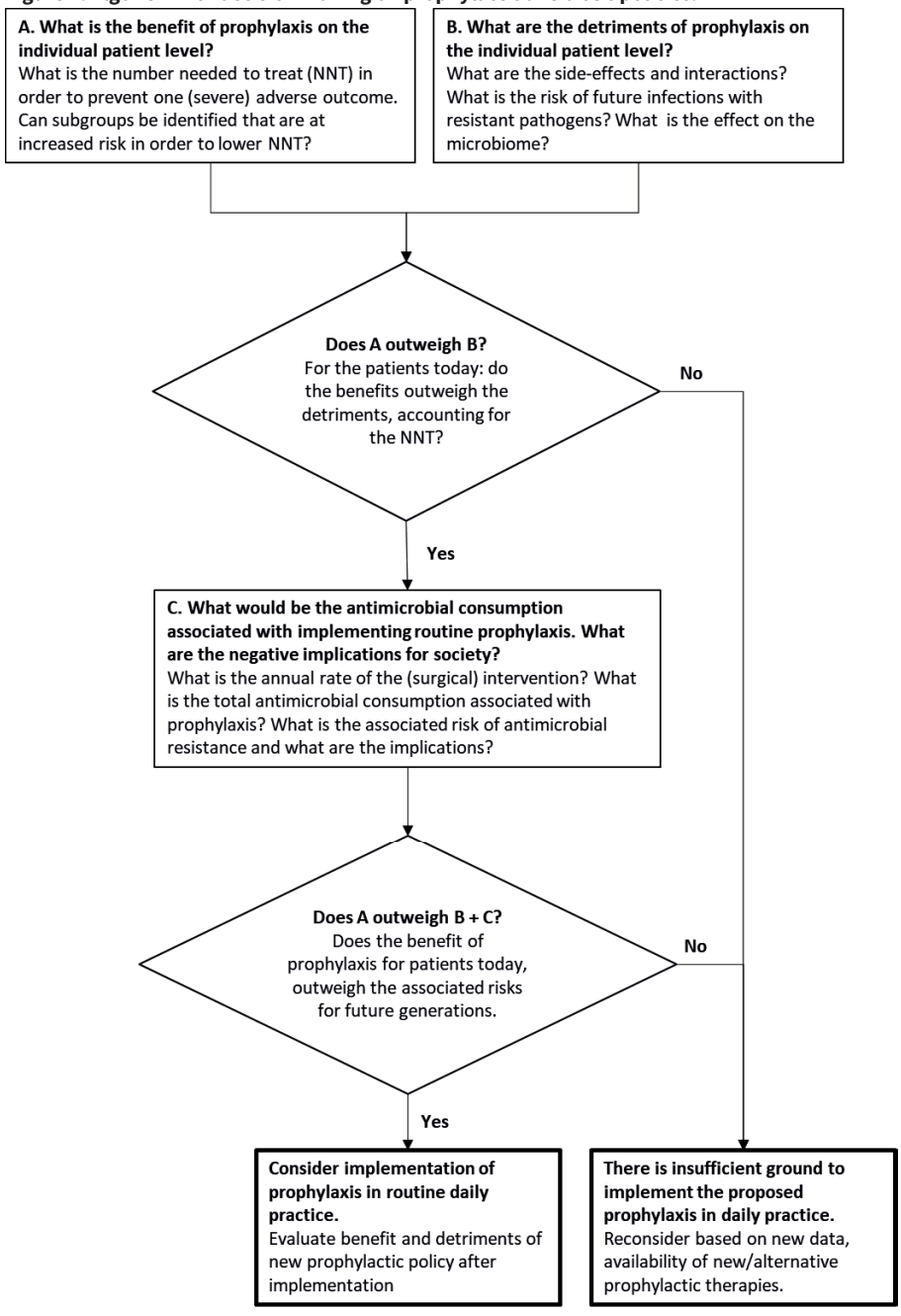
The following letter was written in response to a randomized controlled study that investigated the use of preoperative oral antibiotics in colon surgery, the ORALEV trial. In this study, patients were randomized to receive either oral prophylaxis with ciprofloxacin and metronidazole or placebo. As less surgical site infections occurred in the intervention group, the authors conclude that oral prophylaxis should be implemented in daily practice. In our letter we illustrate how using a systematic approach to decide on antibiotic therapy – as described in the first part of this Chapter- may result in a different conclusion.

Merel M.C. Lambregts, Mark G.J. de Boer

Lancet Gastroenterol Hepatol. 2020; 5(9):800-801.

We read with great interest the Article by Eloy Espin Basany and colleagues reporting the results of the ORALEV trial, which examined the use of preoperative oral antibiotics in colon surgery.[1] The authors concluded that oral prophylaxis with ciprofloxacin and metronidazole the day before colon surgery should be routinely adopted. However, a statistically significant effect on infectious complications might not be enough to support their conclusion. To come to a change in antibiotic policy, a systematic approach is warranted, that comprises more than the effect of prophylaxis on infectious complications alone (Figure). From the data presented by Espin Basany and colleagues,[1] we calculate that the number needed to treat (NNT) to prevent one surgical-site infection (primary endpoint) is approximately 16 (95% CI 9–58), which appears low. However, most of the infections were superficial. When focusing on more severe complications—eg, deeper infections and organ space infections—the difference is small (16 of 269 patients in the control group vs seven of 267 patients in the preoperative antibiotics group) and not statistically significant. Antibiotic prophylaxis did not have any effect on the need for an intervention (drainage or re-operation) or duration of hospital stay. Furthermore, microbiological data to support or oppose the findings were not provided. Hence, it remains unclear to what extent the proposed prophylaxis prevents (serious) infectious complications. The benefit of any preventative treatment must be weighed against the side-effects across the entire exposed population. Both antibiotics used in the ORALEV trial have side effects. The safety profile of quinolones has fallen into disrepute cause of the association with vascular complications. Although in the context of 1-day preoperative prophylaxis, the effect on the microbiome will be low compared to prolonged therapy, even a single dose has an impact.[2] Even if the benefits of preoperative antibiotics outweighed the risks at the individual patient level, there is a third aspect that should be given thought. Today's guidelines have responsibilities towards future generations as well, and should safeguard the long-term efficacy of antibiotics. Even though the prophylaxis proposed in the ORALEV study is given only for 24 h, the associated antimicrobial consumption is considerable, since colon surgery is a high frequency procedure worldwide.(3) Quinolones should be prescribed with caution because of concerns about development of antibiotic resistance. Decreased susceptibility to quinolones rises mainly by single-step mutations, as reflected by increasing resistance rates globally.[4] Balancing the interests of patients with the—often opposed— interest of (near) future generations, is a substantial bioethical dilemma, but should be considered part of our professional duty.[5] As such, we believe that Espin Basany and colleagues' statement that oral prophylaxis the day before colon surgery should be routine practice worldwide appears premature.

Figure 1. Algorithm for decision making on prophylactic antibiotic policies.



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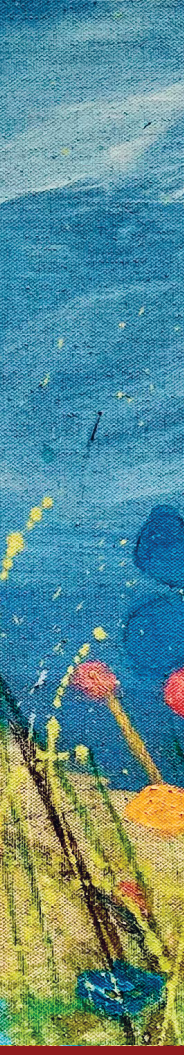


9

General discussion and summary

Antimicrobial resistance (AMR) represents a serious clinical and public health challenge. The emergence of drug resistant bacteria has been paralleled by a stagnation in the antibiotic development pipeline. Currently, the biggest threat is posed by the antimicrobial resistant ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter species) pathogens.[1] These pathogens are characterized by potent drug resistance mechanisms and are a leading cause of severe multidrug resistant infections, especially in the nosocomial setting. The acquisition of antimicrobial resistance genes by ESKAPE pathogens and other multidrug resistant organisms (MDRO) has reduced the treatment options for serious infections, and increased the death rates due to treatment failure worldwide.[2]

Infections with pathogens with reduced susceptibility to antibiotics are associated with higher mortality compared to infections with their more susceptible counterparts.[3] Data suggest that this disparity may -in part- be the result of a mismatch of empiric therapy.[3,4] Therefore, the changing epidemiology of AMR requires constant adaptation of antimicrobial policy guidelines. Increasing resistance in major human pathogens, demands further broadening of the empiric therapy with the aim to ensure adequate coverage. At the same time, this leads to more consumption of broad-spectrum antibiotics and contributes dramatically to the rising prevalence of resistance. Strategies to target the use of antibiotics in the empiric setting are needed to escape from this vicious cycle of increasing antimicrobial consumption and development of resistance in human pathogens.

No matter the strategy, empiric antibiotic therapy is inevitably accompanied by a certain degree of uncertainty, as is ubiquitous in medicine.[5] Uncertainty about the pathogen and the antimicrobial susceptibility pattern, are among the primary concerns. However, uncertainty is not limited to the microbiological aspect alone. This thesis addressed the uncertainties that are associated with empiric antibiotic therapy, how they affect daily decision making, and how they can be tackled in antibiotic policy making and antibiotic stewardship. In this chapter the results of these studies are summarized, and the potential implications are discussed.

FROM UNCERTAINTY TO PROBABILITY

Time to positivity as a tool in empiric antimicrobial treatment

At the time of the first assessment of the patient, the clinical diagnosis often remains uncertain. Blood cultures are essential in the diagnostic process, in particular when the source of the infection is not yet evident and the presence of bacterial infection is ques-

tionable.[6] Historically, diagnosing or excluding bloodstream infection is the weakest link in the diagnostic process, as bacterial growth of blood samples in culture media takes several days. Because of the modernisation of blood culture methods, and the development of continuous monitoring systems, the time to positivity (TTP) of blood cultures has been reduced substantially during the past decades. In **Chapter 2** we describe the potential of time to positivity (TTP) in the diagnostic approach of patients with suspected bacterial infections. The study shows that, in patients with bacteraemia, the majority of blood cultures reached positivity within 24 hours. The probability of blood culture positivity after 24 hours was 1.8% (95% CI 1.46-2.14%). The knowledge that the probability of bacteraemia is very low when blood cultures have remained negative for 24 hours is valuable for clinical decision making. In particular if further diagnostics aimed at identifying bacterial infection have not revealed an infectious source, the antibiotic therapy deserves to be re-assessed.

For the application of this probability to the bedside, the pre-test probability of bloodstream infection (BSI) in the individual patient should be considered. The pre-test probability is largely dependent on the clinical syndrome, for example septic versus non-septic patients, but may be difficult to estimate. Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. However, the majority of patients in whom blood cultures are obtained, does not fulfill the sepsis criteria and have a relatively lower pre-test probability of BSI. When the pre-test probability is high, for example in septic shock, the probability of bacteraemia at T=24 may rise accordingly. On the other hand, in patients with sepsis and septic shock, bacterial load is likely to be relatively high, and therefore TTP may actually be shorter.[7] So, when it comes to the probability of BSI at T=24 hrs., the shorter TTP may – at least to some extend- counteract the relatively high prevalence of BSI in septic patients.

A second factor to consider with regard to TTP, is the patient population. TTP may differ between patient populations with BSI, either because of patient characteristics or because of the specific distribution of pathogens.[8] Patients with neutropenia constitute a highly relevant subpopulation. During neutropenia, i.e an absolute neutrophil count below 0.5×10^9 cells/L, patients are more susceptible to bacterial bloodstream infections, which are associated with substantial morbidity and mortality.[9] However, it is notoriously difficult to distinguish bacterial infection from viral of fungal infection or non-infectious pathology in this patient population.[10] **Chapter 3** shows that the finding in the general population – that the probability of BSI is low after 24 hours – also applies to patients with neutropenia. For some of the major pathogens, such as *Staphylococcus aureus*, Enterobacterales and *Pseudomonas aeruginosa*, median TTP was low in patients with neutropenia as compared to the general patient population. This may be explained

by the fact that in the (near) absence of neutrophils, the bacterial load is higher, reflected in a low TTP. In patients with neutropenia, excluding bacteraemia at an early time point is at least as important as in the general population, as the differential diagnosis of febrile neutropenia is broad. A low probability of BSI at T=24 hrs. may warrant early diagnostics, i.e. additional imaging looking for insidious fungal infections.

Although guidelines advise extensively on the initial choice of empiric antibiotics in sepsis, there is limited research on the safety of de-escalation of antibiotic therapy, in immunocompetent nor immunocompromised patients. Currently, in immunocompetent adults, the consensus is to discontinue antibiotic therapy when blood cultures remain negative for 48 hours up to 96 hours and no primary site of infection has been identified. With the results from Chapter 2 and 3, the 48 hour timespan should be questioned. The current broad spectrum empirical treatment of 48 hours may thus be unnecessarily longer than the time that is needed to diagnose bacteraemia. In the meanwhile patients are exposed to potentially toxic therapy, antimicrobial resistance is enhanced and health care costs increased. Both in the general patient population and in patients with neutropenia, the potential gain is significant. The benefit of a TTP-guided de-escalation approach would not be limited to the individual patient. Considering the vast number of patients that present each day with suspected bacterial infections, it would impact overall antimicrobial consumption as well.

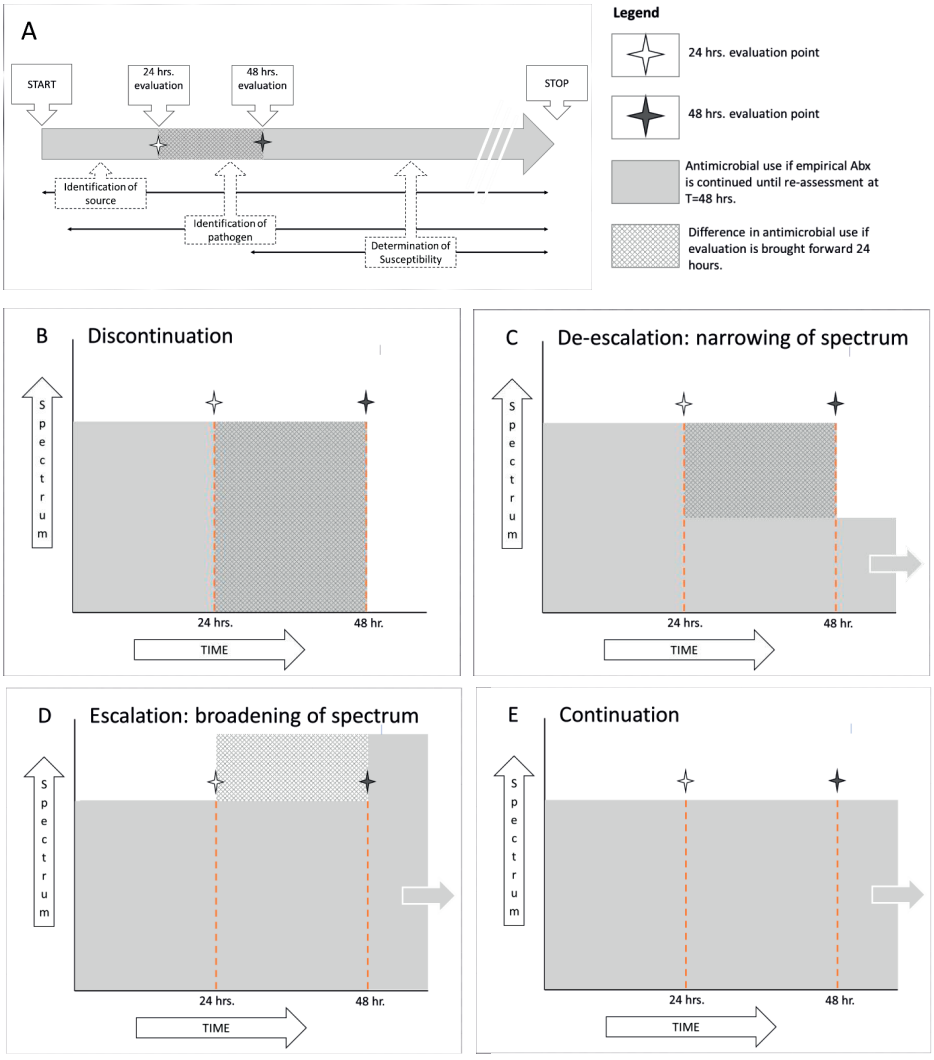
In addition to its value in the assessment of the probability of BSI, TTP may also be helpful in determining the probability of BSI with a specific class of pathogens. The distribution of pathogens is relevant, as this may guide early de-escalation strategies. For example, **Chapter 3** shows that in patients with febrile neutropenia, the probability of BSI with a Gram-negative aerobic pathogen is very unlikely when blood cultures have remained negative for 24 hours. These results were confirmed in a recent prospective study.[11] Guidelines for the treatment of febrile neutropenia recommend empirical treatment for a minimum of 48-96 hours. To address the relatively high prevalence of colonization with MDRO's in patients with onco-haematological disease, the recommended regimens are rather broad spectrum and include reserved antimicrobial agents. In the unlikely event of a BSI with a TTP of more than 24 hours, the pathogens are most often Gram-positive and/or anaerobic. Therefore, there is no rationale to delay the reassessment of the spectrum of Gram-negative antimicrobial treatment beyond 24 hours, because of pending blood culture results, as current international guidelines recommend to do.[12] So, in addition to the potential value for the duration of antimicrobial therapy in general, TTP may provide guidance with respect to the spectrum of empiric therapy, at different points in time.

Further research is needed to assess whether the duration of empirical antibiotic therapy and/or its spectrum can be safely reduced using TTP. Informing the physician about the remaining probability of blood culture positivity in his patient at T= 24 hours, could in itself be an intervention that affects diagnostic strategy and/or empirical therapy. Obviously, blood culture positivity is merely one of the factors that guide re-assessment of empirical therapy. Knowledge of a low probability cannot directly be translated to a potential for safe de-escalation. The clinical re-evaluation of the patient and the results obtained with other diagnostics, i.e. microbiological tests and imaging, are at least equally important. The outcome of re-assessment at 24 hours may therefore be continuation of antibiotic therapy or even escalation, despite the preliminary blood culture negativity. The different scenarios are depicted in figure 1. The real potential of TTP in decision making, is that it enables incorporating the factor time in the differential diagnosis of bloodstream infection. With TTP, antimicrobial therapy may be tailored to optimally fit the probability of BSI versus alternative (infectious or non-infectious) syndromes.

In **Chapter 4** TTP is used as part of a clinical rule in patients with *Staphylococcus aureus* bacteraemia (SAB). The purpose of this decision rule was not to diagnose BSI with *S. aureus*, but to differentiate between uncomplicated and complicated SAB. A risk score, composed of both clinical data and TTP was developed and validated externally. The risk score performed fairly well in predicting complicated SAB. The risk score is however insufficient to guide decision making 'standing on its own', but enables a more accurate assessment of the probability of complicated SAB. This chapter illustrates that TTP may not merely be used for the assessment of the probability of BSI over time, but also for risk assessment and prognosis in SAB specifically.

There are limitations to the use of TTP in clinical practice. TTP reflects the bacterial load in the blood and the microbial growth rate, but it is merely an indirect measure. As a result, the use of TTP in clinical practice is hampered by many confounding factors, most importantly variation in the volume of blood in the bottles and variation in transportation logistics. The time from collection of the blood culture sample to loading of the bottle differs between hospitals. This affects TTP, limiting the generalizability of the results, both in this thesis and in other publications. Future studies should be of a multicenter, prospective design and account for these aspects. It is nevertheless worth supporting further efforts to make use of the valuable information that TTP carries, that up till now remains hidden for clinicians.

Figure 1. Effect of early (24 hrs.) compared to late (48 hrs.) re-evaluation of empiric antimicrobial therapy on antimicrobial consumption in 4 different scenarios.



Legend *A) The timeline of antimicrobial therapy*, in a patient with suspected bacterial infection. The source of infection and/or the causative pathogen, cannot always be identified and the timing is variable. Re-evaluation of empirical antimicrobial therapy at 24 hours, compared to 48 hours, has a potential impact on antimicrobial consumption of 24 hours and is largely dependent of the findings at reassessment. In all exemplary scenario's (B to E) the patient presents with sepsis of unknown origin and empiric treatment with a third generation cephalosporin is started. *B) Therapy is discontinued*. Example: the patient is stable at re-assessment, blood cultures are negative and there are no signs of localized infection. *C) Therapy is de-escalated* to a narrower spectrum. Example: blood cultures have remained negative at T=24 hours, and re-assessment reveals pneumonia. Therapy is narrowed to penicillin *D) Therapy is escalated* to a broader spectrum. Example: at the 24 hour re-assessment, the patients is hemodynamically unstable and deteriorating, empiric therapy is broadened by adding an aminoglycoside. *E) Continuation*. Example: At T=24 the patient is clinically stable. Blood cultures have remained negative. The most probable source is a urinary tract infection. Therapy is continued awaiting urine cultures.

Increasing antimicrobial resistance and the empiric treatment of sepsis and bacteraemia

Previous chapters of this thesis provide insight in the probability of bloodstream infection at different points in time. The next question is whether the causative pathogen is susceptible to the institutional antibiotic sepsis therapy. Empiric antibiotic treatment needs to be tailored to the local setting, accounting for the local epidemiology of pathogens. Worldwide the prevalence of pathogens with resistance to empiric sepsis therapy is increasing. When to change standard sepsis therapy to a broader spectrum, is a recurrent dilemma. Using local clinical and microbiological data, **Chapter 5** provides insight in the probability of a mismatch of empiric therapy if different antibiotic strategies were to be applied. The study shows that treatment adequacy rate can be increased, without increasing inappropriate reserve antimicrobial consumption, by tailoring antimicrobial therapy based on the probability of infection with a MDRO. We proposed a method to calculate the probability of adequate empiric therapy in a predefined population and to calculate the associated antimicrobial consumption. The number needed to treat (NNT) provides insight into the number of patients that need to be treated with a reserve antimicrobial agent to prevent an antibiotic mismatch in one patient. With the proposed method, different antibiotic strategies can be compared.

To draw conclusions from the estimated NNT of different antibiotic strategies, it is essential to consider the consequences of a mismatch in BSI. Although antibiotic therapy may be the cornerstone in the treatment of bacterial infections, the magnitude of the effect of a mismatch on patient survival is still a matter of debate. To decide on antibiotic therapy, and which adequacy rate of empiric therapy is – or is not- to be accepted, knowledge on the effect of a mismatch in patient outcome is essential.

Chapter 6 shows that, in a cohort of patients with BSI, a mismatch of empiric therapy was not independently associated with 14 day mortality. Disease severity scores were relatively low in the patient cohort, and therefore the results are not applicable to patients with severe sepsis and septic shock.[13] In these patients there are theoretical grounds and previous studies indicating that delays in instituting adequate antimicrobial therapy are indeed causally linked to mortality. Nevertheless, the data described in Chapter 6 suggest that, overall, the magnitude of the effect of adequate empiric therapy in BSI may be overestimated in daily clinical practice. Mortality in BSI is multifactorial and empiric antibiotic therapy may merely be a piece of the bigger puzzle. A correct diagnosis, adequate fluid resuscitation, adjustment of antibiotics based on culture results, and source control, may be even more important determinants of patient survival. The fact that adequate empiric therapy may not be the 'holy grail', is relevant when

evaluating the NNT to prevent a mismatch of antibiotic therapy. Ultimately, we do not aim to treat the micro-organism, but the patient that has the infection.

FROM PROBABILITY TO DECISION MAKING

Decision making in clinical practice

As described in previous chapters, prescribing antimicrobial therapy -by its very nature- involves decision making under uncertainty.[14,15] Under such uncertainty, antimicrobial prescribing is not solely driven by an objective consideration of the available facts, as no human behaviour is. It is driven by attitudes and values, in response to intrinsic and extrinsic stimuli. For example social team dynamics and personal reputation, among others, may be prominent determinants of prescription behaviour. In **Chapter 7**, a theoretical framework was developed to describe the determinants of antibiotic prescription behaviour. Decision making under uncertainty is – and will always be- entangled with medical practice. Therefore medical students should be educated on the determinants of their own professional behaviour to raise awareness of the complexity of the decisional environment.[16] Education on the non-medical factors, such as social team dynamics, that may influence the decisions doctors make in daily practice, is underrepresented in medical curricula.[14]

Teaching the clinical examples of cognitive biases in decision making creates awareness and may increase the resistance of medical students to these effects. An illustration is the propensity to resolve uncertainty by action rather than inaction and how this is likely to result in overly broad antibiotic therapy. A successful balance of certainty and uncertainty can only be achieved if professionals are aware of just how complex the decisional environment is and what the pitfalls are.

Education on determinants of decision making in medicine should not stop with attaining the medical degree. Some of the strongest determinants of prescription behaviour, such as hierarchy and team dynamics, become even more apparent on the working floor. Discussions in peer group meetings may raise alertness to social aspects that influence medical decision making, and provide doctors with experience and tools to recognize and counteract potentially undesirable factors.

On a different level, knowledge of the determinants of antibiotic prescribing may be used for stewardship purposes.[17] For example, in order to efficiently improve adherence to antibiotic guidelines, it is essential to identify the determinants of non-compliance and target the improvement strategies accordingly. Further research should therefore

focus on quantifying the relative importance of individual determinants of antibiotic prescribing.[18]

Antibiotic policy making

The first part of this thesis addresses uncertainties associated with empiric therapy and provides a starting point to estimate the probability of BSI and antimicrobial resistance. It enables the adjustment of empiric antimicrobial therapy to the local pathogen prevalence and susceptibilities, as current guidelines on antibiotic stewardship stress to do.[19] However, even the most advanced calculations, will not solve the central question: when to escalate empiric therapy to a broader spectrum. Ultimately it needs to be decided which adequacy rate and which NNT are acceptable. This is a question that may only be answered when both clinical data, local epidemiology and ethics are combined in a balanced way. A method to determine the antimicrobial resistance threshold above which antibiotic therapy should be adjusted to a broader spectrum, has never been universally agreed upon.

In **Chapter 8** we have constructed a framework to combine clinical and epidemiological data with ethics, to address antibiotic policy dilemma's. The first part of the framework is aimed at retrieving the required clinical and epidemiological (local) data, identifying the uncertainties and estimating probabilities as discussed in the first part of this thesis. The second part builds on the available data, by putting them in an ethical perspective. In a moral deliberation session, involving all relevant stakeholders, the dilemma is evaluated. The framework does not aim to deliver 'the correct answer', but it structures the different aspects of antibiotic policy dilemmas in an era of antimicrobial resistance.

The ethical aspects involving antimicrobial therapy are complex, as the consequences of today's antibiotic policy transcend the individual patient, and even the current generation. It may be because of this complexity, that the ethical aspects often remain implicit in today's antibiotic guidelines on empiric therapy. Regardless of the method or framework that is used, guidelines should report thresholds, e.g. the resistance rate at which a change of antimicrobial class is recommended. More importantly, both the scientific and ethical considerations that lie at the base of the recommendations, should be made explicit. This transparency would enable local antibiotic policy makers, to translate international guidelines into local policy. Furthermore it may launch and support the debate on important questions, such as which degree of uncertainty is acceptable in empiric therapy, and how the interests of current and future generations relate to each other. As these questions are relevant for each dilemma on empiric antibiotic therapy, regardless of country and setting, more research should be directed on how to better integrate this ethical dilemma into antibiotic policy making.

CONCLUSIONS

In conclusion, it is essential that strategies are developed and implemented to optimize empiric therapy in those who need it, while minimizing exposure to broad-spectrum therapy in patients who will not benefit from it. Prediction tools to estimate the risk of BSI, antimicrobial resistance and/or complications, allow the targeting of antimicrobial regimens and support de-escalation strategies. These strategies should incorporate local epidemiology and the severity of the clinical syndrome, while balancing the importance of a match of empiric therapy against the pitfalls of overuse of broad-spectrum therapy. To design those strategies, thresholds should be determined on which uncertainties are -and are not- tolerable. To this aim ethics should be incorporated into antibiotic policy making explicitly.

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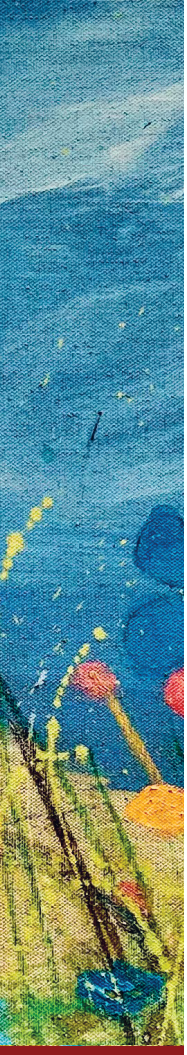
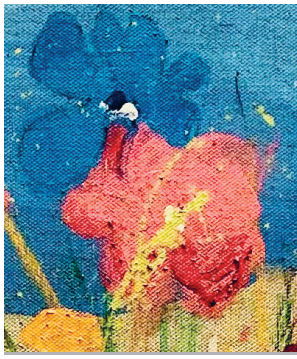




Nederlandse samenvatting

Antibiotica vormen de hoeksteen van de behandeling van bacteriële infecties. Het eerste antibioticum, penicilline, werd ontdekt in 1928. Penicilline is een antibacteriële stof die ingrijpt op de synthese van de bacteriële celwand, waardoor de bacterie ten gronde gaat. De ontdekking had een groot effect op de overleving van patiënten met infecties. Sinds de ontdekking van penicilline zijn er ook antibiotica ontwikkeld die ingrijpen in andere essentiële processen in de bacterie, zoals de aanmaak van bacteriële eiwitten. Onder blootstelling aan antibiotica kunnen bacteriën echter eigenschappen ontwikkelen die het werkingsmechanisme van een specifiek antibioticum, of een groep antibiotica, teniet doen. Hierdoor ontstaat er antibioticaresistentie. Bacteriën die resistent zijn tegen één of meerdere groepen antibiotica noemen we bijzonder resistente micro-organismen (BRMO).

De belangrijkste factor in het ontstaan van antibioticaresistentie is de selectiedruk door gebruik van antibiotica, waarbij resistente bacteriën worden uitgeselecteerd. Binnen enkele jaren na introductie van een nieuw antibioticum in de kliniek wordt, zonder uitzondering, het eerste resistentiemechanisme aangetoond. Hoe groter de druk van antibiotica in de omgeving, hoe groter het overlevingsvoordeel van de bacteriën met resistentie-eigenschappen, en derhalve hoe sterker de uitselectie van resistente bacteriën. De afgelopen decennia nam het gebruik van antibiotica wereldwijd fors toe, zowel in de zorg als in de veehouderij. Zo wordt antibioticaresistentie een steeds groter probleem.

Antibioticaresistentie is daarmee één van de grootste bedreigingen voor de volksgezondheid geworden. De ontwikkeling van nieuwe antibiotica is al geruime tijd gestagneerd, terwijl resistentie voor de bestaande middelen verder toeneemt. Een post-antibiotisch tijdperk, waarbij simpele bacteriële infecties niet meer behandeld kunnen worden is een reëel vooruitzicht.

Empirische behandeling van infectie

Een groot deel van het antibiotica verbruik vindt plaats in de empirische setting. Empirische antibiotica therapie is de behandeling met antibiotica die wordt gegeven zolang de verwekker en de gevoeligheid nog onbekend zijn. Door de toenemende prevalentie van resistentie is de voorafkans op een BRMO als oorzakelijk pathogeen toegenomen. De toenemende prevalentie van BRMO's vraagt om het verbreden van de empirische antibiotische therapie. Echter, diezelfde verbreding gaat weer gepaard met een hogere antibiotische druk en dus meer resistentieontwikkeling.

Dit proefschrift is gericht op potentiele aangrijpingspunten die deze vicieuze cirkel kunnen doorbreken. In het eerste gedeelte van dit proefschrift worden tools onderzocht

om de diagnostische onzekerheid in de empirische fase te verminderen. Het tweede gedeelte is gericht op de incorporatie van onzekerheid in de besluitvorming en de ontwikkeling van richtlijnen.

(On)zekerheid

Onzekerheid is onlosmakelijk verbonden met empirie. Bij de eerste presentatie is vaak nog onzeker of er sprake is van een bacteriële infectie, met name als het focus van de infectie niet duidelijk is. Het uitsluiten van een bloedbaaninfectie – bacteriemie- is dan een belangrijke stap in het diagnostische proces. Voor het diagnosticeren van bacteriemie zijn we afhankelijk van bloedkweken en daarmee van de (snelheid van) bacteriële groei. Van oudsher wordt gewacht tot de bloedkweken 48 tot 72 uur negatief zijn gebleven voordat bacteriemie onwaarschijnlijk wordt geacht.

In **hoofdstuk 2** is de tijd tot positief worden van de bloedkweek (time to positivity, TTP) onderzocht bij patiënten met bacteriemie. De TTP is gedefinieerd als de tijd tussen afname van de bloedkweek en het positieve signaal in de incubator. De studie toont aan dat de TTP met hedendaagse technieken zodanig is verbeterd dat de kans op bacteriemie zeer klein is als bloedkweken 24 uur negatief zijn gebleven. In de onderzochte patiëntenpopulatie is de kans dat een bloedkweek nog positief wordt na T=24 uur slechts 1.8%. Deze kennis is van waarde bij de herbeoordeling van de patiënt op T=24 uur en heeft potentieel gevolgen voor de differentiaaldiagnose, diagnostische vervolgstappen en empirische behandeling.

Om deze bevindingen toe te passen in de dagelijkse praktijk zijn een aantal zaken van belang. Ten eerste is de TTP afhankelijk van de logistiek in het ziekenhuis, zoals transporttijden van de bloedkweken naar het laboratorium. Vertraging hierin beïnvloedt de TTP. Ten tweede is het van belang om de individuele patiënt voor ogen te houden. De kans op bacteriemie op T=24 bij een bepaalde patiënt is afhankelijk van een aantal factoren. De belangrijkste factor is de voorafkans dat er sprake is van bacteriemie. Deze kans is bijvoorbeeld hoger bij ernstig zieke patiënten, zoals de patiënt in septische shock. Daarnaast zijn er patiëntengroepen waarbij op theoretische gronden de TTP anders zou kunnen zijn, bijvoorbeeld bij patiënten met een afweerstoornis.

Een specifieke patiëntengroep betreft de patiënten met neutropenie. Bij neutropenie is het aantal neutrofielen verminderd. Neutrofielen zijn witte bloedcellen die een belangrijke rol spelen bij het verwijderen van micro-organismen uit de bloedbaan. Neutropenie treedt frequent op als bijwerking van chemotherapie voor bijvoorbeeld kanker. Bij deze patiënten zijn de bron van de infectie, het type pathogeen en de afweer substantieel anders vergeleken met de algemene patiëntenpopulatie. Al deze

aspecten kunnen de TTP beïnvloeden en daarmee de kans op bacteriemie op T=24 uur. **Hoofdstuk 3** toont aan dat, ondanks deze verschillen, de bevindingen uit hoofdstuk 2 ook gelden voor hemato-oncologische patiënten met neutropenie. Bij patiënten met neutropenie is het onderscheid tussen bacteriële infecties en andere oorzaken van koorts, zoals schimmelinfecties of geneesmiddelenreacties moeilijk vast te stellen en is de mortaliteit van bacteriële infecties hoog. Daarom is het feit dat bacteriemie al op T=24 uur onwaarschijnlijk gemaakt kan worden van belang voor de vervolgstappen op diagnostisch en therapeutisch vlak.

Prospectief onderzoek is nodig om te bepalen of TTP veilig gebruikt kan worden om empirische behandeling met antibiotica te versmallen of zelfs te verkorten. Hierbij moet rekening gehouden worden met specifieke patiënt categorieën en moet er onderscheid gemaakt worden tussen verschillende klinische syndromen.

Dat TTP ook voor andere klinische vraagstukken relevant kan zijn wordt duidelijk in **hoofdstuk 4.** TTP is een indirecte maat voor de hoeveelheid bacteriën (bacteriële load) in het bloed. Hoe meer bacteriën, hoe korter de TTP. In deze studie is de waarde van TTP onderzocht bij patiënten met *Staphylococcus aureus* bacteriemie (SAB). Bij dit ziektebeeld is het onderscheid tussen gecompliceerde en ongecompliceerde bacteriemie van belang. Gecompliceerde bacteriemie gaat vaker gepaard met endocarditis en metastatische infectie. Het onderscheid tussen gecompliceerde en ongecompliceerde SAB is van belang voor de dosering van antibiotica en de behandelduur. Echter, in de klinische praktijk is de differentiatie tussen gecompliceerde en ongecompliceerde bacteriemie aanvankelijk lastig te maken. Omdat bij gecompliceerde bacteriemie de bacteriële load op theoretische gronden hoger is, is in deze studie gekeken naar de diagnostische waarde van TTP bij patiënten met SAB. Er is een score ontwikkeld bestaande uit klinische factoren, routine laboratorium bepalingen en TTP, met als doel het onderscheid te kunnen maken tussen gecompliceerde en ongecompliceerde bacteriemie. De negatief voorspellende waarde van de SAB-risicoscore in het validatiecohort was 0.83 (95%CI 0.68-0.92). Daarmee presteert de score beter dan bestaande scores. De SAB-risicoscore kan de klinische praktijk ondersteunen in het differentiëren tussen ongecompliceerde en gecompliceerde bacteriemie.

Antimicrobiële resistentie en de empirische behandeling

Er zijn grote geografische verschillen in de prevalentie van resistentie. Wereldwijd wordt daarom aanbevolen om de empirische behandeling te baseren op de lokale resistentiecijfers en aan te passen op geleide van veranderingen in de epidemiologie. Een uniforme methode om lokale resistentiecijfers te vertalen naar antibiotisch beleid is echter nog niet beschikbaar.

In **hoofdstuk 5** wordt een stappenplan beschreven waarmee verschillende empirische antibioticaregimes met elkaar vergeleken kunnen worden. Op basis van lokale klinische en epidemiologische gegevens kan op die manier inzicht worden verkregen in het aantal patiënten dat adequaat behandeld zou worden en de totale antimicrobiële consumptie die ermee gepaard gaat. De number needed to treat (NNT) dat hiermee verkregen wordt, reflecteert het aantal patiënten dat met een breed spectrum middel behandeld moet worden om 1 patiënt adequaat te behandelen. De studie toont aan dat de NNT fors omlaag gebracht kan worden door risicostratificatie toe te passen. Bij risicostratificatie wordt in de keuze van de empirische therapie rekening gehouden met de voorafkans op infectie met een resistent pathogeen. Voorbeelden van patiënten met een hogere kans op infectie met een BRMO zijn onder andere patiënten die voorbehandeld zijn met antibiotica en patiënten die drager zijn van een BRMO. Door reserve antimicrobiële middelen in te zetten bij deze patiënten met een hoger risico op infectie met een BRMO, kon de NNT in deze studie met 83% worden verlaagd.

Of een bepaalde NNT wel of niet acceptabel is, is mede afhankelijk van de gevolgen die te verwachten zijn van inadequate empirische therapie voor de individuele patiënt. Antibiotica vormen de hoeksteen van de behandeling van infecties, maar in welke mate inadequate therapie in de empirische fase de klinische uitkomst bepaalt, is een onderwerp van discussie. In het onderzoek beschreven in **hoofdstuk 6** is het effect van een mismatch van de eerste antibiotische gift op de 14-dagen mortaliteit bij patiënten met bacteriemie onderzocht. In dit retrospectieve onderzoek is gebruikt gemaakt van propensity score methoden, om het risico op vertekening (confounding) te beperken. In de studiepopulatie was een inadequate empirische behandeling niet geassocieerd met 14-dagen mortaliteit. Ook was er geen effect op 30-dagen mortaliteit of opnameduur. De resultaten zijn niet van toepassing op patiënten met (ernstige) sepsis, aangezien deze populatie te weinig vertegenwoordigd was in het studiecohort. De studie toont echter dat in patiënten die klinisch stabiel zijn, het effect van adequate empirische therapie mogelijk beperkt is. Dat is van belang omdat de negatieve effecten van breedspectrum therapie zoals toxiciteit, resistentieontwikkeling en *Clostridioides difficile* infecties, relatief zwaarder gaan wegen als de positieve effecten van antibiotica beperkt zijn.

Omgaan met onzekerheid

Onzekerheid in de klinische praktijk en voorschrijfgedrag

In de eerste zes hoofdstukken van dit proefschrift worden klinische en microbiologische data gebruikt om onzekerheden omtrent diagnose en prognose te beperken, ter ondersteuning van de besluitvorming. Eliminatie van alle onzekere factoren is echter niet mogelijk. Patiëntenzorg en onzekerheid zijn onlosmakelijk met elkaar verbonden.

Het feit dat beslissingen moeten worden gemaakt in onzekerheid, heeft invloed op het voorschrijfgedrag van artsen. In **hoofdstuk 7** zijn de diverse determinanten van voorschrijfgedrag beschreven en geplaatst in een theoretisch kader. Het theoretisch kader is gebaseerd op de *Theory of Planned Behaviour*. Deze theorie gaat er vanuit dat gedrag bepaald wordt door de specifieke cognities die mensen hebben bij een bepaald (doel)gedrag. Door middel van een systematische review zijn de determinanten van antibiotica voorschrijfgedrag geïdentificeerd. Uit de analyse blijkt dat naast de medisch inhoudelijke aspecten ook sociale en logistieke factoren het voorschrijfgedrag van artsen beïnvloeden. Belangrijke determinanten blijken hiërarchie, sociale teamdynamiek, tijdsdruk en risicovermijding te zijn. Om voorschrijfgedrag te kunnen verbeteren, is het essentieel om deze factoren te (er)kennen en mee te nemen in de ontwikkeling van antibiotic stewardship interventies.

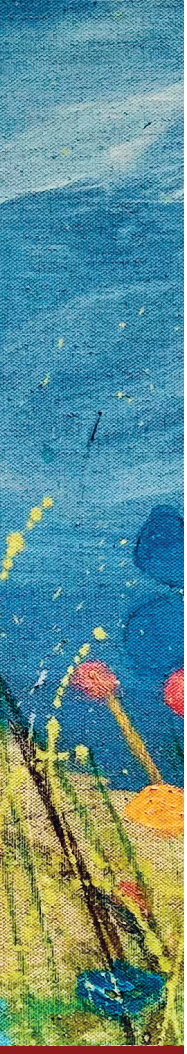
Onzekerheid en het opstellen van richtlijnen

Richtlijnen zijn essentieel ter ondersteuning van het voorschrijfgedrag van artsen. In **hoofdstuk 5** is een stappenplan voorgesteld om verschillende empirische antibiotica regimes tegen elkaar af te zetten door berekening van de NNT. Echter, zelfs de meest geavanceerde berekeningen kunnen de centrale vraag niet beantwoorden: wanneer is een breder antibiotisch regime geïndiceerd? Dit is in essentie een ethische afweging.

Hoofdstuk 8 beschrijft een methode om antibioticabeleid dilemma's te behandelen, waarbij klinische data, lokale epidemiologie en ethische afwegingen worden geïntegreerd. Op basis van bestaande dilemma's is een stappenplan ontwikkeld bestaande uit drie fases: data exploratie & data evaluatie (fase 1), ethische evaluatie (fase 2) en haalbaarheid & evaluatie (fase 3). In de eerste fase worden de beschikbare data op een structurele wijze beschreven en geëvalueerd. Hierbij is de NNT, zoals beschreven in hoofdstuk 5 een belangrijke component. In de tweede fase worden de ethische afwegingen geëxpliciteerd. Ethische afwegingen zoals *goed-doen versus niet schaden* spelen een rol bij de totstandkoming van elke medische richtlijn. Echter, specifiek bij richtlijnen over antibioticabeleid zijn de ethische afwegingen multidimensionaal. Antibiotica moeten immers beschouwd worden als een schaars goed. Ons voorschrijfgedrag van vandaag heeft niet alleen invloed op de betreffende patiënt, maar ook op de maatschappij en op toekomstige generaties. In fase 2 worden deze verschillende ethische aspecten op structurele wijze besproken. Na fase 2 wordt het beleid van voorkeur geformuleerd. Fase 3 is vervolgens gericht op de haalbaarheid en re-evaluatie. De ontwikkelde methode heeft als belangrijkste doel het structureren en expliciteren van de complexe ethische afwegingen bij het opstellen van antibioticabeleid.

Conclusie

Het is essentieel dat strategieën worden ontwikkeld om empirische therapie te verbreden voor degenen die het nodig hebben, terwijl de blootstelling aan breedspectrumtherapie bij patiënten die er geen baat bij hebben tot een minimum wordt beperkt. Dit proefschrift biedt handvaten om lokale epidemiologie en risicopredictie te vertalen naar empirisch antibioticabeleid. Uiteindelijk moet het belang van adequate empirische therapie worden afgewogen tegen de nadelen van overmatig gebruik van breedspectrumtherapie, zowel op individueel patiëntniveau als op populatieniveau. De dynamische epidemiologie van antibioticaresistentie en de complexe ethische aspecten vormen hierbij een uitdaging. Het structureren en verhelderen van de afwegingen die worden gemaakt is essentieel om de volgende stappen hierin te kunnen maken.



Nawoord

Er hebben heel veel mensen bijgedragen aan dit proefschrift, op heel veel verschillende manieren en ik ben iedereen heel dankbaar. Ik kan hier dus nooit volledig zijn. Maar, het niet benoemen van de mensen die écht onmisbaar waren, is in mijn ogen wetenschappelijk onjuist.

Allereerst, Leo en Mark, heel veel dank voor de kansen die jullie mij geboden hebben en alle steun en begeleiding gedurende het hele proces. En voor jullie vertrouwen. Jullie ideeën en adviezen worden ontzettend gewaardeerd. Het is fijn om te weten dat ik zowel "op links" als "op rechts" altijd kan aankloppen voor wijze raad.

Voor alle projecten was microbiologische expertise essentieel. Veel dank aan de afdeling microbiologie, en in het bijzonder aan Martha en Sandra, voor de prettige samenwerking. Jullie ideeën en kritische blik zijn van grote waarde geweest.

Naast de raakvlakken met de microbiologie, waren er ook projecten met een ethisch en/of gedragswetenschappelijk aspect. Beiden onderwerpen lagen behoorlijk ver buiten mijn comfortzone, wat wel geïllustreerd wordt door het aantal word-files in de betreffende mapjes (419, and counting). Martine, Babette, Henk en Eric, dank voor jullie uitleg en oneindige geduld. Ik heb gigantisch veel van jullie geleerd.

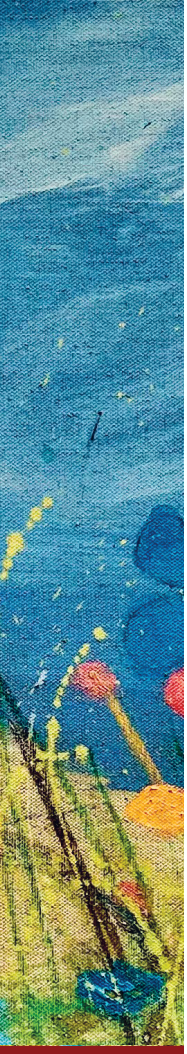
Omgevingsfactoren moeten niet worden onderschat. De goede sfeer en collegialiteit op de afdeling infectieziekten, en alle collega's daar, hebben zeker bijgedragen aan dit boekje. Het is een luxe om op de C5 te mogen werken. Hetty, Geert en Henk, jullie zijn fantastische kamergenoten. Dank voor jullie hulp, niet gelimiteerd tot dit proefschrift. Opa's stoel stond - ook na mijn vertrek - altijd klaar. Anna, 'Feestmacarons' en 'troostmacarons' eten in tropische temperaturen. Ik kan me geen beter werkklimaat voorstellen. Nooit gedacht dat ik bij mijn 'guidance committee' op een kamer zou belanden, maar dat blijkt inderdaad heel 'guiding'.

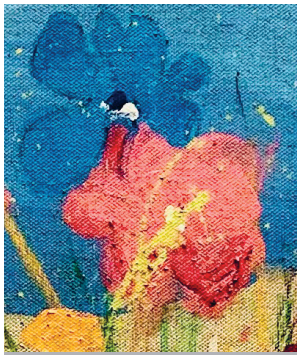
Het is onmogelijk alle mensen te bedanken die het mogelijk gemaakt hebben om door te gaan, toen de basis wegviel. Graag noem ik in het bijzonder de Groningers voor allerlei vormen van hulp, variërend van een diepvries vol noodmaaltijden tot (meestal ongevraagde..) adviezen. Jullie stonden telkens weer klaar om een probleem op te lossen, ongeacht mijn humeur. Jeroen, Aad, Pieter, Monique, Jolein, Karlijn en Joost: een boekje schrijven kan niet zonder een dak boven je hoofd. Zonder jullie hulp was ik nog aan het klussen geweest en was er van een boekje geen énkele sprake.

Karin en Elly, jullie gaven me de mogelijkheid links en rechts achterstallig schrijfwerk in te halen, door met heel veel liefde voor Anne en Tom te zorgen. Karin, een vijfde oma is

voor ons alledrie ontzettend waardevol. Kitty en Liesbeth, ‘Hotel Essenpark’ kan ik aan iedere haperende promovendus aanbevelen. Dank voor al jullie support, van ver en van dichtbij.

Lieve Anne en Tom. Jullie schilderden de kaft, het enige onderdeel van dit hele proefschrift waar maar 1 versie van is, omdat het gelijk goed was. En jullie bijdrage ging nog veel verder dan dat. Jullie zijn het aller-, aller-, allerbelangrijkste. Dit boekje is er echt dankzij jullie.



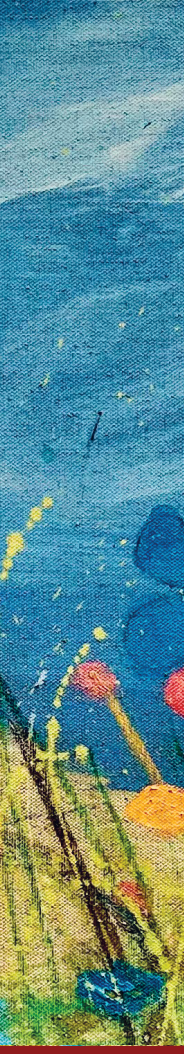


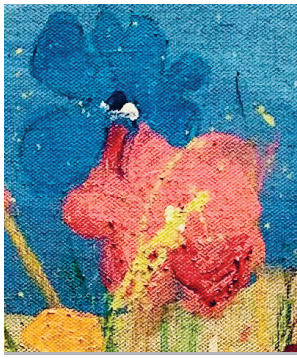
Curriculum Vitae

Merel werd geboren op 20 juli 1985, in Tilburg. Samen met haar broer Joost, groeide ze op in Wassenaar. In 2003 behaalde zij haar gymnasium diploma *cum laude* aan het Christelijk Gymnasium Sorghvliet in Den Haag. Zij vertrok naar Groningen voor de studie geneeskunde aan de Rijks Universiteit Groningen. Tijdens haar studie was zij werkzaam als lid van het nierperfusieteam. Na een bestuursjaar als secretaris van het KNMG studentenplatform, liep zij coschappen bij de Isala Klinieken in Zwolle, met een keuzestage tropengeneeskunde in Rwanda en een semi-arts stage interne geneeskunde (dr. Alleman). In 2010 behaalde zij *cum laude* de master geneeskunde. Hierna startte zij met de opleiding tot internist in het Alrijne ziekenhuis Leiderdorp en het Leids Universitair Medisch Centrum (opleiders dr. Janssen en prof. dr. de Fijter).

Zij koos voor het aandachtsgebied infectieziekten, eveneens in het LUMC (opleider prof. dr. Visser). In die periode werden dochter Anne (2015) en zoon Tom (2017) geboren. De interesse voor onderzoek op het gebied van antibiotic stewardship begon tijdens de differentiatie infectieziekten en leidde tot een promotietraject (prof. dr. Visser, dr. de Boer) en een onderbreking van de opleiding voor een stage klinische epidemiologie in het LUMC (prof. dr. Dekkers).

Na de registratie als internist-infectioloog, werd zij aangesteld bij de afdeling infectieziekten (LUMC). Naast klinische en poliklinische patiëntenzorg, is zij lid van het Regionaal Coördinatieteam Antibioticaresistentie Holland West en doet zij onderzoek op het gebied van antibiotic stewardship, zoals beschreven in dit proefschrift.





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