Antibiotic Stewardship

Clinical decision support systems to improve antibiotic use in hospitals

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van antibioticagebruik in ziekenhuizen

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General introduction and outline of the thesis

Antibiotic resistance

It was on a September morning in 1928 that the biologist, Alexander Fleming (1881–1955), accidentally discovered one of the world's first antibiotic drugs, penicillin. Returning from a two-week summer vacation with his family, he made the discovery from a contaminated Petri dish. When sorting through the petri dishes he had set aside, and that had been long unattended, he discovered the dishes contained colonies of a bacterium called Staphylococcus. On one dish he noticed something striking: a clear zone, without bacterial growth, surrounded a mold spore, that had grown on the dish while he had been away [1]. The mold, called Penicillium notatum, turned out to contain a powerful antibiotic, which about a decade later, during World War II, was turned into a drug that saved millions of lives. Infectious diseases that were deadly, could now be completely cured with penicillin. Striking is the difference in death rate from bacterial pneumonia between World War I, which was 18 percent and World War II, during which it fell to less than 1 percent [2]. The introduction of penicillin as treatment for bacterial infections marked the beginning of the so called 'golden era' of antibiotic therapy. Later Fleming wrote about this day the now famous words: '*When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer. But I guess that was exactly what I did.*' Unfortunately the successful use of penicillin was compromised by the development of resistance. Consequently, many of the progress in treatment of infections of the prior years was threatened in the year 1950 [3]. However, the discovery of penicillin was the start of the era of antibiotic therapy and many other antibiotics have been discovered since then. Actually, most of the antibiotic classes that we use nowadays have been discovered between 1940 and 1962. Alongside the discovery and introduction of these new antibiotics there has also been discovery of resistance to these antibiotics soon afterwards. Antibiotic resistance is a natural occurring process used by bacteria in order to survive [4]. Several mechanisms may result in the selection of antimicrobial resistant bacteria. Resistance to beta-lactam antibiotics, the most widely used class for treatment of bacterial infections, occurs for example as a result of inactivation of the antibiotic by enzymes, the so-called beta-lactamases. These beta-lactamases break open the beta-lactam ring, which is a molecule structure these class of antibiotics have in common. Other resistance mechanisms are a decreased permeability of the bacterial membrane and efflux of antibiotics [5]. Resistance genes can be transferred to or by other bacteria [4]. To solve the resistance problem, new antibiotics were introduced by the pharmaceutical industry. However, starting around 1980, the antibiotic pipeline has dried up [3]. Only in the last 6 years the status of the antibacterial pipeline has improved, but the number of new antibiotic drugs still remains insufficient [6]. Unfortunately, decades after the successful

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introduction of the first antibiotic drug penicillin, bacterial infections have become life threatening again [3, 7]. As the World Health Organization stated: '*Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill*' [8]. Overuse and inappropriate use of antibiotics are seen as contributing factors to this problem [9-14]. Overuse of antibiotics occurs around the world, despite advices against it [15]. In many countries, antibiotics are available without a medical prescription and this over the counter availability contributes to the overuse of antibiotics [15, 16]. In addition, studies have shown that about 30–50% of antibiotics (for hospitalized patients) are being prescribed inappropriately [17-24]. A range of cases fall under the description 'inappropriate antibiotic use', such as the unjustified use of antibiotics, antibiotics being prescribed in an inappropriate dose, route or duration, and antibiotics prescribed in a too broad spectrum. Besides the association with the development of antimicrobial resistance, inappropriate use of antibiotics is also associated with increased healthcare costs and adverse patient outcomes [20, 21]. The need to use more expensive, alternative antibiotics when first-line antibiotics fail in the treatment of infections and longer hospital stays leads to this increased healthcare costs. Illustrative for the burden of antibiotic resistance is the prediction made by the Organization for Economic Co-operation and Development that in the next 30 years around 2.4 million people in Europe, North America and Australia will die from infections with resistant microorganisms [25]. Dealing with antimicrobial resistance complications will cost up to US$3.5 billion per year [25]. Besides the overuse and inappropriate use of antibiotics in humans, antibiotic resistance seems to be driven by several other factors, such as: the over- and misuse of antibiotics in animals, healthcare transmission of resistant bacteria and sub-optimal tools/methods for rapid diagnoses [26]. In animals, antibiotics are used to prevent infections and for growth promotion, which in some countries accounts for no less than approximately 80% of total consumption of medically important antibiotics [27]. The most important route in which antibiotic resistant bacteria in animals transmit to humans is the foodborne route, but transmission can also occur via direct contact or the environment. Transmission of resistant bacteria also occurs from human to human, often in hospitals and long-term care facilities. Because multiple factors contribute to the antibiotic resistance problem a multifaceted approach, focused on the different contributing aspects seems to be the approach with the best chance of success [28]. In recent years several initiatives have been developed by several organizations, such as the World Health Organization (WHO) and the Infectious Diseases Society of America (IDSA) to address the antibiotic resistance problem [6, 27, 29, 30]. These initiatives address several common areas which acquire attention, such as the importance of more judicious use of antibiotics in both human and animals, infection prevention and promoting research aimed at developing new antibacterial drugs.

Antibiotic stewardship

A recurrent and important component in different initiatives to promote more judicious use of antibiotics, thereby preserving the effectiveness of these drugs, is through the implementation of Antibiotic Stewardship Programs (ASPs) [24, 31-33]. Antibiotic stewardship is used in human healthcare within hospitals, but also outside hospitals and in animal health (veterinary antimicrobial stewardship) [34]. Antibiotic stewardship is most frequently described in terms of its primary goal: 'to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance' [24]. In 2012 this description was updated in a consensus statement from the IDSA, the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS): 'antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration' [33, 35]. Antibiotic stewardship has 3 recognizable dimensions: a) the structural prerequisites, b) objectives (the 'what') and c) improvement interventions (the 'how') [36, 37]. An important structural prerequisite is the presence of a multidisciplinary antimicrobial stewardship team (AST). This team is ideally composed of the following core members: an infectious disease physician, a clinical pharmacist, a clinical microbiologist, an information system specialist, an infection control professional and a hospital epidemiologist [24]. Antibiotic stewardship programs aim at achieving a range of objectives, such as a timely switch from intravenous (iv) to oral administration and guideline-adherent empirical antibiotic prescribing. To achieve the different possible objectives a wide variety of antibiotic stewardship interventions are possible. Some examples of these interventions are: prospective audit of antimicrobial use with intervention and feedback to the prescriber. This is done by trained individuals (physicians or pharmacists), who assess antimicrobial therapy and give recommendations regarding the selection, dose, route and duration of prescribed antibiotic(s), when this is not appropriate/suboptimal. Other examples of antibiotic stewardship interventions are optimization of antimicrobial dosing based on relevant parameters and a systematic plan for switching from parenteral to oral antibiotic treatment [24]. Quality indicators are useful to measure/follow if antibiotics are appropriately used. These are 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality, and hence change in the quality, of care provided' [38]. A performed systematic literature review of published quality indicators for appropriate antibiotic use in hospitalized adult patients showed that the most frequently mentioned indicator is whether empirical antibiotic therapy is prescribed in concordance with guidelines (71% of

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included studies) [39]. A timely switch from iv to oral antibiotic therapy was the second most frequently mentioned indicator [39]. There is probably an association between guideline-adherent empirical therapy and a reduction of mortality. The same applies to switching from iv to oral antibiotic therapy. However studies regarding this subject are of low quality and therefore firm conclusions cannot be drawn [40]. A growing body of evidence shows that ASPs can optimize antibiotic treatment by clinicians [41]. High certainty evidence exists that interventions to improve antibiotic prescribing are effective in increasing antibiotic policy compliance and reduction of treatment with antibiotics. A reduction of 1.12 days in length of stay can probably be achieved with antibiotic stewardship interventions [41]. In addition antibiotic stewardship is associated with a reduction of adverse events associated with antibiotic use, such as clostridium difficile infections and antibiotic resistance [42, 43].

Antibiotic stewardship in the Netherlands and worldwide

Although antibiotic resistance rates in the Netherlands are relatively low compared to other countries, the increasing resistance of some bacteria has (and is) giving cause for concern and alertness [44]. Antimicrobial stewardship programs were implemented in many countries during the 1990s and 2000s [34]. In 2014, upon suggestion by the Dutch Working Party on Antibiotic Policy (SWAB) and endorsed by the Dutch Health Inspectorate, ASTs were also established in all hospitals in the Netherlands. The development and implementation of ASPs and their activity across the world varies considerable, with implementation rates of ASPs that vary from 14% in Africa to about 70% in Europe and North America. Recognized main barriers are a lack of funding, personnel or information technology, and prescriber opposition [45, 46]. A lack of information technology is an often cited barrier in low and middle income countries [47]. Financial considerations were barriers to the establishment of an antimicrobial stewardship program in 36% of cases in a survey by Pope and colleagues. In about 27% of cases opposition from prescribing physicians was a barrier [48].

Clinical decision support systems

The efficiency of stewardship interventions can be improved with the support of information technology, especially given the increasing demands on the time of clinicians and healthcare resources to meet antimicrobial stewardship standards [49]. The technological advances over the past years, which have resulted in generally well developed information technology in developed countries has brought many advantages in health care. Many physicians nowadays cannot remember or have never worked with the traditional paper

based health records. The development of new computer technology in the 1960s and 1970s made the development of Electronic Health Records (EHRs) possible, which has changed our health care system [50]. This technology has provided many benefits, because of its many abilities including, but not limited to, the easy storing and retrieving of data, the ease and speed with which patient information can be communicated and the readability of all this information. However, the shift from paper based health records to EHRs did not come without a struggle, which was related to the initial costs and acceptance by physicians [51]. EHRs have undergone tremendous development during the years, with the early EHRs having limited storage and most of them not having the option to enter orders (computerized physician order entry (CPOE) [50]. The advent of EHRs, CPOE (including electronic prescribing) brought the potentially very valuable possibility of developing clinical decision support systems (CDSSs). An often quoted definition of a CDSS is the following, proposed by dr. Hayward of the Centre for Health Evidence: '*Clinical decision support systems link health observations with health knowledge to influence health choices by clinicians for improved health care*' [52]. More recently the Office of the National Coordinator for Health Information Technology has given the following definition: '*Clinical decision support provides clinicians, staff, patients or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care*' [52]. Clinical decision support systems exist in different forms, they can, for example, be integrated in the EHR or may be stand-alone software programs, be knowledge based or non-knowledge based (using a form of artificial intelligence/machine learning algorithms), be activated automatically or 'on demand', be interruptive or non-interruptive [52]. They have been developed for a wide variety of areas in medicine: laboratory result alerting [53], blood product ordering [54], drug and parenteral nutrition dosing [55, 56] and much more. CDSSs to support appropriate use of antibiotics have been developed since 1980 and many have been developed since then [57]. They target a variety of aspects of antibiotic prescribing, such as the choice of antibiotic(s) [58, 59], route of administration [60], dosing [61-63] and de-escalation of antibiotics [64, 65].

CDSS and antibiotic stewardship

With the prescription of antibiotics physicians have to take many elements into account, such as the most appropriate spectrum of activity, the dose, route of administration and cost-effectiveness. Antibiotics are mostly prescribed by non-experts in infectious diseases, which may lead to a decreased quality of antibiotic prescribing [66]. The earlier mentioned health care information technologies EHR, CPOE and CDSS can improve antimicrobial

decisions by incorporating data on for example drug-drug interactions, allergies and renal function [24] and can therefore play an important role in antimicrobial stewardship. It's for this reason that the IDSA and the SHEA suggested to incorporate CDSS for prescribers into ASPs [33]. As part of an ASP, CDSSs can play an important role by covering a part of the activities of an AST. This is attractive given the fact that ASTs are labor intensive and thus expensive [67, 68].

CDSS for IV to oral antibiotics switch therapy

One of the most cost-effective and safe objectives of an ASP is the timely switch from iv to oral antibiotic therapy [40]. A promising stewardship intervention to facilitate a timely switch is a CDSS that automatically generates reminding alerts [69, 70]. Developed CDSSs to facilitate a timely iv to oral switch use local iv to oral switch criteria [71, 72] or use very general rules, such as a certain duration of iv therapy and/or an active order for scheduled oral medications [73, 74]. This limits their general applicability and acceptance. In addition, using more specific rules will probably also improve the specificity of these systems. Improving specificity is important because over alerting can cause alert fatigue. However, a wide variation exists in iv to oral antibiotic switch criteria and their defining measurable values [75-77], which compromise the development of a specific and generally applicable CDSS for iv to oral antibiotic switch therapy.

CDSS for empirical antibiotic therapy

Another important objective of ASPs is the use of empirical antibiotic therapy according to guidelines [39], which is associated with a relative risk reduction for mortality [40]. Several CDSS for empirical antibiotic therapy have shown potential benefits in terms of improving empirical antibiotic prescribing [58, 59, 78-80]. However, in many of these studies the CDSS was not assessed while or after the end-users, the physicians themselves, used the system [59, 78, 79]. Although these studies have shown potential improvements in antibiotic prescribing, possible problems related to implementation (such as willingness and ability of users to use the CDSS) and problems related to the use of the system by the physician themselves were not taken into account. Therefore, it is not clear whether these results can be repeated in real clinical settings. In addition, the development of these systems has been poorly reported, which hinders learning effectively from previous successes and failures. Therefore, the need for detailed description of system design has been addressed [81].

Outline of this thesis

This thesis focuses on CDSS for antibiotic prescribing/antibiotic stewardship. It contributes to the following objectives:

- To evaluate the usefulness of a consensus-based clinical decision support system, to optimize a timely switch from intravenous to oral antibiotics

- To evaluate the use of a clinical decision support system for empirical antibiotic therapy and the uptake of its recommendations according to a systematic guidance for the development, validation and implementation

To effectively promote the appropriate use of antibiotics it is important to gain insight in the magnitude of the problem and areas of improvement for antibiotic use. In **Chapter 2** we determined the prevalence of inappropriate antibiotic use and identified areas in which improvements of prescription can have an important impact hospital-wide. For this purpose a cross-sectional point prevalence survey is performed, using a standardized assessment method.

One of the possible stewardship interventions is the early, safe switch of an iv to oral antibiotic therapy, which is often referred to as 'low-hanging fruit', because it is one of the most obtainable targets within a stewardship program. However, although there is overlap in the iv-to-oral antibiotic switch criteria a considerable variation exists in their operationalization and they are often subjective. In **Chapter 3** we describe a consensus procedure, the so called RAND-modified Delphi procedure, which is used to reach consensus on a set of operationalized iv-to-oral antibiotic switch criteria that all have to be met in adult hospitalized patients for a safe switch after 48–72 hours of iv therapy. These developed measurable conditions are a first step towards standardized iv-to-oral switch criteria. To improve antibiotic use in an effective and sustainable manner however, more is needed than only guidelines and instructions. The specific and generally applicable criteria, on which consensus is reached in this study, offer the opportunity to develop a generally applicable CDSS to remind physicians about switching from iv to oral antibiotic therapy.

In **Chapter 4** we present the development and validation of a CDSS algorithm to facilitate a timely switch from iv to oral antibiotics. This algorithm is based on the operationalized consensus switch criteria described in Chapter 3 and generates reports with iv to oral antibiotic switch candidates which are directed to the infectious disease specialist of the AST. To validate this algorithm and to assess its usefulness in daily clinical practice we used a standardized validation strategy.

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Another possible objective of ASPs, often described as one of the most important, is guideline-adherence when prescribing empirical antibiotic therapy. We have developed a CDSS for empirical antibiotic treatment in adult hospitalized patients, which combines relevant patient information with relevant local antibiotic treatment guidelines. The CDSS is developed to be used by physicians when prescribing empirical antibiotic therapy. A poor usability of CDSS negatively affects their acceptance and effectiveness and can result in medication errors, potentially compromising patient safety. For this reason it is important to well test the usability of these systems before implementation in clinical practice. In **Chapter 5** we describe the assessment of the usability of a developed CDSS for empirical antibiotic drug prescription and provide elements that have to be considered to avoid usability problems.

Several CDSSs to improve empirical antibiotic prescribing have been developed and assessed over the years and have shown benefits in terms of improving empirical antibiotic prescribing. The development of these systems have been poorly reported. Because of a heterogeneous and disjointed approach to reporting CDSS interventions a need exists for a systematic reporting framework [57]. In **Chapter 6** we give a detailed description of the development and implementation of a CDSS to assist and improve empirical antibiotic choices made by physicians, using a systematic reporting framework. We assess the usefulness of this framework and evaluate the use of the CDSS and uptake of its generated advices. In **Chapter 7**, the general discussion, we summarize and discuss the main results of this thesis. Furthermore we give recommendations for future research. We end this thesis with a summary and final conclusions.

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Point prevalence of appropriate antimicrobial therapy in a Dutch university hospital

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Abstract

Purpose: Antimicrobial stewardship teams have been shown to increase appropriate empirical antibiotic therapy, reduce medical errors and costs in targeted populations, but the effect in non-targeted populations is still unclear. The aim of this study was to determine the prevalence of inappropriate antibiotic use in a large university hospital and identify areas in which antimicrobial stewardship will be the most effective.

Methods: In a point prevalence survey we assessed the appropriateness of antibiotic therapy using an electronic surveillance system in combination with a standardized method for duration of therapy, dosage, dosage interval, route of administration and choice of antibiotic drug. Patients using at least 1 antibiotic drug were included.

Results: Among 996 patients admitted in the surveyed wards, 337 patients (33.8%) used one or more antibiotic drugs. 221 patients (22.2%) used antibiotic medication therapeutically, with a total of 307 antibiotic prescriptions. Antibiotic therapy was deemed inappropriate in 90 (29.3%) of these prescribed antibiotics, with an unjustified prescription as the most common reason for an inappropriate prescription. Use of fluoroquinolones, amoxicillin/clavulanic acid and a presumed diagnosis of fever of unknown origin, urinary tract infection and respiratory tract infection were associated with inappropriate antibiotic therapy.

Conclusions: Our study provides insight into (in)appropriateness of antibiotic prescriptions in a tertiary care center in the Netherlands and identifies areas for improvement. The use of an electronic surveillance system for this point prevalence study is easy to use and may serve as a baseline measurement for the future effect of antibiotic stewardship.

Introduction

Antibiotics are an indispensable part of modern medicine. However, as with all drugs, antibiotics may have adverse effects and medication errors can occur in prescribing. Another untoward effect of antibiotics is the selection of antibiotic resistant bacteria. In 2007, more than 8,000 excess deaths in Europe were associated with blood stream infections caused by methicillin-resistant Staphylococcus aureus (MRSA) and third-generation cephalosporin-resistant Escherichia coli [1]. This mortality is only a fraction of the total burden of disease associated with antibiotic resistance [1]. The U.S. Centers for Disease Control and Prevention (CDC) estimated that each year at least 2 million people in the USA acquire infections with antibiotic-resistant bacteria, with at least 23,000 deaths as a direct result of these infections [2]. Although in the Netherlands antimicrobial resistance is low compared to other countries [3], antimicrobial resistance here is also increasing [4].

A clear relationship has been found between the percentage of resistant strains and antimicrobial use [5]. In addition, only around 60% of empirically started antibiotics are considered appropriate [6-8]. Finding a balance between adequate antibiotic use for the individual patient, avoidance of selection of antibiotic resistance, and medication errors is the key role of Antibiotic Stewardship Teams (ASTs) [9]. ASTs have been shown to increase appropriate empirical antibiotic therapy and reduce medical errors and costs [5, 10, 11]. Moreover, by narrowing down earlier broad-spectrum treatment, the development of antimicrobial resistance will decrease [5, 11]. In a hospital-wide rollout of antimicrobial stewardship, AST intervention was associated with a large reduction in targeted antimicrobial utilization among patients receiving at least 3 days of antimicrobial therapy, but no significant change was observed hospital-wide [12].

The aim of this study was to determine the prevalence of inappropriate antibiotic use and to identify the areas on which ASTs can have an important impact hospital-wide.

Materials and methods

Setting

The Erasmus MC, University Medical Centre Rotterdam is a 1,320-bed tertiary care center in Rotterdam with all medical specialties available. In 2012, there were 41,773 admissions and 286,155 bed days.

Cross-sectional point prevalence survey

The point prevalence survey of antimicrobial use was performed on May 4th and May 16th 2013. Patients were selected with E-Surveillance, an electronic surveillance system, which has been operational in our hospital since 2011 [13, 14]. Originally, it was developed as a tool to automatically select patients suspected of having hospital-acquired infections from a hospital-wide point-prevalence population. In this system patient census data, antibiotic prescriptions, individual antibiotic treatment, infectious disease consultancy reports, laboratory data, microbiological results, vital signs, surgical reports and radiology reports are integrated. We used E-surveillance to execute a set of algorithms designed for this study. First, the point prevalence population was automatically created. The study population consisted of all patients in all clinical departments of the Erasmus MC [including a 32-bed general intensive care unit (ICU)], with the exception of the cardiothoracic ICU (18 beds), pediatric (200 beds), and psychiatric wards (77 beds). Then, all patients using at least one antibacterial for systemic use (ATC code starting with J01) on May 4th or May 16th 2013 were marked, with the exception of those patients that received their antibacterial prophylactically. An algorithm differentiated between therapeutic and prophylactic use of the antibacterial based on our hospital's antibiotic policy. The following antibiotic drugs were defined as prophylaxis and excluded by the E-Surveillance system: cotrimoxazole at a dose of 480 mg, amoxicillin/clavulanic acid given once, and cefazolin started preoperatively, intraoperatively or in a postoperative period without another clear indication. Antibiotics given regarding a prophylactic protocol, such as selective decontamination of the digestive tract, antibiotics for patients with neutropenia, chronic obstructive pulmonary disease (COPD) and feneticillin within a period of 2 years after splenectomy were also defined as prophylaxis.

Review of antibiotic policy

Antibiotic drugs were also considered to be prophylactic if they were recorded as such in patient progress notes. Relevant data elements, such as age, sex, ward, and prescribed antibiotic(s), were retrieved from the E-Surveillance database. The appropriateness of antibiotic therapy was determined for each individual patient by both a clinical microbiologist and an infectious disease consultant, using the standardized method developed by Gyssens et al. [15]. Infection information from the admission day until the prevalence day could be used to assess the appropriateness of antibiotic therapy. Discrepancies were discussed by the reviewers until consensus was reached. Relevant parameters associated with antibiotic use were evaluated and the following classifications were used: appropriate prescription, inappropriate prescription due to incorrect use, incorrect choice or unjustified prescription,

and insufficient records for categorization. To evaluate the different relevant parameters a flow chart was used by the reviewers for each prescription, which resulted in classification of the prescription into one of the possible categories shown in Table 2.1. Antibiotic drug prescriptions could be placed in more than one category, if inappropriate for more than one reason. All data were reviewed in E-Surveillance and, when indicated, by chart review.

Prescribing therapeutic antibiotics was considered justified for an infection that was either community-acquired or nosocomial. A community-acquired infection was defined as documented or suspected infection within 48 h after admission with fever (>38°C) and/or elevated infection parameters (C-reactive protein >10 mg/l, white cell count >11 x 10^9/l or erythrocyte sedimentation rate >20 mm/h). A nosocomial infection was defined as infection meeting the CDC criteria and occurring at least 48 h after admission.

The definition of appropriateness of antibiotic therapy was based on the current local antimicrobial treatment guidelines, which is in line with the national guidelines (http://www.swabid.nl) and available microbiological results.

The antibiotic prescription was defined as inappropriate due to unjustified prescription, when the use of an antibiotic was not indicated because no infection was present. The antibiotic drug prescription was also considered to be inappropriate when the administered antibiotic drug was not in line with the antibiotic guidelines, in case of allergy to the prescribed antibiotic drug, or when a more effective, less toxic, less expensive and/or less broad-spectrum alternative agent was available. Additionally, antibiotic drug prescription was considered inappropriate in case of incorrect duration, incorrect dosage, incorrect dosage interval, and/or incorrect route of administration (Table 2.1). For an incorrect dosage kidney and liver function were taken into account, as well as the (available) antibiotic concentration in blood. The route of antibiotic administration was considered incorrect when a patient was able to switch from intravenous (iv) to oral antibiotic drugs when iv drugs had been given for 48 h, the signs and symptoms of infection had improved, and an oral alternative was available. Criteria that needed to be fulfilled were hemodynamically stable; afebrile (i.e. temperature <38°C for 24 hours); diagnosis and/or pathogen known or highly probable; oral intake possible; absence of factors interfering with drug resorption and/or bioavailability; no contra-indications for oral antibiotics and no significant interaction with other medication.

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Table 2.1. Categories evaluation of the appropriateness of antimicrobial drug therapy (ADT)

Categories	Absolute frequency	Percentage of total number of prescriptions
I. Appropriate ADT	199	64.8
II. Inappropriate ADT, due to incorrect use:	21[a]	6.8
a. Improper duration	10	3.3
b. Improper route	6	2.0
c. Improper dosage interval	10	3.3
d. Improper dosage	8	2.6
III. Inappropriate ADT, due to an incorrect choice:	25[a]	8.1
a. Allergy to the prescribed antibiotic drug	0	0
b. Less broad-spectrum alternative agent	9	2.9
c. Less expensive alternative agent	7	2.3
d. Less toxic alternative agent	4	1.3
e. More effective alternative agent	15	4.9
IV. Inappropriate ADT, due to unjustified prescription: use of any antimicrobial is not indicated	48	15.6
V. Insufficient information	18	5.9

[a] Four antibiotic prescriptions were inappropriate due to incorrect use and choice

Results

Antibiotic use and demographics

At the start of the survey, a total of 996 patients were admitted on the included wards, of which 337 patients (33.8%) were using one or more antibiotic drugs. Antibiotic drugs were used prophylactically in 116 patients, these patients were excluded from the analysis. 221 patients (22.2%) used antibiotic medication therapeutically, with a total of 307 antibiotic prescriptions. The median age of patients receiving antibiotic therapy was 62.6 year and 42% was female. In nearly half of the patients (45.3%), a clinical microbiologist or infectious diseases specialist was consulted. Twenty patients were admitted on both point prevalence dates. These patients used a total of 64 antibiotic drugs. On both days, 15 of these antibiotics were still prescribed for the same diagnosis. Most patients 68.3% (151/221) were treated with one antibiotic drug, 57 patients (25.8%) were treated with two and 13 (5.9%) were treated with three or more antibiotic drugs. Combinations of beta-lactam antibiotics plus or minus beta-lactamase inhibitors were the most commonly prescribed antibiotic class, followed by fluoroquinolones.

Appropriateness of antibiotic therapy

In total, 90 (29.3%) of the 307 prescribed antibiotics were classified as inappropriate antimicrobial drug therapy (Table 2.1). More specifically, for 48 (15.6%) prescriptions there was no indication for antimicrobial therapy. 25 (8.1%) prescriptions were an incorrect choice of antibiotic drug, for which a more effective, a less toxic or a less expensive alternative agent was available. Interestingly, in nearly 36% of the incorrectly chosen antibiotics, therapy could have been narrowed down. 21 (6.8%) of the prescribed antibiotic drugs were used incorrectly, mostly due to an incorrect duration of therapy or an improper dosage interval (Table 2.1).

Appropriateness of antibiotic therapy according to antibiotic class, diagnosis, and ward

The rate of inappropriate antibiotic therapy varied from nearly 50% for broad-spectrum antibiotic drugs to 10% for narrow spectrum penicillins (Table 2.2). Antibiotic drugs

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Table 2.2. Appropriateness of antibiotic prescriptions according to the class of antibiotic[a]

Antimicrobial agent	Number of prescriptions (% of total)	Number of inappropriate prescriptions	Proportion of inappropriate prescriptions (95% confidence interval)	OR[b] for inappropriate prescriptions (95% confidence interval)
Fluoroquinolones	37 (12.1)	18	0.49 (0.33-0.64)	Reference
Amoxicillin/clavulanic acid	34 (11.1)	15	0.44 (0.29-0.61)	0.88 (0.34-2.29)
Meropenem	28 (9.1)	5	0.18 (0.08-0.36)	0.24 (0.07-0.77)
Cefalosporins, second generation	27 (8.8)	10	0.37 (0.22-0.56)	0.63 (0.22-1.74)
Piperacillin/tazobactam	26 (8.5)	8	0.31 (0.17-0.50)	0.50 (0.17-1.46)
Glycopeptides	22 (7.2)	1	0.05 (0.01-0.22)	0.05 (0.01-0.39)
Narrow-spectrum penicillin[c]	19 (6.2)	2	0.11 (0.03-0.31)	0.12 (0.02-0.59)
Penicillins with extended spectrum[d]	18 (5.9)	3	0.17 (0.06-0.39)	0.21 (0.05-0.88)
Macrolides	16 (5.2)	6	0.38 (0.18-0.61)	0.75 (0.22- 2.60)
Cefalosporins, third generation	15 (4.9)	2	0.13 (0.04-0.38)	0.17 (0.03- 0.85)
Metronidazole	12 (3.9)	2	0.17 (0.05-0.45)	0.20 (0.04- 1.04)
Aminoglycosides	12 (3.9)	2	0.17 (0.05-0.45)	0.25 (0.05-1.34)
Polymyxins[e]	10 (3.3)	4	0.40 (0.17-0.69)	1.00 (0.22-4.63)
Clindamycin	9 (2.9)	1	0.11 (0.02-0.44)	0.13 (0.01-1.11)
Trimethoprim/sulfonamide	9 (2.9)	6	0.67 (0.35-0.88)	2.00 (0.43-9.26)
Other[f]	13 (4.2)	5	0.38 (0.18-0.64)	0.83 (0.22-3.23)
Total	307 (100)	90		

[a] Eighteen prescriptions could not be assessed because of insufficient information
[b] OR: odds ratio
[c] Narrow spectrum penicillin: penicillin, and flucloxacillin
[d] Penicillins with extended spectrum: amoxicillin and piperacillin
[e] Polymyxins: colistine
[f] Other: linezolid, nitrofurantoine, rifampicin, doxycycline, sulfadiazine

used as empirical therapy in our hospital, such as amoxicillin/clavulanic acid and second-generation cephalosporins, had a higher rate of inappropriate prescriptions than drugs that are more often used in targeted therapy, such as glycopeptides and third generation cephalosporins. Antibiotic therapy prescribed for respiratory tract infections (30.6% of

Table 2.3. Appropriateness of antibiotic therapy by diagnosis[a]

Diagnosis	Number of prescriptions (% of total)	Number of inappropriate prescriptions	Proportion of inappropriate prescriptions (95% confidence interval)	OR[b] for inappropriate prescriptions (95% confidence interval)
Respiratory tract infection	94 (30.6)	36	0.38 (0.29-0.48)	reference
Bacteremia	68 (22.1)	11	0.16 (0.09-0.27)	0.33 (0.15-0.72)
Intra-abdominal infection	22 (7.2)	4	0.18 (0.07-0.39)	0.36 (0.11-1.16)
Urinary tract infection	20 (6.5)	9	0.45 (0.26-0.66)	1.53 (0.55-4.22)
Skin and soft tissue infection[c]	15 (4.9)	1	0.07 (0.01-0.30)	0.13 (0.02-1.0)
Fever of unknown origin	13 (4.2)	8	0.69 (0.42-0.87)	3.06 (0.86-10.90)
Other[d]	75 (24.4)	21	0.40 (0.30-0.51)	0.63 (0.33-1.22)
Total	307 (100)	90		

[a] Per antibiotic prescription on date X, 18 prescriptions could not be assessed because of insufficient information
[b] OR: odds ratio
[c] Skin and soft tissue infection: erysipelas, cellulitis, hydradenitis suppurativa, panaritium, decubitus
[d] Other: less than 10 prescriptions per diagnosis

Table 2.4. Appropriateness of antibiotic therapy by medical specialization[a]

Medical specialization	Number of prescriptions (% of total)	Number of inappropriate prescriptions	Proportion of inappropriate prescriptions (95% confidence interval)	OR[2] for inappropriate prescriptions (95% confidence interval)
Lung diseases	57 (18.6)	16	0.28 (0.18-0.41)	reference
Surgery	53 (17.3)	17	0.32 (0.21-0.45)	1.25 (0.55-2.82)
Internal medicine	45 (14.7)	12	0.27 (0.16-0.41)	1.03 (0.42-2.48)
Hematology	25 (8.1)	9	0.36 (0.20-0.55)	0.49 (0.15-1.65)
Neurosurgery	18 (5.9)	8	0.44 (0.25-0.66)	2,.28 (0.75-6.94)
Gastroenterology/hepatology	16 (5.2)	6	0.38 (0.18-0.61)	1.71 (0.52-5.58)
Neurology	14 (4.6)	6	0.43 (0.21-0.67)	1.92 (0.58-6.42)
Cardiology	14 (4.6)	6	0.43 (0.21-0.67)	2.20 (0.64-7.55)
Urology	12 (3.9)	2	0.17 (0.05-0.45)	0.64 (0.12-3.35)
Orthopedics	10 (3.3)	3	0.30 (0.11-0.60)	1.10 (0.25-4.78)
Thoracic surgery	10 (3.3)	2	0.20 (0.06-0.51)	1.71 (0.26-11.20)
Other[b]	33 (10.7)	8	0.24 (0.13-0.41)	0.98 (0.36-2.65)

[a] Per antibiotic prescription on date X, 18 prescriptions could not be assessed because of insufficient information
[b] Other: less than 10 prescriptions per medical specialization. Medical specialization in this category: ear, nose and throat; oncology; dermatology; geriatrics; gynecology; radiotherapy

the total prescriptions) was inappropriate in 38% and for urinary tract infections (20% of the total prescriptions) in 45% (Table 2.3). Most antibiotic drugs were prescribed on only three wards: lung diseases (18.6%), surgery (17.3%) and internal medicine (14.7%). Of all the medical specializations, neurosurgery has the highest percentage of inappropriate antibiotic drug therapy (44 %) (Table 2.4).

Discussion

In our tertiary care hospital, antibiotic drugs are used in 33.8% of the adult patients in general wards and 22.2% is used therapeutically. Of the patients prescribed antibiotics therapeutically, 90 (29.3%) antibiotic prescriptions were inappropriate. The highest percentage of inappropriately prescribed antibiotic drugs was due to unjustified use, i.e. no antibiotic use was deemed indicated. Improper dosing intervals and incorrect duration were also commonly found, as well as prescription of an antibiotic drug when a more effective alternative was available. Urinary tract infection and respiratory tract infection were the infections with the highest inappropriate antimicrobial drug therapy. Our data offer areas of possible intervention by antimicrobial stewardship. In the future repeated audits of the appropriateness of antimicrobial therapy will give insight into the effectiveness of interventions aimed at improving antibiotic drug use and, thus, the effect of ASTs.

Point prevalence surveys are useful tools to assess appropriate antibiotic use [7]. However, the required time investment and limited human resources can constitute a barrier to perform such surveys. The time investment depends on the size of the hospital, the kind of patients, the experience of the reviewer, and a possible combination with other surveys, such as point prevalence studies of infections. The time needed to perform these surveys has been reported to be 10-20 minutes per patient (personal communication with dr. P.R. Ingram [16] and I. Willemsen [7]). Our study is, to our knowledge, the first to use a computer-based surveillance system to estimate the point prevalence of antibiotic use. With the use of our electronic surveillance system, with automatic selection of patients and extraction of data needed, it took us 5-10 minutes per patient. Using E-Surveillance, we could determine the prevalence of antibiotic drugs in a shorter time period than other methods, circumventing laborious efforts of inspection and collection of data on the wards [7, 16].

The prevalence of antibiotic use corresponds to the Dutch point prevalence study in 32 hospitals by the Prevention of Nosocomial Infections through Surveillance (PREZIES) network which showed that 32% of all admitted patients (N=9,599) received antibiotic drugs [17]. An Australian hospital-wide point prevalence study showed 47% inappropriate

antibiotic drug use in 199 adult patients from all wards of a tertiary hospital using also the method developed by Gyssens et al. [15, 16]. In contrast to our study, in which risk factors for inappropriate antibiotic prescribing included respiratory infections, fluoroquinolone or amoxicillin/clavulanic acid use and neurosurgical care, Ingram et al. found bone/joint infections, creatinine level >120 mmol/l, carbapenem or macrolide use and being under the care of the aged care/rehabilitation team to be risk factors. In a Dutch study 10 years ago in a 1,350-bed teaching hospital including all medical specialties, inappropriate antibiotic use was 37%, with fluoroquinolone use being the only statistically significant risk factor [7]. The higher inappropriate use in the other 2 studies may be explained by a difference in time [7], country [16], and the fact that we did not include antibiotic drugs that were given prophylactically. Another explanation might be that in about half of the patients in our study an infectious disease specialist or clinical microbiologist was involved, probably leading to a lower rate of inappropriately prescribed antibiotic therapy [5, 10-12].

Inappropriate use of antibiotic drugs is an important determinant in the development of antimicrobial resistance [18, 19]. For instance, in Europe, antimicrobial resistance is higher in the south of Europe where much more antibiotic therapy is prescribed compared to Northern Europe [3, 20]. Our study and others [7, 16] have shown that inappropriate use of antibiotic drugs is high, partly because of unjustified antibiotic prescription [21-23]. This may be explained by insecurity about a diagnosis of infection [24], as shown by insufficient documented information for antibiotic use in medical records [25]. Our study provides insight into the areas of inappropriate antibiotic use and, thus, for areas in which interventions may be successful. The importance of identification of such areas was shown in the rollout of antimicrobial stewardship in a tertiary hospital in Toronto. Among patients meeting stewardship criteria a 21% reduction in targeted antibiotic utilization was shown, whereas no significant change was found in all admitted patients [12].

Our study has some limitations. With the electronic surveillance system we used, access to the medical records of patients on cardiac and thoracic ICUs was lacking. Since antibiotic use is high in ICUs, the prevalence of antibiotic use in our hospital may have been lower than expected. However, our results were in concordance with the antibiotic use in other hospitals as shown by the PREZIES data [17]. Another aspect is the inclusion of antibiotics that were prescribed on both days. These antibiotics were included in the analysis because the time difference of 12 days may have resulted in a change of appropriateness of antibiotic therapy, such as for instance duration of therapy.

One of the methods to optimize antibiotic stewardship is a clinical decision support system (CDSS) [9, 26]. Different studies have shown that a CDSS leads to more appropriate antibiotic

treatments [27-31]. The surveillance system used in this study has been developed to easily determine infection rates in specialized patient populations, such as postoperative wound infections in surgical patients [13] and will be developed further as an early warning system for nosocomial infections [14]. This system might be upgraded to an integrated computer-assisted decision support system. However, our study has shown that nearly 6% of patients could not be evaluated for appropriateness of antibiotic use due to insufficient information. This has to be taken into account when a CDSS will be introduced.

In conclusion, our study provides insight into the appropriateness of antibiotic prescriptions in a tertiary care center in the Netherlands and identifies areas for improvement. We used an electronic surveillance system, thereby making the point prevalence study less time consuming and laborious. A point prevalence study for antibiotic use can be an effective tool to assess the effect of antibiotic stewardship either by an antibiotic stewardship team or a CDSS.

Conflict of interest
The authors declare that they have no conflict of interest.

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Development of operationalized intravenous to oral antibiotic switch criteria

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Abstract

Objectives: Despite huge overlap in suggested criteria for a safe intravenous (iv) to oral antibiotic switch, there is considerable variation in their operationalization. The objective of this study was to develop a set of measurable conditions that should be met in adult hospitalized patients for a safe iv to oral switch.

Methods: A RAND-modified Delphi procedure was performed to develop a set of operationalized iv to oral switch criteria. Switch criteria and their accompanying suggested measurable conditions were extracted from the literature and appraised by a multidisciplinary expert panel during two questionnaire rounds with an in-between face to face meeting. In a final step, the experts could approve the set of developed operationalized switch criteria.

Results: Seven switch criteria and 41 accompanying measurable conditions extracted from the literature were appraised. Sixteen measurable conditions that operationalize six switch criteria were selected: (1) stable systolic blood pressure; and the absence of (2) fever, (3) under temperature, (4) malabsorption syndrome, (5) short bowel syndrome, (6) severe gastroparesis, (7) ileus, (8) continuous nasogastric suction, (9) vomiting, (10) (severe) sepsis, (11) fasciitis necroticans, (12) central nervous system infection, (13) Staphylococcus aureus bacteremia and (14) endovascular infection. In addition (15) the patient should be cooperative and (16) adequate antimicrobial concentration should be achievable at the site of infection by oral administration.

Conclusions: These operationalized criteria can be used in daily clinical practice. Future use of these criteria in audits and as rules in clinical decision support systems will facilitate the performance and evaluation of iv-oral switch programs.

Introduction

To optimize clinical outcome, while minimizing toxicity and to reduce costs and emergence of antimicrobial resistance, various stewardship interventions can be part of Antimicrobial Stewardship Programs (ASPs). The implementation of a program for early switch from intravenous (iv) to oral antibiotic therapy is one of these interventions [1-4].

Numerous studies have demonstrated the equal efficacy of an early iv to oral switch to a full course of iv therapy [5, 6]. This early switch has many advantages, such as reduced incidence of catheter-related infections, a decreased hospital length of stay and significant decreases in costs [4, 7, 8]. The iv to oral switch criteria that can be found in the literature mostly overlap. However, there is a considerable variation in their operationalization and they are often subjective [9-11]. Reaching consensus on the operationalization of the criteria for a safe switch to oral antibiotics is important to guide physicians involved in antibiotic prescribing and to achieve uniformity of switch practices in hospitals.

The aim of this study was to reach consensus on a set of iv to oral antibiotic switch criteria, and the measurable conditions that operationalize this set of switch criteria, that should be met in adult hospitalized patients for a safe switch after 48-72 h of iv therapy.

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Methods

Study design

A RAND-modified Delphi procedure was used to reach consensus among an international, multidisciplinary expert panel (for its composition: see the supplemental data and the acknowledgements) on a set of iv to oral antibiotic switch criteria and the measurable conditions that operationalize these criteria.

Literature search and expert consultation

First, a systematic literature search was performed using the following databases: Embase, Medline, Web of science, Scopus, Cochrane, PubMed and Google scholar. Only articles in the English language published after the year 2000 were included. For complete search strings see supplementary data (S3.1). Each article reporting on the development and appraisal of criteria for the iv to oral antibiotic switch published between January 2001 and September 2014 was individually evaluated by two reviewers. A list of unique iv to oral antibiotic switch criteria, with measurable conditions that operationalize these criteria, was extracted from the included studies. Before the Delphi procedure started the criteria

were presented to the experts to check whether we grouped the criteria appropriately and whether they agreed with the formulation of the criteria.

RAND-modified Delphi procedure – brief description

Using the information from the literature search the procedure included four steps. In *STEP 1*, the measurable conditions that operationalize iv to oral antibiotic switch criteria were included in a questionnaire. Experts were asked to appraise the relevance and safety of these measurable conditions on a 9 point Likert scale. Measurable conditions with a median score of 7, 8 or 9 were accepted if there was agreement. Agreement was defined as >70% of the scores in this top tertile (7, 8 or 9). If the median score was <7 the measurable condition was rejected. The measurable conditions with a median score of 7, 8 or 9 and disagreement (i.e. ≤70% of the scores in the top tertile) were discussed during the face to face meeting. During *STEP 2* the identified areas of disagreement were discussed at a face to face meeting. After reaching agreement on the measurable conditions, *STEP 3* followed to appraise the relevance of the iv to oral switch criteria using a questionnaire. The same consensus rules as described above were applied. In *STEP 4* the experts were asked to approve the final set of switch criteria and the measurable conditions that operationalize them (Figure 3.1). A complete description of the procedure can be found in the supplementary data (S3.2).

Results

Expert panel

The experts (n=19) were clinical microbiologists (n=6), infectious disease consultants (n=7) and clinical pharmacists (n=6) from the Netherlands, Belgium, USA and the UK.

Literature search and expert consultation

Our literature search resulted in 1,568 articles, of which 86 contained potential iv to oral antibiotic switch criteria (Figure S3.1). A list of eight unique iv to oral switch criteria was extracted from the included studies, with 41 measurable conditions. The experts suggested to rephrase the switch criterion 'an oral variant of the antibiotic has to exist' into 'an oral variant of the antibiotic with good bioavailability has to exist'. Furthermore the switch criteria 'clinical improvement should be observed' and 'signs and symptoms related to the infection have to be resolved or improved' were merged, because these criteria were believed to be similar, resulting in a final set of seven switch criteria (Table S3.1).
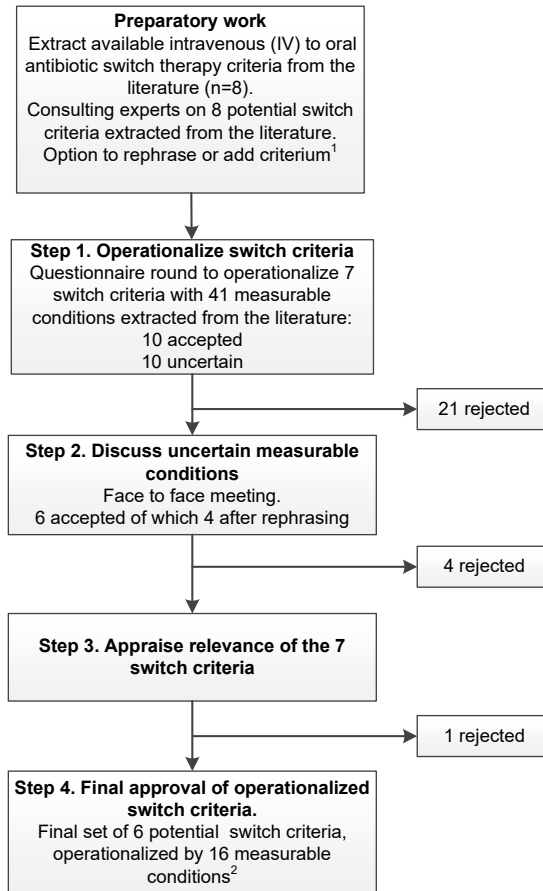
Figure 3.1. Steps in the RAND Delphi procedure.
1. Two criteria were rephrased, one duplicate criterion was removed, no criteria were added. **2.** One of the switch criteria is not operationalized, because no operationalization is found in the literature.

STEP 1 Questionnaire 1

Eighteen experts completed and returned the questionnaire (response rate 94.7%). Ten of the 41 measurable conditions were accepted and 21 were rejected. The experts achieved no agreement on 10 potential measurable conditions, which operationalize six different iv to oral antibiotic switch criteria. No new measurable conditions were suggested.

STEP 2 Face to face meeting

Nine experts attended the meeting. Four measurable conditions were rejected during this meeting and six measurable conditions were accepted, of which four were accepted after rephrasing (Table S3.1).

STEP 3 Questionnaire 2

Eighteen experts completed and returned the questionnaire (response rate 94.7%). Six of the seven iv to oral antibiotic switch criteria were accepted. No additional criteria were suggested.

STEP 4 Final approval

All experts (n=19) returned the document and approved the set of operationalized switch criteria (Table 3.1). The final set consisted of 16 measurable conditions: (1) Stable systolic blood pressure. Absence of: (2) fever, (3) under temperature, (4) malabsorption syndrome, (5) short bowel syndrome, (6) severe gastroparesis, (7) ileus, (8) continuous nasogastric suction, (9) vomiting, (10) (severe) sepsis, (11) fasciitis necroticans, (12) central nervous system infection, (13) Staphylococcus aureus bacteremia and (14) endovascular infection.

Table 3.1. Switch criteria, and operationalized criteria, that should all be met in adult hospitalized patients for a safe iv to oral switch

A. Vital signs should be good or improving.
    Systolic blood pressure should be stable without inotropics or fluid resuscitation.

B. Signs and symptoms related to the infection have to be resolved or improved.
    Temperature should be below 38.3℃[1] without antipyretics.
    Temperature should be >36℃.

C. The gastrointestinal tract (GIT) has to be intact and functioning.
    Absence of the following conditions:
      malabsorption syndrome;
      short bowel syndrome;
      severe gastroparesis;
      ileus;
      continuous nasogastric suction.

D. The oral route should not be compromised.
    No vomiting.
    Patient should be cooperative.

E. Absence of contra-indicated infections.
    Adequate antimicrobial concentrations are not achievable at the site of infection by oral administration.
    Absence of the following infections:
      (severe) sepsis;
      fasciitis necroticans;
      CNS infection;
      Staphylococcus aureus bacteremia;
      endovascular infection (e.g. endocarditis).

F. An oral variant[2] of the antibiotic with good[3] bioavailability has to exist.

[1] chosen by the experts
[2] oral variant can be another antibiotic with appropriate microbiological profile
[3] 60-90%, in accordance with the literature

In addition (15) the patient should be cooperative and (16) adequate antimicrobial concentration should be achievable at the site of infection by oral administration.

Discussion

With this study, using a RAND modified Delphi procedure, we developed a set of operationalized iv to oral antibiotic switch criteria that all have to be met in adult hospitalized patients for a safe switch after 48-72 hours of iv therapy. These operationalized criteria can be used in daily clinical practice, by antibiotic stewardship teams and by attending physicians. Additionally, they may facilitate auditing iv to oral antibiotic switch practices on a specific ward or hospital, and enable comparisons between hospitals or regions.

Since iv to oral switch is one of the most cost-effective stewardship interventions, several iv to oral antibiotic switch programs are being used and implemented in hospitals [9]. In addition, the switch from iv to oral is one of the recently developed structure and process indicators that characterize ASPs among different countries and healthcare systems [12]. However, although early iv to oral switch has been advocated for many years, uptake has been difficult at both the national and individual level [13]. A recommendation for national uptake is that a consensus document with switch criteria should be developed with involvement of stakeholders [14]. Our criteria were defined by national and international experts from involved medical disciplines, which are the key stakeholders for such a consensus.

The present study has several strengths. First, a RAND modified Delphi procedure was used, in which a systematic literature search and input from an international multidisciplinary expert panel were combined [15]. This study design enabled us to include experts of different regions and areas of expertise semi-anonymously, so that domination by powerful individuals was avoided in the questionnaire rounds. Clinical microbiologists, infectious diseases consultants and clinical pharmacists from both teaching and non-teaching hospitals participated in the study. Given the high response rate in all study rounds, we were able to include various relevant perspectives, which we believe strengthened the results of our study.

Our study also has limitations that should be mentioned. Not all experts could attend the face to face meeting and all experts who joined this meeting were from the Netherlands. However, all disciplines and hospital types were represented during this meeting. We also asked all experts for approval of the final set of operationalized switch criteria and for any final remarks. Considering the 100% response and approval rate, we believe that the fact that not all experts could attend the face to face meeting did not influence the validity or reliability of our study results.

The developed measurable conditions are a first step to standardized iv to oral switch criteria. However, to improve antibiotic use in an effective and sustainable manner, more is needed than only guidelines and instructions [16]. Electronic reminders generated by a clinical decision support system (CDSS) are believed to have a great potential to facilitate a timely iv to oral switch [3, 17-19]. The specific and general applicable criteria we developed offer the opportunity to develop a general applicable CDSS to remind physicians of switching from iv to oral therapy.

In conclusion, with a RAND modified Delphi procedure we developed a set of six iv to oral antibiotic switch criteria operationalized by 16 measurable conditions. These operationalized criteria have to be all met in adult hospitalized patients for a safe switch after 48-72 hours of iv therapy.

Transparency declarations

All authors: no conflict.

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Supplementary data

Table S3.1. Results of the Delphi study: 1st questionnaire, face to face meeting and 2nd questionnaire

Iv to oral switch criteria	1st questionnaire Median	% in top tertile	Conclusion	Face to face meeting	2nd questionnaire Median	% in top tertile	Conclusion
I. Vital signs have to be stable							
1. Heart rate should be below a certain beats per minute	5	16.67	Rejected				
2. No need for intravenous fluid administration	5.5	33.33	Rejected				
3. Respiratory rate should be below a certain breaths/minute	6	33.33	Rejected				
4. An improved oxygenation towards normal (for this patient)	7	55.56	Uncertain	Rejected			
5. Systolic blood pressure should return towards normal (for this patient)	7	66.67	Uncertain	Rephrased into number 5a			
5a. Systolic blood pressure should be stable without inotropics or fluid resuscitation				Result from rephrasing number 5	8	87.50	Accepted
6. Mental status should return towards normal (for this patient)	7	66.67	Uncertain	Rejected			
II. Signs and symptoms related to the infection have to be resolved or improved							
7. Temperature should be below a certain threshold (without Paracetamol)	7	27.78	Uncertain	Rephrased into number 7a			
7a. Temperature should be below 38.3°C * without antipyretics * this threshold is chosen by the experts				Result from rephrasing number 7	7	75.00	Accepted
8. Temperature should be > 36°C	7	50.00	Uncertain	Accepted			
9. The white cell count should be normalized	4.5	27.78	Rejected				
11. C-reactive protein (CRP) serum level should be <100 mg/L	5	22.22	Rejected				
12. If CRP was >10 mg/L, the level should have decreased at least 20% in the last 48 hours	5.5	44.44	Rejected				

Table S3.1 continues on next page.

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Table S3.1. *Continued*

Iv to oral switch criteria	1st questionnaire			Face to face meeting	2nd questionnaire		
	Median	% in top tertile	Conclusion		Median	% in top tertile	Conclusion
III. There should be no immunosuppression					4	12.50	Rejected
13. No uncontrolled diabetes mellitus	4	0.00	Rejected				
14. No kidney failure (Se-creatinine >300 μmol/L)	3	0.00	Rejected				
15. No hematological conditions, such as lymphoma and myeloma	3	11.11	Rejected				
16. No severe neutropenia (absolute neutrophil count <0.5 x *10⁹/L)	7	61.11	Uncertain	Rejected			
17. No use of immunosuppressive biologicals (like tumor necrosis factor inhibitors)	5	27.78	Rejected				
18. No use of prednisolone >10 mg/day or equivalent	4	11.11	Rejected				
19. Absence of HIV/AIDS	3.5	16.67	Rejected				
20. Absence of cystic fibrosis	3	11.11	Rejected				
21. Absence of asplenia	4	16.67	Rejected				
22. No organ transplantation	4	16.67	Rejected				
IV. The gastrointestinal (GI) tract has to be intact and functioning					8	87.50	Accepted
22. Absence of malabsorption syndrome	9	83.33	Accepted				
23. Absence of motility disorder	7	61.11	Uncertain	Rephrased into number 23a			
23a. Absence of severe gastroparesis				Result from rephrasing number 23			
24. Absence of short bowel syndrome	7.5	72.22	Accepted				
25. Absence of ileus	9	100.00	Accepted				
26. Absence of continuous nasogastric suction	7	77.78	Accepted				
27. Absence of diarrhea	5	22.22	Rejected				

|		Median	%	Result	Notes
V.	**The oral route should not be compromised**	8	87.50	Accepted	
28.	No vomiting	9	88.89	Accepted	
29.	No nausea	5	33.33	Rejected	
30.	No 'Nil by mouth'	6.5	44.44	Rejected	
31.	No swallowing disorder	6	38.89	Rejected	
32.	Not unconscious	7.5	55.56	Uncertain	Rejected
33.	Not uncooperative	7	55.56	Uncertain	Accepted
VI.	**There should be no contra-indicated infections**	8	87.50	Accepted	
34.	Optimal antimicrobial concentrations are not achievable at the site of infection by oral administration (for example undrained abscesses and meningitis)	9	100.00	Accepted	
35.	Absence of severe sepsis	9	94.44	Accepted	
36.	Absence of severe soft tissue infection	7	61.11	Uncertain	Rephrased into number 36a
36a.	Absence of fasciitis necroticans				Result from rephrasing number 36
37.	Absence of osteomyelitis	5	33.33	Rejected	
38.	Absence of septic arthritis	6	38.89	Rejected	
39.	Absence of CNS infection	9	100.00	Accepted	
40.	Absence of Staphylococcus aureus bacteremia	9	77.78	Accepted	
41.	Absence of endovascular infection	8	83.33	Accepted	
VII.	**An oral variant of the antibiotic with good bioavailability has to exist**	8	87.50	Accepted	

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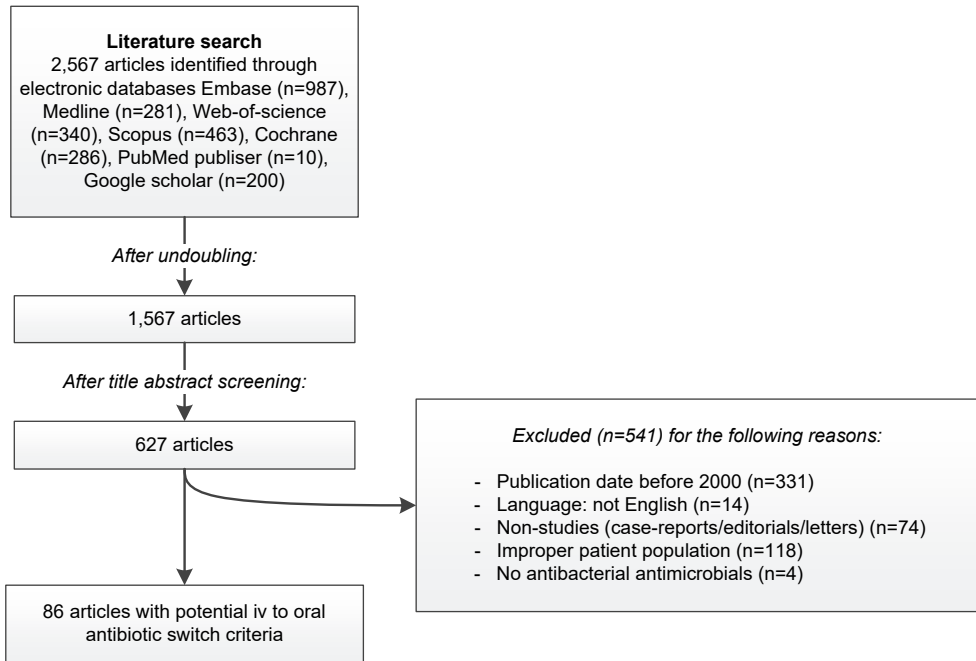
Figure S3.1. Flowchart literature search to identify available criteria and measurable conditions for an iv to oral antibiotic switch.

S3.1. Systematic literature search

Search strings

Embase.com

('antibiotic agent'/exp OR 'antiinfective agent'/de OR 'antibiotic therapy'/de OR 'antimicrobial therapy'/de OR (antibiotic* OR antibacter* OR antiinfect* OR antimicrob* OR (anti NEXT/1 (biotic* OR bacter* OR infect* OR microb*)) OR abyssomicin OR acetomycin OR actinorhodine OR aditoprim OR agglomerin OR alafosfalin OR aldecalmycin OR alisamycin OR allicin OR ambruticin OR angucycline OR ansamitocin OR ansamycin OR aplasmomycin OR aristeromycin OR asukamycin OR atpenin OR auricularum OR aurograb OR avilamycin OR bafilomycin OR baliz OR baquiloprim OR beroline OR betafectin OR betamipron OR boromycin OR borrelidin OR brilacidin OR butalactin OR cadazolid OR calcimycin OR carbadox OR chloramphenicol OR ciadox OR cinoquidox OR citrinin OR concanamycin OR coumamycin OR coumamycin OR cryptosporin OR cycloheximide OR dalfopristin OR dealanylalahopcin OR dioxidine OR echinomycin OR edeine OR efepristin OR emimycin OR endusamycin OR eperezolid OR epiderstatin OR epiroprim OR ethylhydrocupreine OR evernimicin OR everninomicin OR flopristin OR fosmidomycin OR furaquinocin OR furazidin OR furazolium OR fusafungine OR fusidate OR 'fusidic acid' OR grisein OR hatomamicin OR hedamycin OR heliomycin OR hidamicin OR iclaprim OR ikarugamycin OR inostamycin OR kalafungin OR kelfiprim OR kidamycin OR kinamycin OR lactacystin OR lactivicin OR laidlomycin OR lasalocid OR lavanducyanin OR lefamulin OR linezolid OR linopristin OR lonomycin OR lotilibcin OR lydicamycin OR lysocellin OR macrolide OR malyngolide OR manumycin OR methylenomycin OR mikamycin OR monensin OR mureidomycin OR mycolog OR myxothiazol OR narasin OR negamycin OR nybomycin OR olaquindox OR paldimycin OR patulin OR pentalenolactone OR platensimycin OR pleuromutilin OR pluramycin OR polyactin OR polyfungin OR posizolid OR pristinamycin OR prothracarcin OR 'pseudomonic acid' OR pyrroxamycin OR quinomycin OR quinupristin OR radezolid OR radicicol OR ranbezolid OR retapamulin OR simaomicin OR simocyclinone OR spectinomycin OR squalamine OR streptogramin OR streptovitacin OR tedizolid OR terdecamycin OR tetracycline OR tetronasin OR tetronomycin OR tetroxoprim OR thiolactomycin OR tibezonium OR tizoxanide OR toyocamycin OR 'trichostatic acid' OR trichostatin OR trimethoprim OR triostin OR trospectomycin OR tuftsin OR tutofusin OR urdamycin OR validamycin OR valnemulin OR vernamycin OR 'virginiae butanolide' OR virginiamycin OR volpristin OR 'zibrofusidic acid' OR zorbamycin):ab,ti) AND ('intravenous drug administration'/exp OR intraven*:lnk OR (intraven* OR iv OR 'i v'):ab,ti) AND ('oral drug administration'/exp OR oral:lnk OR

'enteral drug administration'/exp OR enteral:lnk OR 'buccal drug administration'/exp OR (oral OR 'p o' OR 'per os' OR po OR enteral OR buccal OR sublingual OR sublabial OR supralingual):ab,ti) AND ('to oral' 'to po' OR 'to p o' OR 'from intravenous' OR 'from iv' OR 'from i v' OR switch* OR conver* OR transition* OR stepdown* OR step-down OR shift*):ab,ti AND (time/de OR 'decision making'/exp OR 'clinical decision making'/de OR 'practice guideline'/de OR checklist/exp OR model/exp OR 'decision tree'/de OR 'decision support system'/de OR 'health care policy'/de OR 'clinical assessment'/de OR 'clinical assessment tool'/de OR 'hospital policy'/de OR 'treatment planning'/de OR (decision* OR decide* OR timing OR criteri* OR checklist* OR guideline* OR protocol* OR model OR polic* OR strateg* OR planning* OR (clinical* NEAR/3 assess*) OR tool* OR barrier* OR facilitator*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP)

(exp "Anti-Bacterial Agents"/ OR "Anti-Infective Agents"/ OR (antibiotic* OR antibacter* OR antiinfect* OR antimicrob* OR (anti ADJ (biotic* OR bacter* OR infect* OR microb*)) OR abyssomicin OR acetomycin OR actinorhodine OR aditoprim OR agglomerin OR alafosfalin OR aldecalmycin OR alisamycin OR allicin OR ambruticin OR angucycline OR ansamitocin OR ansamycin OR aplasmomycin OR aristeromycin OR asukamycin OR atpenin OR auricularum OR aurograb OR avilamycin OR bafilomycin OR baliz OR baquiloprim OR beroline OR betafectin OR betamipron OR boromycin OR borrelidin OR brilacidin OR butalactin OR cadazolid OR calcimycin OR carbadox OR chloramphenicol OR ciadox OR cinoquidox OR citrinin OR concanamycin OR coumamycin OR coumamycin OR cryptosporin OR cycloheximide OR dalfopristin OR dealanylalahopcin OR dioxidine OR echinomycin OR edeine OR efepristin OR emimycin OR endusamycin OR eperezolid OR epiderstatin OR epiroprim OR ethylhydrocupreine OR evernimicin OR everninomicin OR flopristin OR fosmidomycin OR furaquinocin OR furazidin OR furazolium OR fusafungine OR fusidate OR "fusidic acid" OR grisein OR hatomamicin OR hedamycin OR heliomycin OR hidamicin OR iclaprim OR ikarugamycin OR inostamycin OR kalafungin OR kelfiprim OR kidamycin OR kinamycin OR lactacystin OR lactivicin OR laidlomycin OR lasalocid OR lavanducyanin OR lefamulin OR linezolid OR linopristin OR lonomycin OR lotilibcin OR lydicamycin OR lysocellin OR macrolide OR malyngolide OR manumycin OR methylenomycin OR mikamycin OR monensin OR mureidomycin OR mycolog OR myxothiazol OR narasin OR negamycin OR nybomycin OR olaquindox OR paldimycin OR patulin OR pentalenolactone OR platensimycin OR pleuromutilin OR pluramycin OR polyactin OR polyfungin OR posizolid OR pristinamycin OR prothracarcin OR "pseudomonic acid" OR pyrroxamycin OR quinomycin OR quinupristin OR radezolid OR radicicol OR ranbezolid OR retapamulin OR simaomicin OR simocyclinone OR

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S3.2. RAND-modified Delphi procedure – complete description

Study design

A RAND-modified Delphi technique was used to reach consensus on a set of iv to oral antibiotic switch criteria and the measurable conditions that operationalize these criteria. In this study first a systematic literature search was performed. Using the information from the literature, the Delphi process included four steps: a first step to operationalize the iv to oral antibiotic switch criteria, a second step to discuss the areas of disagreement identified during the first step, a third step to appraise the relevance of the iv to oral switch criteria and a final step to approve the final set of operationalized switch criteria.

Expert panel selection

We invited 33 experts by e-mail to participate in this study. Experts were clinicians who have published in the field of antibiotic therapy and clinicians with expertise in iv to oral antibiotic switch, identified through our systematic literature or recommended by other experts. Other selection criteria that were used were geographic diversity, diversity of practice setting (teaching and non-teaching hospitals) and discipline (clinical microbiologists, infectious diseases consultants and clinical pharmacists were selected).

RAND-modified Delphi procedure

STEP 1 Questionnaire 1

The first questionnaire, sent by e-mail to all experts, aimed to operationalize the iv to oral antibiotic switch criteria. The operationalizations for each of the switch criteria were presented as measurable conditions, including threshold values, that could be used in clinical practice to check whether the patient fulfills these criteria. We asked the experts to appraise the relevance of the measurable conditions on a 9 point Likert scale (1= not relevant, 9= very relevant), while considering the following questions:

- Is the condition alone or in combination clinically relevant?
- Do these conditions apply to all hospitalized adult patients treated with intravenous antibacterial drug therapy?
- Does the measurable condition alone or in combination have to be minimally achieved in a patient to fulfill the switch criterion in question so that (regarding this specific criterion) a safe switch is warranted?

They were also given the answer option 'I don't know'.

The experts could rephrase the measurable conditions (e.g. by adapting the suggested threshold values) and they could add measurable conditions.

Consensus rules

Measurable conditions with a median score of 7, 8 or 9 were accepted if there was agreement. Agreement was defined as >70% of the scores in this top tertile (7, 8 or 9). If the median score was <7 the measurable condition was rejected. The measurable conditions with a median score of 7, 8 or 9 and disagreement (i.e. ≤70% of the scores in the top tertile) were discussed during the face to face meeting.

STEP 2 Face to face meeting

All experts were invited to a face to face meeting to discuss the measurable conditions with disagreement identified in the first questionnaire round with the aim to achieve consensus on these areas. The measurable conditions which operationalize the iv to oral switch criteria with a median score of 7, 8 or 9 with disagreement were discussed during this meeting. The discussion resulted in acceptance of the measurable condition, acceptance after rephrasing, or rejection.

STEP 3 Questionnaire 2

After defining the operationalization of the iv to oral switch criteria, the experts were asked to appraise the relevance of the iv to oral switch criteria in the decision to safely switch from iv to an oral antibiotic on a 9 point Likert scale. This was done by e-mail. The same consensus rules as described above were applied.

STEP 4 Final approval

A final list was composed with the set of general applicable iv to oral antibiotic switch criteria, which are operationalized by measurable conditions. This final list was sent by e-mail to all of the experts, to ask them for approval and to give the experts the opportunity to make any final remarks.

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A clinical decision support system algorithm for intravenous to oral antibiotic switch therapy: validity, clinical relevance and usefulness in a three-step evaluation study

H. Akhloufi | M. Hulscher | C.P. van der Hoeven |
J.M. Prins | H. van der Sijs | D.C. Melles | A. Verbon

Abstract

Objectives: To evaluate a clinical decision support system (CDSS), based on consensus-based intravenous to oral switch (IVOS) criteria, which identifies IVOS candidates.

Methods: A three-step evaluation study of a stand-alone CDSS with electronic health record interoperability was performed at the Erasmus University Medical Centre in the Netherlands. During the first step, we performed a technical validation. During the second step, we determined the sensitivity, specificity, negative (NPV) and positive predictive value (PPV) in a retrospective cohort of all hospitalized adult patients starting at least one therapeutic antibacterial drug between 1 and 16 May 2013. ICU, paediatric and psychiatric wards were excluded. During the last step the clinical relevance and usefulness was prospectively assessed by reports to infectious disease specialists. An alert was considered clinically relevant if antibiotics could be discontinued or switched to oral therapy at the time of the alert.

Results: During the first step one technical error was found. The second step yielded a PPV of 76.6% and a NPV of 99.1%. The third step showed that alerts were clinically relevant in 53.5% of patients. For 43.4% it had already been decided to discontinue or switch the intravenous antibiotics by the treating physician. In 10.1%, the alert resulted in an advice to change antibiotic policy and was considered useful.

Conclusions: The prospective cohort study shows that the alerts were clinically relevant in more than 50% (n=449), and useful in 10% (n=85). The CDSS needs to be evaluated in hospitals with varying activity of ID consultancy services as this probably influences usefulness.

Introduction

One of the most cost-effective and safe objectives of a hospital antimicrobial stewardship program is the timely switch from intravenous (iv) to oral antibiotic therapy [1]. A timely iv to oral switch (IVOS) has many advantages, such as reduced incidence of catheter-related infections and a decreased hospital length of stay [1-3]. However, up to two third of patients eligible for an IVOS remain on iv antibiotics longer than necessary [4-6]. A possible explanation is that reassessment of iv started antibiotics is often not done, for instance due to time constraints and change of staff [7]. In addition, different IVOS criteria are being used to determine whether a patient can be switched from iv to oral antibiotic therapy [8]. To address the latter issue, an international Delphi procedure was recently performed to reach consensus among international experts on a set of IVOS criteria that have to be met in adult hospitalized patients for a safe IVOS after 48-72 h of iv therapy [9]. This resulted in the development of six IVOS switch criteria, operationalized by 16 measurable conditions. For example the IVOS switch criterion 'Signs and symptoms related to the infection have to be resolved or improved' is operationalized by the following two measurable conditions: temperature should be below 38.3°C without antipyretics and above 36°C (Table 4.1).

These operationalized consensus criteria are a first step towards standardized IVOS criteria. However, to improve appropriate antibiotic use in an effective and sustainable manner, more is needed than guidance and instructions [10]. A promising stewardship intervention to facilitate a timely IVOS is a clinical decision support system (CDSS) that automatically generates reminding alerts [11, 12]. Earlier studies on CDSS have shown that an important pitfall, which can impede the success of a CDSS, is alert fatigue. To prevent alert fatigue a well-designed CDSS with a high specificity and sensitivity is crucial.

We developed such a CDSS algorithm that is based on the operationalized consensus criteria for IVOS [9]. In this study, we validated this CDSS algorithm, and assessed its clinical relevance and usefulness in daily clinical practice.

Materials and methods

Setting

This study was conducted at the Erasmus University Medical Centre (Erasmus MC) in Rotterdam, the Netherlands, a 1,237 bed tertiary care center. The Erasmus MC uses an electronic health record (EHR) with integrated computerized prescriber order entry (CPOE). This system integrates patient data, medication prescriptions, laboratory data,

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surgical reports and radiology reports. The Department of Medical Microbiology and Infectious Diseases of this hospital provides an active infectious disease (ID) consultancy service, in which ID consultants actively give the attending physicians antibiotic advices. They are also being consulted for antibiotic advice in nearly half of the patients using antibiotic therapy [13].

Study population

The study population for the technical and the retrospective clinical validation was extracted from the CPOE and consisted of all hospitalized adult patients starting at least one antibacterial drug (ATC code J01) between 1 and 16 May 2013. Adult ICU patients were included and patients on the cardiothoracic ICU and the paediatric and psychiatric wards were excluded. Patients using prophylactic antibiotics were also excluded. Cotrimoxazole at a maximum daily dose of 480 mg and cefazolin given once were always considered prophylaxis. Antibiotics given according to a local prophylaxis protocol were also defined as prophylaxis. This was assessed manually. The same criteria were used for the prospective study.

IVOS algorithm

A multidisciplinary team, consisting of an ID specialist, clinical microbiologists, hospital pharmacist experienced in decision support, Information Technology (IT) team and a researcher developed the CDSS algorithm. The consensus-based and operationalized criteria [9] were translated into a computer-interpretable format. All adult hospitalized patients with at least one iv antibiotic prescription for a duration of at least 84 h were selected by the algorithm. This relatively long time period was chosen because we wanted to evaluate the contribution of the CDSS on top of usual (switch) care. An alert indicating that the patient could be safely switched was generated when the conditions described in Table 4.1 were met. A report with all patients with an alert was automatically generated on a daily basis and directed to the ID specialist of the Antibiotic Stewardship Team. Criterion E '*Absence of contra-indicated infections*' could not be translated into the CDSS algorithm. The same applied to criterion F '*An oral variant of the antibiotic with good bioavailability has to exist, including other antibiotics with appropriate microbiological profile*'. These criteria were left to the discretion of the ID specialist. An overview of the included antipyretics (used to assess criterion B), inotropics and fluid resuscitation (used to assess criterion A) can be found in Table S4.1 and Table S4.2.

Validation strategy

A validation strategy developed by Scheepers et al., which we modified, was used [14]. The development and validation strategy developed by Scheepers et al. consists of four steps. The first step is a retrospective technical validation to confirm that the used CDSS parameters are correctly linked to the data in the EHR. During the second step, all alerts are assessed for clinical relevance, actionability and usefulness by an expert team. In step 3 the CDSS is adjusted to assure prospective correct alerts in daily clinical practice. The fourth step is to optimize suitability of the CDSS in practice, which is done by continuous technical and therapeutic maintenance after implementation. In our study, the fourth step was left out.

Technical validation

The technical validation of the CDSS algorithm was performed to check whether the CDSS algorithm creates technically valid definitions. This was done by assessing if the parameters in the algorithm were correctly linked to the correct parameters in our EHR. For example, for the algorithm rule 'systolic blood pressure should be stable without inotropics or fluid resuscitation', it was checked if the correct EHR data (the systolic blood pressure in our EHR for this patient on the day of assessment by the CDSS) were transferred to the algorithm for a correct interpretation of the systolic blood pressure. We also checked for this algorithm rule whether the correct inotropics or fluid resuscitation were transferred and if alerts were suppressed in case of a predefined dose (see Table S4.2 for these inotropics and fluid resuscitation and doses). For the algorithm rule 'temperature should be below 38.1°C for a duration of 24 h (notification when antipyretics are used)' and 'temperature should be above 36°C for a duration of 24 h, it was checked if the correct temperature from our EHR was transferred to the algorithm and if the duration of 24 h was correctly applied by the algorithm rule. We also checked if the correct antipyretics were transferred and if a notification was generated if the daily dose exceeded a predefined dose (see Table S4.1). For the algorithm rule 'patient uses oral medication or no systemic medication at all' we checked if the data in our EHR regarding the medication of patients and route of administration were correctly transferred to the algorithm. We also checked if the alerts were suppressed in case of total parenteral nutrition use. For the algorithm rule 'alert suppressed in case of Staphylococcus aureus bacteremia' we checked if the data in our EHR regarding S. aureus bacteremia were correctly transferred.

Retrospective clinical validation

All alerts generated by the IVOS algorithm were assessed for clinical relevance, actionability, and usefulness. An alert was clinical relevant if the patient was able to switch from iv to oral

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antibiotic therapy (fulfilled Delphi switch criteria A-E (Table 4.1). By chart review, two reviewers (H.A. and T.M.) determined which patients should have been switched, using the IVOS criteria mentioned in Table 4.1 as the gold standard. Discrepancies between the generated alerts and the gold standard were analyzed, discussed with a third reviewer (A.V.) and if needed small modifications to the CDSS algorithm were made (for example no suppression of alert, but a notification, when antipyretics are used).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used to express the quality of the CDSS algorithm, using the consensus-based and operationalized IVOS criteria (Table 4.1) as the gold standard. The sensitivity was calculated by dividing the number of patients that were able to switch from iv to oral antibiotic therapy (fulfilled Delphi switch criteria A-E, Table 4.1) identified by the IVOS algorithm (the true positives) by the total number of patients that were able to switch from iv to oral antibiotic therapy. The specificity was calculated by dividing the number of patients that were not able to switch from iv to oral antibiotic therapy for which no alert is generated (the true negatives) by the IVOS algorithm by the total number of patients that were not able to switch from iv to oral antibiotic therapy. The PPV was calculated by dividing the number of true positives by the total number of alerts. The NPV was calculated by dividing the number of true negatives by the total number of patients without alerts.

An alert was actionable if an oral variant of the antibiotic with good bioavailability existed, including other antibiotics with appropriate microbiological profile (fulfilled Delphi switch criteria A-F (Table 4.1).

Alerts were useful if they were both clinical relevant and actionable. We also assessed how many patients for which the alerts were useful had been switched to oral antibiotic therapy within 24 hours after fulfilling the Delphi switch criteria for the first time.

Prospective evaluation of usefulness in daily practice

We then implemented the CDSS algorithm in daily clinical practice, linking the algorithm to the database of our EHR. Each day the CDSS algorithm generated a report with patients fulfilling the switch criteria. This report was automatically sent to the ID specialist of the Antibiotic Stewardship Team. The ID specialist then assessed whether the patient could switch to oral therapy and contacted the treating physician if this was possible. The ID specialist noted the performed action in the system by categorizing the alert in the system. The categories that could be selected were: 1. no action. 2. antibiotic had already been discontinued or switched to oral therapy. 3. new advice given. The main category 'no action' includes the following categories: advice would not change policy; patient died; not possible

yet to switch to oral antibiotic. This category was considered not clinically relevant. The second main category includes the following categories: patient will soon be or has just been switched to oral antibiotic; and antibiotic discontinued or discontinuation scheduled at short notice. This category was considered clinically relevant. The main category 'new advice given' includes the following categories: new advice given; advice to discontinue antibiotic; advice to switch from iv to oral antibiotic; and advice to change antibiotic to a smaller spectrum. This category was considered clinically relevant and useful.

We then assessed the clinical relevance and usefulness of the CDSS algorithm in clinical practice during the implementation period January until April 2017.

Results

Technical validation

The retrospective study population consisted of 200 adult hospitalized patients using antibiotics during the 2-week study period. The median age of these patients was 61 years (interquartile range: 26) and 45% were female. The parameters in the CDSS algorithm were linked to the correct parameters in the EHR in 99.5% of the cases. One case was considered technically incorrect because the algorithm identified the patient as a suitable candidate for switching while fluid resuscitation was being prescribed. The NaCl infusion 1000 mL formulation used for resuscitation was not included in the original CDSS algorithm. This was included in the CDSS redesign.

Retrospective clinical validation

The algorithm generated a switch alert for 72 of the 73 patients that could have been switched according to the consensus-based switch criteria A-E [9] (Table 4.1), resulting in a sensitivity of 98.6%. Of the 127 patients that should not be switched according to the gold standard, the CDSS algorithm generated an alert in 22 patients, resulting in a specificity of 82.7%. The false positive alerts were mainly caused by presence of an infection considered a contra-indication for switching, such as central nervous system infection, endocarditis, empyema or sepsis. These patients could not be identified with the CDSS algorithm, because criterion E could not be translated into a computer interpretable format in this EHR. Overall the CDSS algorithm had a NPV of 99.1% and a PPV of 76.6%. Sixty of the 73 patients eligible for IVOS received an antibiotic for which an oral variant was available. Ten patients could not be switched at the moment of the alert because no oral variant, including other antibiotics with appropriate microbiological profile, were available. These

patients could not be identified with the CDSS algorithm, because criterion F could not be translated into a computer interpretable format. Three patients could not be switched because the gastrointestinal tract was not functioning properly, these patients were not identified with IVOS algorithm criterion C (Table 4.1). Thus, 73 of the 200 patients should

Table 4.1. Clinical rule iv oral antibiotic switch based on operationalized and consensus based switch criteria [9]

Iv oral antibiotic switch criteria	IVOS algorithm
A. Vital signs should be good or improving when bad	
Systolic blood pressure should be stable without inotropics or fluid resuscitation	Systolic blood pressure >90 mmHg (alert suppressed if inotropics or fluid resuscitation is used)
B. Signs and symptoms related to the infection have to be resolved or improved	
Temperature should be below 38.3℃ without antipyretics	Temperature below 38.1℃ for a duration of 24 h (notification when antipyretics are used)
Temperature should be >36℃	Temperature above 36℃ for a duration of 24 h
C. The gastrointestinal tract (GIT) has to be intact and functioning	Patient uses oral medication or no systemic medication at all (alert suppressed in case of total parenteral nutrition use)
Absence of the following conditions:	
malabsorption syndrome	
short bowel syndrome	
severe gastroparesis	
ileus	
continuous nasogastric suction	
D. The oral route should not be compromised	Patient uses oral medication or no systemic medication at all (alert suppressed in case of total parenteral nutrition use)
No vomiting	
Patient should be cooperative	
E. Absence of contra-indicated infections	Not possible to translate into a computer interpretable format[a]
Adequate antimicrobial concentrations are not achievable at the site of infection by oral administration	
Absence of the following infections:	
(severe) sepsis	
fasciitis necroticans	
CNS infection	
Staphylococcus aureus bacteremia	Alert suppressed in case of S. aureus bacteraemia
endovascular infection (e.g. endocarditis)	Not possible to translate into a computer interpretable format[a]
F. An oral variant of the antibiotic with good bioavailability has to exist, including other antibiotics with appropriate microbiological profile	Not possible to translate into a computer interpretable format[a]

[a] Except for S. aureus bacteraemia, which was assessed by the algorithm. Assessment of criteria which could not be translated into a computer interpretable format was left to the discretion of the ID specialist.

have been switched to oral antibiotic therapy based on the Delphi criteria and for 60 of these patients a suitable oral alternative antibiotic was available.

Eighty-five percent (51/60) of the patients that could have been switched to oral antibiotic therapy were not switched within 24 hours after fulfilling the Delphi switch criteria for the first time.

Prospective evaluation of usefulness in daily practice

The CDSS algorithm generated 840 IVOS alerts for 840 prescriptions in 773 different patients during the period of January until April 2017. In 379 of the alerts (45%) the ID specialist had already been consulted prior to the alert. For 391 prescriptions (46.5%) an alert was generated that would not change the antibiotic policy, for example because of presence of sepsis (Table 4.2). These sepsis patients could not be identified with the CDSS algorithm, because criterion E could not be translated into a computer interpretable format. 449 (364+85) alerts (53.5%) were clinically relevant. In 364 of these clinical relevant alerts the iv antibiotic had just been discontinued or switched to oral therapy. Despite a very active ID consultancy service and the (relatively late) generation of an alert, 84 h after start of therapy, the IVOS alert resulted in an advice to change the antibiotic policy in 85 (10.1%) prescriptions. These advices varied from switching to stopping or changing antibiotics.

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Table 4.2. Actions following the alerts[a] in clinical practice

Categories	Already in consultation[b]	Consultation not needed	New consultation	Total
No action: advice would not change the antibiotic policy	257	134	N/A	391 (46.5%)
Antibiotic had already been discontinued or switched to oral therapy (clinically relevant)	70	293	1	364 (43.3%)
New advice given (clinically relevant and useful)	52	1	32	85 (10.1%)
Total	379	428	33	840 (100%)

[a] Alerts were given 84 h after start of iv antibiotics to the Antibiotic Stewardship Team
[b] Consultation by the ID consultancy service

Discussion

In this study we validated a CDSS algorithm, which generates reports with IVOS candidates directed to the ID specialist of the Antibiotic Stewardship Team and assessed its usefulness in daily clinical practice. In the retrospective validation cohort (n=200), the CDSS algorithm

had a sensitivity of 98.6%, and a specificity of 82.7% compared to the gold standard of the Delphi switch criteria [9]. This resulted in a PPV of 76.6% and a NPV of 99.1%. These results indicate that the CDSS algorithm is a valid instrument to identify IVOS candidates.

In the prospective clinical cohort, 85/840 alerts (10.1%) were considered both clinical relevant and useful, and resulted in an antibiotic advice. Of the 840 alerts, 364 (43.4%) were clinically relevant, but antibiotics were already switched or discontinued by the treating physician or this was scheduled at short notice. This may be explained by the fact that the CDSS alerts were generated 84 h after start of the iv antibiotics. This relatively long time period was chosen to evaluate the contribution of the CDSS on top of usual (switch) care. With a shorter interval to the alert or in a setting with a less active ID service these clinically relevant alerts might also be potentially useful.

The use of a CDSS to facilitate appropriate antibiotic use, such as a timely IVOS, is being recommended [15]. Various other interventions to facilitate a timely switch have been assessed, such as education and the introduction of IVOS guidelines [6]. These strategies have shown to be successful in decreasing the use of iv antibiotics. CDSSs have the advantage of not being dependent on the attending physician. Because misconceptions about efficacy of oral antibiotic treatment can lead to unnecessary prolonged use of intravenous antibiotics [16, 17], educational strategies remain important. Educational messages could be incorporated into the CDSS or communicated by the ID specialist.

Our CDSS is the first IVOS CDSS based on IVOS criteria for which consensus was reached within an international, qualified selected expert panel. A standardized identification of IVOS candidates is valuable, because there exists a wide variation in the criteria that physicians use to determine if a patient is able to switch to oral antibiotics [8, 18, 19]. Other reported IVOS CDSS algorithms used local criteria [20, 21], or used very general rules, such as a certain duration of iv therapy or/and an active order for scheduled oral medications or an oral diet [18, 22]. Of the 840 alerts, 391 (46.5%) generated by our CDSS were not clinically relevant and therefore had no consequences for the antibiotic policy. An explanation for this is that not all Delphi IVOS switch criteria could be translated into the CDSS, because only coded or numerical data can be effectively used in a CDSS format. Assessment of criteria such as presence of an intravascular focus or sepsis, which could not be translated into the CDSS, was left to the discretion of the ID specialist. Because over-alerting may cause alert-fatigue the further improvement of the CDSS is important. With advanced coding of data in EHR the efficacy of the CDSS can be improved, thereby also reducing this risk of alert-fatigue.

To our knowledge only the study of Lammers et al. used the same validation strategy to validate their IVOS CDSS algorithm [14, 23]. They found a comparable percentage of

parameters in their CDSS algorithm which were linked to the correct parameters in the EHR (98.9%) and in their retrospective study a similar PPV (82.1%) was found. In our retrospective validation cohort, 85% (51/60) of the patients that could have been switched to oral antibiotic therapy remained on iv therapy for at least 24 h after fulfilling the switch criteria. This is a higher percentage compared to other studies, reporting that 38.6%-73.9% of patients that are eligible for an early IVOS remained on iv antibiotics longer than necessary [4-6]. Possible explanations for this difference are a retrospective versus prospective setting, the used IVOS criteria, time after which IVOS had to take place, implemented IVOS interventions and included departments. Sevinc et al. for example prospectively assessed all antibiotic prescriptions for the departments of internal medicine, surgery and pulmonology [6], while we assessed this retrospectively in all departments, except for the cardiothoracic ICU and paediatric and psychiatric wards.

This study has strengths and limitations. A strength of this study is that we developed a technically well-validated IVOS CDSS, which is based on IVOS criteria for which consensus was reached within an international, qualified expert panel using a Delphi procedure. Another strength is that we assessed the usefulness of this CDSS in daily clinical practice for a large group of patients. The study has also some limitations that should be taken into account when interpreting the results. Cases categorized as 'advice would not change the antibiotic policy' may also include cases in which earlier advice was given by the ID specialist to discontinue or switch the iv antibiotic. These alerts were also correct, but not classified as clinically relevant. Therefore, the potential usefulness of the IVOS CDSS is probably higher in a setting with a less active ID consultancy service. Since in 379 of the alerts (45%) the ID specialist had already been consulted prior to the alert, we expect that the CDSS would be more effective in facilitating antimicrobial stewardship teams in hospitals without an active ID consultancy service. However, it should be noted that the active ID consultancy service in our hospital provides an additional step in patient safety. It is important to be aware of possible unsafe situations, for example when an alert is generated for a patient with an infection for which a switch is contraindicated. This is possible in a hospital setting without coding of the diagnosis of the patient in the EHR, such as in our EHR. Of great importance is that these decision support systems should always be seen as an aid, with the definite decision still being at the physician's discretion. Moreover, a setting without an active ID consultancy service will have an influence on the NPV and PPV. Further research of the CDSS should therefore include non-academic hospitals without an active ID consultancy system to assess the safety, NPV, PPV and usefulness in these settings.

In conclusion, this study shows that a CDSS based on IVOS criteria developed with a Delphi procedure is effective in helping antimicrobial stewardship teams to select candidates for

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IVOS. Moreover, even in a hospital with an active ID consultancy service this CDSS had additional value to increase IVOS rates. In an era of increasing use of EHR, this IVOS CDSS has the potential to improve the quality of antibiotic use. With further coding of data in EHR the efficacy of the IVOS CDSS can be improved.

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Supplementary data

Table S4.1. Overview of included antipyretics in the CDSS

Antipyretics	Daily dose[1]	ATC code
Paracetamol	>=2000 mg	N02BE01
Acetylsalicylic acid	>=3000 mg	N02BA01
Carbasalate calcium	>=3600 mg	B01AC08
Aceclofenac		M01AB16
Alclofenac		M01AB06
Diclofenac	>=75 mg	M01AB05
Indometacine		M01AB01
Meloxicam		M01AC06
Piroxicam		M01AC01
Dexibuprofen		M01AE14
Dexketoprofen	>=50 mg	M01AE17
Fenoprofen		M01AE04
Ibuprofen	>=1600 mg	M02AA13
Ketoprofen		M01AE03
Naproxen	>=600 mg	M01AE02
Tiaprofenic acid		M01AE11
Fenylbutazon		M02AA01
Propyphenazone		N02BB04
Celecoxib		M01AH01
Etoricoxib		M01AH05
Nabumetone		M01AX01
Prednisone		A07EA03

[1] A notification will be generated if the daily dose is similar or exceeds the mentioned dose. If no dose is mentioned a notification will be generated irrespective of the dose.

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Table S4.2. Overview of the included inotropics and fluid resuscitation in the CDSS

Inotropics	ATC code	Fluid resuscitation (a total dose of minimal 500 mL is required)
Etilefrine	C01CA01	Glucose 3.3%-NaCl 0.3% infu 250 mL
Isoprenaline	C01CA02	Glucose 3.3%-NaCl 0.3% infu 500 mL
Norepinephrine	C01CA03	Glucose 2.5%-NaCl 0.45% infu 250 mL
Dopamine	C01CA04	Glucose 2.5%-NaCl 0.45% infu 500 mL
Norfenefrine	C01CA05	Glucose 2.5%-NaCl 0.45% infu 1000 mL
Phenylephrine	C01CA06	Glucose 5%-NaCl.0.45% infu 500 mL
Dobutamine	C01CA07	Glucose 5%-NaCl 0.9% infu 500 mL
Oxedrine	C01CA08	Albumine
Metaraminol	C01CA09	Voluven (hydroxyethyl starch)
Methoxamine	C01CA10	Volulyte (hydroxyethyl starch)
Mephentermine	C01CA11	Ringer (Lactate)
Dimetofrine	C01CA12	Gelatine
Prenalterol	C01CA13	Glucose 10%-NACL 0.45% INFU 500 mL
Dopexamine	C01CA14	Sodium chloride infu 0.65% 500 mL
Gepefrine	C01CA15	Sodium chloride infu 0.9% 1000 mL PRIMING
Ibopamine	C01CA16	Sodium chloride infu 0.9% 1000 mL VIAFLO
Midodrine	C01CA17	Sodium chloride infu 0.9% 250 mL
Octopamine	C01CA18	Sodium chloride infu 0.9% 250 mL ECOFLAC
Fenoldopam	C01CA19	Sodium chloride infu 0.9% 250 mL VIAFLO
Cafedrine	C01CA21	Sodium chloride infu 0.9% 500 mL VIAFLO
Arbutamine	C01CA22	Sodium chloride infu 3% 250 mL
Theodrenaline	C01CA23	
Epinephrine	C01CA24	
Amezinium metilsulfate	C01CA25	
Ephedrine	C01CA26	
Combinations	C01CA30	
Etilefrine, combinations	C01CA51	

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A usability study to improve a clinical decision support system for the prescription of antibiotic drugs

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Abstract

Objective: A clinical decision support system (CDSS) for empirical antibiotic treatment has the potential to increase appropriate antibiotic use. Before using such a system on a broad scale, it needs to be tailored to the users preferred way of working. We have developed a CDSS for empirical antibiotic treatment in hospitalized adult patients. Here we determined in a usability study if the developed CDSS needed changes.

Methods: Four prespecified patient cases, based on real life clinical scenarios, were evaluated by 8 medical residents in the study. The "think-aloud" method was used, and sessions were recorded and analyzed afterwards. Usability was assessed by 3 evaluators using an augmented classification scheme, which combines the User Action Framework with severity rating of the usability problems and the assessment of the potential impact of these problems on the final task outcomes.

Results: In total 51 usability problems were identified, which could be grouped into 29 different categories. Most (n=17/29) of the usability problems were cosmetic problems or minor problems. Eighteen (out of 29) of the usability categories could have an ordering error as a result. Classification of the problems showed that some of the problems would get a low priority based on their severity rating, but got a high priority for their impact on the task outcome. This effectively provided information to prioritize system redesign efforts.

Conclusion: Usability studies improve lay-out and functionality of a CDSS for empirical antibiotic treatment, even after development by a multidisciplinary system.

Introduction

Misuse and overuse of antimicrobial drugs have contributed to the selection of resistant bacteria, which occurs worldwide and has been estimated to contribute to an extra mortality of 10 million people by 2050 [1]. Studies have shown that about 30-50% of antibiotics are being prescribed inappropriately [2-4], and empirically started antibiotics are considered appropriate in only around 60% of the prescriptions [5-7]. Guideline-adherent empirical therapy is associated with a relative risk reduction for mortality of 35% and is therefore described as one of the most important objectives of antimicrobial stewardship programs [8,9]. The use of a clinical decision support system (CDSS) is a promising method to improve guideline-adherent empirical therapy [10-14]. As part of antimicrobial stewardship, a CDSS can play an important role to prescribe antimicrobial drugs appropriately and according to the guidelines.

CDSSs to support appropriate use of antibiotics have been developed since 1980 [15] and have increased in number in the last years. These systems combine relevant individual patient information with a computerized knowledge base to support decision-making in individual patients. By integrating relevant clinical data and evidence-based guidelines, these systems can help physicians to effectively manage all relevant information necessary for decision making in an increasingly complex clinical practice environment [16]. These systems are considered potentially highly valuable tools to improve clinical decision making and thereby quality of healthcare [15,16]. CDSSs to support appropriate use of antibiotics target a variety of aspects, such as optimizing antimicrobial dosing [17-19] or supporting antimicrobial de-escalation [20,21]. Most of these systems however focus on antimicrobial prescribing [15,22,23]. It has been shown that CDSS can increase confidence of general practitioners in their antibiotic prescriptions [24]. The systems that are designed to support antimicrobial prescribing in secondary care tend to focus more on a broader population than in primary care, where the systems are often focused on specific syndrome presentation in adults [15]. We have developed a CDSS for empirical antibiotic treatment in hospitalized adult patients, which combines relevant patient information with relevant local antibiotic treatment guidelines. Several other CDSSs for empirical antibiotic prescription have been developed. These CDSS differ on different aspects. Some systems use expert rules to predict the pathogen's susceptibility to antibiotics, using antibiotic susceptibility profiles from patients with similar characteristics [11,13,25], but don't take into account for example the antibiotic resistance history of the patients of interests or presence of neutropenia [13,25], like our system does. Others use causal probabilistic networks to predict the probability of a bacterial infection, site of infection and pathogens and their susceptibility to antibiotics. The CDSS we developed generates antibiotic advices based on relevant guidelines. Like many other

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CDSS for empirical antibiotic therapy input of the physicians was needed in our system for the generation of an antibiotic advice [10-13, 25].

CDSS for empirical antibiotic therapy have shown benefits in terms of improving empirical antibiotic prescribing [10-14]. However, in many of these studies the CDSS was not assessed while or after the end-users, the physicians themselves, used the system [10, 12, 13].

An important issue with the implementation of CDSSs is that they are, until now, not frequently used despite their potential benefits [26]. Studies have shown that poor usability negatively affects CDSS acceptance and effectiveness [27, 28]. Poorly designed CDSS have a negative impact on the use of these systems and can result in medication errors, potentially compromising patient safety [27, 28]. Therefore, the usability of these systems need to be well tested before being implemented in clinical practice. For this purpose we used an augmented classification scheme developed by Khajouei et al. [27] to test the usability of our developed CDSS for empirical antimicrobial therapy. This augmented classification scheme combines the User Action Framework (UAF), a standardized validated classification framework, with severity rating of the usability problems and the assessment of the potential (clinical) impact of these problems on the final task outcomes [27]. To our knowledge no other studies have assessed and described the usability of a developed CDSS for antimicrobial drug prescription using this systematic framework.

The aim of this study was to detect usability problems in our developed CDSS for empirical antimicrobial therapy, to rate the severity of these problems, and to determine the impact on the task outcome.

Materials and methods

Setting

This study was conducted at the Erasmus MC, University Medical Center in Rotterdam, the Netherlands, a tertiary care center with all medical specialties available. The Erasmus MC uses an electronic health record (EHR) with integrated computerized prescriber order entry (CPOE) which was introduced in December 2001.

Clinical Decision Support System (CDSS)

A rule-based CDSS for empirical antibiotic treatment in adult patients was built as a web application by a multidisciplinary team of clinical experts and information and communications technology (ICT) professionals (Figure 5.1). The system has been

developed to give empirical antibiotic treatment advice for the following infections: pneumonia, sepsis, urinary tract infections, meningitis and secondary peritonitis.

The developed CDSS combines relevant electronic patient information derived from the Erasmus MC electronic medical record (such as kidney function, microbiological results from the previous 6 months and presence or absence of neutropenia) with relevant local antibiotic treatment guidelines, which are in line with national guidelines (http://www.swabid.nl). The result is an indication driven advice that is patient specific and in accordance with current guidelines. Relevant patient information were as much as possible automatically extracted from our EHR, to which the CDSS was connected. To generate an appropriate antibiotic advice some information input, which could not be automatically extracted from our hospital information system, had to be entered manually by the user (for example the working diagnosis).

Figure 5.1. The developed CDSS, which combines relevant electronic patient information with relevant local antibiotic treatment guidelines.

Testing the usability of the CDSS

To identify usability problems in the design of a CDSS, different usability evaluation methods can be used. One of the methods to assess usability is the use of surveys, for example the often used System Usability Scale [29, 30]. This is a validated survey instrument, which consists of 10 items that have to be rated on a 5-point agreement scale [29]. It is a relative quick and easy instrument to use and it covers areas such as user satisfaction, efficiency of use and

system effectiveness [31]. This method has already been used for assessing the usability of a CDSS for antibiotic prescription [24, 32]. We did not use this survey instrument, because it does not provide insight in details or causes of identified problems. Other usability evaluation methods, which are often used are the heuristic evaluation, the cognitive walkthrough and the think aloud method [33]. The first two mentioned methods are expert-based methods, whereas the think aloud method is a user-based method. With the heuristic evaluation potential usability problems are uncovered using heuristics, which are recognized usability principles [34]. An example of a heuristic is 'provide help and documentation'. We did not use this method because the used heuristics are often very generally described, making them multi interpretable, resulting in different outcomes. This method is also highly dependent on skills and experience of the evaluator to improve the results overall [33]. With the cognitive walkthrough a usability expert simulates a new user by walking through the system step-by-step using typical tasks and details about the user's background. This is a really structured approach, however it is a very tedious method, time consuming and the results are affected by the task description and given details about the user's background [33]. We have chosen to use the think aloud method [35], because this method is a very rich source of data regarding usability problems. This is a user-based usability evaluation method where participants have to verbalize their thoughts during the execution of a set of specified tasks. It provides detailed insight into usability problems actually experienced by end-users of the system. Of added value is that this method provides insight in the causes of the identified problems. The verbal data are used to evaluate the system's design on usability flaws.

The usability study was performed in 2 steps. During the first step residents completed tasks using the CDSS and during the second step the usability of the system was assessed using the data that were collected during the first step. During the first step 15 medical and surgical residents were invited by e-mail to participate in the study. Residents were invited as participants in this study, because they are the intended users of the CDSS. Selection of residents was based on: I) diversity in discipline, II) prescribers of different antimicrobial drugs, III) years of residency and IV) not being involved in the development or analysis of the CDSS. Eight residents (3 from internal medicine, 2 from surgery, 2 from medical microbiology, 1 from neurology) participated in this study. The residents were on average 31 years old, and in their first to 6th year(s) of residency and 4 were female.

The residents were given a short demonstration of the CDSS before the usability test. The CDSS was not used in the hospital before the study. Four test cases were developed based on real life clinical scenarios (for description of these test cases see Table S5.1). The test cases were assessed on correctness, completeness and clearness by clinical experts in our study team. During the usability test, participants were asked to complete the tasks of antimicrobial

drug prescription while an observer watched, listened with minimum interruption and recorded (audiotaped and videotaped) the entire test session. All participants used the same web browser during the test and completed all four test cases.

Evaluating the usability of the CDSS

During the second step usability of the system was assessed using the data that were collected during the first step. This assessment was done by 3 unblinded evaluators, a physician, a hospital pharmacist experienced in clinical decision support and a researcher in the field of quality. Assessment was done by 2 evaluators, independently of each other. One of these primary evaluators had not been involved in the development of the CDSS. Disagreements in the sets of usability problems were resolved in discussion with a third evaluator. For this assessment an augmented classification scheme developed by Khajouei et al. was used [27]. This augmented classification scheme combines the User Action Framework (UAF), a standardized validated classification framework, with severity rating of the usability problems and the assessment of the potential (clinical) impact of these problems on the final task outcomes [27]. Each cycle of the user system interaction, which contains 4 phases (planning, translation, physical actions and assessment) was assessed. Planning is the phase of the user system interaction cycle including all cognitive actions by users to determine *what* to do. In the translation phase users determine *how* to accomplish the intentions that emerge during the planning phase. The phase in which the actions are being carried out by manipulating user interface objects is the physical action phase. The assessment phase is about the perception, interpretation and evaluation of the resulting system state by the user. Usability problems were identified using the videotapes of the cases and classified under different subcategories to the most detailed level using the UAF hierarchy [27]. Severity rating of usability problems was performed using the Nielsen's classification [35]. This severity rating is based on the (potential) impact of the problem on the users, the (potential) persistence of the problem and the frequency with which a problem (might) occur(red).

Results

In total, 51 usability problems were identified in the usability evaluation studies, of which 7 in the planning phase (Table 5.1), 28 in the translation phase (Table 5.2), 4 in the physical actions phase (Table 5.3) and 12 in the assessment phase (Table 5.4). These 51 usability problems could be grouped into 29 different categories. A description and illustration of some of these usability problems can also be found in Figures 5.2 and 5.3. Figure 5.4 shows the final screen with a patient specific antibiotic advice generated.

Table 5.1. Usability problems in the UAF planning phase with their severity and potential effect on task outcome

ID No.	Level 1	Level 2	Level 3	Level 4	Description of usability problem	No.[1]	Severity	Identifying potential outcomes[2]
1	Planning	Users model of the system	Users ability to determine what to do first		It is not immediately clear for the user which diagnosis has to be chosen in case of urosepsis (two possible pathways). The first information input that had to be entered manually by the user is the diagnosis. This is done by selecting one of the diagnosis in a drop down menu. For the diagnosis urosepsis the user has two possible pathways, namely the user can select sepsis, with sepsis focus urogenital tract or high urinary tract infection.	3	2	None (both pathways same result)
2		Goal decomposition	Users ability to determine what to do next		User has to answer if patient has an aspiration pneumonia. Because user doesn't know user chooses the answer 'no'. The option 'unknown' does not exist in the system.	1	0	Wrong antibiotic
3		Goal decomposition	Users ability to determine what to do next		Information is missing about what has to be filled in when the existence of neutropenia is unknown.	2	2	Wrong antibiotic
4		Users knowledge of system state, modalities			When entering a new patient identification number nothing happens.	1	2	None

[1] The number of usability problems with the same classification path, in the interaction of different or the same user with the system
[2] The mentioned outcomes are potential and did not have to occur

Table 5.2. Usability problems in the UAF translation phase with their severity and potential effect on task outcome

ID No.	Level 1	Level 2	Level 3	Level 4	Description of usability problem	No.[1]	Severity	Identifying potential outcomes[2]
5	Translation	Existence	Existence of a way		The user calculates, or even guesses, the BMI with a calculator outside the system.	8	3	Wrong dosage
6		Existence	Existence of a way		The user calculates the needed dosage of gentamicin with a calculator outside the system. The user mentions that it would be helpful if the dosage is calculated by the system.	3	4	Wrong dosage
7		Existence	Existence of a way		User has to fill in the weight and body height of the patient. This information is not automatically retrieved from the hospital information system. User expresses the wish that dosage of antibiotic is calculated with automatic retrieved weight and body height.	1	2	Wrong dosage
8		Existence	Existence of a way		The user has to select a working diagnosis from a drop down menu. After selecting a working diagnosis it is not clear how to go back to the previous step in the system.	1	3	None
9		Presentation	Perceptual issues	Noticeability	The user does not know (immediately) how to perform a request for another patient.	4	1	None
10		Presentation	Perceptual issues	Noticeability	The user does not use the filter to assemble possible resistant micro-organisms in the resistance overview profile, which shows the culture history (if filter is not being used resistant micro-organisms can be overlooked).	1	0	Wrong antibiotic

Table 5.2 continues on next page.

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Table 5.2. Continued

ID No.	Level 1	Level 2	Level 3	Level 4	Description of usability problem	No.[1]	Severity	Identifying potential outcomes[2]
11		Presentation	Perceptual issues	Noticeability	User does not view the overview of AST[3], and the materials (for example sputum, urine and blood) in the resistance overview profile which shows the culture history.	2	0	Wrong antibiotic
12		Presentation	Perceptual issues	Noticeability	Overview of resistance, which shows the culture history, is not seen immediately.	1	2	Wrong antibiotic
13		Presentation	Perceptual issues	Noticeability	Mouse over info about difference between HAP[4] and CAP[4] is not viewed.	3	2	Wrong antibiotic
14		Presentation	Perceptual issues	Noticeability	Mouse over info about severity of pneumonia is not viewed. Argument for severity classification is not correct.	3	2	Wrong antibiotic
15		Presentation	Perceptual issues	Noticeability	User overlooks the information provided about the ESBL[5] positivity of the patient.	1	0	Wrong antibiotic

[1] The number of usability problems with the same classification path, in the interaction of different or the same user with the system
[2] The mentioned outcomes are potential and did not have to occur
[3] AST: Antibiotic Susceptibility Tests
[4] HAP: hospital acquired pneumonia, CAP: community acquired pneumonia
[5] ESBL: extended spectrum betalactamase

Table 5.3. Usability problems in the UAF physical action phase with their severity and potential effect on task outcome

ID No.	Level 1	Level 2	Level 3	Level 4	Description of usability problem	No.[1]	Severity	Identifying potential outcomes[2]
16	Physical actions	Manipulating objects	Physical layout		To view the complete resistance overview, which shows the culture history, the user has to scroll down in the resistance viewer. The user does not scroll down in this viewer.	1	2	None
17		Manipulating objects	Preferences and efficiency		User wants to review the culture history, when advice is generated, but this is not possible (functionality not available). User thinks this is not convenient, because the user wishes to review this history while consulting an infectious diseases consultant.	1	4[3]	None
18		Manipulating objects	Preferences and efficiency		Physician mentions that she misses a button (button does not exist in the system). There is only the possibility to answer 'yes' or 'no' on the question if patient has been abroad. She mentions there has to be a button 'unknown'.	1	2	None
19		Perceiving physical objects	Perceiving objects as they are being manipulated		The user tries to click through the resistance viewer, which shows the culture history. This is not possible (this functionality is not available in the system)	1	1[3]	None

[1] The number of usability problems with the same classification path, in the interaction of different or the same user with the system

[2] The mentioned outcomes are potential and did not have to occur

[3] The difference in severity between these 2 usability problems stands out. The usability problem 'The user tries to click through the resistance viewer, which is not possible' is scored as 1 (cosmetic problem), because it has a low impact on the user interaction, the problem only occurred once and is a usability problem which is not persistent.

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Table 5.4. Usability problems in the UAF assessment phase with their severity and potential effect on task outcome

ID No.	Level 1	Level 2	Level 3	Level 4	Description of usability problem	No.[1]	Severity	Identifying potential outcomes[2]
20	Assessment	Feedback	Content and meaning	Completeness and sufficiency of meaning	The user questions what to do with 'Advice number'.	1	0	None
21		Information display	Content and meaning	Error avoidance	The message 'No relevant cultures known' is confusing. This message only refers to cultures in this hospital	2	1	Wrong antibiotic
22		Information display	Content and meaning	Error avoidance	The user wonders why the resistance overview includes empty fields.	1	3	Wrong antibiotic
23		Information display	Content and meaning	Error avoidance	The advice does not clearly indicate for what antibiotic the trough level has to be determined.	2	2	Determining medication dosage for the wrong antibiotic
24		Information display	Content and meaning	Error avoidance	Physician reads essential information accompanying the advice, but prescribes the wrong antibiotic which is contrary to this information.	1	2	Wrong antibiotic
25		Information display	Content and meaning	Layout and grouping	The final advice already appears earlier under a mouse over (which can be confusing).	1	2	None

26	Information display	Content and meaning	Layout and grouping	The resistance overview displays the results of a bone marrow biopsy, which confuses the physician.	1	2	Wrong antibiotic
27	Information display	Existence	Human memory aids	It is not clear whether the resistance viewer also takes resistance into account determined in other hospitals.	1	0	None
28	Information display	Presentation	Perceptual issues > noticeability	Not clear whether the user realizes the Gentamicin doses has to be adjusted.	1	2	Wrong dosage
29	Information display	Presentation	Perceptual issues > noticeability	The physician does not read the text which states that the Gentamicin dose has to be adjusted in case of a too high body mass index.	1	3	Wrong dosage

1 The number of usability problems with the same classification path, in the interaction of different or the same user with the system
2 The mentioned outcomes are potential and did not have to occur

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Figure 5.2. Some usability problems in the CDSS for empirical antibiotic therapy.

Figure 5.3. The resistance viewer in the CDSS for empirical antibiotic therapy and illustration of 2 usability problems.
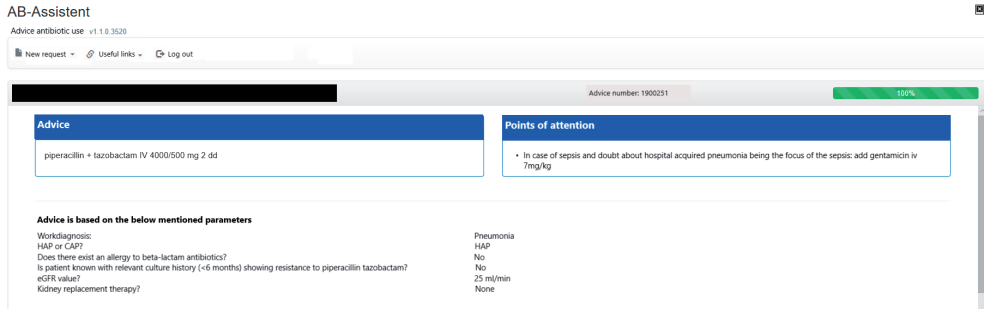
Figure 5.4. Final screen of the CDSS for empirical antibiotic therapy with a patient specific antibiotic advice.

Planning

Seven (14%) of the identified usability problems were found in the planning phase of user-system interaction (Table 5.1). The usability problems in this phase were mainly caused by the user's difficulties in choosing the correct diagnosis (two possible pathways), lack of a third option such as an 'unknown' button, and perceived lack of information (user is not provided with information about the system state, when entering a new patient identification number fails).

Classification of the problems with the augmented scheme showed that some of the problems would get a low priority based on their severity rating, but got a high priority for their impact on the task outcome. For example, the severity of the usability problems leading to the prescription of wrong antibiotics was rated as minor or no problem while the impact of prescribing the wrong antibiotic can be high.

Translation

Twenty-eight (55%) of the usability problems concerned the translation phase (Table 5.2). The usability problems in this phase were mainly caused by the fact that the mouse over functions were not noticed or correctly used, and that extra patient information (culture results) were not noticed by users. Also, the needed doses of gentamicin and the BMI were calculated with a calculator outside the system or guessed, leading to wrong dose advices.

Most usability problems had low severity ratings. Only one usability catastrophe (severity rating of 4) was observed when the gentamicin dose had to be calculated and users did look for a calculator, which was not available in the CDSS. The users expressed the need for a calculator. Not only the usability problem had a high severity rating of 4, but the impact of the problem is high too.

Physical actions

Four (8%) of the usability problems were encountered in the phase of physical actions (Table 5.3). One of these usability problems was caused by the layout of an object, for instance the scroll down button that had to be used. Another usability problem in this phase was the lack of user control over screen objects as these objects were being manipulated. For example, the user tried to click through the resistance viewer, but this was not possible. Two usability problems in this phase concerned the failure of the system to meet specific preferences of users for performing physical actions. One of these problems was the inability to review the culture history when the CDSS had generated an advice. This problem was rated as severity 4, although it would not lead to a wrong medication selection. The user indicated that this problem had a great impact on him, because he wanted to review the culture history during the consultation of an infectious disease specialist when an advice is generated.

Assessment

In total 12 (24%) of the 51 identified usability problems were classified in the assessment phase (Table 5.4). These problems concerned the existence, presentation, content and meaning of system feedback about the course of the user-interaction and the display of information resulting from users' actions.

Not all the problems, that influence the outcome were highly severe problems since three of the problems potentially resulting in wrong antibiotic selection were assigned severity 2, and one problem assigned severity 1. The UAF classification showed that 4 (33%) of the problems concerning the assessment phase of interaction were caused by absent or unclear information displayed after the user's action to avoid errors. The remaining eight (67%) problems in this phase were caused by the absence, poor presentation or noticeability of information or feedback displayed after the users' actions.

A general striking finding was that four users indicated that they would not indiscriminately follow the advice given, because they were aware of the fact that the CDSS was recently developed and might contain errors.

Discussion

With the augmented scheme for classifying and prioritizing usability problems described by Khajouej et al. [27] we found 51 usability problems in different phases of the user system interaction. Most usability problems were found in the translation phase (55%). Testing the usability of a CDSS with this scheme proved to be a simple, but effective way to identify

usability problems and prioritize system redesign efforts. With the use of the augmented UAF the existence of usability problems, that were not foreseen, were identified. Also, the frequency of problems of CDSS use, the severity and potential impact of these problems on task outcome were identified. Assessing usability of a CDSS is important to increase the chance of its adoption.

This study is the first to report usability testing of a CDSS for empirical antibiotic treatment in adult patients using the systematic framework developed by Khajouei et al. [27]. A strength of this study is that we used the standardized and validated UAF, augmented with a severity rating based on Nielsen's classification and the assessment of potential effect of the problem on the task outcome. This approach enables the report of existing usability problems in an accurate, complete and consistent way. This is needed for guiding and prioritizing system redesign efforts. Some limitations of this study should also be recognized. Firstly, we could have missed usability problems because of the small group of participants. However, the group of 8 participants was a well representative group, composed out of residents from different disciplines and different years of residence. In addition, about 80% of usability problems can be discovered with only 8 participants and the more severe a problem is, the more likely it will be uncovered within the first few subjects [36-38]. Studies to determine the optimal number of participants for a usability study have shown that the complexity of the study itself is an important factor to consider [37, 38]. Because the tasks the user had to perform in our study were simple and really straightforward we think that 8 participants were enough to detect most usability problems. Another limitation is that participants may have modified their behavior and reported thoughts in response to their awareness of being observed during the usability test. This so-called Hawthorne effect is inherent to simulated usability studies and not possible to rule out [39]. Because all participants were residents, lack of experience could have contributed to the existence of certain usability problems. These problems will probably not be experienced by medical specialists. However, given the fact that residents and specialists with not much experience in antibiotic prescribing, will be the mainly end-users/are the intended users of the CDSS, these problems are important to discover and take into account in the system redesign.

In this usability study participants completed tasks of antimicrobial drug prescription using four prespecified test cases which were based on real life clinical scenarios. In a setting with real patients, the physician knows his or her patients and can answer certain questions about a patient better than with the use of a prespecified case, such as the question if the patient has neutropenia. It could therefore be that certain usability problems will not exist or exist less in a setting with real patients which are known by the user. However, this only applies for usability problems where continuing in the system is not possible without

knowing certain information (for example neutropenia or if the patient has been abroad). In addition other usability problems could also be revealed when using this CDSS in real clinical conditions.

With this study we found that some of the residents did not follow the advice that was given by the CDSS without thought. They were aware of the fact that the CDSS was recently developed and might contain errors. We also found that time has been invested in the development of functionalities, which were not (optimally) used. An example is presenting mouse over information in addition to certain questions, providing relevant information to the user. Our study showed that these help texts were often not used, which prompted us to enlarge the information icon that makes this help text appear when moving the cursor towards the information icon. Also, simple improvements such as the introduction of a calculator and patient information that is automatically retrieved from the hospital information system such as weight and body height are worthwhile investments. Another simple modification we made to the CDSS is the introduction of a new option, namely the option to review the culture history in the final screen when an antibiotic advice is generated. With these alterations in the system design we made the CDSS more specific to users' needs. For ultimate system usability, iterative usability evaluation during the development and implementation of CDSS are important [28, 40, 41].

Conclusion and recommendations

Our study revealed several usability problems in different phases of the interaction between the intended user and a CDSS developed for empirical antibiotic treatment, the severity of these problems and the impact on the task outcome. It shows that even though the CDSS has been developed by a multidisciplinary team of clinical experts and ICT professionals, many usability problems can exist that are not foreseen. Assessing usability before CDSS implementation is recommended for improving CDSS adoption, effectiveness and safety. When designing a CDSS the following elements have to be considered to avoid usability problems:

- 'When a question has to be answered with a yes or no also provide the answer 'unknown'. If answering with yes or no is necessary for the system to generate an advice, provide users with this information.

- Make it easy to do right by providing calculators for everything that has to be calculated (the recommended dosage of an antibiotic drug, BMI etc.).

- Retrieve as much information as possible automatically from the hospital information system.

- Pay attention to the noticeability of relevant information (for example mouse over info with relevant explanatory information/definitions, resistance overview with information that is relevant for the final antibiotic advice).

- Provide users with information that is clear and as specific as possible and avoid reporting of irrelevant, confusing information.

Acknowledgements

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Supplementary data

Table S5.1. The four test cases that were used to test the usability of the CDSS

Test case 1	Man, 45 years old (height 1.80 m, weight: 100 kg), presents to your emergency room with symptoms of an urosepsis. Patient has an impaired kidney function (eGFR 66 ml/min). You decide to admit patient and start antibiotic therapy.
Test case 2	Female, 70 years old (height 1.55 m, weight: 65 kg), is transferred from nursing home *Leeuwenhoek* to your hospital because of a pneumonia. She has an impaired kidney function (eGFR=25 ml/min), but does not use any renal replacement therapy.
Test case 3	Female, 64 years old (height 1.60 m, weight: 80 kg) is admitted to your department with a suspected urinary tract infection. She uses the medicine Tacrolimus, because of a kidney transplantation she underwent 5 years ago. She has a 40 degree fever. You would like to prescribe antibiotic therapy. Patient does not have any allergies or a history of antibiotic resistance. She has a good kidney function.
Test case 4	Man, 48 years old (height 1.65 m, weight: 80 kg), is admitted to your hospital with an intracerebral hematoma, complicated by oedema, for which an external ventricular drain is placed. Patient is transferred to your department and develops meningitis with cerebrospinal fluid leakage. Patient does not have any allergies or a history of antibiotic resistance. Patient has a good kidney function. You would like to prescribe antibiotic therapy.

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The development and implementation of a guideline-based clinical decision support system to improve empirical antibiotic prescribing

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Abstract

Background: To describe and evaluate a clinical decision support system (CDSS) for empirical antibiotic therapy using a systematic framework.

Methods: A reporting framework for behavior change intervention implementation was used, which includes several domains: development, evaluation and implementation. Within the development domain a description is given of the engagement of stakeholders, a rationale for how the CDSS may influence antibiotic prescribing and a detailed outline of how the system was developed. Within the evaluation domain a technical validation is performed and the interaction between potential users and the CDSS is analyzed. Within the domain of implementation a description is given on how the CDSS was tested in the real world and the strategies that were used for implementation and adoption of the CDSS.

Results: Development: a CDSS was developed, with the involvement of stakeholders, to assist empirical antibiotic prescribing by physicians. Evaluation: Technical problems were determined during the validation process and corrected in a new CDSS version. A usability study was performed to assess problems in the system-user interaction. Implementation: In 114 patients the antibiotic advice that was generated by the CDSS was followed. For 54 patients the recommendations were not adhered to.

Conclusions: This study offers a guidance for the development and validation of a CDSS for empirical antibiotic therapy and shows the usefulness of the systematic framework for reporting CDSS interventions. In addition it shows that CDSS recommendations are not always adhered to which is associated with incorrect use of the system.

Background

To improve quality of antibiotic prescriptions and thereby help to control the emergence and spread of antibiotic resistance, several Antibiotic Stewardship Programs (ASPs) have been developed [1-3]. These programs are ideally administered by an Antimicrobial Stewardship Team (AST), a multidisciplinary team composed of an infectious disease physician, a clinical pharmacist with infectious diseases training, a clinical microbiologist, an infection control professional and a hospital epidemiologist [4]. One of the most important objectives of these ASPs is the use of empirical antibiotic therapy according to guidelines [5, 6], which has been associated with a relative risk reduction for mortality [5]. However, whereas empirical antibiotic therapy has been shown to be significantly more appropriate after consultation of an infectious disease specialist, for the majority of patients antibiotics are prescribed by their attending physician.

Using specific strategies to promote antibiotic prescribing according to the guidelines seems necessary, since it is generally not effective to passively disseminate guidelines [7]. Clinical decision support systems (CDSSs) can link patient data with an electronic knowledge base with clinical guidelines to improve decision making. As the use of electronic medical records increases and new information technologies are being developed, CDSSs for antimicrobial stewardship have gained widespread interest [8-10]. As part of an ASP, CDSSs can play an important role by taking over part of the activities of an AST. This is attractive given the fact that ASTs are labor intensive and thus expensive [11, 12].

Several CDSS to improve empirical antibiotic prescribing in hospitalized patients have been developed and assessed over the years [13-18]. These systems have the potential to improve empirical antibiotic prescribing [13-17], but the development of these systems has been poorly reported. The need for detailed description of system design has been addressed [9]. From the many systems that have been developed to improve antibiotic prescribing, none have been very successfully implemented in clinical practice. Unfamiliarity with the system and a vague description or no description at all of the development of these systems may play a role in the lack of success of CDSS in clinical practice until now. In addition the literature describes a need for a systematic reporting framework, because of a heterogeneous and disjointed approach to reporting CDSS interventions [8]. In this study we describe in detail the development, evaluation and implementation of a CDSS using the reporting framework for behavior change intervention implementation and following the key components for reporting CDSS identified by Rawson et al. [8]. Using this framework a CDSS intervention can be evaluated in a systematic manner taking into account several domains, including development, evaluation and implementation. This study offers a guidance for the development and validation of a

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CDSS for empirical antibiotic therapy. It is, to our knowledge, the first to use this framework to report on a CDSS intervention for antimicrobial therapy and evaluate the usefulness of it.

Methods

Setting

This study was conducted at the Erasmus MC, University Medical Centre, a 1,125 bed tertiary care center in Rotterdam. A total of 31,923 patients were admitted to this hospital in 2018. The Erasmus MC uses an electronic health record (EHR) with integrated computerized prescriber order entry (CPOE). The Department of Medical Microbiology and Infectious Diseases of this hospital provides an active Infectious Diseases (ID) consultation service, in which ID consultants pro-actively give the attending physicians recommendations about antibiotic use.

Clinical decision support system – development

A web-based clinical decision support system for empirical antibiotic therapy for adult hospitalized patients was developed by a multidisciplinary team. This team consisted of an ID specialist, clinical microbiologists, a hospital pharmacist experienced in decision support, an Information Technology (IT) team and a researcher.

The CDSS was iteratively developed through biweekly meetings between the multidisciplinary team. During these meetings several items were discussed. Items that were discussed included which and how extra information should be provided in the system to increase the ease of use and limit errors, such as the CURB-65 score for pneumonia severity. This was done in light of the many residents and fellows working in our hospital. Other important items that were discussed were which known cultures should be presented in the system (all cultures or only recent ones, all cultures or only those relevant for the working diagnosis) and how recent the automatically extracted data should be (eGFR value and neutrophil value). Other discussed items were for example the formulation of questions, how we could show the user the progression of her or his advice request, which information should accompany the generated antibiotic advice and from what age the existence of pregnancy should no longer be asked for. Consensus was needed for optional and extra manual input by the physicians when using the CDSS, since information in the hospital information system can be missing or inaccurate. For example fluctuating information, such as the weight or renal function, may not be continuously updated and therefore be outdated at the time of use of the CDSS.

During the development of the system, different infectious disease consultants were asked for feedback resulting in improvements in lay-out or functionality. The developed CDSS is based on the local antibiotic treatment guidelines, which are in line with the national guidelines (https://adult.swabid.nl). By generating patient specific antibiotic advices, based on relevant guidelines, this system makes it physicians easy to appropriately prescribe antibiotics. The system takes into account all relevant parameters, such as kidney function, culture history and pregnancy. This decreases the risk of overlooking a relevant parameter and increases the chance of optimal antibiotic prescribing. The CDSS was based on frequently occurring infections in our hospital. In addition we also included several infectious diseases on request of physicians. We performed a usability study as part of the development and evaluation phase [19], resulting in stakeholders being engaged in the further development and fine-tuning of the CDSS. The results of the usability study enabled us to make the CDSS more specific to users' needs (for example by adding calculators). A description of the usability study is given under the heading 'clinical decision support system-evaluation'.

Clinical decision support system – evaluation

We used two steps to evaluate the CDSS before we implemented the system in clinical practice. During the first step we used a retrospective technical validation to confirm that the used CDSS parameters were correctly linked to the data in the EHR. During the second step a usability study was performed using realistic clinical scenarios to assess the interaction between the potential end user and the developed system.

Step 1

Flowcharts were first developed on paper and checked for correctness by the development team. Thereafter, the CDSS was built and technically and clinically tested using real patient data to trigger an antibiotic advice. Automatically extracted data were checked on correctness in our EHR. All generated antibiotic recommendations were manually and automatically checked on correctness using local current guidelines and developed flowcharts.

Step 2

To improve lay-out, functionality we performed a usability study [19]. We used a user-based usability evaluation method, where participants had to verbalize their thoughts during the execution of a set of specified tasks using the CDSS. Sessions were recorded and analyzed afterwards by 3 evaluators using an augmented classification scheme. The severity of the identified usability problems was rated and the potential impact of these problems on the final task outcomes was assessed.

After these tests the CDSS was made available for use, by providing the link to the web-based system in our hospital information system. An overview of the CDSS characteristics, development and evaluation can be found in Table 6.1.

Table 6.1. Description and evaluation of the clinical decision support system for empirical antibiotic therapy (following the identified reporting criteria by Rawson et al [1])

Description of decision support tool	
Type of decision support provided	- Antibiotic (empirical) prescribing - Dose optimization - Duration of therapy - Route of administration
Platform on which it is provided	- Web-based
Infrastructure	- Rule-based
System development	
Rationale for development	- Makes it easy to do right by generating patient specific antibiotic advices, based on relevant guidelines. - Decreasing the risk of overlooking a relevant parameter in antibiotic prescribing. - Stakeholders were involved in the development of the system with the use of a usability study. Diagnoses were included in the system on request of stakeholders.
Previous feasibility/pilot testing	- A usability study was performed to assess the interaction between the system and user. With this study we also assessed whether the generated advices would be followed and identified potential negative outcomes/errors.
Evidence supporting evaluation	- A usability study provides detailed insight into usability problems experienced by end-users of the system. It also provides insight in the causes of identified problems.
How the tool is implemented	- A demonstration was given before implementation. - The use of the CDSS was regularly promoted by visiting departments. Medical pocket cards were developed as promotional material for the system. - An active infectious disease consultancy service system is provided in the hospital where the CDSS is implemented. ID consultants were instructed to remind physicians to use the CDSS.
Study design	
Justification for study design	- Descriptive/observational study. This study design is selected to describe the use of the developed CDSS and adoption of its recommendations.
Outcome measure selection	- Evaluation of the adoption of generated advices.

[1] Rawson TM, Moore LSP, Hernandez B, Charani E, Castro-Sanchez E, Herrero P, et al. A systematic review of clinical decision support systems for antimicrobial management: are we failing to investigate these interventions appropriately? *Clin Microbiol Infect* 2017; **23**(8): 524-32.

Clinical decision support system – implementation

The CDSS was demonstrated on the different clinical departments before implementation. During the implementation period (December 2016 until May 2017) the departments were visited on a regular basis to promote the use of the CDSS and answer questions regarding the system. In addition we designed medical pocket cards as promotional material for the system. During the implementation period, each advice that was generated by the CDSS was checked the same day by a clinical infectious disease consultant.

Data collection

To assess the performance of the CDSS during the implementation period, a data file was created with relevant patient data, which was automatically retrieved from our hospital information system. All adult patients in all clinical departments of the Erasmus MC, with the exception of one-day admissions, using at least one antibacterial drug for systemic use (ATC code starting with J01) in the implementation period of the CDSS were selected. Patients that received only prophylactic antibiotics were excluded. The following antibiotic drugs were defined as prophylaxis: all antibiotics given for a duration of less than 48 hours, cotrimoxazole at a dose of 480 mg and cefazolin started pre-, intra-, or postoperatively without another clear indication (manually assessed). Antibiotics given regarding a prophylactic protocol, such as selective decontamination of the digestive tract, antibiotics for patients with neutropenia, chronic obstructive pulmonary disease (COPD), and pheneticillin within a period of 2 years after splenectomy were also defined as prophylaxis. Relevant data such as age, sex, ward, prescribed antibiotic(s), infectious disease consultations and advised antibiotic(s) by the CDSS were automatically retrieved. For every patient for whom the CDSS was used, it was assessed by chart review whether the antibiotic(s) advised by the CDSS were (partly) followed or not. If only one of the recommended drugs or a different route or dosage regimen was prescribed, this was categorized as partly followed. Cases of doubt were discussed by two of the researchers (HA and AV).

The study was carried out in accordance with relevant guidelines and regulations and according to the Dutch Medical Research in Humans Act, medical ethical approval was not required and patients did not need to provide informed consent, since their data were handled anonymously by the researcher.

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Results

Clinical decision support system – development

Our CDSS included the following diagnoses: sepsis, pneumonia, urinary tract infections, fever of unknown origin (with suspicion of bacterial infection), meningitis, secondary peritonitis and liver abscess. The diagnoses secondary peritonitis and liver abscess were included on request of physicians. For each diagnosis, a flowchart to map relevant information for the choice and duration of the antibiotic was developed such as the working diagnosis and, for example, whether a pneumonia was community or hospital acquired (Figure 6.1). To determine the right dose and dosing interval, flowcharts were designed for different antibiotics by mapping relevant factors such as renal function, weight or body mass index and pregnancy (Figure 6.2). In addition, factors such as allergies, and antibiotic susceptibility in the previous 6 months were incorporated in the CDSS in order to deviate from the first choice empiric antibiotic if necessary. The clinical decision support system was built as an interactive system, automatically extracting as much relevant patient information as possible from our hospital information system to which it was connected. Automatically extracted patient data were patient identification number, birth date, sex, admission ward, culture history, kidney function and absolute neutrophil count. To generate an appropriate antibiotic advice some information input, which could not be automatically extracted from the hospital information system, was needed from the prescriber such as the working diagnosis.
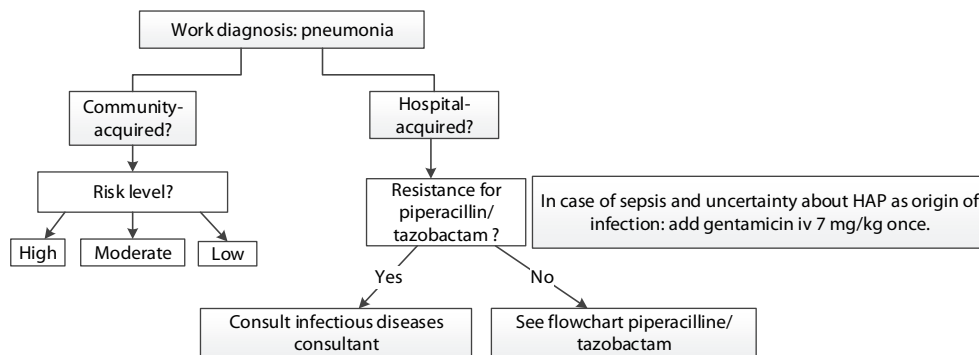

Figure 6.1. Part of the flowchart developed for the working diagnosis pneumonia.
For the complete flowchart of high and moderate risk community acquired pneumonia see Supplementary Figure S6.1. HAP is hospital acquired pneumonia. Risk level was assessed using the CURB-65 score.
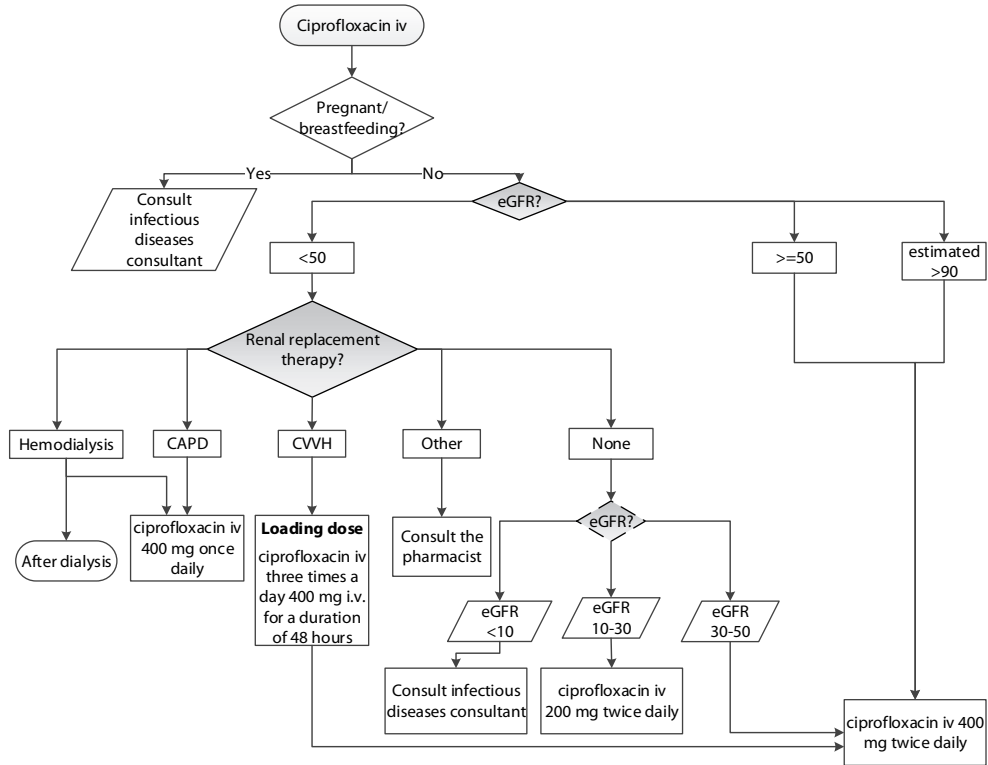
Figure 6.2. The flowchart for ciprofloxacin iv with all relevant information that the CDSS takes into account.

Clinical decision support system – evaluation

Step 1

The recommendations by the CDSS were all in accordance with the local antibiotic guidelines. Some bugs in the CDSS, such as an incorrect threshold value and no generated advice in the end screen, were found with the automatic technical tests, which were corrected in a new version of the CDSS.

Lay-out

For all diagnoses, the physician has to manually fill in the working diagnosis and answer a few questions in the different predefined pathways (Figure 6.3). We added mouse over information for items that might not be clear, such as what an IgE mediated allergy is or needed knowledge of criteria, for example severity of CAP. In the example shown in Figure 6.3, after answering the question about allergy the choice of antibiotic is clear and should be refined by incorporating culture results. The appropriate antibiotic is given

and the physician is obligated to check the antibiogram of previous cultures before he/ she can proceed with the program (for an example see Supplementary Figure S6.2). Only culture results from the previous 6 months were presented. Antibiotics were preselected by the CDSS based on the working diagnosis and relevant parameters. Dosing regimen was refined by using the eGFR and in case of gentamicin using (ideal) body weight. Only eGFR values were presented with date and time of eGFR determination if determined less than 1 week before consulting the CDSS.

Figure 6.3. The clinical decision support system for empirical antibiotic therapy for pneumonia.
HAP is hospital acquired pneumonia. CAP is community acquired pneumonia. Patient data are not from an existing patient.

Step 2

During the usability study a total 51 usability problems were identified, grouped into 29 different categories. Most (n=17/29) of the problems were cosmetic problems or minor problems. Eighteen (out of 29) of the usability categories could have an ordering error as a result [19].

Clinical decision support system – implementation

During the implementation period the CDSS was used 184 times, of which 15 times for patients who did not have any signs of infection or were not admitted to the hospital (trying

out/testing the system). The median age of patients for which the CDSS was used was 64 years and 44.4% (75/169) was female. The CDSS was mostly consulted for the diagnosis pneumonia (hospital acquired and community acquired) (62/169), followed by urinary tract infection (58/169). The CDSS was mainly used by physicians working at the internal medicine department. All recommendations given by the CDSS were correct for the presumed working diagnosis.

Clinical decision support system – recommendations and adoption

The CDSS was used to generate antibiotic advice for clinical practice for 169 patients: for 141 patients an antibiotic advice was given, including dose and route and for 28 patients the advice was to consult an infectious disease consultant. The most commonly recommended drug for pneumonia was piperacillin with tazobactam and for urinary tract infections nitrofurantoin. In 114 patients (67.4%) the advice that was generated by the CDSS was completely (n=91) or partly (n=23) followed. We found several explanations for the deviation from the advised antibiotics(s) by the CDSS (Figure 6.4). Some physicians filled in or used the system incorrectly, they for example tried to fit in a diagnosis or a wrong diagnosis was filled in. We also found that a reconsideration of the working diagnosis/ differential diagnosis or the wish of the physician to prescribe an oral alternative instead of the advised intravenous antibiotic could explain the discrepancy in prescribed antibiotic(s) and the generated advice by the CDSS. The same applies to not correctly filled in allergies (not manually entered or entered while no allergy existed), the use of the system for directed therapy instead of empirical therapy and the use of the system while a bacterial infection was absent. The 15 patients that were used to test/try out the CDSS did not have any signs of infection or were not admitted to the hospital.

Discussion

We have developed, validated and implemented a CDSS to assist and improve empirical antibiotic choices in adult hospitalized patients. In line with the proposed systematic framework by Rawson et al. [8], this study offers a guidance for the development and validation of a CDSS for empirical antibiotic therapy and shows the usefulness of a systematic framework for reporting CDSS interventions. The CDSS was mostly consulted for the diagnosis pneumonia, and urinary tract infection. The advice of the CDSS was 100% correct given the data that were filled in. In 67.4% the advice that was generated by the CDSS was followed (completely or partly). For cases in which the CDSS advice was not followed by the physician, half of them filled in or used the system incorrectly. A CDSS
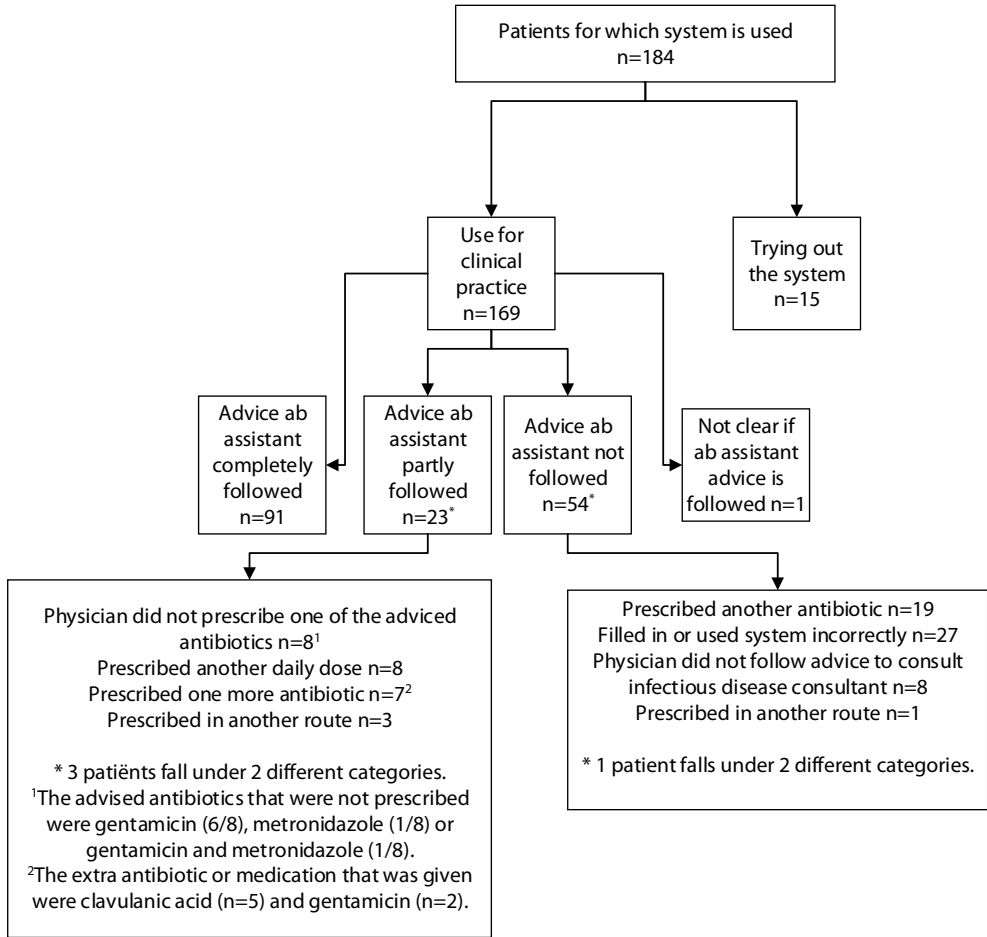
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Figure 6.4. Use of the CDSS and adoption of its recommendations.

for empirical antibiotic therapy has the potential to increase guideline adherent therapy. However, CDSS recommendations are not always adhered to and this could be explained mostly by incorrect use of the system.

This study is, to our knowledge, the first study that uses systematic approach, in which the development, validation and implementation of a CDSS for empirical antibiotic therapy are described in detail. The used reporting framework provides a structured overview of many important aspects of a CDSS intervention. It gives an understanding of the rationale for why and how a CDSS was developed and how its effectiveness was evaluated [20, 21]. Following this framework ensures reporting on these different aspects and when applied also by others will enable a more easy comparison between the different CDSS. Several

important aspects are not included in this framework, such as: the composition of the team that developed the CDSS, type of CDSS (active or a passive), guidelines on which the CDSS is based, rationale for using these guidelines, commercial or noncommercial CDSS, setting for which the CDSS was developed. We propose that these key components should also be considered when reporting on CDSS interventions.

In the implementation domain we found that a factor that compromised the potential of the CDSS is that not all recommendations were followed. Because in half of these non-followed recommendations the system was filled in or used incorrectly, training in its use is recommended. During this training attention can be given to assessing the relevance of previous cultures, because this can be difficult. Physicians could have been testing/trying out the system using data of the admitted patients with signs of infection. For this reason it is recommended to provide test patients, specially created for this purpose. Incorrect use of the system was because physicians for example tried to fit in a diagnosis. In the development phase we decided to include the most common infections in our CDSS. Such an approach has also been applied in another study in which a need for assistance with empirical antibiotic choices when less common infections were present was expressed [14]. In this study the following foci of infection were included: blood, wound, lower respiratory tract, abscess and urinary tract. In our and their study the most common diagnosis for which the CDSS was used was respiratory tract infection. The inclusion of more diagnoses is recommended to tackle the problem of incorrect use of the system because physicians tried to fit in a diagnosis. However, the choice of diagnoses accompanied by an antibiotic advice should be in balance with the amount of work associated with the inclusion of the specific infection and use of the system for these extra infections.

A similar non-adherence to CDSS recommendations has been described before [22] [23]. However a wide range in adherence to CDSS recommendations has been reported [24], which may be explained by differences in CDSS usability, type of CDSS recommendation (fine-tuning or a complete antibiotic advice), local hospital environment and culture [25]. Other explanations for not following CDSS recommendations are the complexity of patient cases, other infectious disease diagnoses that present similarly or a reconsideration of the working diagnosis [18]. In our study, the wish of physicians to prescribe an oral alternative and/or reconsideration of the working diagnosis were also reasons for not following the CDSS recommendation. Monitoring reasons to deviate from CDSS recommendations is important to further optimize (the implementation of) a CDSS.

A strength of this study is that the CDSS was operated by the physicians themselves, which gives insight in their use of this CDSS after implementation and in the acceptance of the

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recommendations. In many studies regarding CDSS for empirical antibiotic prescription, the system was not used by the end-users, the attending physicians, who are the most frequent antibiotic drug prescribers [13, 15, 16, 22]. Although these studies have shown improvements in antibiotic prescribing, possible problems related to implementation and use of the system by physicians were not taken into account. Therefore, it is not clear whether these results can be repeated in a "real clinical setting" that we used. Another strength of this study is that a report is given on how stakeholders were involved before implementation to justify intervention design. Very few studies on CDSS report pre-deployment stakeholder analysis [8]. Other developed CDSS for empirical antibiotic therapy were tested in a limited number of departments [13, 17, 18], or only in hospitalized patients with bloodstream infection [16, 26] or pneumonia [18, 27]. Our CDSS was implemented in a tertiary hospital with a wide variation of departments, which has the risk of less focus on departments or diseases in which antibiotics are used most frequently. However, by targeting a broader population of physicians more use can be expected. In addition, physicians who prescribe less antibiotics benefit more from being assisted with antibiotic choices using this system, because of less experience in prescribing this medicines. For this reason we feel it is important to also include these prescribers.

A recently published study describes the development and implementation of a similar CDSS [28]. However, this CDSS is developed for primary care and is not linked to a hospital information system. This system is a less advanced system, which is not able to automatically extract data which makes the recommendations less individualized and accurate. In addition, it is not clear how often the system could have been used and what the real uptake of recommendations is, because details of antibiotic prescriptions were not collected [28].

Conclusions

In conclusion, we developed a CDSS for empirical antibiotic therapy for adult hospitalized patients and gave a guidance of its development, validation and implementation. We have shown the usefulness of a systematic framework for reporting CDSS interventions. In addition, our data indicate that CDSS recommendations are not always adhered to and incorrect use of the system plays an important role in this.

Acknowledgements

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Ethics approval

According to the Dutch Medical Research in Humans Act, medical ethical approval was not required and patients did not need to provide informed consent, since their data were handled anonymously by the researcher [MEC-2016-101]

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Conflicts of interest

None.

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Supplementary data
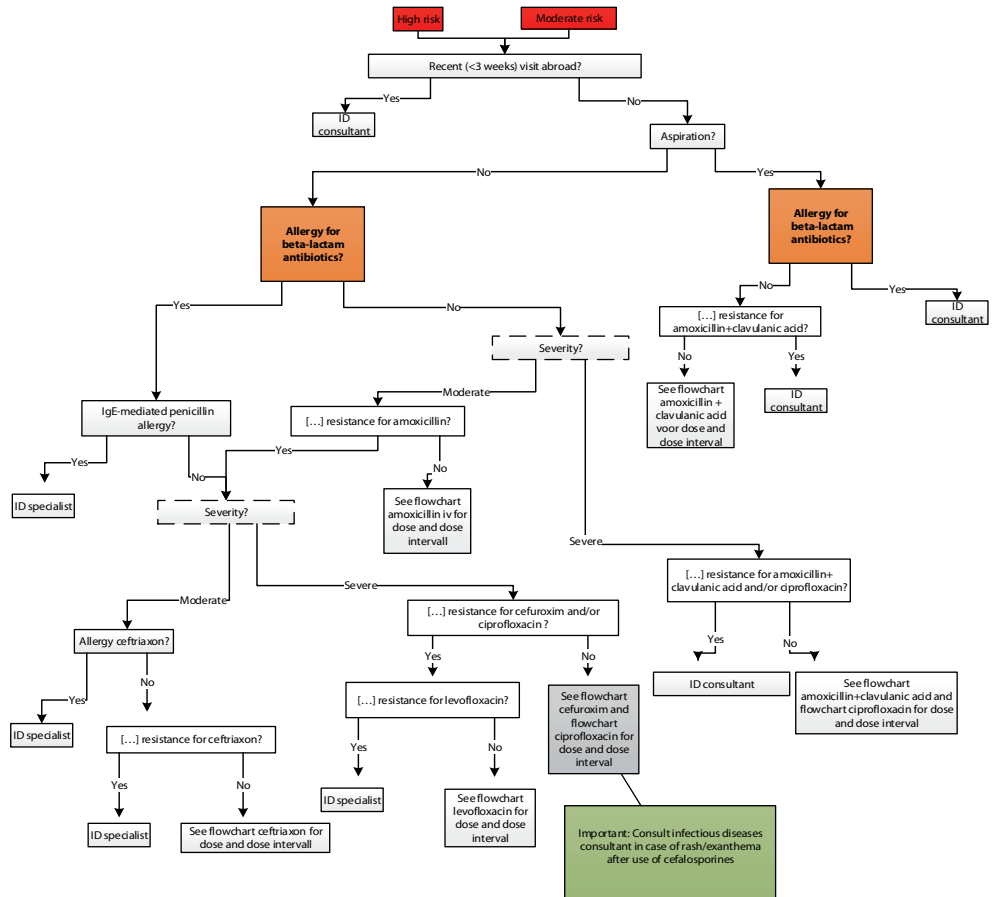
Supplementary Figure S6.1. Complete flowchart of high and moderate risk community acquired pneumonia.

Supplementary Figure S6.2. The resistance viewer in the CDSS for empirical antibiotic therapy.

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Summary and discussion

Antibiotic resistance has become a major global health problem, accelerated by the over- and misuse of antibiotics [1-6]. Antimicrobial stewardship has been implemented in many countries worldwide to promote the appropriate use of antibiotics by promoting the selection of the optimal antibiotic drug regimen, route of administration, dose and therapy duration [7, 8]. Information technology such as clinical decision support systems can improve antimicrobial decisions and can therefore play an important role in antimicrobial stewardship [9]. The main objective of this thesis was to provide insight in the aspects involved in the development, validation and implementation of a clinical decision support system to improve antibiotic prescribing. This thesis also provides insight in the magnitude of the problem of inappropriate prescription of antibiotics in our hospital and areas for improvement.

This chapter provides an overview of our main findings. In addition, an interpretation and description of these findings in light of current literature is given. We will describe lessons learned and provide recommendations for the development, validation and implementation of clinical decision support systems for antibiotic stewardship. Finally suggestions for future research will be given.

Main findings

Inappropriateness of antibiotic prescriptions and areas of improvement.

To effectively improve antibiotic prescriptions, insight into the (in)appropriateness of these prescriptions is helpful. The point prevalence survey described in **Chapter 2** revealed the prevalence of inappropriate antibiotic use in our tertiary care center and identified areas in which antimicrobial stewardship teams could have an important impact hospital wide. The study showed that antibiotics were used in about one third of adult patients in general wards. About two third of these patients used these antibiotics therapeutically, mainly on the following three wards: pulmonology, surgery and internal medicine. In about 45% of the patients a clinical microbiologist or infectious disease specialist was consulted. Approximately 30% of prescribed therapeutic antibiotics were classified as inappropriate mainly due to lack of indication for any antimicrobial therapy (15.6%). Antibiotics were chosen incorrectly in 8.1% of prescriptions with a more effective, less toxic, or less expensive alternative agent that was available. 6.8% of antibiotics were used incorrectly, mostly due to an incorrect duration of therapy or an improper dosage interval. As expected, broad-spectrum antibiotic drugs and antibiotic drugs used for empirical therapy were more often inappropriately prescribed than drugs for targeted therapy in our hospital. Infections of

the urinary and respiratory tract had the highest inappropriate antimicrobial drug therapy percentages. This study revealed insight into the appropriateness of antibiotic prescriptions in a tertiary care center in the Netherlands and identified areas for improvement. An important area of improvement is that an indication for antimicrobial therapy is often lacking. In addition it seems that empirical antibiotic therapy are more often inappropriately prescribed. We developed an interactive CDSS that can be used by physicians when prescribing empirical antibiotic therapy. This CDSS provides the physician with a patient tailored specific antibiotic advice, accompanied by the correct dose, dosage interval and duration. In addition we developed a CDSS to identify candidates that are able to switch from intravenous (iv) to oral antibiotics, to promote a timely switch.

Development of operationalized iv to oral antibiotic switch criteria

Timely iv to oral antibiotic switch is one of the most cost-effective stewardship interventions and is seen as 'low hanging fruit', referring to being a relatively easy to obtain stewardship intervention. For this reason several iv to oral antibiotic switch programmes are being used and implemented in hospitals. Iv-to-oral switch criteria, found in literature, mostly overlap, but a considerable variation exists in the operationalization of criteria which are often subjective [10-12]. In addition, uptake of early iv-to-oral switch has been difficult and the development of a consensus document with switch criteria with involvement of stakeholders has been recommended [10]. In **Chapter 3** such a consensus document is described. This consensus has been developed by an international, multidisciplinary expert panel, using a RAND-modified Delphi procedure.

The set of operationalized iv-to-oral antibiotic switch criteria have to be all met in adult hospitalized patients for a safe switch after 48-72 hours of iv therapy. The following switch criteria, with their operationalized criteria, should all be met in adult hospitalized patients for a safe iv-to-oral switch:

- Vital signs should be good or improving: systolic blood pressure should be stable without inotropics or fluid resuscitation;
- Signs and symptoms related to the infection have to be resolved or improved: temperature should be <38.3°C without antipyretics and above 36°C;
- The gastrointestinal tract (GIT) has to be intact and functioning: absence of the following conditions: malabsorption syndrome, short bowel syndrome, severe gastroparesis, ileus and continuous nasogastric suction;
- The oral route should not be compromised: no vomiting and patient should be cooperative;

- Absence of contraindicated infections: adequate antimicrobial concentrations are not achievable at the site of infection by oral administration. Absence of the following infections: (severe) sepsis, fasciitis necroticans, CNS infection, S. aureus bacteraemia, endovascular infection (e.g. endocarditis);
- An oral variant of the antibiotic with good bioavailability has to exist.

A clinical decision support system to promote the early switch from intravenous to oral antibiotic therapy

The consensus-based and operationalized criteria (**Chapter 3**) were translated into a computer-interpretable format to develop a clinical decision support algorithm (**Chapter 4**). This algorithm was validated and its clinical relevance and usefulness in daily clinical practice was assessed. The algorithm had a sensitivity of 98.6% and a specificity of 82.7% compared with the gold standard of the Delphi switch criteria, which resulted in a positive predictive value of 76.6% and a negative predictive value of 99.1%. These results indicate that this iv-to-oral antibiotic switch algorithm is a valid instrument to identify iv to oral switch (IVOS) candidates. About 10% of generated alerts by the iv-to-oral antibiotic switch algorithm were considered both clinically relevant and useful and resulted in an antibiotic advice to the treating physician by the infectious disease specialist of the antibiotic stewardship team. This algorithm is expected to be more effective in facilitating antimicrobial stewardship teams in hospital settings with no or a less active infectious diseases consultancy team.

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A clinical decision support system for empirical antibiotic therapy

Using a clinical decision support system is a promising method to improve guideline adherent empirical antibiotic therapy [13-16], which is one of the most important objectives of antimicrobial stewardship. Clinical decision support systems for empirical antibiotic therapy have been developed since many years. However the development of these systems have been continuously poorly reported. A web-based clinical decision support system for empirical antibiotic therapy for adult hospitalized patients was developed by a multidisciplinary team (**Chapter 5 and 6**). A detailed description of the development of this system can be found in **Chapter 6**. Before implementation in clinical practice we improved lay-out and functionality with a usability study using the think aloud method (**Chapter 5**), which is important because a poor usability negatively affects CDSS acceptance and effectiveness [17, 18]. In total 51 usability problems were found in different phases of the user system interaction, which contains 4 phases (planning, translation, physical actions and assessment). Most usability problems were found in the translation phase (55%). In this

phase users determine how to accomplish the intentions that emerge during the planning phase. This study revealed many existing usability problems that were not foreseen, even though the system was developed by a multidisciplinary team of clinical experts and information and communications technology professionals. To improve CDSS adoption, effectiveness and safety it is recommended to assess usability before its implementation. When designing a CDSS the following elements have to be considered to avoid usability problems:

- When a question has to be answered with a yes or no also provide the answer 'unknown'. If answering with yes or no is necessary for the system to generate an advice, provide users with this information.
- Make it easy to do right by providing calculators for everything that has to be calculated (the recommended dosage of an antibiotic drug, BMI etc.).
- Retrieve as much information as possible automatically from the hospital information system.
- Pay attention to the noticeability of relevant information (for example mouse over info with relevant explanatory information/definitions, resistance overview with information that is relevant for the final antibiotic advice).
- Provide users with information that is clear and as specific as possible and avoid reporting of irrelevant, confusing information.

After this usability assessment we implemented the CDSS in our hospital for a duration of 6 months by making it available through our hospital information system (**Chapter 6**). The system was used for 184 patients, mainly for the diagnosis pneumonia (67/184), followed by urinary tract infection (65/184). In 108 patients (58.7%) the antibiotic advice that was generated by the CDSS was completely (n=90) or partly (n=18) followed, but this was not the case for about one third the antibiotic advice that was generated by the CDSS. In about 47% of these patients physicians decided to prescribe another antibiotic drug than the antibiotic drug that was recommended by the CDSS. In **Chapter 6** we showed that incorrect use of the system plays an important role in not always adhering to the recommendations of the CDSS. In 8% physicians were testing the CDSS, using patients who did not have any signs of infection or were not admitted to the hospital. For this reason we recommend to provide test patients, specially created for this purpose when implementing a CDSS. We used a systematic framework to offer a guidance for the development and validation of a CDSS for empirical antibiotic therapy and showed the usefulness of this framework for reporting CDSS interventions (**Chapter 6**).

Methodological considerations

CDSSs can be divided into two different types: active or passive CDSS. While passive systems require initiation and/or input by the user, active CDSS provide decision support actively without initiation or input by the user. This thesis focuses on the development and implementation of these two different types of CDSSs to support appropriate/evidence based antibiotic prescribing. One CDSS was developed to promote an early switch from iv to oral antibiotics and the other to improve guideline adherent empirical antibiotic therapy. The CDSS algorithm to facilitate an early switch from iv to oral antibiotics is an active system, while the CDSS that we have developed for empirical antibiotic therapy is a passive system, which requires initiation and input from the physician. We have encountered different problems, which are related to this aspect. With the passive system which had to be initiated by the physician and data had to be manually entered we found that in case of non-adherence to CDSS recommendations physicians often used the system incorrect. In addition, low use of these CDSSs is a known problem and an obstacle in achieving their potential. With the active system alert fatigue is an important aspect to take into account, which is a well-known problem related to an active CDSS [19, 20]. We found that 46.5% of alerts generated by this active CDSS were not clinically relevant and therefore had no consequences for the antibiotic policy. This can be explained by the fact that not only coded or numerical data can be effectively used in a CDSS format. We did not specifically assess alert-fatigue in our study, but to reduce this risk, advanced coding of data in EHR, would be helpful.

We have used several methodologies to assess the developed CDSS. The iv to oral switch algorithm has been developed using consensus criteria which were developed with a RAND Delphi procedure. After we developed this algorithm we performed a quantitative study. We have assessed the test/algorithm performance (sensitivity, specificity, positive and negative predictive value) and assessed the usefulness in clinical practice. For the CDSS that we have developed for empirical antibiotic therapy we performed both qualitative as quantitative research to assess important aspects regarding the usability of a CDSS (qualitative) and to assess the use and uptake after its implementation (quantitative). The use of both these methodologies are complementary. While the qualitative study gives insight in causes for suboptimal/incorrect use of the system, the quantitative study shows the quantity of CDSS use and adherence to its recommendations.

For the iv to oral switch algorithm we first performed a study striving for consensus criteria, because we assumed a CDSS based on evidence- and expert based criteria would improve acceptance. Criteria and their measurable parameters in literature were subjective and slightly different from each other and not in a computer interpretable format.

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In contrast to the active iv oral switch algorithm, more interaction exists between the passive CDSS for empirical antibiotic therapy and the user. This system needs initiation and input from the user. In addition, the iv oral switch algorithm was directed to ID-specialists, while the passive empirical therapy CDSS was mentioned to be used by all prescribers. Usability plays a much greater role for these reasons with this system. To improve acceptance, efficacy and safety of our CDSS for empirical antibiotic therapy we performed a usability study. With this study we also involved future users of the system, which we thought would be helpful to improve CDSS acceptance. We have implemented and studied our CDSSs in a tertiary care hospital in Rotterdam (the Erasmus MC) with an active ID consultancy system. This of course has implications for the generalizability of our results. This will be discussed in more detail below.

Implication for practice

Setting priorities

The (inappropriate) of antibiotics in hospitals contributes with no doubt to the growing challenge of antibiotic resistance. Therefore, an important first step is to gain insight in this inappropriate use to set priorities and develop specific actions /strategies in the fight against antibiotic resistance. Our study (**Chapter 2**) and multiple other studies have shown that inappropriate use of antibiotics in European hospitals is high, ranging from 30 to 50% [21-23]. Our findings underline the importance and need of antimicrobial stewardship and offer areas of possible intervention by antimicrobial stewardship teams. Interventions of antimicrobial stewardship should focus on reducing the unnecessary prescription of antibiotics, which is an important area of improvement (**Chapter 2**). This survey also showed that nearly 6% of patients could not be evaluated for appropriateness of antibiotic use due to insufficient information in the hospital information system. Missing data in the hospital information system has consequences for the development and the (im)possibilities of a CDSS. Especially for an active CDSS, which generates alerts/advices without input or request of a user. In case of a passive CDSS, input can be requested of a user to add missing information that is relevant for an advice. This has to be taken into account when a CDSS will be introduced. It is recommended, especially if information is missing, that the information on which an advice/alert is based is directly viewable or accessible from the advice/alert given. The point prevalence survey which we have used to assess the appropriateness of antibiotic use in our hospital has proven to be a useful instrument for this purpose. Other acknowledged methods exist to assess the quality of antibiotic use in hospitals, for example the use of quality indicators or the monitoring of quantitative antibiotic use [24]. Quality indicators (QIs) are 'a measurable

element of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality, of care provided' [25]. Quality indicators to measure the appropriateness of antibiotic use in the treatment of all bacterial infections in hospitalized patients were not available yet at the moment of our survey. However, at this moment such quality indicators have been developed and validated in a clinical setting [26]. These indicators describe/define appropriate antibiotic use from start to discontinuation of antibiotics [26], and appear to be associated with a shorter length of hospital stay [27]. These quality indicators can be used to measure performance retrospectively, but can also be used prospectively as the basis for developing different types of clinical decision aids [28]. The CDSS that we have developed (**Chapter 4, 5 and 6**) aims to improve/optimize these indicators (4 of 9 indicators), namely: 1. Systemic antibiotic therapy should be switched from iv to oral antibiotic therapy within 48-72 hours on the basis of the clinical condition and when oral treatment is adequate. 2. Empirical systemic antibiotic therapy should be prescribed according to the local guideline. 3. An antibiotic plan should be documented in the case notes at the start of systemic antibiotic therapy. 4. Dose and dosing interval of systemic antibiotics should be adapted to renal function. The other quality indicators are: - before starting systemic antibiotic therapy at least two sets of blood cultures should be taken; - take cultures from suspected sites of infection as soon as possible, preferably before antibiotics are started; -change empirical to pathogen-directed therapy if culture results become available; - perform therapeutic drug monitoring at steady state; - discontinue antibiotic therapy if infection is not confirmed. The maximum duration of empirical systemic antibiotic treatment should be 7 days. These quality indicators should also be used in antibiotic stewardship to measure appropriateness of antibiotic use and are ideally also a target for other CDSS in the future.

Consensus on iv to oral antibiotic switch criteria.

Although robust scientific evidence about which iv to oral antibiotic switch criteria have to be minimally met for a safe iv to oral switch in hospitalized patients is missing, physicians must nonetheless make the decision to switch on a regular basis. The operationalized criteria in **Chapter 3** are developed using a modified-RAND Delphi procedure [28], in which a systematic literature search and input from an international multidisciplinary panel composed of experts from involved medical disciplines is combined. These criteria can be used in daily clinical practice, by antibiotic stewardship teams and by attending physicians and are an important step towards improving the (national) uptake of an early switch from iv to oral antibiotics. It is recommended that these consensus criteria are being disseminated [10]. Especially since a striking lack of awareness of iv to oral switch guidance is one of the barriers to iv to oral switch programs [10]. When introducing such programs it is

recommended to annually audit them to measure success or areas of improvement [10]. The developed criteria may facilitate auditing iv-to-oral antibiotic switch practices on a specific ward or hospital, and enable comparisons between hospitals or regions. To improve iv-to-oral antibiotic switch practices in an effective and sustainable manner, more is needed than instructions and guidelines [29]. A CDSS that reminds physicians to switch their patients to oral antibiotics has great potential. Earlier developed CDSS for this purpose have been developed using local criteria [30, 31]. Other CDSS for this purpose use very general rules, such as a certain duration of iv therapy or/and an active order for scheduled oral medications or an oral diet [32, 33]. This limits their general applicability, acceptance and specificity. The developed consensus criteria can be used to build a system, which is general applicable.

Iv to oral antibiotic switch alerts in clinical practice

A CDSS, based on consensus criteria (**Chapter 3**), is effective in facilitating antibiotic stewardship teams by offering a preselection of iv to oral switch candidates (**Chapter 4**). It is plausible to assume that this saves time and work in comparison with a situation in which antibiotic stewardship teams have to assess all admitted patients with an iv antibiotic on the possibility to switch from iv to oral antibiotics. About one third of admitted patients in a hospital receive antibiotic drugs (**Chapter 2**), which in our hospital were in total 337 patients (on both May 4th and May 16th 2013) (**Chapter 2**). A daily assessment by an antibiotic stewardship team of all these patients is not feasible. A CDSS has the potential to preselect patients which qualify for iv-oral switch. For instance, our CDSS algorithm generated 840 alerts in 773 different patients during a period of 4 months, which is a number of patients that is feasible to asses for the antibiotic stewardship team; an average of 10 per day (standard deviation: 4). The number of clinical relevant and useful alerts can be increased by further optimization of the CDSS algorithm, for example by introducing the possibility to switch off/delay alerts for a certain duration for patients with infectious diseases for which a relatively long duration of iv therapy is needed (for example endocarditis). Our CDSS algorithm was not able to exclude or delay an alert for these patients, because criteria that contain a diagnosis could not be translated into a computer interpretable format (**Chapter 3**). Improving this is important, because over alerting can lead to alert-fatigue, a well-known problem related to an active CDSS [19, 20].

Since in the Netherlands, in approximately 60% of the hospitals funding for antibiotic stewardship programs is lacking and if a budget is provided less than indicated by the staffing standard [34], a CDSS that saves work seems ideal. However, only 9% of Dutch hospitals have dedicated IT support for stewardship teams [34]. Improving this will create more possibilities for the development and improvement of several CDSSs.

A CDSS for empirical antibiotic therapy

In addition to the active CDSS algorithm for iv to oral switch, we developed a passive CDSS for empirical antibiotic therapy. It is recommended to assess usability before implementation of a CDSS, especially with a lot of user system interaction, to improve its adoption, effectiveness and safety. For this, the augmented UAF (systematic framework developed by Khajouei et al. [17]) can be used, as it is a simple, but effective way to identify usability problems and prioritize system redesign effort (**Chapter 5**). For ultimate system usability, iterative usability evaluation during the development and implementation of CDSS is important [18, 35]. Residents do not always follow advice of the CDSS without considering the correctness and applicability of the recommendation (**Chapter 5**), which is positive, because these systems should always be seen as an aid. The definite decision is always at the physician's discretion and too much reliance on a CDSS may have a negative impact on the skills of the user. There may be good reasons to deviate from a guideline, so also from a CDSS based on a guideline. In this light it is also important to note that the uptake of CDSS in hospitals is hindered by the concern of clinicians that their professional autonomy or critical thinking may be reduced by the system [36]. Related to this concern is the fear that the advice of a CDSS can be used against them in medico-legal procedures. This goes both ways; on the one hand the CDSS clearly reveals the discrepancy between (several) guidelines and contextualized decisions [36]. Thus not following or not using the CDSS can be used against the physicians for which this discrepancy is important in the decision making (for example when the kidney function or BMI of a specific patient should be taken into account). On the other hand introduction of technology can cause new types of error. Thus, blindly following the CDSS advices can be used against the physicians. For this reason it is important that the legal consequences of (not) following CDSS advices become clear in context of liability [37].

One of the elements that have to be considered to avoid usability problems is to retrieve as much information as possible automatically from the hospital information system (**Chapter 5**). Several challenges exist in achieving this, such as required data not being available in the EHR (**Chapter 2**) or data being unreliable. An example of unreliable data in the EHR is the (alleged) presence/absence of an allergy. Another challenge is data not always being coded in a standardized terminology in the EHR. For example, we found that we could not retrieve the diagnosis automatically from our EHR, because clinical users use free text to record the diagnosis. For this reason the diagnosis is one of the data that had to be entered manually. This however could also be seen as an advantage in light of maintaining physicians 'autonomy' as this gives control over the CDSS.

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Since not all antibiotic guidelines were present in the CDSS, we assessed in how many patients the system could be used (data not published). During the implementation period of the CDSS, 3,349 patients received at least one antibiotic for systemic use. From these 3,349 patients we randomly selected 248 patients to manually check whether the patients had one of the diagnosis included in the CDSS. In this proportional stratified random sample of 248 patients all departments were reflected. From these 248 patients, 100 patients received at least one antibacterial drug as empirical antibiotic therapy for one of the diagnosis included in the CDSS, which is equivalent to 40.3% (95% CI 34.3-46.3) of patients. That means that of the 3,349 patients that received at least one antibiotic for systemic use, 1,349 patients received this antibiotic(s) as empirical antibiotic therapy for one of the included diagnosis in the CDSS. The CDSS was used 184 times, of which 15 times for patients who did not have any signs of infection or were not admitted to the hospital (trying out/testing the system). Thus the system was used for 12.5% (184-15)/1,349) of patients for which it could be used.

This low use existed despite the development by a multidisciplinary team, usability testing (**Chapter 5**), followed by improving the system and promotion of use on a regular basis in clinical practice. A low level of CDSS use is found in several studies [38-43]. In one study, the study design was adjusted because of potential CDSS underutilization. In this study the researchers performed preintervention interviews, which showed that clinicians perceived excessive time would be required for the use of the CDSS. For this reason an antimicrobial management team was organized that used the CDSS and made the clinicians aware of CDSS recommendations [40]. This clearly illustrates the problem with the use of CDSSs. In this study an Internet-based decision support tool was used for empirical antibiotic advice for community acquired pneumonia. A detailed description of the tool is missing in the study publication. The system was not connected to an EHR. Therefore automatic extraction of relevant information from the EHR was not possible and all relevant information for an antibiotic advice had to be entered in the system. This may have contributed to the perception of the clinician that excesive time would be required for the use of the CDSS.

A relatively high rate of adoption (57.5%) was demonstrated in a study of CDSS/clinical prediction rules (the Heckerling Clinical Decision Rule for pneumonia and the Walsh clinical prediction for streptococcal pharyngitis) in primary care [44]. The authors speculate that this high rate is because of their development process which was comprehensive and user-centered. Like us, they performed usability testing and collaborated with a multidisciplinary team. Beside this, they performed focused user training on clinical decision support and their multidisciplinary team included also clinical decision support specialists. Our CDSS was developed by a multidisciplinary team, composed of an infectious disease physician, a clinical pharmacist with infectious diseases training experienced in clinical

decision support, a clinical microbiologist, an infection control professional and a hospital epidemiologist. To improve use, we recommend to add an expert on implementation of CDSS to the development team. This way implementation issues can be taken into account in an early stage of CDSS development. Another important aspect that has probably contributed in a positive way to the higher adoption rates of the earlier mentioned CDSS/prediction rules in primary care, is the blending of the system in the clinical workflow [44]. The clinical prediction tool appeared on the screen when the provider entered one or more relevant keywords in certain fields during a clinical encounter. We found a low use of our CDSS for empirical antibiotic therapy, which may be explained by it being a passive and new system. At the moment of empirical antibiotic prescribing, physicians had to realize that a CDSS could assist them and find the link to the system in our EHR. A reminder in the CPOE and direct access from the CPOE (fitting in the work process) could be an option to improve CDSS use. A system not being integrated into workflows is one of the barriers that is often described in literature [45]. To improve integration into workflow we recommend making CDSS also accessible at the point of care as smartphone application. Especially since smartphone use among clinicians is increasing.

Multiple other barriers to use a CDSS are described in literature, such as the earlier mentioned fear that such a system will compromise professional autonomy. Other barriers which are mentioned in the literature, include: a poor usability [17,18], and absence of technical support and training [45]. Although CDSSs have high potential in improving guideline adherent therapy their low use is a major barrier in reaching their potential. In addition, because of this low use, measuring clinical outcome is challenging, given the fact that a large sample size is needed to find significant differences in important outcome measures.

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Our CDSS and other CDSS for antibiotic therapy: differences and similarities

CDSSs to support appropriate use of antibiotics have been developed since 1980 [38]. These systems have targeted a variety of aspects, such as optimizing antimicrobial dosing or supporting antimicrobial de-escalation. Most of these systems however focus on antimicrobial prescribing [38]. CDSSs to promote an early iv to oral antibiotic switch have been developed before. However, none of the CDSS for an early iv to oral switch are based on international consensus criteria. Earlier developed CDSSs to promote an early iv to oral antibiotic switch have been developed using local criteria [30,31] or very general rules, such as a certain duration of iv therapy or/and an active order for scheduled oral medications or an oral diet [32,33]. This limits their general applicability, acceptance and specificity.

Many CDSSs that are developed for more general antibiotic prescription focus on a specific infectious disease, mostly respiratory tract infections [46, 47-54 55, 56] or are developed/ implemented/tested only in or for a specific department, such as the emergency department [53, 57-59] or the intensive care [60-63], or in a limited number of departments [13, 16, 55]. In our CDSS for empirical antibiotic therapy, the most common infections were included and our CDSS was implemented in a tertiary hospital with a wide variation of departments. Several CDSSs have been specifically developed to improve empirical antibiotic therapy for hospitalized patients [13-16, 64]. The CDSSs, specifically developed for empirical antibiotic therapy differ on varying aspects. Some systems use expert rules to predict the pathogen's susceptibility to antibiotics, using antibiotic susceptibility profiles from patients with similar characteristics [14, 15, 65], but don't take into account for example the antibiotic resistance history of the patients of interest, or presence of neutropenia [15, 65], like our system does. Other systems use causal probabilistic networks to predict the probability of a bacterial infection, site of infection and pathogens and their susceptibility to antibiotics. The CDSS we developed generates antibiotic advices based on relevant guidelines. Like many other CDSS for empirical antibiotic therapy, input of the physicians was needed in our system for the generation of an antibiotic advice [13-15, 64, 65].

It is important to note however that a good comparison between the different CDSSs is difficult, because of a heterogeneous and disjointed approach to reporting CDSS interventions [38]. Following Rawson's framework [38] ensures a structured overview of many important aspects of a CDSS intervention. Use by others is recommended and will enable a more easy comparison between the different CDSSs. Several important aspects are not included in this framework, such as: the composition of the team that developed the CDSS, type of CDSS (active or a passive), guidelines on which the CDSS is based, rationale for using these guidelines, commercial or noncommercial CDSS, setting for which the CDSS was developed. We propose that these key components should also be considered when reporting on CDSS interventions.

Implications for future research

Iv to oral switch algorithm

The iv to oral switch algorithm proved to be a valid instrument to identify IVOS candidates. With this algorithm a report containing all eligible patients for IVOS was automatically generated on a daily basis and directed to the ID specialist of the Antibiotic Stewardship Team. The ID specialist then assessed whether the patient could switch to oral therapy and

contacted the treating physician if this was possible. It is important and interesting to use future research to assess the number of patients that have been switched to oral antibiotics by the treating physician after this contact. Future research should focus on the effect of this algorithm on outcomes, such as length of stay, readmission rates and costs.

A report with iv to oral switch candidates saves work in comparison with a situation in which the ID specialist has to assess all patients with an iv antibiotic on the possibility to switch to oral antibiotics. However, alert fatigue may still be a problem. For this reason future research should take this aspect into account. With advanced coding of data in EHR the efficacy of the CDSS can be improved, thereby also reducing this risk of alert fatigue. This also provides the opportunity to direct the alerts generated by this algorithm directly to the treating physician in the future. We expect the additional value of the algorithm to be even more in a setting with no or a less active ID service. Research is needed in these settings to evaluate this assumption.

CDSS for empirical antibiotic therapy

The 6-month time period may have been too short to improve use/uptake of the CDSS for empirical antibiotic therapy, since it has been shown that continued use of these systems improves their acceptance [55, 66-68]. Future research should aim to assess use and uptake of CDSS for a longer duration. To gain more insight in the specific barriers to CDSS use in our hospital further research is useful. With an understanding of these specific barriers a specific action plan may be developed to generate interest and improve use of this CDSS and the uptake of its advice. Improving CDSS use and uptake is important to achieve its full potential and also to justify the costs that are associated with development and maintenance of these systems. With more use of the CDSS (with a longer implementation/study period and tackling of specific barriers) a larger sample size can be created for future studies that measure differences in important outcome measures, such as the susceptibility of cultured micro-organism for the prescribed antibiotic before and after implementation of the CDSS. A multicenter approach is recommended to facilitate appropriate sample size. Besides an appropriate sample size this also provides the option to assess differences of implementation in different settings. We expect that the developed CDSSs will be of more value in a hospital with less active ID consultancy systems. In addition, given the fact that first-line care and long-term care include the highest antibiotic prescription rates the implementation and research of CDSS to improve antibiotic use should ideally also be extended to these settings. Because new resistance mechanisms emerge and spread globally, implementing and assessing CDSS in low- and middle-income countries (where antimicrobial resistance is high) is an important future target.

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To help increase the use of a passive CDSS, such as our CDSS for empirical antibiotic therapy, enabling access at the point of care as a smart phone application is recommended. Especially since smartphone use among clinicians is increasing.

Future research should also focus on smartphone based CDSS, because smartphones are increasingly being used by physicians. It is interesting to study the utilization, acceptability and impact of such a CDSS. The Erasmus Medical Center will participate in an international randomized, multicenter clinical trial evaluate the impact of an antimicrobial stewardship smartphone application for the hospital setting [69].

Artificial intelligence / Machine learning CDSS

The CDSSs described in this thesis, like most current CDSSs, use algorithms/rules to generate alerts (iv to oral switch algorithm) or an advice. Changes in guidelines have to be followed by manually changing the algorithms/rules on which the CDSS is based. In the world of health technology another field, that has drawn increasing interest, are CDSSs using artificial intelligence/machine learning. With artificial intelligence/ human learning, systems are able to create/add algorithms/rules themselves. These systems learn automatically from data, and their performance is therefore depending on the quantity and quality of available data. For this reason most of these systems in infectious diseases target domains with high quality and large databases, such as certain patient populations in the ICU. With the availability of more of such databases this is an important future development to focus on and to study. It is important that attention is paid to the transparency of algorithms/rules on which these systems are based. Especially since an important barrier to use a CDSS is the concern of clinicians that their professional autonomy or critical thinking may be reduced by the system. With systems that are able to manage and act relatively fast on large amount of information, it is imaginable that these systems may be equal or better in decision-making than clinicians (in the future), and this concern becomes even more pertinent.

Final remarks

The studies described in this thesis resulted in valuable insights in relevant aspects involved in the development, validation and implementation of a clinical decision support system to improve antibiotic prescribing. The developed (active) iv to oral switch algorithm proved to have good test performance and the added value of this algorithm in identifying iv to oral switch candidates was shown. Important general usability problems that have to be taken into account when developing a passive CDSS for empirical antibiotic therapy have been described. Finally the usefulness of a systematic framework for reporting CDSS interventions was shown.

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Summary in Dutch
Nederlandse samenvatting

Antibiotica resistentie is wereldwijd een groeiend probleem en vormt een bedreiging voor de volksgezondheid. Overmatig en onjuist gebruik van antibiotica dragen hier in belangrijke mate aan bij [1-6]. Om deze reden wordt 'antimicrobial stewardship' wereldwijd geïmplementeerd. Dit zijn activiteiten die worden ingezet om resistentie-ontwikkeling te beheersen door te bevorderen dat de optimale antibiotica, toedieningsweg, dosering en therapieduur worden gekozen [7,8]. Informatie technologie, zoals beslissingsondersteunende systemen, kunnen hierin een belangrijke rol spelen [9]. Het hoofddoel van dit proefschrift is om inzicht te verkrijgen in relevante aspecten ten aanzien van de ontwikkeling, validatie en implementatie van beslissingsondersteunende systemen voor antibiotica gebruik. Met dit proefschrift wordt de bruikbaarheid van een algoritme onderzocht dat kandidaten selecteert voor de switch van intraveneuze naar orale antibiotica. Daarnaast wordt een beslissingsondersteunend systeem geëvalueerd dat ontwikkeld is om empirische antibiotica juist voor te schrijven. Voor de rapportage hiervan wordt gebruik gemaakt van een recent ontwikkeld systematisch raamwerk, waarvan tevens de bruikbaarheid wordt beoordeeld. Dit proefschrift verschaft ook inzicht in de grootte van het probleem van onjuist antibioticagebruik in het Erasmus MC en laat zien op welke aspecten hierin verbetering te behalen valt.

Onjuist gebruik van antibiotica

Om het gebruik van antibiotica in het ziekenhuis te verbeteren is het allereerst belangrijk om inzicht te krijgen in de grootte en de aard van het probleem. Met een puntprevalentie studie (beschreven in **Hoofdstuk 2**) is dit onderzocht. Dit is een studie waarmee het vóórkomen van bepaalde gegevens op 1 specifiek 'punt' in de tijd wordt gemeten (in onze studie 2 specifieke dagen). Met deze studie is inzichtelijk geworden hoe vaak antibiotica onjuist worden voorgeschreven in ons ziekenhuis en wat er beter kan. Deze verbeterpunten kunnen de antimicrobial stewardship teams (ASTs) richting geven. De studie heeft aangetoond dat ongeveer een derde van de volwassen patiënten in ons ziekenhuis antibiotica kreeg voorgeschreven. Ongeveer twee derde van deze patiënten gebruikte deze antibiotica voor therapeutische doeleinden, voornamelijk op de volgende drie afdelingen: longziekten, chirurgie en interne geneeskunde. In ongeveer 45% van de patiënten werd een klinisch microbioloog of specialist infectieziekten geconsulteerd. Er werd gebruik gemaakt van een gestandaardiseerde methode om de antibiotica therapie te beoordelen. Ongeveer 30% van de therapeutische antibiotica voorschriften werd geclassificeerd als onjuist, vooral door het ontbreken van een indicatie voor antimicrobiële therapie (15,6%). In 8,1% van de antibioticumvoorschriften had een ander, effectiever, minder toxisch of goedkoper antibioticum de voorkeur. Bij 6,8% van de antibioticavoorschriften was het doseerinterval,

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de therapieduur, dosering of toedieningsweg incorrect. Onjuiste voorschriften zagen we vaker bij breed spectrum antibiotica en bij antibiotica die vaker empirisch worden toegepast (als nog niet bekend is welk micro-organisme de infectie veroorzaakt). Bij infecties van de urine- en luchtwegen zagen we het hoogste percentage onjuist antibiotica gebruik. Deze studie heeft inzicht verschaft in zowel de kwantiteit als kwaliteit van antibioticagebruik in een tertiair ziekenhuis in Nederland en het belang van antimicrobial stewardship bevestigd. Omdat in de helft van de onjuist geclassificeerde antibiotica een indicatie voor een antibioticum ontbreekt, is het voorschrijven op indicatie een belangrijk punt waar ASTs zich op zouden moeten richten. Het is bij empirische therapie van belang dat er een werkdiagnose (indicatie) is, het antibioticum hierbij past en deze diagnose ook wordt vastgelegd. Het lijkt er namelijk op dat met name deze empirische antibiotica onjuist worden voorgeschreven. De puntprevalentie meting is een bruikbaar instrument gebleken om de juistheid/onjuistheid van antibiotica te onderzoeken. Een andere methode om de kwaliteit van antibioticagebruik te onderzoeken is het gebruikmaken van kwaliteitsindicatoren. Dit zijn meetbare aspecten binnen de zorg die gebruikt kunnen worden om de kwaliteit van zorg te toetsen [10]. Algemene kwaliteitsindicatoren voor antibioticagebruik in ziekenhuizen, die van hoge kwaliteit zijn en tevens zijn gevalideerd, zijn in 2015 ontwikkeld (gevalideerd in 2016) [11-13]. Voorbeelden van deze indicatoren zijn:

a. Empirische systemische antibiotica dienen te worden voorgeschreven volgens de lokale richtlijn.
b. Bij het starten van systemische antibiotica dient een antibioticumplan (naam antibioticum, dosering, toedieningsweg, toedieningsinterval en geplande duur) te worden gedocumenteerd.
c. De dosering en doseerinterval van systemische antibiotica dienen te worden aangepast aan de nierfunctie.
d. Systemische antibiotica dienen geswitcht te worden van intraveneuze naar orale therapie binnen 48-72 uur op basis van de klinische conditie en wanneer orale therapie adequaat is.

Bovenstaande indicatoren zijn samen met de resultaten uit onze puntprevalentie studie richtinggevend geweest voor het ontwikkelen van de beslissingsondersteunende systemen die beschreven zijn in dit proefschrift. We hebben op basis van de kwaliteitsindicatoren een algoritme ontwikkeld dat eenvoudig en snel patiënten identificeert die kunnen switchen van intraveneuze naar orale antibiotische therapie. Daarnaast hebben we op basis van de resultaten van onze puntprevalentiestudie en meerdere kwaliteitsindicatoren een beslissingsondersteunend systeem ontwikkeld dat te gebruiken is door artsen bij het voorschrijven van empirische antibiotica. Dit systeem genereert een patiënt specifiek

advies, waarbij rekening wordt gehouden met alle belangrijke parameters. Zo worden bijvoorbeeld de dosering en het doseerinterval aangepast aan de nierfunctie. Daarnaast genereert het systeem een compleet advies met de naam van het antibioticum, dosering, toedieningsweg en het toedieningsinterval. Omdat dit systeem niet gekoppeld is met het ziekenhuisinformatiesysteem (ZIS) is het niet mogelijk deze informatie automatisch op te laten slaan in het ZIS. Koppeling met het ZIS is aanbevolen om deze functionaliteit (automatisch documenteren van een antibioticumplan) mogelijk te maken.

Consensus over iv orale switch criteria

Antibiotica worden vaak onnodig lang via de intraveneuze toedieningsweg toegediend. Om een tijdige switch te stimuleren wordt aangeraden om een consensus document met iv orale switch criteria te ontwikkelen [14]. Een tijdige switch van intraveneuze (iv) naar orale antibiotica is een van de meest kosteneffectieve stewardship interventies. Het wordt gezien als 'laaghangend fruit', waarmee bedoeld wordt dat de interventie relatief snel en eenvoudig resultaat geeft. Veel ziekenhuizen zijn hiermee bezig, maar de iv orale switch criteria die beschreven worden in de literatuur variëren nogal en zijn vaak subjectief van aard [14-16]. We hebben een RAND-gemodificeerde Delphi-studie uitgevoerd om tot consensus te komen en deze is beschreven in **Hoofdstuk 3**. Een internationaal, multidisciplinair expert panel bereikte consensus over geoperationaliseerde criteria waaraan minimaal moet worden voldaan om veilig naar oraal te kunnen switchen na 48-72 uur iv therapie. Het gaat om de volgende criteria:

- Vitale parameters moeten goed zijn of verbeteren: de systolische bloeddruk dient stabiel te zijn zonder hartversterkende medicatie of vochttoediening;
- Symptomen gerelateerd aan de infectie dienen afwezig te zijn of verbeterd: geen koorts (temperatuur <38,3°C zonder gebruik van koortsverlagende middelen) en geen ondertemperatuur (temperatuur >36°C);
- Het maagdarmkanaal moet goed functioneren: de volgende zaken moeten afwezig zijn: malabsorptie syndroom, short bowel syndroom, ernstige gastroparese, ileus en een maaghevel;
- Afwezigheid van gecontra-indiceerde infecties, dat wil zeggen infecties waarbij adequate concentratie van antimicrobiële middelen op de plaats van infectie niet te bereiken is met orale toediening, (ernstige) sepsis, fasciitis necroticans, infectie van het centrale zenuwstelsel, S. aureus bacteriemie, endovasculaire infectie (bijv. endocarditis);
- De orale route moet mogelijk zijn: de patiënt moet coöperatief zijn en niet braken;

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- Een orale variant van het antibioticum met een goede biologische beschikbaarheid dient beschikbaar te zijn.

Switchen van intraveneuze naar orale antibiotica met behulp van een beslissingsondersteunend systeem

De op consensus gebaseerde en geoperationaliseerde criteria (**Hoofdstuk 3**) zijn omgezet naar een format dat door de computer te interpreteren is om zo een beslissingsondersteunend algoritme te kunnen ontwikkelen. Dit algoritme genereerde lijsten met kandidaten voor de switch van intraveneuze naar orale therapie. Deze lijsten werden gebruikt door de specialisten infectieziekten van het Erasmus MC om behandelend artsen te wijzen op een mogelijke switch (**Hoofdstuk 4**). Dit algoritme is gevalideerd en de klinische relevantie en bruikbaarheid van de alerts die het genereert zijn onderzocht. Hiervoor is gebruik gemaakt van een gestandaardiseerde ontwikkel- en validatie methode, waarbij verschillende stappen zijn doorlopen [17]. Gedurende de eerste stap is een retrospectieve technische validatie verricht, om te kunnen bevestigen dat de systeemparameters correct gelinkt zijn met de relevante data in ons ziekenhuisinformatiesysteem. Gedurende de tweede stap zijn alle alerts onderzocht op klinische relevantie, uitvoerbaarheid en bruikbaarheid. Gedurende stap drie zijn de alerts aangepast naar en getest in een prospectieve setting. Het algoritme bleek een sensitiviteit te hebben van 98,6% en een specificiteit van 82,7%. De positief voorspellende waarde van het algoritme bedroeg 76,6% en de negatief voorspellende waarde 99,1%. Het iv orale switch algoritme blijkt een valide instrument om kandidaten te selecteren die kunnen switchen van de intraveneuze toedieningsweg naar de orale. Ongeveer 10% van de alerts die door het algoritme werden gegenereerd waren zowel klinisch relevant als bruikbaar en dit resulteerde in een advies door de specialist infectieziekten aan de behandelend arts. Het Erasmus MC heeft een consultsysteem, waarbij de specialist infectieziekten actief bijdraagt aan het bevorderen van goed antibioticagebruik. We vonden zelfs in deze setting een toegevoegde waarde van het algoritme. Met dit algoritme is een goed begin gemaakt in de filtering van patiënten die zouden kunnen switchen van iv naar orale therapie.

Een beslissingsondersteunend systeem voor empirische antibiotische therapie

Eén van de belangrijkste doelstellingen van antibiotic stewardship is het juist voorschrijven van empirische antibiotica. We hebben om deze reden tevens een beslissingsondersteunend systeem ontwikkeld dat door artsen is te gebruiken bij het voorschrijven van empirische antibiotische therapie voor volwassen patiënten in het ziekenhuis. Dit web gebaseerd systeem is ontwikkeld door een multidisciplinair team, bestaande uit een onderzoeker, een ziekenhuisapotheker, artsen-microbioloog, internist-infectiologen en een ICT team.

Om de acceptatie, effectiviteit en veiligheid van een dergelijk systeem te verbeteren wordt aanbevolen om de bruikbaarheid ervan te onderzoeken voordat implementatie plaatsvindt [18, 19]. Een onderzoek naar de bruikbaarheid van het ontwikkeld systeem is te vinden in **Hoofdstuk 5**. In totaal werden 51 bruikbaarheidsproblemen gevonden in verschillende fasen van interactie tussen gebruiker en het systeem. De verschillende fasen van interactie tussen gebruiker en systeem zijn: planning, omzetting, fysieke actie en beoordeling. De meeste bruikbaarheidsproblemen werden gevonden in de omzettingsfase. Gedurende deze fase bepalen gebruikers hoe zij de intentie die tijdens de planningsfase opkwam, kunnen bereiken. De verrichte studie heeft vele bruikbaarheidsproblemen aan het licht gebracht die niet waren voorzien, ondanks het feit dat het systeem ontwikkeld was door een multidisciplinair team bestaande uit klinische experts en ICT professionals. Om het gebruik, de effectiviteit en de veiligheid van beslissingsondersteunende systemen te verbeteren wordt aangeraden om de bruikbaarheid ervan te beoordelen voordat deze worden geïmplementeerd. Bij het ontwikkelen van een interactief beslissingsondersteunend systeem gelden de volgende algemene adviezen:

- Geef bij een vraag die beantwoord dient te worden met een 'ja' of een 'nee' ook de optie 'onbekend';
- Maak het gemakkelijk voor de gebruiker om het goed te doen (bijv. door het systeem te voorzien van calculators voor het berekenen van dosering, BMI etc.);
- Haal zoveel mogelijk informatie automatisch op uit het ziekenhuisinformatiesysteem;
- Besteed aandacht aan de zichtbaarheid van relevante informatie (bijv. informatie icoon waarachter belangrijke definities of aanvullende informatie verscholen ligt);
- Voorzie de gebruikers van informatie die duidelijk en specifiek is en voorkom gebruik van irrelevante, verwarrende informatie.

Na dit bruikbaarheidsonderzoek implementeerden we het beslissingsondersteunend systeem in ons ziekenhuis voor een duur van 6 maanden door de link naar het systeem beschikbaar te maken in het ziekenhuisinformatiesysteem (**Hoofdstuk 6**). Alhoewel beslissingsondersteunende systemen voor (empirische) antibiotische therapie sinds vele jaren worden ontwikkeld [20], worden ze niet of slecht beschreven in de literatuur. Een goede vergelijking van de verschillende systemen is moeilijk, omdat het rapporteren over beslissingsondersteunende systemen niet op gestandaardiseerde wijze gebeurt [20]. Een gedetailleerde en gestructureerde omschrijving van de ontwikkeling van ons systeem is te vinden in **Hoofdstuk 6**. Hierbij hebben we een systematisch raamwerk van Rawson gevolgd en beoordeeld [20].

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Het systeem werd gebruikt voor 184 patiënten, waarvan de meesten de werkdiagnose pneumonie (67/184) of urineweginfectie (65/184) hadden gekregen. Het antibioticumadvies dat gegenereerd werd door het beslissingsondersteunend systeem werd compleet (n=90) of gedeeltelijk (n=18) opgevolgd (58,7%). Een derde van de adviezen die het systeem genereerde werd niet opgevolgd. In 47% van de patiënten waarvoor het advies niet werd opgevolgd besloot de arts een ander antibioticum voor te schrijven dan geadviseerd door het systeem. Het systeem werd in 8% getest door de artsen, waarbij gebruik werd gemaakt van patiënten die geen tekenen van infectie hadden of niet opgenomen waren in het ziekenhuis.

Dit proefschrift heeft geleid tot waardevolle inzichten in relevante aspecten bij de ontwikkeling, validatie en implementatie van een beslissingsondersteunend systeem. Het ontwikkelde actieve iv orale switch algoritme bleek goede test karakteristieken te hebben en een meerwaarde te hebben in het selecteren van kandidaten voor de switch van intraveneuze naar orale antibiotische therapie. Er bestaan tevens andere iv orale switch algoritmes, echter geen van deze algoritmes zijn gebaseerd op iv orale switch criteria waarover consensus is bereikt in een internationaal expert team. Vervolgonderzoek met betrekking tot het iv oraal switch algoritme zou zich moeten richten op de vraag of dit algoritme zorgt voor een afname van onnodig intraveneus antibiotica gebruik. We verwachten dat dit algoritme effectiever is in ziekenhuizen met geen of een minder actief consultsysteem dan in ons ziekenhuis. Nader onderzoek hiernaar wordt aanbevolen en zal dit moeten uitwijzen. We hebben met dit proefschrift de relevantie belicht van het testen van de bruikbaarheid van een interactief beslissingsondersteunend systeem voordat het geïmplementeerd wordt. Daarbij hebben we op basis van dit onderzoek enkele algemene adviezen gegeven die bij het ontwikkelen van een interactief beslissingsondersteunend systeem gelden. Het gestandaardiseerde schema dat gebruikt werd bleek een simpele en effectieve methode om de bruikbaarheid van het systeem te onderzoeken en prioriteiten te stellen in het herontwerpen van het systeem. Het bruikbaarheidsonderzoek toonde aan dat adviezen niet blindelings werden opgevolgd door de artsen, omdat het beslissingsondersteunend systeem nieuw was en zij niet zeker waren of het geen fouten zou bevatten. Adviezen werden beoordeeld op correctheid en toepasbaarheid. Dit is positief, want de uiteindelijke beleidskeuze ligt bij de arts.

We hebben gezien dat adviezen die gegenereerd worden door het beslissingsondersteunend systeem niet altijd werden opgevolgd. Als adviezen niet werden opgevolgd was er vaak sprake van incorrect gebruik van het systeem. Het systematisch raamwerk dat werd gebruikt om de ontwikkeling, evaluatie en implementatie van het systeem te evalueren bleek bruikbaar. Het vergelijken van de verschillende beslissingsondersteunende systemen wordt vergemakkelijkt als ook andere onderzoekers dit raamwerk hanteren. Enkele relevante aspecten die ontbreken in dit raamwerk zijn: de samenstelling van het team dat

het beslissingsondersteunend systeem heeft ontwikkeld, type beslissingsondersteunend systeem (actief of passief?), eventuele richtlijnen waarop het beslissingsondersteunend systeem is gebaseerd, motivering voor het gebruiken van deze richtlijnen, commercieel of niet commercieel en de setting waarvoor het systeem is ontwikkeld. Wij adviseren deze aspecten ook te omschrijven bij het beschrijven van een beslissingsondersteunend systeem.

Met een analyse die later is verricht hebben we gezien dat het systeem weinig gebruikt is na implementatie. Het systeem is namelijk gebruikt in slechts 12,5% van de patiënten waarvoor het geschikt was. Dit heeft ons verbaasd, omdat het systeem ontwikkeld is door een multidisciplinair team, de eindgebruiker betrokken is geweest bij de ontwikkeling door middel van een bruikbaarheidsonderzoek en er sprake was van technische ondersteuning. Daarbij heeft de gebruiker veel controle en keuze mogelijkheid in het systeem. Het systeem is computer gebaseerd, geeft specifieke aanbevelingen, en deed dit op het moment dat deze aanbevelingen nuttig waren. Dit zijn alle kenmerken die belangrijk zijn voor succes [21]. Om meer inzicht te krijgen in de specifieke barrières in ons ziekenhuis is nader onderzoek hiernaar geïndiceerd. Om het gebruik van het beslissingsondersteunend systeem en de opvolging van de gegenereerde adviezen te verbeteren is het belangrijk dat deze barrières zo veel mogelijk worden weggenomen. De periode van 6 maanden waarin het beslissingsondersteunend systeem voor empirische therapie is geïmplementeerd en onderzocht kan te kort zijn geweest. Onderzoek laat zien dat de acceptatie van dit soort systemen toeneemt over de tijd [22-26]. Toekomstig onderzoek moet streven naar een langere studieduur. Om het effect te onderzoeken van dit soort systemen op belangrijke uitkomstparameters is het nodig dat het voldoende wordt gebruikt. Het wegnemen van bestaande barrières en een langere studieduur zal naar verwachting zorgen voor meer gebruik. Om te zorgen voor een grotere gebruikersgroep en het verschil in verschillende settings te kunnen onderzoeken adviseren we om soortgelijk toekomstig onderzoek in samenwerking met meerdere ziekenhuizen te verrichten. Omdat smartphones steeds meer worden gebruikt door artsen raden wij aan beslissingsondersteunende systemen ook hierop beschikbaar te maken in de vorm van een app. Het is interessant om in de toekomst te onderzoeken hoe vaak een dergelijke app wordt gebruikt en wat het effect ervan is op het voorschrijven van antibiotica.

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Addendum

List of publications
Contributing authors
About the author
PhD portfolio
Acknowledgements / Dankwoord

List of publications

Akhloufi H, van der Sijs H, Melles DC, van der Hoeven CP, Vogel M, Mouton JW [†], Verbon. The development and implementation of a guideline-based clinical decision support system to improve empirical antibiotic prescribing. *Submitted for publication.*

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About the author

Hassana (Hassna) Akhloufi was born in Amsterdam, the Netherlands, on January 26st 1989. In 2007, she finished her secondary education at the Norbertuscollege in Roosendaal. In the year 2008, after one year of studying law at the Erasmus School of Law, she started medical school at the Erasmus University Medical Center in Rotterdam. In 2012 she obtained her Bachelor of Medical Science and about 2 years later, she interrupted her medical school, during the Master period, to perform research at the department of Internal Medicine, section of Infectious Diseases. She investigated the quality of antibiotic use in the Erasmus Medical Centre in Rotterdam. Not long after this, she started her PhD trajectory and in the years that followed her research focused on several facets, related to the development, evaluation and implementation of clinical decision support systems for antibiotic therapy. As part of a multidisciplinary team she developed different algorithms/clinical decision support systems to improve antibiotic prescribing and facilitate antibiotic stewardship teams in their work. She was supervised by dr. I.H. van der Sijs in collaboration with prof. dr. A. Verbon.

In 2017 she restarted her medical school to finish her Master Medicine, which she completed in 2019. After receiving her medical degree in 2019 she fully focused on her research again on clinical decision support systems for antibiotic therapy. In 2020 she started as a nursing home physician in addition to her research work.

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Courses

2014   Workshop Systematic Literature Retrieval (in Pubmed)

2014   Workshop Endnote

2014   Workshop on Microsoft Excel 2010: Advanced

2015   Introduction to data-analysis

2015   Consultation center for Patient Oriented Research Course

2015   Research integrity

2016   Basic course in legislation and organization for clinical researchers (BROK)

2017   Biomedical English Writing Course for MSc and PhD-students

(Inter)national conferences and seminars

2014   Erasmus MC PhD day, Erasmus Medical Center, Rotterdam

2014-2018   Journal Club Department of Infectious Diseases, Erasmus Medical Center, Rotterdam

2015   Point prevalence study of appropriateness of antimicrobial therapy in a Dutch university hospital, Science Days Internal Medicine, Erasmus Medical Center, Antwerp, Belgium (oral presentation)

2015   Regional Clinical Evening Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands

2015-2016   Infectious diseases Science Day, Erasmus Medical Center, Rotterdam

2016   Organization Infectious Disease Science Day, Erasmus Medical Center, Rotterdam

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2016   CDSS to optimize antimicrobial stewardship, Reference meeting Antimicrobial Stewardship, Erasmus Medical Center, Rotterdam, the Netherlands (oral presentation)

2016   Development of operationalized intravenous to oral antibiotic switch therapy criteria using the RAND Delphi method, Infectious diseases Science Day, Erasmus Medical Center, Rotterdam, the Netherlands (oral presentation)

2016   Development of operationalized intravenous to oral antibiotic switch therapy criteria, ID week, Infectious Diseases Society of America (IDSA), New Orleans, Lousiana, USA (poster presentation)

2017   A clinical decision support system to facilitate antimicrobial stewardship. Internal Medicine Research Meeting, Erasmus Medical Center, Rotterdam, the Netherlands (oral presentation)

2017   Development of operationalized intravenous to oral antibiotic switch therapy criteria. Science Days Internal Medicine, Erasmus Medical Center, Antwerp, Belgium (poster presentation)

2017   A computer assisted decision support system to optimize antibiotic stewardship. National Centre for One Health - Antimicrobial Resistance (NCOH-AMR) symposium, NCOH, Leiden, the Netherlands (oral presentation)

2018   A clinical decision support system increases intravenous to oral switch therapy. European Congress of Clinical Microbiology and Infectious Diseases, ESCMID, Vienna, Austria (poster presentation)

2018   A clinical decision support system to increase intravenous to oral switch therapy. International Forum on Quality and Safety in Healthcare, Institute for Healthcare Improvement (IHI) and BMJ, Amsterdam, the Netherlands (poster presentation)

2018   Supporting personalized antibiotic treatment choices: implementation of a clinical decision support system. Dutch Working Party on Antibiotic Policy (SWAB) symposium, personalized medicine in the treatment of infectious diseases, Utrecht, the Netherlands (oral presentation)

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حسنة