Improving antibiotic use for complicated urinary tract infections
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Introduction
Chapter 1

This general introduction will firstly provide a brief overview of the relevance of appropriate antibiotic use for patients with a complicated urinary tract infection. Secondly, it will narrow down to the process of improving antibiotic use in these patients, including the development of guidelines, quality indicators and improvement strategies. Finally, it ends with a summary of the outline of the thesis.

**Emergence of antibiotic resistance**

The discovery of antibiotics in the 1930s led to a dramatic reduction in illness and death from infectious diseases. Antimicrobial agents fundamentally changed health care in the twentieth century by making bacterial infectious diseases curable. However, the extensive use of antimicrobial drugs in veterinary and human (health care) practice has resulted in the emergence and dissemination of resistant organisms, endangering the efficacy of these drugs [1]. Nowadays, the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) has recognized antimicrobial resistance as one of the greatest threats to human health worldwide [1-3]. Although the resistance problem in the Netherlands is relatively limited, antibiotic resistance is increasing [4].

Urinary tract infections (UTIs) are among the most prevalent infectious diseases [5,6], substantially contributing to antibiotic use in the hospital setting. Most UTIs in hospital are so-called complicated UTIs, defined as a UTI with one of the following characteristics: male gender, pregnancy, any functional or anatomical abnormality of the urinary tract, immunocompromising disease or medication, or a UTI with symptoms of tissue invasion or systemic infection [7]. As shown in several studies, the volume of antibiotic use is an important driver for the emergence of resistance [8-10]. In the Netherlands, resistance rates of *Escherichia coli* – the most common pathogen causing UTIs – are increasing to nearly all antibiotics which are used for its treatment. For example, at Dutch hospital departments, *E. coli* resistance to ciprofloxacin increased from 5% in 2004 to 14% in 2012 [4,11]. To control this increase in antibiotic resistance, appropriate antibiotic use for patients with a complicated UTI is extremely relevant.

**Adequacy of UTI guidelines**

Recommendations on appropriate antibiotic therapy are described in national and international treatment guidelines, e.g. of the Infectious Diseases Society of
Guidelines aim to be a support for clinical decision making and decrease unwanted variability in practice [14]. These guidelines are increasingly developed according to quality criteria, based on a systematic literature search evaluated by a multidisciplinary panel of experts [15]. To improve the consistency and quality of (reporting of) guideline development worldwide, in 2001, the AGREE-instrument (Appraisal Instrument for Guidelines, Research and Evaluation) has been launched [16]. According to these international criteria, in the Netherlands the Dutch Working Party on Antibiotic Policy (SWAB) developed many so-called ‘evidence-based’ antimicrobial treatment guidelines, including the “The SWAB guideline for antimicrobial treatment of complicated urinary tract infections” [17].

An important element of antimicrobial treatment guidelines are recommendations on adequate empirical therapy, i.e. therapy covering the in vitro susceptibility of the isolated pathogens. Expected causative pathogens with their local resistance percentages are the basis for these empirical treatment recommendations. Therefore, recent Dutch resistance rates of uropathogens were taken into consideration for the development of the SWAB guideline for complicated UTIs [11]. However, the prevalence of bacterial resistance to antibiotics is a dynamic phenomenon [4,11,18]. As a consequence, the adequacy of guideline recommendations on empirical antibiotic treatment should be evaluated regularly in the real-life setting to ensure the effectiveness of (adherence to) guidelines. This requires setting up dedicated studies to collect from individual patients data about treatment and pathogen resistance. An alternative (less time-consuming) method to assess guideline effectiveness is currently being developed, using a drug resistance index to communicate trends in resistance [19].

Additionally, to keep guidelines up to date, also other recommendations than empirical treatment recommendations (e.g. on diagnostic procedures) should be evaluated regularly for their appropriateness. For example, UTI treatment guidelines differ in their recommendations whether to collect blood cultures in those patients or not [12,13,17,20]. Studies are needed to reach a consensus on this point.

**Appropriate antibiotic use and quality indicators**

Although guidelines can be considered as descriptions of appropriate care, medical literature points out that 30-40% of patients are not treated in accordance with guidelines [21,22]. The findings for antibiotic care are similar, and assessments have found that up to 50% of hospital antibiotic use is
**Box 1. Set of Quality Indicators [32]**

<table>
<thead>
<tr>
<th>Quality indicators</th>
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<tbody>
<tr>
<td>1. Perform a urine culture</td>
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<tr>
<td>2. Prescribe empirical therapy in accordance with the national guideline</td>
</tr>
<tr>
<td>3. Switch from intravenous to oral therapy within 72 h on the basis of the clinical condition</td>
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<tr>
<td>4. Tailor antibiotic treatment on the basis of culture results</td>
</tr>
<tr>
<td>5. Use fluoroquinolones selectively (oral therapy, or in case of anaphylaxis to beta-lactam antibiotics)</td>
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<tr>
<td>6. Duration of antibiotic therapy should be at least 10 days (in accordance with the national guideline)</td>
</tr>
<tr>
<td>7. Treat UTI in men in accordance with the national guideline*</td>
</tr>
<tr>
<td>8. Replace catheter after initiation of antibiotic treatment</td>
</tr>
<tr>
<td>9. Adapt antibiotic dose according to renal function</td>
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</tbody>
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* Additional QI for men with a UTI. QI applies to (denominator) all men with a UTI, including those with a chronic prostatitis. It evaluates (numerator) whether they were treated in accordance with the guideline regarding the empirical therapy and treatment duration and, in case of chronic prostatitis, whether they were treated with culture-guided therapy for the recommended duration.

inappropriate [23-25]. The importance of appropriate antibiotic use (i.e. guideline adherence) has been emphasized by studies in patients with a lower respiratory tract infection or sepsis, showing associations between appropriate antibiotic use and improved clinical outcome, decreased bacterial resistance and reduced costs [26-30]. For patients with a complicated UTI, the relation between appropriate antibiotic use and (clinical) outcome has been less investigated.

To measure and improve the appropriateness of antibiotic use, first, a valid and reliable assessment of current practice is needed. To translate key recommendations from guidelines into measurable elements, quality indicators (QIs) are developed. They are defined as measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality, and hence the quality of care provided [31]. For several infectious diseases, QIs has been designed previously [32,33]. For complicated UTIs, QIs were based on the treatment recommendations from the corresponding Dutch SWAB guideline [17]. According to the international recommended methodology, a 3-step modified Delphi approach among experts was used [34] to systematically develop a set of nine QIs [32], defining
appropriate antibiotic use for patients with complicated UTIs (box 1). In a pilot study, a large room for improvement on most QIs was demonstrated [32], which is in line with earlier reports in patients with uncomplicated UTIs [35,36].

**Improving antibiotic use for complicated urinary tract infections**

In response to the emerging resistance problem and high rates of inappropriate antibiotic use, the Infectious Diseases Society of America and the Society of Hospital Epidemiologists of America have recommended the introduction of Antimicrobial Stewardship Programs [37]. They can be considered as ‘a menu of interventions that can be designed and adapted to fit the infrastructure of any hospital’ [38]. This menu suggests various interventions - audit and feedback, formulary restriction and preauthorization requirements, education, guidelines etc. - of which it has been shown that they might effectively improve antibiotic prescribing in hospitals [23]. However, the question is: which interventions work in a particular setting, e.g. to improve antibiotic use for patients with a complicated UTI? The answer is complex, as there is no superior (combination of) intervention(s) that can be used to effectively improve antibiotic use in all situations [39]. To successfully improve appropriate antibiotic use, interventions have to be well attuned to the problems, the target group and the setting in which the improvement has to take place [40]. We need to gain insight into the current appropriateness of antibiotic use and into determinants (e.g. patient, professional and hospital characteristics) that influence appropriate use. Various determinants on various levels might play a role, e.g. in patients with pneumonia blood cultures were more often collected in patients who were more severe ill [41-43]. Furthermore, in these patients, treatment at the emergency department, rather than at the ward, resulted in timely administration of antibiotics [42]. This information can be incorporated in the development of improvement interventions and enhance their effectiveness. For patients with a complicated UTI, determinants of appropriate antibiotic use have never been identified.

Another factor that complicates the decision for one (or more) of the antimicrobial stewardship interventions, is that direct comparisons of the efficacies of different interventions are scarce [23,44]. As stated in two recently updated Cochrane reviews, head-to-head comparisons (i.e. two interventions to each other) in a methodological powerful design are urgently needed to extent the current evidence for effectively improving antibiotic prescribing [23,45]. A cluster-randomized trial design is considered to be the ideal for these kinds of studies [23].
Combining this lack of evidence with the demonstrated room for improvement regarding antibiotic use for patients with complicated UTIs [32], we initiated in 2008 the QUality of Antibiotic use in uTI patients (QUANTI) trial: a cluster-randomized trial of two interventions, or strategies, to improve antibiotic use for patients with a complicated UTI. The objective of this trial was to assess the effectiveness, measured as the before-and-after-intervention performance on the previously developed quality indicators [32], of two improvement strategies: 1) a Multi-Faceted Strategy, based on a earlier developed effective strategy (including education, feedback sessions, reminders and the initiation of local process analysis) to improve antibiotic use for patients with lower respiratory tract infections [46] and 2) a Competitive Feedback Strategy, i.e. providing professionals with non-anonymous comparative feedback on the departments’ appropriate antibiotic use for patients with complicated UTIs. This strategy endorses the increasingly common trend to release performance data –either individually or publicly- with the aim of improving healthcare performance [47].

The QUANTI-trial was performed at the Internal Medicine and Urology departments of 19 university and non-university hospitals located throughout the Netherlands. For both baseline and post-intervention measurement, a minimum number of 50 patients per department was included. These large patient cohorts are the basis of most studies described in this thesis.

Outline of the thesis

In Chapter 2, we investigate in a real-life setting the adequacy (i.e. covering the in vitro susceptibility of the isolated pathogens) of the guideline-recommended treatment options in our national SWAB guideline for the empirical treatment of complicated UTIs one to two years after publication. Additionally, we evaluate the adequacy of the actually prescribed antimicrobial therapy for patients who were treated with guideline-adherent therapy, as well as for patients who were not treated in accordance with the guideline.

In Chapter 3, we present an alternative method to estimate the adequacy of empirical treatment guidelines by calculating a drug resistance index. Whereas conventional methods, as described in chapter 2, requires setting up dedicated studies, the index-based estimate of adequacy can be derived from resistance and consumption data routinely collected by existing surveillance programmes, e.g. Nethmap in the Netherlands [4,11]. In this chapter, we investigate the applicability of this index-based approach.

In Chapter 4, we aim to address the question whether it is recommended to collect in patients with a complicated UTI both a urine and blood culture.
Furthermore, we want to identify for which group of patients collection of a blood culture seems most useful.

**Chapter 5** evaluates the association between appropriate (i.e. guideline-adherent) antibiotic use for patients with a complicated UTI and their length of hospital stay. Appropriate antibiotic use was defined by a previously developed valid set of guideline-based quality indicators [32].

**Chapter 6** presents the QUANTI-trial’s baseline measurements, i.e. the appropriateness of antibiotic use for patients with a complicated UTI (defined by the valid set of QIs) in 38 Dutch hospital departments. Additionally, we investigate which patient, department and hospital characteristics determine appropriate antibiotic use.

In **Chapter 7**, we compare in a cluster-randomized study design the effectiveness of two strategies to improve antibiotic use for patients with a complicated UTI and aim to identify determinants of successful improvement.

In the general discussion, the main results of this thesis are summarized and discussed, followed by final conclusions and implications for further research.
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