Improving antibiotic use for complicated urinary tract infections
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Chapter 2

Adequacy of an evidence-based treatment guideline for complicated UTIs in the Netherlands and the effectiveness of guideline adherence

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Abstract

Guideline recommendations on empirical antibiotic treatment are based on literature, expert opinion, expected pathogens and resistance data, but their adequacy in the real-life setting is often unknown. We investigated the adequacy of the Dutch evidence-based guideline-recommended treatment options for patients with complicated urinary tract infections (UTIs) two years after guideline publication and, additionally, the adequacy of actually prescribed empirical therapy, for patients treated with guideline-adherent versus non-guideline-adherent therapy.

A retrospective, observational multicentre study included 810 patients with a complicated UTI without special conditions and 174 with a urinary catheter. Susceptibility patterns of cultured uropathogens were compared with guideline-recommended treatment options, which included specific recommendations for patients with a catheter, and with actually prescribed empirical therapy. We considered inadequate coverage rates (ICRs) below 10% as acceptable.

Of the recommended regimens for patients with a UTI without other conditions, only the guideline-recommended combination of amoxicillin-gentamicin was acceptable (ICR 6%). For patients with a catheter, ICRs of recommended regimens ranged from 3-24%. In patients with a UTI without other conditions actually prescribed guideline-adherent therapy resulted in less broad-spectrum, but not in less adequate therapy; in patients with a catheter actually prescribed guideline-adherent therapy resulted in a higher coverage rate than prescribed non-guideline-adherent therapy.

Due to continuously changing resistance rates and differences between the epidemiologies of uropathogens assumed in the guideline and those in real-life, regular real-life assessments of recommended treatment options are necessary. Guideline adherence seems to be effective to increase coverage rates without prescribing unnecessary broad regimens.
Introduction

Adequate antibiotic therapy is correlated with improved clinical outcomes for patients, less development of resistance and lower costs [1-11]. Recommendations on adequate antibiotic therapy are described in international literature and in national and international treatment guidelines. These guidelines are increasingly developed according to international quality criteria, based on a systematic literature search evaluated by a multidisciplinary panel of experts [12]. In addition to published literature, expected pathogens and local resistance data are important determinants in the development of guideline recommendations for adequate empirical treatment. The prevalence of bacterial resistance to antibiotics is a dynamic phenomenon [13-14]. Guideline recommendations on empirical antibiotic treatment should therefore not only be based on the latest literature, expert opinion, expected pathogens and resistance data; information on their adequacy in the real-life setting should also be incorporated.

In the present study we evaluated the adequacy of empirical treatment options as recommended in the Dutch national guideline for complicated urinary tract infections (UTIs) and the adequacy of the actually prescribed therapy for UTIs in the real-life setting, soon after publication of this guideline. This guideline was released in 2006 by the Dutch Working Party on Antibiotic Policy (SWAB) and disseminated through the different national scientific societies [15]. According to the methodology used in the guidelines of the Infectious Diseases Society of America (IDSA), our national guideline was developed based on a review of the published evidence, in which the strength of the recommendation and quality of evidence were graded using published criteria [16-17]. Also taken into consideration were recent Dutch resistance rates of uropathogens [18].

The objective of the present study was to investigate whether the separate guideline-recommended empirical treatment options were adequate as measured by the susceptibility patterns of the cultured uropathogens. Furthermore, we evaluated 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.
*without systemic symptoms*
Methods

Setting and population
The study population was derived from the baseline measurement of a clustered randomised controlled trial testing a multifaceted implementation strategy to improve the quality of antibiotic use for complicated UTIs in hospitals (http://www.trialregister.nl; NTR1742). This study provided us the opportunity to address the above mentioned research questions. We defined a complicated UTI as a UTI with symptoms of tissue invasion or systemic infection (pyelonephritis, urosepsis, prostatitis) or a UTI with one of the following characteristics: male gender, any functional or anatomical abnormality of the urinary tract, pregnancy, or immunocompromising disease or medication. Participating in this study were the urology and internal medicine departments of 19 Dutch hospitals. The patients from these hospitals were representative for the patient population in Dutch hospitals since university, teaching and non-teaching hospitals located throughout the Netherlands participated. Consecutive patients with complicated UTIs were retrospectively selected from the hospital files using formal inclusion criteria: adult (≥ 16 years) inpatients/outpatients diagnosed in 2008 by an internist or an urologist (or a resident of these specialties) with a complicated UTI as main diagnosis, and in whom antibiotic treatment was started. For all retrieved patients (n=1964) the study researcher verified whether or not the UTI was complicated according to the study definition. A minimal number of 50 patients per department was included. If required to reach a sufficient number, patients from 2007 were also selected. Excluded were patient groups for whom the Dutch national guideline does not provide therapy advice, i.e. patients with a nephrostomy or double J-stent, patients with a UTI after a urological procedure or a UTI caused by a fungus or a mycobacterium, and patients who were currently being treated for another infection or had been transferred from or to another hospital. Finally, from the above-described study population we selected the patients with a positive urine culture (n=1073) (Figure 1). A urine culture result was considered ‘positive’ when a bacterial pathogen was cultured and reported by the microbiology laboratory together with a susceptibility pattern.

Data collection
From February to November 2009 the study coordinator (VS), together with a trained research assistant, collected the following data for each patient: age, sex, comorbidity (diabetes, immunodeficiency, pregnancy, abnormalities of the urogenital tract), the presence of a urinary catheter (≤ or > 10 days), the primary diagnosis, the bacterial pathogen(s) and their susceptibility pattern(s), and the prescribed empirical antibiotic treatment. Data were retrospectively collected.
Box 1. Dutch SWAB guideline for antimicrobial therapy of complicated UTIs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment and Duration</th>
</tr>
</thead>
</table>
| **General** | Amoxicillin + gentamicin iv., 2nd or 3rd generation cephalosporin iv.  
Second choice: amoxicillin-clavulanic acid iv.  
Duration: at least 10 days  

Fluoroquinolones only if β-lactam antibiotics cause anaphylaxis or if the entire course of treatment is oral. |
| **UTI + catheter > 10 days** | β-lactam antibiotic with addition of a fluoroquinolone or gentamicin  
Duration (without systemic symptoms): 5 days  
Duration (with systemic symptoms): at least 10 days |
| **UTI + catheter ≤ 10 days** |  
- with systemic symptoms: See: ‘General’  
- without systemic symptoms: No empirical treatment (only based on urine culture result)  
  Duration: 5 days |
| **Pyelonephritis in pregnancy** | 2nd or 3rd generation cephalosporin iv.  
Second choice: amoxicillin-clavulanic acid iv.  
Duration: at least 10 days |
| **Cystitis in pregnancy or women with diabetes** | Amoxicillin-clavulanic acid or nitrofurantoin (not close to delivery)  
Duration: at least 5 days |
| **Infected kidney cyst** | A fluoroquinolone or a β-lactam antibiotic with aminoglycoside.  
Second choice: trimethoprim-sulfamethoxazole (TMP-SMX)  
Duration: 4-6 weeks |
| **Chronic prostatitis** | No empirical treatment (only based on urine culture result).  
A fluoroquinolone is first choice and TMP-SMX second choice.  
Duration: at least 28 days |
from admission sheets, medical and nursing records, medication charts, and microbiology reports.

**Outcome measures**
The recommended treatment options that were evaluated originate from our national guideline, which was released by the SWAB in 2006. This guideline comprises a general recommendation for patients with complicated UTIs, as well as recommendations for subpopulations with special conditions, e.g. patients with urinary catheters, pregnant women, and men with chronic prostatitis (Box 1).

1) **Coverage rate of the separate guideline-recommended treatment options**
We determined the coverage rate of each single guideline recommended treatment option proposed in the Dutch SWAB guideline for complicated UTIs [15]. The coverage rate was determined by the susceptibility patterns of the actually cultured uropathogens (see further: *Definitions and assumptions*). All patients from the UTI subgroup for whom the recommendation was applicable were evaluated as if they would receive the specific guideline-recommended therapy option(s).

2) **Coverage rate of actually prescribed empirical therapy**
We next evaluated the coverage rate of the actually prescribed empirical therapy. The coverage rate was again determined by the susceptibility patterns of the actually cultured uropathogens (see further: *Definitions and assumptions*). We defined empirical therapy as the first prescribed (combination of) antibiotics, before identification of the causative uropathogen. If the initial therapy was adapted to a previous positive urine culture this therapy was not called ‘empirical’ and these patients were excluded from the present analysis.

Therapy in accordance with the guideline was defined as guideline-adherent therapy, and therapy not in accordance with the guideline as non-guideline-adherent therapy.

**Definitions and assumptions**
*Adequate coverage:*
The guideline-recommended treatment options and the actually prescribed therapy were considered *adequately covering* if the cultured uropathogen was reported to be susceptible to the (recommended or prescribed) antibiotic. If more than one uropathogen was cultured, all uropathogens had to be susceptible. If a combination of antibiotics was recommended or prescribed the uropathogen(s) had to be susceptible to at least one of the antibiotics.
Chapter 2

Box 2. Intrinsic resistance of common uropathogens [19]

<table>
<thead>
<tr>
<th>Uropathogen</th>
<th>Intrinsic resistance (for UTI recommended antibiotics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>none</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>amoxicillin</td>
</tr>
<tr>
<td>Proteus spp</td>
<td>nitrofurantoin</td>
</tr>
<tr>
<td>Pseudomonas aeruginos</td>
<td>amoxicillin/ amoxicillin-clavulanic acid, first, second and third generation cephalosporins (no ceftazidime), trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>cephalosporins, amoxicillin/ amoxicillin-clavulanic acid</td>
</tr>
<tr>
<td>Citrobacter spp</td>
<td>amoxicillin, cephalosporins</td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>aminoglycoside, fluoroquinolone</td>
</tr>
<tr>
<td>Staphylococcus spp</td>
<td>none</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>cephalosporins, aminoglycoside, fluoroquinolone</td>
</tr>
</tbody>
</table>

Inadequate coverage (resistance, including intrinsic resistance):
A guideline-recommended or prescribed empirical therapy was considered inadequately covering in case of resistance (including intrinsic resistance) of the cultured uropathogen.
We classified a microorganism resistant if the cultured uropathogen was reported to be resistant to the recommended or prescribed antibiotic. Intrinsic resistance for the various microorganisms is listed in Box 2 [19]. Intrinsic resistance overruled reported susceptibility, e.g. if a Citrobacter spp. was reported to be susceptible to cefuroxime it was considered inadequately covering due to intrinsic resistance.
In case of more than one uropathogen we assumed there was inadequate coverage if at least one of the uropathogens was (intrinsic) resistant. If a combination of antibiotics was recommended or prescribed we classified the uropathogen(s) inadequately covered if the uropathogen(s) was (intrinsic) resistant to both antibiotics. If the cultured uropathogen was reported ‘intermediate susceptible’ to the recommended or prescribed antibiotic it was also considered inadequately covered. There was one exception to this: if the uropathogen was reported intermediate susceptible for amoxicillin-clavulanic acid, the uropathogen was considered to be susceptible if amoxicillin-clavulanic acid was recommended or prescribed intravenously, because for complicated UTIs this was current practice in the Netherlands at that time.
Inadequate coverage rate:
We defined this as the percentage of the cultured uropathogen(s) that was inadequately covered by a guideline-recommended or prescribed empirical therapy, due to resistance (including intrinsic resistance).

Assumptions in case of unreported susceptibility
Not all microbiology laboratories used the same antibiotic panel for reporting susceptibility. If the susceptibility of a uropathogen to the recommended or prescribed antibiotic was not reported and there was no intrinsic resistance, the susceptibility to this antibiotic could sometimes be extrapolated from overlapping susceptibility patterns of antibiotics. We made the following assumptions: 1) if a uropathogen is reported susceptible/resistant to tobramycin it is also considered susceptible/resistant to gentamicin and vice versa; 2) if a uropathogen is reported susceptible to a certain generation cephalosporin (e.g. first-generation cephalosporin) it is also considered susceptible to higher generations cephalosporins (e.g. second-generation cephalosporin); 3) if a uropathogen is reported resistant to a certain generation cephalosporin (e.g. third-generation cephalosporin) it is also considered resistant to lower generations cephalosporins (e.g. second-generation cephalosporin). An exception to assumptions 2) and 3) is ceftazidime, because its susceptibility pattern cannot be derived from and assigned to lower generations cephalosporins. 4) if a uropathogen is reported susceptible to norfloxacin it is also considered susceptible to ciprofloxacin; and 5) if a uropathogen is reported resistant to ciprofloxacin it is also considered resistant to norfloxacin.
If the unreported susceptibility could not be extrapolated from the susceptibility of related antibiotics or explained by intrinsic resistance, we classified it as ‘susceptible’.

Analysis
Descriptive statistics were used. Frequencies, percentages and averages were calculated with the SPSS 16.0 software. We considered inadequate coverage rates below 10% as acceptable [16]. Actually prescribed therapy could be guideline-adherent or non-guideline-adherent and we compared inadequate coverage rates between both groups with the $X^2$ test.

Results

Study population characteristics
The study population consisted of 1073 patients, distributed over the seven treatment categories described in the Dutch SWAB guideline for complicated UTIs (Figure 1). For each diagnosis category the SWAB guideline provides treatment recommendations (Box 1). Due to the small sample size of five of the
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complicated UTI (n=810)</th>
<th>UTI + catheter &gt; 10days (n=174)</th>
<th>Total (n=984)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years: median (range)</td>
<td>69 (16-102)</td>
<td>67 (18-95)</td>
<td>70 (16-102)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>387 (48)</td>
<td>134 (77)</td>
<td>521 (53)</td>
</tr>
<tr>
<td>Outpatient, n (%)</td>
<td>176 (22)</td>
<td>25 (14)</td>
<td>201 (20)</td>
</tr>
<tr>
<td>Hospital acquired UTI (≥ 3 days hospital stay)</td>
<td>37 (5)</td>
<td>11 (6)</td>
<td>48 (5)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>158 (20)</td>
<td>46 (26)</td>
<td>204 (21)</td>
</tr>
<tr>
<td>History of abnormalities of the urinary tract (anatomical and/or functional), n (%)</td>
<td>143 (18)</td>
<td>105 (60)</td>
<td>248 (25)</td>
</tr>
<tr>
<td>Renal transplant, n (%)</td>
<td>29 (4)</td>
<td>2 (1)</td>
<td>31 (3)</td>
</tr>
<tr>
<td>Patients treated in university hospital, n (%)</td>
<td>170 (21)</td>
<td>66 (38)</td>
<td>236 (24)</td>
</tr>
<tr>
<td>Number of uropathogens in culture: 1, 2 or 3, n (%)</td>
<td>737: 65: 8</td>
<td>127: 37: 10</td>
<td>864 : 102 :</td>
</tr>
<tr>
<td>Empirical treatment, n (%)</td>
<td>641 (79)</td>
<td>139 (80)</td>
<td>780 (79)</td>
</tr>
</tbody>
</table>

### Table 2. Isolated uropathogens in patients with a positive urine culture

<table>
<thead>
<tr>
<th>Uropathogen</th>
<th>Complicated UTI (n=810)</th>
<th>UTI + catheter &gt; 10days (n=174)</th>
<th>Total (n=984)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli, n (%)</td>
<td>553 (62)</td>
<td>90 (39)</td>
<td>643 (57)</td>
</tr>
<tr>
<td>Klebsiella spp, n (%)</td>
<td>82 (9)</td>
<td>24 (10)</td>
<td>106 (10)</td>
</tr>
<tr>
<td>Proteus spp, n (%)</td>
<td>56 (6)</td>
<td>20 (9)</td>
<td>76 (7)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa, n (%)</td>
<td>45 (5)</td>
<td>20 (9)</td>
<td>65 (6)</td>
</tr>
<tr>
<td>Citrobacter spp, n (%)</td>
<td>9 (1)</td>
<td>5 (2)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Enterobacter spp, n (%)</td>
<td>12 (1)</td>
<td>5 (2)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Streptococcus spp, n (%)</td>
<td>13 (2)</td>
<td>7 (3)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>Staphylococcus spp, n (%)</td>
<td>19 (2)</td>
<td>18 (8)</td>
<td>37 (3)</td>
</tr>
<tr>
<td>Enterococcus spp, n (%)</td>
<td>69 (7)</td>
<td>24 (10)</td>
<td>93 (8)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>30 (4)</td>
<td>18 (8)</td>
<td>48 (4)</td>
</tr>
<tr>
<td>Missing, n (%)</td>
<td>3 (&lt;1)</td>
<td>0 (0)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Total uropathogens, n (%)</td>
<td>891 (100)</td>
<td>231 (100)</td>
<td>1122 (100)</td>
</tr>
</tbody>
</table>
seven categories, we focused on patients with a
urosepsis/pyelonephritis/complicated UTI without special conditions (n=810)
and on patients with a UTI and a urinary catheter in place for > 10 days
(n=174). Table 1 presents the characteristics of the 984 analysed patients, and
Table 2 summarises the 1122 cultured microorganisms. *Escherichia coli* was
the most frequently isolated micro-organism (57%).

Coverage rate of the separate guideline-recommended treatment options

 Patients with a complicated UTI without other conditions
We evaluated all patients from this subgroup (n=810) as if they would receive
any of the five guideline-recommended therapy options. For patients with a
complicated UTI without other conditions the combination of amoxicillin and
gentamicin had the highest coverage rate (inadequate coverage rate of 6%)
(Figure 2a). All other recommended regimens had an inadequate coverage rate
of > 10% of patients. Second-generation cephalosporins had the highest
inadequate coverage rate, i.e. 24% (of which intrinsic resistance was 16%), the
inadequate coverage rate for third-generation cephalosporins was 18% (intrinsic
resistance 16%), for amoxicillin-clavulanic acid 14% (intrinsic resistance 7%)
and for ciprofloxacin it was 23% (intrinsic resistance 9%). *Enterococcus* species
usually have low virulence, and it is debatable whether they should be covered
in empirical therapy. Leaving out enterococci (7%) decreased the inadequate
coverage rate for some regimens (Figure 2b): third-generation cephalosporins
now had an inadequate coverage rate of 10%. All other regimens remained
inadequately covering in > 10% of patients.

 Patients with a UTI and a urinary catheter in place for > 10 days
We next evaluated patients from this subgroup (n=174) as if they would receive
any of the guideline-recommended therapy options. For patients with a UTI and
a urinary catheter in place for > 10 days the combination of amoxicillin-
clavulanic acid with gentamicin had the highest coverage rate (inadequate
coverage rate of 3%). The combination of amoxicillin and a fluorquinolone
had the highest inadequate coverage rate (24%). Excluding enterococci
decreased the inadequate coverage rates for the regimens of a cephalosporin
combined with gentamicin or a fluorquinolone, making a third-generation
cephalosporin with gentamicin the most adequate recommendation (inadequate
coverage rate of 2%). Figure 3 shows the inadequate coverage rates for all
guideline recommended treatment options for this subgroup (Fig 3a and 3c), as
well as the inadequate coverage rates if in these patients the general
recommendations for patients with a complicated UTI would have been
followed (Fig 3b and 3d). Following the general recommendations resulted in
substantially higher inadequate coverage rates.
Figure 2. Inadequate coverage rates of the separate guideline-recommended treatment options in patients with a complicated urinary tract infection without other conditions: a) including and b) excluding Enterococcus spp.

a. Including Enterococcus spp. (n=810) b. Excluding Enterococcus spp. (n=771)
Figure 3. Inadequate coverage rates of the separate guideline-recommended treatment options in patients with a urinary tract infection and a urinary catheter in place for >10 days, concerning: a) guideline-recommended treatment options for this subgroup, and b) general guideline-recommended treatment options (for patients without a catheter). Rates including Enterococcus spp are shown in a and b (n=174), and rates excluding enterococci in c and d (n=167).

a. Recommendations for subgroup (n=174) with catheter

b. General recommendations
Table 3. Prescribed empirical therapy in the study population (n=780).

<table>
<thead>
<tr>
<th>Prescribed empirical therapy n (%)</th>
<th>Complicated UTI (n=641)</th>
<th>UTI + catheter &gt; 10 days (n=139)</th>
<th>Total (n=780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin + gentamicin</td>
<td>30 (5)</td>
<td>6 (5)</td>
<td>36 (5)</td>
</tr>
<tr>
<td>second-generation cephalosporins</td>
<td>164 (26)</td>
<td>28 (20)</td>
<td>192 (25)</td>
</tr>
<tr>
<td>third-generation cephalosporins</td>
<td>150 (23)</td>
<td>40 (29)</td>
<td>190 (24)</td>
</tr>
<tr>
<td>(including ceftazidime)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amoxicillin + clavulanic acid, intravenous fluoroquinolones, oral</td>
<td>45 (7)</td>
<td>10 (7)</td>
<td>55 (7)</td>
</tr>
<tr>
<td>fluoroquinolones, intravenous</td>
<td>75 (12)</td>
<td>10 (7)</td>
<td>85 (11)</td>
</tr>
<tr>
<td>- β-lactam antibiotics cause anaphylaxis</td>
<td>1 (&lt;1)</td>
<td>7 (5)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>- no anaphylaxis for β-lactam antibiotics</td>
<td>18 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second or third-generation cephalosporin with addition of gentamicin</td>
<td>60 (9)</td>
<td>15 (11)</td>
<td>75 (10)</td>
</tr>
<tr>
<td>Second or third generation cephalosporin with addition of a fluoroquinolone</td>
<td>2 (&lt;1)</td>
<td>2 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>amoxicillin + clavulanic acid with addition of gentamicin</td>
<td>25 (4)</td>
<td>3 (2)</td>
<td>28 (3)</td>
</tr>
<tr>
<td>amoxicillin or amoxicillin + clavulanic acid with addition of fluoroquinolone</td>
<td>13 (2)</td>
<td>3 (2)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>58 (9)</td>
<td>15 (11)</td>
<td>73 (9)</td>
</tr>
<tr>
<td>Total</td>
<td>641 (100)</td>
<td>139 (100)</td>
<td>780 (100)</td>
</tr>
<tr>
<td>Treated according to the SWAB guideline</td>
<td>465 (73)</td>
<td>39 (28)</td>
<td>504 (65)</td>
</tr>
</tbody>
</table>

Printed bold: guideline-concordant therapy

Coverage rate of actually prescribed empirical therapy: guideline-adherent versus non-guideline-adherent therapy

Patients with a complicated UTI without other conditions

Of the 810 patients from this subgroup empirical therapy was started in 641 patients (79%). In 465 of these 641 patients (73%) treatment was in accordance with the guideline. Non-guideline-adherent therapy involved in the majority of patients the addition of an extra antibiotic to the original guideline-recommended antibiotic, e.g. the addition of gentamicin to a second or third-generation cephalosporin (60/176; 34%). See further table 3. Inadequate coverage rates were basically the same for actually prescribed guideline-adherent and non-guideline-adherent therapy (Fig. 4a and 4c).
Patients with a UTI and a urinary catheter in place for > 10 days
Of 139 empirical treated patients guideline adherence was 28% (39/139). The majority of the prescribed non-guideline-adherent regimens consisted of a β-lactam antibiotic without addition of gentamicin or a fluoroquinolone, e.g. a third-generation cephalosporin (40/100; 40%). See further table 3. In patients with a urinary catheter in place for > 10 days, actually prescribed non-guideline-adherent therapy had higher inadequate coverage rates than guideline-adherent therapy (p=0.077 including enterococci vs. p=0.047 excluding enterococci) (Fig. 4b and 4d).

Discussion

In a real-life setting this study evaluated the adequacy of the the guideline-recommended treatment options in our national SWAB guideline for the empirical treatment of complicated UTIs one to two years after publication. Of the recommended antimicrobial therapy options for complicated UTIs in patients without other conditions, only the combination of amoxicillin and gentamicin was adequate, with a rate of inadequate coverage below 10%. Had patients with a UTI and a catheter in place for > 10 days been treated with the general recommended therapy for patients with a complicated UTI the inadequate coverage rates were above 30%, with the exception of the combination amoxicillin/gentamicin (12%). It is known that the spectrum of uropathogens causing UTIs in patients with urinary catheters differs widely, and that resistance to first-line antibiotics is common [20-22]. Specific guidelines for this subgroup recommend initiation of empirical treatment with broad-spectrum antibiotics based on local susceptibility patterns [17, 20], but the adequacy of different broad-spectrum regimens in this subgroup has not been evaluated before. Our data support the need for the specific guideline recommendations for patients with a UTI and a catheter in place for > 10 days.

A possible explanation for the high rate of inadequate guideline recommendations is that the range of uropathogens found in the present study was broader than assumed in our national guideline, i.e. the guideline was based on the susceptibility pattern of the most common uropathogen, *E.coli*. Furthermore, bacterial resistance rates continue to change over time. We collected our data during 2007/2008, whereas the national guideline (published in 2006) was based on data from 1998-2004. The reliance on data and literature from recent years is inherent in the process of developing guidelines. However, the dynamics of bacterial resistance might warrant frequent updates in particular of antimicrobial treatment guidelines.
Figure 4. Inadequate coverage rates of the prescribed empirical therapy, categorized into guideline-adherent and non-guideline-adherent therapy: a, for patients with complicated urinary tract infection (UTI) without other conditions, and b, for patients with a UTI and a urinary catheter in place for > 10 days. Rates including enterococci are shown in a and b, and rates excluding enterococci are shown in c and d.

a. Complicated UTI without other conditions

b. UTI and a catheter in place > 10 days

Inadequate coverage rate (%)

<table>
<thead>
<tr>
<th>Guideline-adherent</th>
<th>Non-guideline-adherent</th>
</tr>
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<tbody>
<tr>
<td>n=465</td>
<td>n=176</td>
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Inadequate coverage rate (%)

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<thead>
<tr>
<th>Guideline-adherent</th>
<th>Non-guideline-adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=39</td>
<td>n=100</td>
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</tbody>
</table>

Inadequate coverage rate (%)

<table>
<thead>
<tr>
<th>Guideline-adherent</th>
<th>Non-guideline-adherent</th>
</tr>
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<tbody>
<tr>
<td>n=451</td>
<td>n=170</td>
</tr>
</tbody>
</table>

Inadequate coverage rate (%)

<table>
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<tr>
<th>Guideline-adherent</th>
<th>Non-guideline-adherent</th>
</tr>
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<tbody>
<tr>
<td>n=36</td>
<td>n=97</td>
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</table>
In the total study population guideline adherence was 65%: 72% in patients with a complicated UTI without other conditions and only 28% in patients with a UTI and a catheter in place for > 10 days. The reason why inadequate coverage rates of actually prescribed guideline-adherent therapy and non-guideline-adherent therapy for patients with a UTI without other conditions were basically the same, might be that non-guideline-adherent therapy often means broader treatment, i.e. addition of gentamicin to a cephalosporin or amoxicillin+clavulanic acid. This broader empiric antibiotic therapy does not contribute to lowering the rate of inadequate coverage in this group, but does increase the selection of antimicrobial resistance [23]. However, for the special group of patients with a catheter, treatment in accordance with the guideline had higher coverage rates than non-guideline-adherent therapy.

In our study, Enterococcus species were 8% of the isolated uropathogens in patients with a positive urine culture. Because Enterococcus species usually have low virulence, it is debatable whether they should be covered in empirical therapy. Enterococci have a high intrinsic resistance rate and omitting them from the analysis decreased the inadequate coverage rates of many recommended antibiotic regimens. Particularly in patients with a catheter this resulted in some guideline-recommendations now becoming adequately covering, because enterococci have intrinsic resistance to some of the recommended regimens for this subgroup, i.e. the combination of cephalosporin with a fluoroquinolone or gentamicin.

Our study has several strengths. We evaluated the guideline published in 2006 in patients with UTIs diagnosed in 2007/2008. This had the advantage that in 2008 the guideline was no longer ‘new’ and was presumably known to the prescriber. To our knowledge, this is the first study to compare the empirical treatment recommendations from an evidence-based national guideline with the susceptibility patterns of (uro)pathogens cultured in the real-life setting within two years of publication. Furthermore, we included a large number of hospitals from all over the Netherlands and collected data on a large number of patients. Therefore, these findings are largely representative for the entire population. Because data were extracted manually from medical charts they are more comprehensive and reliable than data obtained from administrative databases designed for other purposes.

This study has two important limitations. First, because the study was a retrospective multicentre trial, antibiotic susceptibility reporting was not standardised and in several hospitals susceptibility was not reported for all antibiotics. Most of the susceptibilities that were not reported could be extrapolated from the susceptibility of related antibiotics or explained by
intrinsic resistance (see Methods). However, in the case that unreported susceptibility could not be extrapolated we classified it as ‘susceptible’, resulting in overestimation of the coverage rate of certain antibiotics. On the other hand, classifying them as missing cases (the alternative option) would have underestimated the coverage rate of antibiotics. For example, in the latter case the coverage rate of second-generation cephalosporins would be underestimated in hospitals that routinely report only on third-generation cephalosporins and not on second-generation cephalosporins, because resistance could be extrapolated (a third-generation cephalosporin resistant microorganism is also second-generation cephalosporin resistant) whereas susceptibility could not. We decided to favour an overestimation of coverage rates rather than an underestimation; however, this must be taken into account when interpreting the study data.

The second limitation is that, in 2008, laboratories in the Netherlands still used the CLSI/CRG criteria. Resistance rates following the EUCAST criteria are in some instances higher, because many EUCAST breakpoints are lower than the CLSI breakpoints [24]. For example, application of the EUCAST breakpoint for resistance of *E. coli* for cefuroxime (MIC > 8 mg/L) instead of the CLSI breakpoint (MIC > 16 mg/L) results in 3% additional resistant cases [25]. This implies that inadequate coverage rates using the EUCAST criteria might have been a fraction higher.

A final limitation of our study is inherent to most retrospective studies, i.e. that information is inevitably incomplete. In 18 of the 19 Dutch hospitals the urine culture results and susceptibility patterns were part of the electronic patient record and therefore easy to find. However, information on the physician’s decision-making at the start of therapy was sometimes difficult to retrieve. Incidentally, we may have considered the therapy as ‘empirically started’ whilst the physician took the result of a previous urine culture into account; in this case adherence to recommended empirical therapy was not applicable.

In conclusion, in the dynamic field of continuously changing bacterial resistance rates regular real-life assessments of guideline-recommended treatment options are necessary; this applies even when the guidelines are developed according to international quality criteria and adapted to local resistance data. This is the case in the Netherlands, where recent and detailed resistance data were available during the development of the guideline [18]. This study shows that if such information would have been available at the moment the guideline was developed, part of the treatment recommendations for patients with complicated UTIs would have been changed. In addition, the results endorse specific recommendations for patients with a catheter in place
Adequacy Dutch UTI guideline for > 10 days and the need for their implementation in daily practice. Guideline adherence seems to be effective to increase coverage rates without prescribing unnecessary broad regimens.
References


25. EUropean Committee on Antimicrobial Susceptibility Testing. MIC- and Inhibition zone diameter distributions of microorganisms without and with resistance mechanisms. Available at: http://mic.eucast.org/Eucast2/ (last accessed 12 March 2013).