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Appropriate antibiotic use for patients with urinary tract infections reduces length of hospital stay

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Abstract

Background
To define appropriate antibiotic use for patients with a complicated urinary tract infection (UTI), we developed in a previous study a key set of four valid, guideline-based quality indicators (QIs). In the current study, we evaluated the association between appropriate antibiotic use for patients with a complicated UTI, as defined by these QIs, and length of hospital stay (LOS).

Methods
A retrospective, observational multicentre study included 1,252 patients with a complicated UTI, hospitalized at Internal Medicine and Urology departments of 19 university and non-university Dutch hospitals. Data from the patients’ medical charts were used to calculate QI performance scores. Multilevel mixed model analyses were performed to relate LOS to QI performance (appropriate use or not). We controlled for the potential confounders gender, age, (urological) comorbidity, febrile UTI and ICU admission < 24 h.

Results
Prescribing therapy in accordance with local hospital guidelines was associated with a shorter LOS (7.3 days vs. 8.7 days; P = 0.02), as was early intravenous-oral switching (4.8 days vs. 9.1 days; P < 0.001). There was an inverse relationship between the proportion of appropriate use in a patient (QI sumscore/number of applicable QIs) and LOS (9.3 days for lower tertile vs. 7.2 days for upper tertile; overall P < 0.05).

Conclusion
Appropriate antibiotic use in patients with a complicated UTI seems to reduce length of hospital stay and therefore favours patient outcome and health care costs. In particular, adherence to the total set of QIs showed a significant dose-response relationship with a shorter LOS.
Background

In patients with a lower respiratory tract infection or sepsis, appropriate antibiotic use has been associated with improved clinical outcome, including the clinically relevant endpoints mortality, admission to intensive care units (ICUs) and length of stay, decreased bacterial resistance, and reduced costs [1-5]. For patients with a complicated urinary tract infection (UTI), the evidence is limited [6-7]. To define appropriate antibiotic use for patients with a complicated UTI, we developed in a previous study a valid set of guideline-based quality indicators (QIs) [8]. We identified four key indicators for appropriate antibiotic use in these patients, i.e.: perform a urine culture before starting treatment, prescribe empirical treatment in accordance with the national guideline, switch from intravenous (i.v.) to oral treatment within 72 hours of starting treatment, and tailor antibiotic treatment on the basis of culture results.

The aim of this study was to evaluate the association between appropriate antibiotic use for patients with a complicated UTI and their length of hospital stay. Length of hospital stay (LOS) is an important outcome, because it reflects the recovering time of patients, affects the risk of in-hospital complications, and determines hospital costs [9]. Secondary outcomes were ICU admission and in-hospital mortality.

Methods

Study population and data collection

We conducted a retrospective observational cohort study, which was part of the baseline measurement of a cluster randomized controlled trial testing a multifaceted stewardship program to improve the appropriate use of antibiotics in patients with a complicated UTI in hospitals (http://www.trialregister.nl; NTR 1742). The departments of Internal Medicine and Urology of 19 university, teaching and non-teaching hospitals located throughout the Netherlands participated. Included were adults (≥ 16 years) who were admitted and diagnosed in 2008 or 2007 with a complicated UTI (including catheter-associated UTIs), and in whom antibiotic therapy was started. We defined a complicated UTI as a UTI with one of the following characteristics: male gender, any functional or anatomical abnormality of the urinary tract, pregnancy, immunocompromising disease or medication, or a UTI with symptoms of tissue invasion or systemic infection (pyelonephritis, urosepsis, prostatitis) [10]. Exclusion criteria were hospital-acquired UTIs [11], UTIs for which the Dutch national guideline does not provide a treatment recommendation (i.e. UTIs in patients with a nephrostomy or after a urological
procedure), current treatment for another infection, transfer from/to another hospital, and direct admission to an ICU (i.e. treatment not initiated at the department of Internal Medicine or Urology).

Between February and November 2009 the study researcher (VS) and a trained research assistant collected data from medical- and nursing charts. QI performance was calculated for each patient using previously constructed algorithms. The ethics committee assessed the study and concluded that our study was deemed exempt from their approval.

**Quality indicators and definitions**

**Perform a urine culture before starting treatment**
A urine culture performed at the same date as starting treatment (or, when admitted after 9 PM, the next day) was considered as ‘performed before starting treatment’.

**Prescribe empirical therapy in accordance with the national guideline**
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 culture, this therapy was not called ‘empirical’ and these patients were excluded for this indicator. Prescribing in accordance with the guideline was judged in relation to the at that moment current Dutch national guideline for complicated UTIs [12] (indicator 2A). This guideline contains a general recommendation for patients with a complicated UTI, as well as recommendations for subpopulations with special conditions, e.g. patients with urinary catheters, pregnant women, and men with chronic prostatitis.

In most hospitals, a local hospital guideline was available: it was usually derived from the national guideline, with treatment recommendations based on local resistance data. If a local hospital guideline was available, adherence to the local hospital guideline was examined as well, creating an additional QI ‘Prescribe empirical treatment in accordance with the local hospital guideline’ (indicator 2B).

**Switch from intravenous to oral treatment within 72 hours of starting treatment**
This indicator was applicable to the subgroup of patients who started with i.v. antibiotic treatment and fulfilled the criteria for a safe early switch. These criteria were: haemodynamic stability, no gastrointestinal problems at 48 h after admission, no *Staphylococcus aureus* in the blood culture and the availability of an adequate oral antibiotic, based on culture result, or the availability of oral equivalent of the i.v. antibiotic [13].

**Tailor antibiotic treatment on the basis of culture results**
This QI applied to all patients with a positive culture result (denominator) and assessed the proportion of patients (numerator) that received tailored final antibiotic treatment. Final antibiotic treatment was considered ‘tailored’ when it
was in accordance with the resistance pattern of the cultured microorganism, regardless whether a change of therapy had been performed or not. If possible, broad antibiotic therapy should be tailored to narrow therapy. The following antibiotics were considered as ‘broad’: cephalosporins and all combinations of antibiotics (e.g. amoxicillin and gentamicin). Antibiotics with a narrow spectrum were: fluoroquinolones, amoxicillin, and trimethoprim-sulfamethoxazole (TMP-SMX). When the culture result showed that the microorganism was sensitive to amoxicillin, we classified amoxicillin and not co-amoxiclav as narrow spectrum. Nitrofurantoin and fosfomycin are not indicated for the treatment of complicated UTI.

Definitions Length of hospital stay was defined as the number of days between admission and discharge, regardless the number of hours, because the precise time of discharge was often not available. The minimum LOS was 1 day, because admission and discharge on the same day was considered outpatient care. Urological comorbidity was defined as an anatomical abnormality of the urinary tract, a history of urolithiasis, or neurological urinary retention. Other comorbidity included the following diseases: cardiovascular disease, diabetes mellitus, immunocompromising disease, and kidney disease. A febrile UTI included pyelonephritis, urosepsis, acute prostatitis and UTI with systemic symptoms (temperature >38ºC, haemodynamic instability or delirium, as described by the attending physician). Non-febrile complicated UTIs were cystitis/chronic prostatitis in men, UTIs without systemic symptoms in catheterized patients, and cystitis in diabetic or immunocompromised women.

Analysis To compare LOS between groups (appropriate use (or not) as defined by the specific QI), we performed multilevel (mixed model) analyses, because of the hierarchical structure of our study (patients nested within departments and departments nested within hospitals). In this analysis we took account of the variability associated with each level of nesting. We performed a model with a random intercept and all other variables fixed. To investigate a possible relationship between performance on the total set of QIs and LOS, we first calculated in each patient the proportion of appropriate antibiotic use, defined as the patient’s QI sumscore divided by the number of QIs that applied to that specific patient. Including the key indicators but excluding the QI ‘Prescribe empirical treatment in accordance with the local hospital guideline’, the number of QIs that applied to a patient varied between 1 and 4. Next, we investigated the relationship between the proportion of appropriate use and the LOS by using mixed models. We controlled in all analyses of our main outcome parameter (LOS) for age, gender, urological comorbidity, other comorbidity, febrile versus non-febrile UTI and ICU.
admission within 24 hours. We performed an additional subgroup analysis excluding patients who died during hospital stay.

To compare dichotomous outcomes (ICU admission and in-hospital mortality) between groups (appropriate use (or not) as defined by the specific QI), we performed binary logistic regression analysis and adjusted for age, (urological) comorbidity and febrile UTI. Data were entered in SPSS software, version 20. A value of $P < 0.05$ was considered statistically significant.

Table 1. Baseline characteristics of 1,252 hospitalized patients with a complicated urinary tract infection

<table>
<thead>
<tr>
<th>Total</th>
<th>$n=1,252^* $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>63.1 (21.5) **</td>
</tr>
<tr>
<td>Male sex</td>
<td>513 (41.0)</td>
</tr>
<tr>
<td>Urological comorbidity (anatomical and/or functional abnormalities of urinary tract)</td>
<td>286 (22.9)</td>
</tr>
<tr>
<td>Comorbidity, other (cardiovascular disease, diabetes mellitus, immunocompromising disease, kidney disease)</td>
<td>610 (48.8)</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>215 (17.2)</td>
</tr>
<tr>
<td>Febrile UTI; non-febrile UTI</td>
<td>1083 (86.6); 167 (13.4)</td>
</tr>
<tr>
<td>Internal medicine ward; Urology ward</td>
<td>890 (71.1); 362 (28.9)</td>
</tr>
<tr>
<td>Patients treated in university hospital</td>
<td>292 (23.3)</td>
</tr>
<tr>
<td>Days of hospital stay, mean (SD)</td>
<td>8.0 (8.2)</td>
</tr>
<tr>
<td>ICU admission necessary</td>
<td>36 (2.9)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>32 (2.6)</td>
</tr>
</tbody>
</table>

**QIs for appropriate antibiotic use:**

<table>
<thead>
<tr>
<th>QIs</th>
<th>$n=1,250$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Perform a urine culture before starting treatment</td>
<td>1003 (80.2) **</td>
</tr>
<tr>
<td>2A. Prescribe empirical treatment in accordance with the national guideline</td>
<td>765 (65.6)</td>
</tr>
<tr>
<td>2B. Prescribe empirical treatment in accordance with the local hospital guideline</td>
<td>455 (46.3)</td>
</tr>
<tr>
<td>3. Switch from intravenous to oral treatment within 72 hours of starting treatment</td>
<td>295 (54.3)</td>
</tr>
<tr>
<td>4. Tailor antibiotic treatment on the basis of culture result</td>
<td>610 (71.7)</td>
</tr>
</tbody>
</table>

* missing data in $\leq 4$ patients; percentages were calculated with the denominator excluding missing cases

** numbers are $n$ (%), unless otherwise indicated
Results

Study population
The study population consisted of 1,252 hospitalized patients treated for a community-acquired complicated UTI at a department of Internal Medicine or Urology. The mean patient age was 63.1 years, 41.0% were men, and 22.9% had urological comorbidity. The mean LOS was 8.0 days. Not every QI applied to all included patients, therefore the sample sizes of the QIs varied (table 1). Concerning the performance on the QIs, a urine culture was performed in the majority of patients (80.2%). Empirical treatment was in 65.6% prescribed in accordance with the national and in 46.3% in accordance with the local hospital guidelines.

Of all patients in whom a urine culture was performed and in whom intravenous antibiotic treatment was started (n=914), 50% fulfilled all criteria for a safe early switch, while in patients without a urine culture in whom intravenous antibiotic treatment was started (n=221) this was the case in only 39% (OR 1.5; 95% CI 1.1-2.1; P=0.005). Of all patients treated with i.v. antibiotics fulfilling the criteria for a safe early switch, 54.3% was switched to an oral antibiotic within 72 hours after admission. In 851 patients the culture results were positive, enabling culture-guided final antibiotic therapy. In 71.7% of these patients final antibiotic treatment was as tailored as possible. The patients’ baseline characteristics and performances on the QIs are listed in Table 1.

Quality indicators and outcome
Associations between appropriate antibiotic use (as defined by the four QIs) and LOS are listed in Table 2. Length of hospital stay was not different for patients in whom a urine culture had been performed compared to those in whom no urine culture was performed.

A positive association was demonstrated between prescribing empirical therapy in accordance with the local hospital guideline and LOS (7.3 days in patients treated according to the local hospital guideline vs. 8.7 days in patients not treated according to the hospital guideline; P = 0.02). Treatment in accordance with the national guideline was not related to a shorter LOS. Another statistically significant association was found between an early i.v.-oral switch and a shorter LOS (4.8 days vs. 9.1 days; P < 0.001). Tailoring antibiotic treatment on the basis of culture results was not associated with LOS. Excluding patients who died during hospital stay (n=32) did not influence mean LOS (8.0 days) or the above mentioned associations between appropriate antibiotic use and LOS.

Table 3 shows the associations between the QIs and ICU admission and in-hospital mortality. The numbers of events were relatively small, but prescribing
empirical therapy in accordance with the local hospital guideline was associated with a lower rate of ICU admission.

### Table 2. Associations between quality indicators and LOS

<table>
<thead>
<tr>
<th>Quality Indicator</th>
<th>Length of stay (LOS), mean (SD)</th>
<th>P value a</th>
<th>P value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No urine culture</td>
<td>8.1 (8.2)</td>
<td>0.23</td>
<td>0.16</td>
</tr>
<tr>
<td>Guideline adherence - national</td>
<td>7.6 (7.3)</td>
<td>0.13</td>
<td>0.32</td>
</tr>
<tr>
<td>Guideline adherence - local</td>
<td>7.3 (5.9)</td>
<td>0.004</td>
<td>0.02</td>
</tr>
<tr>
<td>Early iv-oral switch</td>
<td>4.8 (3.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tailored antibiotic treatment</td>
<td>8.7 (9.1)</td>
<td>0.60</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Variables in bold are associated with shorter LOS

* missing data on LOS in 2 patients

a Data not adjusted for possible confounding variables

b Data adjusted for age, gender, urological comorbidity, other comorbidity, febrile UTI and ICU admission < 24h
Table 3. Associations between quality indicators and ICU admission\textsuperscript{a} and in-hospital mortality

<table>
<thead>
<tr>
<th>Quality Indicator</th>
<th>ICU admission\textsuperscript{b} (n%)</th>
<th>(P) value</th>
<th>In-hospital mortality\textsuperscript{b} (n%)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture (n=1,247)</td>
<td>Urine culture ((n=1000)) 34 (3.4) 2 (0.8)</td>
<td>0.06</td>
<td>25 (2.5) 7 (2.8)</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>No urine culture ((n=247))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guideline adherence - national (n=1,164)</td>
<td>Empirical therapy in accordance with national guideline ((n=762)) 20 (2.6)</td>
<td>0.62</td>
<td>17 (2.2)</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>Empirical therapy not according to national guideline ((n=402)) 13 (3.2)</td>
<td></td>
<td>11 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Guideline adherence - local (n=980)</td>
<td>Empirical therapy in accordance with local guideline ((n=453)) 8 (1.8)</td>
<td>0.03</td>
<td>11 (2.4)</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>Empirical therapy not according to local guideline ((n=527)) 20 (3.8)</td>
<td></td>
<td>12 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Early iv-oral switch (n=543)</td>
<td>Fulfilling criteria of safe switch and iv-oral switch &lt; 72 h ((n=295)) 1 (0.3)</td>
<td>0.06</td>
<td>2 (0.7)</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Fulfilling criteria of safe switch and no iv-oral switch &lt; 72 h ((n=248)) 7 (2.8)</td>
<td></td>
<td>2 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Tailored antibiotic treatment (n=851)</td>
<td>Final treatment culture-guided and as tailored as possible ((n=610)) 22 (3.6)</td>
<td>0.59</td>
<td>10 (1.6)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Final treatment not culture-guided and as tailored as possible ((n=241)) 7 (2.9)</td>
<td></td>
<td>5 (2.1)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}ICU admission after initial admission to Internal Medicine or Urology ward
\textsuperscript{b}missing data on ICU admission and in-hospital mortality in 3 patients
Data adjusted for age, urological comorbidity, other comorbidity and febrile UTI
**Performance on the total set of QIs**

The proportion appropriate use in each patient was related to LOS (figure 1). To many patients only 3 out of the 4 QIs applied: the QI regarding i.v. to oral switching involved only 43% of patients. Therefore, we divided the proportions in 3 tertiles (0-33%, 34-67% and 68-100%), and compared their association with LOS.

A statistically significant association was demonstrated between a higher proportion of appropriate antibiotic use and a shorter LOS (overall P-value < 0.05; figure 1). In patients in the upper tertile of appropriate antibiotic use, the mean LOS was 7.2 days, compared to 9.3 days for those in the lower tertile of appropriate antibiotic use.

**Figure 1.** Performance on the total set of QIs (proportion of appropriate antibiotic use) and LOS
Discussion

Prescribing empirical therapy in accordance with the local hospital guideline and an early i.v.-oral switch both correlated with a shorter length of hospital stay in patients with a complicated UTI. Additionally, a higher proportion of appropriate antibiotic use as defined by the quality indicators was associated with a shorter length of stay.

To our knowledge, this study is the first to evaluate in patients with a complicated UTI the relationship between appropriate antibiotic use and LOS. The major strength of this study is the broad and large population of interest (including men, and patients with all kinds of comorbidities), from many hospitals and different departments. Our study population represents the everyday clinical case-mix of patients hospitalized with a community-acquired complicated UTI. Further, the set of validated QIs comprised various aspects of appropriate antibiotic use in these patients, instead of one single element of it. ICU admission and in-hospital mortality occurred rarely in our study population. Length of hospital stay, on the other hand, turned out to be a very useful outcome measure. Many factors have been identified as independent predictors for LOS [14]. We therefore controlled for potential confounders (gender, age, urological comorbidity, other comorbidity, febrile UTI and ICU admission within 24 hours), and did not find any significant differences compared to the unadjusted analyses.

Our study has a few limitations. First, this is a retrospective chart review study, although there were few missing data. Second, no severity of illness score was calculated in our patients, as there is no scoring system specific for UTI patients. We neither used any general severity of illness score. However, we assume that the variables febrile UTI and ICU admission within 24 hours approach severity of illness and we adjusted our analyses for these variables. The early i.v.-oral switch could only be evaluated in the subgroup of haemodynamic stable patients without gastrointestinal problems. Finally, due to its observational design, associations between appropriate antibiotic use and LOS could be demonstrated, but causal relationships cannot be deduced.

Statistically significant associations have been established between guideline adherence and LOS [2,3,5] and between an early i.v.-oral switch and LOS [15] in patients with pneumonia. Nevertheless, despite its obvious and proven benefits, also shown in our study, an early switch to oral therapy cannot be considered routine clinical practice yet [13,16,17]. For complicated UTIs fewer studies are available, but two studies showed a relation between inadequate antibiotic therapy (i.e. not covering the in vitro
susceptibility of the isolated pathogens) and increased LOS in specific subgroups of UTI patients [6-7]. In the same patient cohort, we showed that guideline adherence indeed increased the percentage of patients receiving adequate antibiotic therapy [18], hence a positive effect of guideline adherence on LOS in UTI patients seems plausible.

An explanation for the demonstrated better adherence to the national guideline (65.6%) compared to the local guideline (46.3%) could be that the national guideline provides five possible empirical treatment recommendations, of which the local hospital guideline usually selects a number of options, depending on local resistance data.

We found no relationship between performing a urine culture and LOS. Our results are in contrast to those of Hood et al., who demonstrated that obtaining a urine culture was associated with a shorter LOS [19]. There are no other studies showing a relationship between culturing and patient outcome. However, in clinical practice a (positive) culture result might be useful to switch from i.v. to oral treatment. Of all our patients in whom a urine culture was performed and in whom intravenous antibiotic treatment was started 50% fulfilled all criteria for a safe early switch, while in patients without a urine culture in whom intravenous antibiotic treatment was started this was the case in only 39%. So indirectly, our study highlights the value of urine culturing by enabling the possibility of safe early switching to oral treatment. Additionally, a (positive) culture result is required to tailor antibiotic therapy on the basis of culture results, contributing to the containment of the development of bacterial resistance [20]. No associations were shown between tailoring antibiotic treatment on the basis of culture results and LOS. Further studies are needed to assess the more specific value of culturing and tailoring in terms of patient outcome, resistance and costs.

Even more important, our study shows that not adherence to one single QI, but adherence to a comprehensive set of QI ultimately influences patient outcome. While performance on the individual QIs in some cases lacked an association with LOS, performance on the total set of (applicable) QIs showed a significant inverse relationship with LOS.

In conclusion, appropriate antibiotic use in patients with a complicated UTI seems to reduce their length of hospital stay with more than two days and therefore favours patient outcome and healthcare costs. A half-day reduction of LOS in pneumonia patients had a substantial cost impact [9]. For patients with a complicated UTI, among the most prevalent infections in the hospital, appropriate antibiotic use can save enormous costs.
Appropriate antibiotic use reduces LOS

References


