MAJOR ARTICLE

Appropriate Antibiotic Use for Patients With Urinary Tract Infections Reduces Length of Hospital Stay

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(See the Editorial Commentary by Marwick and Nathwani on pages 170–2.)

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 4 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 multicenter study included 1252 patients with a complicated UTI, hospitalized at internal medicine and urology departments of 19 university and nonuniversity 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 sex, age, (urological) comorbidity, febrile UTI, and intensive care unit admission <24 hours.

Results. Prescribing therapy in accordance with local hospital guidelines was associated with a shorter LOS (7.3 days vs 8.7 days; $P = .02$), as was early intravenous-oral switching (4.8 days vs 9.1 days; $P < .001$). There was an inverse relationship between the proportion of appropriate use in a patient (QI sum score/number of applicable QIs) and LOS (9.3 days for lower tertile vs 7.2 days for upper tertile; overall $P < .05$).

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

Keywords. antibiotic use; urinary tract infection; length of hospital stay; intravenous-oral switching; guideline adherence.

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 4 key indicators for appropriate antibiotic use in these patients: perform a urine culture before starting treatment, prescribe empirical treatment in accordance with the national guideline, switch from intravenous 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 (LOS). 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.

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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 nonteaching hospitals located throughout the Netherlands participated. Included were adults (aged ≥16 years) who were admitted and diagnosed in 2007 or 2008 with a complicated UTI (including catheter-associated UTIs), and in whom antibiotic therapy was started. We defined a complicated UTI as a UTI with 1 of the following characteristics: male sex, 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 (ie, 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 (ie, treatment not initiated at the department of internal medicine or urology).

Between February and November 2009 the study researcher (V.S.) 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 to be 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 then-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 (eg, 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 the 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 intravenous antibiotic treatment and fulfilled the criteria for a safe early switch. These criteria were hemodynamic stability, no gastrointestinal problems at 48 hours 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 intravenous 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) who received tailored final antibiotic treatment. Final antibiotic treatment was considered "tailored" when it was in accordance with the resistance pattern of the cultured microorganism, whether a change of therapy had been performed or not. If possible, broad-spectrum antibiotic therapy should be tailored to narrow-spectrum therapy. The following antibiotics were classified as broad spectrum: cephalosporins and all combinations of antibiotics (eg, amoxicillin and gentamicin). Antibiotics with a narrow spectrum were fluoroquinolones, amoxicillin, and trimethoprim-sulfamethoxazole. When the culture result showed that the microorganism was sensitive to amoxicillin, we classified amoxicillin and not amoxicillin/clavulanic acid as narrow spectrum. Nitrofurantoin and fosfomycin are not indicated for the treatment of complicated UTI.

Definitions

LOS was defined as the number of days between admission and discharge, regardless of 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 ≥38°C, hemodynamic instability, or delirium, as described by the attending physician). Nonfebrile 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 sum score 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, sex, urological comorbidity, other comorbidity, febrile versus nonfebrile 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 analyzed using SPSS software, version 20. A value of $P < .05$ was considered statistically significant.

Table 1. Baseline Characteristics of Hospitalized Patients With a Complicated Urinary Tract Infection

Characteristic	Total (N = 1252)[a]
Age, y, mean (SD)	63.1 (21.5)[b]
Male sex	513 (41.0)
Urological comorbidity (anatomical and/or functional abnormalities of urinary tract)	286 (22.9)
Comorbidity, other (cardiovascular disease, diabetes mellitus, immunocompromising disease, kidney disease)	610 (48.8)
Urinary catheter	215 (17.2)
Febrile UTI; nonfebrile UTI	1083 (86.6); 167 (13.4)
Internal medicine ward; urology ward	890 (71.1); 362 (28.9)
Patients treated in university hospital	292 (23.3)
Length of hospital stay, d, mean (SD)	8.0 (8.2)
ICU admission necessary	36 (2.9)
In-hospital mortality	32 (2.6)
QIs for appropriate antibiotic use:	
1. Perform a urine culture before starting treatment	n = 1250 1003 (80.2)[b]
2A. Prescribe empirical treatment in accordance with the national guideline	n = 1167 765 (65.6)
2B. Prescribe empirical treatment in accordance with the local hospital guideline	n = 983 455 (46.3)
3. Switch from intravenous to oral treatment within 72 hours of starting treatment	n = 543 295 (54.3)
4. Tailor antibiotic treatment on the basis of culture result	n = 851 610 (71.7)

Abbreviations: ICU, intensive care unit; QI, quality indicator; SD, standard deviation; UTI, urinary tract infection.

[a] Missing data in ≤4 patients; percentages were calculated with the denominator excluding missing cases.

[b] Data are presented as No. (%) unless otherwise indicated.

RESULTS

Study Population

The study population consisted of 1252 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 prescribed in accordance with the national guidelines in 65.6% of patients and in accordance with the local hospital guidelines in 46.3%.

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, whereas in patients without a urine culture in whom intravenous antibiotic treatment was started (n = 221), this was the case in only 39% (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.1–2.1; $P = .005$). Of all patients treated with intravenous antibiotics fulfilling the criteria for a safe early switch, 54.3% were 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 4 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.

Table 2. Associations Between Quality Indicators and Length of Hospital Stay

Quality Indicator	LOS, d, Mean (SD)[a]	*P* Value[b]	*P* Value[c]
Urine culture (n = 1248)			
Urine culture (n = 1001)	8.1 (8.2)	.23	.16
No urine culture (n = 247)	7.4 (7.9)		
Guideline adherence–national (n = 1165)			
Empirical therapy in accordance with national guideline (n = 763)	7.6 (7.3)	.13	.32
Empirical therapy not according to national guideline (n = 402)	8.5 (9.7)		
Guideline adherence–local (n = 982)			
Empirical therapy in accordance with local guideline (n = 455)	7.3 (5.9)	.004	.02
Empirical therapy not according to local guideline (n = 527)	8.7 (9.6)		
Early IV-oral switch (n = 542)			
Fulfilling criteria of safe switch and IV-oral switch <72 h (n = 294)	4.8 (3.5)	<.001	<.001
Fulfilling criteria of safe switch and no IV-oral switch <72 h (n = 248)	9.1 (7.7)		
Tailored antibiotic treatment (n = 850)			
Final treatment culture-guided and as tailored as possible (n = 609)	8.7 (9.1)	.60	.92
Final treatment not culture-guided and as tailored as possible (n = 241)	9.0 (9.4)		

Variables in bold are associated with shorter LOS.

Abbreviations: IV, intravenous; LOS, length of hospital stay; SD, standard deviation.

[a] Missing data on LOS in 2 patients.

[b] Data not adjusted for possible confounding variables.

[c] Data adjusted for age, sex, urological comorbidity, other comorbidity, febrile urinary tract infection, and intensive care unit admission <24 hours.

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; $P = .02$). Treatment in accordance with the national guideline was not related to a shorter LOS. Another statistically significant association was found between an early intravenous-oral switch and a shorter LOS (4.8 days vs 9.1 days; $P < .001$). 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 3. Associations Between Quality Indicators and Intensive Care Unit Admission[a] and In-hospital Mortality

Quality Indicator	ICU Admission[b], No. (%)	*P* Value	In-hospital Mortality[b], No. (%)	*P* Value
Urine culture (n = 1247)				
Urine culture (n = 1000)	34 (3.4)	.06	25 (2.5)	.77
No urine culture (n = 247)	2 (0.8)		7 (2.8)	
Guideline adherence–national (n = 1164)				
Empirical therapy in accordance with national guideline (n = 762)	20 (2.6)	.62	17 (2.2)	.73
Empirical therapy not according to national guideline (n = 402)	13 (3.2)		11 (2.7)	
Guideline adherence–local (n = 980)				
Empirical therapy in accordance with local guideline (n = 453)	8 (1.8)	.03	11 (2.4)	.71
Empirical therapy not according to local guideline (n = 527)	20 (3.8)		12 (2.3)	
Early IV-oral switch (n = 543)				
Fulfilling criteria of safe switch and IV-oral switch <72 h (n = 295)	1 (0.3)	.06	2 (0.7)	.93
Fulfilling criteria of safe switch and no IV-oral switch <72 h (n = 248)	7 (2.8)		2 (0.8)	
Tailored antibiotic treatment (n = 851)				
Final treatment culture-guided and as tailored as possible (n = 610)	22 (3.6)	.59	10 (1.6)	.98
Final treatment not culture-guided and as tailored as possible (n = 241)	7 (2.9)		5 (2.1)	

Data adjusted for age, urological comorbidity, other comorbidity, and febrile urinary tract infection.

Abbreviation: ICU, intensive care unit; IV, intravenous.

[a] ICU admission after initial admission to internal medicine or urology ward.

[b] Missing data on ICU admission and in-hospital mortality in 3 patients.

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 of the 4 QIs applied;

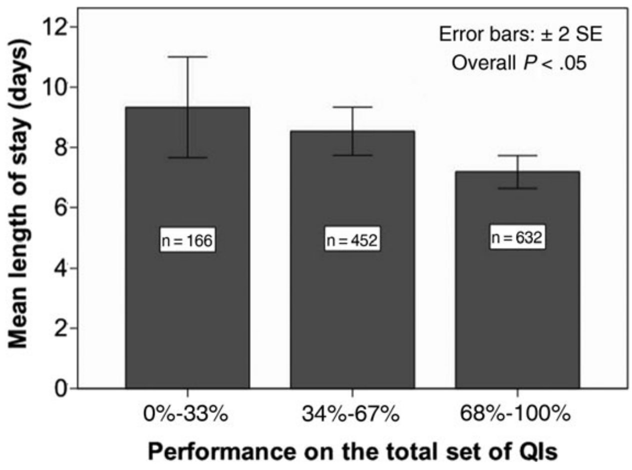

Figure 1. Performance on the total set of quality indicators (proportion of appropriate antibiotic use) and length of hospital stay. Abbreviations: QI, quality indicator; SE, standard error.

the QI regarding intravenous to oral switching involved only 43% of patients. Therefore, we divided the proportions into 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 $P < .05$; 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.

DISCUSSION

Prescribing empirical therapy in accordance with the local hospital guideline and an early intravenous-oral switch both correlated with a shorter LOS 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 LOS.

To our knowledge, this study is the first to evaluate the relationship between appropriate antibiotic use and LOS in patients with a complicated UTI. 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 1 single element of it.

ICU admission and in-hospital mortality occurred rarely in our study population. LOS, 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 (sex, 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 intravenous-oral switch could only be evaluated in the subgroup of hemodynamic 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 intravenous-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 yet be considered routine clinical practice [13, 16, 17].

For complicated UTIs fewer studies are available, but 2 studies showed a relation between inadequate antibiotic therapy (ie, 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 5 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 intravenous 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, whereas this was the case in only 39% of patients without a urine culture in whom intravenous antibiotic treatment was started. 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 adherence to a comprehensive set of QIs, not to one single QI, ultimately influences patient outcome. Although 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 by more than 2 days and therefore favors 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.

Notes

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