Predicting the Need for Radiologic Imaging in Adults with Febrile Urinary Tract Infection

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Background. Radiologic evaluation of adults with febrile urinary tract infection (UTI) is frequently performed to exclude urological disorders. This study aims to develop a clinical rule predicting need for radiologic imaging.

Methods. We conducted a prospective, observational study including consecutive adults with febrile UTI at 8 emergency departments (EDs) in the Netherlands. Outcomes of ultrasounds and computed tomographs of the urinary tract were classified as “urgent urological disorder” (pyonephrosis or abscess), “nonurgent urologic disorder,” “normal,” and “incidental nonurological findings.” Urgent and nonurgent urologic disorders were classified as “clinically relevant radiologic findings.” The data of 5 EDs were used as the derivation cohort, and 3 EDs served as the validation cohort.

Results. Three hundred forty-six patients were included in the derivation cohort. Radiologic imaging was performed for 245 patients (71%). A prediction rule was derived, being the presence of a history of urolithiasis, a urine pH ≥7.0, and/or renal insufficiency (estimated glomerular filtration rate, ≤40 mL/min/1.73 m²). This rule predicts clinically relevant radiologic findings with a negative predictive value (NPV) of 93% and positive predictive value (PPV) of 24% and urgent urological disorders with an NPV of 99% and a PPV of 10%. In the validation cohort (n=131), the NPV and PPV for clinically relevant radiologic findings were 89% and 20%, respectively; for urgent urological disorders, the values were 100% and 11%, respectively. Potential reduction of radiologic imaging by implementing the prediction rule was 40%.

Conclusions. Radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule.

Fever in patients with urinary tract infection (UTI) represents the presence of tissue inflammation that is considered to reflect acute pyelonephritis or urosepsis syndrome [1, 2]. It usually presents with mild disease, but it may cause substantial morbidity and mortality [3, 4]. Therefore, in clinical practice, the risk of complications should be assessed and alertness for underlying urologic abnormalities is part of the approach to the individual patient [5]. In this respect, ultrasonography of the urinary tract is frequently performed. It is noninvasive, readily available, portable, radiation free, and sensitive in detecting urinary obstruction and pyonephrosis [6–8]. Computed tomography (CT) is considered to be superior, but its use is limited as it requires potentially nephrotoxic contrast-enhancement [8, 9]. Nevertheless, routine performance of imaging studies in UTI are reported to be of little value, because the incidence of underlying abnormalities is low [10]. In particular, it has been advocated to perform radiologic imaging to those who remain febrile despite receipt of 3 days of active antimicrobial treatment [10–14]. Furthermore, imaging might be considered in men, diabetic persons, and patients with relapsing UTI or symptoms of urolithiasis [9, 15–17]. However, the scientific basis of these recommendations predominantly relies on expert opinion and small, observational, single-cen-
ter studies limited to young female patients [11, 16]. The clinical significance of radiologic imaging in men has been doubted in one study [18].

Nowadays, most patients with acute pyelonephritis are managed as outpatients, whereas those who present to emergency departments (EDs) are characterized by advanced disease with higher risk of complications [4, 19–21]. Therefore, redefining who will benefit from radiologic imaging is needed in order to guide efficient use of radiography. To address this issue, we prospectively observed patients with febrile UTI, with the aim of developing a clinical prediction rule that identifies those at risk for underlying abnormalities.

PATIENTS AND METHODS

Study design and setting. We conducted a prospective, observational, multiple-center cohort study with the aim of predicting different disease outcomes in adults with febrile UTI. Here, we focused on patients who presented to EDs and the prediction of radiologic outcomes.

Consecutive adults with febrile UTI were considered for enrolment in the study, and those who met the entry criteria and provided written informed consent were included. Eight EDs in 7 hospitals, serving one single area of the Netherlands, participated. Recruitment took place from January 2004 through November 2008, but each hospital started at different time points.

Clinical and radiologic outcome was evaluated during 3 months of follow-up. The study was approved by the local ethics committee.

Inclusion and exclusion criteria. Inclusion criteria were as follows: age, ≥18 years; fever (defined as a tympanic temperature of ≥38.0°C and/or a history of fever and chills ≥24 h before presentation); at least 1 symptom of UTI (dysuria, frequency, urgency, perineal pain, flank pain, or costovertebral tenderness); and a positive nitrite dipstick test result or leukocyturia, as defined by a positive leukocyte esterase dipstick test result or the presence of >5 leukocytes/high-power field in a centrifuged sediment. Exclusion criteria were current treatment for urolithiasis or hydronephrosis, pregnancy, known allergy to fluoroquinolones, receipt of hemodialysis or peritoneal dialysis, a history of transplantation, or known presence of polycystic kidney disease.

Procedures. Patients were empirically treated according to local guidelines (β-lactams, with or without aminoglycoside, for inpatients and a fluoroquinolone for outpatients). Decisions about antimicrobial treatment, hospitalization, and radiologic imaging were based on clinical judgment by the physician in charge.

Blood and urine samples were obtained for culture and were analyzed using standard microbiological methods, as described elsewhere [22]. The urine pH was measured locally by standard

Clinical data were collected by qualified research nurses or the clinical investigators (C.v.N, B.P.C.H., and T.N.B.) by reviewing the medical record completed with an interview by telephone or in person using a standardized questionnaire. All patients were contacted at enrolment and 28–32 days and 84–92 days thereafter to assess clinical and urological outcome. Radiologic data were taken from the electronic radiologic records.

Definitions and outcome measures. All radiologic studies—ultrasonography and/or CT—performed during 3-month follow-up were reviewed. The outcome was classified as “urgent urological disorder” (pyonephrosis, renal abscess, or obstructive renal stones), “nonurgent urologic disorder” (all other urological disorders with consequences for treatment), “clinically irrelevant findings” (including findings attributable to acute pyelonephritis), and “incidental nonurological disorders.”

This classification was done by the clinical investigators (C.v.N., B.P.C.H., and T.N.B.) on the basis of the final written radiologic report.

The primary end point was a clinically relevant urologic disorder, as detected by radiologic imaging, being the combination of all “urgent urological disorders” and “nonurgent urologic disorders.” Secondary end points were urgent urological disorders and the duration of fever, as defined by the interval from enrolment until the first day with a maximum body temperature <38.0°C.

Acute uncomplicated UTI was defined as UTI in women without known functional or anatomic abnormalities of the urinary tract [12, 23].

Model development. The selection of potential predictors was based on known risk factors for complicated outcome of febrile UTI, such as the development of struvite stones. Therefore, a history of urolithiasis was included, as was a urine pH ≥7.0, because struvite will only precipitate in an environment with a pH of at least 7.2 [14, 24–26]. In addition, the glomerular filtration rate (GFR) may be halved once a pyelum is completely obstructed. Thus, we choose an estimated GFR, as expressed by the modification of diet in renal disease formula (MDRD), ≤40 mL/min/1.73 m² which is 50% of the median value of our study population [27]. Other potential risk factors included were: diabetes mellitus, male sex, history of urinary tract disorder and failure of prior antimicrobial treatment [15, 16, 20].

In the event that no radiologic imaging was performed, the radiologic outcome was considered to be normal provided that the clinical and urological outcome during the 3-month follow-up period was unremarkable. However, this method does not exclude the possibility of an asymptomatic nonurgent urologic disorder. Therefore, a model was constructed to allow imputation for this (nonradiology) group, as follows. First, a logistic
normal distribution were analyzed using the Mann-Whitney test and the Wilcoxon test, respectively. Categorical variables were analyzed using the chi-square test. Measures for association were expressed as odds ratios (ORs) for disease with their 95% confidence intervals (CIs) for categorical variables. The aforementioned selected variables were put into a multivariate logistic regression model. For each of the imputation datasets above, we repeated our calculations, such that the model was rerun 100 times. A 2-tailed P value of <.05 was considered statistically significant. Statistically significant variables in the multivariate model were used to formulate a prediction rule. The discriminative power of the prediction rule was determined by calculating its sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

RESULTS

A total of 346 patients were included in the derivation cohort, 245 (71%) of whom underwent radiologic imaging. The median age was 70 years (interquartile range, 49–80 years), and 41% were male. The majority of patients had flank pain and shaking chills (Table 1). Radiologic imaging was significantly associated with female sex, history of urolithiasis, absence of indwelling urinary catheter, and the presence of flank pain or shaking chills (Table 1).

Microbiological findings. The results of urine cultures, which were performed for 322 patients (93%), were as follows: Escherichia coli, 182 patients (57%); other uropathogens, 69 (21%); and no significant bacteriuria, 71 (22%). Forty-eight patients (65%) with no significant bacteriuria were pretreated for UTI. Blood cultures were performed in 319 patients (92%). Bacteremia was present in 95 (30%) of these patients and predominantly involved E. coli in 75 (79%) of the 95 cases.

Radiologic outcome. In total, 268 ultrasounds and 81 CTs of the urinary tract were performed. Of these imaging studies, 50% were done ≤24 h after presentation and 75% were done ≤72 h after presentation. Of the 245 patients who underwent radiologic imaging, 175 (71%) were classified as having normal findings, 14 (6%) were classified as having urgent urologic disorders, 32 (13%) were classified as having nonurgent urologic disorders, and 24 (10%) were classified as having incidental nonurological disorders. More details about the specific radiologic findings are outlined in Table 2. During follow-up, 3 patients were lost to follow-up and 15 died.

Of the 101 patients who did not undergo radiologic imaging, 8 patients died (2 deaths were related to urosepsis, and 6 were related to an underlying comorbidity), and 2 were lost to follow-up. These 10 were excluded from further analysis. For the remaining 91 patients, the clinical, including urological, outcome was unremarkable, except for 1 patient who required treatment for nonobstructive renal stones. Comparing this patient with the previously described imputation model, we found that the imputation model predicted the highest probability Pnonurgent for this patient. Therefore, we set this patient as having a nonurgent urologic disorder and included the patient as a fixed case within each of the 100 simulated datasets. In addition, the simulations added an average of 7 additional other cases across 100 simulation repeats as having a nonurgent urologic disorder. Thus, 8 (9%) of the 91 patients had a presumed nonurgent urologic disorder (Table 2).

Derivation of the prediction rule. In the multivariate analysis, the following predictors were significantly associated with the primary end point: history of urolithiasis; urine pH, ≥7.0; and MDRD, ≤40 mL/min/1.73 m² (Table 3). Comparing model results across the 100 imputation-based analyses revealed that male sex could also be a significant predictor (Table 3).

To account for the relative impact of each variable, points were assigned to each predictor on the basis of the β coefficient in the logistic regression equation. Different cutoff values were used to calculate the corresponding predictive values with respect to radiologic outcome. To obtain sufficient sensitivity, a cutoff value of ≥1 point had to be used while male sex was
Table 1. Baseline Characteristics of Patients at Presentation with Febrile Urinary Tract Infection (UTI)

| Characteristic                        | Total (n = 346) | Radiology performed (n = 245) | No radiology performed (n = 101) | P
|---------------------------------------|-----------------|-------------------------------|----------------------------------|------
| Age, median years (IQR)              | 70 (49–80)      | 68 (43–80)                    | 72 (54–80)                       | .174
| Male sex                             | 140 (41)        | 88 (36)                       | 52 (52)                          | .008
| Present antibiotic UTI treatment     | 124 (36)        | 94 (38)                       | 30 (30)                          | .140
| Present urinary catheter             | 33 (10)         | 17 (7)                        | 16 (16)                          | .011
| History of urolithiasis              | 39 (11)         | 34 (14)                       | 5 (5)                            | .015
| Urinary tract disorder\(^b\)         | 94 (27)         | 66 (27)                       | 28 (28)                          | .896
| History of UTI                       | 157/340 (46)    | 42/98 (43)                    | 115/242 (48)                     | .472
| Diabetes mellitus                    | 58 (16)         | 40 (16)                       | 18 (18)                          | .753

**Fever duration.** Duration of fever could be evaluated in 300 of 346 patients in the derivation cohort. The outpatients presumably continued to be febrile but did not measure or record their body temperatures. The median duration of fever was 2 days. After 1, 2, 3, and 4 days, 38%, 65%, 82%, and 90% of patients, respectively, were afebrile. Duration of fever ≥3 days was not associated with any clinically relevant radiologic finding (univariate OR, 1.17; 95% CI, 0.61–2.23) or any urgent clinically relevant radiologic finding (univariate OR, 1.40; 95% CI, 0.47–4.15).

**Validation of the prediction rule.** Of 144 patients included in the validation cohort, 94 (65%) underwent radiologic imaging (84 ultrasounds and 23 CTs). During follow-up, 3 patients died and 4 were lost to follow-up. Of the 50 patients who did not undergo radiologic imaging, 3 patients died (all deaths were related to an underlying comorbidity) and 10 were lost to follow-up; these 13 patients were excluded from further analysis. The remaining 37 patients all had unremarkable clinical and urological follow-up findings. Using similar methods for imputation, a mean of 6 different patients was 100 times randomly imputed as having a nonurgent urologic disorder.

Classification of radiologic outcome revealed the following: of 131 evaluable patients, 95 (73%) had ‘normal findings, 6 (5%) had urgent urologic disorders, 13–19 (10%–15%) had nonurgent urologic disorders, and 17 (13%) had incidental nonurological disorders.

The discriminative performance of the prediction rule (≥1 point) in this cohort was acceptable, with an NPV of 89% for any clinical relevant radiologic finding and an NPV of 100% for any urgent relevant radiologic finding. The mean NPV for any clinical relevant radiologic finding of the multiple imputation models was 87%. Sensitivity, specificity, and PPV are shown in Table 4.
Table 2. Radiologic Outcome of Patients with Febrile Urinary Tract Infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of patients</th>
<th>Radiology</th>
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<tbody>
<tr>
<td></td>
<td>(n = 245)</td>
<td>(n = 91)</td>
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<tr>
<td>Clinically relevant findings (n = 47)b</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urgent urologic disorders</td>
<td>14 (6)</td>
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<tr>
<td>Pyonephrosis</td>
<td>13 (5)</td>
<td>...</td>
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<tr>
<td>Pyonephrosis with ureteropelvic junction stenosis</td>
<td>1 (1)</td>
<td>...</td>
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<tr>
<td>Nonurgent urologic disorders</td>
<td>32 (13)</td>
<td>1 (1)b</td>
<td></td>
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<tr>
<td>Nonobstructive renal stones</td>
<td>19 (8)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Urologic malignancy</td>
<td>5 (2)</td>
<td>...</td>
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<tr>
<td>Ureteropelvic junction stenosis</td>
<td>3 (1)</td>
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<tr>
<td>Enterovesical fistula</td>
<td>2 (1)</td>
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<tr>
<td>Other</td>
<td>3 (1)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>No indication for radiologic imaging</td>
<td>175 (71)</td>
<td>90 (99)</td>
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<tr>
<td>Clinically irrelevant findings</td>
<td>165 (67)</td>
<td>...</td>
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<tr>
<td>Normal or findings attributable to acute pyelonephritis</td>
<td>5 (2)</td>
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<tr>
<td>Benign prostatic hyperplasia</td>
<td>3 (1)</td>
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<tr>
<td>Other</td>
<td>2 (1)</td>
<td>...</td>
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<tr>
<td>Incidental nonurological disorders</td>
<td>24 (10)</td>
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<tr>
<td>Aortic aneurysm</td>
<td>3 (1)</td>
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<tr>
<td>Diverticulitis</td>
<td>2 (1)</td>
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<tr>
<td>Choledocholithiasis</td>
<td>2 (1)</td>
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<tr>
<td>Liver metastases</td>
<td>2 (1)</td>
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<tr>
<td>Other</td>
<td>15 (6)</td>
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</table>

a Presumed radiologic outcome. Of 101 patients, the outcome could not be assessed for 10: 8 patients died, and 2 were lost to follow-up. The clinical and urological outcome of the evaluable patients was unremarkable in 90 patients, and 1 patient required additional treatment for renal stones.

b On the basis of logistic modeling, a mean of 7 extra patients were randomly assigned to this category; thus, clinically relevant findings range from n = 47 to n = 54.

Potential reduction in radiologic imaging. In total, radiologic imaging was performed in 339 (69%) of 490 patients, including 357 ultrasounds and 104 CTs. Of the 490 patients, 203 (41%) had a prediction score ≥ 1 point. Thus, implementing the prediction rule might potentially lead to 40% (relative reduction) or 28% (absolute reduction) reductions in radiologic imaging studies.

DISCUSSION

We present a simple clinical prediction rule to be used at EDs for selective use of radiologic imaging in adults presenting with febrile UTI. This rule might lead to a 40% reduction in the number of imaging studies without losses in the findings of critically relevant outcomes, such as pyonephrosis and renal abscess. To the best of our knowledge, this is the first study to have derived and validated a prediction rule to predict the need for radiologic imaging in adults with febrile UTI.

The present study has several strengths. First of all, the participating patients reflect the daily practice of emergency medicine, with the majority experiencing underlying comorbidities for which radiologic imaging is almost routinely considered. Second, the prediction rule was not only derived but also validated on a representative cohort gathered at multiple centres. Furthermore, the clinical prediction rule consists of readily available patient characteristics, which should make it easily applicable to routine practice of EDs. Finally, the prediction rule is based on factors that are biologically correlated with complicating stones in UTI [24–26]. Therefore this prediction rule may also be useful in other settings.

However, our study has also some limitations. First, the sample size is relatively small, but according to the rule of thumb (1 predictor for 10 outcomes), the study still had reliable power [28]. In addition, compared with previous studies that addressed risk factors for urinary tract abnormalities in patients with UTI, our study is the largest prospective study thus far [11, 14, 16, 18]. Second, we considered the radiologic outcome of patients without imaging to be normal provided that the clinical outcome was unremarkable. Over a 3-month period, the presence of an urgent urological disorder will likely become apparent, but nonurgent urologic disorders would not necessarily have become clinically evident. Thus, the real presence of such conditions may have been underestimated. Therefore,
we additionally tested 100 models with imputation of nonurgent urologic disorders to account for the impact of variability of imputation. The outcome of these models was not significantly different, indicating that such underestimation has limited impact on the final predictive value of the prediction rule.

On the basis of known risk factors for complicated outcome, we used readily available variables for predictive modelling. The cutoff values of continuous variables were chosen on the basis of limitations in our dataset. For MDRD, a cutoff value of 25 mL/min/1.73 m² was chosen as a marker of a 50% decline in renal function. This was because, in the majority of participants, the preexistent GFR was unknown. It could well be that a decrease in GFR at an individual level is a better predictor. The use of this prediction rule in a population with high frequency of preexistent renal failure should, therefore, be performed with caution. Nevertheless, in daily practice, a prior estimated GFR of patients is often unknown. In addition, we chose a urine pH ≥7.0 as the cutoff value, although struvite calculi only precipitate in an environment with a pH of at least 7.2 [24, 25]. In fact, we noticed that a cutoff value of ≥7.5 had similar sensitivity but better specificity (data not shown), but our data were limited, because the urine dipsticks used in the validation cohort rounded the urine pH to whole values—either 7.0 or 8.0, with the former value providing higher sensitivity.

We found clinical relevant abnormalities of the urinary tract in 19% of the patients who underwent radiologic imaging. This is comparable to previous studies involving both men and women [15, 18, 29–32]. However, we did not find an association between fever duration and elevated risk of underlying urinary tract abnormality [11, 13, 14, 30]. This is probably...
because, in our study, the majority of patients with pyonephrosis underwent draining before the third day of antimicrobial treatment. However, the predictive value of fever duration has been questioned in previous studies showing similar fever patterns as in our study [32, 33]. Additional studies are needed to address this issue in more detail but, we advocate the implementation of our prediction rule because it predicts urgent urological complications at presentation rather than after 3 days of treatment. Additional research is required on modification and validation of this prediction rule in different settings and larger cohorts. Moreover, because this study does not prove that implementation of the prediction rule indeed saves radiologic imaging and costs, prospective studies evaluating the cost-effectiveness are essential.

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