The Impact of Empirical Management of Acute Cystitis on Unnecessary Antibiotic Use

Warren J. McIsaac, MD, MSc; Donald E. Low, MD; Anne Biringer, MD; Nicholas Pimlott, MD, PhD; Michael Evans, MD; Richard Glazier, MD, MPH

Background: Guidelines for the management of acute cystitis support empirical antibiotic treatment; however, up to half of symptomatic women have negative urine cultures.

Objective: To determine whether empirical treatment leads to unnecessary antibiotic prescriptions in women with symptoms of acute cystitis.

Methods: A cohort of 231 women (defined as females aged 16 years and older) presenting to family physicians' offices with symptoms of cystitis underwent a standardized clinical assessment, urine dip testing, and culture. Recommendations for urine testing and antibiotic treatment under 3 empirical strategies were compared with observed physician management and a logistic regression model for the outcomes of antibiotic prescriptions, urine culture testing, and unnecessary antibiotics, defined as a prescription where the subsequent urine culture was negative.

Results: There were 123 positive urine cultures (53.3%). Physicians prescribed antibiotics to 186 women (80.9%), of whom 74 (39.8%) were culture negative. Unnecessary antibiotic use was similar for 2 guidelines recommending empirical antibiotic treatment without testing for pyuria (41.4% and 40.6%). Treating women with classic cystitis symptoms and pyuria would have decreased unnecessary antibiotic use (26.2%; \( P = .02 \)) but resulted in fewer women with confirmed urinary tract infection receiving immediate antibiotics (66.4% vs 91.8% usual care; \( P < .001 \)). A derived prediction model incorporating testing for pyuria and nitrites would also have reduced unnecessary antibiotic use (27.5%; \( P = .03 \)), but more women with confirmed urinary tract infection would have received immediate antibiotics (81.3%; \( P = .01 \)).

Conclusions: Empirical antibiotic treatment of acute cystitis in women without testing for pyuria promotes unnecessary antibiotic use. A simple decision rule provides for prompt treatment of infected women while reducing antibiotic overuse and unnecessary urine testing.

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Urinary tract infections (UTIs) account for 0.9% to 2.1% of an estimated 700 million office visits each year in the United States. An antibiotic is prescribed in 58% of encounters, representing 5% of all antibiotic prescriptions to adults. In recent years, antibiotic resistance among common uropathogens has been increasing. At the same time, physicians have been advised that empirical antibiotic treatment without culture is appropriate in cases of uncomplicated UTI. The majority of these occur in women; however, up to half of women with symptoms suggestive of UTI do not demonstrate significant bacteriuria on culture. As a result, empirical treatment may promote unnecessary antibiotic use, which has been associated with increased levels of antimicrobial resistance.

To assess the impact of empirical management of uncomplicated UTI on antibiotic use, a cohort of women presenting to family physicians with symptoms suggesting a UTI were assessed. Recommendations from 3 empirical strategies were applied retrospectively to the cohort to determine what would have been the rates of antibiotic prescribing and unnecessary antibiotic use had physicians followed these recommendations. The latter was defined as prescriptions of antibiotics to women with negative urine cultures. The empirical management strategies were then compared with the actual care provided by the study physicians. In addition, we sought to determine whether any other combination of clinical findings and urine testing were more helpful in guiding initial prescribing decisions.
SUBJECTS AND METHODS

The study took place in 4 urban academic family medicine clinics affiliated with the Department of Family and Community Medicine of the University of Toronto, Toronto, Ontario. These clinics have more than 70 full- and part-time physician staff, 52 residents, and in excess of 150,000 patient visits per year. The cohort of women was prospectively enrolled between January 1, 1998, and January 7, 2000. Women (defined as females aged 16 years and older) presenting with urinary tract symptoms for which the treating physician considered UTI a possible diagnosis were eligible for the study. No attempt was made to further define an eligible case, to encourage physicians to enroll cases representative of their usual practice.19 The study was explained to eligible women by a research assistant or a non-treating physician, and consent was obtained. Ethics approval for the study was obtained from the University of Toronto research ethics board.

Physicians completed a standardized clinical assessment to determine symptoms, risk factors for UTI,20,21 and physical findings. Patients were excluded if they had been taking antibiotics in the previous 7 days, were immunocompromised, were pregnant, or were following up a previously diagnosed UTI. A urine sample was obtained for dipstick testing with leukocyte esterase and nitrite test strips (Multistix 5; Bayer, Inc, Etobicoke, Ontario) and submitted for culture. Urine cultures were processed at the usual laboratory to which the clinics referred their samples. These included 3 tertiary care academic teaching hospitals and 1 commercial laboratory. The gold standard for a diagnosis of a UTI was a positive culture with more than 100,000 colonies of a single organism per milliliter, or 10^2 to 10^5 colonies of coliform organisms per milliliter.6 At the time of the initial visit, and before culture results were available, physicians recorded their diagnosis and treatment decisions. The physicians were free to treat patients in their usual fashion. For each woman, the recommendations from 3 strategies recommending empirical antibiotic treatment were applied retrospectively on the basis of the presenting clinical findings and the results of the urine dip testing, where relevant.22,23 Stamm and Hooton6 recommended empirical treatment without the need for urine cultures in patients with typical symptoms (defined as dysuria, frequency, and urgency) and pyuria, either microscopically or on leukocyte esterase testing. The Group Health Cooperative of Puget Sound introduced a clinical guideline in their health maintenance organization that offered telephone treatment without urine testing, or an office visit, to women with symptoms of dysuria or urgency.7 Those accepting telephone management were offered antibiotic treatment, while those requesting an office visit were treated at the discretion of the health care provider.

The Protocol Steering Committee of the British Columbia Medical Association recommended no testing for patients with classic symptoms of a UTI (not defined) where the physician planned to prescribe an antibiotic.24 If a suspected UTI was not initially treated, a culture was recommended if there was either pyuria or nitrites. For all 3 strategies, it was assumed that a urine culture would be ordered where an antibiotic was not prescribed or dip testing was positive, as appropriate to the particular approach. The culture results from groups of women with similar symptoms or dipstick findings in the cohort were used to determine what culture results would have been under these strategies.

We also assessed whether any other combination of clinical and urine dip test findings was more predictive of a positive urine culture. The association of individual clinical findings and dipstick results with culture results was assessed by means of a χ² or Fisher exact test as appropriate. Variables associated with a positive urine culture (P<.25) were retained for multivariate modeling by means of backward stepwise multiple logistic regression.22,23 The final model retained only variables that were independently associated with the outcome of a positive urine culture (P<.05). Recommendations for empirical antibiotic use and urine culture testing were developed on the basis of the probability of a positive urine culture and compared with the other strategies.

The sensitivity and specificity of each strategy and of observed physician management was determined in relation to the decision to initiate antibiotics. If a strategy recommended immediate antibiotic therapy and the culture result was positive, then the prescribing decision was considered appropriate (sensitivity of the prescribing decision). If an antibiotic was not recommended and the urine culture was negative, then this was considered appropriate for a negative case (specificity). An antibiotic prescription was classed as unnecessary if the subsequent urine culture result was negative.

The outcomes assessed, therefore, were antibiotic prescriptions, unnecessary antibiotics, urine culture use, and the sensitivity and specificity of each strategy. These outcomes were determined for the 3-empirical treatment strategies (classic symptoms and pyuria, of Puget Sound guideline,7 and British Columbia Protocol Steering Committee guideline24) and the derived management approach (logistic model), and compared with actual treatment of the cohort of women by the physicians (usual care) by means of a χ² test.

The sample size calculation determined that 108 persons with infection were needed to detect whether any combination of dipstick testing and clinical findings had a sensitivity for identifying a positive urine culture of at least 90%, with the lower 95% confidence interval (CI) being no less than 75% and 90% power.24 A pilot study found a prevalence of infection of 46% in this setting, so that the sample size was estimated to be 235.

RESULTS

A total of 231 women were assessed. The average age of these women was 43.9 years (range, 20-92 years). More than half were married or in common-law relationships and had had a previous history of a UTI (Table 1). Thirty-six women (17.5%) came to the office after 1 day of symptoms, approximately one third (72/206) presented within 2 days, and one third (72/206) waited more than 5 days. More than 80% of women asked (119/143) thought they had a UTI, and almost three quarters thought they needed an antibiotic. The most frequent symptoms were frequency (85.7%), dysuria (78.4%), and urgency (77.5%). The physicians’ diagnosis was UTI in 92.3% of cases. This was somewhat higher (95%) if there was dysuria, with or without other symptoms. An antibiotic was pre-
A positive urine culture was more likely if symptoms had been present for only 1 day (odds ratio [OR], 2.83; 95% CI, 1.07-7.45), burning or discomfort on urination (OR, 3.97; 95% CI, 1.66-9.30), postvoid urgency (OR, 0.45; 95% CI, 0.21-0.98), a positive leukocyte test (>trace) (OR, 2.38; 95% CI, 1.16-4.83), a positive nitrite test (OR, 5.49; 95% CI, 1.89-15.99), and blood on dip testing (>trace) (OR, 2.35; 95% CI, 1.14-4.84). Postvoid urgency was dropped from the model, as the direction of the association lacked clinical sensibility and the univariate association was weak. Blood on dip testing was also dropped, as the reduced model without this factor was found to perform as well. The area under the receiver operating characteristic curve for the 4 remaining variables was 0.79.

Table 2 shows the rate of positive urine cultures in relationship to the number of these 4 clinical characteristics present. Fewer than 2 findings were associated with a relatively low rate of positive cultures (15.8%-27.9%), whereas 2 or more characteristics were associated with a high positive culture rate (62.9%-100.0%; P<.001). Therefore, a management algorithm was devised suggesting that a urine culture be obtained where fewer than 2 of the 4 characteristics were present and antibiotic treatment without culture be given for those with 2 or more findings (UTI rule).

The Figure illustrates how prescribing rates were estimated for each empirical strategy, using the Puget Sound algorithm as an example. Three women with a final diagnosis of pyelonephritis were excluded and 39 who reported a vaginal discharge were not considered eligible for telephone management, as per the algorithm. In a previous report, 40% of women accepted telephone management and were considered to have been prescribed antibiotics. Applying this percentage would result in 69 women in the current cohort receiving telephone treatment and 104 requesting an office visit. Physicians in the current study prescribed antibiotics to 85.5% of women presenting with dysuria or urgency. Applying this to the estimated 60% of women who would be seen by physicians at an office visit under the Puget Sound guideline would mean 88.9 women would receive antibiotic treatment without culture being given for those with 2 or more findings (UTI rule).

Table 2. Number of Clinical Findings Derived From Multiple Logistic Regression (Symptoms for 1 Day, Dysuria, Positive Leukocyte† or Positive Nitrite† Test) and Rate of Positive Urine Cultures

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Culture Result, No. (%)</th>
<th>Likelihood Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>0</td>
<td>16 (84.2)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>1</td>
<td>44 (72.1)</td>
<td>17 (27.9)</td>
</tr>
<tr>
<td>2</td>
<td>26 (37.1)</td>
<td>44 (62.9)</td>
</tr>
<tr>
<td>3</td>
<td>7 (15.9)</td>
<td>37 (84.1)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>6 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td>93 (46.5)</td>
<td>107 (53.5)</td>
</tr>
</tbody>
</table>

*More than trace. †More than negative.  §Likelihood ratio for 0 and 1 category combined. ¶Likelihood ratio for 2, 3, and 4 category combined.  ©2002 American Medical Association. All rights reserved.
of 88.9 persons) compared with 32.0% where physicians did not immediately prescribe antibiotics (or 4.8 of 15 persons). Those latter women were assumed to have undergone urine culture testing. The estimated numbers of persons in each category of the Figure have been rounded to the nearest whole number for convenience. This approach was also followed for women without dysuria or urgency, or reporting vaginal discharge. The other empirical management strategies were similarly evaluated.

Table 3 summarizes the antibiotic use, unnecessary antibiotic prescriptions, culture use, and the sensitivity for identifying UTI of all strategies compared with observed physician management (usual care). All strategies would have reduced urine culture testing compared with usual physician care (P<.01). Both treating classic symptoms with pyuria and the UTI rule would have reduced unnecessary antibiotic use compared with usual care (34% and 31% reductions, respectively; P<.005). The Puget Sound and British Columbia Protocol Steering Committee guidelines were the most sensitive for treatment of UTI at initial presentation before culture results, but were the least specific, resulting in high levels of unnecessary antibiotic use similar to that observed for usual care. Following the classic approach or the derived management algorithm would have reduced initial antibiotic prescriptions by 40% and 26%, respectively (P<.001), and urine culture testing by 40% and 54%, respectively (P<.001). The UTI rule had a significantly higher sensitivity for treating subsequently confirmed UTI cases at initial presentation (81.3%) than did the classic approach (66.4%; P=.001).

There is wide variation in how physicians manage acute uncomplicated cystitis. In one study, physicians proposed 82 different treatment regimens. Half reported they would treat typical UTI symptoms over the telephone, whereas the other half would not. Another study comparing microbiologists, urologists, and general practitioners found similar variations in management and concluded, “there is a need for evidenced-based rather than consensus-directed guidelines.”

Empirical antibiotic treatment of acute, uncomplicated cystitis has been advocated on the basis of the predictable set of pathogens that are found and the high rate of negative, and therefore unnecessary, urine cultures that are submitted. Empirical treatment can help to decrease unnecessary urine testing. However, guidelines and treatment recommendations need to be evaluated for their impact on a variety of clinical outcomes. We found that, although empirical management can reduce the number of unnecessary urine cultures substantially, some strategies are associated with high levels of unnecessary antibiotic use. Given the accumulating evidence of a causal relationship between antibiotic resistance and antibiotic overuse, the impact of empirical management on unnecessary antibiotic use is an important consideration.

Antibiotic resistance is a growing problem in urinary tract infections. Escherichia coli, which accounts for up to 80% of uncomplicated cystitis in young women, demonstrates resistance to trimethoprim-sulfamethoxazole in up to 18% of isolates, and 38% are resistant to ampicillin. Sulfamethoxazole-trimethoprim is frequently recommended as first-line therapy. A Welsh study compared rates of antibiotic resistance in urinary tract isolates from different community-based groups of general practitioners and found a direct correlation between rates of antibiotic resistance and community rates of antibiotic prescribing. If further resis-
It is also relevant that women with uncomfortable symptoms due to UTI receive timely antibiotic treatment. Although usual physician management and 2 empirical strategies resulted in the greatest number of women receiving immediate antibiotic treatment, the severity of their symptoms and willingness to wait for culture results was not directly assessed. We observed that 35% of women waited more than 5 days before visiting their physician, suggesting that some were perhaps less bothered by their symptoms and may have been willing to wait for culture results. The use of classic symptoms and pyuria proposed by Stamm and Hooton resulted in the fewest women with UTI receiving antibiotics immediately. However, the original description of this approach also included abrupt onset and severe symptoms as being relevant to the diagnosis of cystitis. We were not able to model these factors with this cohort and so may have underestimated the sensitivity of this approach.

The management algorithm derived by means of logistic regression modeling (UTI rule) would have reduced urine culture testing compared with usual care and the classic approach. It would also have reduced unnecessary antibiotic use compared with usual care and the Puget Sound and British Columbia protocols and resulted in more women with positive urine cultures being treated immediately with antibiotics than would the classic approach. The UTI rule also allows for telephone treatment if women have symptoms for 1 day and dysuria. Komaroff et al were among the first to propose that explicit clinical strategies could help improve the cost and quality of medical care with the use of UTI as the model. However, their algorithm and another decision rule are somewhat more complex, which may be less appealing to busy practitioners.

Prediction rules have been proposed as a method for incorporating research evidence into practice. However, validation in independent patient populations is a prerequisite, as they may not perform well if the disease prevalence in the new setting differs from that in the population in which the prediction rule was originally derived. We found that the prevalence of positive cultures in this study was similar to reports in other general practice settings. Antibiotic prescribing by these family physicians was also similar to the 82% to 86% reported in other studies. A Canadian study had a somewhat lower prescribing rate (63%) but also included children. Although such observations suggest that the algorithm will likely perform similarly in other general and family practice clinics, the validity of the algorithm still requires independent confirmation.

Guidelines recommending empirical treatment of women presenting to family physicians with symptoms suggestive of an uncomplicated UTI without urine testing result in high rates of unnecessary antibiotic use. In the face of emerging antibiotic resistance among uropathogens, these strategies require reevaluation. The use of classic symptoms combined with testing for pyuria limits unnecessary antibiotic use but may leave symptomatic women untreated until urine culture results are available. The simple UTI decision rule described in this article results in prompt treatment of most infected women and, at the same time, limits unnecessary urine culture testing and antibiotic prescriptions. The rule requires validation in an independent population, and its acceptability to patients needs to be assessed, as some women will be advised to delay antibiotic treatment until culture results are available.

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From the Mt Sinai Family Medicine Centre (Drs McIsaac and Biringer) and Department of Microbiology (Dr Low), Mt Sinai Hospital, Family Healthcare Research Unit, Department of Family and Community Medicine (Drs McIsaac, Pimlott, Evans, and Glazier) and Department of Laboratory Medicine and Pathobiology (Dr Low), University of Toronto, Department of Microbiology, The Toronto Hospital (Dr Low), Family Medicine Unit, Women’s College Hospital (Dr Pimlott), Family Medicine Unit, University Health Network–Toronto Western Division, Toronto (Dr Evans), and Department of Family and Community Medicine and Inner City Health Research Unit, St Michael’s Hospital (Dr Glazier), Toronto, Ontario.

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Corresponding author: Warren J. McIsaac, MD, MSc, Mt Sinai Family Medicine Centre, 600 University Ave, Room 413, Toronto, Ontario, Canada MSG 1X5 (e-mail: wmcsisaac@mtsinai.on.ca).

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