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The Natural Course of Uncomplicated Lower Urinary Tract Infection in Women Illustrated by a Randomized Placebo Controlled Study

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This prospective, multicentre, randomized, double-blind and placebo controlled study was performed to describe the natural course of uncomplicated lower urinary tract infection (UTI). A total of 1143 women 18 y and above, consulting at 18 primary health care centres in northern Sweden for symptoms suggestive of UTI were included. The symptoms urgency, dysuria, suprapubic pain and loin pain were registered, and urine cultures performed at inclusion and follow-up visits 8–10 d and 5–7 weeks later. Associations between all symptoms and bacteriuria or bacterial counts were unpredictable. Eradication of symptoms and bacteriuria and combinations of them were studied in 288 patients placebo treated for 7 d, of whom 39% dropped out after the first follow-up visit. The spontaneous cure rate of symptoms was 28% after the first week, and 37% had neither symptoms nor bacteriuria after 5–7 weeks. Considering the high dropout rate after the first follow-up visit, the spontaneous cure rate of symptoms and bacteriuria was calculated to 24% at the end of study. We conclude that patient near-laboratory tests are required to establish the diagnosis of lower UTI, and the guidelines for diagnosis of UTI need to be revised.

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INTRODUCTION

Urinary tract infection (UTI) is the second most common group of bacterial infections after those of the respiratory tract. Acute uncomplicated lower UTIs in women are dominating (1) and most often handled by general practitioners in primary health care (PHC) (2). Studies of UTI usually focus on bacteriology, drug resistance and bacteriological outcome of antibiotic therapy in selected patient groups, despite guidelines for evaluation of treatment of UTI requiring eradication of both bacteriuria and symptoms (3). However, the clinical presentation and duration of symptoms before treatment are seldom reported (4–6). Common UTI symptoms are frequency, urgency, dysuria and suprapubic pain, while low back/flank or loin pains are often considered as symptoms of pyelonephritis (3).

The cut-off limit for significant bacteriuria (SBU) was established by Kass to \(10^7\) colony forming units (CFU) per ml in midstream urine for patients with pyelonephritis and asymptomatic bacteriuria (7). However, this limit was later applied also to patients with lower symptomatic UTI, although in many studies about 50% of the patients had bacteriuria. The cut-off limits were intensively discussed (8–12) before new guidelines for diagnosis of UTI were established in 1992 in USA (3) and 1993 in Sweden (13). According to these guidelines the limits for SBU vary between \(10^7\) and \(10^5\) CFU/ml depending on uropathogens, gender and type of urine sample. New Swedish (14) and European guidelines (15) were established in the y 2000, classifying the uropathogens as primary, secondary, doubtful, and usually urethral or genital flora. Moreover, minor changes in cut-off limits for SBU were stated.

Age, symptom duration and bladder incubation time are considered to influence the frequency of symptoms and bacteriuria (1, 3, 13, 16). The natural course of uncomplicated UTI has previously been sparsely documented in a few minor studies (17–19). Therefore a comprehensive larger study is needed to better understand the nature of UTI, and preferably in a placebo controlled study design.

The aim of the present study was to describe the natural course of suspected uncomplicated lower UTI in women by evaluating the presence of symptoms and bacteriuria and their spontaneous cure rates, as well as the combinations of them during 1 week of placebo therapy and a 5–7 weeks follow-up period.

MATERIAL AND METHODS

Inclusion

Women 18 y and above with symptoms suggestive of lower UTI: urgency (U), dysuria (D), suprapubic pain (S) or loin pain (L) were invited to participate. The study was performed at 18 PHC centres in the county of Västerbotten in northern Sweden between April 1995 and December 1997. The severity of each symptom was graded as none, light, moderate or severe (score 0–3) and a total symptom score of \(\geq 2\) was required for inclusion in the study to allow evaluation of improvement. The ethics committee of Umeå University approved the study. All patients gave their signed informed consent before inclusion.

Exclusion

The exclusion criteria were: pregnancy/planned pregnancy, antibiotic therapy for UTI within the last month or unapproved drug treatment within 3 months prior to inclusion, known/suspected penicillin allergy, genital infection, complicating factors (diabetes or abnormality of the urinary tract), 1 or more signs of pyelonephritis
Uropathogens were quantified as 10^3 to 10^4 and counting the number of colony forming units in CFU/ml. The Maryland, USA) and incubated at 35°C for 18 to 20 h before counting the number of colony forming units in CFU/ml. The uropathogens were also classified into 4 groups: Gram-positive bacteria were primarily identified by catalase reaction. Staphylococci were identified by DNAse activity and novobiocin susceptibility and enterococci/streptococci by esculin, CAMP-reaction and agglutination reactions (Streptex Murex Biotech Ltd. Dartford, England). Coagulase negative staphylococci, other than S. saprophyticus, were identified by the API 20 E system (API bio Merieux sa, France). Gram-positive bacteria were identified by DNase activity and novobiocin susceptibility and enterococci/streptococci by esculin, CAMP-reaction and agglutination reactions (Streptex Murex Biotech Ltd. Dartford, England). Coagulase negative staphylococci, other than S. saprophyticus, were denoted ‘other CNS’. The uropathogens were also classified into 4 clinically relevant groups: E. coli, Gram-negatives other than E. coli, staphylococci and Gram-positives other than staphylococci (20).

Natural course

The clinical course was focused on eradication of symptoms and the bacteriological course on the proportion of negative cultures at first and at follow-up visits. The natural course of lower UTI was described by the spontaneous eradication of both symptoms and bacteriuria.

Statistics

The software used for statistical calculation was SPSS 11.0 (SPSS Inc., Chicago, IL). Comparison of proportions was done using the χ² test. Analysis of variance with post hoc tests and Bonferroni correction was used when mean values were compared (21).

RESULTS

Of 1162 enrolled women, 19 were excluded (11 had missed cultures and 8 had a symptom score < 2 at consulting). Of the remaining 1143 included patients (Fig. 1), 288 patients (P0) were randomized to placebo therapy of whom 11 (4%) patients dropped out before the first follow-up visit (P1). Another 111 (39%) dropped out after the first follow-up visit (P2), mainly due to persisting symptoms, and received treatment with other antibiotics than pivmecillinam. The remaining 166 patients (P3) fulfilled the study. Another 425 patients fulfilled the inclusion criteria but refused participation in the study and served as controls (reject log, Fig. 1). The baseline characteristics of placebo treated patients did not significantly differ from the antibiotic treated patients. However, the control patients were older, had shorter symptom duration but did not differ in their symptomatology, bladder incubation time or bacteriuria (data not shown).

The bacterial counts at inclusion among the 1143 patients were: 20% had negative culture, 5% had 10^3 CFU/ml, 9% had 10^4 CFU/ml and 67% had ≥ 10^5 CFU/ml, Table I.

Mixed floras in 55 episodes were classified as negative culture, while 45 episodes with 1 dominating species were classified as uropathogens. The most frequent uropathogens in the cultures at inclusion were E. coli (62.1%), followed by ‘other CNS’ (4.9%), Klebsiella (2.7%), S. saprophyticus (2.6%) and enterococci (2.2%).

The percentage of symptoms at inclusion were: urgency, 96% [mean value of symptom score (m) = 2.0 (range 0–3)]; dysuria, 88% (m = 1.8); suprapubic pain, 60% (m = 0.9) and loin pain, 40% (m = 0.6), Fig. 2. The mean score for all symptoms (UDSL) was 5.3 (range 2–12). The symptoms urgency and dysuria each had positive association to bacteriuria and bacterial counts (21), with significant differences between negative culture and 10^4 CFU/ml and ≥ 10^5 CFU/ml (p < 0.05), while suprapubic pain and loin pain had negative associations (p < 0.05), Fig. 2. Thus, there were no associations between all symptoms and bacteriuria or bacterial counts. We found no significant differences in mean scores of symptoms or combinations of all symptoms between the species (Table I) or Gram groups of bacteria.

Among all the 1143 patients the symptom duration varied considerably (76% ≤ 7 d and 13% ≥ 15 d). The mean duration of symptoms was 10 d and the median duration was 4 d (SD 19.5 d).

The age distribution was: 22% up to 24 y, 50% aged 25 to 54 y and 28% 55 y and above. Compared to women 55 y and above, women up to 24 y had shorter symptom duration (78% ≤ 7 d vs 52% ≥ 15 d), lower frequency of E. coli (55%...
higher frequency of staphylococci (15% vs 3%, data not shown).

At inclusion 57% of all the patients had a bladder incubation time \( \geq 4 \) h and 75% of those had high bacterial counts \( (\geq 10^5 \text{ CFU/ml}) \). There were no differences in bladder incubation time between the age groups, but compared to women up to 24 y, women aged 55 y and above had fewer negative cultures (13% vs 22%) and higher frequency of high bacterial counts \( (\geq 10^5 \text{ CFU/ml}, 75\% \text{ vs } 64\%)\).

The natural course of UTI was described among the 288 placebo treated patients. At inclusion we found no differences in mean symptom scores between patients who dropped out or fulfilled the study plan, but the dropouts had higher bacterial counts. However, at the first follow-up visit these patients still had high symptom scores and therefore most of them received antibiotics and left the study \( (P = 4) \), and thus 58% attended the last follow-up visit \( (P_3, n = 166) \), Fig. 1.

We found that bacterial species as well as bacterial counts varied considerably during the time of study within the patients (data not shown). Among the 97 patients with \( \geq 10^5 \text{ CFU/ml} \) at inclusion, 47% had spontaneous eradication of bacteriuria with negative cultures \( (< 10^5 \text{ CFU/ml}) \), while 40% had unchanged counts at the end of study. Of the 42 patients with negative cultures at inclusion, 83% remained negative after 8–10 d, as did 69% at the end of study. However, among all the 166 patients fulfilling the study \( (P_3) \), 45% had negative cultures after 8–10 d and 57% at the end of study, Table II.

The symptoms registered in patient diaries during placebo therapy and at the follow-up visits are shown in Fig. 3. Patients free from symptoms slowly increased during the first week. At d 7, approximately 75% of patients were free from suprapubic and loin pain, 45% from urgency and dysuria, and 30% from all symptoms. Corresponding proportions at end of study were 90, 70 and 55%, respectively.

Patients infected with E. coli and staphylococci had similar and slow eradication rates of all symptoms during placebo therapy compared with patients with other Gram-negatives and other Gram-positives than staphylococci. The latter groups had eradication rates similar to those with negative cultures, Fig. 4.

28% of the patients were cured from all symptoms at the first follow-up visit compared with 54% at the second follow-up visit. Negative culture and no symptoms at those visits were found in 21% and 37% of the patients, respectively, Table II.

**DISCUSSION**

The present study is a comprehensive placebo controlled study describing the natural course of lower UTI in women. It is unlikely that a similar study will be performed, as international ethical recommendations of the World Medical Association in the year 2002 do not support placebo therapy (22). The included patients are representative for women consulting PHC for uncomplicated lower UTI as we found no significant differences in symptoms or bacteriuria between the included patients and the control group (reject log). Only a few placebo controlled studies have been published, with low numbers of patients, and mainly focused on evaluating the efficacy of treatment with various antibiotics in relation to placebo. Also, symptoms were only briefly reported, if at all (17–19). Thus, these studies were inadequate to describe the natural course of lower UTI.
In most studies _E. coli_ has been reported as the dominant species of UTI in PHC (23), which was confirmed in this study. _S. saprophyticus_ is usually the second most common species and classified as a primary pathogen according to the current Swedish (14) and European guidelines (15). However, in our study 'other CNS' than _S. saprophyticus_ was the second most common group of bacteria. Whether 'other CNS' have become more virulent or have been neglected in earlier studies, or have not been reported as uropathogens, is unknown. The spontaneous eradication rate in patients with staphylococcal induced UTI was similar to that for _E. coli_ during the first week of infection. Moreover, at inclusion no significant differences in mean symptom scores were found between different bacterial species. Our results indicate that 'other CNS' have similar symptoms and clinical and bacteriological course as _E. coli_. Thus, 'other CNS' may be underestimated as uropathogens, and the present classification in primary, secondary and doubtful uropathogens as stipulated in these current guidelines can be questioned. It is often presumed that there is a positive association between symptoms and bacteriuria with increasing symptom scores corresponding to higher bacterial counts (15, 24). This was confirmed for urgency and dysuria, but not for suprapubic pain and loin pain, or for all symptoms. Thus, the overall association between symptoms and bacteriuria was unpredictable. Therefore rapid and patient near-diagnostic tests are required to establish the presence of bacteriuria and to confirm the diagnosis of lower UTI.

### Table 1. Relation between bacteriuria and mean values of all symptoms score among all 1143 patients at inclusion

<table>
<thead>
<tr>
<th>Species</th>
<th>Symptom score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No.&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Symptom score&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No.&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Symptom score&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No.&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Symptom score&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No.&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>5.7</td>
<td>38</td>
<td>5.5</td>
<td>70</td>
<td>5.3</td>
<td>602</td>
<td>5.3</td>
<td>710</td>
<td>62.1</td>
</tr>
<tr>
<td>CNS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.9</td>
<td>7</td>
<td>5.2</td>
<td>6</td>
<td>5.8</td>
<td>43</td>
<td>5.7</td>
<td>56</td>
<td>4.9</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.0</td>
<td>2</td>
<td>4.0</td>
<td>1</td>
<td>4.8</td>
<td>28</td>
<td>4.7</td>
<td>31</td>
<td>2.7</td>
</tr>
<tr>
<td><em>S. saprophyticus</em></td>
<td>5.0</td>
<td>2</td>
<td>4.0</td>
<td>4</td>
<td>5.9</td>
<td>26</td>
<td>5.8</td>
<td>30</td>
<td>2.6</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.7</td>
<td>3</td>
<td>6.2</td>
<td>6</td>
<td>6.0</td>
<td>16</td>
<td>6.0</td>
<td>25</td>
<td>2.2</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>4.3</td>
<td>3</td>
<td>4.7</td>
<td>10</td>
<td>3.8</td>
<td>6</td>
<td>4.4</td>
<td>19</td>
<td>1.7</td>
</tr>
<tr>
<td><em>Citrobacter spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.6</td>
<td>14</td>
<td>5.6</td>
<td>14</td>
<td>5.6</td>
<td>14</td>
<td>5.6</td>
<td>14</td>
<td>1.2</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6.1</td>
<td>13</td>
<td>6.1</td>
<td>13</td>
<td>6.1</td>
<td>13</td>
<td>6.1</td>
<td>13</td>
<td>1.1</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>5.0</td>
<td>2</td>
<td>4.8</td>
<td>5</td>
<td>4.9</td>
<td>7</td>
<td>4.9</td>
<td>7</td>
<td>0.6</td>
</tr>
<tr>
<td><em>Proteus spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.0</td>
<td>2</td>
<td>6.0</td>
<td>4</td>
<td>5.7</td>
<td>6</td>
<td>5.7</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td><em>Alpha streptococci</em></td>
<td>5.3</td>
<td>3</td>
<td>5.3</td>
<td>3</td>
<td>5.3</td>
<td>3</td>
<td>5.3</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td><em>Pseudomonas spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6.0</td>
<td>2</td>
<td>6.0</td>
<td>2</td>
<td>6.0</td>
<td>2</td>
<td>6.0</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td>4.0</td>
<td>2</td>
<td>4.0</td>
<td>2</td>
<td>4.0</td>
<td>2</td>
<td>4.0</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Gram-positive rods</td>
<td>5.0</td>
<td>1</td>
<td>5.0</td>
<td>1</td>
<td>5.0</td>
<td>1</td>
<td>5.0</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>5.0</td>
<td>1</td>
<td>5.0</td>
<td>1</td>
<td>5.0</td>
<td>1</td>
<td>5.0</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Negative culture</td>
<td>5.1</td>
<td>223</td>
<td>5.5</td>
<td>53</td>
<td>5.4</td>
<td>102</td>
<td>5.4</td>
<td>765</td>
<td>5.3</td>
</tr>
<tr>
<td>Total</td>
<td>5.1</td>
<td>223</td>
<td>5.5</td>
<td>53</td>
<td>5.4</td>
<td>102</td>
<td>5.4</td>
<td>765</td>
<td>5.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Negative culture defined as < 10<sup>3</sup> CFU/ml or mixed culture without 1 dominating species; <sup>b</sup>mean symptom score; <sup>c</sup>number of isolates; <sup>d</sup>coagulase negative staphylococci other than _S. saprophyticus_; <sup>e</sup>species.

In most studies _E. coli_ has been reported as the dominating species of UTI in PHC (23), which was confirmed in this study. _S. saprophyticus_ is usually the second most common species and classified as a primary pathogen according to the current Swedish (14) and European guidelines (15). However, in our study ‘other CNS’ than _S. saprophyticus_ was the second most common group of bacteria. Whether ‘other CNS’ have become more virulent or have been neglected in earlier studies, or have not been reported as uropathogens, is unknown. The spontaneous eradication rate in patients with staphylococcal induced UTI was similar to that for _E. coli_ during the first week of infection. Moreover, at inclusion no significant differences in mean symptom scores were found between different bacterial species. Our results indicate that ‘other CNS’ have similar symptoms and clinical and bacteriological course as _E. coli_. Thus, ‘other CNS’ may be underestimated as uropathogens, and the present classification in primary, secondary and doubtful uropathogens as stipulated in these current guidelines can be questioned. It is often presumed that there is a positive association between symptoms and bacteriuria with increasing symptom scores corresponding to higher bacterial counts (15, 24). This was confirmed for urgency and dysuria, but not for suprapubic pain and loin pain, or for all symptoms. Thus, the overall association between symptoms and bacteriuria was unpredictable. Therefore rapid and patient near-diagnostic tests are required to establish the presence of bacteriuria and to confirm the diagnosis of lower UTI.

In a recent meta-analysis of 464 studies of acute uncomplicated UTI in women, only 9 reported on the symptomatology, of which 5 were classified as high quality studies (25). In this meta-analysis it was also found that frequency and dysuria had a positive association with bacteriuria, while suprapubic pain and flank pain had a negative association, and thus the authors concluded that suprapubic and flank pain were not useful for diagnosis of UTI.

In the present study most patients had the classical UTI symptoms urgency and dysuria. However, as many as 60% also had suprapubic pain, and 40% loin pain, without signs of pyelonephritis. Therefore, these 2 latter symptoms should not be neglected, but instead be actively asked for and, if found, the contemporary presence of bacteriuria should be...
confirmed by laboratory diagnostic tests. We suggest that antibiotics should be prescribed for symptomatic bacteriuria and not for symptoms only. This is in contrast to the increasing habit of prescribing antibiotics for symptoms only without urinalysis, even by telephone, as recommended in the current Norwegian guidelines (24). Such management probably causes an undesired over-consumption of antibiotics.

In the present study loin pain was more common compared to that found in a previous study from PHC in the same region (6), and another Swedish study (25), but similar to a Norwegian study (26). In these studies, as well as in those included in the meta-analysis (25), only presence or absence of symptoms was recorded. We consider that our use of graded symptom scores and patient diaries gives a more complete evaluation of the symptomatology, and probably is more sensitive to evaluate the predictive values of symptoms.

The spontaneous resolution of all symptoms in the placebo group was surprisingly low both during and after the first week (28%), and after 6 weeks (54%), although the symptom scores were reduced for most patients at both follow-up visits. Furthermore, only 13% of the patients were free from all symptoms and had negative cultures after 1 week, compared with 37% after 6 weeks. However, the cure rates at the end of study were likely to be too high, and not representative for all placebo treated patients due to the high dropout rate after the first follow-up visit. Therefore, the cure rates for all symptoms and the combination of all symptoms and bacteriuria was calculated at the last follow-up visit to 36% and 24%, respectively. The great individual variations between different bacterial counts and uropathogens between inclusion and at the follow-up visits need to be further analysed. If these variations are true, and not due to sampling procedures, this may explain the difficulties in the definition of UTI, as well as to establish the optimal point of time for evaluation of cure.

In conclusion, the natural course of uncomplicated lower UTI in women was studied by the presence and eradication of symptoms and bacteriuria and the combinations of them. The associations between symptoms and bacteriuria or bacterial counts were unpredictable, and thus rapid and patient near-laboratory tests are required for diagnosis of UTI. ‘Other CNS’ than S. saprophyticus was the second most common group of bacteria with a spontaneous eradication similar to that for E. coli, indicating that the present classification in primary, secondary and doubtful uropathogens as in the current guidelines seems not to be clinically relevant, and needs to be revised. The spontaneous resolution of all symptoms and bacteriuria was surprisingly low.

ACKNOWLEDGEMENTS

We express our gratitude to all women in the county of Västerbotten who participated and made this study possible. We also thank the GPs and staff at the following 18 PHC centres in the county of

<table>
<thead>
<tr>
<th>Visits</th>
<th>Placebo groups</th>
<th>Number of patients</th>
<th>Negative culture$^a$</th>
<th>No symptoms$^b$</th>
<th>Negative cultures and no symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^c$</td>
<td>P0</td>
<td>288</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>P1</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2$^d$</td>
<td>P2</td>
<td>277</td>
<td>31</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>P3</td>
<td>166</td>
<td>45</td>
<td>43</td>
<td>21</td>
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<tr>
<td></td>
<td>P4</td>
<td>111</td>
<td>9</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>3$^e$</td>
<td>P3</td>
<td>166</td>
<td>57</td>
<td>54</td>
<td>37</td>
</tr>
</tbody>
</table>

$^a$Negative culture defined as $<10^3$ CFU/ml or mixed culture without 1 dominating species; $^b$free from all symptoms; $^c$at inclusion; $^d$after 8–10 d; $^e$after 5–7 weeks.
REFERENCES