Urinary tract infections in general practice patients: diagnostic tests versus bacteriological culture

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Objectives: Urinary tract infections (UTIs) are common bacterial infections encountered in general practice. For the optimal treatment the general practitioner (GP) should rely on the results of diagnostic tests and recent antimicrobial susceptibility of uropathogens.

Patients and methods: In total 1993 female patients (11–70 years) with complaints of an acute uncomplicated UTI were included. The performance characteristics of the diagnostic tests used were determined and compared with the antibiotic prescription rate. The antibiotic therapy (agent and duration), the uropathogens and the antibiotic susceptibility of Escherichia coli were determined for each age group.

Results: The positive predictive value (PPV) (96%) and the specificity (94%) of the nitrite test were high for all samples. A negative nitrite with a positive leucocyte-esterase (LE) test showed a high PPV (79%) and sensitivity (82%). When both nitrite and LE tests were negative ~50% of the samples were culture positive. Of the patients, 94% of those with a positive nitrite test and 71% of those with a negative nitrite and positive LE test were prescribed antibiotics, mostly nitrofurantoin and trimethoprim. Nitrofurantoin prescriptions decreased and those of fluoroquinolones increased with increasing age. Nitrofurantoin was equally prescribed for 3–7 days in all patients. Trimethoprim was mostly prescribed for 3 days in patients aged 21–50 years and for 5 days in the other patients. E. coli, the uropathogen mostly isolated, decreased in frequency with increasing age. Proteus mirabilis was found more in the oldest patients and Staphylococcus saprophyticus in the younger patients. The antimicrobial susceptibility of E. coli was not age related. The lowest percentages were found for amoxicillin (67%) and trimethoprim (77%). Fluoroquinolone resistance was emerging in the older patients.

Conclusions: For female patients with symptoms of an acute uncomplicated UTI a positive nitrite test or a negative nitrite test with a positive LE test confirmed UTI whereas a negative nitrite together with a negative LE test did not rule out infection. For empirical treatment GPs should take into account the changing aetiology with increasing age. Prudent use of antibiotics in general and more specifically fluoroquinolones remains recommended. As trimethoprim resistance reached 20% it might be advisable to no longer use it as therapy of first choice for acute uncomplicated UTIs in The Netherlands.

Keywords: UTIs, nitrite and leucocyte-esterase test, antimicrobial resistance, E. coli

Introduction

An acute uncomplicated urinary tract infection (UTI) is one of the most common bacterial infections in women.1–3 It is estimated that as many as 60% of all women report having had a UTI at least once in their lifetime.4,5 The majority of UTIs are caused by Escherichia coli followed by Staphylococcus saprophyticus, mainly in younger women. Klebsiella, Proteus and Enterobacter species are isolated less frequently.6,7

For the diagnosis of a UTI the general practitioner (GP) can rely, besides the symptoms of the patient, on the results of the nitrite and leucocyte-esterase (LE) dipstick tests performed on urine samples. In the first revision of the ‘Urinary Tract Guidelines’ of the Dutch College of General Practitioners...
(NHG)\(^8\) a urine sample with a positive nitrite test is considered positive and a specimen with a negative nitrite together with a negative LE test is considered negative. Furthermore, urine specimens of symptomatic female patients should be considered as culture positive at \(\geq10^2\) cfu/mL and are called low count bacteriuria.\(^8\)

Several studies in The Netherlands on the antibiotic susceptibility patterns of uropathogens showed an increased resistance to widely used agents like trimethoprim and amoxicillin.\(^9\) However, most information concerning the isolated uropathogens and their antimicrobial susceptibility was derived from samples sent in by the GPs, after prior (once or twice) therapy failure had occurred.\(^10\) Therefore, these samples are likely to reflect a sample bias. Consequently an underestimation of the antibiotic susceptibility percentages of uropathogens from patients with an acute uncomplicated UTI is to be expected.\(^11\)–\(^13\)

Recent data on the antimicrobial susceptibility of uropathogens isolated from patients with an acute uncomplicated UTI visiting their GP, i.e. the ‘unselected’ uropathogens, are needed for the set-up of evidence-based guidelines such as those of the NHG.

Therefore a study on acute uncomplicated UTIs in non-pregnant female patients between 11 and 70 years of age attending 21 general practices from the Sentinel Station of The Netherlands Institute for Health Services Research (NIVEL) was performed. In these patients care as usual of the GP concerning diagnostic procedures (i.e. nitrite and LE tests) and the treatment prescribed (choice and duration of the antimicrobial agent) were compared with the bacteriological culture results and the antimicrobial susceptibility of all the unselected \(E.\ coli\) isolates, the most important uropathogen, was determined.

Materials and methods

Patients and urine sample processing

The patient population of the 21 general practices from the Sentinel Station of NIVEL participating in the study accounts for \(~1\%\) of the Dutch population and is representative of age, gender, regional distribution and degree of urbanization.

From January 2003 until December 2004 the GPs recorded the care as usual, i.e. the results of the diagnostic tests (nitrite and LE test) and the therapy prescribed (agent and duration), for non-pregnant female patients aged between 11 and 70 years with symptoms of an acute uncomplicated UTI. An acute uncomplicated UTI was defined as an infection with one or more of the following symptoms: dysuria, stranguria, urinary frequency or urgency without the presence of fever >38°C. Patients were included by the GP when they had complaints of an acute uncomplicated UTI as defined above and a fresh voided (midstream) urine specimen was delivered.

The urine sample was used for diagnostic purposes by the GP, i.e. nitrite dipstick and/or LE test. Subsequently a dipslide (Uriline, 56508, BioMérieux, Plainview, NY, USA) was prepared according to the manufacturer’s instructions and sent by mail to the laboratory of Medical Microbiology of the University Hospital Maastricht, The Netherlands for isolation and identification of the uropathogens and antibiotic susceptibility testing.

On the day of arrival, the dipslide was incubated overnight at 37°C (if necessary). Bacterial growth on the dipslides was recorded from no growth to \(10^7\) cfu/mL according to the manufacturer’s instructions and considered positive at \(\geq10^5\) cfu/mL. Identification was performed using standard biochemical tests.\(^14\) If there remained any doubt about the identification API 20E, API20 NE, API 20 Strep or API Staph tests (BioMérieux) were used depending on the Gram stain of the microorganism. The isolated uropathogens were stored at \(–70°C\) until further analysis.

Antimicrobial susceptibility testing

MICs for the \(E.\ coli\) isolates were determined according to NCCLS criteria\(^15\) using the microbroth dilution method with Mueller–Hinton II broth cation-adjusted (Becton, Dickinson and Company, Sparks, USA), an inoculum of \(5 \times 10^5\) cfu/mL and overnight incubation at 37°C. The MIC plates with freeze-dried antibiotics were provided by MCS Diagnostics BV (NLDMCS1, Swalmen, The Netherlands). The following antimicrobial agents (range in mg/L) were tested: amoxicillin (0.06–128), co-amoxiclav (0.06–128), trimethoprim (0.03–64), co-trimoxazole (0.03–64), norfloxacin (0.03–64), ciprofloxacin (0.008–16) and nitrofurantoin (0.5–512). The reference strains \(E.\ coli\) ATCC 35218 and ATCC 25922 were used as control strains. The breakpoints for susceptibility were in accordance with the NCCLS guidelines.\(^15\)

Statistical analysis

The performance of the diagnostic tests, i.e. the positive predictive value (PPV), the negative predictive value (NPV), the sensitivity and the specificity of all samples, was calculated for the nitrite test alone and for the LE test in the case of a negative nitrite test using culture \(\geq10^5\) cfu/mL as gold standard. Samples with a negative nitrite and an unknown LE test result or both test results unknown were excluded for this analysis. For the analysis of the therapy prescribed (agent and duration), the causative uropathogens and the susceptibility of the \(E.\ coli\) isolates, the patients were divided into three age categories: 11–20, 21–50 and 51–70 years.\(^16\) For the analysis of the prescribed therapy, norfloxacin, ciprofloxacin and ofloxacin therapy were combined as the fluoroquinolones group.

For the statistical analysis the program SPSS 11.0 for Windows was used. To detect significant differences between the age groups and the prescribed treatment, the bacteriological culture results and the antimicrobial susceptibility of the \(E.\ coli\) isolates the Mann–Whitney \(U\)-test was performed. A \(P\) value of \(<0.05\) was considered significant.

Results

In total, 1993 non-pregnant women with a mean age (±SD) of 43 ± 17 years were enrolled in the study, half of which belonged to the age group 21–50 years.

The nitrite test was performed by the GP in 1892 of the 1993 patients. The PPV of the nitrite test was 96% and the specificity 94%. The NPV and sensitivity were 30% and 44%, respectively. In the case of a negative nitrite test result, the PPV of the LE was 79% and the sensitivity 82%.

Furthermore, 94% of the patients with a nitrite-positive urine sample received antimicrobial therapy. The majority of patients (71%) with urine samples negative for the nitrite test and positive for the LE test did receive antimicrobial therapy. One-fifth of the patients with urine samples showing both negative nitrite and negative LE tests were prescribed antibiotics.

Of all the patients, 70% were prescribed antibiotic therapy. Nitrofurantoin followed by trimethoprim were the agents prescribed most frequently in all the patients (57–68% and 18–23%, respectively). The former agent was less prescribed in the oldest age category than in the youngest one. The
Proteus mirabilis of found in the oldest patients (Table 1). The frequency of isolation most frequently in all age groups, was proportionally less

P. mirabilis 69 66 65 66

E. faecalis 43 3 3

Pseudomonas spp. 2 2 2 2

14 4 4 14

K. pneumoniae

Acinetobacter spp. 2 4 4 4

Other Gram-negatives 7 7 9 8

S. saprophyticus b 7 4 0.5 3

E. faecalis 4 3 3 3

Other Gram-positives 6 6 7 6

Table 1. Percentages of uropathogens isolated for each age group

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>11–20</th>
<th>21–50</th>
<th>51–70</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>69</td>
<td>66</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Other Gram-negatives</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>S. saprophyticus b</td>
<td>7</td>
<td>4</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other Gram-positives</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

aSignificant difference between the youngest and oldest patient groups (Mann–Whitney U-test; P < 0.02).
bSignificantly lower percentage in the oldest patients compared with those of both the other groups (Mann–Whitney U-test; P = 0.000).

prescription rate of the fluoroquinolones (5–15%) increased with increasing age. The duration of the treatment regimen prescribed in this patient population ranged from 3 to 7 or more days. Nitrofurantoin therapy was prescribed with the same frequency in all age groups as a 3, 5 or 7 day regimen. The majority of the patients aged 21–50 years old (80%) were prescribed a 3 day course of trimethoprim; a 5 day course was given to the other patients. Fluoroquinolones were mostly prescribed for 7 days in all the patients.

Of all samples received, 8% (161/1993) showed no growth and 13% (249/1993) showed a mixed (contaminated) culture. For the analysis of the causative uropathogens for each age category, both groups were excluded. E. coli, the uropathogen isolated most frequently in all age groups, was proportionally less found in the oldest patients (Table 1). The frequency of isolation of Proteus mirabilis and S. saprophyticus was age dependent, i.e. the prevalence of P. mirabilis increased and that of S. saprophyticus deceased with increasing age. The highest frequency of isolation of S. saprophyticus was found for the youngest age group.

No significant differences in susceptibility percentages of the E. coli isolates were found between patients of the three age groups. The lowest susceptibility percentages were found for amoxicillin (67%) and trimethoprim (77%). Fluoroquinolone susceptibility was slightly lower in the patients over the age of 21 years.

Discussion

This study in non-pregnant female patients of 11–70 years of age among 21 general practices throughout The Netherlands was a nationwide study on acute uncomplicated UTIs dealing with the care as usual of the GP, i.e. nitrite and LE test and the antibiotic therapy prescribed, bacteriological culture and the antimicrobial susceptibility of unselected E. coli isolates.

The nitrite dipstick test was very accurate in predicting a UTI (PPV = 96%) and GPs prescribed in >90% of these patients antimicrobial therapy as recommended by the NHG. Furthermore, according to the NHG guidelines the LE test can be used to exclude a UTI in combination with a negative nitrite. The daily practice data of this study showed that the GP used the LE test often to confirm a UTI as 71% of the patients with a negative nitrite and positive LE test were treated with antibiotics. When both diagnostic tests showed a negative result ~20% of the patients were treated with antibiotics whereas in almost 50% of these samples a positive culture (≥10^3 cfu/mL) was found. This discrepancy between the prescription rate (20%) and the percentage of culture positive urine samples (50%) might be explained by the low cut-off value we used for positive culture. In the latest recommendation of the NHG, however, it is stated that for symptomatic women a ‘low count’ bacteriuria can be caused by 10^2–10^4 cfu/mL and these infections should be considered as UTIs. Furthermore, as bacteria need over 4 h to convert nitrate into nitrite at a level that is reliably detectable, the time span might have been too short before collection of these urine samples and false negative test results could be obtained. Also, the biochemical reaction detected by the nitrite test is associated with members of the Enterobacteriaceae family but not with other uropathogens like S. saprophyticus, Pseudomonas spp. or enterococci. Indeed, in the nitrite and LE negative samples of this study E. coli were significantly less frequently found, but Acinetobacter spp., other Gram-negatives and Gram-positives and Enterococcus faecalis were more often found (data not shown). In addition, by lowering the cut-off value for a positive urine sample to ≥10^3 cfu/mL more low count urine samples are considered culture positive in which insufficient bacteria might be present to reduce nitrate into adequate amounts of nitrite for detection by the dipstick test. False positive nitrite test results were seen in 4% of the patients and might be due to anaerobic or fastidious microorganisms unable to grow on the uricult dip-slide. False positive LE results when the nitrite test was negative were found in 186 (21%) urine samples and might be caused by the presence of leucocytes of the vaginal fluid in the urine or the specimen might contain eosinophils, which can act as a source of esterases.

The antibiotic treatment prescribed most frequently in our patient population was in accordance with the NHG guidelines. However, the oldest patients were prescribed nitrofurantoin less often and fluoroquinolones more frequently than both of the younger groups. GPs might have altered their prescribing habits as nitrofurantoin is known to cause side effects, such as nausea, vomiting, allergic and other reactions, especially in older women. Furthermore, older women more often have a history of UTI and thus will have received therapy more often in the past. Fluoroquinolone therapy was also prescribed for longer durations in these older women as compared with the other antibiotics probably to be sure of full eradication of the more resistant uropathogens.

The uropathogens isolated in this patient population were similar to those in other studies, however, (significant) changes were found with increasing age of the patients tested. In post-menopausal women, owing to the loss of oestrogen and consequently the depletion of vaginal colonization with lactobacilli, other Gram-negative bacteria besides E. coli can enter the urinary tract more easily and cause an infection. The percentage of S. saprophyticus in the study of Christiaens et al. among patients between 15 and 50 years old (9%) was similar to the percentage found in our patients of 11–20 years (7%) but higher than that in our patients of 21–50 years (4%).
This difference with our patients was probably caused by the differences in age groups.

The antimicrobial susceptibility data were analysed for E. coli isolates only as this was the most prevalent uropathogen isolated. The susceptibility percentages were similar for all agents tested with the exception of amoxicillin in the youngest age group. However, a tendency to an increasing fluoroquinolone resistance was found in the oldest patients. The susceptibility percentages of isolates from public health laboratories were lower compared with our data.\(^9,10\) As in both studies most urine specimens analysed were sent in by the GP after prior therapy failure or recurrent UTI, these ‘selected’ isolates were more often exposed to antibiotics and thus more resistant.

In conclusion, for symptomatic female patients between 11 and 70 years of age a urine sample with a positive nitrite test or with a negative nitrite test together with a positive LE test should be considered indicative of a UTI and the patient should be treated accordingly. However, when both nitrite and LE tests are negative, a UTI cannot be excluded and the samples should be further investigated by culture. Furthermore, the GP should take into account the age of the patient when prescribing antibiotic treatment as the aetiology of a UTI is influenced by it. Prudent use of fluoroquinolones is strongly recommended as resistance is already emerging in the oldest patients. In addition, for an optimal empirical therapy actual data on antimicrobial resistance percentages of unselected uropathogens are required and these data should be made available to the GPs for implementation in their daily practice. Finally, as trimethoprim susceptibility in E. coli isolated in this study decreased to \(~80%\) it might be advisable to limit its use as first agent in the treatment of an acute uncomplicated UTI in The Netherlands.

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Transparency declarations

None to declare.

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