Evaluation of the Nitrite and Leukocyte Esterase Activity Tests for the Diagnosis of Acute Symptomatic Urinary Tract Infection in Men

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For 422 male patients with symptoms indicative of a urinary tract infection, nitrite and leukocyte esterase activity dipstick test results were compared with results of culture of urine samples. The positive predictive value of a positive nitrite test result was 96%. Addition of results of the leukocyte esterase test did not improve the diagnostic accuracy of the nitrite test.

Despite the obvious genitourinary differences between the sexes, management of lower urinary tract infections (UTIs) in men is based largely on standards developed from studies of women. This has helped foster misconceptions that, among other problems, add needless complexity and expense to diagnosis and treatment of male patients [1]. General practitioners care for the majority of men with UTIs [2]. In men, a UTI is diagnosed by a colony count in voided urine of $\geq 10^5$ colony forming units (CFU)/mL, which has a sensitivity and specificity of 97% [3]. Because culture of urine is costly and it takes $\geq 24$ h before results are known, the use of simpler and faster diagnostic methods, such as the nitrite dipstick test and the leukocyte esterase activity (LE) dipstick test, would be preferable.

In the female population with symptoms indicative of UTI, Dutch guidelines postulate that a positive nitrite test result indicates a high probability for UTI, in which case empirical antibiotic treatment is started. In the instance of a negative nitrite test result, microscopic examination and urine culture is the next step for further analysis [4]. To our knowledge, the value of the dipstick tests has not been evaluated in men with symptoms indicative of UTI. In this study, the nitrite and LE tests were evaluated in a general practice setting among adult men presenting with symptoms indicative of UTI; urine culture was used as the reference standard.

Materials and methods. From January 2003 through December 2004, 21 general practices participating in The Netherlands Institute for Health Services Research sentinel project monitored personal, diagnostic, and therapeutic information for consecutive male patients aged $\geq 18$ years who had symptoms indicative of a UTI (i.e., acute signs of dysuria and urinary frequency and/or urgency, without the presence of a temperature $\geq 38^\circ$C), without systemic symptoms, foreign body, history of urological problems, urine catheter, or suspicion of sexually transmitted disease. The patient population of these practices included $\sim 1\%$ of the Dutch population and was representative of age, sex, regional distribution, and degree of urbanization.

Patients suspected of having a UTI provided a fresh voided (midstream) urine sample as part of usual care, which was used by the general practitioner or practice nurse to perform a dipstick test with nitrite and/or leukocyte esterase activity, according to the manufacturer’s instructions, within 2 h of voiding. Any change in color of the dipstick was considered a positive test result [5]. Subsequently, a dipslide test (Uriline) was performed according to the manufacturer’s instructions, and the results were sent by mail to the Laboratory of Medical Microbiology of the University Hospital Maastricht (Maastricht, The Netherlands). At the laboratory, the uropathogens were isolated and identified, as described elsewhere [6, 7]. Growth of $\geq 10^3$ CFU/mL was considered to be a positive result of a urine culture [3]. In the instance of culture of $>1$ microorganism, only the predominant microorganism was considered.

Sensitivities, specificities, and positive and negative predictive values of both the nitrite and LE tests were calculated, separately and in combination. The sensitivities and specificities of the nitrite and LE tests were compared using the McNemar test. To determine the combined diagnostic performance of both tests and to determine the additional diagnostic value of age, a logistic regression analysis was performed, and the different diagnostic strategies were compared with receiver operating characteristic curves and areas under the curve. SPSS for Windows, version 11.0.1 (SPSS), was used.

Results. In total, 422 men with symptoms indicative of UTI...
were enrolled in the study. The mean age was 57 years (range, 18–104 years); 35% were 18–50 years of age, 39% were 51–70 years of age, and 26% were >70 years of age. Two hundred thirty-six men (56%) had a positive urine culture result. Of these positive culture results, 23 yielded $10^4$–$10^5$ CFU/mL, 35 yielded $10^5$–$10^6$ CFU/mL, 52 yielded $10^6$–$10^7$ CFU/mL, and 95 yielded $\geq 10^7$ CFU/mL. In the majority of the samples (91%), 1 species was cultured. None of the samples were contaminated (i.e., contained >2 microbial species). Of the patients aged 18–50 years, 29% had positive urine culture results; of the patients aged 51–70 years, 38% had positive results; and of those aged >70 years, 33% had positive results. The most frequently isolated uropathogens were Escherichia coli (48%) and non–E. coli gram-negative bacteria (36%), resulting in 84% gram-negative bacteria.

The nitrite test was not performed for 11 patients, the LE test was not performed for 20 patients, and results of both tests were lacking for 14 patients. The age distribution was not significantly different between these patients and the evaluated patients. Of the 25 patients with an unknown nitrite test result, 8 (32%) had a positive urine culture result; of the 34 with an unknown LE test result, 22 (65%) had a positive urine culture result. Of the 377 patients with known nitrite and LE test results, 212 (56%) had a positive urine culture result.

For all patients for whom both the nitrite test and the LE test were performed, the sensitivity of the nitrite test was 47%, and the specificity was 98%; the sensitivity of the LE test was 78%, and the specificity was 59%. When these parameters were calculated for all patients who underwent either test, the values changed only marginally. Addition of the results of the LE test did not improve the sensitivity or specificity of the nitrite test (table 1).

When both test results were combined using a logistic regression analysis, the area under the curve of the combination of both tests was 0.80 (95% CI, 0.76–0.84). Furthermore, addition of age as a diagnostic variable to both tests resulted in a minimal increase of the area under the curve to 0.81 (95% CI, 0.77–0.86).

The positive predictive value of a positive nitrite test result was 96%. In the instance of a negative nitrite test result, the probability of disease was 41%; addition of a negative LE test result decreased this probability to 27%, and a positive result increased it to 55%.

Discussion. In adult men presenting with acute symptoms indicative of a UTI, the nitrite test had a sensitivity of 47% and a specificity of 98%. The positive predictive value of this test was high (96%), with a negative predictive value of 59%. The positive and negative predictive values of the LE test were less than those of the nitrite test, and addition of the results of the LE test to those of the nitrite test did not substantially improve the predictive values.

<table>
<thead>
<tr>
<th>Diagnostic test, result (no. of patients with result)</th>
<th>Culture result, no (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nitrite</strong></td>
<td></td>
</tr>
<tr>
<td>Positive (104)</td>
<td>100 (47)²</td>
</tr>
<tr>
<td>Negative (273)</td>
<td>112 (53) 161 (98)³</td>
</tr>
<tr>
<td><strong>LE</strong></td>
<td></td>
</tr>
<tr>
<td>Positive (232)</td>
<td>165 (78)³</td>
</tr>
<tr>
<td>Negative (145)</td>
<td>47 (22) 98 (59)³</td>
</tr>
<tr>
<td><strong>Nitrite, positive</strong></td>
<td></td>
</tr>
<tr>
<td>LE, positive (91)</td>
<td>88 (42) 3 (2)</td>
</tr>
<tr>
<td>LE, negative (13)</td>
<td>12 (6) 1 (1)</td>
</tr>
<tr>
<td><strong>Nitrite, negative</strong></td>
<td></td>
</tr>
<tr>
<td>LE, positive (141)</td>
<td>77 (36) 64 (39)</td>
</tr>
<tr>
<td>LE, negative (132)</td>
<td>35 (17) 97 (59)</td>
</tr>
</tbody>
</table>

a Growth of $\geq 10^7$ CFU/mL.

b Sensitivity.

c Specificity.

Our study was limited by the fact that, for 45 patients (12%), no nitrite and/or LE test results could be obtained. The missing nitrite and LE test data may be secondary to the fact that, according to the general practitioner guidelines in The Netherlands, the LE test should not be performed when results of the nitrite test are positive [4]. Another disadvantage of the nitrite test is that the causative microorganism and its antibiotic susceptibility are not known. However, in our study, the majority of the cultured bacteria were gram-negative bacteria, suggesting that empirical therapy can be started in men without symptoms of complicated UTI, pending culture results.

In a recent meta-analysis, the sensitivity of the nitrite test (45%–60%) was shown to be lower than that of the LE test (48%–86%) among most female populations, whereas the specificity of the nitrite test was higher (85%–98% vs. 17%–93%) [6, 8]. The positive predictive value of the nitrite test has been reported to be ∼96% [6]. The general practitioner guidelines recommend starting empirical antibiotic therapy in women with symptoms indicative of UTI when nitrite test results are positive [4]. However, in contrast to female UTIs, there are no studies evaluating empirical therapy for male UTIs. Therefore, we suggest that, after a positive nitrite test result, empirical therapy be started, pending results of the urine culture. Further studies are warranted to evaluate empirical therapy for male UTI.

The cutoff value of $\geq 10^7$ CFU/mL to diagnose a UTI is based on 1 study [3]. Although this cutoff value is recommended in the Dutch guidelines [9], a cutoff value of $\geq 10^5$ CFU/mL may be used by general practitioners or laboratory staff. If bacteriuria were defined as colony count $\geq 10^5$ CFU/mL, 23 of
UTIs would have been missed; a similar result was described by other researchers [3]. When we recalculated our data with a cutoff of $\geq 10^9$ CFU/mL, the nitrite and LE tests yielded sensitivities of 60% and 82%, respectively, and specificities of 95% and 53%, respectively.

In men, UTIs become increasingly frequent with age and functional disability [10, 11], but bacteriuria in elderly men tends to be intermittent, episodic, and more complex to diagnose [11]. We showed that the performance of the tests did not change with increasing age and that the tests are valuable for all men aged $\geq 18$ years who have an acute symptomatic UTI.

In conclusion, for symptomatic male patients aged $\geq 18$ years, a positive nitrite test result should be considered to be indicative of a UTI, and the patient should be treated empirically, pending culture results. However, when the nitrite test yields negative results, a UTI cannot be excluded, and urine samples should be further investigated by culture, without start of empirical therapy.

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References