Predictive value of the urinary dipstick test in the management of patients with urinary tract infection-associated symptoms in primary care in Indonesia: a cross-sectional study

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ABSTRACT

Objective To assess the test characteristics of a urine dipstick test in predicting a positive urine culture in an outpatient setting in Indonesia.

Design Cross-sectional study.

Setting Two outpatient clinics in Medan, Indonesia.

Participants 616 consecutively enrolled participants suspected of having a urinary tract infection.

Outcome measures The primary outcome is the estimates of accuracy (sensitivity, specificity, predictive values) where urine culture is the reference test. The secondary outcome is the post-test probability of a positive urine culture.

Results The optimal test characteristics were obtained when index test positivity was defined as any leucocyte esterase reaction and/or a nitrite reaction and reference test positivity was defined as a urine culture with a growth of at least $10^5$ colony-forming units/mL (sensitivity: 88.2% (95% CI 81.6 to 93.1), negative predictive value: 93.0% (95% CI 88.9 to 95.9)). The post-test probability of a positive urine culture after a negative urinary dipstick test was 7% in the obstetric/gynaecology clinic and 8% in the internal medicine clinic.

Conclusion The use of a urine dipstick test in a rule-out strategy can reduce the need for urine culture and avoid the prescription of (ineffective) antibiotics in a non-urology outpatient setting.

INTRODUCTION

Urinary tract infection (UTI) is the most common reason to prescribe antibiotic treatment in primary care, which is, in general, given empirically on the basis of clinical signs and symptoms.

Conclusion The strength of the study is its population-based setting representing a typical clinical conduct in Indonesian outpatient clinics, giving the results a clear impact for care provided.

Strengths and limitations of this study

- The main limitation of the study is its restriction to two purposely chosen health facilities.
- The number of positive reference tests (urine culture) is limited for some of the definitions for positivity used, resulting in rather wide CIs around the accuracy estimates.

A urine culture will provide support for the diagnosis of UTI, in addition to clinical symptoms and the presence of potential risk factors, identify the causative organism, and steer adequate antimicrobial treatment. In many low-income and middle-income countries (LMICs), the laboratory capacity to perform urine culture is limited, or urine culture is too expensive to be offered routinely in primary care. The use of a point-of-care test that predicts the result (positive or negative) of urine culture in patients with UTI-associated symptoms would greatly enhance the efficiency of clinical diagnostics and care, and of use of resources. The urine dipstick test, which detects the presence of leucocytes and/or nitrite in urine specimens within minutes, is such a test. Urine dipstick

selection of resistance. Coupled with the fact that the clinical manifestation of a UTI mimics that of other syndromes, empirical treatment for UTI leads, in a setting of high prevalence of AMR, to an overprescribing of inadequate therapy, resulting in additional morbidity for the patients and costs for the healthcare system.

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tests are, however, not routinely used in the primary care setting in many LMICs.

The prevalence of AMR in uropathogens is alarmingly high in Indonesia, both in inpatients and outpatients. A population-based AMR survey in Medan and Bandung showed that empirical oral therapy for UTIs in outpatients is only possible when having access to nitrofurantoin or fosfomycin. The prevalence of resistance against fluoroquinolones, the drugs of first choice according to Indonesian treatment guidelines, was above 40% in *Escherichia coli* (72% in urology clinics) and above 25% in *Klebsiella pneumoniae* (84% in urology clinics). The same survey showed that the empirical treatment with a fluoroquinolone was appropriate in just one-third of the outpatients receiving these drugs. Urine culture and antimicrobial susceptibility testing could have prevented the prescription of inappropriate therapy.

We aimed to assess the performance of the dipstick test to assist clinicians in deciding whether to send a urine sample for culture or not. The primary objective is to estimate the test characteristics of the urine dipstick test in relation to the results of a urine culture in patients suspected of having a UTI, from two primary care outpatient clinics in Medan, Indonesia.

METHODS

Design and setting

The study was a cross-sectional survey in which data collection was planned before the performance of the index test (dipstick test) and the reference test (urine culture). The study was embedded in a larger study on estimating the prevalence of AMR in UTIs using a lot quality assurance sampling approach. The survey took place in two purposively selected outpatient clinics in the primary care setting in Medan, Indonesia: one for obstetrics/gynaecology and one for internal medicine.

Population and procedures

Adult patients (age ≥18 years) with a clinical suspicion of UTI were eligible to be enrolled in the study. UTI was defined according to the guidelines of the Centers for Disease Control and Prevention. Participants were included consecutively during the entire time frame in which participants were enrolled in the facility for the main study. Each participant provided, after written informed consent, a clean-catch mid-stream urine specimen for dipstick test and culture. Urine specimens were immediately stored at 2°C–8°C until initial processing in the laboratory of Adam Malik General Hospital (a tertiary care facility), which occurred within 8 hours of urine collection.

Sample size

The sample size was based on the duration of the primary study in the selected health facilities. This duration depended on the collection of 44 positive urine cultures with *E. coli* and/or *K. pneumoniae*, needed for classifying the facility as having a high or low prevalence of AMR (F Ginting et al., submitted, 2018).

Test methods

The index test consisted of the Combur 10 urinary dipstick test (Roche Diagnostic, Germany) and was performed according to the manufacturer’s instructions, directly after receiving the participant’s urine in the outpatient facility. We used multiple definitions of a positive index test, based on combinations of the leucocyte esterase test result and the nitrite test result.

The urine was stored in a cool box on receipt until transport to the central laboratory (within 4 hours of collection), where it was stored in a refrigerator (2°C – 8°C). The reference test was performed within 24 hours after the initial receipt of the urine.

The reference test was a standard urine culture in which urine was inoculated onto a MacConkey agar plate (Oxoid, Thermo Scientific, UK) using calibrated loops (10 μL) and incubated at 37°C for 18 hours. We used three different definitions for a positive reference test, being growth of at least $10^5$ colony-forming units per millilitre (cfu/mL), at least $10^4$cfu/mL or $10^3$cfu/mL. The latter two definitions use thresholds to define culture positivity that are commonly used in clinical practice. The concentration of $10^3$ cfu was used to account for the potentially limited growth in a setting with large-scale over-the-counter sales of antibiotics, and therefore with a high probability of prior antibiotic treatment, interfering with bacterial growth.

Laboratory technicians reading the culture plates were not aware of the dipstick test results, while the study nurses performing the urine dipstick test were not aware of any clinical information other than the participant being suspected of having a UTI, through the screening procedure.

Data analysis

All analyses were a priori specified in a data analysis plan. For each combination of index and reference test, we calculated the dipstick test characteristics (sensitivity, specificity, positive predictive value, negative predictive value) for a positive urine culture, with associated 95% CIs. For the index test definition with the optimal test characteristics (based on the Youden Index), we calculated the probability of a positive culture (post-test probability), given the prevalence of positive cultures in the population (pretest probability), stratified by index test results (positive or negative). This approach is preferred over the commonly used receiver operating characteristic curve with its associated area under the curve (AUC). The AUC provides a single estimate of test accuracy. It does not provide direct insight into the probability of a positive urine culture by dipstick result. Our approach of calculating post-test probabilities for different pretest probabilities does exactly that, and thereby aids the care provider directly in his/her clinical assessment of the patient, the need for additional diagnostic tests, and the decision to start empirical therapy.
Neither the index nor the reference test could have an indeterminate result. Participants without a result on either of the index and/or the reference test were excluded from the analyses. Data were analysed using STATA V.14.

Patient and public involvement
The study is directly relevant to patients’ experiences, given the fact that they, in general, bear the cost of urine culture. There was no patient or public involvement in the design, conduct and analysis of the study, nor in the recruitment of participants. There are no planned dissemination activities towards patients or the general public.

Table 1  Baseline characteristics

| Site                        | Obstetrics/gynaecology | Internal medicine | Total       |
|-----------------------------|------------------------|-------------------|-------------|
|                             | n=313      | %  | n=303      | %  | n=616      | %  |
| Female                      | 313        | 100| 159        | 52.5| 470        | 76.3|
| Missing                     | –          | –  | 2          | 0.7 | 3          | 0.5 |
| Age, years (median (IQR))   | 30         | 28–36| 54        | 48–62| 42        | 30–54|
| Dysuria                     | 78         | 24.9| 161        | 53.1| 239        | 38.8|
| Missing                     | 1          | 0.3| 5          | 1.7 | 6          | 1.0 |
| Polyuria                    | 231        | 73.8| 146        | 48.2| 377        | 61.2|
| Missing                     | 1          | 0.3| 5          | 1.7 | 6          | 1.0 |
| Urgency                     | 38         | 12.1| 30        | 9.9 | 68         | 11.0|
| Missing                     | 1          | 0.3| 5          | 1.7 | 6          | 1.0 |
| Lower abdominal pain        | 246        | 78.6| 161        | 53.1| 407        | 66.1|
| Missing                     | 1          | 0.3| 2          | 0.7 | 3          | 0.5 |
| Haematuria                  | 2          | 0.6| 3          | 1.0 | 5          | 0.8 |
| Missing                     | 1          | 0.3| 2          | 0.7 | 3          | 0.5 |

Figure 1  Participants included and tests performed.

RESULTS
The study included 616 patients, of whom 3 were excluded from further analysis due to missing dipstick test results (n=1) and missing culture results (n=2) (figure 1). Patients’ characteristics are reported in table 1. None of the participants reported an adverse event during the study. The cross-tabulations of the results of the index and reference test are reported in table 2, together with the accuracy estimates and their 95% CIs.

Sensitivity decreases rapidly when the definition of a dipstick positive test required an increasingly strong test reaction for leucocyte esterase, regardless of the definition of culture positivity. A positive dipstick test definition requiring both a leucocyte esterase reaction and a nitrite reaction results in low sensitivities, but high specificities, leading to high negative predictive values when using culture positive definitions with the threshold of growth of at least $10^4$ cfu/mL or $10^5$ cfu/mL. The dipstick test positivity definition of at least 1+ leucocyte esterase reaction and/or a positive nitrite reaction provides the highest sensitivity and the highest negative predictive value, regardless of the culture positivity definition. This definition for a positive index test provided the highest Youden Index (131.7) when the definition of culture positivity was set at $10^3$ cfu/mL or more.

The post-test probabilities of a positive urine culture given the pretest probability (prevalence) and dipstick
### Table 2: Test characteristics by dipstick test and culture definitions

| Dipstick | Sensitivity | Specificity | PPV | NPV |
|----------|-------------|-------------|-----|-----|
|          | n=613       |             |     |     |
|          | Lens        | Ref         | lb  | ub  | lb  | ub  | lb  | ub  | lb  | ub  | Est 95% CI |
|          | Pos Neg Pos | Growth ≥10^3 cfu/mL |     |     |     |     |     |     |     |     |                   |
| L        | ≥1+ any     | 119 17 136 | 87.5 80.7 92.6 | 44.4 39.9 49.0 | 31.0 26.4 35.9 | 92.6 88.4 95.6 | 130.94 |
|          | ≥2+ any     | 62 74      | 54.4 45.7 63.0 | 72.8 68.5 76.7 | 36.3 29.6 43.3 | 84.8 81.0 88.2 | 126.16 |
|          | 3+ any      | 17 119     | 12.5 7.5 19.3 | 94.3 91.8 96.2 | 38.6 24.4 54.5 | 79.1 75.5 82.4 | 105.84 |
| Any pos  | 25 111     | 18.4 12.3 25.9 | 91.0 88.1 93.4 | 36.8 25.4 49.3 | 79.6 76.0 82.9 | 108.37 |
| ≥1+ or pos | 120 16     | 88.2 81.6 93.1 | 44.4 39.9 49.0 | 31.2 26.6 36.1 | 93.0 88.9 95.9 | 131.68 |
| ≥2+ or pos | 84 52     | 61.8 53.1 70.0 | 67.3 62.9 71.5 | 35.0 29.0 41.4 | 86.1 82.1 89.4 | 128.06 |
| 3+ or pos | 34 102     | 25.0 18.0 33.1 | 86.6 83.2 89.5 | 34.7 25.4 45.0 | 80.2 76.5 83.6 | 110.58 |
| ≥1+ and pos | 24 112     | 17.7 11.7 25.1 | 91.0 88.1 93.4 | 35.8 24.5 48.5 | 79.5 75.9 82.8 | 107.64 |
| ≥2+ and pos | 15 121     | 11.0 6.3 17.5 | 96.4 94.4 97.9 | 46.9 29.1 65.3 | 79.1 75.6 82.4 | 106.47 |
| 3+ and pos | 8 128      | 5.9 2.6 11.3 | 98.7 97.3 99.5 | 57.1 28.9 82.3 | 78.6 75.1 81.9 | 103.62 |

| Dipstick | Index Ref | Growth ≥10^6 cfu/mL |
|----------|-----------|---------------------|
| 1+ any   | 40 10 50  | 80.0 66.3 90.0 38.9 34.9 43.1 |
| 2+ any   | 27 23     | 54.0 39.3 68.2 68.6 64.6 72.4 |
| 3+ any   | 7 43      | 14.0 5.8 26.7 93.4 91.1 95.3 |
| Any pos  | 14 36     | 28.0 16.2 42.5 90.4 87.7 92.7 |
| ≥1+ or pos | 41 9     | 82.0 68.6 91.4 38.9 34.9 43.1 |
| ≥2+ or pos | 32 18    | 64.0 49.2 77.1 63.1 58.9 67.1 |
| 3+ or pos | 16 34     | 32.0 19.5 46.7 85.4 82.2 88.3 |
| ≥1+ and pos | 13 37    | 26.0 14.6 40.3 90.4 87.7 92.7 |
| ≥2+ and pos | 9 41     | 18.0 8.6 31.4 95.9 93.9 97.4 |
| 3+ and pos | 5 45     | 10.0 3.3 21.8 98.4 97.0 99.3 |

Continued
**Table 2 Continued**

| Dipstick | Index | Ref | Growth=10^5 cfu/mL |
|----------|-------|-----|-------------------|
|          | Pos   | Neg | Pos               |
| ≥1+      | any   | 32  | 6 38 84.2 68.8 94.0 |
|          | any   | 27  | 5 36.8 31.8 45.0 |
| ≥2+      | any   | 33  | 5 86.8 71.9 95.6 |
|          | any   | 29  | 4 36.8 45.2 54.9 |
| Any      | pos   | 12  | 26 31.6 34.3 34.3 |
|          | pos   | 27  | 11 71.1 54.6 48.6 |
| ≥1+ or   | pos   | 33  | 5 86.8 71.9 95.6 |
|          | pos   | 27  | 11 71.1 54.6 48.6 |
| ≥2+ or   | pos   | 33  | 5 86.8 71.9 95.6 |
|          | pos   | 27  | 11 71.1 54.6 48.6 |
| Any      | pos   | 12  | 26 31.6 34.3 34.3 |
|          | pos   | 27  | 11 71.1 54.6 48.6 |
| ≥1+ and  | pos   | 11  | 27 29.0 15.4 21.8 |
|          | pos   | 29  | 15.2 45.9 31.8 |
| ≥2+ and  | pos   | 7   | 31 18.4 7.7 34.3 |
|          | pos   | 3 7 18.4 7.7 34.3 |
| 3+ and   | pos   | 4   | 34 10.5 2.9 24.8 |
|          | pos   | 4   | 34 10.5 2.9 24.8 |

Any, any test result (0–3+ (leucocyte esterase); negative or positive (nitrite); cfu, colony-forming units; est, estimate; L, leucocyte esterase; lb, lower bound; N, nitrite; neg, negative; NPV, negative predictive value; pos, positive; PPV, positive predictive value; ref, reference test; ub, upper bound.

**Figure 2** Post-test probabilities for levels of pretest probabilities for the definitions of positive dipstick and positive culture. The definitions of positive dipstick and positive culture used in Figure 2. The 45° line indicates a similar pretest and posttest probability. All other lines below this 45° line indicate an increased posttest probability above the 45° line indicate a decreased posttest probability. The prevalence of a positive urine culture in the outpatient clinic for internal medicine was 21%. This gives a probability of 30% and 7% when the dipstick test is positive and negative, respectively. These probabilities are 50% and 8% in the outpatient clinic for obstetrics/gynaecology, with a prevalence of positive urine cultures of 24%.

**DISCUSSION**

The study shows that the urine dipstick test is an adequate tool to assess the probability of a positive urine culture in outpatients with UTI-associated symptoms. Given the test characteristics, the dipstick test should be used as a rule-out strategy, rather than a rule-in strategy, in this setting. A negative dipstick test (no reaction for leucocyte esterase nor nitrite) is indicative of a low probability of a positive urine culture.

The prevalence of a positive urine culture in the outpatient clinic for internal medicine was 21%. The prevalence of urine culture positivity is defined as at least 10^5 cfu/mL. The prevalence of a positive urine culture in patients with UTI-associated symptoms is 2%. The prevalence of positivity defined as at least 10^5 cfu/mL is negative remains below 5%. This is most striking when the prevalence of a positive culture when the dipstick test is negative. These probabilities are 50% and 8%, respectively, in the outpatient clinic for obstetrics/gynaecology, with a prevalence of positive urine cultures of 24%.
urine culture, making the diagnosis of UTI unlikely and empirical antimicrobial therapy unwarranted. Implementing this strategy in non-urology outpatient facilities in Indonesia could lead to a considerable reduction in the prescription of antibiotics, thereby contributing to combating AMR.

Using a rule-out strategy leads to a number of missed UTI diagnoses, the consequences of which should be judged by the treating physician. Uncomplicated UTI is self-limiting in large patient groups, making an initial missed diagnosis likely to be a minor event. But in pregnant women, a missed UTI diagnosis could lead to serious complications for both the mother and the unborn child.6-10 The test characteristics in our study were nearly similar in the obstetrics/gynaecology and internal medicine clinic, where the rule-out strategy would miss 8% and 5% positive cultures, respectively.

There is wide variety in the reported role and usefulness of the urine dipstick tests in the diagnosis of UTI. Our results are in line with a meta-analysis including 14 studies that support the use of the dipstick test in a rule-out strategy. The pooled pretest probability was 20% in this meta-analysis, with a post-test probability of 52% for a positive dipstick test and 5% for a negative dipstick test.11 However, the setting of the different studies varied considerably and included general practice, antenatal care, emergency department and hospitalised patients. In the five studies conducted in the antenatal care setting, none reported a post-test probability of over 5% with a negative dipstick test results (leucocyte esterase and/or nitrite reaction).11 A similar conclusion was drawn by another meta-analysis reporting population-specific estimates, with a post-test probability of a negative test of 5% in the antenatal care setting, although of 12% in the setting of general practitioners.12 Both reports indicate that care setting and patient population are the main sources for the heterogeneity of the findings. The results are contradictory to an older meta-analysis, concluding that in many clinical settings the post-test probability of a positive culture with a negative dipstick test was too high to dismiss the diagnosis of a UTI.13

The common use of the urine dipstick is by interpreting a positive result as a tool to support the diagnosis of UTI (rule-in strategy) and as an indication to start antibiotic treatment. Physicians need to have clear guidance on the interpretation of test results in their own clinical setting to make them feel comfortable to use the less frequent rule-out strategy. The rule-out strategy is used in a variety of other clinical settings, including the use of faecal calprotectin in the screening for organic bowel disease in the primary care setting,14 and the use of D-dimer in the diagnosis of deep venous thrombosis in the emergency department.15

Interventions to reduce antibiotic prescription, including the use of point-of-care tests, have been proven effective in hospital patients in a recently updated Cochrane review.16 Such strategies should also work in the outpatient setting when implemented correctly. However, clinical practice might be hard to change as described by a study from the Thai–Myanmar border, in which antibiotic prescriptions were compared with the results of a urine dipstick test and urine microscopy. Despite proper guidance on using the dipstick test result in a rule-out strategy for UTI, over 50% of participants with UTI-associated symptoms but with a negative dipstick result were prescribed antibiotics.17

Strengths and weaknesses

The strength of the study is its population-based setting. The two selected health facilities represent typical clinical conduct in Indonesian outpatient clinics. As such, the results have external validity. The main limitation of the study is its restriction to just two purposively chosen health facilities. Generalisation to other settings might be difficult, especially to the urology outpatient setting, where UTI-associated symptoms might be a result of a very different underlying disease pattern. Although a prospective study, the implementation was dictated by the duration of the initial study in the selected health facilities. Despite a considerable number of participants, the number of positive reference tests (urine culture) is limited, especially with a definition for positivity that requires a larger concentration of cfu. This resulted in rather wide CIs around the accuracy estimates.

Most Gram-positive micro-organisms will not cause a nitrite reaction in the dipstick test, although the leucocyte esterase reaction can still be positive. A history of UTI caused by a Gram-positive organism would necessitate a culture in further clinical management, regardless of any dipstick test result. The same holds true for pregnant women with asymptomatic bacteriuria, who need a culture for adequate identification of recommended antimicrobial treatment. This latter group was not part of our study, which was restricted to patients with UTI-associated symptoms.

CONCLUSION

In a setting with a high prevalence of AMR in uropathogens, when there are limited opportunities left for empirical antibiotic treatment, the use of a urine dipstick test in a rule-out strategy can reduce the need for urine culture and avoid the prescription of (ineffective) antibiotics.

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