

Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study

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Executive summary

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Executive summary

Objectives

- To estimate independent clinical and dipstick predictors of infection and develop clinical scores.
- To test the clinical scores in an independent sample.
- To understand the natural history of urinary tract infection (UTI) and its key determinants.
- To perform a randomised controlled trial comparing management using the clinical and dipstick score with commonly used alternative management strategies.
- To estimate the resource use associated with each management strategy and estimate cost-effectiveness.
- To understand women's understanding of and concerns about the presentation and management of UTI, and particularly their responses to being asked to delay antibiotics.

Design

Six studies were carried out:

- a validation development study for diagnostic clinical score and diagnostic dipstick score (training study)
- a validation study for scores developed in study 1 (testing study)
- an observational study of the natural history of UTI
- a randomised controlled trial of scores developed in study 1
- an economic analysis of the randomised controlled trial
- a qualitative study of patients in the randomised controlled trial.

Setting

The setting was primary care.

Subjects

In total, 427 women aged 17–70 with suspected UTI participated in study 1; 434 participated

in study 2; 843 participated in study 3; 309 participated in the randomised controlled trial; and 21 participated in the qualitative study.

Methods

Validation studies

Independent clinical and dipstick predictors were estimated for diagnosis based on the European urinalysis guidelines standards for bacteriuria.

Observational study

Independent predictors of symptom severity and duration were estimated.

Randomised controlled trial

Patients were randomised to five basic management approaches:

- empirical antibiotics
- empirical delayed antibiotics (by 48 hours)
- target antibiotics based on a higher symptom score (two or more of urine cloudiness, smell, nocturia, dysuria)
- target antibiotics based on dipstick results (nitrite or both leucocytes and blood)
- target antibiotics based on receipt of a positive mid-stream specimen of urine (MSU) result.

Advice on self-care was also controlled by randomisation.

Qualitative study

A total of 21 participants from the trial participated in a recorded semistructured interview, which was analysed using the constant comparative method.

Economic study

NHS resource use was estimated using data in GP notes, and effectiveness was estimated by the number of days for which symptoms were rated as moderately bad by patients.

Results

The validation development study

In total, 62.5% of women had confirmed UTI (i.e. symptoms suggestive of UTI and bacteriuria). Only nitrite, leucocyte esterase (+ or greater) and blood (haemolysed trace or greater) independently predicted diagnosis (multivariate odds ratios 6.36, 4.52 and 2.23 respectively). A dipstick rule – based on having nitrite or both leucocytes and blood – was moderately sensitive (77%) and specific (70%) [positive predictive value (PPV) 81%, negative predictive value (NPV) 65%]. Predictive values were improved by varying the cut-point: the NPV was 73% for all three dipstick results being negative, and the PPV was 92% for having nitrite and either blood or leucocyte esterase. A clinical rule – based on having two of urine cloudiness, offensive smell, reported moderately severe dysuria and moderately severe nocturia – was less sensitive (65%) (specificity 69%, PPV 77%, NPV 54%). The NPV was 71% for none of the four clinical features and the PPV was 84% for three or more features.

The validation testing study

In total, 66% of women had confirmed UTI. The predictive values of nitrite, leucocyte esterase (+ or greater) and blood (haemolysed trace or greater) were confirmed (independent multivariate odds ratios of 5.56, 3.49 and 2.12 respectively). The dipstick rule – based on the presence of nitrite or both leucocytes and blood – was moderately sensitive (75%) but less specific (66%) (PPV 81%, NPV 57%). Predictive values were improved by varying the cut-point: the NPV was 76% for all three dipstick results being negative, and the PPV was 92% for having nitrite and either blood or leucocyte esterase.

Urine offensive smell was not found to be predictive in this sample; for a clinical score using the remaining three predictive clinical features (urine cloudiness, dysuria and nocturia) the NPV was 67% for none of the features and the PPV was 82% for three features.

The observational study of the natural history of urinary tract infection

Women in this study were nested in studies 1 and 2. A total of 684 women provided symptom information and 511 had both laboratory results and complete diaries. Symptoms rated by the

patient as a moderately bad problem or worse lasted an average of 3.25 days for infections sensitive to antibiotics. After adjusting for other predictors, when compared with sensitive infections, resistant infections lasted 56% longer [95% confidence interval (CI) 22–99%, $p < 0.001$], those with no antibiotic treatment 62% longer (95% CI 13–131%, $p = 0.008$) and those associated with urethral syndrome 33% longer (95% CI 14–56%, $p < 0.001$). Symptom duration was shorter if the doctor was perceived to be positive about diagnosis and prognosis and longer with frequent somatic symptoms, a previous history of cystitis, urinary frequency and more severe symptoms at baseline. Infections with no antibiotic treatment and also antibiotic-resistant infections were also associated with more severe frequency and dysuria symptoms after presentation.

The randomised trial

In total, 66% of the MSU group had laboratory-confirmed UTI – i.e. similar to the validation and observational studies. There were differences in antibiotic use between antibiotic management groups (immediate antibiotics 97%, MSU 81%, dipstick 80%, symptom score 90%, delayed antibiotics 77%, likelihood ratio test $p = 0.011$) and also in the use of MSUs at the initial consultation (23%, 89%, 36%, 33% and 15% respectively, $p < 0.001$), but little difference in symptomatic outcomes. Women suffered 3.5 days of moderately bad symptoms if they took antibiotics immediately. Those commencing antibiotics after 48 hours subsequently reconsulted less (hazard ratio 0.57, 95% CI 0.36–0.89) but also suffered a 37% longer duration of symptoms (95% CI 11–68%, $p = 0.003$), mainly in the MSU group (70% longer duration; other groups $\leq 21\%$ longer duration). Advice to use bicarbonate or cranberry juice had no effect on any outcome.

The economic analysis

The MSU group was more costly over a period of 1 month but not over a period of 1 year. There were modest non-significant differences in the estimates of effectiveness. To allow for the uncertainty of estimates we estimated cost-effectiveness acceptability curves for the strategies, which suggest that if a day of moderately bad symptoms is given a low value, i.e. less than approximately £10, then immediate antibiotics is likely to be the most cost-effective strategy. For values over £10 the dipstick strategy becomes the most likely to be cost-

effective. Because of the uncertainty we can never be more than 70% certain that the dipstick strategy is the most cost-effective.

The qualitative study

Several important features associated with women's health-seeking behaviour and their experiences of consulting for a UTI were identified, as well as their general attitudes towards and understanding of UTI, its aetiology and treatment. A fear of spread to the kidneys and the appearance of blood in the urine were two organic symptoms that particularly triggered worry and, in turn, seeking help. The generalised impact of symptoms on vocational and leisure activities was considerable and women expressed these as important triggers for seeking help. When patients are asked to delay taking antibiotic medication, i.e. they are essentially asked to 'wait some more', the sometimes protracted, uncomfortable and worrying journey that people have taken from 'person to patient' needs to be acknowledged. Some patients who had negative experiences of delay indicated that they had not felt validated in their expressions of bodily change and were threatened by such delay because, it seemed, the rationale for not taking the antibiotics was unclear.

Conclusions

- A clinical score is of limited value in increasing diagnostic precision, and dipstick results modestly improve diagnostic precision, but both of these diagnostic strategies have poor NPVs; they should not be used to rule out infection.
- Being positive about the diagnosis and natural history for patients with suspected UTI may help symptom resolution, and doctors can provide useful information on the natural history for patients (patients with a past history and those with high somatisation and severe baseline symptoms will have more severe symptoms lasting longer than 3 days).
- Immediate antibiotics targeted using dipsticks with a delayed prescription as backup or an empirical delayed prescription both achieve

similar symptom control to immediate antibiotics and reduce antibiotic use.

- Dipsticks are likely to be cost-effective if the value of saving a day of moderately bad symptoms is valued at £10 or more, but caution is required given the considerable uncertainty surrounding the estimates.
- If women are asked to delay taking antibiotics, great care is needed in both acknowledging the triggers to consult and particular worries and explaining the rationale for not using antibiotics immediately.

Implications for practice

Although all of the strategies trialled are acceptable, to both achieve good symptom control and reduce antibiotic use clinicians should probably either offer a 48-hour delayed antibiotic prescription to be used at the patient's discretion or target antibiotic treatment by dipsticks (positive nitrite or positive leucocytes and blood) with the offer of a delayed prescription if dipstick results are negative.

Suggestions for research

- Trials are needed of alternative diagnostic approaches (e.g. microscopy, dipsticks combined with dipslides).
- Further research is needed to estimate quality of life and model cost-effectiveness of the different strategies.
- More research is needed into the use of alternatives/complements to antibiotics (e.g. herbal medicines).

Publication

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The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Second, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA Programme as project number 97/14/06. The contractual start date was in September 2001. The draft report began editorial review in July 2007 and was accepted for publication in October 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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