Point-of-care tests for urinary tract infections to reduce antimicrobial resistance: a systematic review and conceptual economic model

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Scientific summary

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Scientific summary

Background

Urinary tract infections (UTIs) are one of the most common causes of infection worldwide. The accurate and timely diagnosis of UTIs is crucial to ensure that appropriate treatment is started to help resolve symptoms, improve quality of life and reduce the risk of complications such as pyelonephritis, kidney failure and sepsis. In the ongoing public health challenge of antibiotic resistance, it is important that antibiotics are prescribed only when necessary and that they target the causative organism of the infection.

However, UTIs can be difficult to diagnose. Currently they are diagnosed by a general practitioner (GP) based on symptoms and laboratory-based urine culture. Dipstick tests can be used to help make a quicker diagnosis in some people, for example children or women aged < 65 years. Dipstick tests involve dipping a specially treated paper or plastic strip into a urine sample to identify the presence of leukocyte esterase, nitrites and blood. However, these tests are not very accurate at diagnosing UTI, and they do not provide any information on the pathogenic cause or on antibiotic resistance. The GP will often prescribe antibiotics before knowing the culture results, which can take up to a week to receive. Some people may therefore be given antibiotics unnecessarily, and some will be given the wrong antibiotics.

Novel point-of-care tests (POCTs) can be conducted in a near-patient setting and can quickly diagnose a UTI. Some can also tell which pathogen is causing the infection and which antibiotic will work best.

Objectives

This project aimed to determine whether POCTs for people with suspected UTI have the potential to be clinically effective and cost-effective to the NHS.

We defined the following objectives to address this overall aim.

- Objective 1: what is the impact on clinical outcomes of using POCTs to diagnose UTI, with or without additional pathogen identification and antimicrobial sensitivity testing (AST)?
- Objective 2: what is the accuracy of POCTs for UTI diagnosis, pathogen identification and AST?
- Objective 3: what is the technical performance (other than accuracy) of POCTs for UTI?
- Objective 4: what are the costs, from a UK NHS and Personal Social Services perspective, of using POCTs for UTI diagnosis, pathogen identification and AST?
- Objective 5: how might a conceptual model be specified in terms of structure and evidence required for parametrisation in order to estimate the cost-effectiveness of POCT for UTI diagnosis, pathogen identification and AST?

Methods

Clinical effectiveness review

A systematic review was conducted in line with published guidance.

Data sources

Four databases and two trial registries were searched. Additional non-bibliographic search methods included searching trial registries, screening reference lists of reviews and study reports, hand-searching relevant websites and reviewing information submitted by test manufacturers.

Study selection and review methods

Studies were eligible for inclusion if they were published during or after the year 2000, enrolled patients with suspected UTI, and evaluated a POCT in scope:

- rapid tests giving results < 40 minutes – Astrego PA-100 system, Lodestar DX, TriVerity, Uriscreen, UTRiPLEX
- culture-based tests giving results in up to 24 hours – Flexicult Human, ID Flexicult, Diaslide, Dipstreak, Chromostreak, Uricult, Uricult Trio, Uricult Plus.

For objective 1, studies had to be randomised controlled trials (RCTs) or non-randomised studies of interventions, set in primary care or the community and use standard care as the reference standard. For objective 2, only diagnostic test accuracy studies were eligible for inclusion. Studies of any design were eligible for objective 3. Studies had to report data on prespecified outcomes to be eligible:

- Objective 1 – any outcome related to antibiotic use/prescription, morbidity, mortality, UTI-associated healthcare resources, health-related quality of life.
- Objective 2 – test accuracy in detecting UTI, identifying pathogens or assessing susceptibility to antimicrobials.
- Objective 3 – test failure rate, ease of use/acceptability, time to results, health-related quality of life, any outcome related to antibiotic use/prescription, UTI-associated healthcare resources, test costs, clinical outcomes. Title and abstract screening was conducted by two reviewers independently. Inclusion assessment, data extraction and risk-of-bias assessment were performed by one reviewer and checked by a second reviewer. Risk of bias was assessed using the RoB 2 tool for RCTs, QUADAS-2 for diagnostic test accuracy studies, and QUADAS-C for comparative accuracy studies.

For each objective, we provided a narrative summary of included study details, risk of bias and results, stratified by POCT. For objective 2, bivariate random-effects meta-analyses were used to pool sensitivity and specificity across studies, separately for each POCT. We presented coupled forest plots of individual study and summary estimates of sensitivity and specificity together with 95% confidence intervals (CIs) to allow visual assessment of results and of heterogeneity across studies. There were not enough studies for formal investigation of heterogeneity, or to stratify analysis based on populations specified in the scope.

Conceptual economic model

We developed a conceptual model to estimate the cost-effectiveness of POCTs for UTI diagnosis, pathogen identification and AST. This represented important short- and long-term costs and quality-of-life impacts on the management of UTIs.

The conceptual model was implemented as a decision tree comparing POCTs with laboratory culture-based tests for UTI. Sensitivity and specificity were informed by the clinical effectiveness review. The decision tree was further informed by screening studies identified by the clinical effectiveness review for any evidence relating to cost-effectiveness or parameters that could inform the conceptual model. This was supplemented by pragmatic searches of Ovid MEDLINE, EMBASE and EconLit for cost-effectiveness studies in UTI. These were supplemented by evidence from National Institute for Health and Care Excellence guidelines, *British National Formulary* costs, and the Personal Social Services Research Unit.

We prioritised tests and populations where evidence was greatest. We also prioritised rapid over culture-based tests and tests that performed AST over those that only identified pathogenic cause and both such tests over those that tested only for UTI.

The decision tree model was implemented in the R statistical programming language (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical effectiveness review

We identified 16 studies for inclusion in the review. All studies were included for objective 2; two were also included for objective 1, while five also provided data for objective 3. Six studies evaluated rapid POCTs (Lodestar DX, *n* = 1; Uriscreen, *n* = 4; UTRiPLEX, *n* = 1) and 12 studies evaluated culture-based POCTs (Flexicult Human, *n* = 4; ID Flexicult, *n* = 2; Uricult Trio, *n* = 3; Uricult, *n* = 1; Dipstreak, *n* = 2). Two studies reported direct comparisons between tests (Flexicult Human and ID Flexicult; Uriscreen and UTRiPLEX). Studies enrolled women, pregnant women, children and people with catheters. There were no data on any other prespecified tests or populations of interest.

Objective 1: clinical outcomes

Two RCTs evaluated the clinical impact of the culture-based test Flexicult Human in women: one compared with standard care (*n* = 653) and the other compared with ID Flexicult (*n* = 376). Both trials were judged as being at low risk of bias. There was no evidence of a difference between intervention groups in the studies' primary outcomes: one evaluated concordant antibiotic use (odds ratio 0.84, 95% CI 0.58 to 1.20) and the other evaluated appropriate antibiotic prescribing (odds ratio 1.44, 95% CI 1.03 to 1.99). Compared with standard care, one study found that the use of Flexicult Human was associated with reduced antibiotic prescribing at initial consultation (odds ratio 0.56, 95% CI 0.35 to 0.88), but no difference was found between groups for other outcomes related to antibiotic use. Neither study reported a difference between intervention groups in duration of symptoms/infection, patient enablement or resource use. There were no data on mortality or health-related quality of life.

Objective 2: diagnostic test accuracy

Sixteen studies reported data on test accuracy. Two studies took place in Wales (*n* = 200 samples; *n* = 144 samples) and one had centres in Wales, England, Spain and the Netherlands (*n* = 289). The other studies were conducted in Israel (two studies; *n* = 795; *n* = 818), Hawaii (one study; *n* = 378), Venezuela (one study; *n* = 150), Mexico (one study; *n* = 108 samples), Philippines (one study; *n* = 200), South Africa (one study; *n* = 374), Republic of Korea (one study; *n* = 151), Argentina (one study; *n* = 2173), Denmark (three studies; *n* = 183 Flexicult Human/*n* = 158 ID Flexicult, *n* = 121 samples, *n* = 117) and Belgium (one study; *n* = 156 Uriscreen/*n* = 292 URiPLEX) (brackets show the number of participants or samples analysed). Twelve studies were conducted in primary or secondary care and four were laboratory-based. Five studies were judged at high risk of bias, eight at unclear risk of bias and three at low risk.

Only three rapid tests were evaluated (six studies). Lodestar DX appeared to be the most promising test. In a laboratory-based study, it had good sensitivity (86%, 95% CI 74% to 99%) and specificity (88%, 95% CI 83% to 94%) for detecting *E. coli*. Uriscreen had modest summary estimates of sensitivity (74%, 95% CI 59% to 84%; four studies) and specificity (64%, 95% CI 41% to 82%). UTRiPLEX had poor sensitivity (21%) but good specificity (94%) in one study recruiting children. Neither Uriscreen or UTRiPLEX provide information on antimicrobial sensitivity or pathogenic cause of infection.

Twelve studies evaluated culture-based tests. Of the culture-based tests evaluated, Dipstreak and Uricult were found to be highly accurate. However, these were assessed by two studies and one study, respectively, and both were conducted in the laboratory and were at high or unclear risk of bias. By contrast, studies of Uricult Trio (an extension of Uricult) in near-patient settings reported more modest

summary sensitivity (73%, 95% CI 63% to 82%) and specificity (70%, 95% CI 52% to 84%). Summary sensitivity for Flexicult Human (three studies) was 79% (95% CI 72% to 85%) and summary specificity was 67% (95% 30% to 90%). For ID Flexicult (two studies), this was 89% (95% CI 84% to 93%) and 70% (95% CI 52% to 84%). Three studies reported data on the accuracy of Flexicult Human in determining antimicrobial sensitivity. Summary sensitivity was 87% (95% CI 83% to 90%), and summary specificity was 93% (95% CI 89% to 95%).

All summary estimates should be interpreted with caution due to heterogeneity across studies.

Objective 3: technical performance

Five studies reported technical performance data. These evaluated culture-based tests only: three on Flexicult Human (n = 653; n = 35; n = 121) and two on Uricult Trio (n = 200; n = 374) Studies reported that POCTs are easier to use and interpret than laboratory tests and produce results more quickly. Clinicians reported that using Flexicult Human had increased their awareness of antibiotic prescribing and positively impacted their prescribing habits. However, they raised concerns regarding limits on when the test can be used, difficulties in result interpretation, limited resources, concerns about prolonging patient discomfort while awaiting test results, and the expense of maintaining a stock of tests. One study reported that Flexicult Human costs £48. (Confidential information has been removed). There were no data on test failure rate or health-related quality of life.

Conceptual economic model

We developed a conceptual model that could be used for a future full economic evaluation of POCTs for UTI and their role in reducing antibiotic resistance. This model identified pathways for benefit from POCTs, namely that they could reduce the use of empiric antibiotics and, by reducing the incidence of UTI complications and improving cure rates, reduce healthcare costs and quality-of-life impacts arising from UTI. Beyond test accuracy, we found only two studies from the clinical effectiveness review with relevant evidence for the economic model. Our pragmatic searches identified only eight cost-effectiveness studies in UTI, none of which modelled POCTs and none of which provided all the evidence needed to inform our economic evaluation. Due to the limited findings on test accuracy, we restricted modelling to a mixed population (Lodestar DX vs. Flexicult Human) and to women with uncomplicated UTI (Lodestar DX vs. Flexicult Human vs. ID Flexicult). Despite our prioritisation of tests and subgroups, broad approach to modelling, and pragmatic approach to searching for evidence, we found that evidence informing our economic model was too weak for results to be meaningful.

Conclusions

Implications for practice

There are few available data concerning the clinical effectiveness and cost-effectiveness of POCTs, particularly rapid POCTs, for people with suspected UTI, making it difficult to determine whether these tests have the potential to be clinically effective and cost-effective to the NHS. There is a clear need for a rapid test that would accurately diagnose a UTI within a short time in GP surgeries or pharmacy settings. Ideally, such tests would also provide information on antimicrobial sensitivity to allow targeted antibiotic use. The only test within scope that meets these criteria is the Astrego PA-100 system. However, there are currently no data available on this test.

Our conceptual model for economic evaluation found potential pathways to benefit from POCTs. They could reduce costs, improve quality of life, reduce antibiotic resistance and reduce complications from UTI. There were insufficient data on test accuracy, targeted versus empiric antibiotic efficacy, or costs and quality-of-life impacts of UTI complications for our model to perform a meaningful comparison.

Strong evidence that POCTs (1) reduce unnecessary antibiotic use, (2) improve symptoms or (3) are cost-effective is needed before such tests are introduced into the NHS.

Recommendations for research

Given the paucity of data on POCTs for diagnosing UTI, further studies are needed to determine whether POCTs for people with suspected UTI have the potential to be clinically effective and cost-effective to the NHS. Ideally, studies would be RCTs with embedded diagnostic test accuracy studies of POCTs and should be conducted in primary care; such studies would provide data on clinical impact and test accuracy. Studies should focus on tests with the greatest potential for clinical impact: the Astrego PA-100 system and Lodestar DX. Either the studies should enrol patients across multiple patient groups of interest (e.g. men, women, pregnant women, children) with results stratified according to patient subgroup, or separate studies should be carried out to determine whether results differ according to subgroups. Studies should also consider the feasibility of introducing rapid POCTs into pharmacy settings.

In addition to further studies on clinical effectiveness, further research on potential cost-effectiveness and impact on antibiotic resistance is needed. This research could build on our conceptual economic model using systematic literature reviews to identify evidence on the efficacy of empiric versus targeted antibiotic treatment of UTI; the efficacy in preventing UTI complications; and both the cost and quality-of-life impacts of these complications.

Study registration

This study is registered as PROSPERO CRD42022383889.

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