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Diagnostic test accuracy of dipstick urinalysis for diagnosing urinary tract infection in febrile infants attending the emergency department

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ABSTRACT

Objective To report the diagnostic test accuracy of dipstick urinalysis for the detection of urinary tract infections (UTIs) in febrile infants aged 90 days or less attending the emergency department (ED).

Design Retrospective cohort study.

Patients Febrile infants aged 90 days or less attending between 31 August 2018 and 1 September 2019.

Main outcome measures The sensitivity, specificity and predictive values of dipstick urinalysis in detecting UTIs defined as growth of $\geq 100\,000$ cfu/mL of a single organism and the presence of pyuria (>5 white blood cells per high-power field).

Setting Eight paediatric EDs in the UK/Ireland.

Results A total of 275 were included in the final analysis. There were 252 (92%) clean-catch urine samples and 23 (8%) were transurethral bladder catheter samples. The median age was 51 days (IQR 35–68.5, range 1–90), and there were 151/275 male participants (54.9%). In total, 38 (13.8%) participants had a confirmed UTI. The most sensitive individual dipstick test for UTI was the presence of leucocytes. Including 'trace' as positive resulted in a sensitivity of 0.87 (95% CI 0.69 to 0.94) and a specificity of 0.73 (95% CI 0.67 to 0.79). The most specific individual dipstick test for UTI was the presence of nitrites. Including trace as positive resulted in a specificity of 0.91 (95% CI 0.86 to 0.94) and a sensitivity of 0.42 (95% CI 0.26 to 0.59).

Conclusion Point-of-care urinalysis is moderately sensitive and highly specific for diagnosing UTI in febrile infants. The optimum cut-point to for excluding UTI was leucocytes (1+), and the optimum cut-point for confirming UTI was nitrites (trace).

Trial registration number NCT04196192.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

- ⇒ Febrile infants under 90 days of age are at high risk of serious bacterial infection (SBI).
- ⇒ Urinary tract infections (UTIs) are the most common SBI in this cohort.
- ⇒ Urinalysis with point-of-care (POC) urine dipstick testing is not recommended by NICE for infants under 90 days of age.

WHAT THIS STUDY ADDS

- ⇒ POC dipstick urinalysis has a moderate sensitivity for diagnosing UTIs in this cohort.
- ⇒ POC dipstick urinalysis has a high specificity for diagnosing UTIs in this cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ POC urinalysis has sufficient diagnostic accuracy to be useful in two clinical scenarios. First, for infants where the decision has been made to perform a septic screen and administer parenteral antibiotics, the presence of nitrites is likely sufficient to confirm a diagnosis of UTI. Promptly diagnosing UTI may reduce the need for further invasive procedures such as lumbar puncture. Second, in settings where microscopy is not available, a negative urinalysis may be sufficient to avoid parenteral antibiotics in an otherwise well appearing infants with reassuring inflammatory markers and white cell count.

INTRODUCTION

Young febrile infants (under 90 days of age) are at high risk of serious bacterial infections (SBIs).^{1–4} The most commonly encountered SBIs are urinary tract infections (UTIs), accounting for 80%–90% of all SBI in this age group.^{1–7} The features of UTI in young infants are typically non-specific and include fever, vomiting, lethargy, irritability and poor feeding.^{8–10} The diagnosis and management of UTIs in the UK is guided by the National Institute for Health and Care Excellence (NICE). The clinical guideline CG54, 'Urinary tract infection in under

16s: diagnosis and management', recommends that all infants under 3 months of age with suspected UTI are referred to a paediatric specialist for assessment.⁸ NICE CG54 recommends that infants under 3 months of age undergo urine laboratory microscopy analysis rather than point-of-care (POC) urine dipstick analysis.⁸ It has, however, been demonstrated that POC dipstick analysis of transurethral bladder catheter (TUBC) samples from febrile infants can be highly sensitive and specific in this age group.^{11–13}

POC urine dipstick testing has several advantages to laboratory microscopy. Urine dipstick testing is quicker, requires fewer resources and can be conducted at sites where laboratory access is not



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available 24 hours a day. Prompt and accurate diagnosis of UTI in febrile infants is important. Increasingly international guidelines, including from mainland Europe and the USA, advocate a tailored approach to the assessment and management of febrile infants, including the community management of well-appearing infants with suspected UTI.^{9–10} Prompt and accurate diagnosis of UTIs in infants under 90 days of age may reduce their length of stay, the need for invasive tests such as lumbar puncture and reduce the use of parenteral antibiotics that may be given ‘just in case’.

The objective of this study was to report the diagnostic test accuracy of urine dipstick testing for the diagnosis of UTIs in febrile infants under 90 days of age presenting to the ED.

METHODS

The data for this diagnostic test accuracy study come from the Febrile Infants Diagnostic assessment and Outcome (FIDO) study.³ The FIDO study was a multicentre cohort study conducted in sites from Paediatric Emergency Research in the UK and Ireland.¹⁴ The study protocol was registered at www.clinicaltrials.gov. This diagnostic test accuracy study has been reported in adherence with Standards for Reporting Diagnostic Accuracy (STARD) criteria for reporting diagnostic test accuracy studies.¹⁵

Participants

This multicentre observational study was conducted at eight paediatric emergency departments (EDs) across the UK and Ireland with one centre in Northern Ireland, one in Scotland, three in England and three in Ireland. Infants up to 90 days of age attending between 31 August 2018 and 1 September 2019 were screened for inclusion by searching clinical software databases. All sites had a dedicated paediatric ED with a combined annual census of approximately 390 000 children. Patients with a recorded fever ($\geq 38^{\circ}\text{C}$) at triage were eligible for inclusion. There were no exclusion criteria for the original FIDO study. Exclusion criteria for this secondary analysis included not having either the index test (Siemens Multistix) or the reference test (urine culture) reported or urine collection via either a urine pad or bag.

Test methods

The index test was the commercially available Siemens Multistix POC urine dipstick test performed on either a clean-catch or TUBC urine sample (table 1). The Siemens Multistix is a semi-quantitative urine test that reports the absence (negative) or presence of leucocytes and nitrites (‘trace’ to ‘3+’). Dipstick urinalysis was performed by clinical staff according to their departmental guidelines and training. The reference standard

was confirmation of UTI defined as growth of $\geq 100\,000$ cfu/mL of a single organism excluding likely contaminants (lactobacilli, corynebacteria and coagulase-negative staphylococci) and the presence of pyuria (>5 white blood cells per high-power field) on laboratory microscopy. Reference testing was performed in accredited laboratories (United Kingdom Accreditation Service (UKAS) or equivalent).

Study procedures

The study was conducted retrospectively and only included anonymised, non-personal, routinely collected clinical data. All infants received usual care, and there were no additional interventions. The index test result was recorded from the medical record. In all instances the index test was performed without knowledge of the urine culture result (reference test).

Data management

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Bristol.¹⁶ REDCap is a secure, web-based software platform designed to support data capture for research studies. Incomplete data sets were excluded from the analysis.

Data analysis

Analysis

The study population was described in terms of demographic characteristics with median age in days and IQR and gender as total and percentage. Simple descriptive statistics (total number and proportion) were used to report urine collection method and urine culture results. The diagnostic accuracy of urine dipstick testing was reported with sensitivity, specificity, negative predictive value and positive predictive value with 95% CI. In situations where the dipstick testing provided an invalid result, the test result was excluded from analysis.

Office for Research Ethics Committees and local research governance

This study uses only routinely collected, non-personal and fully anonymised data.¹⁷ The study was, however, registered with, and approved by, research governance offices at the respective sites.

FINDINGS

A total of 1942 eligible infants were screened, of which 1379 were ineligible (no history of fever or outside of age range); 8 had incomplete data; 13 had urine samples collected from urine pads; and 267 did not have either the index test (Siemens Multistix) or the reference test (urine culture) reported. A total of 275 were included in the final analysis. Figure 1 shows the flow of participants and table 1 shows recruitment by site. The median age of included participants was 51 days (IQR 35.0–68.5, range 1–90), and 151/275 participants were male (54.9%). This was similar to the overall FIDO study reported previously, and demographic data are shown in table 2. The excluded population ($n=280$) was similar to the included population with a similar median age of 58 days (IQR 28–68, range 1–90), similar proportion of male participants 168/280 (60%) and similar rates of culture-positive UTI 16/150 (11%).

Of the 275 included urine samples, 252 (92%) were clean-catch samples and 23 (8%) were TUBC. In total, 38 (13.8%) participants had a confirmed (non-contaminant) UTI. Of these, 35 (92%) were *Escherichia coli*; 2 (5%) were *Klebsiella*; and 1 (3%) was *Enterococcus*. The median length of stay of infants with confirmed UTI was 72 hours (IQR 45–102). The sensitivity

Table 1 Recruitment by site

Site	N	Urinary tract infection
Belfast	16	6
Bristol	39	7
Dublin (Crumlin)	32	8
Dublin (Tallaght)	34	1
Dublin (Temple St)	7	0
Glasgow	92	7
Leicester	20	4
London	35	5
Total	275	38

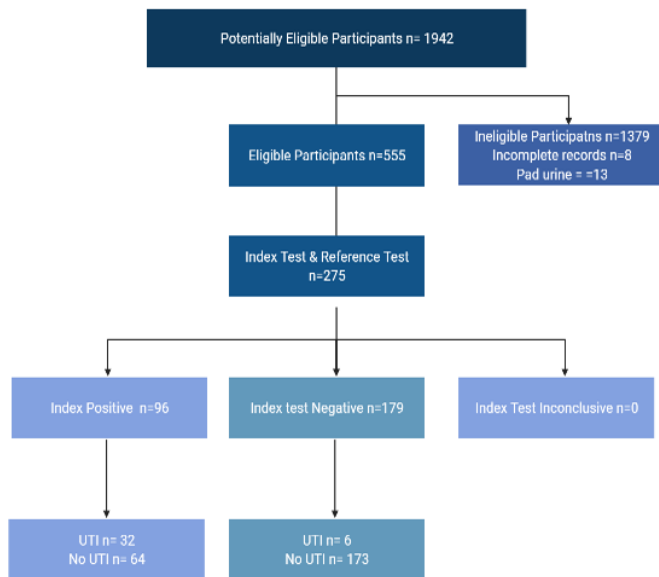


Figure 1 Flow of participants. UTI, urinary tract infection.

and specificity of Siemens Multistix dipstick testing at a range of cut-points are shown in table 3. The most sensitive individual dipstick result for UTI was the presence of leucocytes. Including trace as positive resulted in a sensitivity of 0.84 (95% CI 0.69 to 0.94) and a specificity of 0.73 (95% CI 0.67 to 0.79). Increasing the threshold for positivity to 1+ reduced the sensitivity to 0.82 (95% CI 0.66 to 0.92) and increased the specificity to 0.82 (95% CI 0.76 to 0.87). Increasing the leucocyte positive cut-point to 2+ or 3+ resulted in larger drops in sensitivity to 0.66 (95% CI 0.49 to 0.80) and 0.58 (95% CI 0.41 to 0.74), respectively, and increased specificity to 0.91 (95% CI 0.87 to 0.94) and 0.96 (95% CI 0.93 to 0.98), respectively.

The most specific individual dipstick result for UTI was the presence of nitrites. Including trace as positive resulted in a specificity of 0.91 (95% CI 0.86 to 0.94) and a sensitivity of 0.42 (95% CI 0.26 to 0.59). Increasing the threshold for positivity to 1+, 2+ or 3+ increased the specificity to 0.95 (95% CI 0.91 to 0.97), 0.99 (95% CI 0.97 to 1.00) and 0.98 (95% CI 0.95 to 0.99), respectively, and reduced the sensitivity to 0.42 (95% CI 0.26 to 0.59), 0.16 (95% CI 0.06 to 0.31) and 0.03 (95% CI 0.00 to 0.14), respectively.

The combined accuracy of leucocyte and nitrite testing is also shown in table 3. Requiring both the presence of leucocytes and nitrites was highly specific for UTI in this cohort (0.93 to 1.00) but poorly sensitive (CI 0.00 to 0.093), with both measures highly dependent on the cut-point used. Conversely, the presence of either leucocytes or nitrites demonstrated similar performance characteristics as leucocyte-only testing. Including trace of either leucocytes or nitrites as positive resulted in a sensitivity

of 0.84 (95% CI 0.69 to 0.94) and a specificity of 0.71 (95% CI 0.65 to 0.77), respectively. Increasing the threshold of positivity to 1+ reduced the sensitivity to 0.82 (95% CI 0.66 to 0.92) and increased the specificity to 0.81 (95% CI 0.75 to 0.86). Further increasing the positivity cut-point to 2+ and 3+ reduced the sensitivity to 0.66 (95% CI 0.49 to 0.80) and 0.61 (95% CI 0.43 to 0.76), respectively, and increased the specificity to 0.90 (95% CI 0.86 to 0.94) and 0.94 (95% CI 0.90 to 0.97), respectively.

Interpretation

This is the first report of the diagnostic test accuracy of POC dipstick urinalysis for infants under 90 days of age in the UK and Ireland. In this article, we report that POC urinalysis in infants under 90 days of age has a moderate sensitivity of 0.82 and a specificity of 0.82 for identifying UTIs in this group. The reported test accuracy in this study is slightly lower than results published by Tzimenatos *et al* (USA), Glismeyer *et al* (USA) and Velasco *et al* (Spain), who reported the sensitivity and specificity of urine dipstick testing of febrile infants as between (95% CI 0.83 to 0.94) and (95% CI 0.91 to 0.94).^{11–13} The lower sensitivity and specificity observed in our cohort may reflect differences in sample collection between studies. In the studies by Tzimenatos *et al*, Glismeyer *et al* and Valasco *et al*, urine samples were collected by invasive methods such as TUBC and suprapubic aspiration (SPA). In the FIDO study cohort, 92% of urine samples were collected by non-invasive clean-catch. Non-invasive samples, as recommended by current NICE guidance (CG54), may have higher contamination rates and smaller volumes than TUBC/SPA samples, thereby reducing the test accuracy of POC urine dipstick testing. The FIDO study results likely reflect the current real-world performance of Siemens Multistix in the UK and Ireland.

The optimum cut-point for Siemens Multistix POC dipstick testing from the FIDO study cohort was one plus of leucocytes. At this cut-point the Sensitivity of Siemens Multistix POC dipstick testing was 0.82 and the specificity was 0.82. Lowering the threshold to include trace as a positive had a marginal effect on the sensitivity of the test (0.84) but reduced the specificity to 0.73. A testing strategy of either leucocytes or nitrites positive did not improve the test accuracy (table 3). The presence of nitrites was highly specific for UTI in this cohort. Even at trace levels, the specificity of Siemens Multistix POC urine dipstick was 0.91 for UTI. Nitrite testing was, however, poorly sensitive with a sensitivity of 0.42 at a trace cut-point.

Based on these findings, the absence of leucocytes (using a 1+ cut-point) on urine Siemens Multistix urine dipstick testing has a moderate sensitivity for excluding UTI. In contrast however, the presence of nitrites (trace as cut-point) on Siemens Multistix POC urine dipstick testing could be reliably used to confirm UTI prior to microscopy. This is of potential benefit as early identification of UTI in this cohort could minimise the need for further invasive investigations such as lumbar puncture.

SUMMARY

POC urinalysis with Siemens Multistix is a moderately sensitive and highly specific test to diagnose UTI in febrile infants under 90 days of age. The optimum cut-point to for excluding UTI was leucocytes (1+) and the optimum cut-point for confirming UTI was nitrites (trace).

Strengths/limitations

The strengths of this study are that it is a relatively large study including a number of sites from across the UK and Ireland and

Table 2 Baseline demographic data

	Overall
n	275
Median age (days)	51(IQR35–68.5)
Male gender (n/%)	151 (54.9)
Positive dipstick	100 (36.3)
UTI, n (%)	38 (13.8)
Length of stay proven UTI	72 (IQR 45–102)
UTI, urinary tract infection.	

Table 3 Diagnostic test accuracy of Siemens Multistix testing

Test (positive cut-point)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Leucocyte (trace)	0.84 (0.69 to 0.94)	0.73 (0.67 to 0.79)	0.33 (0.24 to 0.44)	0.97 (0.93 to 0.99)
Leucocyte (1+)	0.82 (0.66 to 0.92)	0.82 (0.76 to 0.87)	0.42 (0.31 to 0.54)	0.97 (0.93 to 0.99)
Leucocyte (2+)	0.66 (0.49 to 0.80)	0.91 (0.87 to 0.94)	0.54 (0.39 to 0.69)	0.94 (0.90 to 0.97)
Leucocyte (3)	0.58 (0.41 to 0.74)	0.96 (0.93 to 0.98)	0.71 (0.52 to 0.86)	0.93 (0.90 to 0.96)
Nitrite (trace)	0.42 (0.26 to 0.59)	0.91 (0.86 to 0.94)	0.42 (0.26 to 0.59)	0.91 (0.86 to 0.94)
Nitrite (1+)	0.42 (0.26 to 0.59)	0.95 (0.91 to 0.97)	0.57 (0.37 to 0.76)	0.91 (0.87 to 0.94)
Nitrite (2+)	0.16 (0.06 to 0.31)	0.99 (0.97 to 1.00)	0.75 (0.35 to 0.96)	0.88 (0.84 to 0.92)
Nitrite (3+)	0.03 (0.00 to 0.14)	0.98 (0.95 to 0.99)	0.17 (0.00 to 0.64)	0.86 (0.82 to 0.90)
Leucocyte or nitrite (trace)	0.84 (0.69 to 0.94)	0.71 (0.65 to 0.77)	0.32 (0.23 to 0.42)	0.97 (0.93 to 0.99)
Leucocyte or nitrite (1+)	0.82 (0.66 to 0.92)	0.81 (0.75 to 0.86)	0.41 (0.30 to 0.53)	0.96 (0.93 to 0.99)
Leucocyte or nitrite (2+)	0.66 (0.49 to 0.80)	0.90 (0.86 to 0.94)	0.52 (0.37 to 0.67)	0.94 (0.90 to 0.97)
Leucocyte or nitrite (3+)	0.61 (0.43 to 0.76)	0.94 (0.90 to 0.97)	0.62 (0.45 to 0.78)	0.94 (0.90 to 0.96)
Leucocyte and nitrite (trace)	0.42 (0.26 to 0.59)	0.93 (0.89 to 0.96)	0.48 (0.31 to 0.66)	0.91 (0.87 to 0.94)
Leucocyte and nitrite (1+)	0.42 (0.26 to 0.59)	0.95 (0.92 to 0.98)	0.59 (0.39 to 0.78)	0.91 (0.87 to 0.94)
Leucocyte and nitrite (2+)	0.16 (0.06 to 0.31)	1.00 (0.98 to 1.00)	1.00 (0.54 to 1.00)	0.88 (0.84 to 0.92)
Leucocyte and nitrite (3+)	0.00 (0.00 to 0.09)	1.00 (0.98 to 1.00)	N/A	0.86 (0.82 to 0.90)

N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value.

the first to report the diagnostic test accuracy of POC dipstick urinalysis in the UK and Ireland. Although retrospective in design, the index test and reference standard were recorded from the medical record and are not at high risk of bias. The index test was always performed before the reference test, and the reference test was performed by technicians unaware of the index test result. The limitations are that the study was performed retrospectively and, as such, will not include all febrile infants that have attended at all sites. (It is, however, reassuring that the reported rates of SBI/IBI are broadly similar to international estimates.) The nature of the retrospective data collection will also bias into the study. The study population was too small to allow for further subgroup analysis, such as by age or symptoms. All sites in this study had dedicated paediatric EDs and the results may not be generalisable to departments without a dedicated paediatric ED.

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Collaborators On behalf of Paediatric Emergency Research in the UK and Ireland

Contributors TW, MDL, DR and J-AM contributed to the design of the study. TW co-ordinated the running of the study including data management and site training. MDL and TW designed the electronic CRFs. MDL, J-AM, DR, RB, SD and MB and SF were site leads. LM and HM provided statistical expertise and performed the statistical analysis. EM, TW and MDL drafted the manuscript. All authors contributed to the data collection and the writing of the manuscript. TW is guarantor of the study.

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Patient consent for publication Not applicable.

Ethics approval National research ethics committee approval was not necessary for this study based on the results from the Health Research Association decisions tool. The study was, however, registered with, and approved by, research governance offices at the respective sites.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data collected during this study will be available (including data dictionaries) on the Queen's University Belfast database within 3 months of completion of the study.

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