PRACTICE

UNCERTAINTIES PAGE

How best to diagnose urinary tract infection in preschool children in primary care?

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Accurate and timely diagnosis of urinary tract infection (UTI) in young children presenting to primary care is important because appropriate treatment may alleviate suffering and help prevent long term sequelae such as renal scarring, poor renal growth, recurrent pyelonephritis, impaired glomerular function, hypertension, end stage renal disease, and pre-eclampsia.[1][2] The prevalence of renal scarring in the general population is unknown, but a systematic review of studies, largely conducted in secondary care, showed 15% of children with an initial episode of UTI had evidence of renal scarring on follow-up dimercaptosuccinic acid (DMSA) scanning, and there was an 8% incidence of UTI recurrence per year.[3]

Among consultations for illness episodes in children aged under 5 years in the UK, approximately 40% comprise infectious diseases and respiratory episodes, while about 10% of presentations comprise non-specific symptoms. Thus identifying which children have a significant UTI (which often also presents with non-specific symptoms) is a key challenge for primary care clinicians.

The diagnosis is further hampered because young children cannot clearly articulate symptoms; when children wear nappies, parents are not aware of the classic dysuria and frequency symptoms as experienced by adults; and obtaining an adequate urine sample can be frustrating, time consuming, and costly.

The precise prevalence of UTI among all acutely unwell children presenting to primary care is unclear. One systematic review of 10 studies, eight of which were conducted in hospital emergency departments, one in US paediatricians' offices, and one in an army medical centre, estimated UTI prevalence at 7%.[4] A large Australian emergency department study published in 2010 found a prevalence of 3.4% in children presenting with a febrile illness.[5] We identified only one small exploratory study

conducted in general practitioner/family physician practices, which found a prevalence of 4%.[6]

It is not surprising then that the diagnosis of UTI is often delayed and may be missed in up to 50% of children presenting to primary care,[7] sometimes due to symptoms being incorrectly attributed to other causes (such as otitis media). The pressure to reduce antibiotic prescribing may reduce the serendipitous treatment of undiagnosed UTI and the consequent prevention of renal sequelae, making accurate diagnosis now even more important than ever.

What is the evidence of the uncertainty?

The 2007 guidelines on the diagnosis, treatment, and long term management of UTI in children by the National Institute for Health and Clinical Excellence (NICE)[8] concluded, after a systematic review, that there is uncertainty regarding the following questions on the diagnosis of UTI in children aged less than 5 years in primary care:

1) What is the accuracy of clinical symptoms and signs?

2) What is the accuracy of the combination of nitrite and leucocyte esterase (LE) dipstick test?

3) How do nappy pad or urine bag sample contamination rates compare to supra-pubic aspiration (SPA) or catheter samples?

To address these uncertainties, we considered relevant studies from our 2006 Health Technology Assessment (HTA) funded systematic review of tests for diagnosing UTI in children,[9] the NICE guidelines,[8] and a systematic literature search of Medline from 2002 (the end date of the HTA review searches) to April 2011. We used a sensitive search strategy combining terms related to UTI with terms relating to "clinical signs and symptoms," "dipstick testing," or "urine sampling," to identify

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studies published since these reports. We included primary studies or systematic reviews that addressed one of the above questions, used urine culture as the reference standard, enrolled children aged 5 years or less, and were conducted in a primary care or emergency department setting in the Western world.

Clinical symptoms and signs

We found one systematic review[10] that included eight primary studies in children aged less than 5 years (n=7892) and three additional primary studies (n=17 462) that fulfilled our inclusion criteria.[5 11 12] Of these 11 studies, nine were conducted in hospital emergency departments, and two in paediatricians' offices; none was conducted in general practices or family physician practices. The web table shows positive and negative likelihood ratios for each clinical sign and symptom together with estimates of the post-test probability of disease for the presence and absence of each symptom based on the prevalences (pre-test probabilities) of UTI of 4% seen in the study by O'Brien[6] and 7% in the study by Shaikh.[4]

The data found show that no individual symptom or sign, or any combination of symptoms or signs, was sufficient to rule in a diagnosis of UTI, though some post-test probabilities (such as 25% for increased capillary refill time, no fluid intake, and supra-pubic tenderness) appear high enough to mandate urine testing and empirical treatment while awaiting culture confirmation. A number of symptoms and signs did not appear to have diagnostic value, including some that were recommended for the diagnosis of UTI by NICE[8] (for example, poor feeding and vomiting). Some symptoms, signs (for example, respiratory), and proposed clinical prediction rules did reduce the probability of UTI to below 2% (given a pre-test probability of 4%) and these may be considered low enough to rule out UTI and avoid the need to obtain urine. These are summarised in table 1⇓.

The largest study, which included almost 16 000 children,[5] derived a clinical prediction rule based on a combination of 27 signs and symptoms. Results were not reported for specific thresholds, but the model was found to have an area under the receiver operating characteristic curve of 0.80 (95% confidence interval 0.78 to 0.82) leading the authors to conclude that a computer assisted diagnostic decision tool based on this model could improve decision making in the emergency department.

Dipstick testing

We identified five primary studies conducted in children aged less than 5 years that assessed nitrite and leucocyte esterase dipstick testing in an emergency department setting,[13 14 15 16 17] all of which were included in our previous HTA review,[6] though our published analysis was not stratified by age <5 years. The age stratified results presented in the web table suggest that nitrite and/or leucocyte esterase positivity are useful for identifying children in whom urine should be cultured to confirm the presence of a UTI with post-test probabilities of between 20% and 84%. If both nitrite and leucocyte esterase are negative, the post-test probability ranged from 1% to 2% (based on pre-test probably of 4% to 7%) and this may be sufficient to rule out UTI without urine culture (table 1).

Urine sampling

The NICE guidelines found "insufficient data to draw conclusions about urine collection bags and urine collection pads" and "low-level evidence that showed that the accuracy of urine collection pads was greatly improved if the pads were not used for longer than 30 minutes."[8] We identified one study

published since these recommendations that reported a sensitivity of 88% and a specificity of 80% for bag samples compared to the recommended (reference) standard of catheter samples in non-toilet trained children.[18] No further studies addressing nappy pads were identified.

Is ongoing research likely to provide relevant evidence?

We searched (8 September 2011) the UK Clinical Research Network Study Portfolio (http://public.ukcrn.org.uk/search) for diagnostic studies of UTI in children and identified the Diagnosis of Urinary Tract infection in Young children (DUTY) study (www.dutystudy.org.uk) and the Epidemiology of Urinary Tract Infection (UTI) in Children with Acute Illness in Primary Care (EURICA) study. DUTY is a diagnostic cohort study designed to derive, validate, and test the efficiency of a diagnostic algorithm (that includes symptoms, signs, and dipstick urinalysis) for UTI in acutely unwell preschool children presenting to primary care. The study will also compare contamination rates between pad and clean catch urine sampling methods and is due to report at the end of 2012. EURICA is designed to estimate the prevalence of UTI in acutely unwell children aged less than 5 years presenting to primary care.

What should we do in the light of the uncertainty?

Many primary care clinicians will question the relatively high prevalence of UTI of 4% and 7% reported in the studies by O'Brien[6] and Shaikh,[4] since prevalences of this level might suggest more children develop complications than we currently appear to observe. There are a number of possible reasons for this high prevalence, including: (1) false positive results due to contamination; (2) false positive results due to asymptomatic bacteriuria;[19] (3) poor recognition of complications due to the limitations of existing tests (such as ultrasound and dimercaptosuccinic acid (DMSA) scans to detect renal scarring); and (4) uncertainty regarding the natural history of, and the development of complications from, UTI in children.

As with many decisions about who to test in primary care, acutely unwell children can be divided into three broad groups; those who on clinical grounds almost certainly do not have a clinically important UTI (no test); those who almost certainly do (test and treat); and the group in the middle for whom there is ongoing uncertainty. Data presented here suggest we may be able to identify some children in the first group (see table 1), but until studies conducted in family physician and general practice settings report both UTI prevalence and the diagnostic value of symptoms and signs, we recommend primary care clinicians adopt a low threshold for urine testing and the use of immediate antibiotics for children testing positive for nitrites or leucocyte esterase, while awaiting culture confirmation.

As to how urine should be sampled, a clean catch approach is always best, especially after cleaning the perineum. Given the absence of clear advantage of the so called pad over bag methods in terms of the risk of contamination, carer or clinician preference and availability and costs of pad or bag should guide the method.

Recommendations for further research

1. How do the presence versus absence of symptoms, signs, and abnormal dipstick urinalysis in preschool children attending primary care with an acute illness correlate with the microbiologically confirmed presence of a recognised urinary pathogen at an adequate concentration?

2. Among preschool children attending primary care with suspected UTI and in whom urine sampling is warranted, what is the effect of of nappy pads, urine bags, or clean catch samples on rates of microbiologically confirmed contamination of urine specimens? (The DUTY study attempts to address both these questions.)

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Table

Table 1| Symptoms and signs and dipstick test results helpful for ruling out urinary tract infection in children <5 years

Clinical signs or symptoms	Age (years)	No of studies	No of children	Prevalence of sign or symptom (%)*	Likelihood ratio (95% CI)	Post-test probability (%)‡	
						Based on 4% prevalence	Based on 7% prevalence
≤2 of: <12 months old; white race; temp ≥39°C; no apparent source of fever; fever for >48 hours	0-2	2[8][9]	1681	NA	0.15 (0.05 to 0.46)[8]; 0.17 (0.10 to 0.46)[9]	0.6; 0.7	1.1; 1.3
Stridor	0-5	1[2]	15 781	1.8	0.20 (0.05 to 0.81)	0.8	1.5
Audible wheeze	0-5	1[2]	15 781	6.4	0.25 (0.13 to 0.48)	1.0	1.8
Circumcised males	0-2	6§[7]	6835	NA	0.33 (0.18 to 0.63)	1.4	2.4
Temp <39°C with a potential source of fever	0-1	1§[7]	945	NA	0.37 (0.16 to 0.85)	1.5	2.7
Abnormal chest sounds	0-5	1[2]	15 781	15.7	0.43 (0.31 to 0.58)	1.8	3.1
Chest crackles	0-5	1[2]	15 781	8.3	0.46 (0.30 to 0.70)	1.9	3.3
Age ≤3 years	0-5	1[2]	15 781	78.5	0.47 (0.37 to 0.61)	1.9	3.4
Did not feel hot	0-5	1[2]	15 781	7.7	0.47 (0.31 to 0.73)	1.9	3.4
Breathing difficulty	0-5	1[2]	15 781	13.7	0.48 (0.35 to 0.66)	2.0	3.5
Dipstick: leucocyte esterase or nitrite negative	0-12	1[11]	246	NA	0.88 (0.71 to 1.1)	3.5	6.2
	0-18	1[12]	243		0.11 (0.04 to 0.28)	0.5	0.8
	0-24	1[14]	491		0.72 (0.55 to 0.94)	2.9	5.1
Dipstick: leucocyte esterase and nitrite negative	0-48	4[10][11][13][14]	4870	NA	0.27 (0.21 to 0.35)	1.1	2.0

*Data on the prevalence of individual features are taken from the study by Craig et al,[2] which enrolled children presenting to an emergency department with fever. Data on the prevalence of features not assessed in this study were not available. Prevalence of these features is likely to vary according to setting.

†The further the likelihood ratio is away from 1 the stronger the evidence for the absence of disease. A likelihood ratio of <0.1 is considered to provide strong evidence to rule out a UTI.[17]

‡Pre-test probabilities (prevalence) selected based on O'Brien et al[3] (4%) and Shaikh et al[1] (7%).

§Studies included in the systematic review by Shaikh et al.[7]