Journal of Paediatrics and Child Health

doi:10.1111/j.1440-1754.2010.01925.x

REVIEW ARTICLE

Diagnosis and management of urinary tract infection in children

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Abstract: A young child presents to their primary health provider with fever and irritability. How likely is a urinary tract infection? How should a urine sample be collected? How accurate are urinary dipsticks and microscopy compared with culture for the diagnosis? What route and type of antibiotics should be used? What imaging is indicated? Diagnosing and treating children with urinary tract infection presents many questions. This review summarises the most relevant recent primary studies, systematic reviews and guidelines.

Key words: prophylaxis; pyelonephritis; urinary tract infection.

Frequency and Clinical Presentation

Urinary tract infection (UTI) occurs in approximately 8% of girls and 2% of boys by 7 years of age.[1] A systematic review of 12 studies of children presenting to emergency departments with fever and no focus showed that approximately 5% of febrile infants (0–2 months) had a UTI.[2] A large Australian study based in a paediatric emergency department[3] identified UTI in 3.3% of children presenting with fever under the age of 5 years.

UTIs can be grouped into asymptomatic bacteruria, cystitis and acute pyelonephritis.

An isolated positive urine culture can be found in children without symptoms (asymptomatic bacteriuria) and should not be treated, because antibiotics may promote symptomatic disease and antibiotic resistance and do not confer any long-term benefit.[4,5] Cystitis occurs when infection is limited to the urethra and bladder; children present with localising symptoms, such as frequency, urgency, dysuria, cloudy urine and lower abdominal discomfort. Pyelonephritis is almost always associated with fever,[6] except in some young infants.[7] On rare occasions, children with UTI can have a negative urine culture, usually in the setting of a renal tract malformation such as an infected cyst or a completely obstructed renal tract, or if they are receiving antibiotic treatment.

Key Points

1. Consider urinary tract infection (UTI) in any child with an unexplained fever or with urinary symptoms.
2. A negative dipstick and/or a normal urine white cell count greatly reduce the likelihood but do not rule out a UTI.
3. Routine prophylactic antibiotics are not justified after a first UTI.
4. A renal tract ultrasound should be done following the first UTI with further imaging contingent upon the ultrasound result.

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Accepted for publication 9 May 2010.

Diagnosis

Sample collection

A recent systematic review of five studies[8] found that clean voided urine samples compared with suprapubic bladder tap showed sensitivity estimates between 75 and 100% and specificity 57% to 100%, and that the concordance between these two methods varied widely. Accordingly, centres may need to determine the performance of voided samples in their own setting before making policy decisions about collection methods. Few appropriate studies are available for pad and nappy collection methods, so their accuracy is uncertain, and contamination rates are higher than alternative methods.[8] Recent guidelines[9] recommend a clean catch sample or, if unobtainable, a urine collection pad, catheter or ultrasound guided suprapubic bladder tap. In practice, clean catch sampling is often the first line collection method with catheter or suprapubic bladder tap collection used if clean catch fails or clinical urgency dictates.

- A urine sample should be obtained by catheterisation, suprapubic bladder tap or clean catch methods in non-toilet trained children

Near patient tests

Dipstick testing of urine is often used to guide early empiric diagnosis and treatment. Systematic review evidence[10] shows that a dipstick has best discriminatory power when interpreted as positive if either leucocyte esterase or nitrite are positive. For example, assuming a 5% prevalence or baseline risk of UTI, when either test is positive, the child would have an 18% probability of UTI and if both results were negative the probability of UTI would be approximately 1%. The predictive

Table 1 Post-test probability of urinary tract infection with varying baseline risk of UTI for the common near patient tests (calculations based on findings in 10.)

	Children with fever (5% baseline risk)		Children who have had 1 previous UTI (20% baseline risk)	
	Positive	Negative	Positive	Negative
	Post test probability of UTI		Post test probability of UTI	
Dipstick				
Leucocyte esterase alone	24	2	72	9
Nitrite alone	56	3	91	18
Leucocyte esterase and nitrite	54	3	90	19
Leucocyte esterase or nitrite	18	1	64	6
Microscopy				
White cell count	22	2	69	11
Bacteria	37	1	82	5
Gram stained bacteria	55	0.3	90	19

UTI, urinary tract infection.

value of tests vary with prevalence, Table 1 provides additional examples as prevalence increases.

Another common screening test for UTI is microscopy for white cells and/or bacteria. Some groups consider the presence of significant numbers of white cells in the urine (pyuria) as necessary for the diagnosis of a UTI.[11,12] However, guidelines[13,14] and recent research studies[15] indicate that pyuria is not required for the diagnosis of UTI. Test performance of pyuria is variable across primary studies, reflecting differing thresholds for positivity, representativeness of participants and quality of reporting. Systematic review[10] results estimate the performance of urine white cell count as very similar to those of leucocyte esterase for both positive and negative results. Microscopy for bacteria has much greater diagnostic discrimination, with positive results showing a similar value to that of nitrite but slightly greater discrimination when results are negative, giving a probability of UTI of about 1%, assuming underlying prevalence of 5% as above.[10,16] A modification of this test to include Gram stain of urine performs even better, with a positive result giving a 55% probability of UTI and a negative result reducing the probability of UTI to 0.3%, using the above assumptions. Despite the apparent better performance of microscopy for bacteria, the most recent guidelines on UTI management[9] recommend microscopy and provide decision structures for interpreting white cell count and unstained bacteria on microscopy in combination. Figure 1 shows a suggested diagnostic flow chart.

- Dipstick testing for nitrite and leucocyte esterase is most useful when results are concordant but false negatives and false positives occur frequently so that a urine culture is always required if a UTI is suspected
- The presence of pyuria is not required for the diagnosis of UTI

Urine culture

UTI is confirmed or excluded based on the number of bacterial colonies grown in culture. The threshold for diagnosis has traditionally varied depending on collection method[13] and in practice also varies across microbiology departments and clinical setting. Table 2 presents an interpretation of AAP guidelines and published literature[10,17]

Acute Treatment

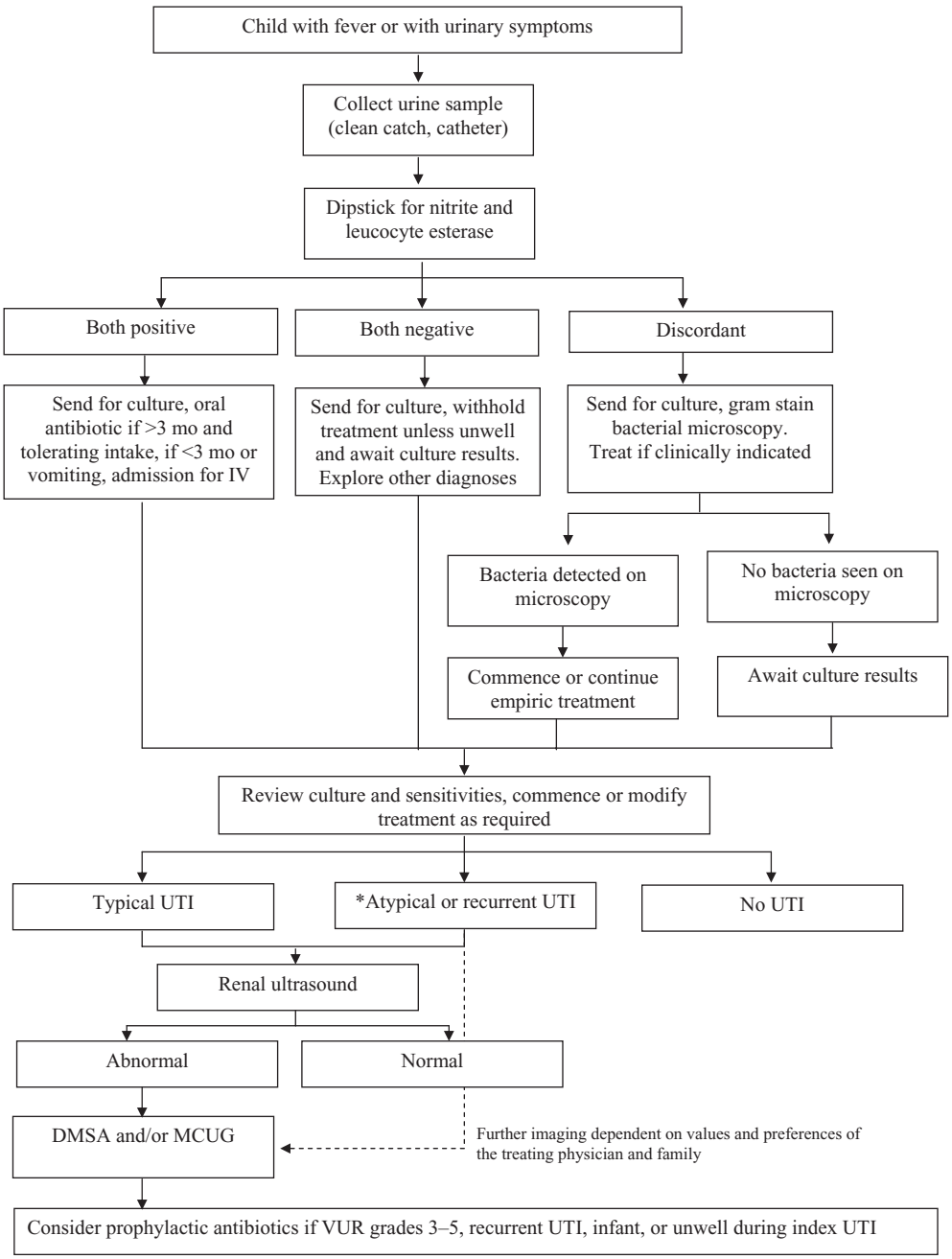
Children 0–3 months

Good quality evidence for treatment choices in very young children is limited because these children are usually excluded from randomised controlled trials. Infants aged 3 months or less with UTI are usually treated with intravenous antibiotics because about 10% have concomitant bacteraemia,[18,19] and the risk of uropathology is probably higher (e.g. posterior urethral valves, obstructed systems)[20] although data on prevalence of uropathies is imprecise. The most likely pathogens in this age group are *Eschericia coli* and *Enterococcus faecalis*, indicating empiric treatment with a beta-lactam antibiotic and aminoglycoside, for example ampicillin and gentamicin, which is the usual empiric choice in the newborn period. Based on current clinical practice, intravenous treatment is usually continued until systemic signs have resolved and followed by an oral antibiotic with a total treatment time of 7–14 days. Evidence to support the duration of therapy is poor and practice will vary. Antibiotic treatment regimens are detailed in Table 3.

- Intravenous antibiotic treatment until afebrile, oral antibiotics for a total treatment duration of 7–14 days

Children >3 months with pyelonephritis

Treatment choices for children over the age of 3 months with clinical pyelonephritis are based on eight randomised controlled trials and summarised in a Cochrane review.[21] This review provides good evidence from three randomised trials (960 children) that oral antibiotics are effective treatment for acute



*Atypical UTI; seriously unwell, poor urine flow, abdominal or bladder masses, raised creatinine, septicemia, failed response to antibiotics, non-*E.coli* organisms

Fig. 1 Diagnostic and treatment flowchart for urinary tract infection in children. VUR, vesicoureteric reflux; UTI, urinary tract infection; IV, intravenous; DMSA, dimercaptosuccinic acid; MCUG, micturating cystourethrogram.

pyelonephritis and this treatment mode is recommended in the most recent guidelines.[9] Admission for intravenous therapy can be limited to seriously unwell (septic appearance) children or those with persistent vomiting. Five trials (534 children) using intravenous antibiotics for 48–72 h followed by oral antibiotics showed no difference in dimercaptosuccinic acid (DMSA) abnormality or resolution of symptoms compared with 7–14 days of intravenous antibiotics.[21] The optimal duration of oral antibiotics for acute pyelonephritis is poorly supported by trial evidence. In clinical practice, between 7 and 10 days of oral antibiotics is usual and similar to the most recent guidelines[9] recommending 7–10 days. Suitable empiric regimens will depend upon local patterns of resistance, local practice regimens are detailed in Table 3.

Table 2 Urine culture microbiological threshold for identifying urinary tract infection

Collection method	Colony forming units per litre	Number of bacterial species	Classification
Voided samples (clean catch, midstream and bag)	$\geq 10^8$	1	Definite UTI
	$\geq 10^7$	1	Probable UTI
	$\geq 10^8$	2	Probable UTI
Catheter samples	$\geq 10^7$	1	Definite UTI
	$\geq 10^6$	1	Probable UTI
	$\geq 10^7$	2	Probable UTI
Suprapubic bladder tap	Any amount	1	Definite UTI
	Any amount	2	Probable UTI

UTI, urinary tract infection.

Table 3 Antibiotics for urinary tract infection, prior to organism identification

Clinical features	Antibiotics
If febrile	Oral cephalexin or Oral trimethoprim-sulphamethoxazole (7–14 days)
If afebrile	Oral cephalexin or Oral trimethoprim-sulphamethoxazole (3 days)
If child aged under 1 month or any age, febrile and/or extremely unwell and not able to tolerate oral	Intravenous ampicillin plus gentamicin (until clinically improved, follow with oral antibiotics until 14 days treatment completed)

Limited data report intramuscular (IM) antibiotic therapy, but suggest no difference between IM plus oral treatment and oral treatment alone.[9]

- Oral antibiotics should be given for 7–10 days unless the child is seriously unwell or unable to take oral antibiotics, in which case intravenous antibiotics are indicated

Children >3 months with cystitis

A large evidence base supports acute treatment options for children with cystitis (22 trials, three systematic reviews[22,23,24]). These data demonstrate that short duration therapy (3–4 days) is as effective as standard therapy (7–14 days) in eradicating urinary bacteria.[22] Single-dose therapy has been less rigorously explored in children and no recommendation can be made. National Institute for Health and Clinical Excellence (NICE) guidelines[9] recommend 3 days of treatment with the choice of antibiotic directed by local guidelines.

- Oral antibiotics for 3–4 days

Renal tract imaging

The aim of renal tract imaging following UTI has been to identify children with abnormalities that increase their risk of recurrent UTI or renal damage. However, identification is only worthwhile if subsequent treatment reduces the risk of further UTI and long-term sequelae. Until recently, little good evidence to support treatment options was available and recommendations for imaging were based on clinical experience and opinion. NICE guidelines[9] suggest reserving imaging for subgroups of children at highest risk of kidney damage and underlying abnormalities. These children include those with atypical UTI, meaning those seriously unwell, with poor urine flow, abdominal or bladder masses, raised creatinine, septicaemia, failed response to antibiotics or non-*E. coli* organisms, as well as children with recurrent UTIs. In practice, Australian paediatricians report that they order renal ultrasounds for most children after first UTI, with micturating cystourethrogram (MCUG) and DMSA scans ordered more selectively,[25] and a trend for much less testing in recent years.[26]

Renal ultrasound is a useful screening test for the detection of obstructive uropathy, and is inexpensive, non-invasive and readily available. MCUG is used to identify vesicoureteric reflux (VUR), which if severe (grades 3–5) has been demonstrated to be a risk factor for repeat UTI[27,28] and the presence or absence of reflux is often used to guide decisions about the need for prophylactic treatment.[29] However, the PRIVENT (Prevention of Recurrent urinary tract Infection in children with Vesicoureteric reflux and Normal renal Tracts) trial[15] demonstrated no difference in treatment effect of prophylactic antibiotics in children with reflux compared with those without. If identification of reflux does not influence management, then a cystogram for all children after first UTI is not justified and recent guidelines do not recommend it..[9] The single clear indication for a cystogram is if ultrasonography demonstrates that obstructive uropathy, because of conditions like posterior urethral valves, is likely. DMSA scan performed soon after acute infection identifies areas of renal parenchymal abnormality assumed to be caused by UTI. Identification of persisting abnormalities is often the basis for repeating the scan one to several years later. DMSA scan is a sensitive test for detecting acute changes in renal parenchyma compared with histopathology (86% sensitivity, 91% specificity[30]). However, short-term studies have demonstrated that many of these abnormalities resolve over time irrespective of whether antibiotic prophylaxis was used.[11,15,27,31] This resolution

over time regardless of treatment suggests little benefit in performing a DMSA after a first infection. Evidence to support imaging practices is generally of low quality and practice is based on what is available. The decision to undertake renal tract imaging should also consider the values and preferences of the treating physician and family. NICE guidelines[9] are complex, with variable recommendations according to age, frequency of UTI and clinical presentation.

A simpler approach would be

- Renal tract sonography in all children
- Micturating cystography and/or DMSA for children with abnormal renal tract sonography.

Preventing UTI recurrence

Approximately 20% of children who have had one UTI experience a symptomatic recurrence.[15,31] Preventing UTI recurrence would avoid further episodes of illness, discomfort and family stress.[6] The likelihood that preventing UTI would prevent clinically important kidney damage is unknown but likely to be very low, given the very low risk of clinically important kidney damage following UTI, and the modest benefit of prophylactic interventions.

Antibiotics

Traditionally, low-dose antibiotics were given to children with reflux or recurrent infections to prevent further infections. Systematic reviews of trials that underpinned this practice demonstrated the inadequacy of the evidence to support the practice.[32,33] Cohort studies of children, followed after UTI, also raised doubt over the effectiveness of treatment.[6] Small inconclusive trials comparing antibiotic prophylaxis with no treatment to prevent UTI continued to be published resulting in increased confusion.[11,31,34,35] In 2009, a large trial of almost 600 children both with and without VUR showed a small benefit in treating children with low dose cotrimoxazole for 12 months compared with placebo.[15] The small reduction in risk of recurrent symptomatic UTI with prophylaxis (from 19% to 13%) should be weighed against the harm of greater bacterial resistance to the prophylactic antibiotic used, in subsequent UTI. The decision to use antibiotic prophylaxis should consider the baseline risk of recurrent UTI, clinical setting and parental factors. It should not be used routinely following uncomplicated UTI[9]

- Antibiotic prophylaxis is not routinely recommended for children after first UTI
- Antibiotic prophylaxis should be considered in children at high risk of serious or recurrent infections – young infants, those with renal tract malformations or recurrent UTI

Reimplantation and endoscopic injection for VUR

A Cochrane review of trials of surgery plus antibiotics compared with antibiotics alone, demonstrated no difference in risk of symptomatic UTI between the groups and no difference in the upper tract outcomes (such as new or worsening kidney damage).[33] There was a small difference in risk of febrile UTIs (a number needed to treat of 15 over 5 years). No new randomised trials have been published since this update, although many case series exist.

- Surgical intervention for reflux could be considered in children with reflux and recurrent febrile UTIs who have failed antibiotic prophylaxis and/or complementary therapies

Circumcision

The Royal Australasian College of Physicians' policy position is that circumcision is not indicated as primary prevention. It could be estimated that between 110 and 140 circumcisions are required to prevent one UTI, while major complications occur in around 2%..[36,37] However, circumcision should be considered in boys with a high risk of recurrent febrile infection, that is boys with previous UTIs and/or high-grade VUR, where the number needed to treat is between 4 and 11, so that the benefits outweigh the risk of adverse effects.

- Circumcision is not recommended after first UTI
- Consider circumcision in boys with recurrent UTI

Complementary therapies

A recent review of trials of complementary therapies, including Vitamin A, probiotics, cranberry, nasturtium and horseradish, methenamine hippurate and UroVaxom showed that most report a treatment benefit.[38] Importantly, however, these studies are generally small, often in sub-groups of people and are frequently poorly reported. Cranberry products have the greatest evidence base for use as prevention of recurrent UTI in women, but little data are available for children. A recent trial of 31 children with reflux,[39] 12 taking cranberry products and 19 cefaclor, demonstrated no difference in rate of recurrent UTI between the groups, but the weak study design (small size, no randomisation or allocation concealment) limits the precision and validity of the findings. While most of these complementary therapy studies suggest a benefit they do not provide assurance of treatment outcome and awareness of further infections should be highlighted.

- Cranberry concentrate may be of some benefit in reducing the risk of UTI

Conclusions

Diagnosis, treatment and follow-up of children with UTI are important issues for general paediatricians and involve multiple decisions. Many steps in the diagnosis and acute care treatment process are well studied and recommendations for sample collection, testing and antibiotic use are possible. Very recent new evidence is available to guide the use of prophylactic treatment but evidence for long-term benefit of renal tract imaging is still lacking.

Acknowledgements

This review was funded by a NHMRC program grant (number 402764). All authors declare no conflict of interest

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