

Urinary tract infections in infants and children: Diagnosis and management

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Recent studies have resulted in major changes in the management of urinary tract infections (UTIs) in children. The present statement focuses on the diagnosis and management of infants and children >2 months of age with an acute UTI and no known underlying urinary tract pathology or risk factors for a neurogenic bladder. UTI should be ruled out in preverbal children with unexplained fever and in older children with symptoms suggestive of UTI (dysuria, urinary frequency, hematuria, abdominal pain, back pain or new daytime incontinence). A midstream urine sample should be collected for urinalysis and culture in toilet-trained children; others should have urine collected by catheter or by suprapubic aspirate. UTI is unlikely if the urinalysis is completely normal. A bagged urine sample may be used for urinalysis but should not be used for urine culture. Antibiotic treatment for seven to 10 days is recommended for febrile UTI. Oral antibiotics may be offered as initial treatment when the child is not seriously ill and is likely to receive and tolerate every dose. Children <2 years of age should be investigated after their first febrile UTI with a renal/bladder ultrasound to identify any significant renal abnormalities. A voiding cystourethrogram is not required for children with a first UTI unless the renal/bladder ultrasound reveals findings suggestive of vesicoureteral reflux, selected renal anomalies or obstructive uropathy.

Key Words: Bacteremia; Cefixime; Cystitis; Gentamicin; Pyelonephritis; Pyuria; Sepsis; UTI; VUR

Urinary tract infections (UTIs) are a common cause of acute illness in infants and children. Guidelines and recommendations on management of UTI were last published by the Canadian Paediatric Society (CPS) in 2004.(1) Since then, meta-analytic reviews investigating the utility of diagnostic tests, radiological assessment and randomized control treatment trials have been published.(2-5) In 2011, the American Academy of Pediatrics markedly revised its clinical practice guideline for diagnosing and managing initial febrile UTI in young children.(6)

The present statement focuses on the diagnosis and management of infants and children >2 months of age with an acute UTI and no known underlying urinary tract pathology or risk factors for a neurogenic bladder. Many of the recommendations for children >3 years of age and all recommendations for managing lower UTIs (cystitis) are based on expert opinion alone because studies are lacking. For infants <2 months of age with a febrile illness, bacterial sepsis must be considered, leading to a different approach to investigation and management. Children with recurrent UTIs, renal abnormalities or pre-existing major medical problems should be managed individually because these patients may require more extensive investigation, and more aggressive therapy and follow-up. A subsequent statement will address antibiotic prophylaxis of UTIs.

Le diagnostic et la prise en charge des infections urinaires chez les nourrissons et les enfants

De récentes études ont suscité des changements majeurs dans la prise en charge des infections urinaires chez les enfants. Le présent document de principes porte sur le diagnostic et la prise en charge des nourrissons et des enfants de plus de deux mois atteints d'une infection urinaire aiguë, sans affection sous-jacente connue des voies urinaires ou facteurs de risque de vessie neurogène. Il convient d'écartier la possibilité d'infection urinaire chez les enfants atteints d'une fièvre inexplicquée qui ne savent pas encore parler et chez les enfants plus âgés ayant des symptômes évocateurs de ce type d'infection (dysurie, urgences mictionnelles, hématurie, douleur abdominale, douleur lombaire ou nouvelle incontinence diurne). Chez les enfants qui sont propres, il faut faire un prélèvement d'urine à mi-jet pour analyse et culture. Chez les autres, le prélèvement par cathéter ou par ponction sus-pubienne est préconisé. L'infection urinaire est peu probable si l'analyse d'urine est complètement normale. La collecte d'urine dans un sac peut être utilisée pour analyse, mais pas pour culture. Une antibiothérapie de sept à dix jours est recommandée en cas d'infection urinaire fébrile. Si l'enfant n'est pas gravement malade et qu'il est susceptible de recevoir et de tolérer chaque dose, on peut lui donner un traitement initial d'antibiotiques par voie orale. Il faudrait soumettre les enfants de moins de deux ans à une échographie des reins et de la vessie après leur première infection urinaire fébrile, afin de détecter toute anomalie rénale d'importance. Lors d'une première infection urinaire, la cysto-urétrographie mictionnelle (CUGM) est inutile, à moins que l'échographie des reins et de la vessie ne donne des résultats évocateurs d'un reflux vésico-urétéral, de certaines anomalies rénales ou d'une uropathie obstructive.

Incidence of UTI

In a 2008 systematic review, approximately 7% of children two to 24 months of age presenting with fever without a source and 8% of children two to 19 years of age presenting with possible urinary symptoms were diagnosed with a UTI.(7) Occurrence rates varied widely depending on age, sex and race. The rate in uncircumcised febrile boys <3 months of age was 20.7% compared with 2.4% in circumcised boys, declining to 7.3% and 0.3%, respectively, in boys six to 12 months of age. However, contamination is very common in obtaining a urine sample from a male when the foreskin cannot be retracted and the rates in uncircumcised males are, undoubtedly, overestimates. In febrile girls, approximately 7.5% <3 months of age, 5.7% three to six months of age, 8.3% six to 12 months of age and 2.1% 12 to 24 months of age had a UTI as the cause of their fever.(7)

Diagnosis of UTI

Clinical features

As previously recommended by the CPS, a urinalysis and urine culture should be obtained from children <3 years of age with a fever (>39.0°C rectal) with no apparent source.(1) A child with rhinitis, cough, wheezing, rash or diarrhea is likely to have a viral infection as the source of fever and need not be investigated for a UTI.

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TABLE 1
Sensitivity and specificity of components of urinalysis, alone and in combination

Test	Sensitivity	Specificity
LE	83 (67–94)	78 (64–92)
NT	53 (15–82)	98 (90–100)
Either LE or NT positive	93 (90–100)	72 (58–91)
Microscopy, WBCs	73 (32–100)	81 (45–98)
Microscopy, bacteria	81 (16–99)	83 (11–100)
LE, NT or microscopy positive	99.8 (99–100)	70 (60–92)

Data presented as % (range). LE Leukocyte esterase; NT Nitrite; WBCs White blood cells. Reproduced with permission from Pediatrics, volume 128, pages 595-610, copyright 2011 by the American Academy of Pediatrics

Although positive urine cultures occur with bronchiolitis, it is probable that most positive urine cultures in infants >2 months of age with bronchiolitis are caused by contamination or asymptomatic bacteruria.(8) The incidence of UTI without fever in preverbal children is not known but positive urine cultures in afebrile young children are much more commonly due to contamination than to UTI. For children ≥ 3 years of age, the presence of urinary symptoms (dysuria, urinary frequency, hematuria, abdominal pain, back pain or new daytime incontinence) can be used as a criterion for requesting a urinalysis and culture.(9) Be wary that prepubertal girls can develop dysuria and a red vulva from poor hygiene or exposure to bubble bath or other irritants;(10) urine cultures will be sterile but this problem is often inappropriately treated as a UTI.

Systematic reviews of the diagnostic accuracy of clinical examination and urinalysis in diagnosing UTI have been published.(10,11) They show that infants with a fever $>39^{\circ}\text{C}$ for >48 h without another source for fever on examination are highly likely to have a UTI. Some studies have proposed a predictive rule for ruling out UTI in girls <24 months of age based on the following features: age <12 months, white race, temperature $>39^{\circ}\text{C}$, fever for >2 days and absence of another source of infection. When there are *no more than one* of these features, the risk for UTI is $<1\%$.(6,12,13) It is unusual for males to have their first UTI after three years of age in the absence of instrumentation of the urinary tract.

Sampling urine

Obtaining urine samples from children who are not toilet trained involves urethral catheterization,(14) suprapubic aspiration (SPA), use of a paediatric urine collection bag or leaving the child with the diaper off and obtaining a clean-catch urine when the child voids. Although collecting urine using a bag for urinalysis is simple and noninvasive, bag samples have a high a rate of contamination (up to 63%), making culture results unreliable for diagnosis of UTI.(15) In some hospital and clinic settings, a bag specimen is used as an initial screen and a subsequent specimen is obtained by catheterization or SPA if the urinalysis is abnormal. For toilet-trained children, a midstream urine sample should be collected. Asking little girls to sit backward on the toilet seat spreads the labia and may prevent contamination. It appears that perineal cleansing may not be necessary before collection of midstream urine,(15) presumably because the first drops of urine wash away contaminants.

Interpreting urinalysis

Rapid urine tests (also known as dipsticks or macroscopic urinalysis) remain useful for diagnosis of UTI. The nitrite test measures the conversion of dietary nitrate to nitrite by Gram-negative bacteria. A positive nitrite test makes UTI very likely (Table 1), but the test may be falsely negative if the bladder is emptied frequently or if an organism that does not metabolize nitrate (including all Gram-positive organisms) is the cause of infection. The leukocyte esterase test is an indirect measure of pyuria and, therefore, may be falsely

TABLE 2
Minimum colony counts that are indicative of a urinary tract infection

	CFU/mL	CFU/L	Comments
Clean catch (midstream)	$\geq 10^5$	$\geq 10^8$	Mixed growth is usually indicative of contamination. Sitting a girl backward on the toilet is a good way to spread the labia when collecting midstream urine
In and out catheter specimen*	$\geq 5 \times 10^4$	$\geq 5 \times 10^7$	Mixed growth is usually indicative of contamination. Specimens from indwelling catheters are less reliable
Suprapubic aspiration	Any growth	Any growth	

*Some laboratories report only to the nearest log; therefore, clinical judgment must be applied for reports of growth of $>10^4/\text{mL}$ or $>10^7/\text{L}$.(6) CFU Colony-forming unit

negative when leukocytes are present in low concentration. A microscopic urinalysis is useful to determine whether there are white blood cells in the urine, which is a sensitive indicator of inflammation associated with infection. Table 1 shows that pyuria is 73% sensitive and 81% specific for diagnosis of UTI. However, the definition of pyuria is not uniform in the literature. The finding of 10 white blood cells per microliter in uncentrifuged urine specimen is reported to be a more sensitive indicator of UTI, but most centres in Canada report the number of white blood cells per high-power field (with >5 being abnormal). Common teaching is that absence of pyuria does not exclude a UTI, especially in infants <2 months of age. However, it has also been argued that febrile UTIs should always result in pyuria, bringing into question whether many infants with positive urine cultures but no pyuria have contamination or asymptomatic bacteruria rather than a UTI.(6) Bacteria and yeast seen on microscopic urinalysis are often contaminants. Debris is sometimes confused with bacteria on an unstained specimen, but the combination of pyuria and bacteruria on urinalysis should raise suspicion for a UTI.(11) According to published literature, a child with a negative urine dipstick for nitrites and leukocyte esterase and no pyuria or bacteruria on microscopic examination has a $<1\%$ chance of having a UTI (Table 1).(6)

Interpreting urine cultures

Urine collection must occur before starting antibiotics because a single dose of an effective antibiotic rapidly sterilizes the urine. For children who are not toilet trained, only urethral catheterization and SPA are considered to be reliable methods for specimen collection for the purpose of culture.(16) A negative bag culture rules out a UTI but a positive result is not useful. See Table 2 for interpretation of urine cultures. However, strict definitions of colony count criteria are operational and not absolute; in rare circumstances, low colony counts can be indicative of a UTI.(6) In previously well children who have not been on antibiotics, UTIs are usually due to *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Citrobacter* species, *Serratia* species or, in adolescent females only, *Staphylococcus saprophyticus*. It is controversial whether enterococci commonly cause UTIs in previously healthy children with no history of recent antibiotic exposure.(17) Mixed growth or growth of other organisms usually indicates that the urine is contaminated.

Other investigations

There is no evidence that documentation of bacteremia in children with UTIs should influence therapy. Blood cultures need not be performed when the diagnosis of UTI is clear unless the child is hemodynamically unstable. Renal function should be monitored when the child has a complicated UTI (see below) or is treated with aminoglycosides for >48 h.

Reassessment when urine culture results are available

When children are started on antibiotics for possible UTI, the diagnosis must be reassessed once the results of all investigations are available and antibiotics stopped if UTI appears to be unlikely.

Treatment of UTI

A series of reports on the treatment of pyelonephritis and the long-term risk of renal scarring has shed new light on treatment strategies.(3,4,18) The risk of permanent renal damage due to acute pyelonephritis in children with normal kidneys is believed to be very low,(19-21) and the need for routine intravenous (IV) antibiotics has been questioned. A Cochrane review of children up to 18 years of age with pyelonephritis found no difference between oral antibiotics (10 to 14 days) and IV antibiotics (three days) followed by oral antibiotics (10 days) with respect to duration of fever or subsequent renal damage. Similarly, no significant differences were found comparing IV antibiotics (three to four days) followed by oral antibiotics, versus IV antibiotics alone for seven to 14 days. (3) Based on these studies, most experts recommend initial treatment with oral antibiotics for febrile UTIs in nontoxic children with no known structural urological abnormality, assuming that they are likely to receive and tolerate every dose.(22) Data on oral therapy is limited for infants two to three months of age, so close follow-up is warranted for this age group. Some experts recommend initial IV antibiotics for this age group.

While waiting for antibiotic susceptibility results for the likely bacterial pathogen, clinicians should make an empirical choice of antibiotics based on local susceptibility patterns.(23) Annually updated susceptibility patterns for community-acquired *E coli* infections should be sought from valid Internet or local microbiology laboratories. The least broad-spectrum antibiotic option should be used. Currently, cefixime is a good choice in most areas. For patients requiring hospitalization, a common IV choice is gentamicin, with or without ampicillin. Clinicians sometimes favour using cefotaxime or ceftriaxone because they are less nephrotoxic than gentamicin, but these cephalosporins are broader spectrum (see Table 3 for dose recommendations). Therapy should be modified to the narrowest spectrum antimicrobial when susceptibility results become available, but it is not necessary to switch outpatients to a different oral antibiotic if the isolate is susceptible to the one that they are on. Aminoglycoside levels and renal function need to be monitored when the aminoglycoside is continued for >48 h.

UTI without fever is usually a lower tract infection (cystitis). Cystitis occurs mainly in postpubertal girls and presents as dysuria and urinary frequency. There are a paucity of studies, but a two- to four-day course of oral antibiotics based on local community-acquired *E coli* susceptibilities is likely to be effective.(24)

When to be concerned that a child has a complicated UTI

Children should receive more extensive assessment when they are hemodynamically unstable, have an elevated serum creatinine level at any time, have a bladder or abdominal mass, have poor urine flow, or are not improving clinically within 24 h or fever is not trending downward within 48 h of starting appropriate antibiotics.(5) A clinician would usually start with a renal and bladder ultrasound (RBUS) to look for obstruction or an abscess. IV rather than oral antibiotics are indicated for complicated UTIs until the child is clearly improving.

What should one do if a multiresistant organism is isolated in urine?

It is increasingly common to isolate an organism that is resistant to the empirical antibiotics that were chosen, even when the child has not previously been on antibiotics. Often the susceptibility

TABLE 3
Antibiotics commonly used to treat urinary tract infections (UTIs) in children two months of age and older, if the isolate is susceptible

Parenteral antibiotics	
Drug	Dosage per day
Ampicillin	200 mg/kg IV/day (divided every 6 h)
Ceftriaxone	50–75 mg/kg IV/IM every 24 h
Cefotaxime	150 mg/kg/day IV (divided every 6 h or 8 h)
Gentamicin	5–7.5 mg/kg IV/IM once per day
Tobramycin	5–7.5 mg/kg once per day
Oral antibiotics	
Drug	Dosage per day
Amoxicillin	50 mg/kg/day (divided in three doses)
Amoxicillin/clavulanate	(7:1 formulation) 40 mg/kg/day (divided in three doses)
Co-trimoxazole	8 mg/kg/day of the trimethoprim component, divided in two doses (0.5 mL/kg/dose)
Cefixime	8 mg/kg/day (given as a single dose)
Cefprozil	30 mg/kg/day (divided in two doses)
Cephalexin	50 mg/kg/day (divided in four doses)
Ciprofloxacin*	30 mg/g/day (divided in two doses)

*The initial choice of antibiotic should be guided by knowledge of local resistance patterns. Cefixime is a common choice for a first febrile UTI, pending susceptibilities. *Not licensed for use in prepubertal children; IM Intramuscular; IV Intravenous*

pattern of the isolate is limited to antibiotics that cannot be given orally or to quinolones, which are not licensed for use in prepubertal children. Quinolone antibiotics should not be used routinely but may be appropriate if the organism is resistant to other oral antibiotics. Commonly, too, the child has shown marked clinical improvement on treatment by the time susceptibilities become available.(25) It is not clear whether clinical improvement is because the organism is susceptible to the high concentration of antibiotic that is achieved in the urine or because the urine was contaminated initially. If the child is now asymptomatic, one approach would be to repeat the urinalysis and urine culture and change therapy only if results are suggestive of a persistent UTI, keeping in mind that even a repeat positive urine culture may be contaminated. If the child remains symptomatic, urinalysis and urine culture should be repeated and the antimicrobial modified pending results.

Imaging: What imaging studies should be performed, and when?

Children with suspected cystitis do not require imaging. Major objectives for conducting diagnostic imaging studies during or after a febrile UTI are to confirm that the child had pyelonephritis and to identify whether severe vesicoureteral reflux (VUR) or structural anomalies are present. Imaging should only be performed when it is likely to alter management. The choice of imaging should be guided by the safety, cost and accuracy of the procedure to be done. In the past, a voiding cystourethrogram (VCUG) was recommended routinely for children between two months and two years of age who had a febrile UTI,(26) but this is no longer recommended practice.

Imaging options

Current common imaging options for children with UTI include renal/bladder ultrasound (RBUS), radiographic (eg, VCUG) and radioisotope (eg, dimercaptosuccinic acid [DMSA]) techniques. At the time of the first acute infection, clinicians will be concerned as to whether the child is predisposed to recurrent urinary infection, because of kidney stones or anatomical anomalies of the kidney, ureter or bladder, which may cause VUR or urinary stasis.

Antibiotic prophylaxis pending results of imaging is no longer advised routinely.

RBUS has become a standard tool for evaluating children <2 years of age with a first febrile UTI during or within two weeks of their acute illness (where practical) because it is convenient, inexpensive and less invasive than VCUG.(27) RBUS reliably detects hydronephrosis, which usually occurs with high grade (grade IV or V) VUR. In one study, 12 of 14 children (86%) with grade IV or V VUR were identified by RBUS alone.(28) Although RBUS is less sensitive at diagnosing grades I to III VUR, many experts question the importance of VUR at these grades because most low-grade VUR resolves spontaneously.(19) RBUS has the advantage of being readily available, radiation free and non-invasive. Thus, RBUS alone is an attractive alternative to performing a VCUG after the first episode of febrile UTI. It is controversial whether there is a need to obtain a RBUS if a high-quality ultrasound reported by an expert can be documented to have shown a normal fetal urinary tract late in pregnancy.(29)

A VCUG is the optimal method for diagnosing VUR and for assessing the degree of VUR and the anatomy of the male urethra. There are several drawbacks to performing a VCUG including expense, exposure to radiation, the risk of causing a UTI and discomfort for the child. A recent change in practice is that antibiotic prophylaxis is no longer recommended for children with grade I through III VUR because the number needed to prophylax for one year to prevent one UTI is probably >10.(30) Therefore, routine imaging of infants with VCUG after the first UTI is no longer suggested unless RBUS is suggestive of selected renal abnormalities or obstruction, or high-grade VUR;(5,28,31) a child with normal kidney structure is not at significant risk of developing chronic kidney disease because of UTIs. A VCUG is usually indicated for children <2 years of age with a second well-documented UTI. Although a VCUG is often postponed until the child finishes antibiotics, there is no evidence that this delay is necessary. It is controversial whether antibiotic prophylaxis is indicated for a VCUG.(5,32)

Where available, a nuclear cystogram (NCG) may be used in place of a VCUG to assess for VUR using radioisotopes. NCG delivers less radiation than a VCUG but is less readily available and provides poor anatomical detail for the male urethra; thus, it can miss posterior urethral valves. It is logical to use NCG in place of VCUG as the initial test for VUR investigation in females and in follow-up studies for both sexes.

A DMSA scan can be used to diagnose acute pyelonephritis (when performed during acute illness) and to identify renal scars (when performed months following the acute illness).(19,33) This method requires exposure to radiation and is not likely to alter management; thus, a DMSA is primarily useful when the diagnosis of acute UTI or of repeated UTIs is in doubt.

Recommendations for physicians:

- Infants from two to 36 months of age with a fever of >39°C and no other source for fever on history or physical examination could have a UTI, and should have urine collected for urinalysis. Unless this test is completely normal, they should then have urine collected by catheter or suprapubic aspirate sent for culture. The present statement does not apply to infants <2 months of age.
- When UTI is suspected in toilet-trained children, a midstream urine sample rather than a catheter or SPA specimen should be submitted for urinalysis and culture.
- Children with possible UTI who require antibiotic treatment immediately for other indications, such as suspected bacteremia, should have urine collected for urinalysis,

microscopy and culture. The test sample should be midstream urine if the child is toilet trained, and a catheter or SPA or clean-catch specimen if not, and obtained before starting antibiotics. Overdiagnosis of UTI is a common problem, leading to overuse of antibiotics and unnecessary imaging. Urines collected by bag should never be used for diagnosis of UTI. Urines with low colony counts, mixed growth or no pyuria are usually contaminated.

- Infants and children with febrile UTI should be treated with antibiotics for seven to 10 days. Oral antibiotics can be administered as initial treatment when the child has no other indication for admission to hospital and is considered likely to receive and tolerate every dose. There is no evidence that children with UTIs and documented bacteremia who have a rapid clinical response to antibiotics require intravenous antibiotics or a longer course of antibiotics. However, all such children need to be assessed by a physician the day that the blood culture is known to be positive. The choice of antibiotic should be guided by the resistance pattern of common urinary pathogens in the community and changed to a less broad spectrum agent, if practical, when the sensitivity of the pathogen is known.
- Children <2 years of age should be investigated after their first febrile UTI with a renal and bladder ultrasound (RBUS) to identify significant renal abnormalities and grade IV or V VUR. A voiding cystourethrogram (VCUG) is not indicated with a first febrile UTI when the RBUS is normal.
- Antibiotic prophylaxis is no longer recommended for grades I through III VUR or pending results of the initial RBUS.
- Children with grade IV or V VUR or a significantly abnormal RBUS should be discussed with a paediatric urologist or nephrologist to determine whether there is an urgent need for a consult and make the best plan for further investigation and management.
- Parents of all children with febrile UTIs, with or without VUR, should be advised that their child needs to be assessed for the possibility of recurrent UTI early in the course of any unexplained fever. Such guidance is especially pertinent in this era, where very few children are on prophylactic antibiotics for UTIs.
- For older children with no fever and presumed cystitis, a two- to four-day course of oral antibiotics is usually adequate.

Future research needs for optimal management of UTI in children:

- Long-term cohort studies to establish the relationship between UTI in infants and young children and reduced renal function and hypertension in adults.
- Less invasive techniques for diagnosis of VUR and better understanding of the contribution of VUR and other risk factors to the development of renal function abnormalities.
- Assessment of optimal treatment strategies (length of therapy, choice of antibiotics) for febrile UTIs and for older children with cystitis.
- Management strategies for infants <2 months of age with UTIs.

Note: Information for parents, 'Urinary tract infections', can be accessed at www.caringforkids.cps.ca

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