Urinary tract infections in children

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Abstract

Urinary tract infection (UTI) is a common bacterial infection that can affect infants and children. The severity of illness depends on microbial virulence and host susceptibility.

It has a number of different ways to manifest itself clinically ranging from a mild cystitis to a presentation with systemic symptoms such as a nonspecific fever, vomiting, failure to thrive or irritability or with significant dehydration and electrolyte imbalance which can be seen in infants in the first 3 months of life. It is therefore a ubiquitous differential diagnosis in many children presenting both in primary care and in the hospital setting.

In most children urinary infections are isolated acute infections from which they recover quickly. In a small minority of children urinary infections can be associated with underlying significant pathology: either they are associated with congenital renal tract malformations such as renal dysplasia and/or hydronephrosis or if they have recurrent infections this may lead to renal scarring, particularly if the infections are associated with systemic symptoms.

Keywords acute pyelonephritis; bladder function; constipation; cystitis; fever; non *Escherichia coli* urine infection; renal scarring; urine infection; uropathogenic *Escherichia coli*

Key points

- Urine for microscopy and culture should not be collected by bag or pad; a clean catch sample should be obtained with the option in hospital of a catheter or suprapubic sample.
- Infections with non *Escherichia coli* UTIs are associated with increased risk of underlying obstructive structural abnormalities.
- Clinical features inform the decision as to which children need renal imaging.
- Children with recurrent UTIs should have a basic clinical assessment of bladder function.
- Genetic differences in innate immunity and uropathogens virulence factors play a key role in the risk of acute pyelonephritis.

Definition

The definition of a urinary tract infection consists of **bacteriuria in the presence of symptoms**. Bacterial growth of more than 10^5 is regarded as the threshold number for a significant bacterial growth; however, the evidence base for this threshold is weak. There is evidence that infants may have urine infections with lower bacterial counts. Although in most instances there is also pyuria this may sometimes be absent. Asymptomatic bacteriuria needs no treatment or investigation.

Causative organisms and host response

The bacteria that cause urinary tract infections originate from gut and perineal flora. The urinary tract is kept sterile by a normal urine flow and the innate (or nonspecific) local immune system. The ability of bacteria to cause urinary infections depends on bacterial virulence factors as well as host factors. Uropathogenic *E. coli* (UPEC) have specific virulence factors which enable them to attack the uroepithelium, one of these is the possession of P fimbriae which increase bacterial adhesion to the mucosa and facilitate its exposure to bacterial toxins. UPEC are cause 70–90% of community acquired urinary tract infections. Following mucosal adhesion the innate immune response is stimulated and various families of Toll like receptors (TLRs) play a key role in the activation of transcription factors, and production of a variety of cytokines, interferons and their regulatory factors. The degree of renal damage has been found to be correlated to high blood and urinary levels of various cytokines, for example Interleukin 6 (IL-6), which induces fever, stimulates hepatocyte production of C reactive protein and acts on the urothelium to produce IgA antibodies. Over the last few years it has become increasingly clear that there is genetic variation in innate immunity, e.g. affecting the expression and function of TLRs, Interferon Regulator Factor 3 (IRF3) and IL-8 receptors, resulting in clinical differences in the host response ranging from being able to tolerate bacteria asymptomatically (asymptomatic bacteriuria) to mounting a severe inflammatory response resulting in acute pyelonephritis. The familial occurrence of recurrent UTI has been known about for some time and may be explained by this type of genetically transmitted defects in single proteins involved in the innate immunity of the uroepithelium to uropathogens. Most children with UTI do not have underlying structural abnormalities and this area of study, which is already seeing major expansion, should provide in the future the tools for identifying children at risk of renal damage as well as enabling the development of specific biological agents to prevent recurrent UTI.

Other bacteria are other coliforms such as Klebsiella as well as organisms such as *Proteus mirabilis*, Pseudomonas, coagulase negative Staphs, Streptococci (e.g. Group B strep, Enterococci), *Staphylococcus aureus* and occasionally *Haemophilus influenzae* as well as others. These non *E. coli* organisms often do not possess the aforementioned virulence factors seen in UPEC and it has been shown that their ability to cause urinary infections depends heavily on the presence of host factors, particularly structural urinary tract abnormalities leading to urinary stasis. Therefore, one of the indications for investigating the urinary tract in children is the type of organism involved in the infection.

Incidence and epidemiology

Reliable measurements of the incidence of UTI in children have been difficult. Epidemiologically strong studies from Sweden

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have reported that around 2% of boys and girls aged less than 2 years have a UTI. Based on evidence extracted from Swedish and UK data, approximately 10% of girls and 3% of boys will have had a UTI before the age 16 years. In infancy, the incidence of UTI in the under 3 months of age is higher in boys most probably reflecting a higher incidence of obstructive congenital urogenital abnormalities in males. After this age, girls have a higher incidence of UTI. Girls are more likely to have recurrences of UTI.

Clinical presentation and differential diagnosis

The clinical presentation can be divided into two types. In a lower tract UTI or cystitis the symptoms are confined to the bladder and consist of dysuria, frequency, incontinence, urgency of micturition and abdominal pain. An upper tract UTI or 'acute pyelonephritis' is defined by the presence of fever ($\geq$38 °C) or other systemic symptoms such as loin pain or vomiting and in infants typically failure to thrive or persistent irritability. Babies under 3 months of age can occasionally present with dehydration, hyponatraemia and hyperkalaemia mimicking the findings in congenital adrenal hyperplasia. The symptoms in the very young children particularly infants are nonspecific and it is safer to assume that they are upper tract in nature.

The diagnosis needs to be confirmed by obtaining a urine specimen which is sent for culture but this is difficult in children still in nappies. Febrile children should be assessed using the 'traffic light system' of the NICE fever guideline and it is recommended that in those with nonspecific fever regardless of the severity of illness should have a urinalysis.

Large numbers of young children present with nonspecific symptoms to primary care and the DUTY study hopes to create an algorithm of presenting symptoms and signs to help select which children should have a urine sample taken.

Urine analysis

There is a significant risk of contamination of the urine sample if urine bags are used and this is slightly less when pads are used and changed every 30 minutes. The gold standard is a suprapubic aspiration (SPA) with ultrasound guidance although recent evidence shows that urethral in out catheterization yields reliable results and is better tolerated. These techniques require training and they are not feasible in primary care. Therefore the best and most practical way to try to obtain a noncontaminated sample is by clean catch and this should be possible in the community. Urine dipsticks with reagent strips to look for the presence of nitrite and leucocyte esterase are useful particularly to rule out UTI, they can be useful to rule in UTI but the likelihood ratios are less. They are unreliable in children under 2 years. There is not enough data on how reliability changes as the child gets older and NICE recommends that children under 3 years should have urgent microscopy rather than urine dipstick for the rapid diagnosis of UTI.

Antibiotics should be started after sending the sample to the laboratory if the dipstick is nitrite positive or bacteria are seen on microscopy. If the dipstick is leucocyte positive or if there is only pyuria on microscopy, the sample should be sent to the laboratory and the decision to start empirical antibiotic treatment for UTI should be based on the clinical findings and the severity of illness. Isolated pyuria can occur in febrile children due to infections, viral or bacterial, other than UTI. In situations when the dipstick is negative for both nitrite and leucocyte esterase but the symptoms point to a UTI, the sample should be sent to the laboratory and the question of empirical treatment with antibiotics prior to the culture results depends on the severity of illness. Febrile children should be assessed according to the NICE fever guideline and careful assessment of very young infants with possible UTI should include a decision about ruling out an associated meningitis in severe ill infants. This is a rare complication.

Management and treatment of UTI

Infants under 3 months with a suspected diagnosis of UTI should be assessed by paediatricians.

The history and examination on all children with confirmed UTI should be recorded and should include the following:

- temperature
- hydration
- history suggesting previous UTI or confirmed previous UTI
- recurrent fever of uncertain origin
- antenatally-diagnosed renal abnormality
- family history of vesicoureteric reflux (VUR) or renal disease
- constipation
- dysfunctional voiding including urine flow
- enlarged bladder
- abdominal mass
- evidence of spinal lesion
- growth
- blood pressure

The vast majority of UTIs in children older than 3 months can be treated orally. Children with cystitis/lower tract symptoms can be treated with a 3 day course of antibiotic. Common and useful antibiotics are trimethoprim, nitrofurantoin (should not be used in AP/upper tract UTI), cephalexin or co-amoxiclav. The resistance of *E. coli* to amoxicillin is currently too high for this antibiotic to be recommended as a first line antibacterial. The choice of antibiotic should ideally be agreed along joint guidelines with the local microbiology department. This is particularly important to contain the emergence of increasingly resistant bacteria. Children with AP/upper tract infection can be treated with a 7–10 days course of oral antibiotics. Exceptions to the initiation of oral therapy include vomiting, evidence of circulatory shock, or the presence of known potential obstruction such as hydronephrosis. Continuing fever at the end of 48 hours in spite of suitable antibiotics should be investigated with at least a repeat urine culture and an ultrasound of the renal tract as urinary obstruction can be a cause for failure to respond to antibiotics. There is no indication for the routine use of antibiotic prophylaxis.

Prevention of UTI

There have been many studies on a variety of interventions to try and prevent UTI in children including antibiotic prophylaxis, cranberry juice, probiotics, circumcision, Vitamin A, etc. The role of antibiotic prophylaxis has been questioned by a number of meta-analyses; it may confer a small protective effect in girls with recurrent infections and VUR. Proanthocyanidin-A present in cranberry juice, inhibits bacterial adhesion to uroepithelial cells,