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Febrile Urinary Tract Infections in Children Less Than 2 Years of Age

Pavel Geier and Janusz Feber
Division of Nephrology, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Canada

1. Introduction

Urinary tract infection (UTI) is a common disease in children. In older children the clinical symptoms, diagnostic approach and treatment are similar to adults, whereas infants and neonates present with less specific symptoms. Children post renal transplantation/on immunosuppressive medication may also present with atypical symptoms. Therefore in this chapter we will focus on acute febrile urinary tract infections in young children (aged 2 months to 2 years) and in children post renal transplantation (Tx).

2. Definition

Based on clinical symptoms, UTI's can be divided into three different groups: asymptomatic bacteriuria (ABU), lower UTI (cystitis) and acute pyelonephritis (AP). AP is an infection of the kidney parenchyma and is the most severe form of UTI. In high risk populations (young children, Tx recipients) the AP can cause significant permanent kidney damage resulting in kidney function impairment (Rintaro Mori et al. 2007; Silva et al. 2010; Ramlakhan et al. 2011).

3. Epidemiology

The exact prevalence of UTI's is difficult to assess due to heterogeneity of studies, which includes children of variable ages and genders. The prevalence of UTI's among febrile young children presenting to the emergency department varies between 3.3 and 5.3% (Hoberman et al. 1993; Shaw et al. 1998).

In contrast, the prevalence of febrile UTI in patients post Tx is much higher reaching 15-33% (John & Kemper 2009).

4. Clinical symptoms

High-grade fever is a common symptom of AP. Loin pain, dysuria and urinary frequency may be present, but in young children these symptoms are difficult to discern. Young children can present with only non specific symptoms such as irritability, vomiting, diarrhea and failure to thrive (Clark et al. 2010).

In young children a high grade fever (> 38°C) was found in 83% of patients diagnosed with AP, followed by poor feeding (28%), diarrhea (25%) and failure to thrive (15%) (Kanellopoulos et al. 2006). In children post Tx the most common clinical symptoms are fever, malaise, graft pain and impaired kidney function (John & Kemper 2009).

5. Diagnosis

An early and accurate diagnosis of AP in young children is very important but can be difficult. Delayed diagnosis and/or inadequate treatment of AP may increase the risk of possible permanent kidney damage (Fernández-Menéndez et al. 2003). On the other hand, a false diagnosis of AP may lead to invasive diagnostic imaging and unnecessary treatment without any benefit to the patient (Anon 1999).

The diagnosis of AP is based on a positive urine culture (Mori et al. 2007; Anon 1999); therefore it is crucial to obtain a reliable urine sample for microbiology. The clean-catch urine sample (midstream urine) is appropriate in toilet-trained children, but may be difficult in younger children. In these patients, reliable urine samples can be obtained either by urine catheter or by suprapubic aspiration (SPA). However, both these methods are invasive and should be performed by skilled personnel (Clark et al. 2010). Therefore, an individualized or stepwise approach is recommended. If a child with symptoms suggesting AP is septic and requires immediate antibiotic treatment, the bladder catheterization or SPA is necessary. If however the patient with symptoms of UTI is not severely sick, a urine sample can be obtained by the most convenient method (for example adhesive urine bag) and sent for urinalysis and microscopy. If this urine sample is negative for leukocyte and nitrites, the likelihood of UTI is low (Mori et al. 2010; Ramlakhan et al. 2011); if however leucocytes and/nitrites are detected, a second urine sample should be obtained by a bladder catheter or SPA and sent for urine culture.

Urine culture is considered positive if it grows ≥ 10^7 colony forming units (CFU) of one organism per liter of urine obtained by catheter or ≥ 10^8 CFU in mid-stream urine. Any quantity of a single organism in the urine obtained by SPA is considered a positive urine culture. The diagnosis of AP is usually based on a positive urine culture, high-grade fever, increased white blood cell count with a shift to the left and/or an elevated C-reactive protein.

While these traditional tests suggest renal parenchymal involvement caused by the UTI, the extent and severity of parenchymal lesion/dysfunction is difficult to prove. Recently, serum procalcitonin level has emerged as a marker of parenchymal damage in UTI's (Leroy & Gervaix 2011; Bressan et al. 2009).

The dimercapto-succinic acid (DMSA) isotope exam has been considered as the gold standard to document renal parenchymal inflammation if performed within the first week of symptoms. This investigation is not performed routinely in every patient, but may be helpful in cases in which the diagnosis cannot be established based on urine culture, clinical and laboratory markers (for example a negative urine culture in children who were started on antibiotics before the urine sample was obtained)(Jaksic et al. 2010).

The most predominant bacteria type causing AP in children is Escherichia coli. In the recent study from UK, E.coli caused 92% of acute UTI's in children younger than five years,

followed by Proteus (3%) and Pseudomonas (2%)(Chakupurakal et al. 2010). In transplant patients, E coli is the cause of UTI's in only 21-71 % of patients followed by Enterococcus sp (15-33%) and Pseudomonas aeruginosa (4-15%) (John & Kemper 2009).

6. Treatment

The choice of antibiotics for the treatment of AP should be done with respect to local resistance patterns. E. coli, the most common bacteria causing UTI's in children, is usually susceptible to cephalosporins of the third generation or amoxicillin/clavulanate (Hodson et al. 2007). Recently published randomized controlled trials have shown that oral antibiotics are as effective as I.V. antibiotics in the treatment of AP (Pohl 2007; Hodson et al. 2007). I.V. treatment can be limited to children with persistent vomiting or who present seriously unwell; children can then be switched to oral antibiotics as soon as the clinical status allows. Antibiotic treatment should be started as soon as a reliable urine sample is sent for culture. The optimal duration of antibiotic therapy remains a matter of debate; at least 10 days are recommended for treatment of AP (Hodson et al. 2007).

Long-term antibiotic prophylaxis after the first febrile uncomplicated UTI has been a matter of heated discussion among pediatricians/nephrologists and urologists. Most authors agree that it is generally not recommended in children with normal renal ultrasound findings, as there is a lack of evidence of any benefit of prophylaxis for the prevention of relapses of symptomatic UTI and development of new kidney damage (Williams et al. 2006; Montini & Hewitt 2009). However, a recently published randomized controlled trial (RCT) showed that, in a subgroup of girls with high grade (III-IV) vesicoureteric reflux (VUR), those patients who received long term antibiotic prophylaxis, developed new scarring less often (Brandström et al. 2010). Another RCT showed a mild reduction in UTI recurrence in the prophylactic group and authors concluded that "it would be reasonable for clinicians to recommend the use of trimethoprim–sulfamethoxazole in children who are at high risk for infection or whose index infection was severe. Established risk factors for urinary tract infection are female gender, vesicoureteral reflux and particularly, recurrent urinary tract infection"(Craig et al. 2009). In view of these controversial opinions on antibiotic prophalaxis, it seems reasonable to consider prophylaxis on an individual basis, especially in girls.

The antibiotic of choice for long-term prophylaxis is trimethoprim/sulfamethoxazole; the usual dose is 2 mg/kg of trimethoprim (TMP) given at bedtime. TMP alone can be used as an alternative, as its efficacy is the same as the combined TMP/sulfamethoxazole, but the TMP has less adverse effects (Nguyen et al. 2010). In children who do not tolerate or who develop resistance to TMP/ sulfamethoxazone, cephalosporins of the first or second generation (cefalexin, cefadroxil at dose of 10 mg/kg/per day (Saadeh & Mattoo 2011)) or nitrofurantoin (1 mg/kg/day) can be considered.

7. Imaging after the first febrile UTI

The American Academy of Pediatrics recommends that children between the ages of 2 months and 2 years undergo renal ultrasound (US) and voiding cystouretrography (VCUG) after the first febrile UTI (Anon 1999). This recommendation was based on the assumption that this imaging would allow the detection of children with obstructive uropathy and VUR who are at risk of recurrent UTI's and, if untreated, at risk of permanent renal damage.

The widespread use of antenatal US in recent decades has significantly changed the pattern of congenital uropathies. Nowadays, the most severe cases are diagnosed antenatally and appropriate investigation and treatment is done during the neonatal period before these children develop a UTI. It is therefore questionable whether VCUG is really necessary in all children after their first febrile UTI. Recently published meta-analysis showed that a) the VUR was detected in 25% of children with the first febrile UTI, but only 2.5% of children had a high grade VUR (grade IV and V); b) the risk of renal scarring increases with the severity/grade of VUR (Shaikh et al. 2010). One may therefore assume that only patients with high grade VUR would be at risk for scarring. However, renal scars can develop even without the presence of VUR (Moorthy et al. 2005). It is therefore difficult to prove whether the scar is a result of UTI alone, or VUR or both. Overall, permanent renal scars have been found in 15% of children after the first UTI (Shaikh et al. 2010).

Other studies in children with normal antenatal US report the incidence of renal scarring ranging between 4.5 to 16.9% (Garin et al. 2006; Hoberman et al. 2003; Shaikh et al. 2010).

In view of the relatively high percentage of renal scarring post UTI, not necessarily related to the presence of VUR, it seems more important to focus on the detection of renal parenchymal damage, rather than detecting VUR at the time of the first UTI. Some authors therefore suggest to perform US and DMSA scans to detect renal scars and limit the VCUG in patients with evidence of renal scarring (Hardy & Austin 2008). The advantage of this so-called top-down approach is that no patient with permanent kidney damage secondary to febrile UTI is missed and that the VCUG is indicated less often.

In conclusion, UTI's are relatively frequent in young children less than 2 years of age and in children post Tx, can present diagnostic dilemmas and may lead to kidney parenchymal damage if untreated or not treated properly in a timely fashion.

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