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Urinary Tract Infection in Children

Hsiao-Wen Chen
Department of Pediatric Urology
Chang Gung Children Hospital
Chang Gung University
Taoyuan,
Taiwan

1. Introduction

Urinary tract infection(UTI) is not uncommon cause of bacterial illness in children,4-8% of children have had an UTI from a population based study (Sureshkumar, Jones et al. 2009). The prevalence of UTIs is quite different between two gender and age with high incidence in girls(1% in male and 3% in female), except the male infants with an incidence of 0.7% compared to the 0.1~0.4% of female infants (Foxman 2002),which is due to bacterias harbor in prepuce of youg infant,there was at least a tenfold increased risk for UTIs in noncircumcised compared with circumcised infant(Thomas, Wiswell et al.1986). The symptomatic UTIs raise a significant anxiety for parents and physician with concerning the potential of associated urinary tract disorders or abnormalities. Furthermore, UTIs recur more than 20% in young population, antimicrobial treatment and further investigation warrant in this circumstances. The most common cause of recurrent UTIs is related to the abnormal urinary tract, such as vesicoureteral reflux (VUR), duplex collecting system , spinal dysraphism with neurogenic bladder, Hinman's syndrome …etc. However, the modalities of clinical survey are still controversial regarding the invasiveness and discomfort of examination, it may be need anesthesia. In addition, imaging for UTIs is bearing risk of radiation exposure, the recent reports advocate that the invasive examination such as voiding cystourethrography(VCUG) should be reserved for those with likelihood of VUR with renal damage or dysplasia from the less invasive studies, such as ultrasoud (US) (Preda, Jodal et al. 2011). Meanwhile, additional subject of management for congenital urinary abnormalities associated with UTIs is ongoing debate. This chapter will review the relevant literatures and examine the practical scenarios to cover the top-down approach of urinary tract infection in children, including pathogenesis, host-defense mechanism of the urinary tract, the comprehension of relationship between UTIs and congenital abnormalities or dysfunction, as well as the up-to-date of treatment concept.

2. Pathogenesis of UTIs

The etiology of UTIs is not well understood, and though to be related to gender, bowel habit, urinary incontinence and congenital abnormalities of urinary tract. The most frequent organism is Escherichia (E. Coli),which is originally an harmless flora in human intestine and has some properties as virulence factors (VFs) to overcome the new environment, with bearing

the ability to colonize and adhere to the uro-epithial cell through its fimbriase (P fimbriae, type-1 fimbria),the prevalence of P fimbriation from patients with severe UTIs such as urosepsis is high as 71% compared with 70% in pyelonephritis and 28% in other sources of infection (Brauner, Leissner et al.1987). The process of invasion acts as cytotoxic/endotoxic effect via lipopolysaccharide, aerobactin and enterochelin production, whereas the process of pyelonephritis occurring so call "Nephropathy" (Gally, Bogan et al. 1993; Olianti, Imperiale et al. 2004). Moreover,several gene polymorphisms such as toll-like receotor-2(TLR2) gene,TLR4 gene,heat shock protein 72(HSPA1B) gene are closely associated with the hosts who were vulnerable to UTIs(Karoly, Fekete et al.2006; Tabel, Berdeli et al.2007). In addition,the micro-organisms can alter the gene expression with changing their phenotype in order to adjust to host environment (Johnson 1991).At the point of host defence,urinary tract of human can fundamentally prevent ascending infection from micro-organisms. For instance, urine bolus excretes from renal calyces into bladder through the eccentric peristalsis of ureter, on the other hand, urine from bladder is not allow to reflux backward into ureter by the antireflux competence of submucosal tunnel subset between ureter and bladder. The regular empty of bladder can also prevent the pathogens stasis within lower urinary tract. For these reasons, most of UTIs in children are incidental and promptly recovery with appropriate antibiotics or correction of daily hygiene. However, a minority need to be paid attention on the risk of morbidities, including nephropathy from the chronic pyelonephritis, associated congenital abnormalities, or voiding disorders.

3. Clinical manifestations

Comparing to the adults the symptoms of UTIs in children are not specific owing to the limitation of the verbal expression, fever or chillness is the most general manifestation (National Collaborating Centre for Women's and Children's Health 2007) and followed with lethargic or irritable presentations. Low urinary tract syndrome such as dysuria, pain on micturiction, frequency, incontinence, suprapubic discomfort may be present.

3.1 Acute pyelonephritis

Acute pyelonephritis (APN) is considered if a febrile UTI associated with excess of CRP (Naber, Bergman et al. 2001; Huang, Huang et al. 2007).On the basis of Technetium-99m dimercaptosuccinic acid scintigraphy(DMSA), Nikfar et al. found procalcitonin concentration test could also be useful in the diagnosis of APN with 77% and 89% of sensitivity and specificity comparing to 80% and 65% of C-reative protein(CRP)(Nikfar, Khotaee et al. 2010). However, DMSA still remains the standard tool for diagnosis of APN (Levitchenko, Lahy et al. 2001). At 6 months after APN, 88% of scars were observed by Parex et al., the overall of scars persisted in 27% after 3 years of follow-up. Additionally, increased number of scars from APN was related to high grade VUR (Parrex, Willi et al 2008).

3.2 Acute lobar nephronia

The progression of APN may cause acute and nonsuppurative renal infection with focal tissue edema and leukocytic infiltration that affect one or more lobules of kidney, so call acute lobar nephronia (ALN), which represents a focal mass effect in US or CT, histology may present with acute pyelonephritis and micro-abscesses (Rosenfield, Glickman et al 1979). Klar et al. report 13 patients with 16 episodes of ALN in 210 hospitalized children with urinary tract infection, the most commen pathogen was *E.coli* (Klar, Hurvitz et al.

1996). It is crucial to differentiate ALN from renal abscess regard to their different pathogenesis and treatment, as the ALN needs antibiotics treated with duration at least 2-3 weeks, whereas renal abscess may recquire drainage in addition to antibiotic control (Mark, Zaontz et al. 1984; Rothore, Barton et al. 1991)

3.3 Cystitis

Cystitis is rare in children and usually present with acute symptoms including suprapubic pain, dysuria, frequency or incontinence, the differentiation to the non-infected lower urinary dysfunction (LUTD) should be made based on the urine finding.The uncommon inflammation of bladder caused by fungus, virus or allergy, sometimes masquerade as bladder tumor in US finding (Friedman, Friedman et al.1993; Rosenberg, Eggli et al.1994).

4. Diagnosis and management strategies

In addition to the clinical manifestations, the diagnosis of UTIs can be definitely based on the finding of urine sample either via clean mid-stream urine directly voided by child or collection of urine by sterile bag attached around the urethra in infants or young children who are unable to void voluntarily, otherwise, catheterization or suprapubic aspiration may be used. UTIs should be considered in an urine sample with pyuria or bacteria (National Collaborating Centre for Women's and Children's Health 2007). The threshold of diagnosis depends upon the access of urine sample collection, the less of false positive rate, the more invasive in the fashion of urine obtaining (Hellerstein 1982). As matter of fact, 80% of general pratitioners recommended the use of an urine bag reported by Kennedy et al., the remaining 20% recommended using a dean catch sample (Kennedy, Glynn et al. 2010).

UTIs should be identified as simple or complicated infection by localization of infectious nidus (Figure 1) and whether a recurrent or atypical UTI(Box 1). In order to facilitate the diagnosis and treatment decision, the differentiation of upper urinary tract infection including kidney or ureter between lower urinary tract including bladder or urethra should be conducted based on the clinical symptoms and signs.

Although the prediction rate of US for abnormalities has been questioned (Zamir, Sakran et al. 2004; Riccabona and Fotter 2009), notwithstanding, many congenital abnormalities of urinary tract have currently been detected by prenatal sonography. US is still considered an ideal tool to examine the urinary tract for children with first UTI for its noninvasiveness, reproducibility and lack of radiation exposure. The subtle architecture of kidney can be investigated in the context of APN including acute focal bacterial nephritis (ALN), renal abscess, pyohydronephrosis or stone associated infection (Klar, Hurvitz et al. 1996; Sureshkumar, Jones et al. 2009). Additionally, US can investigate the children with lower urinary tract dysfunction with estimation of residual urine, bladder outline and capacity (Uehling, Hahnfeld et al. 2000; Dacher and Savoye-Collet 2004).

DMSA scintigraphy remains the important examination in the diagnosis of APN,defects in renal outline without any loss of renal volume can be found, whereas in scarring, the defect is associated with focal loss of renal mass (Piepsz A, Colarinha P et al. 2001). However, a 100% of high negative diagnostic value for detection of renal scarring during the acute stage of infection was reported by Hitzel et al., therefore, the follow-up should be ongoing after 6 months of acute pylonephritis to avoid the negative diagnostic value (Hitzel, Liard et al. 2002).

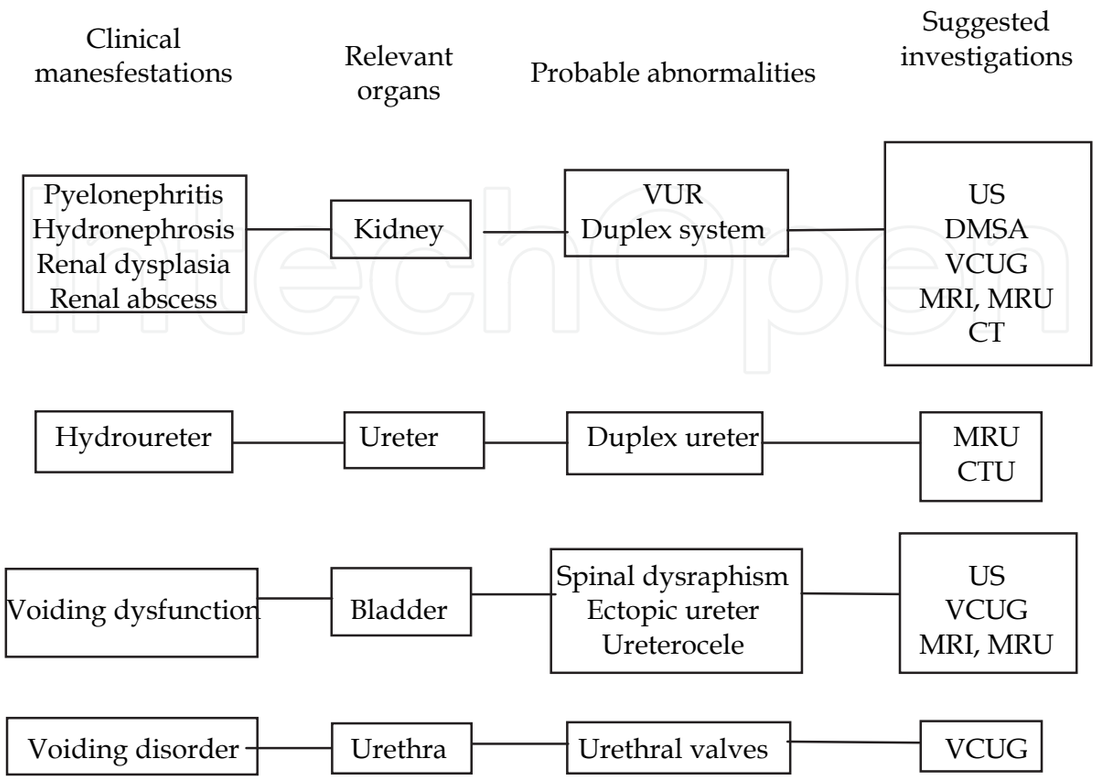

Fig. 1. Algorithm for Investigation of Associated Abnormalities in Children with UTIs.

Atypical (any of the following)

- Septicaemia or patients who looks seriously ill (see NICE guideline [2])
- Poor urine flow
- Abdominal or bladder mass
- Raised creatinine concentration
- Failure to respond to treatment with suitable antibiotics within 48 hours
- Infection with non-Escherichia coli organisms

Recurrent(any of the following)

- Two or more episodes of urinary tract infection with acute pyelonephritis or upper urinary tract infection
- One episode of urinary tract infection with acute pyelonephritis or upper urinary tract infection plus one or more episode of urinary tract infection with cystitis or lower urinary tract infection
- Three or more episodes of urinary tract infection with cystitis or lower urinary tract infection

Box 1. Main characteristics of patients with atypical or recurrent tract infection. Adapted from Rintaro et al.(2007).BJM 25:335:395-396; http://guidance.nice.org.uk/CG54

Magnetic resonance imaging (MRI, MRU) and enhanced CT are recently applied for depiction of APN and renal scarring. As the detection rate is questioning and availability is limited for requirement of sedation and injection of a potentially nephrotoxic medium while performaning the examination, which is reserved for children with doubtful diagnosis or suspicion of congenital abnormalities (Lonergan, Pennington et al. 1998; Kavanagh, Ryan et al. 2005). However, in UTIs with voiding dysfunction, MRI is practical to evaluate the spinal cord and facilitate the diagnosis of abnormalities associated with neurogenic bladder,such as spinal dysraphism with tethered cord (Siomou, Giapros et al. 2009).

VCUG remains a reference examination for VUR, which requires urethral catheterization and radiation exposure, many parents are reluctant to the performance and it is reserved on an individual with likehood of VUR from otherwise noninvasive access, such as DMSA scan or US examination (Herz, Merguerian et al. 2010, Preda , Jodal et al. 2011). However, VCUG permits the effective grading of VUR when the treatment strategy is demanding. Moreover, in case with suspicion of urethral valves or VURD syndrome, VCUG is indispensable to search the urethra, bladder and even voiding function.

5. Nosocomial infection of urinary tract

Urinary tract infection in nosocomial infection is less common in children compared with adults, it encountered the 3rd to 5th most common infection in hospitalized children with incidence varied from 6-42% according to the different denominators (Ford-Jones, Mindorff et al. 1989; Weber, Sheridan et al. 1997; Orrett, Brook et al. 1999). *E. coli* is still the predominant pathogen followed by *Candida* species, *Enterococcus*, *Pseudomonas* species and *Klebsiella* species (Langley, Hanakowski et al. 2001; Prelog, Schieficker et al. 2007). Several risk factors include immunocompromise, broadly antibiotics use, or obstruction of urinary tract can cause nosocomial infection. However, instrustment of the urinary tract is still the most frequent risk for nosocomial urinary tract infection. Therefore, the surveillance of the use of urinary catheter is the main focus for the infection control in hospitalized children.

6. Complex UTIs

Most UTIs are simple and easy to be controlled by antibiotic treatment. Sureshkumar et al. reported female gender,encopresis,daytime urinary incontinence and renal anatomical problems are risk factors associated with UTIs(Sureshkumar,Jones et al.2009).Nonetheless, infants with febrile UTIs or children younger than 2 years of age are highly associated with congenital urinary tract abnormalities.Therefore, many different factors and scenario should be considered when children with recurrent or atypical UTIs,then anatomic or neurological evaluations warrant ongoing.

6.1 VUR and associated abnormalities

VUR encountered the most abnormalities with 25%to 50% of children with UTIs (Smellie, Normand et al. 1981; Downs 1999) which are also related to the hydronephrosis, renal dysplasia, duplex collecting system, or voiding dysfunction. Reflux nephropathy is the main concerning as 13~25% of patients develop end-stage renal disease from the inflammatory and immunological processes(Askari and Belman 1982; Craig, Irwig et al. 2000; Ardissino, Avolio et al. 2004). The risk of developing "Reflux nephropathy" is multiprediposing and related to the host susceptibility and virulence of bacteria(Matsuoka, Nakashima et al. 2006;

Cendron 2008; Coulthard 2008). Although the management of VUR remains controversial, the ultimate goal is to prevent the further renal injury from reflux and repeat UTIs. Not more than 30% of spontaneous resolution rate for mild to moderate grade of VUR and less for high grade (Green field and Wan 1996; Kundson, Austin et al. 2007). Series of literatures reported no significant benefits in control of renal scarring or recurrent UTIs with antibiotic use (Garin, Olavarria et al. 2006). Comparing with antibiotics alone, there is no any additional benefit of surgery except for a reduction of UTIs from a meta-analyses data(Wheeler, Vimalachandra et al. 2003). Surgical correction may at least mitigate the UTIs and process of nephropathy. In addition, several new antireflux techniques have been introduced with less invasiveness or high success rate from 70~98% (Lakshmanan and Fung 2000; Chen, Yuan et al. 2004; Routh, Inman et al. 2010).

Otherwise, the abnormalities associated with VUR such as duplex ureters with an obstruction of one renal moiety, ureterocele, ectopic opening of ureteral orifice that causes incontinence, or reflux associated with urethral valves, then surgical correction should be considered to prevent repeat UTIs and further renal damage.

6.2 Voiding disorders

Children with voiding dysfunction may present with UTIs or VUR as the consequence of urinary stasis and high bladder pressure (Whelan and McKenna 2004; Chen, Mao et al. 2004; Feldman and Bauer 2006). Twenty percent of children with high grade of VUR had lower urinary tract dysfunction by high bladder capacity and increased post-void residual urine(Sillén, Bradström et al. 2010)). Disorder of voiding can be categorized into the sequence of neurogenic abnormalities including spinal dysraphism with tethered cord syndrome, or cerebral palsy(Houle, Vernet et al. 1998; Rendeli, Ausili et al. 2007). In a series reported that urologic symptoms included VUR and renal failure were shown in 33% and 14% of children with spinal dysraphism after a long term follow-up (Silveri, Capitanucci et al. 1997). The non-neurogenic disorders affect the voiding function in children including posterior urethral valves, Hinmain's syndrome, prune belly syndrome(Chaichanamong Kol, Ikeda et al. 2008; Youssif, Dawood et al. 2009; Routh, Huang et al. 2010), which are highly associated with febrile UTI and chronic renal failure (Őborn and Herthelius 2010). The management of UTIs in children associated with voiding dysfunction is complex, the underlying disorders should be appraised when the symptoms are initially presented. The neurologic abnormalities or the urinary tract disorder required accurate evaluations and correction at different times in order to prevent irreversible damage of neurological and renal function.

6.3 Renal abscess

Perirenal or renal abscess and pyonephrosis are not common in UTIs of children, most occur in the urinary tract with obstruction, treatments depend on the individual scenario, subcutaneous drainage of the infection nidus under ultrasound or CT guide to preserve the kidney and antibiotics treatment is the main principle.

6.4 Correction of bowel habit

Several studies showed the relationship between bladder voiding and defecation in constipated children, urinary incontinence and UTIs are caused from the urinary outflow obstruction by bowel distention. Twenty nine to thirty four percent of children with chronic constipation or encopresis were associated with daytime or nighttime urinary incontinence,

moreover, 11% of these children were present with UTIs. Interestingly, treatment of the underlying bowel disorders resulted in improving of urinary incontinence in 63-89% of patients and disappearance of recurrent UTIs in children who had no urinary tract abnormalities (Loening-Baucke 1997;Sureshkumar, Jones 2009).

6.5 Antibiotics treatment

The empirical treatment with ampicilline and gentamycin may be provided once the UTIs were diagnosed and may switch to an appropriate antibiotics when the definitive results of urine culture and sensitivities are available. For upper urinary tract infection, oral antibiotics are not inferior to the parenteral antibiotics, low resisted antibiotics such as cephalosporin is recommended with course for 7-10 days. Parenteral antibiotics can be used in cases of oral antibiotics cannot be used, ceftriaxone or cefataxime for 4-7 days, depends upon the responding of infection control. For lower urinary tract infection, amxocillin, cephalosporin, trimethoprim or nitrofurantoin may be used for 3-7 days. Prophylasis of antibiotics is not recommended for prevention of recurrent UTIs ,which may increase the risk of drug resistance (Hsu, Tan et al. 2010; Nicolau 2011).

6.6 Probiotics

Many experimental and clinical use of probiotics for inflammatory bowel disease with promising results has been extensively reported (Alfaleh, Anabrees et al. 2008; Hedin, Mullard et al. 2010). The application for urinary tract infection is increasing. Certain strains isolated from lactic acid bacteria demonstrated major antimicrobial activity against most of uropathogens in the pediatric urinary tract infection (Lim, Lee et al. 2009). Currently, the benefits for inhibition of UTIs varied according to the types of strains(Abad and Safda 2009), further research on different strains and clinical administration are needed to be ongoing.

7. Conclusion

The prompt diagnosis and treatment of UTIs are considered importantly to prevent subsequent renal damage, particular in very young children. In order to avoid unnecessary examinations or delay in treatment, the abnormalities associated with UTIs should be evaluated under suggested treatment algorithm or guidelines when the clinical manifestations are initially occurred. Although many treatment guidelines or recommendations have been established and need to be adjusted based on the most evidence or consensus, however, the treatment of UTIs in children can be simple or complex according to the scenario of individual.

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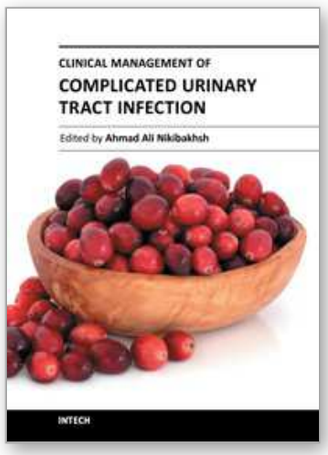

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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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