Review articles
Central Eur J Paed 2018;14(2):167-182
DOI 10.5457/p2005-114.216

Urinary Tract Infections in Children: Never Ending Story

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Received: June 21, 2018
Accepted: August 16, 2018

Key words: Acute pyelonephritis ▪ Cystitis ▪ Renal and bladder ultrasound ▪ Renal scarring in children ▪ Voiding cystoureterography.

The aim of this paper is to provide information from the most important literature on the diagnosis, treatment and further management of urinary tract infections (UTI) in childhood. Following acute viral respiratory tract infections, UTIs are the second, most common infections in children. After febrile UTI, up to 40% of children have permanent renal scarring that may lead to poor renal growth, arterial hypertension, preeclampsia and chronic renal failure. Diagnosis and management of UTI is still one of the most controversial topics of pediatrics. The recent recommendations for the diagnosis, treatment, prophylaxis, and imaging of UTI in childhood based on evidence, or on a consensus of experts are discussed in this review article. **Conclusion** – Prompt diagnosis and treatment of UTI remain of utmost importance. Most existing guidelines recommend renal ultrasound after the first febrile UTI, but cystography only in the presence of risk factors or anomalies on ultrasound. There is still no consensus regarding antibiotic prophylaxis after the first episode of febrile UTI.

Introduction

Urinary tract infections (UTI) include clinical conditions characterized by the growth and multiplication of infectious pathogens within the urinary tract which induce an inflammatory response by the uroepitelial cells in the attempt to destroy and eliminate the pathogens. A genome of bacterial strains and the innate host defense mechanisms determine the severity of UTI and their consequences (1).

Although the problem of UTI has been intensively researched and many papers and guidelines have been published, UTI diagnosis and management are still one of the most controversial topics of pediatrics. At the beginning of this century a revision of the classic theories about UTI pathophysiology and renal scarring resulted in new, less invasive guidelines for UTI management (2-5). Extensive prenatal renal ultrasound examinations showed that most progressive renal scarring, previously considered as an acquired consequence of UTI, is in fact congenital renal hypo dysplasia mainly with a genetic background (6). Recent advances have disclosed that a predisposition to UTI recurrence could be inherited, suggesting that increased susceptibility to UTI is a complex heritable trait influenced by several genes whose deregulation in humans may predispose to recurrent UTI (7). Therefore, the identification of susceptible patients could enable novel strategies in the management of recurrent UTI. In addition, antagonists and agonists of candidate gene products could manipulate host defense mechanisms, offering new therapeutic op-

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tions for UTI treatment (7). In the hope that new diagnostic and therapeutic options will be realized in the near future, the current recommendations for the diagnosis, treatment, prophylaxis, and imaging of UTI in childhood based on evidence, or expert consensus, are discussed here (2-5).

Classification of UTI

UTI may be classified according to the localization of infection, symptoms, episodes and compromising factors (4). According to the localization of the infection UTI are categorized as lower or upper urinary tract infections. Infection of the lower urinary tract or cystitis presents with inflammation of the mucous membrane of the bladder with symptoms including dysuria, frequent voiding, urgency, incontinence, hematuria and suprapubic pain. However, in newborns and infants, these symptoms are rarely detected. Upper urinary tract infection or tubulointerstitial nephritis (pyelonephritis) is a diffuse infection of the renal pelvis and parenchyma, most commonly manifested by systemic features such as high fever, vomiting, abdominal pain or tenderness, malaise, poor feeding, and the presence of leukocyturia. Flank pain is a good diagnostic indicator of acute pyelonephritis in adults and older children, but is not recognized in infants and early childhood. These small children may have such non-specific signs as anorexia, poor weight gain, vomiting and/or diarrhea, lethargy or irritability, convulsions, and hypothermia. In newborns, UTI may induce prolonged hyperbilirubinemia. Thus, the American Academy of Pediatrics (AAP) recommends that infants with elevated direct bilirubin levels should be screened for UTI (2). Severe UTI in childhood may also be accompanied by transient pseudohypoaldosteronism with pronounced hyponatremia, with or without hyperkalemia (8). Acute pyelonephritis is most common during the first year of life, and cystitis is most common in girls after the third year of life.

According to the type of episode of a UTI, they can be divided into first and recurrent infections. Recurrent infection may be unhealed or persistent and reinfection. UTI stratification, according to complication factors, includes uncomplicated and complicated UTI. Uncomplicated UTI is an infection in patients who have a morphologically and functionally normal upper (UUT) and lower urinary tract (LUT), normal kidney function, and a healthy immune system. Complicated UTI occurs in children with known morphological and / or functional problems of the UUT or LUT, in those with an associated metabolic (e.g. diabetes mellitus) or systemic disease (e.g. septicemia, or immunodeficiency), raised serum creatinine, prematurity, or with the presence of foreign objects, such as an indwelling urethral catheter, and also in those without the expected clinical response within 2 days of antimicrobial therapy.

Epidemiology

Urinary tract infection is one of the most common pediatric infections (9-14). In 30% of children with congenital anomalies of the kidney and urinary tract (CAKUT), UTI can be the first sign of the abnormality (13). The incidence of UTI varies in relation to age and sex. The first, symptomatic UTI most often occurs during the infant period. Shaikh et al. found that the overall prevalence of febrile UTI in infants was 7.0% (14). The recurrence rate of UTI in infants with febrile UTI is estimated at 30%, with the majority of recurrences occurring in the first 12 months after the initial infection (15, 16). In the early infant period, the incidence of UTI in boys is higher than in girls, especially in uncircumcised boys, of whom about 20.1% have UTI (17). In the second year and thereafter, UTI is most common in girls: 3% of prepuber-

tal girls and 1% of prepubertal boys are diagnosed with UTI (14, 18, 19). In sexually active adolescents females, UTI was documented in 47/281 (17%) from urine culture results obtained (20).

Etiology

Various infectious agents can cause UTI, but the most of them are Gram negative bacteria (see Table 1). *E. coli* is the leading cause of the first UTI in 90% of girls and in 80% of boys, and the most frequent pathogens in recurrent UTI (9, 10, 19, 21, 22). During infancy, *Klebsiella pneumoniae, Enterobacter, Enterococcus,* and *Pseudomonas* species are more frequent than later in life (18, 19, 22, 23). *Proteus species* is found in 30% of LUT infection in boys, while *Staphylococcus saprophyticus* and *Streptococcus group B* are more frequent among female adolescents and septic neonates, respectively. *Enterococci, Pseudomonas, Staphylococcus aureus, Haemophilus influenzae, Streptococcus B* are a more common cause of UTI in patients with CAKUT and/or low urinary tract dysfunction, than in those with normal urinary tract (4). Fungi (*Candida* species) may also cause UTI, especially after receiving antibiotics or instrumentation of the urinary tract, as well as in immunologically compromised children and those with diabetes mellitus and those subject to immunosupression. *Adenovirus* is a rare cause of UTI and may cause hemorrhagic cystitis. The incidence of non-gonorrheal urethritis caused by Chlamydia trachomatis is 15% to 40%, being the most common among adolescents (24, 25).

Bacterial virulence is in good correlation with the ability to adhere to uroepitelial cells. *E. coli* can express a broad variety of virulence factors involved in the colonization, adhesion, invasion, and survival of host defenses. The ability of *E. Coli*, to cause symptomatic UTI is enhanced by adhesins and toxins (e.g. haemolysin). Adherence to the urinary tract epithelium is the first stage of UTI, enabling the bacteria to resist the hydrodynamic forces of urine flow, and establish infection. Among the more common adhesins produced by *E. Coli* are type 1, P, F1C, S and Auf fimbriae and the Afa/Dr adhesions (26).

Pathophysiology

Urine in the kidneys, ureters, urinary bladder and proximal urethra is normally sterile. The first protection against UTI involves physical barriers (unidirectional urinary flow), epithelial cells and the production of proteins that hinder bacteria adhesion (27). The most common path of spreading UTI is bacteria ascending via the fecal-perineal-urethral route. The entry of bacteria into the urinary bladder can result from turbulent flow during normal voiding, voiding dysfunction, or catheterization. In addition, sexual intercourse or genital manipulation may facilitate the entry of bacteria into the urinary bladder. Rarely, the urinary tract may be colonized during systemic bacteremia (sepsis) or from inflammation processes inside the abdominal cavity.

Table 1. The Most Common Etiology of Urinary Tract Infections (UTI) in Children
E. coli in 80-90% of the first UTI
Proteus in 30% of boys with cystitis
Staphylococcus saprophyticus in 30% of adolescents with UTI
Enterococcus, *Pseudomonas*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus B* in children with urinary tract anomalies and/or dysfunction of low urinary tract
Rare causative agents: *Chlamydia* (adolescents with uretritis), *Mycobacterium tuberculosis* (genitourinary tuberculosis), viruses (adenoviruses-hemorrhagic cystitis), fungi (*Candida albicans*) and parasites (*Schistosoma hematobium*)

Table 2. Predisposing Factors for Urinary Tract Infections
Kidney and urinary tract malformations (congenital or acquired): Vesicoureteral reflux in 30% - 40% and Urinary obstruction in 10%
Low urinary tract dysfunction, congenital or acquired
Constipation
Alteration of the periurethral flora (antibiotic therapy, immunosuppressive drugs)
Anatomic characteristics of female urethra (shorter and wider compared to that in boys)
Immunoglobulin deficiency (most commonly IgA)
Metabolic (diabetes mellitus, deficiency of vitamin A) and electrolytes disorders (hypokalaemia)
Genetic factors (alterations of genes: HSPA1B, CXCR1, CXCR2, TLR2, TLR4, and TGFβ1)

Entry of uropathogens into the urinary tract induces uroepitelial cells to produce mediators of inflammation, until the pathogens are destroyed and eliminated. The functional chemokines and chemokine receptors are crucial for neutrophil recruitment and for neutrophil dependent bacterial clearance. Moreover, the neutrophil-mediated defense is essential for resistance to UTI (7).

Susceptibility to UTI may be increased by any of the factors presented in Table 2. In children, the most common are CAKUT, congenital or acquired low urinary tract dysfunction (LUTD), constipation, and alteration of the periurethral flora by antibiotic therapy. Recent findings suggest that the genome of bacterial strains and the innate host defense mechanisms determine the severity of infection (1). The HSPA1B, CXCR1 & 2, TLR2, TLR4, TGF-β1 genes seem to be associated with an alteration of the host response to UTIs at various levels (7). For example, genetic alteration of TLR4 signaling could modify the host's unresponsiveness to a UTI towards asymptomatic bacteriuria rather than symptomatic pyelonephritis (28).

Circumcision and UTI

For male infants, neonatal circumcision substantially decreases the risk of UTI. Schoen et al. found that during the first year of life, the rate of UTI was 2.15% in uncircumcised boys, versus 0.22% in circumcised boys (17). As reported by Schaikh et al. the risk for UTI in uncircumcised boys is particularly high during the first 3 months of life; in febrile boys younger than 3 months, UTI was present in 2.4% of circumcised boys and in 20.1% of uncircumcised boys (14).

Diagnosis

Prompt diagnosis and initiation of treatment of an UTI is very important to prevent long-term renal scarring. Clinical history and physical examination may suggest a UTI, but its diagnosis is essential, based on the positivity of the urine culture and, significantly, the urine test (2-5).

Laboratory Examinations

Urine culture must be performed before any antimicrobial agent is given. During childhood, the proper collection of urine is essential to avoid false-positive results. In order to choose a particular method, it is important to consider the clinical condition of the patient, the experience of the healthcare team, and the resources of the pediatric or emergency center facilities. In practice, there are four methods for collection of urine: suprapubic aspiration, transurethral catheterization, clean middle urine catch, and sterile plastic bag. Sterile suprapubic urinary bladder aspiration (SPA) is the most reliable way

of taking uncontaminated urine in newborns and infants (success 23%-90%) (2, 3). It is advised to perform the SPA procedure after an ultrasound check for sufficient urine volume in the bladder or, when this is not possible, when the diapers of well-hydrated babies have been dry for more than 30 minutes. Complications of this procedure are rare: transient macrohematuria (2%), microhematuria (urine obtained by this route is not suitable for evaluation of haematuria), the accidental aspiration of intestinal contents (the only risk is urine contamination seen in the growth of mixed bacterial flora). Transurethral catheterization (TC) of the bladder is another way of obtaining urine with minimal contamination. The sensitivity and specificity of urine obtained by TC in relation to that obtained by SPA are 99% and 95%, respectively (3, 29-31). A clean middle urine catch (CMUC) of the first morning urine is the most commonly used method for taking a sample of urine, with a good rate of accuracy. In toilet-trained children the sensitivity and specificity of CMUC are 75%-100% and 57%-100%, respectively (32, 33). CMUC should be done after cleaning the genital area with water and soap, without antiseptic agents. In small children and also in those who do not control voiding, the urine sample may be obtained from a sterile plastic bag (SPB), which, upon washing and drying the periuretral region, is attached to it. If the child does not void within 30 minutes, the bag should be replaced and also it should be removed as soon as the child finishes urination. However, considering false positive findings of about 85%, SPB may only be used for screening for UTI (2, 34). Therefore, SPB can be utilized to perform a dipstick test or microscopy, and a midstream sample can then be collected for urine culture (5). If non-invasive techniques are not possible, than a catheter sample or suprapubic aspirate with ultrasound guidance is done (3).

Only examination of fresh urine is reliable (<1 hour at room temperature, <4 hours at + 4^0C). Microscopy is used to detect white and red blood cells, and bacteria. The presence of a fresh, Gram-stained specimen of uncentrifuged urine correlates with 10^5 colony forming units (CFU) per ml in culture (2). If both pyuria and bacteriuria are positive, there is a high likelihood of a UTI (2). White blood cells casts indicate acute pyelonephritis.

A dipstick is very useful to test urine for nitrite, leukocyte esterase, protein, glucose, and blood (2, 33, 35, 36). A positive test for nitrite in urine has high specificity (about 98%), but low sensitivity (49%) (33, 35, 36). A microscopic finding of more than five leukocytes in urine (74% sensitivity, specificity of 86%) corresponds to dipstick positive leukocyte esterase (74% sensitivity, specificity 87%). Accordingly, a UTI is very likely if a microscopic examination of fresh urine finds bacteria and leukocytes, or positive nitrite and leukocyte esterase on a dipstick (2, 4, 35, 36). A positive dipstick test for blood has poor sensitivity (25%) and high specificity (85%) (35).

Urine culture is mandatory for diagnosis of UTI. In practice, the classical definition of $>10^5$ CFU/ml of voided urine is most commonly used to define a significant UTI. However, it has been well documented that different cut-off levels should be used for SPA, TC, CMUC and SPB (Table 3) (2-5).

The AAP criteria for diagnosis of UTI in children aged 2-24 months are the presence of pyuria and/or bacteriuria on urinalysis and the presence of at least 50,000 colony-forming units (CFU) per mL of a uropathogen of a properly collected urine specimen (2).In neonates and infants younger than 2 months of age, the criteria include the presence of lower amounts of a single pathogen (10,000-50,000 CFU/mL) (2). Mixed cultures indicate contamination (4). For a child whose first urinary finding was normal and febrile, lasting for more than two days without a clear cause of infection, the examination of urine should be repeated.

Table 3. Urine Culture Criteria for Diagnosing Urinary Tract Infections in Children*

Protocol†	Suprapubic aspiration	Transurethral catheterization	Clean middle urine catch	Sterile plastic bag
AAP (2)	Any number of colony forming units (CFU)/ml	Pyuria + 50,000 of CFU/ml	-	False positivity 85%, thus only has value for screening UTI.
NICE (3)	Any number of CFU	>10,000 CFU/ml	>100 000 CFU/ml	>100,000 CFU/ml
EAU/ESP (4)	Any number of CFU/ml (at least 10 identical colonies) (99% probability of UTI)	≥1000-50,000of CFU/ml (80% of the probability of UTI in the first, and 90% in the re-test)	$\geq 10^4$ CFU/ml with symptoms; $\geq 10^5$CFU/ml without symptoms	$\geq 10^5$ CFU/ml
SINePe (5)	Any number of CFU	>10,000 CFU/ml	>100,000 CFU/ml	>100 000 CFU/ml

*Modified from reference 2-5; †Reference; CFU=Colony forming units; AAP=The American Academy for Pediatrics; UTI=Urinary Tract Infection; NICE=The National Institute for Health and Clinical Excelence; EAU/ESPU= European Association of Urology (EAU)/European Society for Urology (ESPU) Pediatric Guidelines Committee; SINePe=Italian Society of Pediatric Nephrology.

In a severely ill, febrile child with a UTI, serum electrolytes, serum creatinine, and blood culture should be done. Blood counts, especially in younger children, should always be done. Procalcitonin and CRP are also useful as a support to evaluate the response to UTI therapy, but their role in the localization of infection - high or low - is controversial. The procalcitonin test seems better suited for ruling in pyelonephritis, but the limited number of studies and the marked heterogeneity between studies prevents us from reaching definitive conclusions (37-39).

Imaging

Compared to the earlier protocols, current protocols for imaging of the urinary tract in children with UTI are more selective and restrictive, by avoiding invasive procedures and by reducing the radiation dose. The recommendations given by these protocols are presented in Table 4.

Renal and Bladder Ultrasound (RBUS)

RBUS is the initial, basic method showing the urinary system. The recent guidelines on UTI in children, published by the AAP (2), the European Association of Urology (EAU) (4), and Italian Society of Pediatric Nephrology (5), have stated consensually that all infants with febrile UTI should undergo RBUS. The protocol of the British National Institute for Health and Clinical Excellence (NICE) (3) is the most selective and only recommends RBUS for children younger than 6 months and for older children if they have an atypical (including a seriously ill child, poor urine flow, abdominal or bladder mass, raised serum creatinine, septicemia, failure to respond to treatment with antibiotics within 48 h and an infection with a non *E Colli*) or recurrent UTI (2). NICE defined reccurent UTI as any of the following: a) two or more episodes of acute pyelonephritis (APN) or upper urinary tract (UUT) infections, b) one episode of APN or UUT infection plus one or more episodes of UTI with cystitis or low urinary tract (LUT) infections, and c) three or more episodes of cystitis or LUT infections.

RBUS serves for estimation of kidney location, size, its echogenicity and corticomedular differentiation, as well as the anteroposterior pelvis diameter with a full and empty bladder, if the ureters are dilated, the urinary bladder wall thickness and residual urine. In the phase of infection, RBUS can give false positive findings, so it is recommended to do it 4-6 weeks after UTI resolution, except if

Table 4. What Do the New Protocols Suggest?

Protocol*	Age of patients	RBUS	VCUG	DMSA scan
APP (2)	2 mos. - 2 yrs.	In all, 4 - 6 wk. after UTI. During the first 48 hrs. of UTI only in patients with high risk	RBUST positive or reccurent UTI	Not indicated after the first UTI
NICE (3)	3 mos. - 3 yrs.	In infants <6 mos. and in those with atypical or recurrent UTI within the first 6 wks.	Infants <6 months with atypical or reccurent UTI	In children aged <3 yrs. and in those with atypical or recurrent UTI, 4 - 6 months after UTI
EAU/ ESPU (4)	The 1st UTI	Early RBUS in all febrile UTI or UTI is associated with pain or haematuria; In all after UTI	VCUG and, if positive, a DMSA scan: All infants with 1st febrile UTI, girls with 1st febrile UTI >1 yrs., boys >1 yr. with recurrent UTI	DMSA scan and, if positive, VCUG. All infants with 1st febrile UTI, girls with 1st febrile UTI >1 yrs., boys >1 yr. with recurrent UTI
Italian† (5)	2 mos. - 3 yrs.	In all within 4-8 wk. after UTI during the first 72 hrs. only if terapeutic response failing	RBUST abnormalities or with risk factors‡	In all, 6 mos. after UTI

*Reference; RBUS=Renal and bladder ultrasound; VCUG= Voiding cystourethrography; DMSA scan=(technetium Tc 99 labeled) dimercaptosuccinic acid scan; AAP=The American Academy for Pediatrics; UTI=Urinary tract infection; NICE=The National Institute for Health and Clinical Excellence; EAU/ESPU=European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) Paediatric Guidelines Committee; †Italian Society of Pediatric Nephrology; ‡Risk factors: RBUS abnormalities, relatives with VUR, Urosepsis, male infants <6 mos. of age, non compliant family, bladder dysfunction, failing therapeutic response within 72 hrs., non *E Coli* UTI.

there is no therapy response within 72 hrs despite the application of the appropriate drug, and/or if there is high suspicion of obstruction or abscess formation. RBUS is relatively inexpensive, non-invasive, and usually readily available. However, RBUS has low sensitivity in detecting VUR, although it may show its indirect signs (40).

Voiding Cystouretrography

The number of techniques available for assessment of VUR is increasing, and a new classification, taking into account their real characteristics (direct/indirect, catheter-using/catheter-free, radiation-giving/radiation-free), has been proposed (41). Of these, the most commonly used are fluoroscopic voiding cystourethrography (VCUG), radionuclide cystography (RNC) and contrast enhanced ultrasound voiding cystography (VUS).

VCUG is still the gold standard for diagnosis of VUR (4). However, it has significant ionizing radiation, while RNC, although highly sensitive, with less radiation exposure, lacks the anatomic resolution of VCUG. More recently contrast enhanced ultrasound voiding cystography (VUS) has become a very popular method for detecting VUR. The main advantage of VUS over the other two is the fact that it does not expose the child to ionizing radiation. Furthermore, VUS is a real time imaging compared to VCUG, which often only gives a snapshot of the procedure. Using radiological VCUG as the reference, the results of voiding urosonography (VUS) were as follows: sensitivity 57%-100%, specificity 85%-100%, positive/negative predictive values 58%-100%/87%-100%, respectively, and diagnostic accuracy 78%-96%. With the exception of two studies, the diagnostic accuracy reported was ≥90% (42).

The AAP (2) and Italian (5) guidelines recommend that VCUG should be performed only if RBUS reveals hydronephrosis, scarring, or other findings suggestive of either

high grade VUR or obstructive uropathy. According to the Italian protocol, additional risk factors are: a positive family history of VUR, septicemia, renal insufficiency, male infants <6 months of age, suspicion of non-compliance of the family, absence of clinical response to antibiotics within 72 hours, and pathogens other than E Coli. In children with febrile UTI presenting none of the risk factors, no further imaging of the urinary tract and of renal parenchyma is recommended (5). The NICE (3) indicates VCUG only in infants with 1st febrile UTI at <6 months of age and in those with recurrent UTI, while the EAU guidelines (4) recommends that, for infants under 1 year, and girls above 1 year, VUR should be excluded by VCUG and/or technetium Tc 99 labeled dimercaptosuccinic acid (DMSA) scan, according to the bottom-up method (VCUG and, if positive, a DMSA scan) or the top-down method (DMSA scan and if positive, VCUG).

Technetium Tc 99 Labelled Dimercaptosuccinic Acid Scan (DMSA Scan)

A DMSA scan is the gold standard for diagnosis of cortical parenchyma defects (renal scarring). The AAP does not indicate a DMSA scan after the 1st febrile UTI (2), while the Italian guidelines recommend that DMSA should be done 6 months after the 1st febrile UTI in all children with an abnormal RBUS, or in whom VUR has been shown (5). NICE limited DMSA scan for children with atypical or reccurent UTI (3), and the EAU guidelines recommend VCUG or DMSA scanning (the bottom-up or the top-down method) after the first episode of febrile UTI, depending on sex, age, and clinical presentation (4).

Tc 99m merkaptoacetiltriglicin (MAG 3) scintigraphy or magnet resonance urography (MRU) is indicated when a urinary tract obstruction is suspected.

Differential Diagnosis

A UTI should be distinguished from asymptomatic bacteriuria (ABU) which indicates colonization of the bladder by non-virulent bacteria that are not able to trigger a symptomatic infectious response (no leukocytes and symptoms).Treatment of ABU is not warranted, because randomized trials have shown that long term outcomes are no different for treated as compared with untreated patients (43).

Treatment

Delay of treatment of a febrile UTI for more than >48 h increases the risk of parenchymal kidney scarring (44-46). Therefore, after taking urine samples for culture, empirical antibacterial therapy is started, and later on it may be changed depending on the sensitivity testing of the isolated pathogens (2). The choice of empirical antibacterial therapy is based on the knowledge of the distribution spectrum of causative organisms and their resistance patterns. The prevalence of antibiotic resistance among European countries during the 2010 - 2012 period showed that *E. coli* had a high resistance to amoxicillin and trimethoprim, and it was variable to cephalosporin. Nitrofurantoin had a good rate of efficacy, with a resistance lower than 5% (47). Unfortunately, resistance to most antibiotics is increasing. Peco-Antic A et al. reported the rising prevalence of extended-spectrum b-lactamase (ESBL) – producing *Enterobacteriaceae* as well as multidrug resistance in newborns and young children treated at the University Children's Hospital in Belgrade for acute pyelonephritis during the 2000-2009 period (48, 49). In Turkey, 49% of children <1 year of age and 38% of

those >1 year of age had ESBL-producing bacteria (50). Antibacterial therapies usually used for the treatment of UTI in children are presented in Tables 5 and 6.

Table 5. Antibacterial Drugs Administered Parenterally for Treatment of Urinary Tract Infections in Children and Adolescents

Chemotherapeutics	Daily dosage		
	Age ≤1 yr.	Age 1–12 yrs.	Adolescents*
Cefepime hydrochloride (4. gen)†	≤ 28 d: 30 mg/kg/D Q 12 hrs.; >28 d: 50 mg/kg/D Q 12 h	60-150 mg/kg IV/IM in 3D	6 g: IV/IM in 3D
Ceftriaxone (3. gen)†,	0–7 d: 50 mg/kg/D Q 24 hrs.; >7 d: BW >2 kg 50-75 mg/kg/D Q 24 hrs.	50-75 mg/kg IV/IM in 1D	2-6 g: IV/IM in 1D
Ceftazidime (3. gen)†	<30 d: 30 mg/kg/D Q 12 hrs.; 1-12 mos. 30-50 mg/kg/Q 8 hrs.	100-150 mg/kg IV in 2-3 D	3-6 g: IV in 2-3 D
Cefotaxime (3.gen)†	0-7 d, BW <2 kg: 100 mg/kg/day divided Q 12 hrs.; >7 d, BW >2 kg: 150-200 mg/kg/divided Q6–8 hrs.	100-200 mg/kg IV in 2–3 D	2-4 g: IV in 2-3D
Cefoperazone (3. gen)†	<30 d: 20-40 mg/kg divided Q6-12 hrs., Max D 80 mg/kg/24 hrs; >30 d Max D 160 mg/kg/24 h	100–150 mg/kg IV in 2-3 D	12 g IV in 2-3 D
Cefuroxime (2 gen)†	<7 d: 25 mg/kg/D Q 12 hrs.; 7-21 d. 25 mg/kg/D Q 8 hrs.; 21-28 d: 25 mg/kg/D Q 8 hrs.	25–100 mg/kg IV/IM in 4 D	750 mg - 1.5 g; IV or IM every 8 hrs.
Ciprofloxacin†	Safety and efficacy not established AAP does not include ciprofloxacin as an empiric treatment option.	20-30 mg/kg IV in 2 D max D 400 mg	200-400 mg/D Q 8-12 hrs.
Gentamycin (aminoglycoside)‡	≤29 gws. 0-7 d: 5 mg/kg/D Q 48 hrs.; ≤29 gws. 8-30 d: 5 mg/kg/D Q 36 hrs.; ≤29 gws. >30 d: 5 mg/kg/D Q 24 hrs.; 30-36 gws. 0-7d: 5 mg/kg/D Q 36 hrs.; 30-36 gws. >7d: 4 mg/kg/D Q 24 hrs. >37 gws: 4 mg/kg/D Q 24 hrs.	5 mg/kg: IV, IM in 1 D; Drag monitoring (in blood 6-10 mg/l)	3–5 mg/kg; Maximum 0.4 g
Amikacin (aminoglycoside)‡	≤29 gws. 0-7d:18 mg/kg/D Q 48 hrs.; 8–28 d: 15 mg/kg/D Q 36 hrs.; >28 d: 5 mg/kg/D Q 24 hrs.; 30–33 gws. 0–7 d: 18 mg/kg/D Q 36 hrs.; >7 d: 15 mg/kg/D Q 24 hrs.; 34–37gws. 0–7d: 15 mg/kg/D Q 24 hrs.; >7 d: 15 mg/kg/D Q 18–24 hrs.; ≥38 gws. 0-7 d: 15 mg/kg/D Q 24 hrs.; >7 d: 15 mg/kg/D Q 12-18 hrs.; ≥1 mo: 15 mg/kg/D Q 24 hrs.	7,5–15 mg/kg IV, IM in 1 D	Max. D 1,5 g
Tobramycin‡	≤29 gws. 0-7 d: 5 mg/kg/D Q 48 hrs.; 8–28 d: 4 mg/kg/D Q 36 hrs.; >28 d: 4 mg/kg/D Q 24 hrs.; 30–33 gws. 0–7d: 4.5 mg/kg/D Q 36 hrs.; >7 d: 4 mg/kg/D Q 24 hrs.; 34-37gws. 0–7 d: 4 mg/kg/D Q 24 hrs.; >7 d: 4 mg/kg/D Q 18–24 hrs.; ≥38 gws. 0-7d: 4 mg/kg/D Q 24 hrs.; >7 d: 4 mg/kg/D Q 12–18 hrs.; ≥1 mo: 5 mg/kg/D Q 24 hrs.	5 mg/kg: IV, IM in 1 D	3–5 mg/kg: IV, IM in 1 D Max: 0.4 g
Imipenem–Cilastatin (carbapenem)§	<7 d: 25 mg/kg/D Q 12 hrs.; 7-28 d: 25 mg/kg/D Q 8 hrs.; 1-3 mos: 25mg/kg/D Q 6 hrs.	50-100 mg/kg IV in 2–4 D	Max dose 4 g
Meropenem (carbapenem) †	<32 gws. <14 d: 20 mg/kg/D Q 12 hrs.; <32 gws. 14-77 d: 20 mg/kg/D Q 8 hrs.; ≥32 gws. ≤7 d: 20 mg/kg/D Q 12 hrs.; ≥32 gws. >7 d: 20 mg/kg/D Q 8 hrs.	30–60 mg/kg IV in 3D	Max dose 6 g

Table 5. Antibacterial Drugs Administered Parenterally for Treatment of Urinary Tract Infections in Children and Adolescents

Chemotherapeutics	Daily dosage		
	Age ≤1 yr.	Age 1–12 yrs.	Adolescents*
Piperacillin + Tazobactam†	≤29 gws. <28 d: 50-100 mg/kg/D Q 12 hrs.; ≤29 gws >28 d: 50-100 mg/kg/D Q 8 hrs.; 30-36 gws. <14 d: 50–100 mg/kg/D Q 12 hrs.; 30-36 gws. >14 d: 50–100 mg/kg/D Q 8 hrs.; 37-44 gws. <7 d: 50-100 mg/kg/D Q 12 hrs.; 37-44 gws. >7 d: 50-100 mg/kg/D Q 8 hrs.; >45 gws. all 50-100 mg/kg/D Q 6 hrs.	150–400 mg/kg IV in 3-4 D	2-4g/D Q 6 hrs.
Trimethoprim (TMP) /Sulfamethoxazol†	2 mos.-2 yr.; 3-6 mg/kg/D Q12 hrs.	8-20 mg/kg: IV in 2-4 D	
Ampicillin	≤29 gws. <28 d: 50 mg/kg Q 12 hrs.; ≤29 gws. >28 d: 30 mg/kg Q 8 hrs.; 30-36 gws <14 d: 50 mg/kg Q 12 hrs.; 30-36 gws. >14 d: 30 mg/kg Q 8 hrs.; 37-44 gws. <7 d: 50 mg/kg Q 12 hrs.; 37-44 gws. >7 d: 30 mg/kg Q 8 hrs.	100-200 mg/kg IV in 3-4 D	3-6 g IV in 3-4 D
Amoxicillin†	Preterm N, BW <4 kg: 20 to 150 mg/kg/day in 3 D; N, BW ≥4 kg-3 mos: 0 to 150 mg/kg/day in 3 D; >3 mos: 20 to 200 mg/kg/day in 3 D	50-100 mg/kg IV in 3 D	1.5-6 g IV in 3 D
Amoxicillin/clavulanic acid (Dosage based on amoxicillin component)†	<3 mos, BW <4 kg: 30 mg/kg Q 12 hrs.; <3 mos, BW >4 kg: 30 mg/kg Q 8 hrs.; >3 mos: 30 mg/kg Q 8 hrs.	60-100 mg/kg IV in 3 D	3.6–6.6 g IV in 3 D

*If different; Gen=Generation; Q=(from Latin "quaque")=Every; D=Dose; IV=Intravenous; IM=Intramuscular; AAP=American Academy of Pediatrics; Max=Maximal; d=Days; N=Neonates; BW=Body weight; †Adjust dose in renal failure; ‡Extreme caution in neonates with renal dysfunction. Caution in concurrent therapy with cephalosporins, potent diuretics, neuromuscular blocking agents, ototoxic and/or nephrotoxic drugs; §Not recommended in pediatric patients with CNS infections because of the risk of seizures and not recommended in children <39 kg with renal impairment; gws=Gestational weeks; §Not recommended in pediatric patients with CNS infections because of the risk of seizures and not recommended in children <39 kg with renal impairment.

Parenteral empirical antibacterial therapy is applied: in children younger than 3 months of age, when the child is severely ill with clinical suspicion of urosepsis, in those with complicated febrile UTI (e.g. upper tract dilatation), in dehydrated patients, in those with vomiting and/or diarrhea, or when parents are not reliable in terms of giving the medicine. A daily single dose of a third-generation cephalosporin and/or aminoglycosides (amikacin) achieves excellent therapeutic results. Once daily administration of aminoglycosides, in patients without pre-existing renal impairment, is as effective as multiple daily dosing, has a lower risk of nephrotoxicity, and there is no greater risk of ototoxicity. Given the additional convenience and reduced cost, once daily dosing should be the preferred mode of administration. Fortunately, the outcome of UTI caused by ESBL-producing bacteria in children appears to be also good even in cases of in vitro documented resistance to empirical intravenous antibiotic therapy (51, 52).

Very few studies have evaluated the transition from parenteral to oral therapy in infants (53). In the premature infant, the bioavailability of most antibiotics is not known, therefore, intravenous therapy is typically preferred (53). In older infants, Benador et al. (54) observed that the risk of renal scarring was not different in infants that received three days of parental therapy followed by seven days of oral therapy, when compared with 10 days of oral therapy. Thus, in older and more mature infants, after the clinical condition has improved, usually after two

Table 6. Antibacterial Agents Given by Oral Route (PO) for Treatment of Urinary Tract Infections in Children and Adolescents

Chemotherapeutics	Daily dosage		
	Age 1-12 yrs.	Age ≤1yr., if different	Adolescents*
Amoxicillin/clavulanic acid (oral) †, ‡	45 mg/kg (amoxicillin fraction); max: 500 mg clavulanic acid per day in 3 D	<3 mo. 30 mg/kg/day in 2D; >3 mos 25-45 mg/kg/day in 2D	250-500 mg/D Q 8 hrs or 500-875 mg/D Q 12 hrs.
Oral cephalosporins			
Ceftibuten (3gen) †	9 mg/kg in 1-2 D	<6 months: Safety and efficacy not established	0.4 g
Cefixime (3 gen) †	8–12 mg/kg in 1-2 D	<6 months: Safety and efficacy not established	0.4 g
Cefpodoxime proxetil (2 gen) †	8-10 mg/kg in 2 D	15 d-6 mos.: 8mg/kg in 2D	0.4 g
Cefuroxime axetil (2 gen) †	20-30 mg/kg in 3 D	No experience in <3 mos.	0.5-1.0 g
Cefaclor (1 gen)*	50-100 mg/kg in 2-3 D	>1 mo: 20-40 mg/kg in 2-D	1.5-4.0 g
TMP/Sulfamethoxazole*	TMP 5-6 mg/kg in 2 D	>2 mos: 8 mg/kg in 2 D	320 mg
Ciprofloxacin†	20–40 mg/kg in 2 D	Due to adverse side effects AAP does not include ciprofloxacin as an empiric treatment option.	750 mg
Nitrofurantoin†	5-7 mg/kg in 4 D	Safety and efficacy have not been established in patients younger than 1 month. It is not recommended for the treatment of febrile UTI because of its limited tissue penetration.	Up to 400 mg/24 h

*If different; Gen=generation; D=Doses per day; PO=Oral; TMP=Trimethoprim; †Adjust dose in renal dysfunction; AAP=American Academy of Pediatrics; ‡Contraindicated when hepatic impairment; d=Days.

to four days, parenteral antibiotic therapy is changed to oral antibacterial therapy, which is called sequential therapy (2, 4). If the causative agent is only sensitive to drugs administered by the parenteral route, it is continued to completely cure the infection. Also, when there is poor therapeutic compliance, parenteral therapy is a more reliable form of treatment. Overall, the duration of treatment in acute pyelonephritis is 10-14 days, and in patients with uncomplicated low urinary tract infection (cystitis), oral treatment should be given for at least 3–4 d (up to 7 days).

Neonates with fever should be routinely hospitalized to undergo a sepsis workup, including urinalysis, and urine culture. When UTI documented, empiric therapy will start with a combination of parenteraly administered antibiotics. Ampicillin and gentamicin are the traditional empiric therapies; however local antibiotic resistance patterns and maternal use of antibiotics before delivery should be considered. The dosing recommendation is given in Table 5. The duration of therapy is 10 to 14 days. Neonates who are older, born full term, and have no genitourinary or associated disorders will receive shorter courses of intravenous antibiotics. Evidence concerning the efficacy of antibacterial prophylaxis after the first episode of UTI is lacking for the neonatal population.

A child with UTI should be hospitalized in the following circumstances: infants younger than three months, severely ill patients (sepsis, dehydration, vomiting), noncompliant parents or guardians, and if the

febrile period lasts for more than three days despite the administration of the appropriate antibacterial drug. For patients with low oral intake or with dehydration, parenteral rehydration must be readily provided. Asymptomatic bacteriuria without leukocyturia, should not be treated by antibiotics unless the UTI causes problems or an operative procedure is planned (4).

Treatment Response in Children with Febrile UTI

Successful treatment of UTI results in sterilization of the urine within the first 24 h, normalization of body temperature within 24-48 h and the disappearance of leukocyturia within 3-4 days after the start of antibacterial therapy. Patients failing to recover are suspected to have treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction. Therefore, immediate renal and bladder ultrasound (RBUS) is necessary.

Antibacterial Prophylaxis

Symptomatic UTI recurrence occurs in at least 20% of children after the first UTI (55). In infancy, the earlier the first UTI occurs, the higher the chance of recurrence (56). Higher grades of reflux, bilateral VUR, and the first infection not caused by E. coli, significantly increase the risk of recurrent UTI (56). Although some prospective randomized studies have questioned the efficacy of antibacterial prophylaxis (ABP) (2-5, 57), well-designed trials have shown that some subgroups of patients clearly benefit from prophylaxis (58-60). To prevent recurrent UTI and/or renal damage, prophylaxis should be considered in the following clinical situations: the presence of prenatal sonographic findings suggestive of uropathies until imaging investigation of the urinary tract has been completed, in the presence of obstructive uropathy until its correction, in the presence of VUR grades III to V, and in patients with bladder and bowel dysfunction (BBD) until its improvement under urotherapy (4, 53, 61). The optimal duration of ABP has not been well established. The Italian protocol suggests 1-2 years (5). Prophylactic antibiotics may be safely discontinued in children with mild / moderate grade VUR when they become toilet-trained (62).

Routine ABP is not indicated in children while clean intermittent catheterization (CIC) is being performed. ABP usage is not protective against the development of symptomatic UTI or new lesions in neurogenic bladder patients receiving CIC. Furthermore, more resistant colonies were observed in the ABP-receiving period (63).

Instructions of current protocols (2-5) on the use of ABP are given in Table 7, while the antibacterial drugs most commonly used for ABP are presented in Table 8.

Table 7. What Do the New Protocols Suggest Concerning Antibacterial Prophylaxis

Protocol*	Antibacterial prophylaxis
AAP (2)	No
NICE (3)	No
EAU/ESPU (4)	Yes, for children with a febrile UTI, BBD, or dilating VUR
Italian† (5)	After APN till VCUG, VUR gradus ≥III, Reccurent UTI

*Reference; AAP=The American Academy for Pediatrics; NICE=The National Institute for Health and Clinical Excellence; EAU/ESPU=European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) Paediatric Guidelines Committee; †Italian Society of Pediatric Nephrology; BBD=bladder and bowel dysfunction; UTI=Urinary tract infection; VUR=Vesicoureteral reflux; APN=Acute pyelonephritis; VCUG=Voiding cystourethrography.

Table 8. Antibacterial Prophylaxis for Urinary Tract Infection*

Antibacterial drug	Prophylactic dosage per day mg/kg†	Limitations in young infants
TMP/Sulfamethoxazole	1 (TMP fraction)	Not recommended <6 wks. of age
Nitrofurantoin	1	Not recommended <3 mos. of age
Cefaclor or Cephalexin	10	No age limitations
Cefixime	2	Not recommended in preterms and newborns
Ceftibuten	2	In Germany, ceftibuten is not approved for infants <3 mos. old (1)
Amoxicillin/clavulanic acid (oral)	15 mg/kg (amoxicillin fraction)	-

*Modified from reference (4); †Prophylactic drug is usually applied in night before going to sleep; TMP=Trimethoprim.

Cranberry juice is increasingly being used to prevent UTI as it has been documented to reduce a number of recurrent UTI (64, 65). Given that cranberry products are harmless, readily available, and may be beneficial, they should be considered for children.

Concluding Remarks

Following acute viral respiratory tract infections, UTIs are the second, most common infections in children. After febrile UTI, up to 40% of children have permanent renal scarring that may lead to poor renal growth, early arterial hypertension, preeclampsia and chronic kidney disease. Although a genetic background for severity of UTI has been recently recognized, prompt diagnosis and treatment of UTI remain of utmost importance. The lowest contamination rates for urine sampling are obtained by SPA and bladder catheterization, while in daily practice a clean middle catch of the first morning urine of is the most commonly used method for taking a sample of urine, with a good rate of accuracy. UTI can be excluded if the dipstick is negative for both leukocyte esterase and nitrites, or if the microscopic analysis is negative for both pyuria and bacteriuria. Urine culture is mandatory for diagnosis of UTI. In practice, the classical definition of $>10^5$ CFU/ml of voided urine is most commonly used to define significant UTI. In neonates and young infants, intravenous antibiotics are usually recommended for treatment of febrile UTI. There is still no consensus regarding the best imaging approach and antibiotic prophylaxis after the first episode of febrile UTI. As suggested by Williams et al. (52) a practical approach would be: (1) RBUS in all children, and (2) VCUG and/or DMSA for children with abnormal RBUS findings. Prophylaxis should be considered for cases of high susceptibility to recurrent UTI and a high risk of renal damage. A child with an anatomical and/or functional urinary tract abnormality should be monitored until the existing abnormality completely heals, and very often during their whole childhood.

Conflict of interest: The author declares that she has no conflict of interest.

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