available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Guidelines

Urinary Tract Infections in Children: EAU/ESPU Guidelines

Raimund Stein [a,*], *Hasan S. Dogan* [b], *Piet Hoebeke* [c], *Radim Kočvara* [d], *Rien J.M. Nijman* [e], *Christian Radmayr* [f], *Serdar Tekgül* [b]

[a] *Division of Paediatric Urology, Department of Urology, Mainz University Medical Centre, Johannes Gutenberg University, Mainz, Germany;* [b] *Hacettepe University, Faculty of Medicine, Department of Urology, Division of Paediatric Urology, Ankara, Turkey;* [c] *Department of Urology, Ghent University Hospital, Gent, Belgium;* [d] *Department of Urology, General Teaching Hospital in Praha, and Charles University 1st Faculty of Medicine, Praha, Czech Republic;* [e] *Department of Urology, Division of Pediatric Urology, University of Groningen, Groningen, The Netherlands;* [f] *Department of Urology, Medical University of Innsbruck, Innsbruck, Austria*

Article info

Article history:
Accepted November 5, 2014

Keywords:
Urinary tract infection
Children
Urine sampling
Diagnosis
Treatment
Antibacterial treatment
Ultrasound
Follow-up imaging
Renal scar
guidelines
EAU
ESPU

EU ✱ ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Context: In 30% of children with urinary tract anomalies, urinary tract infection (UTI) can be the first sign. Failure to identify patients at risk can result in damage to the upper urinary tract.
Objective: To provide recommendations for the diagnosis, treatment, and imaging of children presenting with UTI.
Evidence acquisition: The recommendations were developed after a review of the literature and a search of PubMed and Embase. A consensus decision was adopted when evidence was low.
Evidence synthesis: UTIs are classified according to site, episode, symptoms, and complicating factors. For acute treatment, site and severity are the most important. Urine sampling by suprapubic aspiration or catheterisation has a low contamination rate and confirms UTI. Using a plastic bag to collect urine, a UTI can only be excluded if the dipstick is negative for both leukocyte esterase and nitrite or microscopic analysis is negative for both pyuria and bacteriuria. A clean voided midstream urine sample after cleaning the external genitalia has good diagnostic accuracy in toilet-trained children. In children with febrile UTI, antibiotic treatment should be initiated as soon as possible to eradicate infection, prevent bacteraemia, improve outcome, and reduce the likelihood of renal involvement. Ultrasound of the urinary tract is advised to exclude obstructive uropathy. Depending on sex, age, and clinical presentation, vesicoureteral reflux should be excluded. Antibacterial prophylaxis is beneficial. In toilet-trained children, bladder and bowel dysfunction needs to be excluded.
Conclusions: The level of evidence is high for the diagnosis of UTI and treatment in children but not for imaging to identify patients at risk for upper urinary tract damage.
Patient summary: In these guidelines, we looked at the diagnosis, treatment, and imaging of children with urinary tract infection. There are strong recommendations on diagnosis and treatment; we also advise exclusion of obstructive uropathy within 24 h and later vesicoureteral reflux, if indicated.

* Corresponding author. Division of Paediatric Urology, Department of Urology, Mainz University Medical Centre, Johannes Gutenberg University, Langenbeckstr. 1, 55131 Mainz, Germany.
Tel. +49 6131 171; Fax: +49 (0)613 117 7690.
E-mail address: steinraimund@gmail.com (R. Stein).

http://dx.doi.org/10.1016/j.eururo.2014.11.007

CrossMark

1. Introduction

In 30% of children with urinary tract anomalies, urinary tract infection (UTI) can be the first sign [1]. If we fail to identify patients at risk, damage to the upper urinary tract may occur. Up to 85% of infants and children with febrile UTI have visible photon defects on technetium Tc 99–labelled dimercaptosuccinic acid (DMSA) scanning, and 10–40% of these children have permanent renal scarring [2–4] that may lead to poor renal growth, recurrent pyelonephritis, impaired glomerular function, early hypertension, end-stage renal disease, and preeclampsia [5–10].

Identifying children at risk of renal parenchymal damage and follow-up imaging after UTI is controversial. In these guidelines, we provide recommendations for the diagnosis, treatment, and imaging of children presenting with UTI based on evidence, and when this is lacking, based on expert consensus.

2. Background

UTI is the most common bacterial infection in childhood [11–14], and up to 30% of infants and children experience recurrent infections during the first 6–12 mo after initial UTI [15,16]. In very young infants, symptoms of UTI differ in many ways from those in older infants and children. The prevalence is higher in the first age group, with a male predominance. Most infections are caused by *Escherichia coli*, although in the first year of life *Klebsiella pneumoniae*, *Enterobacter* spp, *Enterococcus* spp, and *Pseudomonas* are more frequent than later in life, and there is a higher risk of urosepsis compared with adulthood [17–19].

The incidence of UTIs depends on age and sex. In the first year of life, UTIs are more common in boys (3.7%) than in girls (2%). This is even more pronounced in febrile infants in the first 2 mo of life, with an incidence of 5% in girls and 20.3% in uncircumcised boys, as demonstrated in one prospective study of >1000 patients using urine specimens obtained by catheterisation [18]. Later, the incidence changes, and about 3% of prepubertal girls and 1% of prepubertal boys are diagnosed with a UTI [17–19].

3. Methodology

Several guidelines on dealing with specific subgroups of UTI are currently available, some of which are driven by economic and health care issues [20–22]. The recommendations in these guidelines were developed by the European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) Paediatric Guidelines Committee after a review of the literature and a search of PubMed and Embase for *UTI* and *newborn, infants, preschool, school, child*, and *adolescent*. A consensus decision was adopted when evidence was low. In these cases, all relevant papers and statements were discussed by all the authors until a consensus was achieved. The same criteria for the levels of evidence and grades of recommendation as in the EAU guidelines were used [23].

4. Classification

The four widely used infection classification systems depend on the site, episode, symptoms, and complicating factors. For acute treatment, the site and severity are the most important.

4.1. Classification according to site

Cystitis (lower urinary tract) is inflammation of the urinary bladder mucosa with symptoms including dysuria, stranguria, frequency, urgency, malodorous urine, incontinence, haematuria, and suprapubic pain. However, in newborns and infants, these symptoms are rarely diagnosed accurately.

Pyelonephritis (upper urinary tract) is diffuse pyogenic infection of the renal pelvis and parenchyma with symptoms including fever ($\geq$38 °C). But unlike adults, infants and young children may have nonspecific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting, or diarrhoea.

4.2. Classification according to episode

Classifications are *first infection* and *recurrent infection*, which is subdivided into unresolved or persistent and reinfection [24].

4.3. Classification according to symptoms

Asymptomatic bacteriuria (ABU) indicates attenuation of uropathogenic bacteria by the host or colonisation of the bladder by nonvirulent bacteria that are incapable of activating a symptomatic response (no leucocyturia or symptoms). In patients with significant bacteriuria, leucocyturia can be present without any symptoms.

Symptomatic UTI includes irritative voiding symptoms, suprapubic pain (cystitis), fever, and malaise (pyelonephritis). In patients with a neurogenic bladder and malodorous urine, it is difficult to distinguish between ABU and symptomatic UTI.

4.4. Classification according to complicating factors

Uncomplicated UTI is an infection in a patient with a morphologic and functional normal upper and lower urinary tract, normal renal function, and a competent immune system.

Complicated UTI occurs in newborns, in most patients with clinical evidence of pyelonephritis, and in children with known mechanical or functional obstructions or problems of the upper or lower urinary tract [25].

5. Diagnostic work-up

5.1. Medical history

The site, episode, symptoms, and complicating factors are identified by taking the patient's history. This includes questions on primary (first) or secondary (recurring)

infection, febrile or nonfebrile UTIs; malformations of the urinary tract (eg, pre- or postnatal ultrasound [US] screening), previous operations, drinking, and voiding habits; family history; whether there is constipation or the presence of lower urinary tract symptoms; and sexual history in adolescents.

5.2. Clinical signs and symptoms

Fever may be the only symptom of UTI, especially in young children [14,26–30]. Newborns with pyelonephritis or urosepsis can present with nonspecific symptoms (failure to thrive, jaundice, vomiting, hyperexcitability, lethargy, hypothermia, and sometimes without fever) [31,32]. Septic shock is unusual, even with high fever [24], unless obstruction is present or the child is otherwise compromised. In older children, lower urinary tract symptoms include dysuria, stranguria, frequency, urgency, malodorous urine, incontinence, haematuria, and suprapubic pain, and for the upper urinary tract, fever and flank pain.

UTI in infancy may also be accompanied by a transient pseudohypoaldosteronism with profound hyponatraemia with or without hyperkalaemia [33,34].

5.3. Physical examination

A complete paediatric physical examination is required to exclude any other source of fever, and especially if the fever has no apparent cause, UTI should be ruled out. Physical examination should search for signs of constipation, palpable and painful kidney, palpable bladder (stigmata of spina bifida or sacral agenesis spine and feet), for genital disorders (phimosis, labial adhesion, postcircumcision meatal stenosis, abnormal urogenital confluence, cloacal malformations, vulvitis, epididymoorchitis), and measure temperature.

5.4. Urine sampling, analysis, and culture

Before any antimicrobial agent is given, urine sampling must be performed. The technique used to obtain urine for urinalysis or culture affects the rate of contamination that in turn influences interpretation of the results, especially in early infancy [29,35].

5.4.1. Urine sampling

5.4.1.1. Newborns, infants, and non–toilet-trained children. In newborns, infants, and non–toilet-trained children, there are four main methods for obtaining urine with varying contamination rates and invasiveness.

A plastic bag attached to the cleaned genitalia is the technique used most often in daily practice. It is helpful when the culture result is negative. UTI can be excluded without the need for confirmatory culture if the dipstick is negative for both leukocyte esterase and nitrite, or microscopic analysis is negative for both pyuria and bacteriuria [36]. As a result of the high contamination rate and high incidence of false-positive results, urine bag culture alone is not sufficiently reliable for diagnosing UTI.

For clean-catch urine collection, the infant is placed in the lap of a parent or nurse holding a sterile foil bowl underneath the infant's genitalia [37]. This is time consuming and requires careful instructing of the parents. There seems to be a good correlation between the results of a urine culture obtained by this method and by suprapubic bladder aspiration (SPA) [20,37]. However, the contamination rates were 26% in clean-catch urine compared with 1% in the SPA group in a 2012 study [38].

Bladder catheterisation may be an alternative to SPA, although the rates of contamination are higher [39]. The risk factors for a high contamination rate using this technique are patients <6 mo of age, difficult catheterisation, and uncircumcised boys [40].

Therefore, in children ≤6 mo of age and uncircumcised boys, use of a new sterile catheter with each repeated attempt at catheterisation may reduce contamination [40]. Otherwise, SPA should be the method of choice. Catheterisation is preferable in children with urosepsis when a permanent catheter may be considered in the acute phase.

SPA is the most sensitive method for obtaining an uncontaminated urine sample. Using US to assess bladder filling simplifies the aspiration [41,42]. Bladder puncture causes more pain than catheterisation in infants <2 mo of age [43]. The Eutectic Mixture of Local Anesthetics, an emulsion containing a 1:1 mixture of lidocaine and prilocaine, can be used topically to reduce pain [44].

5.4.1.2. Toilet-trained children. In toilet-trained children, a clean voided midstream urine sample has a good rate of accuracy [45]. It is important to clean the genitalia beforehand to reduce the contamination rate [46]. In this age group, clean-catch voided urine, preferably midstream, has a sensitivity of 75–100% and a specificity of 57–100%, as shown in five studies using an SPA urine sample as the reference standard [45].

If there is strong suspicion of upper UTI and for the differential diagnosis of sepsis, it is appropriate to obtain an adequate urine sample by catheterisation or SPA [20]. In infants, the use of a bag is reliable only if the dipstick is negative; otherwise, the urine should be obtained through catheterisation or SPA. This is also recommended for exclusion or confirmation of UTI in older children who are severely ill.

5.4.2. Urine analysis

Dipsticks and microscopy are commonly used for urinalysis. Some centres use flow imaging analysis technology.

Most dipsticks test for nitrite, leukocyte esterase, protein, glucose, and blood. A dipstick test that is positive for leucocyte esterase and nitrite is highly sensitive for UTI [20,45,47]. A test that is negative for leukocyte esterase and nitrite is highly specific for ruling out UTI [45]. A few studies have suggested that glucose is also a useful marker [45]. Only one study has looked at the diagnostic accuracy of a dipstick test for blood. It found that blood demonstrated poor sensitivity (25%) and high specificity (85%) [48].

Table 1 – Criteria for urinary tract infections in children from the EAU guidelines on urological infections

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of CFU per millilitre (at least 10 identical colonies)	≥1000–50 000 CFU/ml	$\geq 10^4$ CFU/ml with symptoms $\geq 10^5$ CFU/ml without symptoms

CFU = colony-forming units.
Modified with permission from the European Association of Urology [75].

Microscopy is used to detect pyuria and bacteriuria. Bacteriuria alone has a higher sensitivity than pyuria alone, although if both are positive, there is a high likelihood of UTI [45].

Flow imaging analysis technology is increasingly used to classify particles in uncentrifuged urine specimens [49]. The numbers of white blood cells, squamous epithelial cells, and red cells correlate well with those found by manual methods [20].

5.4.3. *Urine culture*

In patients with negative results on dipstick, microscopic, or automated urinalysis, urine culture is unnecessary if there is an alternative cause of the fever or inflammatory signs. However, if the dipstick and/or urinalysis are positive, confirmation of UTI by urine culture is mandatory.

The classical definition of $>10^5$ CFU/ml of voided urine is still used to define significant UTI in adult women [50,51]. However, the count can vary and be related to the method of specimen collection, diuresis, and the duration and temperature of storage between collection and cultivation [52]. The recent American Academy of Pediatrics (AAP) Guidelines on UTI suggest that the diagnosis should be based on the presence of both pyuria and at least 50 000 CFU/ml in an SPA sample. However, some studies have shown that in voided specimens, ≤10 000 organisms may indicate significant UTI [53,54].

If urine is obtained by catheterisation, 1000–50 000 CFU/ml is considered positive, and any counts obtained after SPA should be considered significant. Mixed cultures indicate contamination (Table 1).

5.5. *Blood test*

Serum electrolytes and blood cell counts should be obtained for monitoring ill patients with febrile UTI. C-reactive protein has a lower specificity for identifying patients with renal parenchymal involvement [55], whereas serum procalcitonin (>0.5 ng/ml) can be used as a reliable serum marker [55–58]. In a severely ill child, blood cultures should be taken as well as US imaging of the urinary tract.

5.6. *Ultrasound*

Early US examination is indicated in children with febrile UTI and urosepsis to discriminate initially between complicated and uncomplicated UTI. It is also indicated if UTI is associated with pain or haematuria, or according to the preference of the treating physician/surgeon.

6. Therapy

Before any antibiotic therapy is started, a urine specimen should be obtained for urinalysis and urine culture. In febrile children with signs of UTI (clinical signs, positive dipstick and/or positive microscopy), antibiotic treatment should be initiated as soon as possible to eradicate the infection, prevent bacteraemia, improve clinical outcome, diminish the likelihood of renal involvement during the acute phase of infection, and reduce the risk of renal scarring [31,59–61]. In children with febrile UTI and no previous normal US examination, US of the urinary tract within 24 h is advised to exclude obstructive uropathy, depending on the clinical situation.

6.1. *Asymptomatic bacteriuria*

In ABU without leucocyturia, antibiotic treatment should be avoided unless UTI causes problems or an operative procedure is planned. In a screening study from Sweden, 2.5% of the boys and 0.9% of the girls <1 yr of age had ABU verified by SPA. Among those infants, one girl and one boy developed symptoms of pyelonephritis close to the time of detection; the others remained asymptomatic. The median persistence of bacteriuria was 2 mo in girls and 1.5 mo in boys [62]. Therefore screening for and treatment of ABU should be discouraged, irrespective of the method of urine sampling.

6.2. *Cystitis in children >3 mo of age*

There are conflicting data concerning the duration of antibiotic therapy in this scenario, although there seems to be an advantage in treating these children for >1–2 d [63–65]. Therefore, in patients with uncomplicated cystitis, oral treatment should be given for at least 3–4 d.

6.3. *Febrile children: administration route*

When choosing between oral and parenteral therapy, these factors should be considered: patient age; clinical suspicion of urosepsis; severity of illness; refusal of fluids, food, and/or oral medication; vomiting; diarrhoea; noncompliance; and complicated febrile UTI (eg, upper tract dilatation).

As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants <2 mo of age, parenteral antibiotic therapy is recommended. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoaldosteronism can

occur in such cases [33,34,66]. Combination treatment with ampicillin and an aminoglycoside (eg, tobramycin or gentamicin) or a third-generation cephalosporin achieves excellent therapeutic results. A daily single dose of aminoglycosides is safer and equally effective as twice daily [66–68].

The prevalence of antibiotic resistance in uropathogenic *E coli* differs markedly among countries, with high resistance in Iran and Vietnam [69]. There are upcoming reports of UTIs caused by extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae in children. In one study from Turkey, 49% of the children <1 yr of age and 38% of those >1 yr of age had ESBL-producing bacteria. Within these groups 83% were resistant to trimethoprim/sulfamethoxazole, 18% to nitrofurantoin, 47% to quinolones, and 40% to aminoglycosides [70]. Fortunately, the outcome appears to be the same as for children with non–ESBL-producing bacteria, despite the fact that initial intravenous empirical antibiotic therapy was inappropriate in one study [71].

The choice of agent is also based on local antimicrobial sensitivity patterns and should be adjusted later according to sensitivity testing of the isolated uropathogen [20]. Not all available antibiotics are approved by national health authorities for use in paediatric populations, especially in infants.

6.4. Duration of therapy in febrile urinary tract infection

The duration of parenteral application is still controversial [20,66,72,73]. The consensus of the guideline panellists, as well as the AAP recommendations, is that parenteral antibiotic therapy should be continued until the child is afebrile, after which oral antibiotics should be given for 7–14 d [20].

If ambulatory (outpatient) therapy is chosen in late infancy, adequate surveillance, medical supervision, and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, close contact with the family is advised [74].

In complicated UTI with uropathogens other than *E coli*, parenteral treatment with broad-spectrum antibiotics is preferred [66]. Temporary urinary diversion may be required in obstructive uropathy, depending on clinical status and/or response to antibiotic therapy.

6.5. Antimicrobial agents

Tables 2–4 list the recommended antibacterial therapies for different urogenital infections [75].

6.6. Prophylaxis

Some prospective randomised studies have challenged the efficacy of antibacterial prophylaxis [76–80]. However, a subgroup of patients, missed by the large randomised studies, benefits from prophylaxis (Table 5). The Swedish reflux study [81] clearly demonstrated that chemoprophylaxis is effective in preventing new renal scars in infant girls with reflux III and IV. No patients in the prophylaxis group developed new renal scars, whereas 8 of 43 girls in the surveillance group and 5 of 42 in the endoscopically treated group had new renal scars at DMSA scanning after 2 yr. None of the 75 boys developed a new renal scar [81].

A recent study compared children with infantile vesicoureteral reflux (VUR) with recurrent UTI (33 male, 11 female; mean age: 3.2 mo) and without recurrent UTI (40 male, 7 female; mean age: 4.8 mo) [82]. They demonstrated that during the first year of life, the earlier the first UTI occurs, the higher the chance of recurrence. Higher grades of reflux, bilateral VUR, and the first infection not caused by *E coli* significantly increase the risk of recurrent UTIs [82]. Clearly, there is a benefit for girls with dilating reflux, and long-term antibacterial prophylaxis should be considered in those cases of high susceptibility to UTI and risk of acquired renal damage.

The recently published Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial including 607 children (280 with a reflux I or II and 322 with a reflux III or IV) demonstrated that antimicrobial prophylaxis with trimethoprim/sulfamethoxazole reduced the risk of recurrence by 50%. In particular, children with a febrile index infection, bladder and bowel dysfunction (BBD), or dilating reflux benefitted from prophylaxis. The number of new renal scars was not different in this study [83].

The indication for using cephalosporins for chemoprophylaxis should be reconsidered in regions with a high incidence of ESBL-producing bacteria in children [70,71].

Cranberry juice is increasingly used to prevent UTI. In one randomised Finnish trial, cranberry juice did not significantly reduce the number of children who experienced recurrence of UTI, but it was effective in reducing the actual number of recurrences and related antimicrobial use [84]. In another study of only 40 children, cranberry juice with high concentrations of proanthocyanidin (37%) reduced the average incidence of UTI over a 12-mo period to 0.4 patient/year with 1.15 in the placebo group [85].

Compliance with prophylaxis is important. In some studies, between 17% and 69% of the patients were compliant [86–88]. Compliance depends greatly on parent and patient education [89].

In boys with phimosis, early treatment should be discussed (local corticosteroid or surgery).

7. Monitoring of urinary tract infection

With successful treatment, urine usually becomes sterile after 24 h, and leucocyturia normally disappears within 3–4 d. Normalisation of body temperature can be expected within 24–48 h after the start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Immediate US examination is necessary, if not performed initially as recommended.

Procalcitonin (among other laboratory inflammatory parameters such as C-reactive protein and leukocyte count) can be used as a reliable serum marker for early prediction

Table 2 – Frequently used antibacterial agents for treatment of paediatric urinary tract infections

Chemotherapeutics	Daily dosage		Application	Comments
	0–12 yr	Adolescents, if different		
Parenteral cephalosporins				
Group 3a (eg, cefotaxime)	100–200 mg/kg		IV in 2–3 D	
Group 3b (eg, ceftazidime)	100–150 mg/kg	3–6 g	IV in 2–3 D	
Ceftriaxone	75 mg/kg	2–6 g	IV in 1 D	
Oral cephalosporins				
Group 3 (eg, ceftibuten)	9 mg/kg	0.4 g	PO in 1–2 D	
Group 3 (eg, cefixime)	8–12 mg/kg	0.4 g	PO in 1–2 D	
Group 2 (eg, cefpodoxime proxetil)	8–10 mg/kg	0.4 g	PO in 2 D	
Group 2 (eg, cefuroxime axetil)	20–30 mg/kg	0.5–1.0 g	PO in 3 D	
Group 1 (eg, cefaclor)	50–100 mg/kg	1.5–4.0 g	PO in 2–3 D	
TMP or TMP/Sulfamethoxazole	5–6 mg/kg 5–6 mg/kg (TMP fraction)	– 320 mg	PO in 2 D PO in 2 D	
Ampicillin	100–200 mg/kg	3–6 g	IV in 3–4 D	Ampicillin and amoxicillin are not eligible for calculated therapy
Amoxicillin	50–100 mg/kg	1.5–6.0 g	PO in 2–3 D* IV in 3 D	
Amoxicillin/clavulanic acid (parenteral)	60–100 mg/kg	3.6–6.6 g	IV in 3 D PO in 3 D	
Amoxicillin/clavulanic acid (oral)	45 mg/kg (amoxicillin fraction); maximum: 500 mg clavulanic acid per day	1500 and 375 mg	PO in 3 D; IV in 3–4 D	
Piperacillin	300 mg/kg per day			
Tobramycin	5 mg/kg	3–5 mg/kg; maximum: 0.4 g	IV in 1 D	Drug monitoring
Gentamicin	5 mg/kg	3–5 mg/kg; maximum: 0.4 g	IV in 1 D	
Ciprofloxacin	Children and adolescents (1–17 yr): 20–30 mg/kg (maximum dose: 400 mg) (parenterally) Children and adolescents (1–17 yr): 20–40 mg/kg (maximum dose: 750 mg) (PO)		IV in 3 D PO in 2 D	Approved in most European countries as second- or third-line medication for complicated UTIs; antibiotic of last resort
Nitrofurantoin	3–5 mg	–	PO in 2 D	Contraindicated in the case of renal insufficiency

D = doses per day; IV = intravenous; PO = oral; TMP = trimethoprim; UTI = urinary tract infection.
* Infants: 2 D; children 1–12 yr: 3 D; adolescents: 2–3 D.
Modified with permission from the European Association of Urology [75].

of renal parenchymal inflammation with a first febrile UTI [56]. In patients with febrile UTI, serum electrolytes and blood cell counts should be obtained.

7.1. *Patients at risk*

Patients at risk are those with antenatally diagnosed uropathy, photopaenia on DMSA scanning after UTI, abnormal US examination (eg, upper urinary tract dilatation, small duplex kidney [or even small/dysplastic kidney], thick bladder wall, postvoid residual urine [if possible, US should always be performed with a full and empty bladder]), ureterocele, posterior urethral valves, urogenital abnormalities, intestinal connections to the perineum, previous UTI, dysfunctional voiding, enlarged bladder, poor urine flow, constipation, abdominal mass, spinal anomaly, family history of VUR, and those with poor family compliance.

If no other cause is found, additional imaging is recommended for those with recurrent fever, poor growth, failure to thrive, or high blood pressure. If the parents refuse further imaging (voiding cystourethrography [VCUG] or DMSA scanning), they must be informed that there is at least a 30% chance of reflux and that renal scarring can develop.

8. Imaging

8.1. *Ultrasound*

Renal and bladder US is advised in all children with febrile UTI to exclude dilatation or anomalies of the upper and lower urinary tract if no improvement is seen within 24 h because some conditions are life threatening. It can be delayed in those with a previous normal US examination, depending on the clinical situation. Abnormal results are found in approximately 15% of cases, and 1–2% have abnormalities that require prompt action (eg, additional evaluation, referral, diversion, or surgery) [20].

In other studies, renal US has revealed abnormalities in up to 37% of cases, whereas VCUG showed VUR in 27% of cases [1]. Dilating VUR (with [intermittent] dilatation of the renal pelvis and calices) was missed by US in 24–33% of cases; in two published series [90,91], 14 of 23 patients with normal US had recurrent pyelonephritis [90], with another study finding the figure to be approximately two of three patients <2 yr of age who presented with febrile UTI [92].

Postvoid residual urine should be measured in toilet-trained children to exclude voiding abnormalities. If pelvic US shows filling of the rectum >30 mm, constipation must

Table 3 – Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of infection*

Diagnosis	Proposal	Application	Duration of therapy	Level of evidence
Pyelonephritis during the first 0–6 mo of life	Ceftazidime and ampicillin* or aminoglycoside and ampicillin*	3–7 d parenterally for at least 2 d after defervescence; then oral therapy†	10 (to 14) d	4
		Newborns: parenteral therapy for 7–14 d; then oral therapy†	Newborns: 14–21 d	
Uncomplicated pyelonephritis (without dilatation or known reflux) after 6 mo of age	Cephalosporin group 3†	Orally (initially parenterally, if necessary)	7 (to 10) d	1b
Complicated pyelonephritis (with dilatation/reflux; severe bladder dysfunction?) and/or urosepsis (all ages)	Ceftazidime and ampicillin* or aminoglycoside and ampicillin*	7 d parenterally; then oral therapy†	10–14 d	4

Modified with permission from the European Association of Urology [75].
* After receipt of microbiologic findings (pathogen, resistance), adaptation of therapy.
† Intravenous (eg, cefotaxime); orally (eg, cefpodoxime proxetil, ceftibuten, cefixime).

Table 4 – Recommended antibacterial treatment for cystitis and cystourethritis

Chemotherapeutics	Daily dosage*	Application
Oral cephalosporins		
Group 1 (eg, cefaclor)	50 (to 100) mg/kg	PO in 2–3 D
Group 1 (eg, cephalexin)	50 mg/kg	PO in 3–4 D
Group 2 (eg, cefuroximaxetil)	20–30 mg/kg	PO in 2 D
Group 2 (eg, cefpodoxime proxetil)	8–10 mg/kg	PO in 2 D
Group 3 (eg, ceftibuten)	9 mg/kg	PO in 1 D
TMP	5–6 mg/kg	PO in 2 D
TMP/Sulfamethoxazole	5–6 mg/kg (TMP fraction)	PO in 3 D
Amoxicillin/Clavulanic acid	37.5–75.0 mg/kg (amoxicillin fraction)	PO in 3 D
Nitrofurantoin	3–5 mg/kg	PO in 2 D

D = dosage per day; PO = oral; TMP = trimethoprim.
* Dosages for children up to 12 yr of age.
Modified with permission from the European Association of Urology [75].

Table 5 – Possibilities for antibacterial prophylaxis

Substance*	Prophylactic dosage per day, mg/kg	Limitations in young infants
Trimethoprim	1	Not recommended <6 wk of age
Trimethoprim	1–2	Not recommended <2 mo of age
Sulfamethoxazole	10–15	
Nitrofurantoin	1	Not recommended <3 mo of age
Cefaclor	10	No age limitations
Cefixime	2	Not recommended in preterms and newborns
Ceftibuten†	2	
Cefuroximaxetil†	5	

* The first-choice antibacterials are nitrofurantoin, trimethoprim, and trimethoprim/sulfamethoxazole; in exceptional cases, oral cephalosporin can be used.
† In Germany, ceftibuten is not approved for infants <3 mo old.
Modified with permission from the European Association of Urology [75]. Modified according to Craig et al [80].

be considered [93–97]. US alone misses up to 33% of patients at risk; therefore, additional imaging is recommended (DMSA/VCUG) (Fig. 1).

8.2. *Renal scintigraphy*

In some children and infants, sedation is required to achieve good quality scanning. A radiation dose of approximately 1 mSv should be taken into account when considering multiple DMSA scans during initial and follow-up imaging [98]. Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage, and they correlate well with the presence of dilating reflux and the risk of further breakthrough infections and future renal scarring [99].

DMSA scanning can be used as a first-line diagnostic procedure based on observations that dilating VUR occurs in most children with an abnormal DMSA scan [90,100]. To exclude reflux early and avoid recurrent UTI, DMSA scanning should be performed within 1–2 mo of the UTI episode. However, these findings are different in newborns. After the first symptomatic community-acquired UTI, most

renal units with VUR grade ≥III had normal early DMSA scanning [101].

8.3. Voiding cystourethrography

VCUG is still the gold standard for the exclusion or confirmation of VUR. The radiation dose can be reduced (eight times lower) by using grid-controlled variable-rate pulsed fluoroscopy rather than continuous fluoroscopy [102]. The radiation dose in children ≤10 yr of age is approximately 0.1–0.55 mSv [103]. Using the techniques available for radiation protection, it is possible routinely to reduce the radiation dose below the lowest reference level valid for newborns [104].

Due to the risk of renal scarring, VCUG or DMSA scanning is recommended after the first episode of febrile UTI, depending on sex, age, and clinical presentation (Fig. 1 and Table 6). Although exclusion of reflux requires investigations that are invasive and unpleasant, as well as costly and time consuming, there is some evidence that not using VCUG and/or DMSA scanning fails to diagnose VUR in patients who are at risk for further renal scarring (sect. 8.1). Two approaches are recommended for the diagnosis of VUR: the bottom-up method (VCUG and, if positive, a DMSA scan) or the top-down method (DMSA scan and, if positive, VCUG) [105].

In one study, the percentage of permanent renal scarring was higher in those with reflux (37%) than in

Table 6 – General and specific recommendations in children with febrile urinary tract infection

General recommendations	<1 yr of age, specific	>1 yr of age, girl specific	>1 yr of age, boy specific	Toilet trained, girl specific	Toilet trained, boy specific
Medical history Anomalies in the pre- or postnatal US Recurrent UTI Family history				Symptoms of LUTS/BBD	Symptoms of LUTS/BBD
Clinical investigation Exclusion of other sources of fever Complete physical examination					
Urine sampling Suprapubic bladder aspiration (most sensitive method) Bladder catheterisation Clean-catch urine collection Plastic bag (useful only if negative for both pyuria and bacteriuria)				Midstream urine sample If urgently needed: bladder catheterisation or suprapubic bladder aspiration	Midstream urine sample If urgently needed: bladder catheterisation or suprapubic bladder aspiration
Blood sample Depending on clinical symptoms/ complicated UTI	Electrolyte Blood cell count Creatinine C-reactive protein Procalcitonin				
Imaging US to exclude upper tract dilatation within 24 h, depending on the clinical situation and medical history					
AB therapy/administration route In uncomplicated UTI, oral AB therapy is possible and gives the same results as parenteral AB treatment	Infants <2 mo of age: parenteral AB therapy				
Duration of therapy Parenteral AB therapy should be continued until the child is afebrile, followed by oral AB for 7–14 d If the child remains febrile, reconsider the administration route and choice of drug, or repeat the US (upper tract dilatation/abscess formation)				Oral AB for 7–14 d (uncomplicated UTI: 7 d; complicated UTI requires longer treatment)	Oral AB for a total of 7–14 d (uncomplicated UTI: 7 d; complicated UTI requires longer treatment)
Follow-up imaging Exclusion of VUR by VCUG and/or DMSA scan	Exclusion of VUR	Exclusion of VUR	Exclusion of VUR after recurrent febrile UTIs	Exclusion of LUTS/BBD	Exclusion of LUTS/BBD Exclusion of VUR only if there is a suspicion
Follow-up therapy Consider prophylaxis		With or without treatment of VUR	Consider treatment of phimosis with or without treatment of VUR	Treatment of BBD/ LUTS with or without treatment of VUR	Treatment of BBD/ LUTS with or without treatment of VUR Consider treatment of phimosis

AB = antibiotic; BBD = bladder and bowel dysfunction; DMSA scan = (technetium Tc 99 labelled) dimercaptosuccinic acid scan; LUTS = lower urinary tract symptoms; US = ultrasound; UTI = urinary tract infection; VCUG = voiding cystourethrogram; VUR = vesicoureteral reflux.

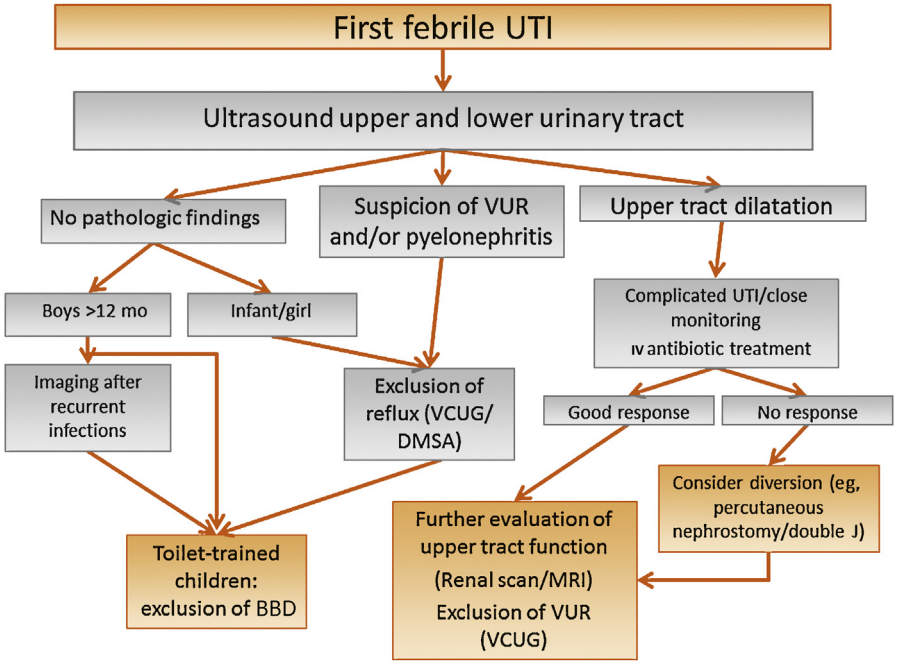

Fig. 1 – Algorithm for assessment and treatment of first febrile urinary tract infection.
BBD = Bladder Bowel Dysfunction; DMSA = dimercaptosuccinic acid; IV = intravenous; MRI = magnetic resonance imaging; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

those without reflux (12%), even if the delay between the onset of symptoms and treatment was shorter for those with reflux (4.3 ± 1.8 d) than for those without reflux (4.9 ± 2.4 d) [106].

The timing of VCUG does not influence the presence or severity of VUR [107,108]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [109,110]. VCUG should be performed after UTI has been treated. To date, no randomised study has demonstrated that it is safe to perform VCUG during ongoing UTI and that the results of VCUG change the treatment.

9. Bladder and bowel dysfunction

BBD is a risk factor for which every child with UTI should be screened at presentation. Correction of lower urinary tract dysfunction is important to decrease the rate of UTI recurrence. If there are signs of BBD during infection-free intervals, further diagnosis and effective treatment are strongly recommended [111–114]. Treatment of constipation leads to a decrease in UTI recurrence [115–117]. Exclusion of BBD is therefore strongly recommended in any child with febrile and/or recurrent UTI, and, if present, treatment of BBD is necessary [118].

10. Conclusions

Figure 1 and Table 6 summarise the general recommendations:

- Classification of a UTI is made according to the site, episode, symptoms, and complicating factors. For acute treatment, the site and severity are of the most importance.
- Immediate US of the kidney and bladder are necessary in patients with febrile UTI to exclude underlying uropathy.
- Treatment of patients with febrile UTIs should be initiated after urine analysis and culture to confirm the diagnosis.
- SPA and catheterisation have the lowest contamination rate for urine sampling. Using a plastic bag (most commonly used in daily practice), UTI can be excluded if the dipstick is negative for both leukocyte esterase and nitrite or microscopic analysis is negative for both pyuria and bacteriuria.
- Prophylaxis has been shown to be beneficial in preventing new renal scars in infant girls with dilating reflux III and IV. Reflux should be excluded in patients with febrile UTIs.
- In toilet-trained children, BBD should be excluded.

Author contributions: Raimund Stein had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stein, Dogan, Hoebeke, Kočvara, Nijman, Radmayr, Tekgül.
Acquisition of data: Stein, Dogan, Hoebeke, Kočvara, Nijman, Radmayr, Tekgül.
Analysis and interpretation of data: Stein, Dogan, Hoebeke, Kočvara, Nijman, Radmayr, Tekgül.
Drafting of the manuscript: Stein, Dogan, Hoebeke, Kočvara, Nijman, Radmayr, Tekgül.
Critical revision of the manuscript for important intellectual content: Stein, Dogan, Hoebeke, Kočvara, Nijman, Radmayr, Tekgül.
Statistical analysis: No statistical analysis was carried out.

Obtaining funding: Tekgül.
Administrative, technical, or material support: Stein, Nijman, Tekgül.
Supervision: Stein, Nijman, Tekgül.
Other (specify): None.

Financial disclosures: Raimund Stein certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Raimund Stein is a company consultant for Grachtenhaus Apotheke, and participates in trials for Bayer Health Care on gonadal function, sexual function, and quality of life in patients with spina bifida. Radim Kočvara participates in trials for Ferring Pharmaceuticals CZ and receives fellowships and travel grants from B. Braun Medical and Ferring Pharmaceuticals CZ. Serdar Tekgül participates in trials for Sanofi Aventis, Astellas, Sanofi, and Pfizer. The other authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

References

[1] Sastre JB, Aparicio AR, Cotallo GD, Colomer BF, Hernandez MC. Urinary tract infection in the newborn: clinical and radio imaging studies. Pediatr Nephrol 2007;22:1735–41.
[2] Jakobsson B, Svensson L. Transient pyelonephritic changes on 99mTechnetium-dimercaptosuccinic acid scan for at least five months after infection. Acta Paediatr 1997;86:803–7.
[3] Benador D, Benador N, Slosman D, Mermillod B, Girardin E. Are younger children at highest risk of renal sequelae after pyelonephritis? Lancet 1997;349:17–9.
[4] Hewitt IK, Zucchetta P, Rigon L, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. Pediatrics 2008;122:486–90.
[5] Fotter R. Paediatric uroradiology. In: Baert AL, Sartor K, editors. Medical radiology: diagnostic imaging. Berlin, Germany: Springer; 2001.
[6] Sacks SH, Verrier Jones K, Roberts R, Asscher AW, Ledingham JG. Effect of symptomless bacteriuria in childhood on subsequent pregnancy. Lancet 1987;2:991–4.
[7] Jacobson SH, Eklof O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. BMJ 1989;299:703–6.
[8] Smellie JM, Prescod NP, Shaw PJ, Risdon RA, Bryant TN. Childhood reflux and urinary infection: a follow-up of 10–41 years in 226 adults. Pediatr Nephrol 1998;12:727–36.
[9] Larcombe J. Urinary tract infection. Clin Evid 2002;7:377–85.
[10] Round J, Fitzgerald AC, Hulme C, Lakhanpaul M, Tullus K. Urinary tract infections in children and the risk of ESRF. Acta Paediatr 2012;101:278–82.
[11] Stull TL, LiPuma JJ. Epidemiology and natural history of urinary tract infections in children. Med Clin North Am 1991;75:287–97.
[12] Marild S, Jodal U. Incidence rate of first-time symptomatic urinary tract infection in children under 6 years of age. Acta Paediatr 1998;87:549–52.
[13] O'Brien K, Stanton N, Edwards A, Hood K, Butler CC. Prevalence of urinary tract infection (UTI) in sequential acutely unwell children presenting in primary care: exploratory study. Scand J Prim Health Care 2011;29:19–22.
[14] Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D. Prevalence of urinary tract infection in febrile infants. J Pediatr 1993;123:17–23.
[15] Mangiarotti P, Pizzini C, Fanos V. Antibiotic prophylaxis in children with relapsing urinary tract infections: review. J Chemother 2000;12:115–23.
[16] Nuutinen M, Uhari M. Recurrence and follow-up after urinary tract infection under the age of 1 year. Pediatr Nephrol 2001;16:69–72.
[17] Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J 2008;27:302–8.
[18] Zorc JJ, Levine DA, Platt SL, et al. Clinical and demographic factors associated with urinary tract infection in young febrile infants. Pediatrics 2005;116:644–8.
[19] Kanellopoulos TA, Salakos C, Spiliopoulou I, Ellina A, Nikolakopoulou NM, Papanastasiou DA. First urinary tract infection in neonates, infants and young children: a comparative study. Pediatr Nephrol 2006;21:1131–7.
[20] Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 201;128:595–610.
[21] Ammenti A, Cataldi L, Chimenz R, et al. Febrile urinary tract infections in young children: recommendations for the diagnosis, treatment and follow-up. Acta Paediatr 2012;101:451–7.
[22] National Institute for Health and Care Excellence (NICE). Urinary tract infection in children: diagnosis, treatment and long-term management. NICE Web site. http://www.nice.org.uk/guidance/cg054.
[23] Shortliffe LMD. Infection and inflammation of the pediatric genitourinary tract. In: Wein AJ, Kavoussi LR, Novick AC, et al., editors. Campbell-Walsh urology. ed. 9. Philadelphia, PA: Saunders; 2007. p. 3232–68.
[24] Craig JC, Irwig LM, Knight JF, Sureshkumar P, Roy LP. Symptomatic urinary tract infection in preschool Australian children. J Paediatr Child Health 1998;34:154–9.
[25] Burns MW, Burns JL, Krieger JN. Pediatric urinary tract infection. Diagnosis, classification, and significance. Pediatr Clin North Am 1987;34:1111–20.
[26] Bonadio WA. Urine culturing technique in febrile infants. Pediatr Emerg Care 1987;3:75–8.
[27] Bauchner H, Philipp B, Dashefsky B, Klein JO. Prevalence of bacteriuria in febrile children. Pediatr Infect Dis J 1987;6:239–42.
[28] Roberts KB, Charney E, Sweren RJ, et al. Urinary tract infection in infants with unexplained fever: a collaborative study. J Pediatr 1983;103:864–7.
[29] Craig JC, Williams GJ, Jones M, et al. The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. BMJ 2010;340:c1594.
[30] Slater M, Krug SE. Evaluation of the infant with fever without source: an evidence based approach. Emerg Med Clin North Am 1999;17:97–126, viii–ix.
[31] Beetz R. Evaluation and management of urinary tract infections in the neonate. Curr Opin Pediatr 2012;24:205–11.
[32] Biyikli NK, Alpay H, Ozek E, Akman I, Bilgen H. Neonatal urinary tract infections: analysis of the patients and recurrences. Pediatr Int 2004;46:21–5.
[33] Tutunculer F, Gunoz H, Bas F, Bundak R, Saka N, Neyzi O. Transient Pseudohypoaldosteronism in an infant with urinary tract anomaly. Pediatr Int 2004;46:618–20.
[34] Nandagopal R, Vaidyanathan P, Kaplowitz P. Transient pseudohypoaldosteronism due to urinary tract infection in infancy: a report of 4 cases. Int J Pediatr Endocrinol 2009;2009:195728.
[35] Tullus K. Difficulties in diagnosing urinary tract infections in small children. Pediatr Nephrol 2011;26:1923–6.

[36] Whiting P, Westwood M, Watt I, Cooper J, Kleijnen J. Rapid tests and urine sampling techniques for the diagnosis of urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr 2005;5:4.
[37] Ramage IJ, Chapman JP, Hollman AS, Elabassi M, McColl JH, Beattie TJ. Accuracy of clean-catch urine collection in infancy. J Pediatr 1999;135:765–7.
[38] Tosif S, Baker A, Oakley E, Donath S, Babl FE. Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: an observational cohort study. J Paediatr Child Health 2012;48:659–64.
[39] Austin BJ, Bollard C, Gunn TR. Is urethral catheterization a successful alternative to suprapubic aspiration in neonates? J Paediatr Child Health 1999;35:34–6.
[40] Wingerter S, Bachur R. Risk factors for contamination of catheterized urine specimens in febrile children. Pediatr Emerg Care 2011;27:1–4.
[41] Buys H, Pead L, Hallett R, Maskell R. Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. BMJ 1994;308:690–2.
[42] Kiernan SC, Pinckert TL, Keszler M. Ultrasound guidance of suprapubic bladder aspiration in neonates. J Pediatr 1993;123:789–91.
[43] Kozer E, Rosenbloom E, Goldman D, Lavy G, Rosenfeld N, Goldman M. Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized, controlled study. Pediatrics 2006;118:e51–6.
[44] Dutta S. Use of eutectic mixture of local anesthetics in children. Indian J Pediatr 1999;66:707–15.
[45] Whiting P, Westwood M, Bojke L, et al. Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model. Health Technol Assess 2006;10:iii–iv, xi–xiii, 1–154.
[46] Vaillancourt S, McGillivray D, Zhang X, Kramer MS. To clean or not to clean: effect on contamination rates in midstream urine collections in toilet-trained children. Pediatrics 2007;119:e1288–93.
[47] Kunin CM, DeGroot JE. Sensitivity of a nitrite indicator strip method in detecting bacteriuria in preschool girls. Pediatrics 1977;60:244–5.
[48] Boreland PC, Stoker M. Dipstick analysis for screening of paediatric urine. J Clin Pathol 1986;39:1360–2.
[49] Mayo S, Acevedo D, Quinones-Torrelo C, Canos I, Sancho M. Clinical laboratory automated urinalysis: comparison among automated microscopy, flow cytometry, two test strips analyzers, and manual microscopic examination of the urine sediments. J Clin Lab Anal 2008;22:262–70.
[50] Kass EH. Asymptomatic infections of the urinary tract. Trans Assoc Am Physicians 1956;69:56–64.
[51] Lohr JA. Use of routine urinalysis in making a presumptive diagnosis of urinary tract infection in children. Pediatr Infect Dis J 1991;10:646–50.
[52] Zorc JJ, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. Clin Microbiol Rev 2005;18: 417–22.
[53] Bollgren I, Engstrom CF, Hammarlind M, Kallenius G, Ringertz H, Svenson SB. Low urinary counts of P-fimbriated Escherichia coli in presumed acute pyelonephritis. Arch Dis Child 1984;59:102–6.
[54] Stamm WE. Measurement of pyuria and its relation to bacteriuria. Am J Med 1983;75:53–8.
[55] Pecile P, Romanello C. Procalcitonin and pyelonephritis in children. Curr Opin Infect Dis 2007;20:83–7.
[56] Kotoula A, Gardikis S, Tsalkidis A, et al. Comparative efficacies of procalcitonin and conventional inflammatory markers for prediction of renal parenchymal inflammation in pediatric first urinary tract infection. Urology 2009;73:782–6.
[57] Mantadakis E, Plessa E, Vouloumanou EK, Karageorgopoulos DE, Chatzimichael A, Falagas ME. Serum procalcitonin for prediction of renal parenchymal involvement in children with urinary tract infections: a meta-analysis of prospective clinical studies. J Pediatr 2009;155, 875–81.e1.
[58] Leroy S, Romanello C, Galetto-Lacour A, et al. Procalcitonin is a predictor for high-grade vesicoureteral reflux in children: meta-analysis of individual patient data. J Pediatr 2011;159, 644–51.e4.
[59] Doganis D, Sinaniotis K. Early antibiotic treatment of pyelonephritis in children is still mandatory. Pediatrics 2009;123:e173–4, author reply e74.
[60] Coulthard MG, Verber I, Jani JC, et al. Can prompt treatment of childhood UTI prevent kidney scarring? Pediatr Nephrol 2009;24:2059–63.
[61] Oh MM, Kim JW, Park MG, Kim JJ, Yoo KH, Moon DG. The impact of therapeutic delay time on acute scintigraphic lesion and ultimate scar formation in children with first febrile UTI. Eur J Pediatr 2012;171:565–70.
[62] Wettergren B, Jodal U. Spontaneous clearance of asymptomatic bacteriuria in infants. Acta Paediatr Scand 1990;79:300–4.
[63] Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. Cochrane Database Syst Rev 2003:CD003966.
[64] Fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. Cochrane Database Syst Rev 2012:CD006857.
[65] Keren R, Chan E. A meta-analysis of randomized, controlled trials comparing short- and long-course antibiotic therapy for urinary tract infections in children. Pediatrics 2002;109, E70–0.
[66] Beetz R, Bachmann H, Gatermann S, et al. Urinary tract infections in infants and children–a consensus on diagnostic, therapy and prophylaxis [in German]. Urologe A 2007;46:112, 114–8, 120–3.
[67] Hodson EM, Willis NS, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev 2007:CD003772.
[68] Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics 2004;114:e111–8.
[69] Ramos NL, Dzung DTN, Stopsack K, et al. Characterisation of uropathogenic Escherichia coli from children with urinary tract infection in different countries. Eur J Clin Microbiol Infect Dis 2011;30:1587–93.
[70] Kizilca O, Siraneci R, Yilmaz A, et al. Risk factors for community-acquired urinary tract infection caused by ESBL-producing bacteria in children. Pediatr Int 2012;54:858–62.
[71] Tratselas A, Iosifidis E, Ioannidou M, et al. Outcome of urinary tract infections caused by extended spectrum (beta)-lactamase-producing Enterobacteriaceae in children. Pediatr Infect Dis J 2011;30:707–10.
[72] Brady PW, Conway PH, Goudie A. Length of intravenous antibiotic therapy and treatment failure in infants with urinary tract infections. Pediatrics 2010;126:196–203.
[73] Magin EC, Garcia-Garcia JJ, Sert SZ, Giralt AG, Cubells CL. Efficacy of short-term intravenous antibiotic in neonates with urinary tract infection. Pediatr Emerg Care 2007;23:83–6.
[74] Mak RH, Wong JH. Are oral antibiotics alone efficacious for the treatment of a first episode of acute pyelonephritis in children? Nat Clin Pract Nephrol 2008;4:10–1.
[75] Grabe M, Bartoletti R, Bjerklund Johansen TE, et al. Guidelines on urological infections. European Association of Urology Web site. http://www.uroweb.org/gls/pdf/19%20Urological%20infections_LR.pdf.
[76] Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary

antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 2006;117:626–32.
[77] Montini G, Rigon L, Zucchetta P, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics 2008;122:1064–71.
[78] Pennesi M, Travan L, Peratoner L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics 2008;121:e1489–94.
[79] Roussey-Kesler G, Gadjos V, Idres N, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol 2008;179:674–9, discussion 679.
[80] Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 2009; 361:1748–59.
[81] Brandstrom P, Jodal U, Sillen U, Hansson S. The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. J Pediatr Urol 2011;7:594–600.
[82] Park S, Song SH, Lee C, Kim JW, Kim KS. Bacterial pathogens in first febrile urinary tract infection affect breakthrough infections in infants with vesicoureteral reflux treated with prophylactic antibiotics. Urology 2013;81:1342–5.
[83] RIVUR Trial Investigators. Hoberman A, Greenfield SP, Mattoo TK, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014;370:2367–76.
[84] Salo J, Uhari M, Helminen M, et al. Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trial. Clin Infect Dis 2012;54:340–6.
[85] Afshar K, Stothers L, Scott H, MacNeily AE. Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. J Urol 2012;188(Suppl):1584–7.
[86] Smyth AR, Judd BA. Compliance with antibiotic prophylaxis in urinary tract infection. Arch Dis Child 1993;68:235–6.
[87] Copp HL, Nelson CP, Shortliffe LD, Lai J, Saigal CS, Kennedy WA. Compliance with antibiotic prophylaxis in children with vesicoureteral reflux: results from a national pharmacy claims database. J Urol 2010;183:1994–9.
[88] Hensle TW, Hyun G, Grogg AL, Eaddy M. Part 2: Examining pediatric vesicoureteral reflux: a real-world evaluation of treatment patterns and outcomes. Curr Med Res Opin 2007;23(Suppl 4):S7–13.
[89] Yiee JH, Baskin LS, Patel N, Yang J, Disandro M. Prospective blinded laboratory assessment of prophylactic antibiotic compliance in a pediatric outpatient setting. J Urol 2012;187:2176–81.
[90] Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Value of ultrasound in evaluation of infants with first urinary tract infection. J Urol 2010;183:1984–8.
[91] Juliano TM, Stephany HA, Clayton DB, et al. Incidence of abnormal imaging and recurrent pyelonephritis after first febrile urinary tract infection in children 2 to 24 months old. J Urol 2013;190(Suppl): 1501–10.
[92] Massanyi EZ, Preece J, Gupta A, Lin SM, Wang MH. Utility of screening ultrasound after first febrile UTI among patients with clinically significant vesicoureteral reflux. Urology 2013;82:905–9.
[93] Burgers R, de Jong TP, Benninga MA. Rectal examination in children: digital versus transabdominal ultrasound. J Urol 2013;190: 667–72.
[94] Berger MY, Tabbers MM, Kurver MJ, Boluyt N, Benninga MA. Value of abdominal radiography, colonic transit time, and rectal ultrasound scanning in the diagnosis of idiopathic constipation in children: a systematic review. J Pediatr 2012;161:44–50.e1–2.
[95] Joensson IM, Siggaard C, Rittig S, Hagstroem S, Djurhuus JC. Transabdominal ultrasound of rectum as a diagnostic tool in childhood constipation. J Urol 2008;179:1997–2002.
[96] Singh SJ, Gibbons NJ, Vincent MV, Sithole J, Nwokoma NJ, Alagarswami KV. Use of pelvic ultrasound in the diagnosis of megarectum in children with constipation. J Pediatr Surg 2005;40:1941–4.
[97] Klijn AJ, Asselman M, Vijverberg MA, Dik P, de Jong TP. The diameter of the rectum on ultrasonography as a diagnostic tool for constipation in children with dysfunctional voiding. J Urol 2004;172:1986–8.
[98] Smith T, Evans K, Lythgoe MF, Anderson PJ, Gordon I. Radiation dosimetry of technetium-99m-DMSA in children. J Nucl Med 1996; 37:1336–42.
[99] Shiraishi K, Yoshino K, Watanabe M, Matsuyama H, Tanikaze S. Risk factors for breakthrough infection in children with primary vesicoureteral reflux. J Urol 2010;183:1527–31.
[100] Quirino IG, Silva JM, Diniz JS, et al. Combined use of late phase dimercapto-succinic acid renal scintigraphy and ultrasound as first line screening after urinary tract infection in children. J Urol 2011;185:258–63.
[101] Siomou E, Giapros V, Fotopoulos A, et al. Implications of 99mTc-DMSA scintigraphy performed during urinary tract infection in neonates. Pediatrics 2009;124:881–7.
[102] Ward VL, Strauss KJ, Barnewolt CE, et al. Pediatric radiation exposure and effective dose reduction during voiding cystourethrography. Radiology 2008;249:1002–9.
[103] Lee R, Thomas KE, Connolly BL, Falkiner M, Gordon CL. Effective dose estimation for pediatric voiding cystourethrography using an anthropomorphic phantom set and metal oxide semiconductor field-effect transistor (MOSFET) technology. Pediatr Radiol 2009;39: 608–15.
[104] Born M, Spiller L, Bachour H, Heydweiller A, Franke I. Dose area product of pediatric VCUG with regard to the strongly lowered German diagnostic reference levels [in German]. Rofo 2013;185: 262–7.
[105] Tekgül S, Riedmiller H, Hoebeke P, et al. EAU guidelines on vesicoureteral reflux in children. Eur Urol 2012;62:534–42.
[106] Oh MM, Kim JW, Park MG, Kim JJ, Yoo KH, Moon du G. The impact of therapeutic delay time on acute scintigraphic lesion and ultimate scar formation in children with first febrile UTI. Eur J Pediatr 2012;171:565–70.
[107] Doganis D, Mavrikou M, Delis D, Stamoyannou L, Siafas K, Sinaniotis K. Timing of voiding cystourethrography in infants with first time urinary infection. Pediatr Nephrol 2009;24:319–22.
[108] Sathapornwajana P, Dissaneewate P, McNeil E, Vachvanichsanong P. Timing of voiding cystourethrogram after urinary tract infection. Arch Dis Child 2008;93:229–31.
[109] Spencer JD, Bates CM, Mahan JD, et al. The accuracy and health risks of a voiding cystourethrogram after a febrile urinary tract infection. J Pediatr Urol 2012;8:72–6.
[110] Mahyar A, Ayazi P, Tarlan S, Moshiri A, Hamidfar M, Barikani A. When is the best time for voiding cystourethrogram in urinary tract infection of children? Acta Med Iran 2012;50:468–72.
[111] Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol 1998; 160:1019–22.
[112] Hoebeke P, Vande Walle J, Everaert K, Van Laecke E, Van Gool JD. Assessment of lower urinary tract dysfunction in children with non-neuropathic bladder sphincter dysfunction. Eur Urol 1999; 35:57–69.
[113] van Gool JD. Dysfunctional voiding: a complex of bladder/sphincter dysfunction, urinary tract infections and vesicoureteral reflux. Acta Urol Belg 1995;63:27–33.
[114] van Gool JD, Kuitjen RH, Donckerwolcke RA, Messer AP, Vijverberg M. Bladder-sphincter dysfunction, urinary infection and vesicoureteral reflux with special reference to cognitive bladder training. Contrib Nephrol 1984;39:190–210.

[115] De Paepe H, Renson C, Van Laecke E, Raes A, Vande Walle J, Hoebeke P. Pelvic-floor therapy and toilet training in young children with dysfunctional voiding and obstipation. BJU Int 2000; 85:889–93.

[116] Loening-Baucke V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics 1997;100:228–32.

[117] O'Regan S, Yazbeck S, Schick E. Constipation, bladder instability, urinary tract infection syndrome. Clin Nephrol 1985;23: 152–4.

[118] Tekgül S, Dogan HS, Hoebeke P, et al. Guidelines on paediatric urology. European Association of Urology Web site. http://www.uroweb.org/gls/pdf/23%20Paediatric%20Urology_LR%20March%2025th.pdf.