Guidelines

Urinary Tract Infections in Children: EAU/ESPU Guidelines

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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.

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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 99m-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 (≥38 °C). But unlike adults, infants and young children may have nonspecific signs such as poor appetite, failure to thrive, 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 pseudohyponatraemia 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 leukocyte 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].
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, $\leq 10$ 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.

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 pseudohypopaldosteronism can

| 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) | $\geq 10^5$ 000 CFU/ml | $\geq 10^4$ CFU/ml with symptoms |
| | $\geq 10^6$ CFU/ml without symptoms |

CFU = colony-forming units.
Modified with permission from the European Association of Urology [75].
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 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 Vescoureteral 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...
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]), ureteroceles, posterior urethral valves, 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 (voiding cystourethrography [VCUG] or DMSA scanning) is recommended for those with recurrent fever, poor growth, failure to thrive, or high blood pressure. If the parents refuse further imaging, 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
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].

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

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

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* After receipt of microbiologic findings (pathogen, resistance), adaptation of therapy.
† Intravenous (eg, cefotaxime); orally (eg, cefpodoxime proxetil, cefibuten, cefixime).

### Table 4 – Recommended antibacterial treatment for cystitis and cystourethritis

<table>
<thead>
<tr>
<th>Chemotherapeutics</th>
<th>Daily dosage</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cephalexins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (eg, cefaclor)</td>
<td>50 (to 100) mg/kg</td>
<td>PO in 2–3 D</td>
</tr>
<tr>
<td>Group 1 (eg, cephalexin)</td>
<td>50 mg/kg</td>
<td>PO in 3–4 D</td>
</tr>
<tr>
<td>Group 2 (eg, cefuroximaxetil)</td>
<td>20–30 mg/kg</td>
<td>PO in 2 D</td>
</tr>
<tr>
<td>Group 2 (eg, cefpodoxime proxetil)</td>
<td>8–10 mg/kg</td>
<td>PO in 2 D</td>
</tr>
<tr>
<td>Group 3 (eg, cefibuten)</td>
<td>9 mg/kg</td>
<td>PO in 3 D</td>
</tr>
<tr>
<td>TMP</td>
<td>5–6 mg/kg</td>
<td>PO in 2 D</td>
</tr>
<tr>
<td>TMP/Sulfamethoxazole</td>
<td>5–6 mg/kg (TMP fraction)</td>
<td>PO in 3 D</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid</td>
<td>37.5–75.0 mg/kg (amoxicillin fraction)</td>
<td>PO in 3 D</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>3–5 mg/kg</td>
<td>PO in 2 D</td>
</tr>
</tbody>
</table>

D = dosage per day; PO = oral; TMP = trimethoprim.

* Dosages for children up to 12 yr of age.

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### Table 5 – Possibilities for antibacterial prophylaxis

<table>
<thead>
<tr>
<th>Substance</th>
<th>Prophylactic dosage per day, mg/kg</th>
<th>Limitations in young infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim</td>
<td>1</td>
<td>Not recommended &lt;6 wk of age</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>1–2</td>
<td>Not recommended &lt;2 mo of age</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>10–15</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1</td>
<td>Not recommended &lt;3 mo of age</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>10</td>
<td>No age limitations</td>
</tr>
<tr>
<td>Cefixime</td>
<td>2</td>
<td>Not recommended in preterms and newborns</td>
</tr>
<tr>
<td>Cefibuten†</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cefuroximaxetil†</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* The first-choice antibacterials are nitrofurantoin, trimethoprim, and trimethoprim/sulfamethoxazole; in exceptional cases, oral cephalexin can be used.
† In Germany, cefibuten is not approved for infants <3 mo old.

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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 | | | | | |
| 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) | | | | | |
| 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 | Infants <2 mo of age: parenteral AB therapy | 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) |
| In uncomplicated UTI, oral AB therapy is possible and gives the same results as parenteral AB treatment | | | | | |
| 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) | | | | | |
| Follow-up imaging | Exclusion of VUR by VCUG and/or DMSA scan | Exclusion of VUR | Exclusion of VUR after recurrent febrile UTIs | Exclusion of LUTS/BBD | Exclusion of LUTS/BBD |
| 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 prophylaxis | | | | | |

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.
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.

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References


