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Review Article

Update of the EAU/ESPU guidelines on urinary tract infections in children

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Summary

Introduction/background
Urinary tract infections (UTIs) are common in children and require appropriate diagnostic evaluation, management and follow-up.

Objective
To provide a summary of the updated European Association of Urology (EAU) guidelines on Pediatric Urology, which were first published in 2015 in European Urology.

Study design
A structured literature review was performed of new publications between 2015 and 2020 for UTIs in children. The guideline was updated accordingly with relevant new literature.

Results
The occurrence of a UTI can be the first indication of anatomical abnormalities in the urinary tract, especially in patients with a febrile UTI. The basic diagnostic evaluation should include sufficient investigations to exclude urinary tract abnormalities, but should also be as minimally invasive as possible. In recent years, more risk factors have been identified to predict the presence of these anatomical anomalies, such as a non-E. Coli infection, high grade fever and ultrasound abnormalities. When these risk factors are factored into the diagnostic work-up, some invasive investigations can be omitted in a larger group of children.

In addition to the treatment of active UTIs, it is also essential to prevent recurrent UTIs and consequent renal scarring. With the increase of antimicrobial resistance good antibiotic stewardship is needed. In addition, alternative preventative measures such as dietary supplements, bladder and bowel management and antibiotic prophylaxis could decrease the incidence of recurrent UTI.

Conclusion
This paper is a summary of the updated 2021 EAU guidelines on Pediatric Urology. It provides practical considerations and flowcharts for the management and diagnostic evaluation of UTIs in children.

Introduction

Urinary tract infections (UTIs) are a common cause of infections in children. These can occur in children with normal urinary tracts, but can also be a harbinger of urinary tract abnormality. Children with UTIs do not only suffer from the clinical symptoms that present with infection, but also risk long term consequences of, especially those presenting with febrile UTI, which includes renal scarring. It is therefore important to prevent recurrent UTIs. A comprehensive diagnostic evaluation, treatment strategy and monitoring of UTIs is therefore required.

This publication is a summary of the updated 2021 European Association of Urology guidelines on Pediatric Urology. A previous summary of these guidelines was published in 2015 [1]. The most important updates include the incorporation of additional risk factors for anatomic abnormalities in the diagnostic evaluation and an updated flowchart. Furthermore, alternative preventative measures for recurrent UTIs are highlighted.

Materials and methods

The EAU/ESPU guidelines on Pediatric Urology are updated at regular intervals. The previous update of the chapter on UTI was performed in 2015 [1]. This chapter has now been updated with current literature from January 2015 until February 2020. A literature search was performed in Medline, Embase and the Cochrane Library. The terms children and urinary tract infections or derivatives hereof were used. A

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total of 1600 English language abstracts were screened for their relevance by LH and RS and 102 full texts were obtained for appraisal. Relevant publications have been used to update the guideline. Publications were deemed relevant when the results would increase the level of evidence or when the publication introduced new evidence about certain topics. An extensive update of the diagnostic evaluation and preventative measures paragraphs was performed by all panel members. A summary of the current evidence and recommendations is presented here.

Epidemiology and aetiology

Urinary tract infections (UTI) represent the most common bacterial infections in children [2,3]. The symptoms may vary according to the age of the child. In neonates there is a male predominance, the prevalence is higher, infections caused by other organisms than E. Coli are more frequent and there is a higher risk of urosepsis [4,5]. A pooled prevalence of 7.8% (CI: 6.6—8.9) of UTI was seen in older children (<19 years) presenting with urinary tract symptoms [4]. The incidence varies with age and sex. The incidence for boys is highest during the first 6 months of life (5.3%) and decreases with age to around 2% for the ages 1—6 years. In girls the incidence is reversed with UTIs being less common during the first 6 months (2%) and increasing with age to around 11% for the ages of 1—6 years [6]. Several risk factors have been identified such as bladder bowel dysfunction, vesicoureteral reflux and obesity [7—9]. Febrile UTIs have been associated with renal scarring and each new febrile UTI increases the risk of renal scarring by 2.8% (CI 1.2—5.8) [10]. The leading causative organism for UTIs has been E. Coli, but over the years other bacteria have been rising in prevalence [11].

Classification systems

Urinary tract infections are classified according to five systems: site, severity, episode, symptoms and complicating factors, of which site and severity are the most important.

1. Classification according to site.

Lower urinary tract infection (cystitis) is an inflammatory condition of the bladder mucosa. Symptoms include dysuria, frequency, urgency, enuresis, hematuria, suprapubic pain and malodorous urine. It may also include epididymitis which is an inflammatory condition of the epididymis. Symptoms include pain and swelling of the hemiscrotum and can be the presenting symptom of lower urinary tract infection.Upper urinary tract infection (pyelonephritis) is a diffuse pyogenic infection of the renal pelvis and parenchyma. Symptoms include fever, chills and flank pain, and could be as severe as septic shock/toxemia.

2. Classification according to severity.

A UTI is classified as mild when children are experiencing mild symptoms and are able to take fluids and oral medication, often due to a lower urinary tract infection. If they suffer from more serious symptoms such as persistent vomiting, dehydration or fever >39 °C this is classified as a severe UTI.

3. Classification according to episode.

First UTI: this may be a sign of anatomical abnormalities and anatomical evaluation is recommended.

Recurrent UTI: can be divided into unresolved, persistent infection and re-infection. In unresolved infection, the initial therapy is inadequate for elimination of bacterial growth in the urinary tract. Persistent infection is caused by a re-emergence of bacteria from a site within the urinary tract that cannot be eradicated (e.g. stones, non-functioning renal segments). The same pathogen is identified in persistent infection. With re-infection each episode can be caused by a variety of new organisms, in contrast to persistent UTI.

Breakthrough UTI: an infection occurring in patients receiving antimicrobial prophylaxis.

4. Classification according to symptoms.

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that do not activate a symptomatic response.

Symptomatic UTI includes irritative voiding symptoms, suprapubic pain, fever and malaise.

5. Classification according to complicating factors.

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal upper and lower urinary tract, normal renal function and competent immune system. Patients can be managed on an outpatient basis, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract.

A complicated UTI occurs in children with known mechanical of functional pathology of the urinary tract. Patients with a complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to exclude the presence of significant abnormalities and when present adequate drainage of the infected urinary tract is necessary.

Diagnostic evaluation

Medical history and clinical evaluation

A detailed medical history includes the question of first or recurrent infections, fetal abnormalities, possible malformations of the urinary tract, prior operations, family history and the presence of bowel or voiding dysfunctions. The physical examination includes a general examination of the throat, lymph nodes, abdomen, genitalia, flank and back. It also includes measurements of body weight, height and temperature. In neonates and infants, the symptoms may be non-specific such as fever, lethargy, vomiting and failure to thrive. In neonates it is important to rule out co-existing meningitis [12]. In toilet trained children cystitis symptoms, suprapubic and flank pain are more often seen.

Urine sampling

Urine sampling has to be performed to exclude or confirm UTI and before any antimicrobial agent is administered.

In neonates, infants and non-toilet trained children there are four main methods to collect urine:

1. Plastic bag attached to the cleaned genitalia. This has a high risk of contamination in about 50—60% [13]; however, it is helpful when the results are negative to rule out a UTI.
2. Clean-catch urine (CCU) collection where spontaneous voiding, with or without tapping or massaging, is collected in a sterile bowl. This has lower contamination rates of approximately 26% [13,14]; however, it is again helpful when the results are negative to rule out a UTI.
3. Transurethral bladder catheterisation is a fast and safe way to obtain a reliable urine sample with a contamination rate of about 10% [14]. Urine collected this way can be used for urine cultures.
4. Suprapubic bladder aspiration is the most invasive method to obtain urine samples with contamination rates of approximately 1% [14] and these samples can be used for urine cultures as well.

It is recommended to use a tw0-step procedure where the CCU urine sample is screened and if positive, a catheter or suprapubic bladder aspiration is used for urine cultures. This may lead to a reduction in invasive procedures [13,14].

In toilet-trained children who can void on demand, the use of clean catch urine, especially midstream, after carefully cleaning of the external genitalia, can be an acceptable technique for obtaining urine for screening and urine cultures [15].

There are three methods that are commonly used for urinalysis screening:

1. Dipstick
2. Microscopy
3. Flow imaging analysis technology

After negative results for the urinalysis (e.g. negative nitrite, leukocyte tests on stick and no pyuria or bacteriuria on urine microscopy), urine cultures are generally not necessary, especially when there is an alternative diagnosis for the fever. In case of a positive urinalysis, confirmation by urine culture is essential. CCU, midstream and catheterisation urine cultures can be considered positive as 10^3-10^4 cfu/ml of a monoculture. With suprapubic bladder aspirates any count constitutes a positive culture. In general mixed cultures are indicative of contamination. In febrile children <4 months of age a cut-off value of 10^3 cfu/ml can be used when clinical and laboratory findings match and a correct sampling method has been used [16]. A negative culture with the presence of pyuria could be due to incomplete antibiotic treatment, urolithiasis and infections caused by *Mycobacterium tuberculosis* or *Chlamydia trachomatis*.

A flowchart was developed as a guide for the basic diagnostic evaluation and subsequent management (Fig. 1).

Imaging

The optimal strategy for the diagnostic evaluation of children with febrile UTI has been changing over time. It is imperative to ensure any abnormalities in the urinary tract are detected with a judicious use of diagnostic tests. An updated diagnostic strategy based on recent literature is presented in Fig. 1.

Ultrasound: renal and bladder ultrasound within 24 h is advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormalities are found in 15% of patients and 1—2% require prompt action (e.g. drainage) [17]. Renal ultrasound should be performed before and after voiding with special attention to the post-void residual urine in toilet-trained children [18]. When perirenal or psoas abscesses or renal masses are seen subsequent CT imaging to exclude xanthogranulomatous pyelonephritis is advised [19].

Radionuclide scanning/MRI: In the acute phase of a febrile UTI (up to six weeks) a dimercaptosuccinic acid (DMSA) scan can demonstrate pyelonephritis by perfusion defects. Changes in clearance of DMSA correlated with the presence of dilating reflux and risk of further pyelonephritis episodes, breakthrough infections and renal scarring [20]. Renal scars can be detected after three to six months [21]. Diffusion-weighted MRI has been shown to accurately diagnose acute pyelonephritis and reveal late renal scars. This could be an alternative to DMSA thereby avoiding radiation exposure [22].

Voiding cystourethrography (VCUG)/urosonography: The gold standard diagnostic test for vesico-ureteral reflux (VUR) is VCUG. VCUG can also exclude the presence of an infravesical obstruction. The timing of VCUG does not influence the presence or severity of VUR [23]. When performed with proven sterile urine, it does not cause any significant morbidity [24]. It is important to diagnose high-grade VUR after the first UTI since this is an important risk factor for renal scarring. The most important risk factors for high-grade VUR and subsequent scarring are: abnormal renal ultrasound, high grade fever and non-E. Coli infections [25—29]. Considering the invasiveness of VCUG and radiation exposure involved [30] we have updated the comprehensive diagnostic strategy using the identified risk factors for VUR to reduce unnecessary use of VCUG for its diagnosis, Fig. 2.

Antibacterial management

Administration route: the choice between oral and parenteral treatment should be based on patient age, clinical suspicion of urosepsis, refusal of fluids, food and oral medication, vomiting, diarrhoea and complicated pyelonephritis. In newborns and infants less than two months of age parenteral antibiotic treatment is recommended, because of the increased incidence of urosepsis and severe pyelonephritis. Electrolyte disorders with life-threatening hyponatremia and hyperkalemia based on pseudohypoaldosteronism can occur in these cases and clinicians should be aware of anatomical abnormalities, such as obstructive conditions [31].

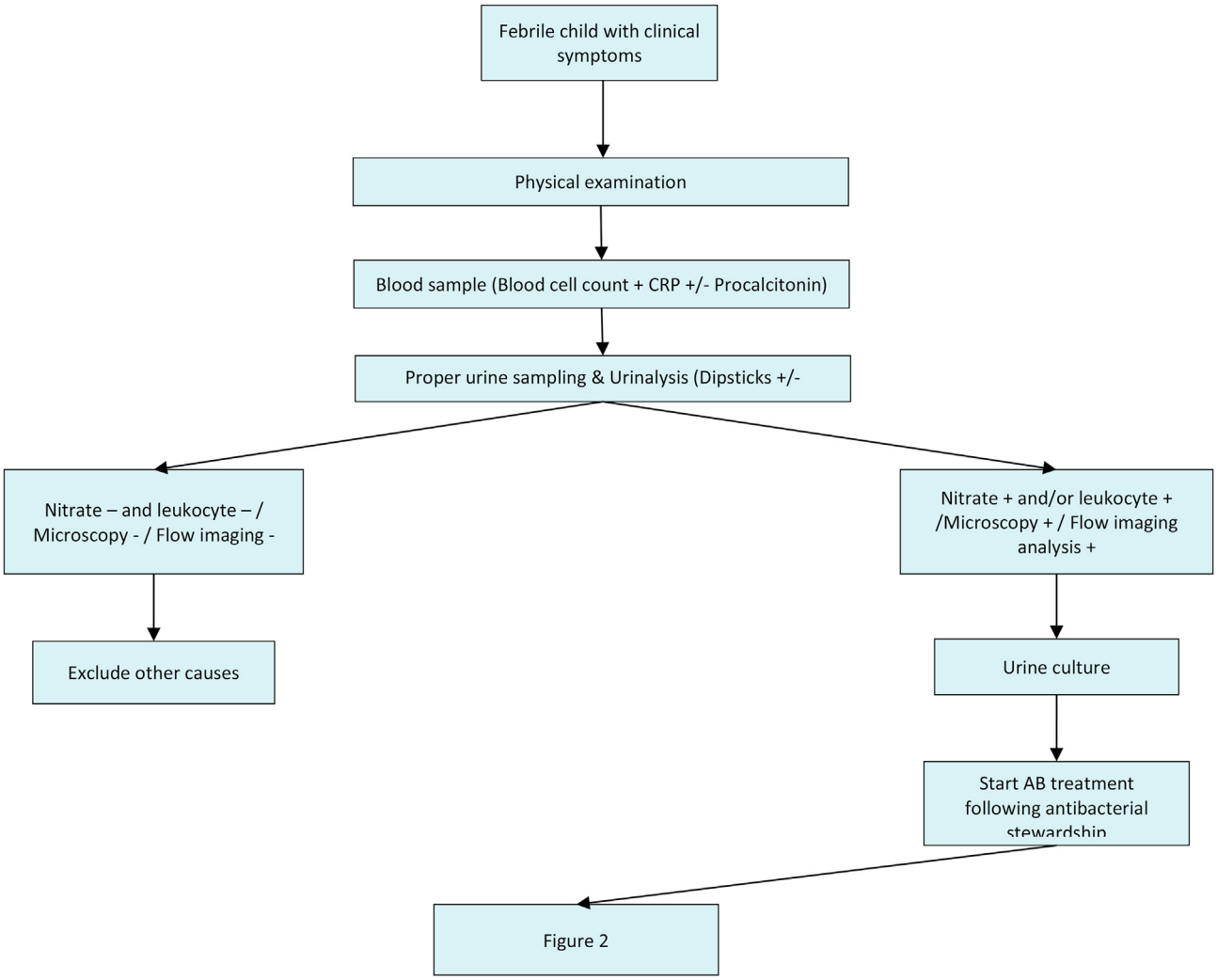

Fig. 1 Flowchart for basic diagnostic evaluation and subsequent management of UTI.

Duration of therapy: Prompt adequate treatment of UTI can prevent the spread of infection and subsequent renal scarring. Outcomes of short courses (one to three days) are inferior to those of seven-to-fourteen-day courses [32]. However, a simple cystitis can be treated with three to five days of antibiotics [33]. No significant difference in recurrent UTIs and rehospitalisation was found between seven day parenteral and longer regimens for UTI in younger infants [34]. In young infants a short course of parenteral treatment with early conversion to oral antibiotics may be considered. When ambulatory treatment is chosen, active surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. Close contact with the family is advised in the initial phase [35]. In complicated UTI, uropathogen other than E. Coli, such as Proteus Mirabilis, Pseudomonas Aeruginosa, are more often the causative pathogens [36]. Temporary urinary diversion such as a stent or nephrostomy might be required in case of failure of conservative treatment in obstructive uropathy.

Antimicrobial agents: There is a significant difference in prevalence patterns of antibiotic resistance of uropathogenic E. Coli in different countries, with increased high resistance patterns in countries outside The Organisation for Economic Cooperation and Development (OECD) [37]. Several risk factors and determinants for UTIs caused by ESBL and non-E Coli bacteria have been identified including history of infection, recent hospitalisation, short-term exposure to antibiotics, and prophylaxis [38,39]. The choice of antibiotics should be guided by good antibiotic stewardship. It is important to be aware of local resistance patterns. These differ between countries and moreover between hospitals. Local antibiotic protocols and web-based recommendations can guide the choice for type of antibiotic therapy. The individual patients' previous cultures should also be taken into account. The daily dosage of

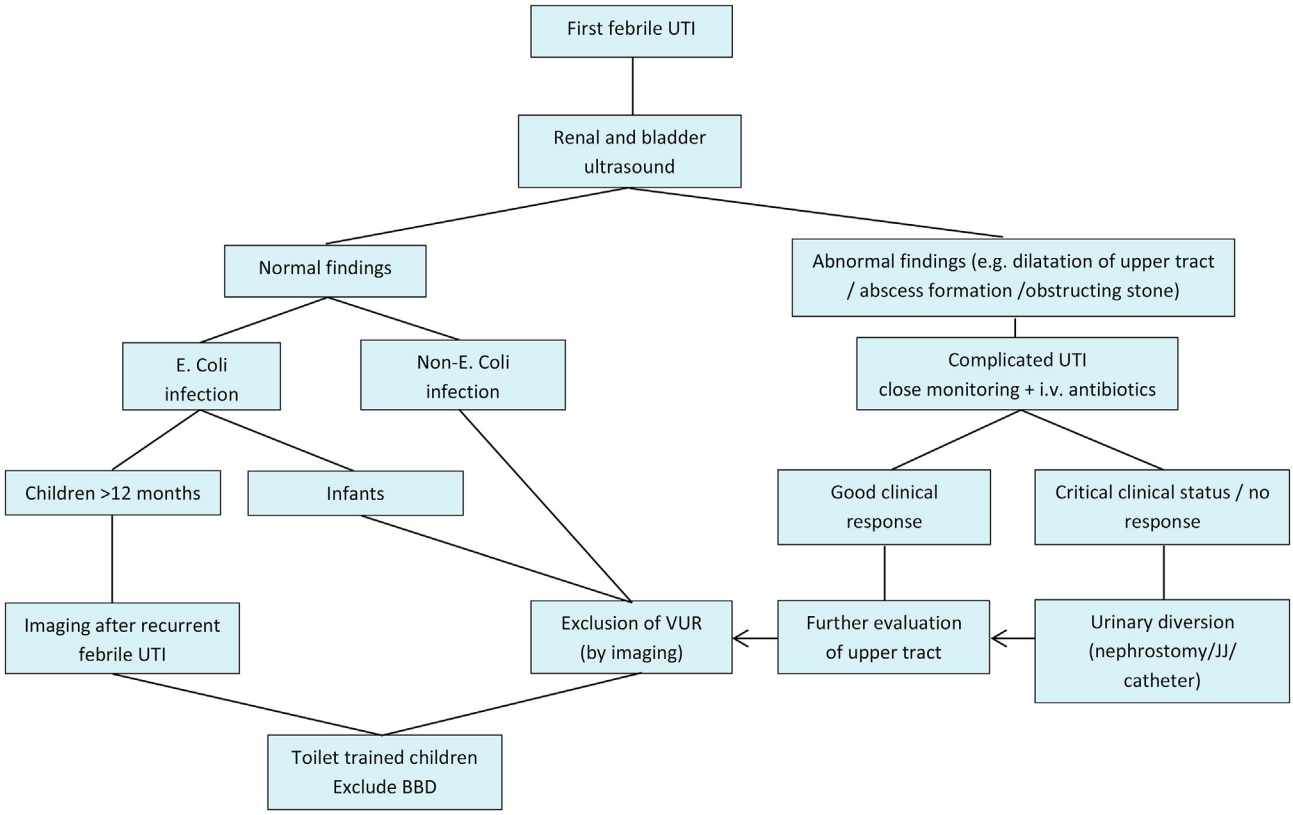

Fig. 2 Flowchart for comprehensive diagnostic evaluation using risk factors.

antibiotics depends on age, weight of the child as well as on renal and liver function.

Preventative measures

Recurrent UTIs are not only problematic because the symptoms are bothersome to children, but recurrent febrile infections will also result in renal scarring [10]. Therefore, it is important to prevent UTI recurrences.

Chemoprophylaxis: Chemoprophylaxis is commonly used to prevent UTIs in children. With increasing resistance rates, one should carefully consider which patients should receive antibacterial prophylaxis, since long-term use has been associated with increased microbial resistance [40,41]. Its use causes a reduction in number of recurrent UTIs, but it did not reduce newly acquired renal damage in children with first and second UTI [41]. However, when used in children with anatomic abnormalities of the urinary tracts a reduction in UTI and subsequent renal scarring was shown [40,41]. Patients with incomplete emptying of the bladder appropriately performing CIC, but still suffering from recurrent UTIs the intravesical application of Gentamicin has been proven effective [42].

Dietary supplements: Cranberry, mostly as juice, has been shown to decrease the risk of UTIs in healthy children, and in children with urogenital abnormalities cranberries appear to be just as effective as antibiotic prophylaxis, even though results were variable between different studies [43]. The results of probiotics are somewhat more conflicting, with one systematic review not ruling out any effect [44] and a randomized controlled trail showing promising results in children with normal urogenital anatomy [45]. A meta-analysis could however not demonstrate a beneficial effect, except as an adjuvant to antibiotic prophylaxis [46]. Even though more studies into supplements are warranted, Vitamin A showed promising results in preventing renal scarring in children with acute pyelonephritis [47,48] and Vitamin E could possibly ameliorate the symptoms of UTI [49].

Prepuce: Use of steroid crème in the presence of physiologic phimosis in boys with UTI significantly reduced recurrent UTIs [50]. In newborns with an anatomical abnormality circumcision may also prevent UTIs [51—53].

Bladder and bowel dysfunction (BBD) is a risk factor for UTI and each child presenting with a UTI should be screened for the presence of BBD. Normalisation of micturition disorders or bladder overactivity is important to lower the rate of

UTI recurrence. Treatment of constipation leads to a decrease in number of UTIs and a multidisciplinary approach is recommended [54]. Exclusion of BBD is strongly recommended in any toilet-trained child presenting with febrile and/or recurrent UTI and should be treated accordingly.

Monitoring of UTI

With successful treatment, urine usually becomes sterile after 24 h and leukocyturia disappears within three to four days. Normalisation of body temperature can be expected within 24—48 h in 90% of patients. The presence of urinary obstruction, congenital uropathy and treatment-resistant uropathogen should be suspected in children with prolonged fever and failing recovery. Repeat ultrasound examination is recommended in these patients. Procalcitonin, C-reactive protein and leukocyte count can be used as reliable serum markers for renal parenchymal inflammation [55]. A cut-off value of 1.0 ng/ml of Procalcitonin has been shown to be predictive of acute pyelonephritis in young children [56]. In patients with febrile UTI, serum electrolytes and blood counts should be followed up.

Summary of evidence

Summary of evidence	LE
Urinary tract infection represents the most common bacterial infection in children less than 2 years of age. The incidence varies depending on age and sex.	1b
Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.	2b
The number of colony forming units (cfu) in the urine culture can vary, however, any colony count of one specimen indicates a high suspicion for UTI	2b
Due to increasing resistance numbers good antibiotic stewardship should guide the choice of antibiotics, taking into account local resistance patterns, old urine cultures (when available) and clinical parameters.	2a
Preventive measures against recurrent UTIs include: chemoprophylaxis (oral and intravesical), cranberries, probiotics and Vitamin A and E.	2a
During acute UTI both DMSA and diffusion-weighted MRI can confirm pyelonephritis or parenchymal damage.	2a

Recommendations

Recommendations	LE	Strength rating
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	3	Strong
Exclude bladder- and bowel dysfunction in any toilet-trained child with febrile and/or recurrent UTI.	3	Strong
Clean catch urine can be used for screening forUTI. Bladder catheterisation and suprapubic bladder aspiration to collect urine can be used for urine cultures.	2a	Strong
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results.	2a	Strong
Midstream urine is an acceptable technique for toilet-trained children.	2a	Strong
The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhea; non-compliance; complicated pyelonephritis.	2a	Strong
Treat febrile UTIs with four to seven day courses of oral or parenteral therapy.	1b	Strong
Treat complicated febrile UTI with broad-spectrum antibiotics	1b	Strong
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	1b	Strong
In selected cases consider dietary supplements as an alternative or add-on preventive measure.	2a	Strong
In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract within 24 h	2a	Strong
In infants, exclude VUR after first epidose of febrile UTI with a non-E. Coli infection. In children more than one year of age with an E. Coli infection, exclude VUR after the second febrile UTI.	2a	Strong

Conflict of interest/funding

None.

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