Review Article

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

Lissette A. ‘t Hoern 1*, Guy Bogaert 2*, Christian Radmayr 2, Hasan S. Dogan 3, Rien J.M. Nijman 4, Josine Quaedackers 5, Yazan F. Rawashdeh 1, Mesnur S. Sitay 6, Serdar Telgujoz 1, Nikita R. Bhatt 7, Raimund Stein 1

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 anatomical 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.

https://doi.org/10.1016/j.jproul.2021.01.037
1477-5131/Crown Copyright © 2021 Published by Elsevier Ltd on behalf of Journal of Pediatric Urology Company. All rights reserved.
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 (UTIs) 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 pyelonephritis [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 and includes a painful 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 colonization 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 or functional abnormalities 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 to prevent 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 two-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, leucocyte tests on stick and no pyuria or bacteruria 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 at 10^5–10^6 cfu/ml of a monokulture. With suprapubic bladder aspiration 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 10^5 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, urethritis 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 postvoid 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 scans 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, diarrhea 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 hypotremia and hyperkalemia based on pseudohyposaidosteronism can occur in these cases and clinicians should be aware of anatomical abnormalities, such as obstructive conditions [31].
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 young 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

Please cite this article as: 't Hoen LA et al., Update of the EAU/ESPU guidelines on urinary tract infections in children., Journal of Pediatric Urology, https://doi.org/10.1016/j.jpursl.2021.01.037
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 trial 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 cream in the presence of 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
urine pathogens should be suspected in children with pro-
longed fever and failing recovery. Repeat ultrasound ex-
amination 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 electro-
lytes 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. Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important. 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. 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. Preventive measures against recurrent UTIs include: chemoprophylaxis (oral and intravesical), cranberries, probiotics and Vitamin A and E. During acute UTI both DMSA and diffusion-weighted MRI can confirm pyelonephritis or parenchymal damage. |
|                                                                                     |    |

**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). Exclude bladder- and bowel dysfunction in any toilet-trained child with febrile and/or recurrent UTI. Clean catch urine can be used for screening for UTI. Bladder catheterisation and suprapubic bladder aspiration to collect urine can be used for urine cultures. Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results. Midstream urine is an acceptable technique for toilet-trained children. 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. Treat febrile UTIs with four to seven days courses of oral or parenteral therapy. Treat complicated febrile UTI with broad-spectrum antibiotics. Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms. In selected cases consider dietary supplements as an alternative or add-on preventive measure. In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract within 24 h. In infants, exclude VUR after first episode 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. |
|-------------------------------------------------------------------------------|----|-----------------|
|                                                                                           | 3   | Strong          |
|                                                                                           | 3   | Strong          |
|                                                                                           | 2a  | Strong          |
|                                                                                           | 2a  | Strong          |
|                                                                                           | 2a  | Strong          |
|                                                                                           | 2a  | Strong          |
|                                                                                           | 1b  | Strong          |
|                                                                                           | 1b  | Strong          |
|                                                                                           | 2a  | Strong          |
|                                                                                           | 2a  | Strong          |

Please cite this article as: ’t Hoen LA et al., Update of the EAU/ESPU guidelines on urinary tract infections in children, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2021.01.037
Conflict of interest/funding

None.

References

[1] Stein R, Dogan HS, Hoebeke P, Kovacova R, Nijman RJM, Radmayr C, et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol 2015;67(4):546–58.

[2] Marfil S, Jodil U. Incidence rate of first-time symptomatic urinary tract infection in children under 6 years of age. Acta Paediatr 1998;87(5):549–52.

[3] 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(1):19–22.

[4] Sakhil N, Morane NE, Bost JF, Farwell MV. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J 2008;27(4):402–8.

[5] Zorc JJ, Levine DA, Platt SL, Dayan PS, Mocci G, Kief W, et al. Clinical and demographic factors associated with urinary tract infection in young febrile infants. Pediatrics 2005;116(3):644–8.

[6] Lademann F, Bittner M, Galasko E. Incidence and morbidity of urinary tract infection in a prospective cohort of children. Acta Paediatrica. International Journal of Paediatrics 2015;104(7):326–9.

[7] Sakhil N, Herberman A, Keren R, Ivanova A, Getman N, Chezy RW, et al. Predictors of antimicrobial resistance among pathogens causing urinary tract infection in children. J Pediatr 2016;171:116–21.

[8] Caffarelli AI, Barzato C, Piacentini G, Management of constipation in preventing urinary tract infections in children: a concise review. European Journal Research 2019;5(2):236–41.

[9] Girer WR, Kratinimos P, Singh S, Guhaap J, Kroutousa I. Obesity as a risk factor for urinary tract infection in children. Clin Pediatr 2016;55(10):952–6.

[10] Sakhil N, Maralami MA, Kuris-Layky M, Herberman A. Association of renal scarring with number of febrile urinary tract infections in children. JAMA Pediatr 2019 Aug 5;173(10):949–52.

[11] Alberici I, Boyeski AK, Drozd D, Emre S, Fischbach M, Horbom J, et al. Pathogenic causing urinary tract infections in infants: A European overview by the ESCAPE study group. Eur J Pediatr 2015;174(9):783–90.

[12] Teuberger M, Pantzlikova A, Cliftord V, Goni G, Rez N, Connell T, et al. The age-related risk of co-existing meningitis in children with urinary tract infection. PlzO 2011;4(1):11.

[13] Kaufman JD, Denver PD, Chandler NA. Risk factors and associated morbidity of urinary tract infections in pediatric surgical patients: a HSQIP pediatric analysis. J Pediatr Surg 2020 Apr;55(4):715–20.

[14] Tosif S, Baker A, Oskay E, Donusah S, Bafi FE. Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: an observational cohort study. J Pediatr Child Health 2012;48(8):659–64.

[15] Valisicourt S, McGilivray 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(6):e1288–93.

[16] Akagawa Y, Kimata T, Akagawa S, Fujishiro S, Kato S, Yamauchi S, et al. Optimal bacterial colony counts for the diagnosis of urinary tract infections in infants. Clin Exp Nephrol 2020 Mar;24(3):253–8.

[17] Whiting P, Woodhead M, Watt I, Cooper J, Kielinen 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(1):4.

[18] Chang SJ, Ticai LP, Hsu CK, Yang SS. Elevated postvoid residual urine volume predicting recurrence of urinary tract infections in toilet-trained children. Pediatr Nephrol 2015;30(7):1131–7.

[19] Stoica I, O’Kelly F, McDermott MJ, Quinn FMJ, Xanthogranulomaticous pyelonephritis in a paediatric cohort (1963-2016): outcomes from a large single-center series. J Pediatr Urol 2018;14(2):e169.

[20] Shirashiki K, Yoshino K, Washinabe M, Matsuyama H, Tanikaze S. Risk factors for breakthrough infection in children with primary vesicoureteral reflux. J Urol 2010;183(4):1527–31.

[21] Quirino KG, Silva JR, Ojiri SJ, Lima CM, Rocha AC, Simoes e Silva AC, et al. Combined use of late phase dimercaptosuccinic acid renal scintigraphy and ultrasound as first line screening after urinary tract infection in children. J Urol 2011;181(1):258–63.

[22] Boakina A, Saloumova D, Havellia J, Kraft G, Stivokel P, Kocvara R, et al. Diffusion-weighted magnetic resonance imaging is more sensitive than dimercaptosuccinic acid scintigraphy in detecting parenchymal lesions in children with acute pyelonephritis: a prospective study. J Pediatr Urol 2018;14(3):269.

[23] Muzi S, Roher K, Hayes W, Wetz M. Timing of voiding cystourethrograph after febrile urinary tract infection in children: a systematic review. Arch Dis Child 2020 Mar;105(3):264–9.

[24] Spencer JD, Bates OS, Mahan JD, Niland ML, Staker SB, Hains ES, et al. The accuracy and health risks of a voiding cystourethrograph after a febrile urinary tract infection. J Pediatr Urol 2012;8(1):72–6.

[25] Pauchard J-Y, Chehade H, Kies C, Girardin E, Cachat F, Gehri M. Avoidance of voiding cystourethrograph in infants younger than 3 months with Escherichia coli urinary tract infection and normal renal ultrasound. Arch Dis Child 2017;102(9):804–8.

[26] Sakhil N, Craig JC, Rivers MM, Da Dalt L, Gardiki S, Herberman A, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. JAMA Pediatr 2014;168(10):893–900.

[27] Rianthavorn P, Tangsamsaksul P. Probabilities of developing vesicoureteral reflux in children with first time simple febrile urinary tract infection, and normal renal and bladder ultrasound. J Urol 2016;196(3):1541–5.

[28] Bahat H, Ben-Ari M, Ziv-Baran T, Neheman A, Youngster I, Goldstein M. Predictors of grade 3-5 vesicoureteral reflux in infants 6-24 months of age. Pediatr Nephrol 2019;34(5):907–15.

[29] Hola G, Wenger TR, Salomonsson P, Knudsen LU, Hadsen JL, Moller S, et al. Selective imaging modalities after first pyelonephritis failed to identify significant urological abnormalities, despite normal antenatal ultrasounds. Acta Paediatr, International Journal of Paediatrics 2017;106(7):1176–83.

[30] Lee LC, Lorenzo AJ, Koyle MA. The role of voiding cystourethrography in the investigation of children with urinary tract infections. Canadian Urological Association Journal – Journal de l’Association des urologues du Canada 2016;10(5–6): 210–4.

[31] Manjappa R, Vaidyanathan P, Kaplowitz P. Transient pseudohypopaldosteronism due to urinary tract infection in infancy: a report of 4 cases. Int J Pediatr Endocrinol 2009;2009:195728.

[32] Roberts KB. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. 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 2011;128(3):595–610.

33. Robinson JL, Le Saux N. Management of urinary tract infections in children in an era of increasing antimicrobial resistance. Expert Rev Anti Infect Ther 2016;14(9):809–16.

34. Denai S, Aroon PN, Shahbanos V, Neuman ML, Balasumth F, Pruitt OA, et al. Parenteral antibiotic therapy duration in young infants with bacteremic urinary tract infections. Pediatrics 2019;144(3):e20183844.

35. Wake RN, 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(1):10–11.

36. Beutel R, Bechmann H, Gatermann S, Keller H, Kiewitz-Brocken F, Neiseit C et al. [Urinary tract infections in infants and children - a consensus on diagnostic, therapy and prophylaxis]. Urologe 2007;46(3):132–8.

37. Bryce A, Hay AO, Lane IF, Thornton HV, Wooldron M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BJU Int (Online) 2016;117:932–939.

38. Foadfara H, Botsari P, Vergato E, Maraki S, Galanakis E. Short-term antibiotic exposure affected the type and resistance of uropathogens similar to long-term antibiotic prophylaxis in children hospitalised for urinary tract infections. Acta Paediatr 2020;109(6):1260–6.

39. Uyar Aku N, Ekinli Z, Dundar D, Baydemir C. Childhood urinary tract infection caused by extended-spectrum beta-lactamase-producing bacteria: risk factors and empiric therapy. Pediatr Int 2017;59(2):176–80.

40. Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev 2019;19(4):CD001534.

41. Abubakr SS, Barry MA. Current status of long-term antibiotic prophylaxis for urinary tract infections in children: an antibiotic stewardship challenge. Kidney Research and Clinical Practice 2019;38(4):441–54.

42. Dray EV, Clemens JQ. Recurrent urinary tract infections in patients with incomplete bladder emptying: is there a role for intravesical therapy? Tram Androl Urol 2017;7:eSuppl 2; S163–70.

43. Durham SL, Stamm PL, Elard LS. Cranberry products for the prophylaxis of urinary tract infections in pediatric patients. Ann Pharmacother 2015;49(12):1349–56.

44. Schwenkert C, Giczi C, Lunacek A, Rehder P, Bartsch G, Oswald J, et al. Interim outcome of the single stage dorsal inlay skin graft for complex hypospadias reparations. J Urol 2006;175(5):1872–7; discussion 6-7.

45. Siddegall-Bujal S, Naqipkhizda R, Hazzah F, Mhane Shafare F, Aasul F. Efficacy of probiotic prophylaxis after the first febrile urinary tract infection in children with normal urinary tracts. J Pediatr Infect Dis Soc 2020 Jul 13;9(3):205–10.

46. Hosseini M, Yousefifard M, Ataei N, Orali A, Mirzay Razaz J, Izadi A. The efficacy of probiotics in prevention of urinary tract infection in children: a systematic review and meta-analysis. J Pediatr Urol 2017;13(5):381–91.

47. Kahleski M, Sharafkhah M, Yousefi Chahar P, Taherzadad H, Raffi M, Kaviani P, et al. Vitamin A supplementation is effective for improving the clinical symptoms of urinary tract infections and reducing renal scarring in girls with acute pyelonephritis: a randomized, double-blind placebo-controlled, clinical trial study. Compl Ther Med 2019;42:49–57.

48. Zhang GQ, Chen J, Zhao Y. The effect of vitamin A on renal damage following acute pyelonephritis in children: a meta-analysis of randomized controlled trials. Pediatr Nephrol 2016;31(3):373–9.

49. Yousefi Chahar P, Kahleski M, Rast S, Rafiee M, Sharafkhah M. Vitamin E as adjuvant treatment for urinary tract infection in girls with acute pyelonephritis. Iran Journal of Kidney Diseases 2015;9(2):97–104.

50. Chen CJ, Satyanarayan A, Schömer BJ. The use of steroid cream for physiologic phimosis in male infants with a history of UTI and normal renal ultrasound is associated with decreased risk of recurrent UTI. J Pediatr Urol 2019;15(5):472–7.

51. Ellisen JS, Dy GW, Fu BC, Holt SK, Gore JL, Merguerian PA. Neonatal circumcision and urinary tract infections in infants with hydrocephrosis. Pediatrics 2018 Jul;141(1):e20173760.

52. Braga LH, D’Cruz J, Rickard M, Jegatheeswaran K, Lorenzo AJ. The fate of primary non-refluxing megaretter: a prospective outcome analysis of the rate of urinary tract infections, surgical indications and time to resolution. J Urol 2016 Apr;195(4 Pt 2):1300–5.

53. Evans K, Aslamakadu N, Nwaiwto D, Demal D, Chirian A, Naughton I, et al. What is the risk of urinary tract infection in children with antenatally presenting dilating vesico-ureteric reflux? J Pediatr Urol 2015 Apr;11(2):93.e1–6.

54. Shaikh Ni, Hoberman A, Keren R, Gotman N, Docimo SG, Mathews B, et al. Recurrent urinary tract infections in children with bladder and bowel dysfunction. Pediatrics 2016;137(1).

55. Kotsalas A, Gardikis S, Tsaklidis A, Mantadakis E, Zissinopoulos A, Delftanes S, et al. Comparative efficacies of procaciolutin and conventional inflammatory markers for prediction of renal parenchymal inflammation in pediatric first urinary tract infection. Urology 2009;73(6):782–6.

56. Zhang H, Yang J, Liu L, Hao B, Mei H, He Y. Diagnostic value of serum procaciolutin for acute pyelonephritis in infants and children with urinary tract infections: an updated meta-analysis. World J Urol 2016;34(3):431–45.