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Clinical Guideline for Childhood Urinary Tract Infection (Second Revision)

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To revise the clinical guideline for childhood urinary tract infections (UTIs) of the Korean Society of Pediatric Nephrology (2007), the recently updated guidelines and new data were reviewed.

The major revisions are as follows. In diagnosis, the criterion for a positive culture of the catheterized or suprapubic aspirated urine is reduced to 50,000 colony forming uits (CFUs)/mL from 100,000 CFU/mL. Diagnosis is more confirmatory if the urinalysis is abnormal. In treating febrile UTI and pyelonephritis, oral antibiotics is considered to be as effective as parenteral antibiotics. In urologic imaging studies, the traditional aggressive approach to find primary vesicoureteral reflux (VUR) and renal scar is shifted to the targeted restrictive approach. A voiding cystourethrography is not routinely recommended and is indicated only in atypical or complex clinical conditions, abnormal ultrasonography and recurrent UTIs. ^{99m}Tc-DMSA renal scan is valuable in diagnosing pyelonephritis in children with negative culture or normal RBUS. Although it is not routinely recommended, normal scan can safely avoid VCUG. In prevention, a more natural approach is preferred. Antimicrobial prophylaxis is not supported any more even in children with VUR. Topical steroid (2-4 weeks) to non-retractile physiologic phimosis or labial adhesion is a reasonable first-line treatment. Urogenital hygiene is important and must be adequately performed. Breast milk, probiotics and cranberries are dietary factors to prevent UTIs. Voiding dysfunction and constipation should be properly treated and prevented by initiating toilet training at an appropriate age (18-24 months). The follow-up urine test on subsequent unexplained febrile illness is strongly recommended. Changes of this revision is not exclusive and appropriate variation still may be accepted.

Key words: Recognition, Diagnosis, Treatment, Imaging studies, Prevention

Introduction

Urinary tract infection (UTI) is the most common bacterial disease in childhood. The incidence is especially high in febrile infants (5-25%), and the recurrence is common after first UTI (12-50%). UTI is frequently associated (15-50%) with primary vesicoureteral reflux (VUR), and reflux nephropathy (renal scars) is a possible cause of childhood hypertension and chronic kidney disease. This concept has led to the aggressive treatment and extensive imaging studies to find primary VUR and renal scar in children

with first UTI[1,2]. Besides, there are some difficulties in diagnosing UTI in young children ; delayed diagnosis from non-specific symptoms and frequent overdiagnosis from contaminated urine specimens. The delay in diagnosis and treatment induce renal scar, and overdiagnosis is responsible for unnecessary antibiotics, radiation exposure and high cost[3].

Recently, most of diffuse and severe renal scars in primary VUR were found to be congenital (dysplasia) rather than acquired. The renal scar after pyelonephritis was at best focal and mild. The role of primary VUR on acquired renal scar and subsequent chronic kidney disease has been diminished[4,5]. Therefore, the recent clinical guidelines were revised from an aggressive approach to a targeted restrictive approach although each updated guidelines have different sensitivity for detecting primary VUR[6-11]. We also need to revise the clinical guideline of the Korean Society of Pediatric Nephrology (KSPN, 2009) although there has been still many controversies.

Step 1. The recognition of UTI

Presenting symptoms and signs for UTI are non-specific in infants and young children and become more specific as the child grows older. Unexplained fever is the most common presenting symptom for UTI in infants. The incidence of UTI in febrile infants (>38.0°C) is around 4-5% and increased more if fever is higher. Female is a major risk factor for UTI, but first UTI commonly develops in male infants, who are uncircumcised. The prevalence of UTI in uncircumcised male infants is 5-20 fold higher than circumcised male and female infants. Physiologic phimosis is the risk factor in uncircumcised male and contributes to the male preponderance (M;F 3-5:1) of UTI in infants, which is contrary to the female preponderance (M;F 1:10) in older children[12,13]. Since early childhood, UTIs usually develops in female and easily diagnosed because of the specific presenting symptoms (high fever, flank pain, vomiting for pyelonephritis and dysuria, voiding dysfunction, turbid urine, suprapubic pain for cystitis)(Table 1). Moreover, febrile UTIs in infants and young children, frequently induce complications such as urosepsis and renal scarring. Urosepsis is common (10%) in young infants (younger than three months) and renal scarring develops (30-60%) after pyelonephritis. Therefore, young febrile infants (<3 months) and children with pyelonephritis are better to be admitted for prompt treatment. Especially, infants and children with toxic symptoms and signs (vomiting, poor feeding, dehydration, lethargy, weak cry, poor response and mottling) should be admitted for initiating parenteral antibiotic therapy.

Recommendation 1: Consider UTI in infants and young children with unexplained fever (>38.0°C). Admit febrile infants younger than three months, infants with toxic symptoms/signs and children with severe pyelonephritis.

Step 2 : Diagnosis

1. Urine collection

Diagnosis of UTI should be prompt and accurate by appropriate urine collection, to prevent therapeutic delay and overdiagnosis There are four collection methods, which are different invasiveness and contamination rates. Clean midstream catch (CMC) is an easy and accurate method in toilet-trained (TT) children. The midstream urine is collected (twice) after simple retraction of the prepuce in uncircumcised male infants and simple separation of labia majora in female children. Suprapubic aspiration (SPA) is a gold standard method in non TT children. The success rate in ultrasound guided SPA is very high (90-100%) although it is invasive. Complication is very rare (hematuria 0.5-2%, intestinal puncture 0.2%). After disinfection of suprapubic area, the urine is aspirated by perpendicular midline puncture with 21-gauge needle, 1 cm above the symphisis pubis[14]. Transurethral catheterization (TUC) is less invasive but more contaminated method than SPA. The success rate is very high (99%) except in severe non-retractile physiologic phimosis. But urethral irritation, urethral stenosis, hematuria and catheter induced UTI are rare inevitable complications. After disinfection of periurethral area, catheter is inserted to catch the urine. Sterile-bag collection (SBC) is the easiest method in non-TT children. But the contamination rate is

Table 1. Presenting Symptoms and Signs of Childhood Urinary Tract Infection(UTI) by Age Groups

Age groups	Diagnosis	Presenting symptoms and signs	
		Common	Less common
Neonates, Infants	UTI	Fever	Vomiting, poor feeding
Young Children (Non-toilet trained)		Irritability	Hematuria Offensive, cloudy urine
Older children (Toilet trained)	Pyelonephritis	High fever	Abdominal pain
		Vomiting	Malaise
		Loin pain	
	Cystitis	Dysuria	Hematuria
		Voiding dysfunction	Offensive, cloudy urine

very high. After washing around the prepuce or the perineum with water or saline, attatch a sterile bag. Immediately after voiding, the urine is collected[15]. Because each method has its merit and fitfall, the ideal method should be selected according to the age, the severity of symptoms and the status of toilet training. In TT children, CMC is a satisfactory method for diagnosis. In non-TT children, SBC is a reasonable method for a screening test, but SPA or TUC is mandatory for accurate diagnosis[2,16]. To ensure the accuracy of the tests, the collected urine specimens must be stored adequately to keep fresh (< 1 hour after voiding at room temperature and <4 hours in refrigerator).

2. Urinalysis

An urinalysis, a rapid screening test to make a presumptive diagnosis of UTI, consists of biochemical dipstick (Multistix) and microscopic sediment analysis. Dipstick urinalysis indicates the presence of leukocyte esterase (LE) or nitrite, and sediment urinalysis indicates the presence of WBC, WBC cast and bacteria. Using either the dipstick or sediment analysis, sensitivity improves at the expense of specificity (Table 2)[7,17].

The LE test can be false negative (6-33%) in early UTI and false positive (8-36%) in other febrile illness, non-specific vaginitis or interstitial nephritis. The nitrite test can be also false negative (18-85%) in early UTI and can be false positive (0-10%) by periurethral/perineal normal flora, Gram (+) or contaminated bacteria. The nitrite test has a relatively high specificity but is not a sensitive marker in children, who empty the bladder frequently because Gram (-) bacteria should be present for at least 4 hours in the bladder to convert the dietary nitrate to nitrite[18]. Therefore, the urinalysis cannot substitute for a urine culture, but it can be valuable in selecting children with a presumptive UTI. A positive nitrite with/without LE, give a presumptive diagnosis of UTI to initiate the empirical antibiotic therapy. A negative test for both nitrite and LE suggests no UTI, although it does not rule out a UTI with certainty (Table 3). Urine WBC cast is very significant finding for pyelonephritis but rapidly resolves (<10 minutes) in the alkali urine.

Table 2. Sensitivity and Specificity of Urinalysis.

Tests	Sensitivity % (range)	Specificity % (range)
Dipstick urinalysis		
Leukocyte esterase (LE)	83 (67-94)	78 (64-92)
Nitrite	53 (15-82)	98 (90-100)
LE or nitrite	93 (90-100)	72 (60-92)
Sediment urinalysis		
White blood cell (WBC)	73 (32-100)	81 (45-98)
Bacteria(bac)	81 (16-99)	83 (11-100)
LE or nitrite or WBC or bac	99.8(99-100)	70 (60-92)

3. Urine culture

To establish a diagnosis of UTI, a significant number of colony-forming units (CFUs) of a single uropathogen, should be cultured on an appropriately collected urine specimen. The traditional criterion (cut off level) for a positive culture was over 10^5 CFU/mL although 10^4-10^5 CFUs/mL were accepted in symptomatic children, who are on fluid therapy, antibiotics pretreatment or disinfection for urine collection. Recently, America Academy of Pediatrics (AAP) reduced the criterion to 50,000 CFUs/mL in the SPA or the TUC urine [7]. The diagnostic rates of the criterion, over 10^5 CFU/mL, were different according to the urine collection method [70-90% (once) or 90-95% (twice) in the clean midstream catch urine, 95-

Table 3. Diagnosis of Presumptive Urinary Tract Infection(UTI) and Empirical Antibiotic Treatment according to Urine Dipstick Test

Urine dipstick	Diagnosis	Antibiotic treatment
Nitrite(+), LE(+)	Possible UTI	Yes
Nitrite(+), LE(-)	Probable UTI	Yes
Nitrite(-), LE(+)	May or may not UTI	Yes or no*
Nitrite(-), LE(-)	No UTI	No

* Depending on clinical conditions
Abbreviation : LE, leucocyte esterase

99% in the SPA urine, 90-95% in the TUC urine and 14-84% in the sterile bag-collected urine]. A positive culture of the sterile bag-collected urine may suggest asymptomatic bacteriuria (ASB), which is not a true UTI[19]. Therefore, a true UTI must be distinguished from ASB. In symptomatic children with a positive SBC urine culture and abnormal urinalysis, the diagnosis is UTI. In asymptomatic children with a positive SBC urine culture and normal urinalysis, the diagnosis is ASB. In febrile infants who has other viral illness, ASB is frequently confused with a true UTI but should be distinguished because antibiotic treatment may do more harm than good. The positive urine culture of mixed uropathogens or non-pathogenic bacterias (coagulase-negative staphylococcus, corynebacterium etc.) means contamination or the normal flora. The pretreatment of antibiotics should be always considered in children with definite symptoms and a negative culture, where ^{99m}Tc-DMSA renal scan is helpful.

Recommendation 2 : Early and accurate diagnosis

1. The ideal method for urine collection : SPA or TUC in non-TT children who are very ill. SBC first in those who are not so ill and then SPA or TUC if an urinalysis is abnormal.

2. Interpretation of urinalysis : A positive nitrite with/without LE give a presumptive diagnosis of UTI. A positive LE only may or may not suggest UTI. A negative test for both nitrite and LE suggests no UTI.

3. A criterion for a positive urine culture in the SPA and TUC urine, is reduced to $5x10^4$CFUs/mL. An abnormal urinalysis (pyuria) can distinguish a true UTI from an ASB. When a urine culture is positive (>10^5 CFU/mL) in the SBC urine, UTI should be diagnosed only in children with both definite symptoms and abnormal urinalysis.

Step 3 : Treatment

The goals of treatment is to eliminate the infection and to prevent renal scarring. Selection and administration of antibiotics should be appropriate.

1. Selection of antibiotics

The empirical antibiotic choice should be based on local antimicrobial susceptibility patterns for isolated dominant uropathogen [Escherichia coli (E. coli)] in the community because they are ever changing and have substantial geographic variability[20]. At first, select the sensitive antibiotics empirically and change to the most susceptible one by the susceptibility result if not improved after 48 hours. The reported resistant rates of antibiotics are variable and changing [low (0-20%) in third generation cephalosporins, aminoglycoside and imipenem, intermediate (20-35%) in amoxacillin-clavulanate or ciprofloxacin, and high (30-85%) in ampicillin or trimethoprim/sulfamethoxazole (TMP/SMX). The emergence of extended-spectrum ß-lactamase (ESBL) producing uropathogens has increased the resistant rates to third generation cephalosporins. Korean antimicrobial resistance monitoring system regularly gives the sensitivity patterns of antibiotics.

2. Administration of antibiotics

Febrile UTI children, who are younger than three months, toxic or unable to retain oral intake, should receive antibiotics parenterally until clinical improvement and followed by oral treatment. A short course (2-4 days) of parenteral treatment is as effective as a longer course (7-14 days) of parenteral treatment. Moreover oral antibiotics alone are as effective as the combinations of parenteral and oral antibiotics in most febrile UTIs and pyelonephritis. If aminoglycosides is chosen, single daily dosing is safe and effective. The majority of cystitis can be easily treated with oral antibiotics. Parenteral antibiotics include third generation cephalosporins and aminoglycoside and oral antibiotics include third generation cephalosporins, amoxacillin-clavulanate, and trimethprim/sulfamethoxazole (TMP/SMX). Aminiglycoside or imipenem is recommended in UTI by extended-spectrum ß-lactamase (ESBL) producing E. coli. (Table 4). For the duration of antibiotics treatment in febrile UTI or pyelonephritis, longer treatment

Table 4. Antibiotics for Oral and Parenteral Treatment of UTI

Antibiotics		Dosage
Parenteral	Ceftriaxone	75 mg/kg/day #1
	Cefotaxime	100-150 mg/kg/day #3
	Ceftazidime	100-150 mg/kg/day #3
	Gentamicin	7.5 mg/kg/day #1-3
	Tobramicin	5 mg/kg/day #1-2
	Amikacin	15-30 mg/kg/day #1-3
	Imipenem	100 mg/kg/day #3-4
Oral	Cefixime	8 mg/kg/day #1
	Cefpodoxime	10 mg/kg/day #2
	Cefprozil	30 mg/kg/day #2
	Cefuroxime axetil	20-30 mg/kg/day #2
	Amoxacillin/clavulanate	20-40 mg/kg/day #3
	Trimethoprim/sulfamethoxazole	8/40 mg/kg/day #2

(>7 days) is more effective than shorter treatment (<7 days) in the success and the relapse rates. The minimal duration should be 7 days. A study, comparing 7, 10 and 14 days was not found. In cystitis, shorter treatment (3-5 days) is as effective as longer treatment (5-7 days)[21-23].

Recommendation 3 : Prompt and adequate antibiotic treatment

Choose the sensitive antibiotics for dominant uropathogen in the community. Oral and parenteral treatment is equally effective in febrile UTI without toxic symptoms. The duration should be 7 to 14 days in febrile UTI and pyelonephritis and 3 to 5 days in afebrile UTI and cystitis.

Step 4 : Urologic imaging studies

The strategy for imaging studies for the past 4 decades, has been focusing to detect primary VUR and renal scar after first UTI. The core imaging studies has been renal and bladder ultrasonography (RBUS), voiding cystourethrography (VCUG) and ^{99m}Tc-DMSA renal scan (DMSA). In primary VUR, the effects of antibiotic prophylaxis and surgical intervention which has been widely performed according to the American Urologic Association (AUA) guideline, have become questionable[4,5]. Therefore, recent clinical guidelines for imaging studies were revised to a more targeted restrictive approach from an aggressive approach that has a questionable benefit and high financial and radiation costs[6-11,24]. RBUS is a basic study that is easy, safe and non-invasive. Widespread application of prenatal ultrasonography has reduced the detection rate of unsuspected urinary abnormalities, but the consequence has not been well defined[25]. Therefore, RBUS is still useful to detect urinary abnormalities and renal infections (pyelonephritis, renal abscess and perirenal abscess), even though UK skipped RBUS in children (>6 months) with simple UTI in the revised guideline. VCUG is an absolute but invasive study to detect primary VUR. Since the role of primary VUR on acquired renal scar, has been challenged, the rationale for performing a routine VCUG after first UTI is also questionable. UK revised to skip VCUG in children with simple UTI[6]. AAP also did not recommend routine VCUG in infants with first febrile UTI and the indications for VCUG were limited to infants who had an abnormal RBUS, atypical or complex clinical conditions and recurrent UTI[7]. DMSA is a gold standard to diagnose pyelonephritis and renal scar. Especially, it is very useful in diagnosing culture negative pyelonephritis in children with definitive symptoms and valuable to detect renal damage in children with normal RBUS. The top-down approach, focusing on diagnosis of pyelonephritis by DMSA, challenged the conventional bottom-up approach, focusing on detection of primary VUR. Normal DMSA can safely avoid invasive VCUG although it is not routinely recommended[26,27].

Recommendation 4 : Targeted restrictive imaging studies.

RBUS is still a basis to detect urinary abnormalities, pyelonephritis, and abscess. VCUG should not be performed routinely after first UTI and is indicated in abnormal RBUS, atypical or complex clinical conditions and recurrent UTI. DMSA is efficacious in diagnosing culture negative pyelonephritis.

Step 5 : Prevention

1. Antibiotic prophylaxis

Antibiotic prophylaxis has been widely used to prevent recurrent UTIs and subsequent renal scarring in children with primary VUR according to the AUA guideline[1,2]. In

the past decade, the beneficial role of antibiotic prophylaxis to prevent renal scar, has been questioned. Moreover, the potential for emergence of antimicrobial resistant bacterias, has been a major concern. Recent randomized controlled trials (RCTs) including the Randomized Intervention for Children with Vesicoureteral reflux (RIVUR) trials do not support the use of antibiotic prophylaxis in children without or with VUR (grade I to IV)[28-30].

2. Physiologic phimosis

Uncircumcised male is listed as an important risk factor for UTI[11]. The tight prepuce in uncircumcised male, designated as physiologic phimosis, had a propensity to be colonized by uropathogens and to develop UTI. Treatment options for physiologic phimosis are neonatal circumcision and topical steroid. AAP policy for neonatal circumcision have turned to positive position because the evidences indicated that potential medical benefits outweigh the risks[31]. However, the Cochrane review (2012) still concluded that more evidences are required for routine neonatal circumcision to prevent UTI[32]. Another option is topical application of steroid. A majority of clinical studies were performed in prepubertal boys, using highly potent steroids with the success rates 68-91%[33]. In infants and younger children with physiologic phimosis, the success rates was much higher (95.1%) even with the least potent hydrocortisone. In infants whose prepuces became completely retractile after topical hydrocortisone, the incidence of recurrent UTI significantly decreased[34].

3. Inadequate urogenital hygiene

Urogenital hygiene (preputial and perineal hygiene) is an another important risk factor for UTI but is frequently ignored. Regular washing can inhibit the adhesion and the growth of uropathogens. The prepuce, the urethra or the perineum is a reservoir for uropathogens. In uncircumcised male infants, simple retraction of prepuce and washing are good preputial hygiene and offer many advantages of neonatal circumcision in eliminating uropathogens. In female infants, simple separation of labia majora and washing are adequate perineal hygiene to eliminate uropathogens. However, there is no clinical study about the effect of urogenital hygiene in preventing ASB or UTI[35].

4. Labial adhesion

Labial adhesion (LA) is defined as complete or partial fusion of the labia minora and is the cause of urethrovaginal reflux and urinary stasis to facilitate the growth of uropathogens. The prevalence was reported as 0.6-5% only in prepubertal girls. Topical steroid or estrogen cream for 2-4 weeks successfully lysed the adhesion without significant side effects in prepubertal girls[36]. LA is listed as a risk factor for childhood UTI in Nelson textbook of Pediatrics[11] but the prevalence in infants and children is unknown and also there is no clinical study in the literature.

5. Dietary factors (breast milk, probiotics, cranberry)

There are some dietary factors to prevent UTI[37]. Breast feeding prevents UTI in infants[38]. Breast milk contains many immunologic factors (sIgA, lactoferrin, oligosaccharides etc) and is a source of lactobacilli. Lactobacilli are acquired at birth as the baby pass through the birth canal and then grow on subsequent breast milk intake. Human colostrum and breast milk are the important natural sources of lactobacilli[39]. Lactobacilli inhibit the growth and the adhesion of uropathogens, and prevent the development of UTI. The beneficial role of lactobacilli are mediated by a number of mechanisms such as production of a biofilm barrier, secretion of antimicrobial compounds and stimulation of innate immunity[40]. A meta-analysis reported that lactobacillus probiotics significantly prevent UTI when a sensitivity analysis was applied[41]. In children, The preventive effect of lactobacillus probiotics was not inferior to antibiotic prophylaxis in children with primary VUR[42,43]. Although the evidence is not definite, considering probiotics mediated activation of the innate immune system, probiotic therapy is a new immunomodulating approach toward UTI in this era of increasing antimicrobial resistance[40]. Cranberry is a traditionally used functional food that contains proanthrocyanidin that inhibit adhesion of p-fimbriated uropathogens to the uroepithelium, prohibit asymptomatic colonization and UTI. RCTs with cranberries showed the effectiveness, significantly more than antibiotics and probiotics in preventing UTIs[44,45]. Breast milk, probiotics and cranberries, the natural diatetary factors, is safe and promising as prophylaxis for UTI[46-49].

6. Voiding dysfunction (VD), constipation and toilet training (TT)

VD, constipation and TT are separately listed as risk factors for UTI but they are interelated[50]. Dysfunctional elimination syndrome (DES) or bladder and bowel dysfunction (BBD) is one form of VD that is associated with constipation. However, voiding dysfunction or constipation should be treated separately and properly. The pathogenesis of VD and constipation is unknown, but maturation delay of neurological bladder and bowel control has been considered, which is related with TT. TT is very important for childhood development, and suggested as the cause of VD and BBD. Regarding the ideal age for TT, the debate has been still ongoing but is defined as 18–24 months in textbooks. Early TT before 18 months was definitely associated with urinary continence and later TT after 24 months was associated with bladder dysfunction[51].

7. Follow–up urine culture

Renal scar increases by the number of recurrent pyelonephritis and is prevented by early treatment. For this reason, children with first UTIs should have the follow-up urine test at the onset of subsequent unexplained febrile illness for early diagnosis. Regular periodic urine culture is not routinely recommended because the detection of ASB is not considered to be useful. ASB is not a cause of further renal damage and has a tendency to disappear spontaneously. Moreover, ASB can progress to symptomatic UTI by more virulent uropathogens, if treated with antibiotics[7]. However, it is unknown whether proper hygiene and probiotics is effective for clearing ASB.

Recommendation 9 : Natural approach for prevention

Antibiotic prophylaxis is not recommended any more in children without or with VUR (grade I to IV). For physiologic phimosis, topical steroid for 2-4 weeks will be a first-line treatment rather than neonatal circumcision. Education for adequate genital hygiene is absolutely required. Labial adhesion should be diagnosed and treated with topical steroid or estrogen for 2-4 weeks. Breast feeding should be encouraged. Probiotics can be a safe, promising agent to prevent UTI in this era of increasing antibiotic resistance. Cranberry is a natural functional food to prevent recurrent UTIs. Early TT at 18-24 month to prevent VD and constipation. Follow-up urine culture should be performed at the onset of subsequent unexplained febrile illness.

Conclusion

The major updates in this revised guideline are as follows: The criterion for a positive culture of the SPA or TUC urine is reduced to 50,000 colony forming uits (CFUs)/mL. Oral antibiotics is considered to be as effective as parenteral antibiotics even in febrile UTI and pyelonephritis. For imaging studies, the traditional aggressive approach is shifted to the targeted restrictive approach. A VCUG is not routinely recommended and indicated only in atypical or complex clinical conditions, abnormal RBUS, abnormal DMSA and recurrent UTIs. DMSA is valuable in diagnosing urine culture negative pyelonephritis and renal scar. For prevention of recurrent UTI, antibiotic prophylaxis is not supported any more. Topical steroid to non-retractile physiologic phimosis is reasonable and a medical alternative to neonatal circumcision. Breast milk, probiotics and cranberries are important dietary factors to prevent UTI. Probiotic prophylaxis can be a natural and safe alternative to antibiotic prophylaxis. The follow-up urine test on subsequent unexplained febrile illness is strongly recommended. Changes of this revision is not exclusive and appropriate variation still may be accepted.

References

1. Elder JS, Peters CA, Arant Jr BS. Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol 1997;157:1846-51.))
2. Peters CA, Skoog SJ, Arant Jr BS, Copp HL, Elder JS, Hudson RG, et al. Summery of the AUA guideline on management of primary vesicoureteral reflux in children. J Urol 2010;184:1134-44.
3. Tullus K. Difficulties in diagnosing urinary tract infections in small children. Pediatr nephrol 2011;26:1923-6.
4. Peters C, Rushton HG. Vesiccoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. J Urol 2010;184:265-73.
5. Salo J, Ikaheimo R, Tapiainen I Uhari M. Childhood urinary tract infection as a cause of chronic kidney disease. Pediatrics 2011;128:840-7.

6. National Institute for Health and Clinical Exellence, "Urinary tract infection in children," NICE, London, UK, 2007, http.//guidance.nice.org.uk/CG54
7. American Academy of Pediatrics. urinary tract infection, Clinical practice guideline for the diagnosis and management of the initial urinary tract infection in febrile infants and young children 2-24 months. Pediatrics. 2011;128:595-610.
8. Ammenti A, Cataldi L, Chimenz R, Fanos V, La Manna A, Marra G, et.al. Italian Society of Pediatric Nephrology. Febrile urinary tract infections in young children. Recommendation for the diagnosis, treatment and follow-up. Acta Pediatr 2012;101:451-7.
9. La Scola C, De mutiis C, Hewitt IK, Puccio G, Toffolo A, Zucchetta P, et al. Different guidelines for imaging after first UTI in febrile infants: yield, cost and radiation. Pediatrics 2013;131:e665.
10. Paintsil E. Update on recent guidelines for the management of urinary tract infections in children: the shifting paradigm. Curr Opin Pediatr 2013;25:88-94.
11. Elder JS, Urinary tract infection. In Behrman RE, Kliegman RM, Jenson HB. Nelson Textbook of Pediatrics, 20th ed. WB Saunders company, 2015, p2556-67.
12. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood. a meta-analysis. Pediatr Infect Dis J 2008;27:302-8.
13. Wiswell TE, Roscelli JD. Corroborative evidence for the decreased incidence of urinary tract infection in circumcised male infants. Pediatrics 1986;78:96-9.
14. Buys H, Pead L, Maskell R. Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. BMJ 1994;308:690-2.
15. Karakan C, Erkek N, Senel S, Akin Gunduz S, Catli G, Tavil B. Evaluation of urine collection methods for the diagnosis of urinary tract infection in children. Med Princ Pract 2010;19:188-9.
16. Al-Orifi, McGillivray D, Tange S, Kramer MS. Urine culture from bag specimens in young children: are the risks too high? J Pediatr 2000;137:221-6.
17. Schroeder AR, Chang PW, Shen MW, Biondi EA, Greenhow TL. Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. Pediatrica 2015;135:965-71.
18. Powell HR, McCredie DA, Ritchie MA. Urinary nitrite in symptomatic and asymptomatic urinary infection. Arch Dis Child 1987;62:138-40.
19. Trautner BW, Grigoryan L. Approach to a positive culture in a patient without urinary symptoms. Infect Dis Clin North Am 2014;28:15-31.
20. Boggan JC, Boggan AMN, Jhaveri R. Pediatric specific antimicrobial susceptibility data and empiric antibiotic selection. Pediatrics 2012;130:e615-22.
21. Bocquet N, Sergent AA, Jais JP, Gajdos V, Guigonis V, Lacour B, et al. Randomized trial of oral versus sequential IV/oral antibiotics for acute pyelonephritis in children. Pediatrics 2012;129:e269-75.
22. Hodson EM, Willis NS, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev 2012;(7):CD003772
23. fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. acute pyelonephritis in children. Cochrane Database Syst Rev 2012;(84):CD006857
24. Rajaraman P, Simpson J, Neta G, Berrington de Gonzalez A, Ansell P, Linet MS, et al. Early life exposure to diagnostic radiation and ultrasound scans and risk of childhood cancer:case-control study. BMJ 2011;342:e472-81.
25. Miron D, Dass A, Saken W, Lumelsky D, Koren A, Horovitz Y. Is omitting post urinary tract infection renal ultrasound safe after normal antenatal ultrasound? An observational study. Arch Dis Child 2007;92:502-4.
26. Preda I, Jodaln U, Sixt R, Hasson S. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. J Pediatr 2007;151:581-4.
27. Bush NC, Keays M, Adams C, Mizener K, Pritzker K, Smith W, et al. Renal damage detected by DMSA, despite normal renal ultrasound in children with febrile UTI. J Pediatr Urol 2015;126:e1-7.
28. Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 2009:361:1748-56.
29. Nagler EV, Williams G, Hodson EM, Craig JC. Long-term antibiotics for preventing recurrnet urinary tract infection in children. Cochrane Database Syst Rev 2011;16(3):CD001534
30. Intervention for Children with Vesicoureteral Rreflux (RIVUR) trial investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014;370:2367-76.
31. American Academy of Pediatrics. Circumcision policy statement. Pediatrics. 2012;130:585-6.
32. Jaqannath VA, Fedorowicz Z, Sud V, Verma AK, Hajebrahimi S. Routine neonatal circumcision for the prevention of urinary tract infection. Cochrane Database Syst Rev 2012;11:CD009129
33. Moreno G, Corbalan J, Penaloza B, Pantoja T. Topical corticosteroid for treating phimosis in boys. Cochrane Database Syst Rev 2014;9:CD008973
34. Lee JW, Cho SJ, Park EA, Lee SJ. Topical hydrocortisone and physiotherapy for nonretractile physiologic phimosis in infants. Pediatr Nephrol 2006;21:1127-30.
35. Osborn LM, Metcalf TJ, Mariani EM. Hygienic care in uncircuncised infants. Pediatrics 1981;67:365-8.
36. Bacon JL, Romano ME, Quint EH. Labial adhesions. J Pediatr Adolesc Gynecol 2015;28:405-9.
37. Kontiokari T, Nuutinen M, Uhari M. Dietary factors affecting susceptibility to urinary tract infection. Pediatr Nephrol 2004;19:378-83.
38. Marild S, Hansson S, Jodal U, Oden A, Svedberg. Protective effect of breast feeding against urinary tract infection. Acta Pediatr 2004;93:164-8.
39 Martin R, Langa S, Revirigo C, Jiminez E, Marin ML, Xaus J, et al. Human milk is a source of lactic acid bacteria for the infant gut. J Pediatr 2003;143:754-8.

40. Amdekar S, Singh V, Singh DD. Probiotic therapy: immunomodulating approach toward urinary tract infection. Curr Microbiol 2011;63:484-90.

41. Grin PM, Kowalewska PM, Alhazzan W, Fox-Robichaud AE. Lactobacillus for preventing recurrent urinary tract infection in women: meta-analysis. Can J Urol 2013;20:6607-14.

42. Lee SJ, Shim YH, Cho SJ, Lee JW. Probiotic prophylaxis in children with persistent primary vesicoureteral reflux. Pediatr Nephrol 2007;22:1315-20.

43. Lee SJ, Lee JW. Probiotic prophylaxis in infants with primary vesicoureteral reflux. Pediatr Nephrol 2015;30:609-13.

44. Salo J, Uhari M, Helminen M, Korppi M, Nieminen T, Pokka T, et al. Cranberry juice for the prevention of recurrence of urinary tract infection in children. a randomized placebo-controlled trial. Clin Infect Dis 2012;54:340-6.

45. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infection. Cochrane Database Syst Rev 2012;10: CD001321

46. Head KA. Natural approach to prevention and treatment of infections of the lower urinary tract. Alternative Med Rev 2008; 13:227-43.

47. Williams GJ, Craig JC, Carapetis JR. Preventing urinary tract infections in early childhood. Adv Exp Med Biol 2013;764:211-8.

48. Beerepoot MA, Geerlings SE, van Haarst EP, van Charante NM, ter Riet G. Non-antibiotic prophylaxis for recurrent urinary tract infection: a systemic review and meta-analysis of randomized controlled trials. J Urol 2013;190:1981-9.

49. Yang SS, Chiang IN, Lin DD, Chang SJ. Advances in non-surgical treatment for urinary tract infection in children. World J Urol 2012;30:69-75.

50. Van Batavia JP, Ahn JJ, Fast AM, Combs AJ, Glassberg KI. Prevalence of urinary tract infection and vesicoureteral reflux in children with lower urinary tract dysfunction, J Urol 2013;190(4 suppl): 1495-9.

51. da Fonseca EM, Santana PG, Gomes FA, Bastos MD. Dysfunctional elimination syndrome: is age at toilet training a determinant? J Pediatr Urol 2011;7:332-5.