British Journal of Medicine & Medical Research
4(3): 927-936, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Urinary Tract Infection in Children

Mohd Ashraf[1*], Kaiser Ahmed[1*], Khurshid Ahmed[1*] and Mohd Mubarik[2]

[1]Department of Pediatrics, GB Pant Hospital, Govt. Medical College Srinagar, Kashmir, India.
[2]Department of Medicine, SKIMS Medical College, Bemina, Srinagar, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author MA conceived the study, performed the critical analysis, wrote the first and re-revised the final draft of the manuscript. Authors Kaiser A, Khurshid A and MM collectively managed the analyses of the study and literature searches. All authors read and approved the final manuscript.

Review Article

Received 1st May 2013
Accepted 25th July 2013
Published 24th October 2013

ABSTRACT

We selected the pediatric urinary tract infection related research and review articles in English language using keywords or phrases such as Infant; children; culture*; Escherichia coli;* fever*, UTI*.

Aims: The purpose of this review is to provide summary of the latest research in particular to the practical aspects of management of *UTI* in children.

Background: Urinary tract infection *(UTI)* is an important medical entity commonly diagnosed during early childhood. Prevalence and incidence of *UTI* varies with age and gender. *UTI* can be missed just on history and clinical examination. Screening of *UTI* in high risk children is important and should be well balanced against cost and risk of missing *UTI.* Despite latest evidence from research there are still controversies in managing *UTI* in children.

Conclusion: Despite major advances in management of *UTI* in neonates and children, uniform guidelines for the imaging and management of recurrent *UTI* are lacking, prompting a multinational large research project to fill in the knowledge gap.

Key words: Infant; children; culture; escherichia coli; UTI.

**Corresponding author: Email: aashraf_05@yahoo.co.in;*

1. INTRODUCTION

Urinary tract infection (*UTI*) by definition is the presence of microorganisms in urinary tract associated with pyuria. *UTI* remain the most common bacterial infection in childhood [1]. The cumulative incidence of UTI in children by 6 years of age is 3%–7% in girls and 1%-2% in boys [1]. Bacteria particularly *escherichia coli* (*E. Coli*)-gram negative rods are the most common cause of UTI, other organisms include viruses, fungi and parasites [1]. Recurrent urinary tract infections can result in chronic kidney disease and hypertension [2]. Over the recent years importance of UTI is well recognized and yet the management controversies are unsettled. This article will provide the latest evidence in the management of UTI in children.

1.1 Epidemiology and Pathophysiology of UTI

The distribution and pattern of UTI varies with age, gender, ethnicity, circumcision in boys, and presence of congenital malformations. During neonatal period and early infancy males are more affected, probably because of anatomical abnormalities and prepuce colonization [3]. About 8% of girls, and 2% of boys experience at least one episode of *UTI* up to the age of 7 [4]. In female infants UTI occurs in 0.1–0.4% and increase up to 1.4% during preschool age and 0.7–2.3% in school age [5].

Approximately 0.2% of circumcised and 0.7% of uncircumcised male infant are at risk, which declines to 0.1-0.2 during 1–5 years and 0.04–0.2 in school age [5]. UTI may lead to transient renal damage in 40% and permanent renal scarring in 5% of patients [6]. Studies have shown that asymptomatic bacteriuria occurs in 1% in infants, 3% in preschool children, and 1% in school age children [7]. Screening studies in emergency departments suggest that up to 5% of children under the age of 2 years presenting with fever have UTI, and over half of these would have been given alternative diagnoses such as otitis media, had the urine not been screened as part of the study [8,9].

UTI had a mortality rate as high as 20% in pre-antibiotic era [10]. Long-term complications of *UTI* associated with renal scarring include hypertension, chronic renal failure, and toxemia in pregnancy. Even though long-term follow-up data are limited, yet one study found that among patients who had renal scarring from pyelonephritis during childhood, 23% developed hypertension and 10% end-stage renal disease [11]. However, more recent studies question the association between pyelonephritis and end-stage renal disease [12].

1.2 Pathophysiology

Mutual interaction of both human host and bacterial factors contribute to the occurrence of *UTI*. Bacterial factors that have been well studied in this condition include adherence, growth factors, and features that allow the bacteria to avoid destruction by the human immune response[13]. In serotypes of *E coli* frequently isolated in *UTI,* bacterial adherence to the uroepithelium is enhanced by adhesins, often fimbriae (pili), which bind to specific receptors of the uroepithelium [14]. The interaction of fimbriae with the mucosal receptor triggers internalization of the bacterium into the epithelial cell, which leads to apoptosis, hyperinfection, and invasion into surrounding epithelial cells or establishment of a bacterial focus for recurrent *UTI* [15] The human defense mechanisms involve many components of the immune system, any of which can vary with genetic background and environmental exposures [16].

Some of these components have been studied in the context of urinary tract infection (e.g., P1 blood type, Lewis blood type), but findings are inconsistent [17]. Recurrence rate of UTI varies from 10 and 30% of children and most of these recurrences occur within 12 months of the primary infection [18,19]. Risk factor(s) for UTI recurrence in children include age less than 6 months, presence of vesicoureteral reflux, congenital genito-urinary malformations, and renal damage detected during first episode of *UTI*, that may be congenital in origin [17]. Other factors, such as dysfunctional voiding, detrusor instability, incomplete bladder emptying, and constipation, are also believed to be risk factors [20-22]. Studies have shown that more than 80% of childhood UTIs are caused by *E. coli*, 10-15% of *UTI*s are caused by the other gram-negative organisms like *Klebsiella, Enterobacter, Proteus*, and *Pseudomonas. Staphylococcus aureus* is usually considered a contaminant, but it can cause illness [23]. Signs that suggest contamination include the absence of symptoms, the recent manipulation or catheterization of the urinary tract under aseptic conditions, the presence of epithelial cells or the absence of leukocytes on urine microscopy, the culture of more than one organism, or a low colony count. Infection with an unusual organism (e.g.,*Pseudomonas)* is commonly associated with recurrent infections (frequently tied with the prolonged use of broad spectrum antibiotics) [24].

It is important to divide *UTI* into lower urinary tract infection, localized to the bladder and urethra (cystitis and urethritis) versus upper tract infection of the ureter, collecting system, and renal parenchyma (pyelonephritis). Ascending bacterial infection of the urinary tract is a complex process that has been associated with bacterial adhesion, virulence, and motility properties of infecting microbes as well as host anatomic, humoral, and genetic factors [25]. The presence of fever, chills, and flank pain has usually been considered clinical evidence of upper tract infection. New technologies like technetium 99m-labeled dimercaptosuccinic acid (*DMSA*) scans to diagnose upper tract infections have demonstrated a wide range of estimates (34 to 70%) for the prevalence of pyelonephritis in children with febrile *UTI* [26,27,28,29].

1.3 Diagnosis

Clinically any febrile child, presenting without any fever localizing sign, is likely to have *UTI*. Neonates often present with very nonspecific symptoms such as an undifferentiated febrile illness, irritability, vomiting, or poor feeding, and, less commonly, with late-onset jaundice or failure to thrive [30]. In infants and todlers the presentation is likely to be also nonspecific, including fever, diarrhea, or vomiting with dehydration, failure to thrive, abdominal/flank pain, foul-smelling urine, and new-onset urinary incontinence, but rarely with more specific urinary symptoms [31]. In cases of serious bacterial infection, signs and symptoms may be subtle. In the older children symptoms and signs may be more specific to the urinary system, and include dysuria, foul-smelling urine, urgency, frequency, new-onset urinary incontinence, or gross hematuria. Systemic symptoms such as fever, abdominal or flank pain, and vomiting are highly suggestive of pyelonephritis. The physical exam is useful to exclude other possible causes for the patient's symptoms. It should be completed in infants and febrile patients.

In older patients, the abdomen and genitalia should be examined, and the costovertebral angles should be palpated. Palpable bladder or abdominal mass, poor urinary flow, poor growth, and elevated BP may be seen with obstructive uropathy or chronic kidney disease and should prompt the clinician to consider abnormalities of the urinary tract [32] .

1.4 Laboratory Diagnosis

The standard laboratory test for diagnosis of UTI is growth of single uropathogenic bacteria in a urine culture from a properly collected urine sample. In neonates and young children,

urine is collected by either suprapubic aspiration (SPA) or urinary catheterization to avoid the contamination from fecal bacteria that colonize the perineal area and distal urethra [33]. When ultrasonographic guidance is used, success rates improve.(34). Various parents and clinician think *SPA* as an invasive method and try to avoid, but tight phimosis or Ibial adhesions form the absolute indications, yet this procedure do need little expertise as well. Urine obtained through catheterization for culture has a sensitivity of 95% and a specificity of 99%, compared with that obtained through SPA [35]. Whether the urine is obtained through catheterization or is voided, the first few drops should be allowed to fall outside the sterile container, because they may be contaminated by colonized bacteria in the distal urethra.

Cultures of urine specimens collected in a bag applied to the perineum have an unacceptably high false-positive rate and are valid only when they yield negative results [36, 37]. With a prevalence of *UTI* of 5% and a high rate of false-positive results (specificity: 63%), a “positive” culture result for urine collected in a bag would be a false-positive result 88% of the time. For febrile boys, with a prevalence of *UTI* of 2%, the rate of false-positive results is 95%; for circumcised boys, with a prevalence of *UTI* of 0.2%, the rate of false-positive results is 99% [38]. Therefore, in cases in which antimicrobial therapy will be initiated, catheterization or SPA is required to establish the diagnosis of *UTI* in infants and toddlers.

Clean catch midstream urine collection is recommended in children who are toilet trained. For a prompt diagnosis, urine is examined by dipstick and microscopy. Urine dipstick is an inexpensive and a readily available technique. The presence of either leukocyte esterase (LE) and/or nitrite is interpreted as a positive dipstick test [39], whereas blood and protein are poor indicators of *UTI.* Urine microscopy is performed to look for the presence of WBC or bacteria, and its sensitivity and specificity are better with uncentrifuged urine and Gram staining of the sample. Urine Gram stain for bacteria has a better sensitivity (91%) and specificity (96%) than all other rapid tests used alone or in combination [39] and can guide specific therapy in addition of diagnosing *UTI* in children.

When uncentrifuged urine is examined microscopically, pyuria is defined by ≥ 10 WBC/mm3 and bacteriuria by the presence of any bacteria per 10 oil immersion field of Gram-stained smear.

1.5 Imaging Studies in UTI

The diagnosis of *UTI* often leads to a radiographic evaluation to look for correctable urinary tract abnormalities that may act as risk factor(s) for *UTI*. Based on the findings of these imaging studies, medical or surgical interventions can then be employed to prevent children from developing future infections or sustaining renal damage. Scarring leading to renal hypertension, and reflux nephropathy leading to chronic renal disease, occur in 10-20% and 10- 25% of patients respectively [40-42].

Thus, the sequential radiographic workup is critical in determining appropriate therapy. Most of the time imaging modalities used for this purpose were a renal and bladder

ultrasonography (*RUS*) and voiding cystourethrogram (VCUG), followed by dimercaptosuccinic acid (DMSA) scan [40]. Patients who have initial photon defects or evidence of parenchymal inflammation are subsequently referred for a VCUG to assess for reflux in addition to a late *DMSA* (6–12 months) to assess for permanent scarring [43], although it cannot differentiate congenital renal dysplasia from the infection induced scarring.

But there is unsettled opinion whether we should go by "bottom up" approach that is starting from RUS through VCUG to DMSA or the top down" that is starting from DMSA to RUS, as both of them have their own merits and demerits.However top down approach is better for research purposes. In "bottom-up" approach, method relies on renal-bladder ultrasound (RUS) to identify anatomic irregularities, obstruction at various places, renal anomalies, abscesses, stones, tumors, and dilations [44] The *VCUG* targets lower urinary tract abnormalities and detects vesicoureteral reflux (*VUR* [44]. Patients diagnosed with reflux or parenchymal deformity may undergo a *DMSA* scan at a later date to assess for scarring. Alternatively, the "top-down" approach targets the kidney at the outset with a DMSA scan to diagnose acute renal parenchymal involvement at the time of the febrile *UTI* [44].

Now it can be assumed reliably, that radiographic evaluation of children with febrile UTIs to identify clinically significant vesicoureteric reflux or renal parenchymal involvement, is that, it demands for solid evidence-based medicine, and puts forward the need for individualized therapy rather than a blanket recommendation regarding the workup and treatment of febrile *UTI* [44] . Latest imaging modalities include, Magnetic resonance urography (*MRU*) which can provide both anatomic and functional data in one study. Due to the improved spatial and contrast resolution, congenital renal dysplasia can be differentiated from acquired renal damage on *MRU* [45].

Another magnetic resonance imaging technique has been developed to perform interactive voiding cystourethrography (i*MRVC*), which involves using a pulse sequence and rapid switching between views to permit prolonged dynamic imaging of the urinary tract [46]. Both *MRU* and i*MRVC* offer exquisite anatomic detail in conjunction with dynamic, functional information without the need for radiation. These tests are expensive to administer, require sophisticated processing techniques, and may require sedation in younger patient populations.

1.6 Immediate Treatment

Neonates with UTI require intravenous antibiotics, because there is an approximately 10% risk of concomitant bacteremia [47,48] and a significant chance of finding uropathology (e.g., posterior urethral valves, obstructed duplex systems, highgrade vesicoureteric reflux [49]. The most likely pathogens in this age group are *E. coli* and Enterococcus faecalis, which require empiric treatment with a β-lactam antibiotic and an aminoglycoside. Usually intravenous treatment is continued until systemic signs have resolved, at which time an oral antibiotic should be given for a total of 7 to 10 days [49]. Treatment choices for children who are more than 2 month old to 2 years has been revised by 2011-AAP guidelines, according to which systematically ill children should be started with IV antibiotics after taking the urine sample for culture and sensitivity and treatment can be revised after the results of antibiotic sensitivity, and oral antibiotic are given once the patient is able to tolerate the orals and responds to IV treatment [38].

Those who are not systemically ill, should get the urine tested and or urine sent for culture, with close watch till the reports come, for the further management (38). There is good

evidence that oral antibiotics are effective treatment for acute pyelonephritis [38]. Intravenous therapy can be limited to children presenting as seriously unwell or with persistent vomiting. Failure rates of oral antibiotics as first-line treatment for children with acute pyelonephritis are less than 5%. The optimal duration of oral antibiotics for acute pyelonephritis is poorly supported by trial evidence. In clinical practice, treatment duration between 7 and 14 days of oral antibiotics is usual. Acute treatment options for children with cystitis is of 3-4 day duration, well supported by large evidence [50].

The choice of empirical treatment depends on type of organisms involved, sensitivity and local resistance patterns. As per the North American Urinary Tract Infection Collaborative Trial report published in 2006 reported, 37.8% *E. coli* are resistance to β-lactam antibiotics and 21 are% *E. coli* are resistance to trimethoprim–sulfamethoxazol (51), However*, E. coli* remains largely sensitive to third generation cephalosporins (ceftriaxone, cefixime), aminoglycosides, and nitrofurantoin [51,52].

In neonates the most likely pathogens are *E. coli* and *E. faecalis*, which require therapy with a β-lactam antibiotic and an aminoglycoside. For pyelonephritis, orally administered antibiotics are second and third-generation cephalosporins. Alternatively, amoxicillin–clavulanate, trimethoprim–sulfamethoxazole (*TMP-SMX*), and first-generation cephalosporins can be used with caution due to increasing resistance of *E. coli* [52]. Fluoroquinolones (ciprofloxacin) are effective for *E. coli* but should not be used as first-line agents due to their safety concerns in children [52]. Parenteral therapy with third- or fourth-generation cephalosporins and aminoglycosides are appropriate for empiric treatment. When enterococcal *UTI* is suspected (associated with urinary catheter, instrumentation of the urinary bladder, or genitourinary abnormalities), ampicillin should be included in treatment options. Gentamicin can be used parenterally as an adjunctive treatment in resistant organisms after knowing the renal functions [53].

1.7 Surgical Management of UTI

With the improvement in techniques and introduction of endoscopic regimens, surgical correction is becoming more acceptable to parents. Most surgical modalities are associated with a very high potential for the correction of *VUR* [54]. However, the final report of the International Reflux Study indicated that at 10-year follow up there was little difference in renal scarring between the medical and surgical groups [54]. But, there was a lower incidence of febrile infections in those children who had surgical correction as compared to those in the medical arm. Options for surgical management include endoscopic, laparoscopic, robotic and open procedures [54]. With the in introduction of the approved injectable agent dextranomer/hyaluronidase [55], acceptance rate of endoscopic treatment for management of *VUR* has risen.

1.8 Prevention of Recurrent Urinary Tract Infection

Role of dysfunctional elimination syndrome is long being debated as a potential cause of recurrent *UTI* [56] Many clinicians advocate treating constipation, ensuring complete bladder emptying and good fluid intake, avoiding local irritation from underclothes and cleanliness. Snodgrass and RIVUR study [56,57] noted a significant correlation between recurrence of *UTI*s and the presence of voiding dysfunction. Maintaining good hygiene, wiping females from front to back during diaper changes or after using the toilet in older girls, while in

uncircumcised males, mild and gentle traction of the foreskin helps to expose the urethral opening, and keeping it clean regularly helps to reduce the *UTI.*

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors state that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

REFERENCES

1. Beetz R. May we go on with antibacterial prophylaxis for urinary 213 tract infections? Pediatric Nephrology. 2006;21:5–13.
2. Quigley R. Diagnosis of urinary tract infections in children. Current Opinion in Pediatrics. 2009;21:194–198.
3. López Sastre JB, Aparicio AR, Coto Cotallo GD, Fernández Colomer B, Crespo Hernández M. Urinary tract infection in the newborn: clinical and radio imaging studies. Pediatric Nephrology. 2007;22:1735–1741.
4. Bauer R, Kogan BA. New developments in the diagnosis and management of pediatric UTIs. Urologic Clinics of North America. 2008;35:47–58.
5. Clark CJ, Kennedy WA, Shortliffe LD. Urinary tract infection in children: when to worry. Urologic Clinics of North America. 2010;37:229–241.
6. Williams GJ, Lee A, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database of Systematic Reviews. 2001;(4)CD001534
7. Linshaw M. Asymptomatic bacteriuria and vesicoureteral reflux in children. Kidney International.1996;50:312–329.
8. Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D. Prevalence of urinary tract infection in febrile infants. J. Pediatr. 1993;123:17-23.
9. Kathy NS, Marc G, Karin LM Noreen MY, Sanford SJ. Prevalence of urinary tract infection in febrile young children in the emergency department. Pediatrics 1998; 102:e16.
10. Hansson S, Martinell J, Stokland E, Jodal U. The natural history of bacteriuria in childhood. Infect. Dis. Clin. North Am. 1997;11:499-512.
11. Jacobson SH, Eklöf O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. Br. Med. J. 1989;299:703-706.
12. Sreenarasimhaiah, S., and S. Hellerstein. Urinary tract infections per se do not cause end-stage kidney disease. Pediatr. Nephrol. 1998;2:210-213.
13. Roberts JA: Factors predisposing to urinary tract infections in children, Pediatr Nephrol 1996;10:517-22.
14. 14 Sussman M, Gally DL. The biology of cystitis: host and bacterial factors. Annu Rev Med. 1999;50:149– 58.

15. Bower JM, Eto DS, Mulvey MA. Covert operations of uropathogenic Escherichia coli within the urinary tract. Traffic 2005;6(1):18–31.
16. Jantausch BA, Criss VR, O'Donnell R, Wiedermann BL, Majd M, Rushton et al: Association of Lewis blood group phenotypes with urinary tract infection in children, J Pediatr 1994;124:863-68.
17. Albarus MH, Salzano FM, Goldraich NP: Genetic markers and acute febrile urinary tract infection in the 1st year of life, Pediatr Nephrol 1997;11:691-94.
18. Panaretto K, Craig JC, Knight JF, Howman-Giles R, Sureshkumar P, Roy LP. Risk factors for recurrent urinary tract infection in preschool children, J Paediatr Child Health1999; 35:454-59.
19. Winberg J: What hygiene measures are advisable to prevent recurrent urinary tract infection and what evidence is there to support this advice? Pediatr Nephrol 1994;8:652.
20. Blethyn AJ, Jenkins HR, Roberts R, Verrier Jones K: Radiological evidence of constipation in urinary tract infection, Arch Dis Child 1995; 73:534-35.
21. Koff SA, Wagner TT, Jayanthi VR: The relationship among dysfunctional elimination syndromes, primary vesicoureteral refl ux and urinary tract infections in children, J Urol 1998;160:1019-22.
22. Lidefelt KJ, Erasmie U, Bollgren I: Residual urine in children with acute cystitis and in healthy children: assessment by sonography, J Urol 1989;141:916-17.
23. Abrahamsson K, Hansson S, Jodal U, Lincoln K: Staphylococcus saprophyticus urinary tract infections in children, Eur J Pediatr 1993;152:69-71.
24. Travis LB, Brouhard BH. Infections of the urinary tract. In: Rudolph. AM, ed. Rudolph's Paediatrics. 12th ed. Stamford: Appleton and Lange,. 1996:1388 1392.
25. Svanborg, C., and Godaly G. Bacterial virulence in urinary tract infection. Infect. Dis. Clin. North Am. 1997;11:513-529.
26. Biggi A, Dardanelli L, Pomero G, Cussino P, Noello C, Sernia O, et al. Acute 266 renal cortical scintigraphy in children with a first urinary tract infection. Pediatr. Nephrol. 2001; 16:733-738.
27. Ditchfield MR, Summerville D, Grimwood K, Cook DJ, Powell HR, Sloane R, et al. Time course of transient cortical scintigraphic defects associated with acute pyelonephritis. Pediatr. Radiol. 2002;32:849-852.
28. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a 272 first febrile urinary tract infection in young children. N. Engl. J. Med. 2003;348:195-202.
29. Lin KY, Chiu NT, Chen MJ, Lai CH, Huang JJ, Wang YT, Chiou YY. Acute pyelonephritis and sequelae of renal scar in pediatric first febrile urinary tract infection. Pediatr. Nephrol. 2003;18:362-365.
30. Lin DS, Huang SH, Lin CC, Tung YC, Huang TT, Chiu NC, et al. Urinary tract infection in febrile infants younger than eight weeks of Age. Pediatrics. Feb 2000;105(2):E20.
31. Garcia FJ, Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. Pediatrics 2002;109(5):846–51.
32. Smellie JM, Hodson CJ, Edwards D, Normand ICS. Clinical and radiological features of urinary infection in childhood. BMJ 1964;5419:1222–6.
33. Djojohadipringgo S, Abdul Hamid RH, Thahir S, Karim A, Darsono I. Bladder puncture in newborns: a bacteriological study. Paediatr Indones. 1976;16(11–12):527–534.
34. Buys H, Pead L, Hallett R, Maskell R. Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. BMJ. 1994;308:690–692.
35. Kramer MS, Tange SM, Drummond KN, Mills EL. Urine testing in young febrile children: a risk-benefit analysis. J Pediatr. 1994;125:6–13.

36. Sorensen K, Lose G, Nathan E. Urinary tract infections and diurnal incontinence in girls. Eur J Pediatr. 1988;148(2):146147.
37. Shannon F, Sepp E, Rose G. The diagnosis of bacteriuria by bladder 291 puncture in infancy and childhood. Aust Pediatr J. 1969; 5):97–100.
38. CLINICAL PRACTICE GUIDELINE: 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;128:595–610.
39. 39. Williams GJ, Macaskill P, Chan SF, Turner RM, Hodson E, Craig JC. Absolute and relative accuracy of rapid urine tests for urinary tract infection in children: a meta-analysis. Lancet Infect Dis. 2010;10:240–250.
40. 40. Herz D, Merguerian P, McQuiston L, Danielson C, Gheen M, Brenfleck L. 5-year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: proof that the top-down approach works. Journal of Urology. 2010;184:1703–1708.[PubMed]
41. Smellie JM, Barratt TM, Chantler C, et al. Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: a randomised trial. Lancet. 2001; 357:1329–1333.
42. Coulthard MG, Verber I, Jani JC, Lawson GR, Stuart CA, Sharma V, et al. Can prompt treatment of childhood UTI prevent kidney scarring? Pediatric Nephrology. 2009; 24: 2059–2063.
43. Coulthard MG. Vesicoureteric reflux is not a benign condition. Pediatric Nephrology. 2009;24:227–308 232.
44 .Michaella M. Prasad* and Earl Y. Cheng.Radiographic Evaluation of Children with Febrile Urinary 310 Tract Infection: Bottom-Up, Top-Down, or None of the Above? Adv Urol. 2012; 716739.
45. Grattan-Smith JD, Little SB, Jones RA. Evaluation of reflux nephropathy, pyelonephritis and renal dysplasia. Pediatric Radiology. 2008;38(1):S83–S105.
46. Arthurs OJ, Edwards AD, Joubert I, Graves MJ, Set PAK, Lomas DJ. Interactive magnetic resonance voiding cystourethrography (iMRVC) for vesicoureteric reflux (VUR) in unsedated infants: a feasibility study. Eur Radiol 2011;21(9):1874-81.
47. Pantell RH, Newman TB, Bernzweig J, Bergman DA, Takayama JI, Segal M,, et al: Management and outcomes of care of fever in early infancy, 2004; JAMA 291:1203-12.
48. Hsiao AL, Chen L, Baker D: Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants, Pediatrics 2006; 117:1695-701.
49. Navarro M, Espinosa L, de las Heras JA, Garcia Meseguer MC, et al: Symptomatic urinary infection in infants less than 4 months old: outcome in 129 cases, An Esp Pediatr 1984;21:564-72.
50. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA: Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children, Cochrane Database Syst Rev (1): CD003966, 2003.
51. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnik LP, et al. . Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) Int J Antimicrob Agents. 327 2005;26:380–388.
52. Fabre R, Merens A, Lefebvre F, Epifanoff G, Cerutti F, Pupin H, et al. 329 Susceptibility to antibiotics of Escherichia coli isolated from community-acquired urinary tract infections. Méd Mal Infect. 2010;40:555–559.
53. Sermin A. Saadeh1 and Tej K. Mattoo. Managing urinary tract infections. Int J Pediatr. 2012; 943653. Published online 2012 July 19.

54. Jodal U, Smellie JM, Lax H, Lax H, Hoyer PF. Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International Reflux Study in Children. Pediatr Nephrol. 2006;21:785-92.
55. Stenberg A, Lackgren G. A new bioimplant for the endoscopic treatment of vesicoureteral reflux: experimental and short-term clinical results. J Urol. 1995;154:800-3.
56. Snodgrass W. Relationship of voiding dysfunction to urinary tract infection and vesicoureteral reflux in children. Urology. 1991;Oct;38(4):341-4.
57. Mathews R, Carpenter M, Chesney R, Hoberman A, Keren R, Mattoo T, et al.Controversies in the management of vesicoureteral reflux: the rationale for the RIVUR study. J Pediatr Urol. 2009 Oct;5(5):336-41

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=306&id=12&aid=2376