Urinary Tract Infections: Pediatrics

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1. Introduction

Urinary tract infection (UTI) refers to inflammatory changes in the urinary tract caused by the presence of an infectious agent. The spectrum of severity may range from a local infection of urinary tract with minor lower urinary tract symptoms to a severe infection with systemic changes and urosepsis. UTI is a common condition in the pediatric population and we will review important concepts including risk factors, evaluation and treatment options related to pediatric UTI. (see *Urology Care Foundation*: **UTIs in Children**)

Keywords

Urinary tract infection (UTI), voiding cystourethrogram (VCUG), renal bladder ultrasound (RBUS), urinalysis, urine culture, antibiogram

2. Epidemiology

Approximately 3.5% of children in the United States will experience a UTI annually and between 1.5-1.75 million outpatient visits for UTI occur each year.[1,2] The predilection for UTI varies by sex, age, and race.[3,4,5] Overall, UTIs are more common in females. The time period during which males are at greatest risk for UTI is during the first year of life. Circumcised males have greater than an 85% reduction in odds of UTI compared with uncircumcised males.[6] In the neonatal period, males are two times more likely to have a UTI compared with females. From 1-6 months the incidence is approximately equal. From 6-12 months the ratio of UTIs in males to females is 1 to 4. Thereafter the incidence of UTI in males decreases dramatically and throughout the remainder of life remains low compared with females. Differences in rate of UTI by race have been reported, namely, Blacks who tend to have lower rates of UTI compared with Whites, Asians, and Hispanics.[3,7,8] The AAP UTI guideline incorporates race as a risk factor in determining the need for UTI evaluation.[9] However, there is concern that the studies from where these data on race and UTI arise are imperfect and use inconsistent and outdated definitions for race/ethnicity potentially contributing to the systemically flawed use of race in medicine.[10] Recently, there has been a call to remove race from the UTI guideline as the effects of the inclusion of race may be that Black children are tested less frequently or require more risk factors to meet criteria for testing.

3. Risk Factors, Genetics, and Pathophysiology

3.1 Risk Factors

Risk factors for UTI include prior UTI, circumcision and phimosis status, **bladder and bowel dysfunction (BBD)**, sexual activity among older ages, presence of genitourinary anomaly, presence of renal scarring, and urologic instrumentation. Approximately 12-30% of children with a symptomatic UTI will have a recurrence.[4,11,12,13] UUncircumcised males have the highest rate of UTI of all gender and age groups, especially among males less than one year of age who are more likely to have physiologic phimosis.[3] The risk of recurrent UTI may be decreased by treating physiologic phimosis with steroid cream.[14,15] Sexually active females have a high risk for UT.[16] Anatomical and functional abnormalities of the urinary tract that may predispose to urinary statis are also associated with an increased risk for UTI including vesicoureteral reflux (see *AUA Guideline*: **Management and Screening of Primary Vesicoureteral Reflux in Children** and *Urology Care*

Foundation: **Vesicoureteral Reflux (VUR) Fact Sheet**), ureterocele, ureteropelvic or ureterovesical junction obstruction, bladder diverticula, posterior urethral valves, neurogenic bladder, and bladder and bowel dysfunction (see *AUA Core Curriculum*: **Urinary Tract Anomalies**).[11,17,18,19,20,21] A recent prospective cohort study combing data from two previously conducted studies (Randomized Intervention for Vesicoureteral Reflux (RIVUR) trial and Careful Urinary Tract Infection Evaluation (CUTIE) study) demonstrated that children with high grade vesicoureteral reflux (HR 1.9, 95% CI 1.1-3.1), bladder and bowel dysfunction (HR 2.1, 95% CI 1.1-3.9), and baseline renal scarring (HR 2.9, 95% CI 1.2 6.8) are at increased risk for recurrent UTI. Moreover, children with any grade of vesicoureteral reflux and bladder and bowel dysfunction were found to have the greatest risk for recurrent UTI (56%).[22] Urologic instrumentation such as catheter placement for voiding cystourethrogram is also a known risk factor for UTI.[23]

3.2 Genetics

The genetics of UTI are incompletely understood and the etiology of UTI is thought to be multifactorial. A higher incidence of UTI has been demonstrated in girls with a family history of UTI and female siblings of girls with UTI have an increased incidence of bacteriuria.[24,25]

Disease severity in UTI is likely a combination of pathogen virulence factors and host susceptibility mechanisms. Likely genetic alterations of the immune response play a role in a child's risk for acquiring UTI and the severity of illness associated with UTI. Ongoing investigation of host immune response pathways and signaling mechanisms is occurring in areas such as Toll-like receptors, interferon regulator factors, and type 1 interferons.[26]

3.3 Pathophysiology

See reference [27]

UTI is usually an ascending infection although hematogenous spread can occur and is most often seen in infants or immunocompromised populations. Most commonly UTIs are caused by bacteria; however fungal (candida) and viral infections (most commonly adenovirus and BK virus) may be seen in immunocompromised patients as well. The mechanism of infection for bacteria is via the intestinal flora that colonize the female introitus or male preputial epithelium. Bacterial virulence factors aid in the colonization and persistence of bacteria. These factors include the following:

1. Fimbriae (Type 1 fimbriae and P fimbriae) which are important for adherence and contribute to the bacteria's ability to ascend to the upper tracts,
2. K antigen which is part of the bacterial capsule and shields bacteria from complement lysis and phagocytosis, and
3. Endotoxin which is a lipopolysaccharide within the cell wall of bacteria that initiates the acute inflammatory response.

4. General Prevention

A strong association between bladder and bowel dysfunction and UTI has been established.[17,28,29] Therefore, good voiding and elimination habits that emphasize regular and complete emptying of the bladder are critical in the prevention of UTI (see *AUA Update Series*: **Evaluation and Management of Lower Urinary Tract symptoms in Children** and *AUA Core Curriculum*: **Voiding Dysfunction**). Furthermore, if constipation is identified this should be aggressively treated. Finally, identification and treatment of conditions that may predispose to urinary stasis are important in the prevention of UTI. In male infants, performing a circumcision or treating physiologic phimosis with a steroid cream may decrease risk of recurrent UTI.[3,14,15]

5. Diagnosis and Evaluation

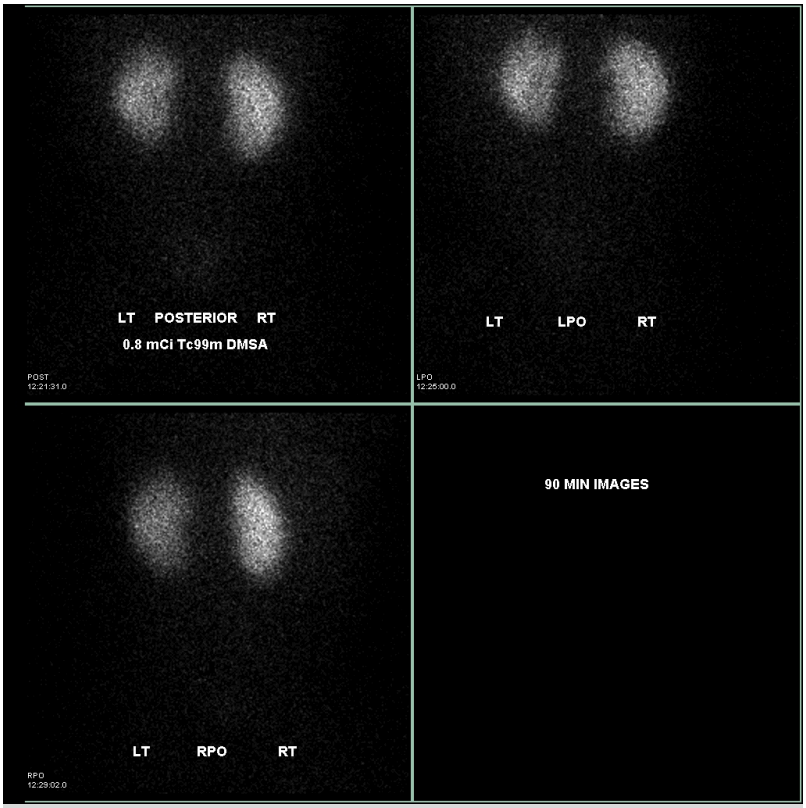

Figure 1: Photopenia of the left upper pole kidney indicating inflammation of the kidney in acute pyelonephritis.

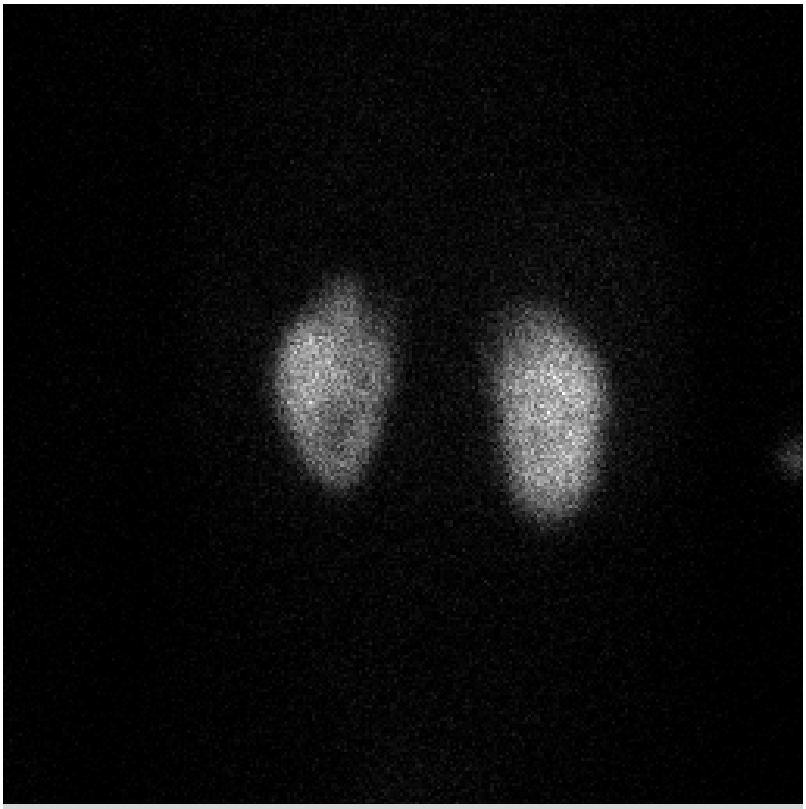

Figure 2: Photopenia of left upper pole kidney in a child six months after active infection indicating scarring.

5.1 History and Physical Examination

The evaluation of all patients presenting with UTI should begin with a medical history and physical exam. In young pediatric patients symptoms are typically nonspecific such as fever, irritability, poor feeding, vomiting, diarrhea, or abdominal distention.[30,31] Older children may complain of dysuria, incontinence, changes in voiding habits, or flank or abdominal pain.[32] Information about the presence, severity, and duration of fever should be obtained. Risk factors for UTI should be elicited such as prior history of UTI, circumcision and phimosis status, presence of genitourinary anomaly, history of abnormal pre or postnatal ultrasounds, family history, and prior genitourinary or gastrointestinal surgery.

Specific findings on physical exam in young children are rare and rather typically consist of fever, failure to thrive, or lethargy. Older children often will have suprapubic or flank tenderness. Assess males and females for palpable abdominal (bladder distention) or flank mass (hydronephrosis) and assess the external genitalia for any anatomic abnormalities. In males examine for phimosis, meatal stenosis, urethral discharge, and testicular tenderness which may be a sign of epididymo-orchitis. In females assess the introitus for discharge and signs of local irritation.

5.2 Urine Testing

See references 32,33,34

Current American Academy of Pediatrics guidelines recommend confirmatory urine testing with urinalysis and culture in the febrile infant from 2-24 months of age prior to antibiotic administration. The National Institute for Health and Clinical Excellence (NICE) guidelines also recommend that infants and children 3-36 months with fever or symptoms and signs of UTI have a specimen collected for urinalysis and culture. There are no US-based guidelines for older children; however, the NICE guidelines recommend urinalysis alone to establish the diagnosis and initiate treatment of a standard UTI in a child greater than 3 years.

Diagnosis of UTI in children 2-24 months is made based on urinalysis that suggests infection (pyuria) and at least 50,000 colonies per mL of a single organism obtained via suprapubic aspiration or catheterization.[34]

5.2.1 Dipstick Urine Testing

Dipstick urinalysis supports clinical information and aids in making the decision to empirically treat a child for UTI.

- Positive leukocyte esterase indicates that WBCs are in the urine and is 95% sensitive for UTI in children with symptoms. False negatives may occur if the urine is collected early in the infection and an inflammatory response has not been mounted. False positives can occur with other conditions that cause inflammation or irritation in the urinary tract such as with urolithiasis.
- Positive nitrite on urinalysis (many gram-negative bacteria produce this substance) has a sensitivity of 30-45%, but a specificity that nears 100%. Since conversion from nitrate to nitrite takes approximately 4 hours there may be false negatives in patients with urinary frequency and in those with infections from yeast or gram positive bacteria. False positives may occur in infrequent voiders.
- Combined positive nitrite-leukocyte esterase on dipstick analysis is 80-90% sensitive and 60-98% specific.
- A dipstick urinalysis obtained by bag specimen that is completely normal generally can rule out a UTI but a bag specimen should not be used to diagnose a UTI. If a bag specimen has an abnormal urine analysis, a catheterized urine specimen should be obtained to diagnose a UTI.

5.2.2 Microscopic Analysis

Microscopic analysis may demonstrate white (WBC) or red blood cell (RBC) casts that are indicative of renal involvement and can help determine if contamination exists by the presence of epithelial cells.

- Greater than 5 WBCs per HPF on an unspun specimen or greater than 10 WBCs on a spun sediment is usually indicative of infection.
- Identification of bacteria on Gram stain has a sensitivity and specificity better than that of a dipstick evaluation for nitrite and leukocyte esterase.

5.2.3 Urine Culture

Urine culture is the gold standard to diagnose UTI:

- Samples collected by suprapubic aspirate or catheterization are less likely to be contaminated than midstream voiding samples from older females and circumcised males, and bag collection specimens in infants. If multiple organisms are present in a voided specimen this is suspicious for contamination and confirmation with a catheterized specimen should be obtained. Cultures obtained by bag specimen should not be used to diagnose UTI. If a urinalysis obtained by bag specimen in infants or young children is concerning for infection, a suprapubic aspiration or catheterized specimen should be obtained for repeat urinalysis and culture.
- > 100,000 CFU/mL on a voided or catheterized specimen and any bacteria on a suprapubic aspirate specimen is considered a positive culture.
- Lower colony counts in symptomatic children, or growth of pathogenic bacteria (e.g. Klebsiella, Pseudomonas) should also be treated.
- Diagnosis of UTI in children 2-24 months is made based on urinalysis that suggests infection (pyuria) and at least 50,000 colonies per mL of a single organism obtained via suprapubic aspiration or catheterization.[34]

5.2.4 Blood Tests

Blood tests are unreliable in diagnosing UTI.

5.3 Imaging

See references 18,34,35

The need for and timing of imaging following UTI remains controversial; it is not typically required in the acute setting, but may be indicated at follow up. [35]

- Consider evaluating all children <5 years after their 1st documented UTI, and all girls, regardless of age, with febrile or recurrent infections, particularly with voiding dysfunction, with a renal bladder ultrasound (RBUS) (see AUA Update Series: **The Role of Ultrasound in Imaging the Urinary Tract in Children**. Nelson CP et al, Col 35, Lesson 17, 2016). However, often RBUS will be normal despite genitourinary anomaly such as VUR and screening RBUS after first, febrile UTI has been shown to not be cost effective.[20,36]
- Need for and timing of VCUG after UTI are controversial: AAP guidelines on UTI management in the patient with a febrile UTI from 2-24 months recommends VCUG after a second febrile UTI unless there is a suspicion of underlying anatomic abnormality (e.g. scarring or hydronephrosis or other abnormality seen on RBUS after the first febrile UTI). There is substantial disagreement with this recommendation; it has been proposed that VCUG be performed after the first UTI since up to 40% of children 1-24 months of age with a single febrile UTI have VUR (20% will have dilating VUR, grade III and above).[20]
- The majority of patients (~90%) with febrile UTI will defervesce within 48 hours of starting antibiotics. Lack of defervesce does not signify an increase in structural or functional abnormalities for most late responders compared with responders.[37]
- DMSA scan may reveal renal inflammation in acute pyelonephritis (**Figure 1**) and/or scarring (**Figure 2**) from previous infection.[38]

6. Treatment

6.1 General Measures

Management of suspected UTI should be based on a combination of factors including likely uropathogen (**Table 1**), clinical status, and reliability of patient and family. Hospitalization might be required based on patient age and clinical status, although infants >2 months and nontoxic children with suspected pyelonephritis can be treated as outpatients as long as compliance with and tolerance of oral antibiotics is not an issue. Less than 1% of patients evaluated for UTI in the outpatient setting require admission. [1]

Table 1. Uropathogen Prevalence by Sex and Visit Setting*

Organism	Male		Female	
	Outpatient	Inpatient	Outpatient	Inpatient
E. coli	50% (48-52)	37% (35-39)	83% (83-84)	64% (63-66)
Enterobacter	5% (5-6)	10% (8-11)	1% (1-1)	4% (4-5)
Enterococcus	17% (16-18)	27% (25-29)	5% (5-5)	13% (12-14)
Klebsiella	10% (9-11)	12% (10-13)	4% (4-5)	10% (9-11)
P. aeruginosa	7% (6-8)	10% (8-11)	2% (2-2)	6% (5-7)
P. mirabilis	11% (10-12)	5% (4-6)	4% (4-4)	2% (2-3)

* Based on national data from TSN (The Surveillance Network).
Prevalence will vary based on region.

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6.2 Antibiotic Treatment

In children, a treatment course for febrile UTI <7days has been shown to be inferior.[39] A recent comparative effectiveness study among 791 children with pyelonephritis demonstrated no difference in clinical outcomes when treated with short duration antibiotic therapy (<10 days, median 8 days) versus long duration (>=10 days, median 11 days) therapy (11.2% vs. 9.4%; OR 1.22, 95% CI 0.75-1.98).[40] The age of the child and comorbid conditions should be considered when selecting antibiotics (e.g. impaired hepatic metabolism in neonates who are less than 2 months old by corrected age and children with hemoglobinopathies). Fluoroquinolones should not be a first line choice and should be limited to resistant uropathogens.

Empiric treatment of acute UTI should be based on local resistance patterns from published antibiograms. (**Table 2**) Escherichia coli remains the most common pediatric uropathogen (>80% of UTIs).[41] Though trimethoprim-sulfamethoxazole is used in approximately 50% of outpatient UTI visits, it is a poor empirical choice for pediatric UTI due to high resistance rates.[1,41] Most uropathogens are susceptible to narrow-spectrum antibiotic agents such as first-generation cephalosporins and nitrofurantoin. However, nitrofurantoin has poor tissue penetration and should not be used for febrile UTI/pyelonephritis. Empiric broad-spectrum antibiotic prescription is appropriate in children at risk for resistant UTI such as those with prior UTI history, recent antibiotic exposure, recent hospitalization, and presence of genitourinary anomaly. [42,43,44] Broad-spectrum antibiotics include broad-spectrum penicillins (antipseudomonal penicillins and β-lactamase/β-lactam inhibitor combination penicillins), macrolides, fluoroquinolones, second-, third-, or fourth-generation cephalosporins, lincosamides, and carbapenems. (**Table 3**)

Table 2. Uropathogen Resistance Rates*

	Percent Antibiotic Resistance					
Antibiotics	**E. coli**	**Enterobacter**	**Enterococcus**	**Klebsiella**	**P. mirabilis**	**P. aeruginosa**
Narrow-spectrum						
TMP/SMX	24	18		15	11	94
Ampicillin	45	78	3	81	12	
Nitrofurantoin	<1	23	<1	17	94	0
Cephalothin	16	96		7	4	
Cefazolin	4	91		7	4	
Gentamicin	4	2		3	5	10
Vancomycin			<1			
Broad-spectrum						
Amox-clav	5	91		4	1	
Cefuroxime	2	33		7	0	
Ceftriaxone	<1	12		2	<1	31
Ceftazadime	<1	15		2	<1	4
Ciprofloxacin	5	1	5	3	3	5
Pip-tazo	1	7		3	<1	5
Imipenem	<1	<1		<1	2	3
Aztreonam	<1	13		3	<1	4

* Based on national data from TSN (The Surveillance Network). Resistance rates will vary based on region. Blanks indicate that testing was not performed for antibiotic to which uropathogens are known to be nonsusceptible.

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Table 3. Details of Common Antibiotic Dosing

Oral Agents	Dose	Common Side Effects	Comments
Amoxicillin-clavulanate	20-40 mg/kg per d in 3 doses	Diarrhea, nausea/vomiting, rash	
Trimethoprim-sulfamethoxazole	8-10 mg/kg/d of TMP in 2 doses	Diarrhea, nausea/vomiting, photosensitivity, rash	Contraindicated less than 6 weeks of age
Cefixime	8 mg/kg/d in 1 dose	Abdominal pain, diarrhea, flatulence, rash	
Cefixime	10 mg/kg/d in 2 doses	Abdominal pain, diarrhea, nausea, rash	
Cefprozil	20 mg/kg/d in 2 doses	Abdominal pain, diarrhea, elevated LFTs, nausea	
Cephalexin	50-100 mg/kg/d in 4 doses	Diarrhea, headache, nausea/vomiting, rash	
Nitrofurantoin	3-5 mg/kg in 2 doses	Nausea, vomiting, bad taste	Contraindicated less than 3 months of age or when GFR <50% or in children with G6PD deficiency
Parenteral Agents	**Dose**	**Common Side Effects**	**Comments**
Ceftriaxone	75 mg/kg/d in 1 dose		
Cefotaxime	150 mg/kg/d divided q6-8h		Single daily dosing acceptable[45]

Ceftazidime	100-150 mg/kg/d divided q8h		
Gentamycin	7.5 mg/kg/d divided q 8h		Single daily dosing acceptable alternative
Tobramycin	5 mg/kg/d divided q8h		
Piperacillin	300 mg/kg/d divided q 6-8 hour		
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6.3 Complementary and Alternative Therapies

The mechanism by which cranberry products are thought to protect against UTI is by inhibiting the bacterial growth and p-pili-mediated adhesion and reducing bacterial biofilm production. [46,47,48] There are currently no formal recommendations on the use of cranberry products to prevent UTI; however, there is some evidence in the literature that cranberry products may be effective lowering UTI recurrence. Regular drinking of cranberry juice (Product: Ocean Spray Cranberry Classic containing 41 grams of cranberry concentrate in 1 liter of juice. Dosing at 5 mL Cranberry juice per kg body weight, with a max dose of 300 mL per day) reduced the overall number of recurrent infections but did not significantly decrease the number of children experiencing at least one UTI recurrence. [49]

D-mannose, which is a sugar related to glucose, has been studied in adult women as a supplement for UTI prevention with small, randomized studies reporting decreased risk of recurrent UTI. [50] No studies or guidelines exist in the pediatric population regarding use of D-mannose for UTI prevention.

Probiotics may favorably alter gastrointestinal flora, but there are limited data and no specific recommendations for their use. [51]

7. Prognosis

The majority of children do not have any long-term sequelae from a single UTI episode. Renal scarring has been found in up to approximately 10% of children after first febrile UTI,[20] however, prompt antibiotic treatment of UTI may prevent renal scarring.[52,53] A recent post hoc analysis by Shaikh and colleagues using data from the RIVUR and CUTIE Trials showed that children who have two febrile UTIs have a substantially higher risk of renal scarring (25.7%, 95% CI 12.5%-43.3%) compared with children with a single febrile UTI (2.8%, 95% CI 1.2%-5.8%). [54]

There is evidence that renal scar development after pyelonephritis occurs more commonly among patients with VUR (3-fold increase in the odds compared with patients without VUR)[55] and a strong predictor of new scar formation among children with VUR presenting with UTI is the presence of previous renal scarring as well as increased severity of VUR.[56,57] Eight randomized controlled trials (RCTs) have studied whether or not prophylaxis prevents recurrent UTI among children with prior UTI history. In the RCTs with low-risk of bias prophylaxis had a protective effect on the development of UTI in children with reflux (pooled odd's ratio, OR=0.51).[58,59] Despite reduction in UTI rates, prophylaxis has not been shown to be associated with decreased rates of new renal scarring.[58,59] Various explanations for this discrepancy in UTI and renal scarring outcomes exist and include the low rate of renal scarring among healthy study subjects, the relatively short follow-up duration of studies that could miss delayed presentation of scar formation, and a potentially lower incidence of scar formation due to early treatment among patients enrolled in trials. However, Wang and colleagues recently performed a secondary analysis of the RIVUR trial data strictly limited to patients who had recurrent UTI during the study and demonstrated that antibiotic prophylaxis was associated with a decrease in the risk of new renal scarring. [60] It is important to note that approximately one half of patients that formed new scars in the RIVUR Trial did not have a recurrent UTI during the study period. Prior studies using RIVUR data that evaluated the association between antibiotic prophylaxis and new scar formation included all children regardless of whether they had a recurrent UTI during the trial. [58,59] A remaining unanswered question is why patients without recurrent UTI develop new renal scarring.

Although there are benefits of antimicrobial prophylaxis, we must weigh these against the potential costs of daily prophylactic therapy including side effects (as outlined above), nonadherence, and antibiotic resistance.[61] A large pharmacy claims study among VUR patients on prophylaxis demonstrated that only about 40% of patients were adherent to prophylactic regimens.[62] Moreover, approximately 25% of parents from the RIVUR trial reported giving the study medication less than 75% of the time.[63] Additionally, a secondary analysis of RIVUR Trial data by Gaither et al. demonstrated that increasing bladder and bowel dysfunction symptom scores had higher levels of non-adherence, and also that non-adherence (taking the study medication <70% of the time) was associated with renal scaring. [64]

In addition, patients on prophylaxis have been found to be at increased risk of resistant infections.[11] An individual patient data meta-analysis of randomized controlled trials of children with VUR being treated with antibiotic prophylaxis compared

to no treatment or placebo showed that prophylaxis increases the risk of multidrug resistant recurrent infections. Patients receiving prophylaxis had 6.4 times the odds (95% CI 2.7-15.6) of developing a multidrug resistant infection and one multidrug resistant infection would develop for every 21 VUR patients treated with prophylaxis.[65]

8. Costs

Freedman, in collaboration with the Urologic Disease in America project, estimated the annual economic burden for inpatient UTI treatment at $180 million.[2] However, this figure grossly underestimates the total cost of UTI given that the majority of UTIs are managed on an outpatient basis. Further contributing to the overall economic burden is the loss of productivity by the parent(s) that often must take time off from work to care for a sick child.

9. Summary

A high index of suspicion is often required for diagnosis of UTI, especially in nonverbal children. Empiric antibiotic treatment of acute UTI should be tailored to the child's age, clinical condition and likelihood for resistant UTI as well as to local antibiotic resistance patterns. History and physical examination and appropriate urine testing are critical determinants for making a UTI diagnosis. Radiographic studies are not usually required in the acute period but are often be employed at follow up to identify anatomic and functional abnormalities of the urinary tract that may predispose to UTIs.

Presentations

Urinary Tract Infections

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