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Work up of Pediatric Urinary Tract Infection

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Abstract

Pediatric UTI costs the healthcare system upwards of 180 million dollars annually, and accounts for over 1.5 million clinician visits per year. Accurate and timely diagnosis of these infections is important for determining appropriate treatment and preventing long-term complications such as renal scarring, hypertension, and end-stage renal disease. Outside of the first 12 months, girls are more likely to be diagnosed with a UTI. About half of boys with UTI will be diagnosed within the first 12 months of life. The prevalence and incidence of pediatric UTI varies by age, race/ethnicity, sex and circumcision status. Diagnosis of UTI is made based on history and exam findings and confirmed with appropriately collected urine. If a bag specimen is negative, this can be used to rule out UTI without the need for confirmatory culture; however positive urinalysis tests from bag specimen warrant further investigation with a catheterized specimen or suprapubic aspiration. Urine culture is the gold standard for diagnosing UTI: Greater than 50,000 CFU on a catheterized specimen or suprapubic aspiration indicate presence of a UTI. Greater than 100,000 CFU on a voided specimen is considered a positive culture. There is no consensus on the need and optimal strategy for imaging in the setting of urinary tract infection in the pediatric population. Prompt recognition of UTI and antibiogram-based, empiric treatment or culture-based, targeted treatment should be initiated within 72 of presentation.

Keywords

pediatric; UTI; guidelines; uropathogen; suprapubic aspiration; vesicoureteral reflux; antibiotic resistance

Introduction

Pediatric urinary tract infection (UTI) is a common cause of presentation to healthcare providers and is an area of concern for parents and clinicians alike. There is a broad

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spectrum of presentations ranging from asymptomatic infection to mild lower urinary tract symptoms, to febrile and systemic illness.

The prevalence and incidence of pediatric UTI varies by age, race/ethnicity, sex and circumcision status[1] (Table 1). While calculating true cumulative incidence is challenging given varied reporting in different clinical settings, likely it is at least 2% in boys and 7% in girls, in the first 6 years of life, with 2.2% of boys and 2.1% of girls having had a UTI before reaching 2 years of age[2, 3]. Controlling for other clinical parameters, Hispanic and white children are more likely to be diagnosed with a UTI than Black children[4]. Outside of the first 12 months, girls are more likely to be diagnosed with a UTI. About half of boys with UTI will be diagnosed within the first 12 months of life, however 80% of girls will be diagnosed at a later age[2]. Circumcision has been shown to have a protective effect on UTI, reducing the odds of infection by 87%, with an even greater effect for boys with recurrent infections or posterior urethral valves[5, 6].

Pediatric UTI costs the healthcare system upwards of 180 million dollars annually, and accounts for over 1.5 million clinician visits per year[3]. Accurate and timely diagnosis of these infections is important for determining appropriate treatment and preventing long-term complications such as renal scarring, hypertension, and end-stage renal disease[7].

History and Physical

One must have a high index of suspicion for UTI in the pediatric population, especially in infants and children under 2 years of age. The evaluation must include a thorough history and the importance of the physical exam in pediatric patients cannot be overstated.

Children under 2 years of age

This is the most challenging population to make the diagnosis of UTI. Presentations are often vague and include irritability, poor feeding, lethargy, jaundice, vomiting, and fever[8]. In evaluating risk factors among children under age 2 presenting to emergency rooms ill appearance, high fever (greater than 39 degrees C), history of UTI, change in urine characteristics (malodor or hematuria), distension and tenderness in the suprapubic area, abdomen, or flanks were associated with UTI[9]. History of a previous UTI, temperature greater than 40 degrees C and suprapubic tenderness are the most useful for diagnosing UTI in febrile infants[10].

Children age 2 to age 12

Toddlers and verbal children are more able to describe their symptoms and localize them to the urinary tract, however given the high prevalence of UTI the lack of localizing symptoms does not rule out UTI in this population.

History—Descriptions of dysuria, frequency, urgency, and urinary incontinence (in a toilet-trained child) increase the likelihood of urinary tract infection diagnosis.

Exam—A thorough exam should include evaluation of external genitalia, with special attention to identify any external lesions, discharge or foreign bodies. Palpation of the abdomen, suprapubic region, and costovertebral angles to elicit tenderness are key[10].

- Special considerations for girls include evaluation for labial adhesions, foreign bodies, vulvovaginitis, and signs of sexually transmitted diseases[11].
- Special considerations for boys include evaluation for phimosis, meatal stenosis, and tenderness in the testes to suggest epididymitis and/or orchitis[12].

Adolescent children

While adolescents are better able to provide history and participate in physical exams, sexual activity is a special consideration for this population that requires additional diagnostic attention. Among surveyed high school students in 2013, 47% have had sexual intercourse and 34% reported having sexual activity in the last 3 months[13]. Sexually transmitted infections (STI) are an important consideration for adolescents with urinary symptoms.

Adolescent Females and UTI

- Adolescent females with urinary symptoms often present with a UTI, STI, or both. Statistics on STI rate vary, with a prospective study finding 29% of adolescent girls with urinary symptoms as having had an STI[14]. Among sexually active females with urinary symptoms, history of STI, more than one partner in the last 3 months, and urinalysis with blood and leukocyte esterase was predictive of STI.
- No specific symptoms or history findings have been shown to reliably predict which adolescent females with urinary symptoms are at increased risk for either UTI or STI[15, 16].
- Current recommendations suggest testing sexually active females with urinary symptoms for UTI as well as STI including Neisseria gonorrhea, Chlamydia, and Trichomonas, especially in those with sterile pyuria[15]. Patients being evaluated or treated for STI should be offered HIV testing[17].

Adolescent Males and UTI

- While the prevalence of UTI among this age group is low, several risk factors have been identified including sexual activity and lack of circumcision[18].
- In adolescent boys with urinary symptoms it is also important to evaluate for balanitis xerotica obliterans, with nearly 35% incidence reported globally[19, 20]. In pubertal males, prostatitis can also present with symptoms of voiding dysfunction[21].

Urine Testing

Clinical and demographic factors should be used to determine the probability of an infection and guide the decision making process to obtain a specimen for analysis. Given the high

false-positive rate of urinary tests it is important to test a population with a high pre-test probability of infection[22, 23].

Urine Specimen Collection in non-toilet trained children

Bag Specimen[24–26]

- The simplest method of using a taped sterile bag to collect the urine is the least reliable, and has been consistently demonstrated to have the greatest contamination rate.
- A positive urine culture from a bag specimen has up to a 75% rate of false positives, with peri-urethral organisms being isolated >98% of the time. Given its low positive predictive value, this method of collection has the lowest diagnostic utility in the clinical setting.
- If a bag specimen is negative, this can be used to rule out UTI without the need for confirmatory culture; however positive urinalysis tests from bag specimen warrant further investigation with a catheterized specimen or suprapubic aspiration.

Urethral Catheterization

- Obtaining a catheterized specimen is a safe, fast, reliable way of collecting urine for analysis in the non-toilet trained population.
- The success of specimen collection depends on the specific anatomy and cooperation of the patient and the technical skill of the medical provider.
- Success rates in the literature have been quoted from 23% to 99%, with increased success using portable ultrasound.
- The possible complications, including trauma and hematuria, have been shown to be minimal.
- The sensitivity and specificity of catheterized specimen is significantly better than a bagged sample, and has a specificity of 83–89% compared to a suprapubic sample, and in samples with greater than 100, 000 CFU/mL approaches 99%.

Suprapubic Aspiration[27–30]

- Arguably the most invasive method of urine collection, it is the most accurate. It is the least likely to be contaminated and any presence of bacteria is indicative of infection.
- Suprapubic aspiration has an advantage for uncircumcised boys with phimosis, or girls with labial adhesions in whom a catheterized specimen is more technically challenging to obtain.
- Despite its advantages, in the clinic or emergency room setting, suprapubic aspiration may prove more challenging to perform in a timely manner, given

the requirement for physician participation and variable success rate per attempt (46% to 97%), though improved with the use of ultrasound.

Urine tests

Dip-stick urinalysis[22, 31, 32]

The most clinically available, affordable, and accessible urine test, and the most widely used in the outpatient setting. The most clinically useful findings are the presence or absence of leukocyte esterase and nitrite in the urine specimen.

- Positive leukocyte esterase is suggestive of inflammation in the urine and the presence of white blood cells (WBC). False positives include other inflammatory conditions, such as Kawasaki disease, appendicitis, gastroenteritis and presence of reactive inflammation, in the case of urinary stone disease. False negatives include urine collected too early in the disease course or in a child with a suppressed immune response. Positive leukocyte esterase is 84% sensitive and 78% specific for diagnosing urinary tract infection.
- Positive nitrite is suggestive of presence of gram-negative bacteria. False negatives include urine collection that has been in the bladder less than four hours, the approximate conversion time from nitrate to nitrite and infection with gram-positive bacteria or non nitrite producing bacteria (namely *enterococci* and *Pseudomonas*). Positive nitrite is up to 50% sensitive and 98% specific for diagnosing urinary tract infection.
- Combined positive nitrite-leukocyte esterase on dipstick analysis is 80–90% sensitive and 60–98% specific. When both are negative, the negative predictive value approaches 100%.

Microscopic Analysis[26, 33–35]

This method of analysis is more expensive and requires more equipment and skilled analysis, compared to a urine dip-stick. Analysis is performed to evaluate presence of white blood cells, red blood cells, and bacteria in the sample.

- Pyuria is the presence of greater than 5 WBC per high power field on a centrifuged sample (10 in an un-centrifuged sample).
- Bacteriuria is the presence of any bacteria per high power field.
- In a centrifuged sample, the presence of both pyuria and bacteriuria is up to 66% sensitive and 99% specific for diagnosing urinary tract infection.
- Comparing a positive urine dipstick and positive microscopic analysis showed no difference between the two methods when correlating with urine culture.

Urine Culture[34, 36]

This is the gold standard for diagnosing UTI and should be processed as soon as possible after collection to maximize diagnostic accuracy.

- Greater than 50,000 CFU on a catheterized specimen or suprapubic aspiration indicate presence of a UTI.
- Greater than 100,000 CFU on a voided specimen is considered a positive culture.
- Diagnosis of UTI in children 2–24 months is made based on the presence of both pyuria and at least 50,000 colonies per mL of a single organism obtained via suprapubic aspiration or catheterization.

Serum tests[37, 38]

Serum markers including complete blood count, blood cultures, serum creatinine, C-reactive protein, erythrocyte sedimentation rate, and pro-calcitonin have all been evaluated as measures for urinary tract infection severity, however, none have been demonstrated to be clinically useful or to alter management.

Imaging

There is no consensus on the need and optimal strategy for imaging in the setting of urinary tract infection in the pediatric population. The role and timing of imaging to evaluate for anatomic abnormalities and renal scarring, after a febrile UTI, is an area of debate. Renal bladder ultrasound (RBUS), voiding cystourethrogram (VCUG), and dimercaptosuccinic acid (DMSA) scan are the most commonly utilized imaging modalities in this population, however their role in diagnosis and management is controversial.

RBUS[39–41]

- Non-invasive, relatively inexpensive, and safe in any age group.
- Most commonly used modality to evaluate for anatomic abnormalities such as duplication, dilation, and obstruction in the genitourinary tract.
- It is an unreliable modality to evaluate for vesicoureteral reflux (VUR), however has been demonstrated to be useful in identifying pyelonephritis.
- For young children with first UTI, RBUS is unlikely to alter clinical management and is not universally recommended.
  - NICE guidelines: Recommend RBUS after first febrile UTI in children under 6 months of age or older than 6 months with atypical or recurrent UTI.
  - AAP guidelines: Recommend RBUS for children 2–24 months of age after first febrile UTI.

VCUG[37, 42]

- Invasive, expensive, and exposes patients to radiation.
- Most commonly used modality to evaluate for VUR.

- NICE guidelines: Recommend VCUG for children under 6 months of age with atypical or recurrent UTI and children 6 months to 3 years with atypical or recurrent UTI and abnormalities on RBUS, poor urine flow or family history of VUR.
- AAP guidelines: Recommend VCUG for children 2 to 24 months of age after the second febrile UTI, and after the first for patients with abnormalities on RBUS or high grade VUR.

DMSA[41, 43–45]

- Time intensive, invasive, expensive and exposes patients to radiation.
- Can provide information about extent of renal inflammation and renal scarring.
- Children with acute DMSA changes are at increased risk for VUR grade III–V on VCUG.
- Both NICE and AAP guidelines do not recommend using DMSA in routine evaluation of first febrile UTI in children.
- The role of DMSA in evaluation of clinically significant renal scarring following infection is still controversial.
  - NICE guidelines: Recommend DMSA 4–6 months after:
    - Atypical or recurrent infection in children under 3 years of age.
    - Recurrent infection in children over 3 years of age.
  - AAP guidelines did not include the use of DMSA in their recommendations.

Treatment

Pediatric UTIs are treated with two purposes: to eliminate the infection and prevent severe systemic illness and to reduce possible long-term complications such as renal scarring and hypertension[41].

The decision to initiate empiric treatment should be based on clinical suspicion of infection based on history and physical exam and positive urinalysis on an appropriately collected urine specimen. The vast majority of patients can be treated as an outpatient if the child is nontoxic appearing, can tolerate oral medications and comply with recommendations[46]. For some patients in whom a urinalysis and clinical picture are concerning for infection antibiotics can be started empirically without awaiting culture results. Alternatively, if the diagnosis is uncertain and child is non-toxic appearing treatment can be delayed until urine culture results are obtained – in both cases medication should be tailored to the antibiotic sensitivities of the urine culture results[10].

The choice of treatment therapy depends on numerous factors, including the child's age, underlying medical problems, illness severity, ability to tolerate oral medications, and most importantly the local resistance patterns to uropathogens (Table 2).

Treatment course[46–48]

A 7–14 day outpatient treatment course is an appropriate regimen.

- NICE guidelines: oral antibiotics for 7–10 days or intravenous antibiotics for 2–4 days followed by oral antibiotics for a total duration of 10 days.
- AAP guidelines: oral or intravenous antibiotics for 7–14 days.

Oral antibiotics[49–51]

Escherichia coli is the most common pathogen, in over 80% of pediatric urinary tract infections. Empiric antibiotics should be based on local resistance patterns, as certain widely used choices are becoming increasingly resistant. Narrow-spectrum antibiotics such as nitrofurantoin and first-generation cephalosporins are more likely to be effective than trimethoprim-sulfamethoxazole, in many communities; however, nitrofurantoin should not be used in febrile UTI treatment and when renal involvement is suspected. Therapy should ultimately be based on the culture organism with the most narrow spectrum agent.

Parenteral antibiotics[46, 50, 52]

For patients who are more ill appearing, have underlying urologic conditions, have had recent urinary infections or have taken antibiotics, immunocompromised patients as well as those with intractable nausea and vomiting inpatient admission and parenteral therapy is appropriate. Empiric choices include ampicillin and gentamicin, third- or fourth-generation cephalosporins, broad-spectrum penicillins, carbapenems, macrolides, and fluoroquinolones.

Renal Scarring[46, 48, 53–55]

It remains controversial whether initiation of treatment within the first 24–72 hours prevents renal damage. In patients who present with ascending infection and renal involvement, there are conflicting data as to whether early treatment can prevent subsequent scarring, as the presence of pyelonephritis has been shown to be associated with scarring, independent of treatment timing. There is evidence to suggest that early treatment helps prevent acute pyelonephritis, and both AAP and NICE guidelines recommend early initiation of treatment.

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Key points

- Given the high false- positive rate of urinary tests it is important to test a population with a high pre-test probability of infection.
- The sensitivity and specificity of catheterized specimen is significantly better than a bagged sample, and has a specificity of 83–89% compared to a suprapubic sample, and in samples with greater than 100, 000 CFU/mL approaches 99%.
- Comparing a positive urine dipstick and positive microscopic analysis showed no difference between the two methods when correlating with urine culture.
- Pediatric UTIs are treated with two purposes: to eliminate the infection and prevent severe systemic illness and to prevent and/or reduce possible long-term complications such as renal scarring and hypertension.

Table 1

Uropathogen Prevalence by Sex and Visit Setting*

	Male		Female	
Organism	**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.

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	
Gentammicin	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.