NCC Pediatrics Continuity Clinic Curriculum: **Urinary Tract Infections**

Goals & Objectives:

- Identify signs and symptoms of urinary tract infections
- Discuss how to properly diagnose urinary tract infections
- List indications for admitting a patient with a UTI
- Compare and contrast UTI management in infants, toddlers, school-age children, and adolescents
- Apply AAP clinical practice guideline to the case of an infant with their first UTI

Pre-Meeting Preparation:

- "Urinary Tract Infections in Children" *(PIR, 2024)*
- Access the Walter Reed Antibiogram via the Darnall Library website using a government computer

Conference Agenda:

- *Review* UTI Quiz
- Complete UTI Cases
- **"Hands-on" Activity:** Review urine dipstick use in the clinic. *Residents and staff may provide their own "mystery samples" for practice dipping.*

Post-Conference: *Board Review Q&A*

Patient Education:

- **Urinary Tract Infection (Male)**
- **Urinary Tract Infection (Female)**
- **Urinary Tract Infections in Young Children**

Additional References:

- **UTI CALCULATOR**
- **"Reassessment of the Role of Race in Calculating the Risk for Urinary Tract Infection"** *(JAMA Peds, 2022)*
- **"Urinary tract infection in children: A narrative review of clinical practice guidelines"** *(Urology Annals, 2023)*
- **"Contemporary Management of Urinary Tract Infection in Children"** *(Pediatrics, 2021)*
- **"Urinary tract infection in children: an overview of diagnosis and management"** *(BMJ Peds, 2019)*
- **Background Commentary of RIVUR Investigators** *(Pediatrics, 2008)*
- **RIVUR Study Website** *(includes Study Description, Toolkits for Parents & Physicians)*
- **"Update of the EAU/ESPU guidelines on urinary tract infections in children"** *(Journal of Pediatric Urology, 2021)*
- **"Conflicting views of physicians and surgeons concerning pediatric urinary tract infections:a comparative review"** *(Pediatric Radiology, 2023)*
- **"Incidence of Pediatric Urinary Tract Infections Before and During the COVID-19 Pandemic"** *(JAMA Open Network, 2024)*

Urinary Tract Infections in Children

Melanie C. Marsh, MD,* Guillermo Yepes Junquera, MD,[†§] Emily Stonebrook, MD,[†¶] John David Spencer, MD,[†¶] Joshua R. Watson, MD[‡§]

*Division of Hospital Medicine, Department of Pediatrics, Advocate Aurora Atrium Health Systems, Chicago, IL
[†]Kidney and Urinary Tract Center, The Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH
[‡]Center for Clinical Excellence, Nationwide Children's Hospital, Columbus, OH
[§]Division of Infectious Diseases and [¶]Division of Nephrology and Hypertension, Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH

PRACTICE GAP

Recognizing and reducing risk of initial and recurrent urinary tract infections (UTIs) are important given the disease burden associated with UTI to patients, families, and the health-care system. Prompt and accurate UTI diagnosis and thoughtful antibiotic management help ameliorate antimicrobial resistance. Reducing recurrent UTI risk includes evaluating a child for factors that augment UTI susceptibility, such as bowel and bladder dysfunction or anatomic kidney or urinary tract disorders.

OBJECTIVES *After completing this article, readers should be able to:*

1. Appropriately diagnose urinary tract infections in children based on clinical manifestations and laboratory testing.
2. Manage urinary tract infections, including optimal antibiotic choice and duration as well as imaging studies.
3. Identify and mitigate risk factors for recurrent urinary tract infections.

ABSTRACT

Despite the American Academy of Pediatrics guidelines for the evaluation, treatment, and management of urinary tract infections (UTIs), UTI diagnosis and management remains challenging for clinicians. Challenges with acute UTI management stem from vague presenting signs and symptoms, diagnostic uncertainty, limitations in laboratory testing, and selecting appropriate antibiotic therapy in an era with increasing rates of antibiotic-resistant uropathogens. Recurrent UTI management remains difficult due to an incomplete understanding of the factors contributing to UTI, when to assess a child with repeated infections for kidney and urinary tract anomalies, and limited prevention strategies. To help reduce these uncertainties, this review provides a comprehensive overview of UTI epidemiology, risk factors,

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ABBREVIATIONS

AAP	American Academy of Pediatrics
BBD	bowel and bladder dysfunction
CFU	colony forming units
IBC	intracellular bacterial community
IV	intravenous
KBUS	kidney and bladder ultrasonography
QIR	quiescent intracellular reservoir
TMP-SMX	trimethoprim-sulfamethoxazole
UPEC	uropathogenic *Escherichia coli*
UTI	urinary tract infection
VCUG	voiding cystourethrogram
VUR	vesicoureteral reflux

diagnosis, treatment, and prevention strategies that may help pediatricians overcome the challenges associated with acute and recurrent UTI management.

EPIDEMIOLOGY AND ETIOLOGY

Urinary tract infection (UTI) is a common infection occurring in childhood. In the United States, pediatric UTI accounts for approximately 1.5 million ambulatory visits and 50,000 hospital inpatient admissions annually. (1)(2) UTI prevalence varies by sex, age, and circumcision status. Females account for 80% to 90% of pediatric UTIs overall. (1)(3) Among males, uncircumcised infants experience the highest UTI prevalence. (4) An estimated 7% to 8% of females and 1% to 2% of males will have at least 1 UTI by age 6 to 7 years. (5)(6)

UTIs are primarily caused by bacteria, and uropathogenic *Escherichia coli* (UPEC) is the most common pathogen, accounting for approximately 80% of UTIs in children. Table 1 displays the relative frequencies of the 6 most common uropathogens encountered among children in a national surveillance database. (7) Less commonly, other enteric gram-negative bacilli such as *Citrobacter* species and *Serratia marcescens* are implicated. Among gram-positive bacteria, enterococci are the most common, but *Staphylococcus saprophyticus* should be considered in female adolescents. (8) In addition, group B streptococcus, *Staphylococcus aureus*, and coagulase-negative staphylococci may be seen in neonates. (9)(10) Viruses and fungi are less common UTI pathogens and are briefly discussed at the end of this review.

UTI PATHOGENESIS

To establish a UTI, uropathogenic bacteria originate from the enteric and vaginal tracts, spread across the perineum, ascend the urethra, and invade the bladder. Our understanding of UTI pathogenesis has been advanced by studying UPEC-associated infections in preclinical models and in clinical settings. To initiate cystitis (ie, infection restricted to the bladder), UPEC produce adhesive organelles called type 1 pili that bind and promote invasion of the superficial bladder urothelium. After internalization, UPEC enter a cytosolic niche called an intracellular bacterial community (IBC). (11)(12)(13) IBCs develop from a single bacterium and consist of an estimated 10^5 organisms encased in a highly organized matrix. In the IBC, UPEC develop filaments that extrude from the infected cell. Filamentous UPEC attach to adjacent epithelial cells, reinvade the urothelium, and create additional IBCs. (14)(15) To limit infection, the host exfoliates infected bladder cells into the urinary stream. After exfoliation, UPEC may invade the underlying basal urothelium and establish a quiescent intracellular reservoir (QIR). In the absence of bacterial replication, QIRs can persist for weeks and are protected from host immune mechanisms and antibiotics. Although the QIR population is small, it is considered a source of recurrent cystitis. (15)(16)

To establish pyelonephritis (ie, kidney infection), uropathogens ascend the ureters and invade the kidney. Specifically, UPEC bind to epithelial cells in the kidney's collecting tubules. Binding to these kidney epithelia depends on the ability of UPEC to produce type 1 pili or P-pili. After binding to kidney tubular cells, cytolytic UPEC strains trigger apoptosis, which facilitates their invasion into the kidney interstitium, promotes kidney inflammation, and impairs kidney functions. (11)(13)

As pathogens ascend the urinary tract, they encounter mechanical and physiologic barriers that limit infection. These factors include the unidirectional flow of urine, changes in urine osmolarity and pH, soluble IgA and Tamm-Horsfall protein, iron-chelating siderophores, and antimicrobial peptides. If pathogens invade the bladder urothelium or attach to kidney epithelial cells, they initiate host responses that exfoliate urothelial cells to promote bacterial clearance or engage pattern recognition receptors, including toll-like receptors, to elicit inflammatory chemokines and cytokines that recruit immune cells to eradicate bacteria. (17)

Table 1. Most Common Uropathogens among Children from a Large US Surveillance Network

	URINARY TRACT INFECTIONS, %	
ORGANISM	FEMALES	MALES
Escherichia coli	83	50
Enterococcus species	5	17
Proteus mirabilis	4	11
Klebsiella species	4	10
Pseudomonas aeruginosa	2	7
Enterobacter species	1	5

Data from Edlin et al. (7)

RISK FACTORS FOR UTI

Although all children are susceptible to UTI, select populations have increased UTI susceptibility.

Young Infants

Neonates and young infants have increased UTI susceptibility because an immature immune system can facilitate bacterial colonization and adhesion to the urothelium. In

addition, elevated androgen levels in males younger than 6 months may heighten UTI risk. (18) In the first year after birth, uncircumcised male children are at increased risk for UTI due to increased concentrations of uropathogens around the external urethral meatus that can potentially colonize the urinary tract and lead to infection. (19)(20)

Anatomic Disorders of the Urinary Tract

Patients with congenital kidney and urinary tract anomalies or inappropriate bladder emptying are at increased risk for UTI. Bladder emptying can be impaired by a functional or anatomic obstruction that occurs with a neurogenic bladder or posterior urethral valves. Impaired bladder drainage facilitates urinary stasis and bacterial replication. Moreover, the need to perform bladder catheterization can heighten UTI risk. (21) Kidney anomalies such as cystic kidney disease or nephrolithiasis may increase UTI risk. Vesicoureteral reflux (VUR) is a UTI risk factor that has been studied extensively. (22) VUR results in urine passing up 1 or both ureters in a retrograde fashion often to the kidneys. The clinical significance of VUR is based on the premise that it predisposes children to acute pyelonephritis by transporting bacteria from the bladder to the kidney, which may lead to kidney injury.

Bowel and Bladder Dysfunction

Bowel and bladder dysfunction (BBD) describes a group of lower urinary tract symptoms combined with bowel disorders, including functional constipation, that prevent appropriate peristalsis and compromise bladder emptying. (23) The most common signs and symptoms of BBD in toilet-trained children are urinary urgency, withholding maneuvers (eg, crossing legs or squatting down to use the heel to apply pressure to the perineum), and daytime wetting. (24) BBD is more common among children with a UTI compared with the general population. As a risk factor for recurrent UTI, BBD disproportionately influences incidence in children with VUR.

Sexual Activity

Sexual activity and the use of spermicides and diaphragms are also UTI risk factors. Intercourse augments UTI by facilitating the transfer of uropathogens from the perineum and genital tract into the urethral meatus. (25)(26)

CLINICAL MANIFESTATIONS

Children with a UTI may present with a variety of signs and symptoms, which may be affected by age and development (Table 2). In verbal children, the presence of lower urinary tract symptoms alone suggests cystitis. In contrast, fever, vomiting, or flank pain suggests upper tract involvement, and pyelonephritis is presumed. Infants, preverbal children, and some medically complex youth are unable to report urinary tract symptoms. In those cases, suspicion for UTI is often triggered by a fever without an apparent focus. In addition, jaundice from direct and/or indirect hyperbilirubinemia that is not explained by another etiology may be a clue in some neonates and young infants with UTI, including those without fever or other signs of illness. (27)(28)(29)(30)(31) Many other conditions may present with signs and symptoms similar to a UTI, as discussed later herein.

DIAGNOSIS

Decision to Test

Given the nonspecific nature of UTI in children, decisions around testing must consider risk factors for UTI, number and severity of signs and symptoms, and the presence or absence of a clinically apparent alternative explanation. For febrile children aged 2 to 23 months in whom UTI is considered, the free, online UTICalc (https://uticalc.pitt.edu) is an excellent resource that incorporates demographic and clinical information to guide decisions about urine testing (and subsequently, empirical treatment). (32)(33) For other groups of children, validated decision support tools are not available, and thus the decision to test is based on clinical suspicion.

Urine Testing

Once the decision to test for a UTI is made, collecting a urine sample is the next step. Clinicians have several options for urine collection depending on the age and development of the child. To collect a urine sample from infants and young children who are incontinent, the American Academy of Pediatrics (AAP) guidelines provide 2 options. (34) Option 1 is to collect urine via catheterization or suprapubic aspiration

Table 2. Clinical Manifestations of Urinary Tract Infections in Children

PREVERBAL CHILDREN	VERBAL CHILDREN
Fever	Lower urinary tract symptoms
Poor feeding	Dysuria
Vomiting	Suprapubic or nonlocalized abdominal pain
Decreased urine output	Urinary frequency
Lethargy	Urgency
Irritability	Enuresis
Jaundice	Hematuria
	Upper urinary tract symptoms
	Fever
	Vomiting
	Flank pain

for urinalysis and culture. Option 2 is to collect urine by noninvasive means (eg, urine bag) for urinalysis; if the results show pyuria, nitrite, or bacteriuria, then a second sample obtained via catheterization or suprapubic aspiration must be obtained for urinalysis and culture. One emergency department showed that by implementing option 2, many children avoided an invasive procedure without prolonging length of stay. (35) Importantly, urine samples collected via bag should not be used for culture because of higher rates of contamination. (36)(37) Likewise, urine collected via cotton balls in neonates should not be cultured. In toilet-trained children, a mid-stream, clean-catch method is recommended.

Making the Diagnosis

Hallmarks of a UTI are pyuria, urinary nitrite, and bacteriuria. (34)(38) Pyuria is defined by urine microscopy with at least 5 white blood cells (WBCs) per high-power field from centrifuged urine or at least 10 WBC/mm^3 from noncentrifuged urine, or detection of leukocyte esterase (as a surrogate marker for pyuria) on urine dipstick analysis. Nitrite is detected when bacteria capable of reducing urinary nitrate to nitrite have incubated in the urine for at least 4 hours. (39) Enteric gram-negative bacteria, *Pseudomonas*, and some staphylococcal species reduce nitrate, whereas streptococci and enterococci do not. Significant bacteriuria may be demonstrated on urine microscopy and ultimately confirmed by growth of a uropathogen in urine culture. In many ambulatory settings, urine microscopy is not available at the point of care, precluding an immediate assessment for WBCs or bacteria.

Many studies have evaluated the test characteristics of urinalysis (dipstick and/or microscopy) for diagnosing UTI, or more accurately, for predicting a positive urine culture. Sensitivity and specificity depend on the population tested (age, sex, comorbidities), urine collection method, urinalysis method used, threshold for positivity of the urinalysis component, and definition of a positive urine culture. Summary data from 3 meta-analyses and 1 large study are shown in Table 3. (40)(41)(42)(43) Enhanced urinalysis, which consists of a urine Gram-stain plus hemocytometer WBC count from uncentrifuged urine, performs better than standard urinalysis but requires additional time and expertise compared with standard urinalysis. (44) Urine Gram-stain is particularly helpful when the child has received antibiotics before obtaining urine for culture.

In febrile children aged 2 to 24 months, the AAP guidelines define UTI as both a urinalysis suggesting infection (pyuria or bacteriuria) and a urine culture that yields at least 50,000 colony forming units (CFU)/mL of a uropathogen. (34) In toilet-trained children, a UTI diagnosis is made in the presence of urinary signs and symptoms, urinalysis suggesting infection, and positive urine culture. A threshold of 50,000 or 100,000 CFU/mL is typically used to define significant bacteriuria from clean-catch specimens.

Uncertainties in Diagnosis

Several factors make the diagnosis of UTI challenging. First, UTI signs and symptoms can be nondescript and overlap with other clinical conditions. A meta-analysis of studies examining signs and symptoms of pediatric UTI found that among preverbal children, fever (temperature >102.2°F [>39°C] and especially >104°F [>40°C]), fever duration longer than 24 hours, and suprapubic tenderness increased the probability of UTI, whereas vomiting, diarrhea, poor feeding, and irritability were of little diagnostic value. (45) Among verbal children, abdominal pain, back pain, dysuria, frequency, and new-onset enuresis were helpful, whereas offensive urine odor had no effect on UTI probability. The absence of any individual symptom was insufficient to exclude a UTI.

Second, pyuria may be caused by many conditions other than UTI, including urethritis, vulvovaginitis, sexually transmitted infections, appendicitis, other acute febrile illnesses, crystalluria or nephrolithiasis, intrinsic kidney disease, and others. (46) The common scenario of a symptomatic child whose urine dipstick is positive for leukocyte esterase but negative for nitrite leads to diagnostic uncertainty.

Third, diagnosing UTI in the absence of pyuria is the subject of debate. The AAP guidelines emphasize the necessity of pyuria, stating that pyuria is the key to distinguishing true UTI from asymptomatic bacteriuria or culture contamination in young, febrile children. (38) Despite historical concerns

Table 3. Summary of Urinalysis Test Characteristics

TEST	SENSITIVITY, %	SPECIFICITY, %	+LR	–LR
Leukocyte esterase	72–83	78–87	3.8–6.1	0.20–0.34
Nitrite	40–53	97–98	15.7–26.5	0.48–0.61
Urine white blood cells	67–85	79–89	3.2–5.3	0.20–0.42

+LR=positive likelihood ratio, −LR=negative likelihood ratio.
Data derived from Downs et al, (40) Gorelick and Shaw, (41) Kazi et al, (42) and Williams et al. (43).

that young infants up to 2 to 3 months old do not reliably demonstrate pyuria, recent studies showed high sensitivity of pyuria in this age group. (9)(47) However, some experts have challenged the inclusion of pyuria in the definition of UTI based on a meta-analysis showing the point prevalence of asymptomatic bacteriuria to be less than 0.5% and a study showing that pyuria was absent in 13% of symptomatic children with positive urine culture results. (38)(48)(49) In addition, compared with UPEC, non–*E coli* pathogens are less likely to result in pyuria. (49)

Fourth, the definition of a positive urine culture is unclear. The AAP guidelines' threshold of 50,000 CFU/mL from catheterized specimens is based on the cutoff point above which most cultures yield a single uropathogen rather than contaminants. (50) However, some studies suggest that the culture threshold defining UTI should be lower than 50,000 CFU/mL. (51)(52) The AAP guidelines point out reasons for low colony counts in some patients (eg, short incubation time in the bladder in infants) and describes the culture threshold as "operational and not absolute." (34) In febrile infants with pyuria, cultures yielding at least 10,000 CFU/mL may be indicative of a UTI. (53)

Fifth, distinguishing between cystitis and pyelonephritis is not clear-cut. When upper urinary tract signs or symptoms are present (Table 2), clinicians typically presume that the patient has pyelonephritis for subsequent management decisions. Fever is considered an upper urinary tract symptom because studies have shown that most children with a febrile UTI have evidence of pyelonephritis on technetium-99m dimercaptosuccinic acid scan, the previous gold standard imaging modality for pyelonephritis that is no longer in clinical use. (54)(55) In addition, serum inflammatory markers have not proved to be of sufficient diagnostic value for pyelonephritis. (56)

Finally, although beyond the scope of this review, assessment of symptoms and test results is even more challenging in children with immunocompromise or anatomic disorders of the urinary tract. Pyuria is often absent in febrile neutropenic children with a UTI. (57) Children with neurogenic bladders are at increased for UTI but also have high rates of asymptomatic pyuria and bacteriuria. (58)(59) Standard criteria to optimally identify those with true infection are lacking.

To minimize diagnostic uncertainty, an expert panel on diagnostic stewardship for UTI recently recommended that ideal reporting of urine culture results should inform clinicians that colony counts greater than 100,000 CFU/mL may not represent a true infection in the absence of symptoms and that treatment for mixed flora or asymptomatic bacteriuria is unnecessary. (60) In addition, culture reports should differentiate between contaminants and typical uropathogens. Finally, identification and testing of isolates should not be automatically reported when more than 2 unique bacterial isolates are present in culture. Implementation of strategies such as these may guide clinicians in not only UTI diagnosis but also appropriate treatment.

MANAGEMENT

Decision to Treat Empirically versus Wait for Culture

During the past 3 decades, *E coli* have developed mechanisms to evade the bactericidal mechanisms of antibiotics routinely prescribed to treat UTIs, such as β-lactams, fluoroquinolones, and aminoglycosides. Up to 90% of *E coli* strains are now resistant to at least 1 unique antibiotic, and *E coli* infections now account for half the estimated global burden of antibiotic resistance. Antibiotic overuse and misuse have accelerated the prevalence of antibiotic resistance among UPEC. (61)

Because it takes approximately 24 hours to receive initial urine culture results, clinical signs and symptoms and urinalysis results are often used to make a presumptive diagnosis of UTI. Studies have shown that among children diagnosed as having a UTI based on symptoms and urinalysis results, almost half have a resultant negative urine culture. (62)(63) If a child with suspected cystitis is well-appearing and does not have fever or other signs of systemic illness, it is reasonable to wait for the culture result before initiating antibiotic therapy. This is particularly pertinent in the current climate of antibiotic overuse and may curtail emerging antimicrobial resistance. (64) However, it is important that reliable follow-up is available, which may include having the patient's or guardian's contact information, identifying the primary care provider, or establishing outpatient follow-up in their medical home.

In children with suspected UTI associated with fever or other upper urinary tract symptoms, prompt empirical antibiotic should be provided while awaiting culture results. Prolonged fever before initiation of antibiotic therapy may increase risk of kidney scar formation. (65)(66) Although previously this relationship has been controversial and potentially confounded by age, recurrent UTI, ethnicity, or BBD, there does seem to be an association when controlling for these factors. (66) Risk of scar increases most steeply after 48 to 72 hours of delay from fever onset to antibiotic initiation. However, 1 study found that for every hour that antibiotics were delayed, the odds of new scarring increased by 0.8%. (66)

Empirical Antibiotics

When considering empirical therapy for UTI treatment, it is important to review local antibiogram data (ie, antibiotic susceptibility patterns) for common uropathogens, as well as any previous urine culture and susceptibility data specific to the child if there is a history of UTI. (38) Given the predominance of UPEC, even in children without nitrite on urinalysis, it is probably unnecessary to cover for *Enterococcus* species empirically. (67) There are several reasonable oral empirical antibiotic options. Nitrofurantoin is a targeted UTI antibiotic that is an excellent empirical choice for treating cystitis in adolescents, where the monohydrate/macrocrystal formulation may be given via a capsule twice daily. However, nitrofurantoin oral suspension for younger children is a less attractive option given poor palatability, the 6-hour dosing interval, and higher cost. Furthermore, nitrofurantoin should not be used to treat suspected pyelonephritis because it does not achieve adequate serum or kidney tissue concentrations. Cephalexin is another narrow-spectrum antibiotic with high UPEC susceptibility in many geographic locations. If local antibiogram data are favorable, cephalexin may be given for children with cystitis or pyelonephritis, at appropriate doses for the indication. (68)

Other empirical options suggested in AAP guidelines include amoxicillin-clavulanate, oral third-generation cephalosporins, and trimethoprim-sulfamethoxazole (TMP-SMX). Amoxicillin alone is usually a poor choice for empirical treatment because of high rates of UPEC resistance, but it may be used for definitive treatment if appropriate based on culture and susceptibility results. Although oral third-generation cephalosporins (cefdinir, cefixime, cefpodoxime) do have a role in UTI treatment, they are broader in spectrum and have less favorable pharmacokinetic properties compared with cephalexin. (69) In addition, clinicians sometimes erroneously assume that susceptibility of urine isolates to intravenous (IV) third-generation cephalosporins (ceftriaxone, cefotaxime) predicts susceptibility to oral third-generation agents, but this is not reliably true. TMP-SMX was previously a commonly used empirical antibiotic for UTI, but resistance among UPEC has increased over time and exceeds 20% in many areas of the United States. (7) Ciprofloxacin is not a wise antibiotic choice for most children. Similar to TMP-SMX, ciprofloxacin resistance is increasing. (7) Furthermore, given concerns regarding its adverse effects, ciprofloxacin should be reserved for treatment of infections for which no reasonable oral alternative exists. (70) In addition, children who are receiving prophylactic antibiotics may have increased risk of resistant organisms, and previous urine cultures should be reviewed when choosing antimicrobial coverage in this population. (71)(72)

For those unable to tolerate enteral agents, IV and intramuscular options can be considered. If a child is otherwise stable to be discharged home, a single dose of intramuscular ceftriaxone 50 mg/kg may be given, followed by an oral antibiotic prescription and close outpatient follow-up. Although there are no clear-cut guidelines on when children require hospital admission for the monitoring and treatment of a UTI, factors for consideration are listed in Table 4. For children hospitalized for IV treatment, appropriate options include cefazolin, ceftriaxone, or dual therapy with ampicillin plus gentamicin. Cefazolin is preferred as a narrow-spectrum empirical option if local susceptibility patterns are favorable.

Definitive Antibiotic Treatment

Once urine culture and susceptibility data are available, antibiotic treatment should be tailored to the most narrow-spectrum agent effective for the infection. In hospitalized children, transition from IV to oral antibiotics should be considered as soon as children are tolerating medications and fluids by mouth. Oral antibiotics are equally as efficacious as IV antibiotics in most children. (73)(74) An approach to guide clinicians on antibiotic administration includes "cascade reporting" of antibiotic susceptibility. When antibiotic susceptibility testing is finalized in a positive urine culture, the cascade reporting preferentially lists antibiotics recommended by the local antimicrobial stewardship

Table 4. Indications for Hospitalization of Children with a Urinary Tract Infection

CATEGORY	INDICATIONS
Social and demographic factors	Age ≤28 d Unreliable access to follow-up
Clinical severity factors	Systemic illness concerning for sepsis Intractable pain Inadequate response or symptom progression despite appropriate enteral antibiotic therapy Concern for urinary tract obstruction or kidney dysfunction requiring intervention or close monitoring
Treatment factors	Inability to retain enteral antibiotic (eg, frequent vomiting) Infection with a multidrug-resistant organism for which an effective enteral antibiotic is unavailable

program or national societies. This strategy promotes antimicrobial stewardship and may reduce antibiotic misuse or overuse. (60)

Duration of Treatment

For cystitis, national US guidelines for treatment duration are lacking, but an antibiotic course of 3 to 4 days seems to be equivalent to longer courses and is endorsed by multiple international organizations. (75)(76)(77)(78)(79) For febrile UTI/pyelonephritis, courses as short as 7 days are supported by comparative effectiveness data and are consistent with AAP guidelines. (34)(80) The recently published Short-Course Therapy for Urinary Tract Infections in Children (SCOUT) randomized clinical trial evaluated 5-day versus 10-day treatment durations for children 2 months to 10 years old meeting strict UTI criteria, 38% of whom were febrile at presentation (94% of those aged 2–23 months). (81) For the primary outcome of treatment failure (occurrence of UTI at or before the day 11–14 follow-up visit), short-course treatment failed noninferiority criteria. However, the low rates of treatment failure overall (4.2% in the short-course group) were encouraging, and 67 children would need to be treated with the longer duration to prevent 1 febrile UTI. A favorable response to treatment is indicated by improvement, and ultimately resolution, of symptoms. Obtaining a urine culture after completing antibiotic therapy as a proof of cure is not recommended. (82)

KIDNEY AND URINARY TRACT IMAGING

Kidney and Bladder Ultrasonography

AAP guidelines recommend kidney and bladder ultrasonography (KBUS) in all infants aged 2 to 24 months with a febrile UTI. (34) In most cases, the KBUS may be performed after the acute UTI process has resolved to minimize transient findings caused by inflammation. Early imaging is recommended to evaluate for a kidney/perinephric abscess or obstructive uropathy if the course is unusually severe or clinical improvement does not occur after 48 hours of appropriate antibiotic therapy. The goal of KBUS is to evaluate for urinary tract anomalies such as obstruction, nephrolithiasis, abdominal mass, or structural kidney anomalies. Although findings such as ureteral dilation and hydronephrosis may suggest VUR, it is not a sensitive imaging modality for VUR diagnosis. (54) KBUS should also be considered in older children with recurrent UTIs, non–*E coli* pathogens, unusually severe presentations, and acute kidney injury, and in male patients (Fig).

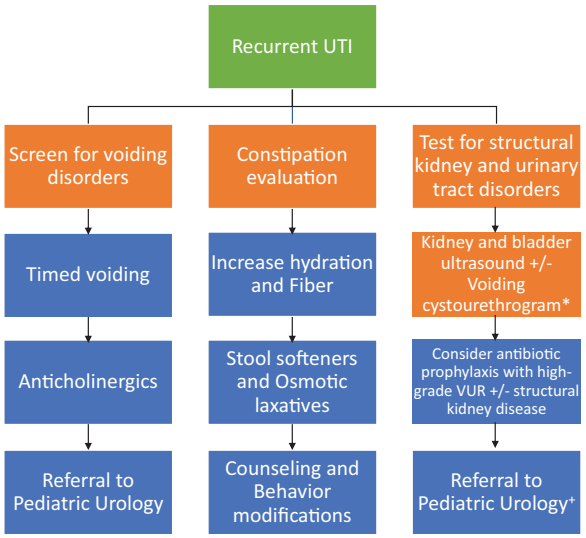

Figure. Suggested management for children with repeated urinary tract infections (UTIs). Stepwise investigation and screening strategies are outlined in the orange boxes, and management strategies are shown in the blue boxes. *A voiding cystourethrogram should be considered if kidney and bladder ultrasonography shows evidence of uroepithelial thickening, hydronephrosis, or hydroureter. +A referral to pediatric urology should be considered for a child with high-grade vesicoureteral reflux (VUR), ureterocele, bladder diverticulum, solitary kidney, horseshoe kidney, kidney size discrepancy greater than 1 cm, kidney cysts, or kidney scarring. Adapted from Khan et al. (83)

Voiding Cystourethrogram

Historical AAP guidelines recommended a voiding cystourethrogram (VCUG) for all children aged 2 to 24 months after their first febrile UTI to accurately identify VUR. Studies after these guidelines were published showed that less than 30% of children undergoing VCUG had VUR and only 10% of those had dilating VUR. (84)(85) As a result, the AAP guidelines were amended and now recommend a VCUG after a febrile UTI in children 2 to 24 months old with an abnormal KBUS, atypical uropathogens or clinical course, known kidney scarring, or family history of structural kidney disease. (34) VCUG should also be obtained, even in the setting of normal KBUS, if a child has recurrent UTI given the limited sensitivity of KBUS to detect VUR as noted previously herein (Fig).

UTI PREVENTION

Antibiotics should be used sparingly for UTI prevention. A major concern of using long-term antibiotic prophylaxis for prevention of recurrent UTI is the development of antibiotic resistance. (86)(87) In the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study, 76% of recurrent UTIs in children receiving TMP-SMX prophylaxis were due to antibiotic-resistant pathogens compared with 28% in the placebo group. (88) Although the RIVUR study

demonstrated a 50% reduction in recurrent UTI for those receiving daily TMP-SMX prophylaxis, this equates to 8 children with VUR being treated with antibiotic prophylaxis for a single child to benefit. (89) Furthermore, these results have not been consistent in other studies or in systematic reviews and meta-analyses. (89)(90) Thus, pediatricians should be highly selective in terms of which patient populations to place on daily antibiotic prophylaxis. Before doing so, they should also consider addressing other variables that can promote UTI (Fig).

Bowel and Bladder Dysfunction

Clinicians can use standardized questionnaires for diagnosing BBD in a primary care setting. These include the Dysfunctional Voiding Scoring System and the Vancouver Symptom Score for Dysfunctional Elimination Syndrome, which can be accessed online or in the following references. (91)(92) Both surveys quantitatively and qualitatively assess constipation, daytime and nighttime wetting, urinary urgency, and difficulty in voiding or stooling. If a child with UTI is suspected of having BBD, pediatricians can recommend a voiding and stooling diary to document frequency of voiding and defecation, volume voided, incontinence, stool characteristics, and fluid intake. An objective measurement of stool can be made using the modified Bristol stool chart for children, available online or in the following reference. (93)

BBD treatment can include managing constipation with hydration, increased fiber intake, and stool softeners. If there is concern for withholding urine or an overactive bladder contributing to UTI, these conditions can be managed with biofeedback or behavioral modifications such as timed voiding (voiding on schedule every 2–3 hours). (23) Oxybutynin, an anticholinergic agent, can be used in children with an overactive bladder. (94) Referral to a pediatric urology practice for evaluation or treatment of voiding disorders may also be considered (Fig). (83)

Antibiotic-Conserving Approaches to Prevent UTI

Due to rising antibiotic resistance rates, antibiotic-sparing options to prevent UTI are needed. There are several approaches that have been investigated, but none of them are recommended as front-line approaches to prevent UTI. The role of hydration in preventing UTI has been tested in several small, historical observational studies. Findings from these studies have recently been summarized in a systematic review in adults and children. (95) However, because of mixed methods and results of the included studies, drawing firm conclusions about the role of hydration in UTI prevention is not possible.

Cranberry-based products are popular, with the active ingredient proanthocyanidin preventing UPEC adhesion to bladder epithelial cells or reducing the formation of bacterial biofilms. Pediatric clinical trials suggest that cranberry products modestly reduce the incidence of UTI in youth with normal urinary tract anatomy. A review of 8 trials using cranberry juice or cranberry extract for UTI prevention concluded that 4 trials had a reduced incidence of UTI with cranberry-based therapy. (96) However, definitive conclusions cannot be made from these trials about the utility of cranberry products in UTI prevention given their differences in cranberry formulations and dosing. Larger, well-designed trials are needed. The value of cranberry in UTI prevention has recently been reviewed. (97)

Probiotics comprising *Lactobacillus* species also show promise in UTI prevention. Probiotics boost endogenous immune defenses, scavenge nutrients needed by bacteria for replication, reduce pH to suppress uropathogen growth, and prevent UPEC binding to urothelial cells. (61)(98)(99) During the past 2 decades, several studies have tested the effects of probiotics on UTI prevention with or without antibiotics. (100)(101)(102) Given the mixed outcomes in these studies, the utility of probiotics for UTI prevention in children is unclear.

D-mannose is a monosaccharide that competitively inhibits UPEC binding to urothelial cells. Given promising preclinical data, synthetic mannosides are now being developed and tested. (103) To date, there are few clinical studies of D-mannose in pediatric UTI prevention. Thus, we can only speculate about the benefits of D-mannose from adult data that show efficacy. However, given the variations in design among different studies, the clinical benefits of D-mannose remain unclear. (97)(104)(105)

Vaccinations are also being developed to prevent UTI. Four vaccines have recently shown promise in randomized controlled trials. The immunogens on which these vaccines are based include whole cell heat-killed bacteria, bacterial cell wall components, nutrient acquisition proteins, and proteins facilitating bacterial adhesion. (106)(107)(108)

Surgical Approaches to Prevent UTI

Male circumcision decreases UTI risk, specifically among neonates, and the AAP supports the benefits of circumcision for UTI risk reduction. (19)(109) In older children, high-grade or dilating VUR surgical correction can reduce UTI susceptibility. Clinical trials comparing medical versus surgical management for recurrent UTI show comparable decreases in UTI incidence and kidney scarring. (110)(111) Thus, surgery is reserved for children whose VUR is unlikely to spontaneously resolve, those with higher risk for pyelonephritis, a history of

kidney scarring, or impaired kidney function. Surgical correction is not recommended for children with low-grade VUR given the high likelihood of spontaneous resolution and low risk of kidney scarring. (83)

VIRAL AND FUNGAL UTI

Adenovirus can cause UTIs in immunocompetent hosts, including urethritis, hemorrhagic cystitis, and nephritis. Treatment is supportive. In hematopoietic stem cell recipients, adenovirus, BK virus, and cytomegalovirus can cause hemorrhagic cystitis. In kidney transplant recipients, BK virus reactivation is associated with nephropathy. Management of these infections in immunocompromised hosts is often multifaceted and beyond the scope of this review. (112)(113) When *Candida* is isolated in urine culture, it may indicate a UTI or colonization. In asymptomatic patients with an indwelling bladder catheter, removal of the catheter without antifungal therapy is typically sufficient. (114) However, for patients who are very-low-birthweight infants, neutropenic, or undergoing a urologic procedure, treatment of asymptomatic candiduria is recommended. Those with symptoms suggesting cystitis or pyelonephritis may also be treated, and fluconazole is the drug of choice for susceptible organisms. Additional evaluation and management recommendations for UTI due to *Candida* in specific patient populations are provided in national guidelines. (114)

CONCLUSIONS

UTI continues to challenge pediatric medical providers. Prompt and accurate diagnosis is important to minimize UTI symptoms, reduce UTI-associated sequelae, and minimize the inappropriate use of antibiotics. With a better understanding of the etiology, pathogenesis, diagnosis, and treatment of UTI, clinicians will be better prepared to manage this common clinical infection.

Summary

- Uropathogenic *Escherichia coli* is the most common cause of urinary tract infection (UTI), followed by other enteric gram-negative bacilli and *Enterococcus* species. (Based on strong research evidence) (7)
- UTICalc is an excellent decision support tool that clinicians may use when considering a UTI in a febrile infant or young child (2–23 months of age). The tool calculates pre-test and post-test probabilities of UTI and guides decisions regarding whether to test and empirically treat for UTI. (Based on strong research evidence) (32)(33)
- A UTI is best defined by the presence of symptoms with inflammation evidenced by pyuria and a urine culture with at least 50,000 colony-forming units per milliliter of a uropathogen. However, challenges surrounding UTI diagnosis include signs and symptoms that are nonspecific, debate around the necessity of pyuria, and uncertainty regarding the optimal culture threshold to define significant bacteriuria. (Based on some research evidence as well as consensus) (34)(38)(53)
- Cephalexin and nitrofurantoin are recommended empirical oral antibiotic choices for UTI (if supported by local antibiotic susceptibility data), usually for 3 to 4 days for uncomplicated cystitis and 7 days for febrile UTI/pyelonephritis. (Based on some research evidence as well as consensus) (75)(80)
- After a first febrile UTI in an infant or young child, clinicians should obtain kidney and bladder ultrasonography (KBUS) to evaluate for urinary tract anomalies. A voiding cystourethrogram is indicated if the KBUS is abnormal or if the child experiences a second febrile UTI. (Based on some research evidence as well as consensus) (34)
- Clinicians should strive to identify and mitigate modifiable risk factors for UTI and recurrence, including bowel and bladder dysfunction (BBD). Assessment for BBD via validated questionnaires, initiation of behavior interventions, and treatment of constipation can begin in the medical home, with referral to specialists in cases refractory to initial interventions. (Based on some research evidence as well as consensus) (23)(24)

Take the quiz! Scan this QR code to take the quiz, access the references and teaching slides, and view and save images and tables (available on May 1, 2024).

PIR QUIZ

1. A 4-month-old previously healthy girl is brought to the office by her parents with a 2-day history of fever that spiked to 102.4°F (39.1°C) today. The parents gave her ibuprofen, which improved her temperature. She has been mildly fussy with mildly decreased breastfeeding. She has not had vomiting or diarrhea. On physical examination, she is alert and smiling at her mother. There is no clear focus of infection on examination. A bag urine specimen for urinalysis resulted with 2+ leukocyte esterase and negative nitrite. Which one of the following is the most appropriate next step in management?

   A. Begin oral amoxicillin therapy.
   B. Bladder catheterization to send urine for culture.
   C. Culture the urine from the bag specimen.
   D. Intramuscular ceftriaxone.
   E. Schedule renal bladder ultrasonography for tomorrow.

2. A 2-month-old boy is brought to the office by his parents after a recent hospitalization of a first-time febrile urinary tract infection (UTI). He was discharged to home 5 days ago on oral amoxicillin as the urine culture grew ampicillin-susceptible *Escherichia coli*. Mom states that he is doing well and is back to his normal self. He is uncircumcised, and his parents are opposed to having him circumcised. Renal bladder ultrasonography noted mild left-sided hydronephrosis, and a voiding cystourethrogram (VCUG) showed grade II vesicoureteral reflux on the left. Which one of the following is the most appropriate recommendation to prevent renal scarring with subsequent UTI(s)?

   A. Advise that he be brought in to be seen for any febrile illness and receive early empirical antimicrobial treatment if evaluation findings are consistent with a UTI.
   B. Begin amoxicillin antimicrobial prophylaxis for 12 months.
   C. Begin azithromycin antimicrobial prophylaxis alternating with amoxicillin antimicrobial prophylaxis every 2 months.
   D. Begin oral oxybutynin.
   E. Schedule for surgical repair of the vesicoureteral reflux.

3. A previously healthy 14-month-old girl is brought to the emergency department (ED) with a 1-day history of fever with the maximum temperature being 102.5°F (39.1°C) last night. Her appetite is mildly decreased but she seems to be having a normal number of wet diapers. She has not had vomiting. She has no known allergies. She is alert and her physical examination is negative for any clear source of infection. A catheterized urine specimen showed 3+ leukocyte esterase, positive nitrites, and 20 to 30 white blood cells per mm^3 on an unspun specimen. Culture is pending. Which one of the following is the most appropriate therapy?

   A. Admit to the hospital for intravenous (IV) vancomycin and gentamicin.
   B. Admit to the hospital for observation pending the urine culture result.
   C. Begin oral amoxicillin therapy.
   D. Begin oral cephalexin therapy.
   E. Begin oral nitrofurantoin therapy.

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2024 *Pediatrics in Review* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *Pediatrics in Review* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2024. To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.

4. A previously healthy 6-week-old girl is admitted to the hospital with fever for approximately 30 hours. She was brought to the ED due to a temperature of 104°F (40°C). She has had decreased oral intake and 1 episode of vomiting. On physical examination she is ill-appearing, but there are no focal findings. A lumbar puncture was performed, and cerebrospinal fluid studies were normal. Catheterized urine was obtained, and urinalysis resulted positive nitrites, 1+ leukocyte esterase, and negative results for blood, protein, and glucose. The microscopic urine noted 15 white blood cells per mm^3 on unspun urine. She was started on IV ceftriaxone in the ED, which has been continued. The urine grew *E coli* susceptible to ceftriaxone and ampicillin and resistant to trimethoprim-sulfamethoxazole. Blood and cerebrospinal fluid cultures have no growth at 3 days. Renal bladder ultrasonography performed today is normal. She is now eating well and appears well. Which one of the following is the most appropriate next step in management?

   A. Change to oral amoxicillin to complete a 7-day course of treatment.
   B. Change to oral amoxicillin-clavulanate to complete a 10-day course of treatment.
   C. Continue IV ceftriaxone to complete a 7-day course.
   D. Change to IV ampicillin to complete a 10-day course.
   E. Obtain aVCUG.

5. A 4-month-old girl is admitted to the hospital for a second febrile UTI. Her history is remarkable for hospitalization for a febrile *E coli* UTI at 2 months of age. Renal bladder ultrasonography with the first UTI was normal. Urine culture with the current UTI is growing extended-spectrum β-lactamase *Klebsiella oxytoca*. She is currently receiving IV meropenem and is now afebrile after 48 hours of treatment. Which one of the following is the most appropriate next step in management?

   A. Add IV ceftaroline.
   B. Computed tomography of the abdomen and pelvis.
   C. Dimercaptosuccinic acid renal scan.
   D. Magnetic resonance imaging of the abdomen and pelvis.
   E. VCUG.

UTI Quiz

1. Percentage of females who will have at least one UTI by 7 years old = ___.

2. Percentage of males who will have at least one UTI by 7 years old = _____.

3. 80% of UTIs are caused by which pathogen? _____.
   Other UTI pathogens include:_____.

4. The gold standard test for diagnosing a UTI is _____. In general, how many colony-forming units/mL of growth from a specimen are required to diagnose a UTI? _____

5. What common condition in children leads to voiding dysfunction and is strongly correlated to recurrent UTIs?

6. List at least 4 host risk factors that predispose to urinary tract infections:

7. Which imaging study is the gold standard for diagnosing VUR?

8. Based on the AAP Clinical Practice Guidelines, what are the indications for performing a VCUG?

UTI Cases

Case 1:

A 4 week old term female presents to the ED with a fever to 102.2F and fussiness that started 12 hours prior. Mother of child was GBS negative and had no history of HSV. The child is still breastfeeding well without emesis and has no focal findings of infection on exam.

Discuss which diagnostic studies you would obtain and your treatment plan including antibiotic choice.

CSF studies are reassuring, but her WBC is 19,000 and the U/A is positive for Leukocyte Esterase, negative for nitrites and urine microscopy shows 20 WBC/hpf. A day into her admission, the urine culture (cath specimen) grows >10,000 cfu of E. Coli, which is resistant to ampicillin.

What imaging study if any would you order?

Discuss discharge criteria, length of treatment (IV vs oral) and whether you would start prophylactic antibiotics.

Case 2:

A 15 month old Caucasian girl is brought to the ED with the complaint of fever to 103 for two days and "acting fussy". She has had no other symptoms, and has a non-focal exam.

What conditions are in your differential diagnosis?

What are some of the symptoms that may accompany UTI in an infant or toddler?

Using Figure 2 from the AAP UTI Clinical Practice Guideline, estimate this patient's risk of having a UTI:

The bag U/A performed in the ED is negative for nitrites, but has trace leukocyte esterase.
How does this influence your thinking?

The parents adamantly refuse a urethral catheterization to obtain a urine culture. The child throws up a dose of tylenol she received 10 minutes prior.
Do you insist on performing a cath U/A? If so, how do you convince the parents?

Discuss treatment options (which antibiotic? IV vs Oral? Duration?), as well as indications for admission and imaging.

Case 3:
A 16-year-old girl presents with 3 days of dysuria, urgency and 1 day of fever to 103F, chills, nausea, emesis, and abdominal pain. **Use the chart below to develop a differential diagnosis and discuss how you would rule in/out that diagnosis:**

Differential Diagnosis	**Pertinent (+) and (-) History and Exam Findings**	**Helpful lab/imaging studies to rule in/out**
Ex. Renal Calculus	Colicky abd pain? CVA tenderness? Hx of prior stones? Medications?	-U/A to eval for microscopic hematuria -Urine microscopy for crystals -CT abdomen

Differential Diagnosis	Pertinent (+) and (-) History and Exam Findings	Helpful lab/imaging studies to rule in/out

Based on the presence of pyuria and a positive urine culture for E.coli you diagnose this patient with pyelonephritis. Two days into her admission and course of IV ceftriaxone she remains febrile to 102 and with rigors. **Are you concerned by these findings? What is the expected clinical course for this patient?**

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UTI Board Review

1. Voiding cystourethrography in a 9-month-old boy who has new-onset febrile urinary tract infection reveals grade II vesicoureteral reflux (VUR). The parents ask you about their son's prognosis.

Of the following, you are MOST likely to explain that
A. approximately 80% of children who have newly diagnosed febrile urinary tract infections have
VUR when tested
B. once VUR is established, no follow-up radiologic testing is indicated
C. males have a worse prognosis than females
D. referral to urology for ureteral reimplantation is warranted
E. unilateral grade II reflux has a high likelihood of resolution within 5 years of the diagnosis

2. A mother brings in her 3-year-old daughter because of daytime urinary incontinence and abdominal pain. The mother explained that the girl was toilet trained at 2 years of age. On physical examination, growth parameters and vital signs are normal, although the girl has mild suprapubic tenderness without associated costovertebral angle tenderness or sacral dimples. Urinalysis shows a urine specific gravity of 1.025, pH of 6.5, 2+ blood, 1+ protein, 3+ leukocyte esterase, and positive nitrite. Urine microscopy demonstrates 5 to 10 red blood cells/high-power field, 20 to 50 white blood cells/high-power field, and 3+ bacteria.

Of the following, the MOST likely etiologic agent is
A. *Enterococcus faecalis*
B. *Escherichia coli*
C. *Klebsiella pneumoniae*
D. *Proteus mirabilis*
E. *Staphylococcus saprophyticus*

3. You employ voiding cystourethrography (VCUG) to evaluate a 4-year-old girl who had a febrile urinary tract infection 1 month ago. The study reveals a smooth-walled bladder, absence of vesicoureteral reflux, and a mildly narrowed urethra.

Of the following, the MOST appropriate management in this situation is
A. administration of prophylactic antibiotics until 6 years of age
B. no treatment
C. placement of the child on a clean intermittent catheterization program
D. repeat VCUG in 6 months
E. urologic consultation for cystoscopic evaluation

4. You are evaluating a 5-year-old girl who has a urinary tract infection. She has had four lower urinary tract infections in the last 2 years, all of which resolved completely with oral antibiotics. She denies symptoms of urgency and frequency. The only significant finding on her medical history is constipation. Results of renal ultrasonography and voiding cystourethrography are normal. Her growth parameters and physical examination findings are normal. You prescribe oral trimethoprim-sulfamethoxazole.

Of the following, the MOST appropriate additional step to help reduce the incidence of further urinary tract infection is to

A. begin an evaluation for immunodeficiency
B. perform renal scintigraphy
C. prescribe a stool softener and regular bowel routine
D. prescribe oral oxybutynin
E. refer her to a pediatric nephrologist

5. A 6-year-old girl is experiencing daytime and nighttime enuresis of 1 month's duration. She achieved daytime continence at age 3 and has been dry at night since age 4. She has no history of fever, but does have some dysuria. The physical examination is remarkable only for suprapubic tenderness. Urinalysis demonstrates a specific gravity of 1.015, pH of 6.5, 1+ blood, trace protein, 3+ leukocyte esterase, and positive for nitrite. Microscopy reveals 2 to 5 red blood cells/high-power field (HPF), 20 to 50 white blood cells/HPF, and 3+ bacteria. Results of a urine culture are pending.

Of the following, the MOST appropriate empiric treatment for this patient is

A. amoxicillin
B. cefixime
C. cephalexin
D. ciprofloxacin
E. trimethoprim-sulfamethoxazole

6. A 16-year-old girl presents with symptoms of burning with micturition and back pain. Her temperature is 101.3°F (38.5°C), heart rate is 88 beats/min, respiratory rate is 14 breaths/min, and blood pressure is 108/64 mm Hg. You can elicit costovertebral angle tenderness on the left side and suprapubic tenderness. Her urinalysis demonstrates a urine specific gravity of 1.025, pH of 6.5, 2+ blood, 1+ protein, 3+ leukocyte esterase, and positive for nitrite. Microscopy reveals 5 to 10 red blood cells/high-power field (HPF), 50 to 100 white blood cells/HPF, 4+ bacteria, and occasional squamous epithelial cells.

Of the following, the MOST likely diagnosis is

A. acute bacterial cystitis
B. acute glomerulonephritis
C. acute pyelonephritis
D. bacterial urethritis
E. nephrolithiasis