Urinary Tract Infections and Vesicoureteral Reflux in Infants and Children

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Objectives After completing this article, readers should be able to:

- 1. Describe the association of urinary tract infections (UTIs) and unexplained fever in infants.
- 2. Discuss the management of a suspected UTI.
- 3. Review the use of radiologic studies to diagnose vesicoureteral reflux (VUR) and to assess renal scar formation.
- 4. Explain the indication for long-term prophylaxis against UTI in patients who have VUR.

Urinary Tract Infections

UTIs are a cause of serious bacterial infections in about 7% of febrile infants and children up to 24 months of age. Patients who experience UTIs comprise about 0.7% of pediatric office visits (2.2% to 2.8% of children), 14% of pediatric emergency department visits, and approximately 13,000 admissions for acute pyelonephritis annually. (1)

Definitions, Epidemiology, and Host Factors

Most UTIs are bacterial infections of the mucosal surface of the urinary tract. The infection may occur anywhere from the urethra to the renal parenchyma (Table 1). (2) A temperature greater than 38.5°C may help to differentiate acute pyelonephritis from lower tract UTIs. In contrast to children who have physical signs or symptoms suggestive of a UTI, asymptomatic bacteriuria is an incidental finding in children who present with no urinary tract complaints, with normal physical examination findings, and with normal results on renal imaging studies. In these instances, antibiotic therapy is not indicated.

A number of host factors, such as age, sex, race, circumcision status, genitourinary abnormalities, and immune status, affect the probability of patients developing UTIs and recurrent UTIs. Although the numbers of infants and children who develop UTIs are significant, the literature is inconsistent, with some studies using prevalence and others using incidence to quantify the number of pediatric patients who have UTIs.

Prevalence is the total number of individuals who experience a UTI within a particular period of time; incidence is the number of individuals who acquire a new UTI during a set period of time. The overall incidence of childhood UTI in girls and boys is 8% and 1% to 2%, respectively. The incidence is greater than 2% in adolescent girls and young adults. The incidence in uncircumcised infant males is 0.7%, but circumcision reduces the incidence threefold. From 1 year of age through school age, the incidence in males is less than 0.2% compared with up to 1.4% in females.

The prevalence of UTI in febrile infants who have no obvious source of infection is about 7% to 9% in those younger than 3 months of age regardless of sex and decreases to about 2% for both males (>3 months of age) and females (>12 months of age). (3)

Diagnosis

The terms used to define and localize UTI vary (Tables 1, 2). The "gold standard" for diagnosing UTI is the urine culture obtained by suprapubic aspiration, urethral catheterization, a "clean catch" midstream specimen, or urine bag collection (least preferable). (4)

Urinalysis by dipstick examination for nitrite and leukocyte esterase (LE) is rapid and easy to perform. The nitrite test demonstrates the presence of gram-negative bacteria in urine that reduce dietary nitrate to nitrite. The nitrite test is 37% sensitive and 100% specific, with a positive predictive value and negative predictive value of 90% and 100%,

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Symptomatic bacteriuria	Upper or lower urinary tract sympt	oms and urine culture with
-,	significant bacterial colony coun	ts (see text and Table 2)
Urethritis	Inflammation of the urethral muco	sa, with symptoms of dysuria,
	counts (<10 ³) (rule out vaginiti	s in sexually active patients)
Acute cystitis	Inflammation of bladder mucosa a	nd symptoms of lower tract

Table 1. Descriptions and Criteria for Urinary Tract Colonization/Infection

flank pain, and other systemic symptoms (eg, vomi	ting
Asymptomatic bacteriuria Urine culture with significant bacterial colony count asymptomatic patient	n an
Complicated bacteriuria Urine culture with significant bacterial colony count associated urologic abnormalities (hydroureter, hydronephrosis, and vesicoureteral reflux)	and

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respectively. (5) LE detects the presence of leukocytes in the urine and is best performed on a fresh specimen. In contrast to the nitrite test, the sensitivity and specificity is 73%, the positive predictive value is 34%, and the negative predictive value is 95%. (A positive predictive value is the proportion of patients who have positive test results and are correctly diagnosed with a clinical condition. The negative predictive value is the proportion of patients who have negative test results and are correctly diagnosed with a clinical condition.) Pyuria (purulent fluid in the urine) without other findings is not adequate to diagnose a UTI and is not a substitute for a urine culture. The presence of leukocytes also may be related to vaginal secretions, dehydration, glomerulonephritis, tuberculosis, or interstitial nephritis and should be differentiated from a UTI.

Microbiology

The most common organism causing UTI in children is Escherichia coli, accounting for up to 70% of infections. Other bacterial pathogens include Pseudomonas aeruginosa (nonenteric gram-negative), Enterococcus faecalis, Klebsiella pneumoniae, group B Streptococcus (predominately in neonates), Staphylococcus aureus (consider other

sites of infection via hematogenous spread, renal abscess, and pyelonephritis), Proteus mirabilis (boys >1 year old and associated with renal calculi), or coagulase-negative Staphylococcus. Fungal UTI can be caused by Candida albicans (associated with instrumentation of the urinary tract); viral UTIs can be caused by adenovirus and BK virus (hemorrhagic cystitis). Most UTIs in sexually active females are caused by *E coli* or *S saprophyticus*. In hospitalized patients, the common nosocomial pathogens are E coli, C albicans, and P aeruginosa.

infections: urgency, dysuria, frequency, and hematuria

tract

Pathogenesis

As the most common pathogen in UTIs, E coli has served as a model for understanding the microbial virulence in UTI. The uropathogenic E coli (UPEC) strains have extraintestinal virulence due to distinctive antigens and genes that enhance virulence. (6) The virulence factors for *E coli* include P-fimbriae, protectins, toxins, and siderophores. The ability of UPEC to adhere to the uroepithelium via cell receptors is related to the presence of hairlike extensions called fimbriae on the cell surface of UPEC. Adhesion of the fimbriae to the host epithelium in a lock-and-key pattern impedes the normal

Table 2. General Criteria to Diagnose a Urinary Tract Infection (2)(4)

Suprapubic Aspiration	Any growth of gram-negative bacilli or >10 ³ colony forming units/mL of gram-positive cocci
Urethral Catheterization	Greater than 10 ³ colony forming units/mL for circumcised males and all females, >10 ⁵ colony forming units/mL for uncircumcised males (if 10 ⁴ to 10 ⁵ colony forming units/mL, consider repeat sample)
Midstream Clean Catch	>10 ⁵ colony forming units/mL. These values pertain to pure, one-pathogen colony growth and should be interpreted based on the child's symptom complex (2)(4)

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"flushing action of urine flow and emptying." (6) The clinical significance of P-fimbriaed *E coli* is higher in patients who have pyelonephritis than cystitis because UPEC virulence may contribute to the parenchymal inflammatory response and injury as well as to the formation of renal scars (Fig. 1).

A strong correlation exists between constipation and recurrent UTI in children. This association is believed to result from compression of the bladder and bladder neck that increases bladder storage pressure and postvoid residual urine volume. Also, a distended colon or fecal soiling provides an abundant reservoir of pathogens. Constipation in children increases the likelihood of urinary incontinence, bladder overactivity, dysfunctional voiding, a large-capacity bladder with poor emptying function, recurrent UTIs, and persistence or progression of VUR.

In a study that involved 366 children ages 4 to 18 years who had symptoms of voiding dysfunction, constipation or encopresis was reported in 30%, day-time wetting (diurnal enuresis) in 89%, night-time wetting (nocturnal enuresis) in 79%, and recurrent UTIs in 60% of the patients. VUR was present in 20% of the patients who underwent voiding cystourethrography (VCUG). (7)

The diagnosis of constipation is based primarily on history and physical examination. Objective criteria to help support a clinical diagnosis are limited. A plain radiograph of the abdomen, obtained routinely during VCUG, may provide objective, noninvasive supporting evidence for constipation in some patients. Treatment of constipation via positive reinforcement, increased fluid and dietary fiber intake, bowel habit training, and use of stool softeners or laxatives judiciously reduces the recurrence of UTIs and increases the resolution of enuresis and uninhibited bladder contractions.

Other host facts predispose to UTI and could lead to infection with less common urinary tract pathogens (Table 3). In adolescents, spermicidal use (in diaphragms, condoms) increases the risk of cystitis by altering the normal vaginal flora, favoring bacterial colonization and enhancing adherence of uropathogenic strains. Sexual intercourse, infrequent voiding pattern, pregnancy, history of cystitis, anatomic abnormalities, VUR, urolithiasis, and presence of a foreign body all can increase the risk of cystitis in adolescent patients or young adults. (8)



Figure 1. Possible pathogenesis for the formation of renal scars due to uropathogenic *E coli* infection. Reproduced with permission from Johnson CE, Corey HE, Elder JS. Urinary tract infections in childhood. *Consensus in Pediatrics.* 2003;1(3).

Clinical Presentation

The symptom complex for UTI is very broad and somewhat depends on the age of the patient. In the first 3 months after birth, the symptoms may be nonspecific and include fever, hypothermia, vomiting, diarrhea, jaundice, difficulty feeding, malodorous urine, irritability, hematuria, or failure to thrive. In infants from 3 to 24 months of age, the symptoms become more specific and increasingly refer to the urinary tract, such as cloudy or malodorous urine, frequency, or hematuria. Unfortunately, some children present only with fever without a clear source of infection. In these cases, the magnitude of the temperature elevation should assist with the evaluation. In our experience, low-grade fevers are more likely to implicate a lower tract infection, whereas temperature elevations greater than 39.0°C are indicative of upper tract infection. Preschool (2 to 6 years of age) and older children are better able to verbalize specific symptoms, such as

Table 3. Host Risk Factors Predisposing to Urinary Tract Infection

- Lack of circumcision of male infants
- Male sex in first 6 to 8 postnatal months
- · Lack of breastfeeding in first 6 postnatal months
- Constipation
- Dysfunctional voiding pattern
- Recent history of antibiotic use for any purpose
- Urinary tract infection in the past 6 months
- Indwelling catheters or intermittent catheterization
- Family history of recurrent urinary tract infection
- Recent sexual intercourse
- Use of a diaphragm for birth control or spermicidal agents

No evidence of increased urinary tract infection risk: Poor hygiene, bubble bath use, urethral caliber, or type of undergarments worn

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abdominal pain, suprapubic pain, costovertebral angle pain, dysuria, urgency, or secondary enuresis in a previously toilet-trained child.

Management and Treatment

Timely appropriate treatment of acute pyelonephritis, particularly in young children, is helpful in preventing renal injury that may lead to scarring with associated complications of hypertension, proteinuria, or even endstage renal disease.

The choice of antibiotic for children and adolescents who have clinical diagnoses of cystitis is based on local antimicrobial susceptibility. In most cases, a 3- to 7-day course of therapy is adequate. Antibiotics used to treat urinary tract infections are shown in Table 4.

The approach to acute pyelonephritis is based on the patient's age and severity of symptoms. We suggest that the initial treatment with oral or intravenous antibiotics be for approximately 10 days; in selected cases, as when there is prolonged fever or renal abscess, treating for up to 14 days may be reasonable. In most cases, when there is appropriate treatment, the cultures become sterile by 48 hours. Infants younger than 3 months of age should be hospitalized to receive intravenous fluids and antibiotics. Indications for hospitalization and intravenous antibiotics for older infants through adolescents include dehydration or the inability to take oral fluids; an ill-appearing infant or child; or patients who have chronic

diseases such as sickle cell disease, diabetes mellitus, immunocompromise, cystic fibrosis, urinary tract abnormalities, or other serious conditions when the infection could compromise the chronic illness. The approach to infants (>3 months of age), children, and adolescents who have acute pyelonephritis and lower tract infections is shown in Figs. 2 and 3.

Radiographic Studies

RENAL ULTRASONOGRAPHY. Renal ultrasonography is the safest and fastest method for detecting congenital renal and urinary tract anomalies as well as hydronephrosis that may be associated with UTI and VUR. Abnormalities include renal dysplasia, ectopic kidney, duplex collecting system, ureteropelvic junction obstruction, and ureterocele. Ultrasonography also is useful in diagnosing renal abscess and acute focal bacterial nephritis (lobar nephronia), which are rare complications of acute pyelonephritis. Ultrasonography is not a good imaging modality for diagnosing VUR because it may produce normal results in low-grade VUR. In high-grade VUR, ultrasonography may provide indirect evidence by demonstrating dilation of the ureter and hydronephrosis.

Ultrasonography is not a sensitive method for diagnosing renal scars or acute pyelonephritis. In comparison to ^{99m}technetium-dimercaptosuccinic acid (DMSA) renal scans, the sensitivity and specificity of renal ultrasonography in diagnosing renal scars are 36% and 94%, respectively. (9) Ultrasonographic abnormalities compatible with a diagnosis of acute pyelonephritis occur in 45% of cases compared with 93% of cases detected by DMSA renal scan. (10) The timing for performing renal ultrasonography after the first UTI is usually within 2 to 4 weeks. For hospitalized patients, renal ultrasonography generally is performed during the hospital stay. Repeat ultrasonography rarely is necessary for patients who have VUR.

VOIDING CYSTOURETHROGRAPHY. Fluoroscopic VCUG is the gold standard for diagnosing VUR. The grading of VUR (Fig. 4) is based on fluoroscopic VCUG appearance. The results of the VCUG, including grading for VUR, can be affected by many factors. These include the size, type, and position of the catheter; rate of bladder filling; height of the column of contrast media; state of hydration of the patient; volume, temperature, and concentration of the contrast medium; and patient's ability to void during the study.

In younger children who have UTIs, particularly those younger than 5 years of age, the VCUG should be obtained as soon as the infected urine has become sterile or when the child has completed the full course of

Table 4. Suggested Treatment of Urinary Tract Infections in Infants, Children, and Adolescents^{1,2}

Location of Urinary Tract Infection	Suggested Therapy ^{1,2}	Selected Common Adverse Reactions of Therapy or Cautions (Pregnancy Risk Factor)
Cystitis Uncomplicated	3-to 7-day Oral Regimen Trimethoprim-sulfamethoxazole (TMP-SMX) administered twice a day ^{2,3} Trimethoprim: 8 to 10 mg/kg per day (≥2 months of age) Adolescents: 160 mg every 12 hours Amoxicillin <3 months: 20 to 30 mg/kg per day ÷ every 12 hours ≥3 months: 25 to 50 mg/kg per day ÷ every 8 hours Adolescents: 250 mg every 8 hours or 500 mg every 12 hours Amoxicillin-clavulanate (doses for amoxicillin component) ⁴ <3 months: 30 mg/kg per day ÷ every 12 hours <40 kg: 25 to 45 mg/kg per day ÷ every 12 hours Adolescents: 875/125 mg every 12 hours Cephalexin 25 to 50 mg/kg per day ÷ every 6 hours Maximum daily dose: 4 g Cefixime 16 mg/kg per day ÷ every 12 hours for day 1, then 8 mg/kg per day ÷ every 12 hours to complete treatment Adolescents: 400 mg ÷ every 12 to 24 hours Cefpodoxime proxetil ≥6 months to 12 years: 10 mg/kg per day ÷	TMP-SMX (C): Nausea, vomiting, anorexia, diarrhea, allergic rash, photosensitivity, dizziness, headache, lethargy. Not recommended for newborns (<2 months of age) or patients with renal insufficiency Cephalosporins: See individual medication
	Maximum daily dose: 800 mg Ciprofloxacin extended-release ⁵ 500 mg once a day for 3 days Nitrofurantoin (>1 month of age) 5 to 7 mg/kg per day ÷ every 6 to 8 hours Adolescents: 50 to 100 mg/dose every 6 hours, macrocrystal/monohydrate 100 mg twice a day	<u>Ciprofloxacin **(C)</u> : Nausea, headache, dizziness, photosensitivity, agitation, insomnia, lightheadedness, anxiety <u>Nitrofurantoin (B)</u> : Caution with impaired renal function, patients with glucose- 6-phosphate dehydrogenase deficiency, anemia, vitamin B deficiency, diabetes mellitus, or electrolyte abnormalities
Recurrent cystitis infections	Consider prophylactic antibiotics Quarter to half daily dose of TMP-SMX, trimethoprim, cephalexin, nitrofurantoin, or ciprofloxacin ⁵ at bedtime	
Acute Pyelonephritis Outpatient Uncomplicated	<u>10-day Oral Regimen</u> ¹ Similar to cystitis except for amoxicillin- clavulanate dosing of 875/125 mg twice a day Ciprofloxacin 500 mg twice a day OR extended- release 1,000 mg once a day ⁵	

(Continued)

Table 4. Suggested Treatment of Urinary Tract Infections in Infants, Children, and Adolescents^{1,2}-continued

Location of Urinary Tract Infection	Suggested Therapy ^{1,2}	Selected Common Adverse Reactions of Therapy or Cautions (Pregnancy Risk Factor)
Hospitalized due to severity of symptoms	Parenteral Regimen (children are defined as ≤12 years) ^{1.6} Gentamicin 6 to 7.5 mg/kg per day ÷ every 8 hours plus ampicillin 100 to 200 mg/kg per day ÷ every 6 hours (maximum dose, 1 g) (specific once-daily dosing of gentamicin is not included in this table) OR Ampicillin plus cefotaxime (see below), depending on age Cefepime <14 days of age: 30 mg/kg per dose every 12 hours 2 months to 16 years (≤40 kg in weight): 50 mg/kg per dose every 12 hours Adolescents: 1 g every 12 hours Cefotaxime >7 days and 2,000 g, infants and children: 150 to 200 mg/kg per day ÷ every 6 to 8 hours Adolescents: 1 to 2 g/day every 6 to 8 hours Ceftriaxone >7 days and 2,000 g, infants and children: 50 mg/kg per day every 24 hours (maximum, 2 g/day) Adolescents: 1 to 2 g every 24 hours Ciprofloxacin ⁵ Children: 10 to 20 mg/kg per 24 hours ÷ every 12 hours Adolescents and adults: 200 to 400 mg/dose every 12 hours	
¹ All dosages are suggestions only. So	me drugs require adjustment for renal disease or specific glomeru	lar filtration rates (GFR). These medications should be

used only by physicians experienced in the treatment/management of infants, children, adolescents, and young adults who have urinary tract infections. The physician should check medication dosing, maximum dosage, labeling, and safety information on all agents before prescribing. For pregnant adolescents, physicians should review Pregnancy Risk Factors before prescribing. ²Local antimicrobial susceptibility should be determined and may influence the therapeutic choice. TMP/SMX should not be used as empiric therapy if the

prevalence of *Escherichia coli* resistance to TMP/SMX is $\geq 20\%$. ³TMP-SMX not recommended for newborns (<2 months of age) or patients who have renal insufficiency.

 4 Amoxicillin-clavulanate 125 mg/5 mL for <3-month-old infants; 200 mg/5 mL or 400 mg/5 mL suspension or 200 mg or 400 mg chewable tablet formulations. ⁵Ciprofloxacin was only approved for patients 18 years of age or older. Recent United States Food and Drug Administration approval for ciprofloxacin has been obtained for use in children 1 to 17 years of age for complicated urinary tract infection and pyelonephritis due to E coli. Oral dosage for children is 20 to 30 mg/kg per day divided twice a day with a maximum dose of 1.5 g/day. Ciprofloxacin is not a drug of first choice due to increased adverse events related to joints or surrounding tissues.

⁶Consider changing to oral therapy following clinical response and a negative urine culture to complete course of therapy. Choice of antibiotic should be based on sensitivity of the pathogen.

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antibiotic therapy. The concept that early performance of VCUG may yield false-positive results for VUR is not supported by results of a study that compared VCUGs

that were performed within 7 days of UTI with those performed 7 days after UTI. (11) Because the procedure requires bladder catheterization, which can be distressing



Figure 2. Suggested evaluation and treatment for suspected acute pyelonephritis. Modified with permission from Johnson CE, Corey HE, Elder JS. Urinary tract infections in childhood. *Consensus in Pediatrics*. 2003;1(3).

to both the patient and the parents, it is important that the diagnosis of UTI be based on an appropriately collected urine sample (catheter collection in non-toilettrained children) that results in significant bacterial growth on culture.

Compared with fluoroscopic VCUG, nuclear cystography exposes the patient to a lower radiation dose and is at least as sensitive in detecting VUR. In fact, some believe that the procedure is more sensitive than fluoroscopic VCUG. However, nuclear cystography does not provide anatomic detail and, thus, does not permit precise grading of VUR or reveal anatomic defects such as ureterocele or bladder diverticulum, which may be associated with VUR. For these reasons, fluoroscopic cystography is preferred for the initial evaluation of children who have UTI and in any situation in which greater anatomic detail is needed. Although some centers use nuclear cystography for evaluating healthy girls who have uncomplicated UTI, this practice is not universally accepted. Nuclear cystography can be used to document resolution of reflux during follow-up or after surgical correction or for screening asymptomatic siblings. With the introduction of low-dose digital-pulsed fluoroscopy, the radiation exposure during the fluoroscopic VCUG has been reduced, and less nuclear cystography is being performed.

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Figure 3. Evaluation of older children and adolescents with signs or symptoms suggestive of a urinary tract infection. Reprinted with permission from Massengill S, Feld LG. Urinary tract infections in adolescents. In: Fisher M, Alderman E, Kriepe R, Rosenfeld WR, eds. *Textbook of Adolescent Health Care.* Elk Grove Village, III: American Academy of Pediatrics; 2010. In press.

RENAL SCAN. DMSA scintigraphy currently is the accepted gold standard for diagnosing acute pyelonephritis and renal scarring. Single-photon emission computed tomography scan DMSA scintigraphy is superior to planar imaging for detection of renal cortical damage. DMSA scintigraphy is more sensitive than ultrasonography intravenous urography (rarely used in children) or computed tomography scan in diagnosing renal scarring. In experimentally induced acute pyelonephritis in the pig model, the sensitivity of DMSA scintigraphy is 92%, when compared with histologic findings. (12) Sensitivity of more than 92% and specificity of more than 98% have been reported in the clinical setting.

Diagnosing acute pyelonephritis by a renal scan does not change clinical management and, hence, is not advisable for routine care. In contrast, a diagnosis of renal scarring (reflux nephropathy) following acute pyelonephritis can have a significant bearing on the future care of the patient, irrespective of VUR resolution. For renal scarring, DMSA scintigraphy ideally should be performed 6 months after acute infection to allow resolution of acute reversible lesions. The interpretation of DMSA results is influenced by intraobserver and interobserver variability, the presence of dysplasia rather than acute pyelonephritis-induced renal scarring, and the sitespecific expertise and methodology used for performing the procedure.

A DMSA renal scan does not differentiate between congenital or acquired renal scarring. Thus, many individuals who have reflux nephropathy do not have renal injury from previous UTIs but rather from preexisting renal disease such as renal dysplasia and injury associated with severe VUR.

All young children who have their first UTI should undergo a renal ultrasonographic examination, unless the patient had previous ultrasonography results reported as normal. All young children who have UTI also should undergo VCUG, with the subsequent manage-



Figure 4. Radiographic grading of vesicoureteral reflux. Reprinted with permission from Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mövius TE. International system of radiographic grading of vesicoureteral reflux. *Pediatr Radiol.* 1985;15:105–109.

ment, including a need for a DMSA renal scan, determined accordingly.

Vesicoureteral Reflux

Natural History

VUR occurs when urine within the bladder flows back up into the ureter and often back into the kidney. The primary concern with VUR is exposing the kidneys to infected urine, which could lead to acute pyelonephritis and renal scarring. All grades of primary VUR have the potential for spontaneous resolution over a period of time. Such resolution is particularly true of mild-to-moderate VUR caused by the lengthening of the submucosal segment of the ureter. As reported by different investigators, the rate of improvement is not consistent because of differences in patient selection, definition of resolution, duration of follow-up, and the use of single versus two negative VCUG studies to confirm resolution of VUR.

In a prospective 5-year follow-up study of children younger than 5 years of age who had primary VUR and radiographically normal kidneys, grade I VUR resolved in 82%, grade II in 80%, and grade III in 46% of the ureters. (13) The resolution rates for grades IV and V over a 5-year period are approximately 30% and 13%, respectively. (14) Grades I through III VUR resolve at a rate of 13% per year for the first 5 years of follow-up and 3.5% per year during subsequent years; grades IV and V VUR resolve at a rate of 5% per year. (15) The rate of resolution is higher in lowgrade VUR compared with high-grade VUR and in nondilated compared with dilated ureters. VUR tends to resolve sooner in African American children. Older age at presentation and bilateral VUR are believed to decrease the probability of spontaneous resolution.

Treatment

Very few patients who have primary low-grade VUR require surgical correction. Studies have shown that the medical management of VUR is as effective as surgical treatment in decreasing the frequency of UTIs or preventing renal scars. (16)(17) The medical management of VUR, as endorsed by the American Academy of Pediatrics, consists primarily of long-term antimicrobial prophylaxis. Antimicrobial agents most appropriate for prophylaxis include trimethoprim-sulfamethoxazole (TMP-SMZ), trimethoprim alone, nitrofurantoin, or cephalexin. In view of increasing resistance of E coli, ampicillin and amoxicillin are less effective as prophylactic agents and are not used for this purpose beyond the first 2 postnatal months. During the neonatal period, it is advisable to avoid using TMP-SMZ. In toilet-trained children, the medication generally is administered at bedtime, although this recommendation is not evidence-based. The prophylactic dose of antimicrobials is one-fourth to one-half of the therapeutic dose for acute infection. The following are suggested dosages for commonly used antimicrobials.

- TMP-SMZ: TMP 2 mg/kg as a single dose or 5 mg/kg of TMP twice per week
- Nitrofurantoin: 1 to 2 mg/kg as a single daily dose
- Cephalexin: 10 mg/kg as a single daily dose
- Ampicillin: 20 mg/kg as a single daily dose
- Amoxicillin: 10 mg/kg as a single daily dose

Medical management is appropriate for all grades of primary VUR, particularly in younger children. Surgical management is reserved for patients who fail medical management by having breakthrough UTIs or persistent VUR, particularly with evidence of progressive renal injury. The duration of antimicrobial prophylaxis and the potential need for surgical intervention, which may include endoscopic injection of a bulking agent to alter ureteral entrance into the bladder and, hence, prevent refluxing of the urine or ureteral reimplantation, depend on the age of the patient, the severity of the VUR, the frequency of UTI, patient tolerance, compliance with antimicrobial prophylaxis, presence and severity of renal scarring, and duration of follow-up. Medical management must include treatment of constipation and voiding dysfunction, if present.

Patients who have VUR and UTI require close monitoring for early diagnosis and treatment of UTI recurrence, changing of antimicrobial prophylaxis if the patient has recurrent breakthrough UTIs, and monitoring of the VUR by periodic VCUG examinations. The timing for follow-up VCUG is not well defined, and some recommend yearly studies. Delaying VCUG from yearly to every 2 years in children who have mild VUR (grades I and II) and every 3 years in children who have moderate/severe VUR (grades III or higher) yields substantial reductions in the average numbers of VCUG examinations and costs, with a modest increase in antimicrobial exposure. (18)

Limitations and Controversies With Antimicrobial Prophylaxis

Potential limitations of long-term antimicrobial prophylaxis to prevent UTIs include drug resistance, gastrointestinal symptoms, skin rashes, hepatotoxicity, hematologic complications with SMZ-TMP, and primarily gastrointestinal symptoms with nitrofurantoin. Compliance with daily administration of the medication over a prolonged period of time can be difficult to sustain. Another limitation of medical management is the need for repeated follow-up VCUGs to monitor the resolution of VUR.

Many investigators have raised doubts about the role of long-term antimicrobial prophylaxis in reducing the frequency of acute pyelonephritis or decreasing the frequency of renal scarring (reflux nephropathy). Some have questioned the validity of the published data because of the study methodology used to reach conclusions. These include a Cochrane review on the effectiveness of long-term antibiotic prophylaxis for preventing UTIs in children, which concluded that most published studies to date have been poorly designed, with biases known to overestimate the true treatment effect. (19) Another systematic analysis, which evaluated the value of identifying VUR after a symptomatic UTI and the effects of various interventions on the occurrence of UTI and subsequent renal parenchymal damage, concluded that it is unknown whether the identification and treatment of children who have VUR confers clinically important benefits and whether any intervention, including antibiotic prophylaxis or surgery for VUR, is better than no treatment. (20) Another systematic analysis, which evaluated the predictability of renal parenchymal damage by diagnosing VUR in hospitalized children who had febrile UTI, revealed VUR to be a weak predictor of renal damage in such children. (21)

Antibiotic Prophylaxis Versus Surveillance Only

A few recent studies have compared antibiotic prophylaxis with surveillance only in children who had primary VUR. One such study included 236 children ages 3 months to 18 years who had acute pyelonephritis. Of these, 218 completed a 1-year follow-up period. A total of 113 children (3 months to 12 years of age) who had grades I through III VUR and 105 children who had no VUR (3 months to 17 years of age) were included in the study. Patients were randomly assigned to prophylactic antibiotic or no prophylaxis. DMSA renal scans were used to document renal scarring. At the end of 1 year, only 13 of the 218 children (5.9%) had developed renal scarring, and no difference was noted in the incidence of UTIs, pyelonephritis, or renal scarring between the prophylaxis and no-prophylaxis groups. (22)

In another study, 225 children who had grades I through III VUR were randomized to daily antibiotic prophylaxis or no prophylaxis. The children ranged from 1 month to 3 years of age. After a follow-up period of 18 months, there was no significant difference in the occurrence of UTIs (17% in treatment group and 26% in untreated control group) between the two groups. No difference was noted on the basis of the grade of VUR. A significant association was found between treatment and the child's sex, with significantly reduced UTIs in boys receiving prophylaxis, particularly in those who had grade III VUR. (23)

The third randomized study recruited 100 children with grades II through IV VUR diagnosed after the first episode of acute pyelonephritis. Children were randomly assigned to receive antibiotic prophylaxis or no prophylaxis. The mean ages of children in the prophylaxis and no-prophylaxis groups were 9 and 8.3 months, respectively. At the end of 2 years, prophylaxis was discontinued and patients were followed for another 2-year period for a total follow-up period of 4 years. DMSA renal scans were performed to diagnose renal scars. There was no difference in recurrence of acute pyelonephritis at 2 years (36% versus 30% for prophylaxis and no prophylaxis, respectively) or 4 years of follow-up. DMSA renal scans showed abnormalities in 0%, 30%, and 67% of children who had grades II, III, and IV VUR, respectively. No significant difference in renal scarring was noted at 2 years, and no new renal scars were found during the 4-year period. (24)

The fourth randomized (also blinded) study included 576 patients, 42% of whom had VUR. The median age of patients at study entry was 14 months. Long-term prophylaxis was associated with a modest reduction (7 percentage points) in the risk of recurrent UTI among predisposed children regardless of the presence of VUR, age, sex, and frequency of previous UTIs. (25)

Some of these important studies had limitations that included lack of blinding, small number of children studied, inadequate urine collection methods in non-toilet-trained children, relatively short duration of follow-up, and wide age group variation in one study. Also, the studies did not address the issue of interobserver variability in the interpretation of DMSA renal scans.

Potential Complications

Reflux nephropathy (RN) initially was defined as renal injury caused by VUR and UTIs. The current understanding is that RN results from one of the two processes. In some patients, especially males, renal dysplasia may be associated with severe VUR (congenital form), and renal injury may not be due primarily to infection. Such patients are primarily boys who have class IV or V VUR; their condition is identified most commonly with the antenatal discovery of renal dilation during fetal ultrasonography. The second mechanism for developing RN is likely due to the combination of VUR and repeated UTIs that occurs primarily before the age of 5 years (acquired form). In these children (more commonly female), the combination of upper tract infection and reflux causes permanent scarring. The risk of kidney damage is greatest in children younger than 2 years of age because of their unique kidney papillary morphology and the delay in diagnosing UTIs due to nonspecific clinical presentations, difficulties in obtaining urine specimens, and the higher prevalence and severity of VUR in smaller children. Although the risk of renal injury is higher in children who have high-grade VUR, the injury can occur even with mild and moderate VUR.

RN generally is asymptomatic, particularly in its early stages, but may cause long-term complications such as hypertension, proteinuria, progressive renal failure, and an increased risk of pregnancy-related complications such as hypertension and preeclampsia. According to the North American Pediatric Renal Trials and Collaborative Studies 2006 annual report, (26) 8% of the 6,405 children who had end-stage kidney disease (ESRD) had RN, which makes it the fourth most common cause of ESRD after obstructive uropathy, renal aplasia/hypoplasia/ dysplasia, and focal segmental glomerulosclerosis.

Hypertension and Proteinuria

Hypertension occurs in up to 20% of children and young adults who have RN and may take 8 years to develop. The exact cause for hypertension due to renal scarring is not known. Hypertension is relatively uncommon in children who have VUR, with an estimated probability of 2%, 6%, and 15% at 10, 15, and 21 years of age, respectively. (27) However, hypertension increases in proportion to the degree of renal injury. (27) In a study of otherwise healthy children and adolescents referred with hypertension, DMSA renal scans revealed renal scarring in 21% of the patients. (28)

Patients who have RN may present with microalbuminuria, persistent proteinuria, or rarely, nephrotic-range proteinuria. The presence of proteinuria suggests a histologic

Summary

- UTIs are frequent infections in infants, children, and adolescents. It is important to perform a urinalysis and urine culture in all children who have no source of a fever and in symptomatic children.
- The most common organism causing UTI in children is *E coli*, accounting for up to 70% of infections. Most UTIs in sexually active females are caused by *E coli* or *S saprophyticus*. In hospitalized patients, common nosocomial pathogens include *E coli*, *C albicans*, and *P aeruginosa*.
- The symptom complex for UTI is broad and somewhat dependent on patient age. In the first three postnatal months, the symptoms may be nonspecific, which requires a high degree of suspicion by the practitioner. In infants 3 to 24 months of age, the symptoms increasingly are urinary tract-specific, such as cloudy or malodorous urine, frequency, or hematuria.
- The choice of antibiotics for uncomplicated cystitis is based on local antimicrobial susceptibility and consideration of previous antibiotic therapy that could contribute to antimicrobial resistance. A short course of therapy of 3 to 7 days is adequate for most patients. For acute pyelonephritis, we suggest initial treatment with oral or intravenous antibiotics for about 10 days.
- The clinical significance of P-fimbriated *E coli* is greater in pyelonephritis than cystitis. The virulence effects of the uropathogenic *E coli* may contribute to the parenchymal inflammatory response/injury as well as to the formation of renal scars with uropathogenic *E coli* infections.
- The current recommendation is for all young children who have a first UTI to undergo renal ultrasonography and VCUG. Very few patients who have primary lowgrade VUR require surgical correction. Studies have shown that medical management of VUR is as effective as surgical treatment in decreasing the frequency of UTIs or preventing renal scars.
- Medical management is appropriate for all grades of primary VUR, particularly in younger children. Surgical management is reserved for patients who fail medical management by having breakthrough UTIs or persistent VUR, particularly with evidence of progressive renal injury. Potential limitations of long-term antimicrobial prophylaxis for VUR include drug resistance, gastrointestinal symptoms, skin rashes, hepatotoxicity, hematologic complications with SMZ-TMP, and mostly gastrointestinal symptoms with nitrofurantoin.
- The approach to the diagnosis of VUR and appropriate treatment may reduce the incidence of renal scars, hypertension, and proteinuria.

diagnosis of secondary focal segmental glomerulosclerosis, which can be confirmed by renal biopsy if kidney size is normal and the diagnosis is uncertain. (29) Proteinuria usually is modest and commonly is associated with hyper-

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tension and renal dysfunction. Chronic kidney disease progresses gradually over 5 to 10 years.

Appropriate management of hypertension or proteinuria includes the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocking agents (ARBs) as renoprotective therapy. A combination of ACE inhibitor and ARB may provide an additional effect of lowering proteinuria. (30) However, it is not known whether this antiproteinuric effect slows the progression of the renal disease. Some patients who have a significantly scarred kidney may benefit from unilateral nephrectomy if the contralateral kidney is sufficiently healthy to sustain long-term renal function.

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PIR Quiz

Quiz also available online at http://www.pedsinreview.aappublications.org.

- 5. A previously healthy 6-month-old girl presents to the emergency department with a 2-day history of poor feeding, frequent emesis, and tactile fever. Physical examination of the fussy baby reveals a temperature of 38.3°C, heart rate of 115 beats/min, blood pressure of 94/59 mm Hg, and no other significant abnormalities. You attempt to feed her, but within 5 minutes she vomits almost the entire feeding. A catheter-obtained urinalysis shows a specific gravity of 1.015; pH of 6.0; 124 white blood cells; 14 red blood cells; and positive nitrites, bacteria, and leukocyte esterase. The most appropriate medical management is:
 - A. Hospital admission and administration of an intravenous cephalosporin.
 - B. Hospital admission and administration of intravenous gentamicin.
 - C. Hospital admission and administration of intravenous vancomycin.
 - D. Hospital discharge and administration of oral amoxicillin.
 - E. Hospital discharge and administration of an oral cephalosporin.
- 6. A 2-year-old boy has a history of recurrent (at least two) urinary tract infections. After the first infection, voiding cystourethrography (VCUG) revealed bilateral vesicoureteral reflux (grade III on the right and grade IV on the left). The most recent VCUG, obtained 6 months ago, revealed grade II VUR on the right and grade I VUR on the left. Since the initial infection, he has been receiving daily antibiotic prophylaxis without breakthrough infections. Of the following, the *most* appropriate management at this time is to:
 - A. Continue antibiotic prophylaxis.
 - B. Discontinue antibiotic prophylaxis and observe.
 - C. Refer to urology for bilateral ureteral reimplantation.
 - D. Refer to urology for reflux surgery.
 - E. Repeat the VCUG every 6 months.
- 7. The test or parameter that offers the *best* positive predictive value and negative predictive value for the detection of a urinary tract infection is:
 - A. Serum white blood cell count.
 - B. Urinary bacteria.
 - C. Urinary leukocyte esterase.
 - D. Urinary nitrites.
 - E. Urinary white blood cell count.
- 8. An 18-year-old girl presents to her pediatrician with a 3-day history of dysuria and frequency. Her past medical history is negative for any urinary tract infections. On physical examination, she has a temperature of 38.7°C and right flank tenderness. Her urinalysis reveals 143 white blood cells with positive leukocyte esterase, bacteria, and nitrites. Of the following, the *most* accurate constellation of statements about her is:

	Diagnosis	Causative Organism	Most Likely Contributing Factor	Recommended Treatment
A.	Acute pyelonephritis	Escherichia coli	Sexual activity	Oral antibiotics
Β.	Acute pyelonephritis	Klebsiella	Immunosuppression	Intravenous antibiotics
C.	Cystitis	Escherichia coli	Undiagnosed vesicoureteral reflux	Intravenous antibiotics
D.	Cystitis	Proteus	Urinary tract obstruction	Intravenous antibiotics
E.	Sexually transmitted disease	Chlamydia trachomatis	Sexual activity	Oral antibiotics

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