

Urinary Tract Infections in Children: Knowledge Updates and a Salute to the Future

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Educational Gaps

1. Evaluating and treating bladder and bowel dysfunction are critical in reducing the risk of urinary tract infections (UTIs).
2. The pathogenesis of *Escherichia coli* infections reveals that quiescent intracellular reservoirs may be antibiotic-protected sources of recurrent infections.

Objectives

1. Review the documentation of UTI and the importance of the urine culture.
2. Understand the controversy over imaging and management of febrile UTIs in children.
3. Recognize the risk factors for recurrent UTIs and strategies for intervention.
4. Update information on the pathogenesis of *E coli* UTIs.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
BBD	bladder and bowel dysfunction
DMSA	dimercaptosuccinic acid
IBC	intracellular bacterial communities
NC	nuclide cystography
PAC	proanthocyanidin
QIR	quiescent intracellular reservoirs
RIVUR	Randomized Intervention for Children with Vesicoureteral Reflux
TLR-4	Toll-like receptor 4
UTI	urinary tract infection
VCUG	voiding cystourethrography

CASE SCENARIO

Ellie is a 7-year-old girl with frequent urinary tract infections (UTIs): 3 in the past 6 months. Her first UTI was discovered at age 3 years. Symptoms include an increase in daytime wetting accidents, dysuria, and foul urine odor. She has not had fever. The culture has yielded *Escherichia coli* resistant to ampicillin and trimethoprim-sulfamethoxazole. The family denies that Ellie has constipation when she has a daily bowel movement. Even without UTIs, she has urgency, squatting, and damp panties during the day. She wipes front to back and takes showers not baths. She is overweight and has been treated with nystatin cream for perineal redness and itching 3 times. At night she has always wet the bed and wears pull-ups. Her evaluation includes normal renal ultrasonographic findings. Family history reveals that her father wet the bed as a child and still goes to the bathroom often. Her mother says she hates to go on a road trip with Ellie and her father because “they know every bathroom between here and Memphis.” The mother has had several UTIs. Ellie’s younger sister had a febrile UTI

at age 3 months and was diagnosed as having bilateral grade 3 reflux for which she is taking prophylactic antibiotics with no more episodes of UTI.

JUST THE STATS, PLEASE

UTIs are a common cause of discomfort, expense, and missed work and school. In addition, UTIs carry a risk of damage to the kidneys and bladder. In 2007, there were 10.5 million ambulatory visits for UTI, approximately 0.9% of all ambulatory visits in adults and children. A fifth of these visits were to emergency departments. Among children, 0.7% of ambulatory visits and 5% to 14% of emergency department visits were for UTIs. The prevalence of UTI in febrile infant girls is approximately 7%; thereafter, the prevalence decreases to 2.1% of cases. A fever in circumcised male infants younger than 3 months was due to a UTI in 2.4%, whereas among febrile uncircumcised male infants 20.1% had a UTI. White febrile infants were more likely than black febrile infants to have a UTI (8% vs 4.7%). The prevalence of symptomatic UTI with or without fever in older children aged 1 to 18 years was 7.8%. (1)

The incidence of UTI spikes during infancy for girls and boys, around the time of toilet training and at the onset of sexual activity in girls, and is usually an ascending infection. In the past, the bacterial organism responsible for UTIs in children was *E coli* 80% to 90% of the time. More recent reviews reveal *E coli* in 54% to 67% of cultures followed by *Klebsiella*, *Proteus*, *Enterococcus*, and *Pseudomonas*. Gram-positive organisms, such as *Staphylococcus saprophyticus* and group B *Streptococcus*, may also cause UTIs in children. Although rare, *Staphylococcus aureus*, *Candida*, *Salmonella*, *Pseudomonas*, and *Proteus* may cause pyelonephritis via the hematogenous and ascending routes.

UTI SYMPTOMS

In infants, signs suggestive of a UTI are high temperature ($\geq 102.2^{\circ}\text{F}$ [$\geq 39^{\circ}\text{C}$]) without another source for more than 24 hours in boys or more than 48 hours in girls. A history of irritability, lethargy, vomiting, or poor feeding may be present, and, on examination, suprapubic tenderness, white race, and lack of circumcision may suggest a higher likelihood of UTI. For verbal children older than approximately 24 months, more specific signs may be helpful: abdominal pain with fever, back pain, new-onset incontinence, dysuria, and frequency. Foul urine odor, in contrast, is not predictive of UTI. (2)(3)

The diagnosis of a UTI can be suspected on the basis of changes in the urinalysis but is verified by culture of a reliable urine sample. In young children before toilet training, a urine sample should be obtained by bladder catheterization or

suprapubic tap. Older children may provide a clean mid-stream voided sample for culture. As noted in the American Academy of Pediatrics (AAP) guidelines for UTI in febrile children younger than 24 months, (3) the urinalysis should be performed within 1 hour at room temperature or 4 hours refrigerated and should support the diagnosis of UTI with some evidence of pyuria or bacteriuria. The culture of a reliable specimen should be plated expeditiously. A significant bacterial count in the urine, however obtained, is greater than 50,000 CFU/mL usually of a single uropathogen. Urine cultures obtained from a bag specimen are unreliable. (4) Urinary nitrites are very specific but not very sensitive. The conversion of urinary nitrates to nitrites takes approximately 4 hours. In the child with frequency, the urine may not be in the bladder long enough for nitrites to be produced. Moreover, some bacteria, notably *Enterococcus*, do not convert urine nitrates to nitrites.

UTI TREATMENT

If the child with suspected UTI has fever or back pain suggestive of pyelonephritis or cystitis symptoms with significant dysuria or is missing school because of UTI symptoms, treatment should be initiated while waiting for the culture results. The increasing rates of antibiotic resistance provide an imperative not to start empiric antibiotic treatment without first obtaining a reliable culture result. With only mild symptoms, postponing treatment until the culture confirms a UTI with sensitivities is preferred. Traditionally, the antibiotic chosen before sensitivities are known was trimethoprim-sulfamethoxazole, but resistance to this antibiotic has increased among uropathogens. If the resistance to trimethoprim-sulfamethoxazole is greater than 20%, as it is in most communities in the United States, another choice for empiric oral initiation should be selected. A first-generation cephalosporin or nitrofurantoin may be used because uropathogens are usually sensitive to these antibiotics. (5) However, nitrofurantoin may not be the best choice for suspected pyelonephritis because of inadequate serum and tissue levels. (3) Local hospitals usually publish an antibiogram, which can be useful when choosing antibiotics. The most useful antibiogram for pediatricians is one that separates adults from children and hospital- from community-acquired infections. When sensitivities are known, the choice should be the least broad spectrum that will be efficacious (eg, cephalexin rather than cefdinir). The 2010 *Pediatrics in Review* article on UTI in children provides an excellent chart on antibiotics and dosing for UTI in children (Table 1). (6)

A new addition for treatment of uncomplicated cystitis due to bacteria with multiple resistances is fosfomycin, which may be effective in a single 3-g oral dose and may make

TABLE 1. **Antibiotics and Dosing for Urinary Tract Infection in Children**

LOCATION OF URINARY TRACT INFECTION	SUGGESTED THERAPY ^{1,2}	SELECTED COMMON ADVERSE REACTIONS OF THERAPY OR CAUTIONS (PREGNANCY RISK FACTOR)
Cystitis Uncomplicated	<p><u>3-to 7-day Oral Regimen</u> 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</p> <p>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</p> <p>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</p> <p>Cephalexin 25 to 50 mg/kg per day ÷ every 6 hours Maximum daily dose: 4 g</p> <p>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 Maximum daily dose: 800 mg</p> <p>Ciprofloxacin extended-release⁵ 500 mg once a day for 3 days</p> <p>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</p>	<p><u>TMP-SMX (C)</u>: Nausea, vomiting, anorexia, diarrhea, allergic rash, photosensitivity, dizziness, headache, lethargy. Not recommended for newborns (<2 months of age) or patients with renal insufficiency</p> <p><u>Cephalosporins</u>: See individual medication</p> <p><u>Ciprofloxacin ** (C)</u>: Nausea, headache, dizziness, photosensitivity, agitation, insomnia, lightheadedness, anxiety</p> <p><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</p>
Recurrent cystitis infections	<p>Consider prophylactic antibiotics Quarter to half daily dose of TMP-SMX, trimethoprim, cephalexin, nitrofurantoin, or ciprofloxacin⁵ at bedtime</p>	
Acute Pyelonephritis Outpatient Uncomplicated	<p><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 day⁷</p>	
Hospitalized due to severity of symptoms	<p><u>Parenteral Regimen (children are defined as <12 years)</u>^{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) <u>OR</u> 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</p>	

Continued

TABLE 1. (Continued)

LOCATION OF URINARY TRACT INFECTION	SUGGESTED THERAPY ^{1,2}	SELECTED COMMON ADVERSE REACTIONS OF THERAPY OR CAUTIONS (PREGNANCY RISK FACTOR)
	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	

TMP-SMX=trimethoprim-sulfamethoxazole.

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intravenous antibiotics for symptomatic bladder infections due to these extended antibiotic spectrum β -lactamase-producing organisms unnecessary.

Phenazopyridine may be used for cystitis symptoms while waiting for improvement in the symptoms. The dose is 12 mg/kg daily divided into 3 doses for 2 days. The dose should be adjusted for reduced glomerular filtration rate and should be avoided if the glomerular filtration rate is less than 50 mL/min/1.73M². This medication is commercially available by prescription or over the counter as a coated tablet but may be compounded to a suspension for young children. The urine turns bright red orange (which obscures accurate urine dipstick readings but will not affect the urine culture) and will stain underwear if the child is incontinent.

Hospitalization is recommended for children younger than 1 month or in older children who require intravenous fluids or intravenous antibiotics for severe illness, especially symptoms of urosepsis, such as hypotension or tachycardia, or lack of response to oral antibiotics, or for children the clinician or family are uncomfortable caring for in an outpatient setting.

Antibiotics are the treatment of choice for symptomatic UTIs. However, children and adults may have asymptomatic bacteriuria, with or without pyuria, which does not require antibiotic treatment. (7) Children, particularly girls, with dysfunctional voiding or bladder and bowel dysfunction (BBD) may have positive urine culture results. If symptoms do not improve with treatment of the UTI, then the positive culture results may be due to the underlying BBD (ie, a UTI is not the cause of the symptoms). Rather than using frequent antibiotics, the underlying bladder dysfunction should be addressed. The offensive odor of infected urine in these incontinent children, however, may need to be treated with antibiotics.

IMAGING AFTER A UTI AND CONSIDERATIONS FOR THE MANAGEMENT OF REFLUX

The appropriate radiographic evaluation of the child with the first documented UTI is currently being reevaluated. The concern is to identify the child with an anatomical abnormality that may predispose him or her to renal scarring from subsequent infection without exposing all children with anatomical abnormalities to unnecessary long-term antibiotic treatment, additional radiographic assessment, or surgery. From the international study of reflux in children in the 1980s until the 2011 recommendations by the AAP, all boys, young girls, older febrile girls, or girls with recurrent infections were imaged from the bottom up with renal ultrasonography and voiding cystourethrography (VCUG) or nuclide cystography (NC) looking for obstruction and reflux. (8) The most common radiographic abnormality after UTI was reflux for which prophylaxis was prescribed until the child outgrew the reflux or had a surgical repair. Normal renal ultrasonographic findings have never been sufficient to rule out reflux because changes in these findings are usually only present with high-grade (ie, grade IV and V) reflux.

To avoid unnecessary studies that involved catheterization and to avoid exposure to pelvic radiation, some advocated a top-down approach, which included renal ultrasonography and a dimercaptosuccinic acid (DMSA) renal scan. If the ultrasonographic or DMSA scan results were abnormal, VCUG was performed. (8) In a retrospective study of 142 children after a first febrile UTI, findings of pyelonephritis were present in all 37 children who were subsequently diagnosed as having grade III to V reflux. Five children with grade I to II reflux had negative DMSA scan results for pyelonephritis. Sixty-four children had pyelonephritis with no evidence of reflux on VCUG performed 1 month later. (9)

Reflux is generally graded using the international system. Grade I describes a whiff of reflux of urine into the distal nondilated ureter from the bladder and does not reach the kidneys. Grade II is reflux that reaches the renal pelvis but does not blunt the calyces or dilate the ureter. In grade III reflux, there is dilation of the ureter and blunting of the calyces, and in grade IV and V reflux, there is progressive dilatation, distention, distortion, and tortuosity of the collecting system.

Several lines of evidence have led to a reassessment of the traditional approaches and renewed interest in research on susceptibility to UTI and renal scarring.

1. The most important goal of detecting reflux was to prevent progressive scarring from reflux and infection that would lead to chronic kidney disease, hypertension, dialysis, and transplantation. With the advent of high-quality prenatal ultrasonography, some fetuses with hydronephrosis were postnatally discovered to have reflux and scarring without ever having a first UTI. This appearance of scarring associated with high-grade reflux is likely due to renal dysplasia. The refluxing ureter develops from a ureteric bud that is slightly ectopic and meets the primordial renal tissue in a slightly ectopic position that does not induce normal branching of the collecting system. (10) Thus, some children with kidney failure previously classified as reflux nephropathy have had dysplasia associated with reflux unrelated to infection. (11)
2. Many children with reflux never have another UTI with or without prophylactic antibiotics.
3. Some early studies suggested that children with and without prophylactic antibiotics had the same number of UTI recurrences (low in both groups), and those receiving prophylaxis were more likely to have resistant bacteria.
4. Children with lower grades of reflux (grades I and II) are less likely to develop scarring and more likely to outgrow reflux spontaneously.

In 2011, the AAP published new guidelines for evaluating first febrile UTIs in children aged 2 to 24 months. Careful attention was paid to the collection of urine samples, interpretation of urine culture results, and treatment of patients with positive urine culture results. This young age was chosen because the immature kidney in the child not yet toilet trained was deemed to be the most susceptible to misdiagnosis and inappropriate management. The recommendations for imaging were more controversial. In a rather strongly worded statement, the AAP recommended that VCUG or NC not be performed after a first febrile UTI if the renal ultrasonographic findings were normal. There was an assumption that most children would not have a recurrent febrile UTI, that prophylaxis was not helpful, and that

high-grade reflux would usually, but not always, reveal some abnormality on renal ultrasonography.

Some physicians believed that extracting the data on children aged 2 to 24 months from 6 studies had serious flaws, including lack of information on circumcision status; inclusion of urine cultures from bag specimens (some studies); lack of blinding to reflux status (most studies), including only one study that compared treatment and placebo; absence of DMSA documentation of scarring (some studies); lack of documentation of adherence with prophylactic antibiotic treatment; and lack of documentation of BBD. Some studies documented a reduction of UTIs with prophylaxis, such as the randomized study in Australia in 2009 of prophylaxis vs no prophylaxis in 576 children, but less than half the children had reflux. (12)

RELATIVELY HOT OFF THE PRESS! THE FIRST OF THE RIVUR STUDY RESULTS

The results from the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial were published in the *New England Journal of Medicine* on June 19, 2014. A total of 607 children with reflux (grade I–IV) were randomized to receive trimethoprim-sulfamethoxazole prophylaxis or no prophylaxis after 1 to 2 carefully documented symptomatic UTIs. The UTI recurrence rate was approximately 30% in the group not receiving prophylaxis. Prophylaxis decreased the recurrent rate by half. Scarring was the same in children with and without prophylaxis at age 2 years: approximately 11% in each group, a few of whom had severe scarring. Stool colonization with resistant *E coli* was more common in the prophylaxis group but did not reach statistical significance. However, among *E coli* UTI recurrences, the resistant *E coli* in the prophylaxis group was significantly higher. Eight children would need to be treated with prophylactic antibiotics to prevent one UTI. (13) In summary, the RIVUR study indicates that prophylaxis can be effective, but the lack of difference in scarring and the increase in antibiotic resistance prevent firm recommendations.

The question may be asked whether there is a way to identify higher grades of reflux more likely to result in recurrent pyelonephritis with scarring because prophylaxis or surgery may be beneficial in this population. Serum procalcitonin has been found to correlate closely with pyelonephritis, reflux, and subsequent scarring. (14)(15)(16) One possible paradigm would be to measure the procalcitonin level in all children suspected of having pyelonephritis. If the level is elevated by 0.5 or more, a DMSA scan should be performed, and those children with positive results would undergo VCUG to look for reflux. Alternatively, those children

with elevated procalcitonin levels (high specificity, 83%; lower sensitivity, 43%) and those with a dilated urinary tract by ultrasonography (lower specificity, 38%; high sensitivity, 87%) would undergo VCUG. (16)

Whether children with reflux are treated with prophylaxis or not, early evaluation of febrile illnesses should be performed with accurate urine sampling and early initiation of antibiotic treatment while waiting for culture results if the urinalysis supports the clinical suspicion for a UTI.

SURGICAL REPAIR OF REFLUX

Surgical correction may be recommended if prophylactic antibiotics and correction of BBD are unable to keep the child free of infection, particularly recurrent pyelonephritis. The International Reflux Study in the 1980s found that surgery reduces the frequency of pyelonephritis compared with medical therapy, but there was no difference in renal scarring between the 2 groups. There are 2 basic surgical approaches: reimplantation and subureteral injection. Reimplantation involves surgically re-creating the intravesical tunnel that normally acts as a one-way valve to allow urine to flow from the kidney to the bladder without backflow. This surgical procedure can be performed intravesically or extravesically via open approach or laparoscopically or robotically, depending on the experience of the urologist. The advantage to the subureteral injection of a nonabsorbable, immobile material that serves as a one-way valve is the absence of a surgical incision because the procedure is performed through a cystoscope but still under anesthesia. The disadvantage is the lower success rate of 75% to 90% with subureteral injection vs 95% to 99% for reimplantation, depending on the grade of reflux and experience of the surgeon. There is an early success yet late failure rate in some children treated with subureteral injection.

The persistence of reflux without UTIs is not necessarily a reason for surgically correcting reflux. Even with no documented UTIs, some clinicians have been concerned that reflux left unrepaired in childhood would lead to pregnancy-related complications, especially maternal pyelonephritis and fetal demise. Concern for these complications in the far distant future does not seem to be a reason to correct reflux in childhood. The evidence to date suggests that renal scarring, not the presence or absence of reflux, puts women at risk for pregnancy-related complications. (17)

IMAGING MODALITIES FOR THE URINARY TRACT

Renal ultrasonography is very helpful for the detection of hydronephrosis but not very useful for detecting the cause of

the hydronephrosis. Pyelonephritis can sometimes be detected on ultrasonography as a localized decrease in echogenicity (due to edema) or a decrease in perfusion of a segment of kidney using power Doppler ultrasonography. Ultrasonography may detect bladder wall thickening from infection or BBD. Ureterocele and duplex kidneys can be seen by ultrasonography, although the nondilated ureter cannot be traced from the kidney to the bladder. Occasionally, a keyhole sign of a dilated posterior urethra associated with posterior urethral valves can be detected, especially when evaluating boys prenatally for hydronephrosis. Discovery of debris in the bladder by ultrasonography may indicate infection, hematuria, crystals, incomplete bladder emptying, or infrequent voiding.

The VCUG involves placing a catheter through the urethra and instilling contrast into the bladder to the point of reaching voiding capacity. Feeding tubes are preferred for infants so that the catheter does not obstruct the urethra. Even in older children, the balloon on the Foley catheter is rarely inflated so that the child can void around the catheter. Cyclic studies, particularly in infants and toddlers, are beneficial if reflux is not seen on the first fill (Fig 1). The VCUG can reveal grading of reflux, reflux into duplex systems, ureteroceles, bladder diverticuli or trabeculations, and especially posterior urethral valves. The NC, in which a nuclear tracer is instilled into the bladder via a catheter, is a lower-radiation alternative if reflux is the only finding that is being monitored. The NC may be especially sensitive for reflux because the radiation comes from the tracer instilled into the bladder; thus, the camera can be turned on during the entire filling and emptying of the bladder unlike the VCUG in which the radiation comes from the fluoroscope, which cannot be turned on during the entire filling and emptying of the bladder. In the future, a solution of bubbles may be instilled via catheter, and ultrasonography could detect the bubbles in the kidney as a manifestation of reflux without exposure to radiation. Generally, however, catheterization remains a procedure in all these studies, generating concern over the stress and pain of catheterization. Some centers use light sedation and others involve Child Life experts, but VCUG performed with the patient under general anesthesia is not believed to accurately represent normal bladder dynamics. Centers with trained professionals who frequently perform these procedures may improve tolerability, quality, and radiation exposure. Studies for reflux can be performed when bladder irritability resolves after appropriate initiation of treatment for the UTI. There is no longer a recommendation for waiting 4 to 6 weeks after an acute infection before performing a study for reflux.

Pyelonephritis can occur without reflux (Fig 2) and even lead to scarring. Therapeutic intervention for recurrent episodes

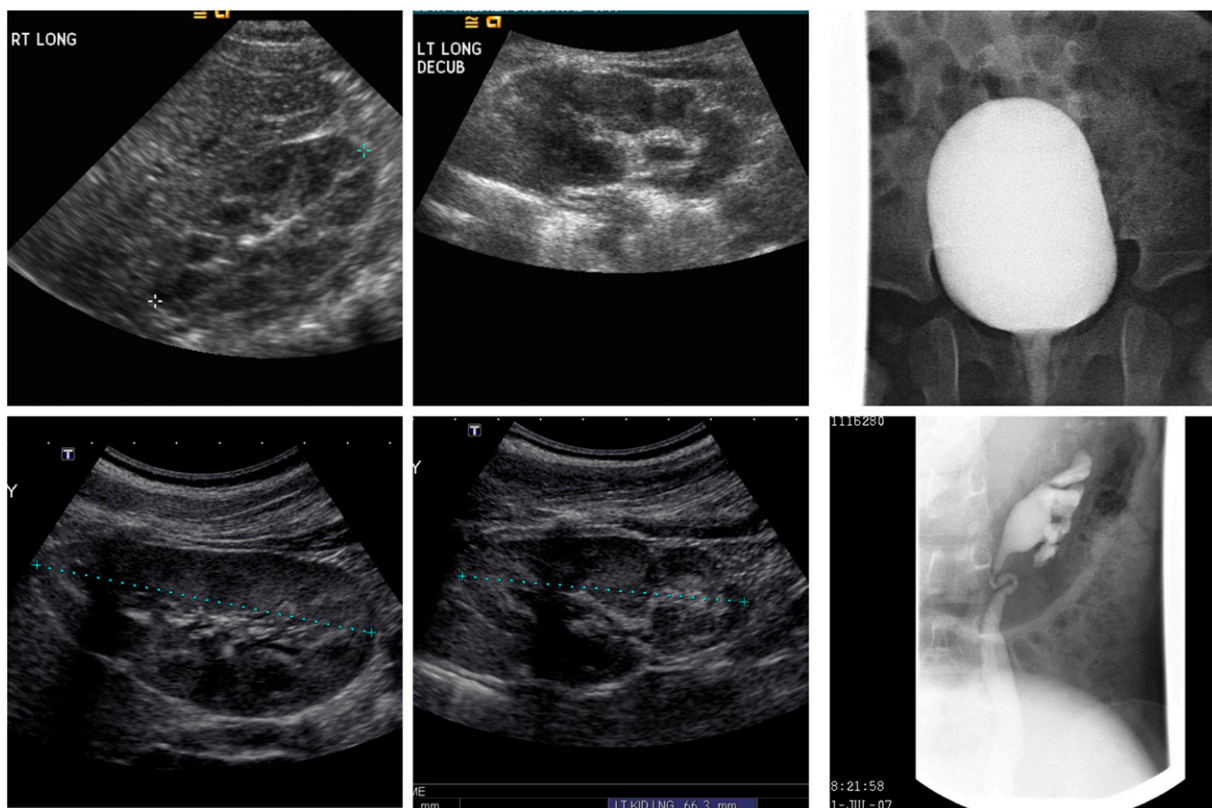
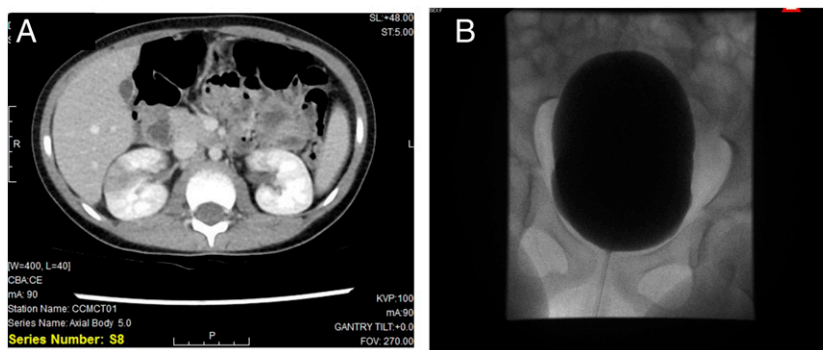


Figure 1. Normal ultrasonographic findings of the right kidney but lower pole scarring of the left kidney. No reflux was seen on initial bladder filling, but cyclic filling revealed reflux into the scarred lower pole.

of pyelonephritis without reflux have included administering prophylactic antibiotics, addressing BBD, and performing PIC (positioning the instillation of contrast) cystography in the operating room where contrast is infused against the ureteral orifice looking for occult reflux that can then be repaired. (18) Figure 3 shows the PIC cystogram that led to correcting occult reflux that reduced episodes of pyelonephritis.

The static DMSA renal scan gives information about the parenchyma and is very sensitive for pyelonephritis and subsequent scarring, although distinguishing between acute and chronic changes is not always easy (Fig 4).

Figure 2. Pyelonephritis and scarring can occur in the absence of reflux. A. On computed tomography, pyelonephritis is seen as a wedge-shaped area of decreased function. B. Voiding cystourethrogram reveals no reflux.



AN UPDATE ON BREAKING THE CYCLE OF RECURRENT UTIS

Lower urinary tract dysfunction combined with constipation has been called the dysfunctional elimination syndrome; however, the new term recommended by the International Children's Continence Society is BBD. BBD greatly increases the risk of UTI and delays the resolution of vesicoureteral reflux if present. (19)

Constipation is a common association with recurrent UTIs. Because parents may not know the bowel habits of their toilet-trained child, a 2-week bowel diary is useful in detecting hidden

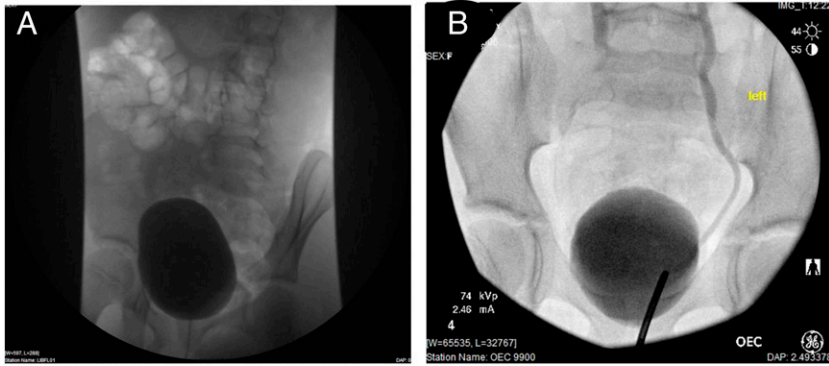


Figure 3. History of vesicoureteral reflux and a new febrile urinary tract infection. A. Voiding cystourethrogram reveals no reflux. B. Intraoperative PIC cystogram reveals reflux, which was repaired with the patient under the same anesthesia.

constipation. The diary includes frequency of stooling, type of stool (using graphics such as the Bristol stool scale), an estimate of quantity, and an assessment of difficulty of passage. Physical examination findings of firm stool in the left lower quadrant or on rectal examination suggest constipation. Ultrasonography through the full bladder may reveal a dilated rectum of more than 3 cm compatible with chronic constipation (Fig 5). Abdominal radiography for constipation may be useful but has been confounded by interobserver variability, suggesting there is no reliable standard. The whole kernel corn or beet transit time is an inexpensive assessment of intestinal motility. The appearance of corn or deep red color from beets after ingestion of these foods should be noted. Normal times vary, but a healthy lifestyle with high fiber, exercise, and fluids usually produces a stool in 12 to 24 hours. Mean transit time in the Western world has been estimated at 48 to 96 hours!

Treatment of constipation starts with a rectosigmoid evacuation and then a maintenance program with monitoring for success. Dietary changes, improved fluid intake, increasing physical activity, and regular toilet times contribute to long-term success. *Lactobacillus* probiotics, in theory, may also improve constipation by the production of lactic acid that stimulates bowel motility.

Constipation, with or without encopresis, is closely associated with UTI. Constipation may lead to lower urinary tract dysfunction, particularly dysfunctional voiding, or both

functional constipation and voiding dysfunction may have a common origin because both the anal sphincter and the external urinary sphincter are striated and both are components of the urogenital diaphragm. (20) Compression of the urethra from a full rectum can prevent complete emptying of the bladder, leading to UTIs.

Functional lower urinary tract disorders, (21) particularly urge incontinence with posturing, infrequent voiding, and dysfunctional voiding, increase the risk of UTIs, especially in girls. Urge incontinence is the name preferred by the International Children's Continence Society in place of the term *overactive bladder*. As the bladder fills, a contraction occurs with little warning, and the child may squat with the heel in the perineum (Vincent curtsy) or grab the genitals or cross the legs. Urethral compression can lead to an automatic relaxation of the bladder so that the child may then stop posturing and go about her play without voiding until the next spasm occurs.

Dysfunctional voiding is the voluntary contraction of the pelvic floor during urine flow. This condition increases pressure in the bladder and may produce turbulent flow or prematurely stop urine flow, resulting in postvoid residuals that may contribute to UTIs. On VCUG, dysfunctional voiding is sometimes seen as a spinning top urethra. At one time thought to represent urethral stenosis requiring urethral dilation, the spinning top urethra is now believed to be almost always functional and not anatomical (Fig 6).

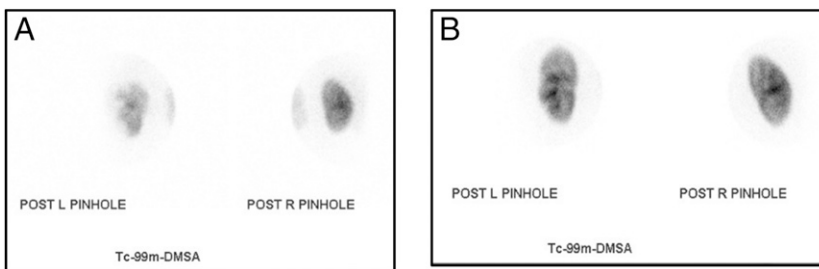


Figure 4. Dimercaptosuccinic acid scan revealing acute pyelonephritis of the left kidney (A) and significant healing with minimal subsequent scarring (B) 2 years later.

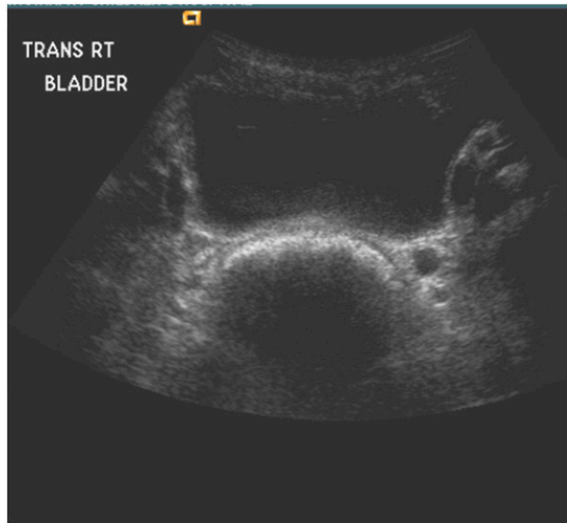


Figure 5. Constipation may be seen on an ultrasonogram as a curvilinear density that decreases ultrasonographic penetration behind a full bladder. The study reveals the close relationship of the bowel and bladder anatomically. A rectal diameter greater than 3 cm suggests chronic constipation.

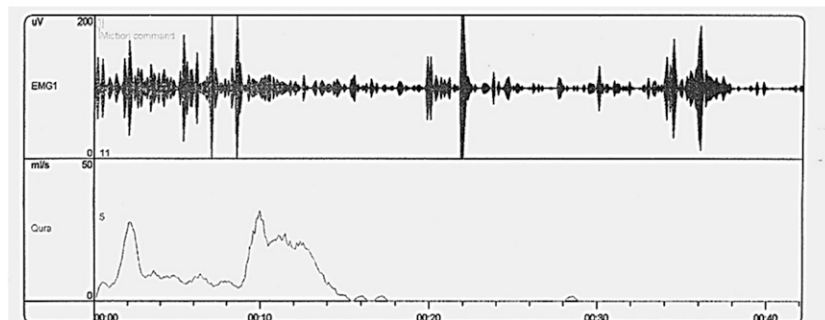
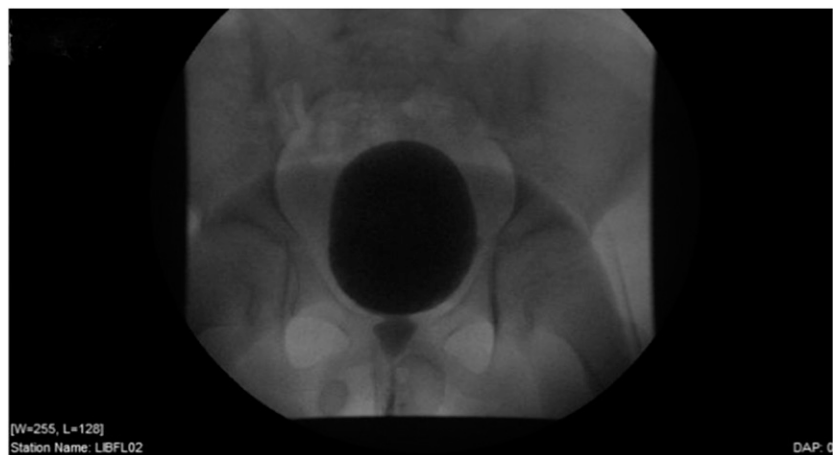
Constipation is very common with dysfunctional voiding because, as mentioned above, urinary and anal sphincters are parts of the same urogenital diaphragm.

Treatment of dysfunctional voiding and urge incontinence may include behavioral (Table 2) and pharmacologic (Table 3) treatment.

Other conditions that increase the risk of UTI include previous UTI, sexual activity, pregnancy, instrumentation of the urinary tract, infrequent voiding, immune deficiency, and stones. Prior antibiotic use, particularly with penicillin or ampicillin, also increases the risk of UTI.

Much attention in the lay press has been devoted to proper wiping techniques, and yet infants may sit in soiled diapers without developing UTIs. Encopresis without constipation has accordingly not been associated with increased risk of UTI. One study of college women with UTIs found no difference in wiping technique front to back vs back to front. (22) However, avoidance of perineal irritation caused by chemicals in bubble baths or excessively chlorinated pools or vulvovaginitis from

Figure 6. The VCUg in the top frame shows the “spinning top urethra” indicating that this girl is tightening the external urethra during voiding when the sphincter should be completely relaxed. Tightening the external sphincter leads to a ballooning of the posterior urethra, increasing pressure during voiding which may allow persistence of reflux. Girls may not empty the bladder completely because tightening the bladder outlet eventually leads to detrusor relaxation. Dysfunctional voiding is also demonstrated in the non-invasive urodynamic study in the bottom frame. The top line is a recording of EMG activity from the pelvic floor, the bottom line is urine flow. Urine flow starts strong then drops off as the pelvic floor activity increases. The non-invasive urodynamics shows that dysfunctional voiding (the “spinning top urethra”) is almost always functional and not anatomic. The tight-appearing urethra does not require urethral dilation. Girls and boys need to be educated on relaxation of the pelvic floor during voiding. Pelvic floor exercises are often prescribed for adult women with stress incontinence but the emphasis is different for children. Through a pelvic floor education program, children are taught to identify the pelvic floor and relax the pelvic floor during voiding (and during defecation since both urethral and anal sphincters are part of the pelvic floor muscle).



Uroflow results	
Peak flowrate	32 ml/s
Time to peak flow	10 s
Voided volume	185 ml
Flow time	17 s
Voiding time	29 s
Delay time	- s
Average flowrate	11 ml/s
Residual urine	39 ml

TABLE 2. Behavioral Interventions for Urge Incontinence and Dysfunctional Voiding

INTERVENTION	REASON	HOW ACCOMPLISHED
Timed voiding	Prevent bladder from filling to the point at which children posture to hold the urine	Voiding schedule, parent or teacher reminders, alarm watch or timer with rewards for going promptly
Increased fluid intake	Ensure that time voiding can be accomplished on schedule	Drink water with every trip to the bathroom, assign a certain amount of fluids (noncarbonated or noncaffeinated)
Urotherapy	Integration of bladder rehabilitation	One-on-one work with health care clinician who reviews timed voids, bowel charts, and fluid intake and teaches pelvic floor relaxation
Proper voiding posture	Empty bladder completely, prevent vaginal reflux	Feet flat on floor or stool, legs spread apart and leaning forward with elbows on knees for girls and prevent trapping penis by the elastic of the underwear and prevent standing on tiptoes to urinate into adult toilet for boys
Address toileting fears	Remove concern for going to the bathroom	Address individual concerns; if dysuria, may use relaxation techniques and phenazopyridine or if fear of automatic flushing toilet, may use sticky note to cover automatic eye

postvoid dribbling (also called vaginal voiding or vaginal reflux) may lead to symptoms that mimic UTI. A red, raw bottom may also inhibit children from going to the bathroom or from relaxing and voiding to completion, all indirectly leading to UTI. Lastly, pinworms or fungal diaper dermatitis may lead to scratching that introduces bacteria into the short female urethra.

ALTERNATIVE PREVENTION STRATEGIES

The increase of resistant bacteria fueled by the overreliance on antibiotics has led to some innovative ways to prevent UTIs in addition to addressing BBD. There has been increased interest in cranberry products with the realization that the active ingredient may be proanthocyanidin (PAC), which is not routinely measured in cranberry juice, pills, or extract and is light and heat sensitive. PAC appears to act by competitively binding the P-fimbriae by which *E coli* attach to the bladder wall. A small randomized, placebo-controlled, blinded study performed with a known quantity of PAC in cranberry juice found a 65% reduction in UTI recurrence in children who had at least 2 culture-documented UTIs in the previous year. (23)

There are a few commercially available products with quantified PAC. The disadvantage is the cost of the product, which is not covered by most insurance.

E coli binds via a FimH adhesin at the tip of the type 1 fimbriae to carbohydrate-rich glycoprotein receptors (rich in D-mannose) on uroepithelium. Providing D-mannose, a sugar not metabolized by the body, should competitively bind *E coli* and thus prevent its attachment to the bladder wall, the first crucial step in an infection. In in vitro and animal studies, D-mannose has been effective. In one study, 308 adult women with recurrent UTIs (defined as 2 UTIs in 6 months or 3 in a year) were treated for an acute infection and then randomized to receive nitrofurantoin, 50 mg/d, or D-mannose, 2 g/d, or no prophylaxis for 6 months. This study was not blinded and did not include children. The rate of recurrent UTI was significantly higher in the group that did not receive prophylaxis (60%) compared with the groups receiving D-mannose (15%) and nitrofurantoin (20%) which did not differ significantly. (24)

Available probiotics in this country are usually strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*. The therapeutic

TABLE 3. Pharmacologic Interventions

TYPE OF MEDICATION	PURPOSE	POTENTIAL ADVERSE EFFECT BUT BY NO MEANS EXHAUSTIVE
Anticholinergics	Prevent bladder spasms and allow successful timed voids	Constipation, heat intolerance, behavioral changes among many more
α -Blockers (off-label)	Relax bladder neck (a muscle that is not under voluntary control so cannot be taught) for improved bladder emptying	Lightheadedness, dizziness, orthostatic hypotension, especially when starting the dose so start right at bedtime; other adverse effects may occur

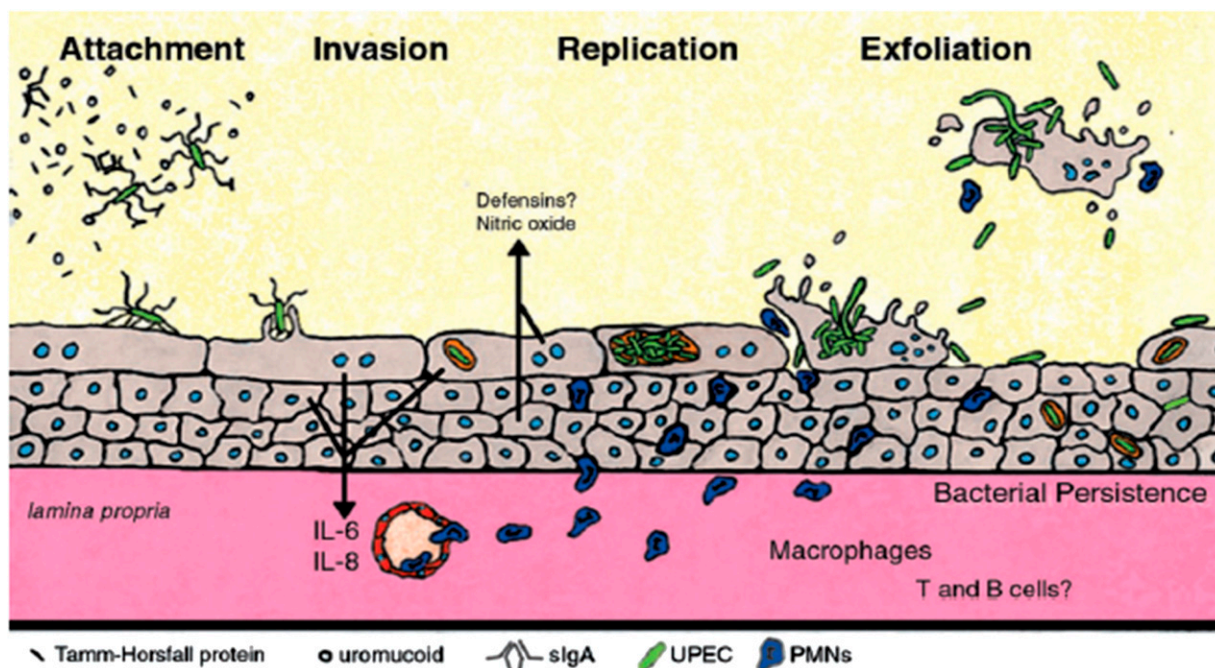


Figure 7. Interplay between uropathogenic *Escherichia coli* and innate host defenses. Reprinted with permission from Mulvey MA, Schilling JD, Martinez JJ, Hultgren SJ. Bad bugs and beleaguered bladders: interplay between uropathogenic *Escherichia coli* and innate host defenses. *Proc Natl Acad Sci U S A*. 2000;97:8829–8835. Copyright 2000, National Academy of Sciences, U.S.A.

benefit of probiotics is in postantibiotic or infectious diarrhea, but theoretically the replacement of uropathogens with relatively benign bacteria may also reduce the recurrences of UTI. Furthermore, there is a theoretical benefit of probiotics on constipation in that the lactic acid produced may stimulate bowel motility. However, the main uropathogenic bacteria in the healthy colon are not lactobacilli but *E coli*. There is a non-uropathogenic *E coli*, Nissle 1917, that eradicates pathogenic bacteria from the gastrointestinal tract. In vitro, Nissle 1917 inhibited or overyielded 40% of *Pseudomonas*, 50% of *E coli*, *Enterococcus*, and *Staphylococcus*, and 100% of *Klebsiella* and *Enterobacter* but 0% of *Serratia* or *Citrobacter*. (25) In the United States, this potential therapy will be regulated by the Food and Drug Administration to ensure safety, and trials are under way.

PATHOGENESIS OF *E COLI* UTI

E coli is the most common cause of UTIs in all ages. The pathogenesis of *E coli* cystitis has been elucidated in mouse models with indirect evidence that the same occurs in humans. The fimbriae of uropathogenic *E coli* allow attachment to the bladder lining via D-mannose receptors. The superficial cells may take up the attached *E coli*, which multiply in the nutrient-rich cytoplasmic environment to create intracellular bacterial communities (IBCs). Some of these bacteria fail to divide and thus become filamentous forms, which are much harder for white blood cells to recognize and phagocytize when the cell

breaks open to release the IBCs. As part of the defense against infection, the bladder lining is shed with the attached bacteria and the IBCs. This loss of the superficial umbrella cells of the bladder then exposes lower layers of the bladder wall to *E coli*. These lower layers of cells may incorporate the *E coli* and, instead of transporting the *E coli* to the lysozyme for digestion, may allow them to be dormant in quiescent intracellular reservoirs (QIRs). *E coli* in QIRs are completely protected from antibiotics and may be the source of recurrent UTI (26) (Fig 7).

Future attempts to prevent this cycle include use of substances that inhibit attachment of the bacteria to the bladder wall (the first step in infection) or to repopulate the colon and/or vagina with nonuropathogenic bacteria. In the meantime, prophylactic antibiotics for some limited time may be beneficial in an attempt to allow the bladder lining to regenerate without harboring the *E coli* again in QIRs and to allow time for correction of BBD.

GENETIC DETERMINANTS OF RISK OF UTI

A risk factor for UTIs in children is to have a mother who has had UTIs, and there is also a hereditary aspect to reflux: reflux will be present in 30% to 50% of siblings or offspring of patients known to have vesicoureteral reflux. Although the detection of reflux before the first infection by screening for reflux with NC may allow caregivers to have a heightened awareness for the early detection of UTI, the knowledge of

reflux may cause families undue worry about something that may never be a problem.

Genetic differences are likely involved in the susceptibility to scarring. There is evidence that Toll-like receptor 4 (TLR-4) on the surface of the bladder activates the inflammatory response and attracts white blood cells to the urothelium. (27) The interleukin 8 receptor is necessary to transport neutrophils across the urinary epithelium. (28) If there are few TLR-4s in the bladder, uropathogens do not induce an inflammatory response and thus do not get effectively cleared, resulting in asymptomatic bacteriuria. Absence of the interleukin 8 receptor means that inflammatory cells are attracted to the urothelium by activation of TLR-4 but cannot enter the urinary space. Thus, neutrophils release cytokines into the tissue, resulting in extensive inflammation and scarring. In the future, more precise selection of children at risk for scarring may be possible with the use of genetic markers. Treatment of host inflammation that actually leads to scarring may be appropriate. (29)

Genetic virulence factors of the bacteria also play a role in pyelonephritis and cystitis, and there is a gradation of virulence factors from *E coli* pyelonephritis to cystitis to normal fecal flora. (30)

CASE SCENARIO CONTINUED

Ellie has had recurrent UTIs.

1. Documentation of UTIs in children is important because some symptoms of other conditions mimic UTIs. The AAP suggests 3 criteria: symptoms, a urinalysis that reveals some inflammatory response or bacteriuria, and a reliable culture. Determining whether UTIs were culture proven is important in determining evaluation and treatment. A report of foul urine odor is not adequate documentation of UTI.
2. UTI risk factors for Ellie are:
 - a. Onset of the UTIs around toilet training time.
 - b. Previous UTI.
 - c. Mother with history of UTIs.
 - d. Lower urinary tract dysfunction as manifested by urgency and urge incontinence even when she does not have a UTI.
 - e. e.Perineal irritation from recurrent vulvovaginitis, which may be postantibiotic fungal infection but could also be postvoid dribbling in a child who is overweight and may not be spreading the labia when she voids.
 - f. Her sibling with reflux is a risk factor for reflux but not necessarily for UTI.
 - g. QIRs may be present but are difficult to prove.
 - h. Constipation that was not immediately apparent because families are often unaware of a 7-year-old child's

bathroom habits; however, a bowel diary revealed daily small pelletlike stools produced with straining.

3. Imaging: renal ultrasonography, and if results are normal, management would include treating BBD and considering concomitant short-term prophylactic antibiotics.
4. On the basis of the sister's reflux, VCUG might be performed, and if it revealed unilateral grade 2 reflux, management would include treating BBD and considering concomitant short-term prophylactic antibiotics. Although Ellie is reaching an age at which most low-grade reflux has disappeared, BBD can lead to its persistence. In addition, if the decision is made to correct reflux surgically, success is greater (particularly with the subureteral injection) if BBD is corrected first. However, the presence of reflux does not change the initial bladder management. An acceptable alternative would be to manage bowel and bladder and only performed VCUG (or NC) for urinary tract dilation noted on ultrasonography or for febrile infections associated with an elevated procalcitonin.
5. Surgery for reflux might be offered for recurrent pyelonephritis or more UTIs after therapy for BBD and with some evidence of damage by DMSA scan.

Summary

- On the basis of some research and consensus, documentation of urinary tract infections (UTIs) is important in children because there is increasing antibiotic resistance and investigation of UTIs may be invasive in children. UTIs are documented by appropriate symptoms, evidence of inflammation or bacteriuria on urinalysis, and a positive culture result of at least 50,000 CFU/mL obtained by reliable methods. (1)(16)(17)(18)(19)(20)
- On the basis of some research and consensus, bladder and bowel dysfunction (BBD) is a contributor to recurrent infections with and without an anatomically normal urinary tract. Treatment of BBD decreases UTIs and improves reflux resolution rates. (1)(2)(3)(9)(15)(21)
- On the basis of research in animal models and some in humans and consensus, the pathogenesis of *Escherichia coli* UTI reveals that bacteria may be protected from antibiotics and host defense mechanisms in quiescent intracellular reservoirs that serve as the source of recurrent infections. (8)
- On the basis of a well-designed randomized clinical trial, prophylactic antibiotics for children with reflux decrease recurrence of UTI but do not affect renal scarring. Therefore, no firm recommendations can be made about imaging after the first febrile UTI. (16) The usefulness of procalcitonin and dimercaptosuccinic acid scans await randomized clinical trials.

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PIR Quiz

1. A previously healthy, 3-month-old girl presents to the emergency department with a 2-day history of temperatures to 102.6°F (39.2°C), fussiness, and 2 episodes of nonbloody, nonbilious emesis. On examination, her vital signs reveal a heart rate of 140 beats per minute, respiratory rate of 30 breaths per minute, blood pressure of 70/40 mm Hg, and a temperature of 101.8°F (38.8°C). She is alert and appears well hydrated, irritable, but consolable, and there are no other pertinent findings on physical examination. You obtain a catheterized specimen, which is sent for urinalysis. It reveals 25 white blood cells per high-power field, 10 red blood cells per high-power field, and positive results for nitrites, leukocyte esterase, and bacteria. The most appropriate management of this patient would be:
 - A. Admit to the hospital and administer intravenous ampicillin.
 - B. Admit to the hospital and administer intravenous ciprofloxacin.
 - C. Admit to the hospital and administer intravenous vancomycin.
 - D. Discharge home and prescribe an oral cephalosporin.
 - E. Discharge home and prescribe oral amoxicillin.
2. A 12-year-old girl comes for a health supervision visit. She is otherwise healthy, is doing very well in school, and takes dance classes. She describes some occasional abdominal pain in the periumbilical area that goes away without any intervention. She also describes some occasional urgency regarding urination. Vital signs are all within normal limits, and she is afebrile. She has not started her menses yet. Your physical examination reveals a healthy young girl. Her abdominal examination reveals normal bowel sounds in all quadrants, no tenderness to palpation, no hepatosplenomegaly, and no masses. You obtain a midstream void specimen for urinalysis. The urinalysis reveals 20 white blood cells per high-power field, 10 red blood cells per high-power field, negative results for nitrites and protein, and a small amount of leukocyte esterase. Of the following, the next best step in management is:
 - A. Amoxicillin antibiotic therapy.
 - B. Observation.
 - C. Renal ultrasonography.
 - D. Trimethoprim-sulfamethoxazole antibiotic therapy.
 - E. Voiding cystourethrography (VCUG).
3. A 15-month-old, uncircumcised male presents to his pediatrician with 4 days of poor appetite, fussiness, and low-grade fever. A clean midstream voided sample is sent for culture. The specimen yields more than 50,000 CFU/mL of *Escherichia coli* sensitive to cephalexin, trimethoprim-sulfamethoxazole, and nitrofurantoin. You administer oral antibiotic therapy. Of the following, the MOST appropriate next test to order is:
 - A. Dimercaptosuccinic acid (DMSA) scan.
 - B. Renal ultrasonography.
 - C. Renal ultrasonography and VCUG.
 - D. VCUG and DMSA scan.
 - E. VCUG.
4. Parents of a 3-year-old girl with recurrent urinary tract infections (UTIs) and grade II reflux are speaking with you about the risks and benefits of using prophylactic antibiotics. Of the following, a TRUE statement is:
 - A. Only those children with higher-grade reflux (grades IV and V) should be receiving prophylaxis.
 - B. Prophylactic antibiotics can be used only for a 6-month period to prevent resistant organisms.
 - C. Prophylaxis can be effective for some children, but the lack of difference in scarring and the increase in antibiotic resistance prevent firm recommendations.
 - D. Prophylaxis has not been found to be beneficial for children with recurrent UTIs.
 - E. The rate of recurrent UTIs is the same in those children who receive prophylaxis as those who are not receiving prophylaxis.

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This journal-based CME activity is available through Dec. 31, 2017, however, credit will be recorded in the year in which the learner completes the quiz.

5. A 4-year-old girl presents for a health supervision visit. She has a history of chronic constipation. She has recently started to have episodes of bed-wetting at night and often experiences urinary urgency and frequency. You are concerned about voiding dysfunction. You start discussing a management plan to relieve her symptoms of constipation and suggest that this will also help with her urinary problems. The parents ask you how the constipation is related to her voiding dysfunction. Of the following, the MOST appropriate response is:
- A. Antibiotic treatment of her UTI will aid in relieving her constipation.
 - B. Constipation is closely associated with UTI and may lead to lower urinary tract dysfunction.
 - C. Diagnosis of pinworm infection will reduce symptoms of constipation.
 - D. Increasing her fiber and water intake will markedly improve her constipation and voiding dysfunction.
 - E. *Lactobacillus* probiotics improve constipation by the production of lactic acid that stimulates bowel motility.

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