MODULE 7: PEDIATRIC URINARY TRACT INFECTIONS

KEY WORDS: Cystitis, vesicoureteral reflux (VUR), dysuria, hematuria, pyelonephritis, hydronephrosis, UTI

LEARNING OBJECTIVES

At the end of this clerkship, the medical student will be able to:

1. Describe the differences in clinical presentation of UTIs in infants and older children
2. Describe the differences in clinical presentation of cystitis and pyelonephritis
3. Identify modifiable and non-modifiable risk factors associated with bacterial, viral, and fungal UTIs in children
4. Describe variations in urologic anatomy that are associated with pediatric UTIs
5. Describe the anatomic, physiologic, and clinical sequelae of repeated and untreated pediatric UTIs
6. Summarize the diagnostic evaluation of pediatric UTIs
7. Outline the operative and non-operative management options for pediatric UTIs

EPIDEMIOLOGY

Pediatric urinary tract infections are common, accounting for over 1.5 million visits to health care providers annually, and over $180 million in spending directed toward diagnosis and treatment. About 2% of males and 7% of females will have at least one UTI by the age of 6 years. Although overall females are more likely to develop UTIs, infant males (particularly those with an intact foreskin) are at increased risk in the first year of life.

CLINICAL PRESENTATION

Children, particularly infants, may present with nonspecific UTI symptoms. Infants in particular may present with fever, lethargy, decreased oral intake, or signs of dehydration. Older children may complain of dysuria, irritative bladder symptoms (urinary urgency and frequency, with or without incontinence), a sensation of incomplete emptying, and flank or abdominal pain. Children of any age may also present with blood in the urine (hematuria), vomiting, or with changes in bowel habits (constipation and/or diarrhea). Importantly, while the presence of fever and systemic symptoms raises concern for pyelonephritis, a fever is not pathognomonic for

kidney infection: in some cases, children may present with cystitis and fever, while others may have renal involvement and present with normo- or even hypothermia.

Children who are immunosuppressed may also have atypical presentations.

PATHOPHYSIOLOGY

Bacteria or fungi (including yeast) can enter the urinary tract through ascending (urethra or bladder) or hematogenous (bloodborne) routes. The most common bacterium isolated in pediatric UTIs is E. Coli, which is commonly found in stool. The ascent of bacteria from the bladder to the kidneys may be mediated by anatomic abnormalities such as vesicoureteral reflux, or by bacterial virulence factors such as pili that enable the bacteria to "climb" toward the kidneys even in the absence of anatomic anomalies.

Fungal UTIs are common in immunosuppressed children, in those with indwelling catheters, and in those with prolonged antibiotic exposure. Fungal UTIs classically occur in children who are immunosuppressed, or those in the Neonatal Intensive Care Unit (NICU), as patients in the NICU often have multiple invasive lines and tubes and have received broad-spectrum antibiotics for prolonged periods. "Fungal balls" may obstruct the collecting system and necessitate percutaneous drainage. Fungal UTIs may not have significant pyuria, but catheterized urine samples will show fungal growth; this can make the clinical differentiation of fungal colonization and infection difficult. Treatment consists of limiting risk factors (removing or changing indwelling lines and tubes, limiting antibiotic use when possible) and administering antifungal agents (fluconazole or amphotericin B).

Like fungal UTIs, viral UTIs typically occur in immunocompromised children in whom normally dormant viruses are activated. Viral UTIs are common in children following organ transplantation or oncology-related immunosuppression, and viral infection can also be associated with hemorrhagic cystitis. Common viruses include BK virus, adenovirus, and cytomegalovirus (CMV). Limiting immunosuppression when possible, and considering antiviral therapy (e.g. ribavirin, cidofovir) can be helpful.

Sterile pyuria is often seen with UTIs caused by acid-fast bacilli such as Mycobacterium tuberculosis.

TABLE 1. Uropathogen Prevalence by Sex and Visit Setting

Table 1

Uropathogen Prevalence by Sex and Visit Setting[*]

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

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

The Table above (Copp 2015) shows nationwide data on the most common bacterial pathogens causing UTI in the inpatient and outpatient settings.

SEQUELAE

Untreated, UTIs may develop into systemic illness (sepsis), damage organs, or have late effects on general health. Examples of spread into adjacent organs include epididymitis and orchitis. Chronic infection of the renal parenchyma (pyelonephritis) has been associated with late effects including renal scarring, poor renal function, and high blood pressure. Renal scarring is most likely in young children with pyelonephritis, and is often seen in children with vesicoureteral reflux. Renal scans using DMSA (dimercaptosuccinic acid) can show differential uptake within the renal parenchyma consistent with renal scarring or dysplasia. One study following children with pyelonephritis-associated scarring for 27 years found a 21% prevalence of hypertension and 10% prevalence of end-stage renal disease. Prompt treatment of suspected UTI in children has been shown to decrease the likelihood of renal involvement, although the data supporting effects on renal scarring are less robust. Treatment should be started as early as possible, and ideally within 24-72 hours of symptom onset.

Xanthogranulomatous pyelonephritis (XGP) is uncommon in children, and develops in the setting of chronic renal obstruction and infection. Nephrectomy is often necessary.

EVALUATION AND MANAGEMENT OF THE CHILD WITH SUSPECTED UTI

A full history and physical examination should be performed. Onset and duration of symptoms, as well as the presence or absence of systemic symptoms (e.g. fever, vomiting, diarrhea) should be recorded. Caregivers should be asked about the child's pre- and post-natal history as well as any family history of urogenital anomalies, current medications, and ill contacts. In children with suspected urinary tract infection, urine should be collected and evaluated for infection. Urine collection using bags in infants is discouraged because of the high risk of contamination; suspected infection on a bagged specimen should be confirmed by collecting urine through suprapubic aspiration or urethral catheterization. In older, toilet-trained children, midstream urine specimens are acceptable options, though care must be taken to adequately cleanse the perineum before voiding and to ensure that midstream urine is collected. Laboratory tests such as complete blood count, basic metabolic panel, C-reactive protein, erythrocyte sedimentation rate, and blood cultures should be performed at the physician's discretion.

In children aged 2-24 months of age, the current AAP UTI Clinical Practice Guideline supports the diagnosis of UTI in children with >50,000 cfu/cc of a single pathogen on appropriately collected urine, in conjunction with findings of inflammation (e.g. pyuria: 10 WBC/hpf on an "enhanced urinalysis" or 5 WBC/hpf on a centrifuged specimen). A 2016 study showed that about one in ten children with symptoms of UTI and bacterial growth on urine culture had no pyuria; in those children, Enterococcus, Klebsiella, and Pseudomonas were more likely to be identified as the causative organism. Fungal UTIs may also present with relatively few white cells in the urine. The presence of nitrites supports the diagnosis of a UTI, although nitrites are more common in urine that has been stored in the bladder for >2 hours.

In children in whom the urine suggests infection, early initiation of antibiotic therapy is critical to minimizing the deleterious effects of infection on the upper tracts. Empiric antibiotic selection is based on the suspected pathogen and local resistance patterns, although it is noteworthy that many hospitals do not have antibiograms specific to pediatric patients. Factors such as ease of use (e.g. taste and number of daily doses) as well as cost should also be considered in efforts to increase adherence. Families should be made aware that antibiotics may be changed based on final culture growth and antibiotic sensitivity; these data are typically available 48-72 hours following urine collection. The duration of antimicrobial therapy is dictated by the age and medical complexity of the child: in general, treatment courses of 7-14 days for most children, although the SCOUT trial is investigating the efficacy of shorter antibiotic courses. When nitrofurantoin is selected as the antibiotic of choice, the minimum duration of therapy should be 7 days. Parents and caregivers should be made aware that, in the setting of pyelonephritis, fevers may persist even in the setting of observed clinical improvement.

The 2011 AAP Clinical Practice Guidelines support obtaining a renal-bladder ultrasound in all children 2-24 months after the first febrile UTI. Recent literature suggests that the cost-effectiveness of screening with a renal-bladder ultrasound may

be increased if sonography is limited to children with a second febrile UTI. Additional testing, such as voiding cystourethrogram, should be obtained if the screening ultrasound demonstrates evidence of collecting system dilatation or renal parenchymal abnormality.

The role of antibiotic prophylaxis in the management of urinary tract infections remains a source of debate. In the setting of high-grade (grade 4-5) vesicoureteral reflux, prophylactic antibiotics appear to decrease the risk of recurrent urinary tract infection. The benefit of antibiotic prophylaxis in lower-grade, "nondilating" (grades 1-3) reflux is less clear. The RIVUR study found that antibiotic prophylaxis was associated with a decreased risk of developing a recurrent UTI, although the number needed to treat was over 5000 doses. Even less clear is the role of antibiotic prophylaxis in the setting of voiding dysfunction: while children on antibiotic prophylaxis had lower rates of renal scarring, bladder-bowel dysfunction was an independent predictor of decreased adherence with medication administration. If antibiotic prophylaxis is considered as an option, a clear endpoint for prophylaxis should be planned and families should be counseled on the risks and benefits of antibiotic prophylaxis, including the possible need for periodic laboratory tests.

Antibiotic stewardship is critical to limit the adverse effects of antibiotic for both individual patients and the community at large; 3.5 million people die in the United States each year from antibiotic-resistant infections. The choice of prophylactic antibiotic should be based on the child's age, any comorbidities, local resistance patterns, and ease of use (e.g. cost, number of daily doses, taste, need for refrigeration). In otherwise healthy term infants, amoxicillin 20 mg/kg daily is frequently used; in infants older than two months, trimethoprim (TMP)-sulfamethoxazole at a dose of 2 mg TMP/kg once daily may be used.

ASSOCIATED CONDITIONS
Anatomic
VUR
Vesicoureteral reflux (VUR), or the retrograde flow of urine toward the kidney, facilitates the exposure of the upper tracts to bacterial pathogens. In high grade (grades 4 and 5) VUR, the risk of UTI may also be increased in part due to the presence of a pseudoresidual volume of urine that arises when the refluxed urine drains from the ureters back into the bladder. Low grade VUR is generally not associated with an increased risk of urinary tract infections in the absence of other anomalies.

In 2011, the AAP released a recommendation (reaffirmed in 2016) that voiding cystourethrogram (VCUG) should be reserved for children with a second febrile urinary tract infection or those in whom the screening ultrasound found sonographic abnormalities in the renal parenchyma or collecting system. In older children with afebrile UTIs, VCUG is generally considered low-yield for the identification of anatomic abnormalities in the absence of other sonographic or physical findings.

A VCUG (see figure) delineates the anatomy within the collecting system, inclusive of the ureters, bladder, and urethra. Thus, it can be used to identify children with VUR and posterior urethral valves; in some cases, ureteroceles and ureteral ectopia may be diagnosed as filling defects and contour abnormalities. Variations in VCUG technique may be associated with differences in radiographic findings, although one multi-institutional study found that the most significant observed difference was in observed bladder capacity rather than in the proportion of children in whom VUR was detected. Nonetheless, as the timing of VUR onset during the filling/voiding cycle is one prognostic factor to be considered when calculating the likelihood of spontaneous resolution, differences in technique should be acknowledged. While the likelihood of spontaneous resolution of VUR has classically been associated with grade (extent of distension of the upper tracts by retrograde contrast), more recent research has identified that the timing of the VUR consent within the filling/voiding cycle as well as the distal ureteral diameter (normalized to the height of a vertebral body) are also important predictive factors.

The AUA Guideline: Management and Screening of Primary Vesicoureteral Reflux in Children is a detailed resource for clinicians.

Posterior Urethral Valves/Myogenic Bladder
Posterior urethral valves are excess tissue in the membranous urethra, just distal to the verumontanum, creating obstruction during voiding and contributing to the development of secondary vesicoureteral reflux and upper tract damage. Improvements in antenatal screening have enabled many of these boys to be identified prenatally, and therapy (bladder decompression followed by endoscopic valve ablation) to be performed fetoscopically or early in the postnatal period. Despite these advancements, half of boys will develop renal insufficiency within the first decade and one in six will develop end stage renal disease. While these data suggest that the baseline risk of renal dysplasia may not be altered by early intervention, optimization of lower tract function and reduction in UTI risk are critical to limit further renal damage in this population.

In the setting of outlet obstruction, the voiding and storage dynamics will be altered by differences in the composition and function of the bladder (specifically collagen and muscle components). Collectively termed the "myogenic bladder," these variations span a wide spectrum and should be managed according to the underlying abnormalities in bladder function.

Ectopic Ureter/Ureteroceles
Ureteral ectopia is present in about 0.05% of children, and occurs when the ureteric bud emerges too proximally in the Wolffian system. As a result, the ureteral orifice opens not in an orthotopic position in the bladder but at or distal to the bladder neck. In girls, the ureter may also drain to the perineum or into the vagina (via a ruptured Gartner's duct cyst). In boys, the ureter may drain into any remnant of the Wolffian system, such as the vas deferens or seminal vesicle, but does not drain to the perineum. Ureteral ectopia can expose the upper tract to bacteria because of the

absence of the antireflux mechanism generated by tunneling the ureter at the ureterovesical junction, and also because of the relative proximity of the ectopic ureteral orifice to the perineum.

Ureteroceles are a cystic dilatation of the distal ureter, and may be associated with obstruction of or less commonly reflux into the affected ureter. Ureteroceles may predispose children to the development of urinary tract infections by obstructing the bladder outlet during voiding, with resulting elevated post-void residuals, or by trapping infected urine in the obstructed ureterocele.

Both ectopic ureters and ureteroceles are definitively treated surgically.

Neurogenic Bladder
Patients with damage to the nerves that innervate the bladder, the pelvic floor, or the external sphincter often have abnormal bladder capacity, difficulty voiding at low pressures, and incomplete bladder emptying. In the pediatric population, children with spinal dysraphism (e.g. myelomeningocele, sacral agenesis) comprise the majority of children with neurogenic bladders, although neurogenic bladder can be seen with spinal cord injury from trauma, surgery, tumor, and vascular accidents. Children with neurogenic bladder may have functional deficits such as difficulty ambulating, lower extremity pain, and abnormal voiding and stooling habits; in some cases, skin abnormalities, such as variable pigmentation or hair distribution over the lower spine, deep sacral dimples, or deviations in the gluteal cleft, may be seen. The exact functional abnormalities associated with neurogenic bladder vary by the nerves involved. Since abnormalities in lower tract function can be associated with an increased risk of damage to the upper tracts, children with neurogenic bladders must be followed carefully.

Urolithiasis
While renal and ureteral stones were once unusual in children, the cumulative incidence has increased in recent years. While kidney stones are generally not independently a risk factor for the development of urinary tract infections, stones traveling down the ureter can cause obstruction and prevent the antegrade flow of infected urine. Urea-splitting bacteria (e.g., Proteus spp) are associated with the development of struvite stones. Bladder stones may serve as a nidus for bacteria and should be considered in children who present with bacterial recurrence or persistence despite appropriate therapy. Bladder stones are most commonly seen in children with concentrated urine and in those who do not completely empty the bladder, such as children who perform intermittent catheterization and those with a bladder augmented with a mucus-producing bowel patch.

Although upper tract urolithiasis is not directly implicated in the development of urinary tract infections, there is considerable overlap in the risk factors (decreased fluid intake, increased dietary salt intake) for the two conditions. More recent research has suggested a possible role for abnormalities in the bowel flora

(microbiome) in children with urinary tract infections as well as those with urolithiasis.

<u>Ureteropelvic Junction Obstruction</u>
Ureteropelvic junction obstruction (UPJO) develops when the flow of urine from the renal pelvis to the ureter is blocked. Obstructions may be "intrinsic" (associated with a defect in the muscular or intimal layers of the ureter or a "high insertion" wherein the ureteropelvic junction is not dependent) or "extrinsic" (usually associated with vascular compression from a lower pole accessory renal artery). Prior to the widespread use of prenatal ultrasonography, UPJO were commonly diagnosed when patients presented with hematuria, UTI, intermittent flank pain, nausea, and vomiting, often after increased fluid intake or diuresis. Persistent pressure on the renal parenchyma from the dilated renal pelvis may be associated with an ipsilateral decrease in renal function. Renal function (estimated renal plasma flow) and drainage can be assessed using MAG-3 nuclear medicine renal scans. Symptomatic patients and those with demonstrated obstruction may be considered for surgical intervention with open or minimally invasive pyeloplasty.

<u>Eagle-Barrett (Prune Belly or Triad) Syndrome</u>
Eagle-Barrett syndrome consists of the triad of deficient or absent anterior abdominal wall musculature (giving the abdomen its characteristic wrinkled appearance), dilated and tortuous ureters, and intra-abdominal undescended testes typically located at the level of the iliac vessels. Even after abdominal wall and urinary tract reconstruction, children with this condition often have urinary stasis, and so instrumentation of the urinary tract should be limited to reduce the risk of introducing bacteria.

Functional
<u>Voiding Dysfunction and Constipation</u>
The relationship between bladder-bowel dysfunction and urinary tract infections is well documented in toilet-trained children. Changes in urodynamic and rectal manometric parameters have been described, including increased voiding pressures and increased post-void residual urine in the setting of increased rectal distension. Additionally, the stool serves as a reservoir of bacteria, and functional constipation is associated with lower urinary tract symptoms. Frequent (every 2-3 hours) voiding, management of constipation, and increased fluid intake may help to decrease lower urinary tract symptoms and UTIs in these children. Children with symptoms refractory to behavioral modification should be evaluated for pelvic floor dysfunction, and may benefit from biofeedback or physical therapy.

<u>Sexual Abuse</u>
Estimates of the prevalence of pediatric sexual abuse vary widely, with some series finding that nearly four in ten children have experienced sexual violence. The signs and symptoms of sexual abuse may be subtle, and physicians must maintain a high index of suspicion for abnormal physical examination findings (e.g. genital abrasions or lacerations), inappropriate demeanor (unexplained fear of the examiner), or

patient statements. Physicians must report suspected sexual abuse to Child Protective Services.

SUMMARY
1. UTIs are common in children and have substantial clinical and economic sequelae.
2. Children with bacterial UTIs may have structural abnormalities of the urinary tract, elimination disorders, or sexual abuse.
3. Risk factors for fungal UTIs include immunosuppression, broad spectrum antibiotics, and invasive vascular and urinary devices.
4. Bacterial pyelonephritis is associated with renal scarring and later renal insufficiency and hypertension.
5. The most common radiologic study for children with UTI is renal and bladder ultrasound. Some children may benefit from VCUG.
6. Antibiotic stewardship, including selection of the proper treatment spectrum and duration, is critical for both treatment and prophylactic antibiotic regimens.
7. Prompt treatment for presumed or proven UTI may decrease renal scarring and late sequelae.

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