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Pediatric Urinary Tract Infections

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The urinary tract is a common site of infection in the pediatric population. Unlike the generally benign course of urinary tract infection (UTI) in the adult population, UTI in the pediatric population is well recognized as a cause of acute morbidity and chronic medical conditions, such as hypertension and renal insufficiency in adulthood. As a result, it is crucial to have a clear understanding of the pathogenesis of UTI, risk factors, indications for diagnostic tests, and the appropriate uses of antimicrobial agents in the management of children with UTI.

Classification

A UTI is defined as colonization of a pathogen occurring anywhere along the urinary tract: kidney, ureter, bladder, and urethra. Traditionally, UTIs have been classified by the site of infection (ie, pyelonephritis [kidney], cystitis [bladder], urethra [urethritis]) and by severity (ie, complicated versus uncomplicated). A complicated UTI describes infections in urinary tracts with structural or functional abnormalities or the presence of foreign objects, such as an indwelling urethral catheter. This model does not necessarily reflect clinical management, however. In children, a simpler and more practical approach is to categorize UTI as a first infection versus recurrent infection. Recurrent infections can be further subdivided into (1) unresolved bacteriuria, (2) bacterial persistence, and (3) reinfection (Fig. 1).

The initial UTI documented by a proper urine culture is the first infection. Infections of the urinary tract generally resolve with adequate treatment in most

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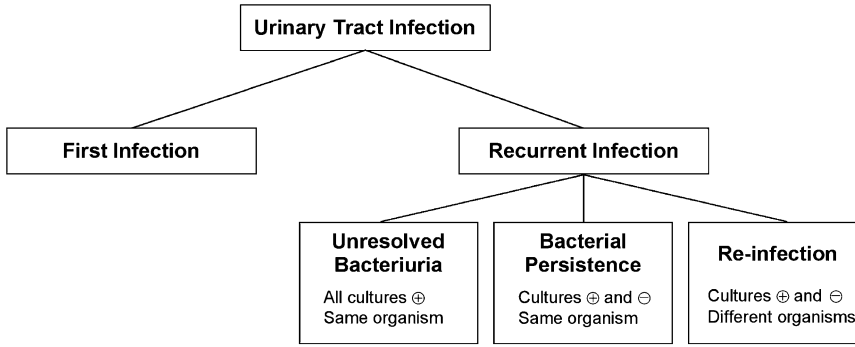

Fig. 1. Functional classification of UTIs.

children. In neonates and infants, however, they are presumed to be complicated because of the high association between urinary tract malformation and concurrent bacteremia, which predispose children to acute morbidity and long-term renal insufficiency [1,2].

The recurrence of a UTI may be caused by several reasons. Unresolved bacteriuria is most commonly caused by inadequate antimicrobial therapy. Subtherapeutic levels of the antimicrobial agents may be a result of noncompliance, malabsorption, suboptimal drug metabolism, and resistant uropathogens unresponsive to attempted therapy [3]. In these cases, infection typically resolves after altering the therapy according to antimicrobial sensitivities determined by a proper urine culture.

Bacterial persistence and reinfection occur after sterilization of the urine has been documented. In the case of bacterial persistence, the nidus of infection in the urinary tract is not eradicated. Characteristically, the same pathogen is documented on urine cultures during subsequent episodes of UTI despite negative cultures after treatment. The uropathogen frequently resides in a location that is shielded from antimicrobial therapy. These protected sites are often anatomic abnormalities, including infected urinary calculi [4], necrotic papillus [5], or foreign objects, such as an indwelling ureteral stent [6,7] or urethral catheters [8], which once infected may not be sterilized. Identification of the anatomic abnormality is essential because surgical intervention (extirpation) may be necessary to eradicate the source of infection (Box 1).

In contrast to bacterial persistence, reinfection is characterized by different pathogens documented on proper urine cultures with each new UTI. UTI most commonly occurs by periurethral colonization [9] and by the fecal-perineal-urethral route [10]. Rarely, a fistula between the urinary tract and gastrointestinal tract serves as the source of reinfection [11]. It is important to note that *Escherichia coli* occurs in many different serotypes, and documentation of what seems to be recurrent *E coli* UTI may, in fact, represent reinfection rather than bacterial persistence [12]. Serotyping (or careful examination of antimicrobial

Box 1. Surgically correctable causes of recurrent infection

Infection stones
Infected nonfunctional renal segments
Infected ureteral stumps after nephrectomy
Vesicointestinal or urethrorectal fistulae
Vesicovaginal fistulae
Infected necrotic papillae
Unilateral medullary sponge kidney
Infected urachal cyst
Infected urethral diverticulum or periurethral glands

Data from Shortliffe LD. Urinary tract infection in infants and children. In: Walsh P, Retik AB, Vaughn Ed, et al, editors. Campbell's urology. 8th edition. Philadelphia: WB Saunders; 2002. p. 1846–84.

sensitivity profile) ultimately can establish a diagnosis of reinfection in equivocal situations. As the pathogenesis of UTI has become better understood, it seems that some element of bacterial persistence is more common than previously thought [13]. Similar to bacterial persistence in abnormal conditions with reinfection such as fistulae, surgery may be necessary to correct the source of infection (Box 1).

Epidemiology

The true incidence of pediatric UTI is difficult to determine because there are varying presentations that range from an absence of specific urinary complaints to fulminant urosepsis. Data from the Urologic Disease in America project, however, suggest that pediatric UTI constitutes a significant health care burden on the American public. The study revealed that infections of the urinary tract affect 2.4% to 2.8% of children every year and account for more than 1.1 million office visits annually. Inpatient hospital costs for children with pyelonephritis total more than $180 million per year in the United States [14].

The epidemiology of pediatric UTI varies based on age and gender (Table 1). During the first year of life, boys have a higher incidence of UTI; in all other age groups, girls are more prone to developing UTI. During the first year of life, the incidence of UTI in girls is 0.7% compared with 2.7% in boys [15]. During the first 6 months, uncircumcised boys have a 10- to 12-fold increased risk for developing UTI [9,16]. In children aged 1 to 5 years, the annual incidence of UTI is 0.9% to 1.4% for girls and 0.1% to 0.2% for boys [17]. The incidence of a UTI is largely unchanged from age 6 to 16 years, with an annual incidence

Table 1
Incidence of pediatric urinary tract infection by age group and gender

Age (y)	Female (%)	Male (%)
<1	0.7	2.7
1–5	0.9–1.4	0.1–0.2
6–16	0.7–2.3	0.04–0.2
18–24	10.8	0.83

of 0.7% to 2.3% for girls and 0.04% to 0.2% for boys [18]. During early adulthood (18–24 years), the annual incidence of UTI in men remains relatively low at 0.83% [19]; however, it increases substantially in women to 10.8% [20].

Uropathogens

Although UTI may be caused by any pathogen that colonizes the urinary tract (eg, fungi, parasites, and viruses), most causative agents are bacteria of enteric origin (Box 2). The causative agent varies based on age and associated comorbidities. *E coli* is the most frequent documented uropathogen. Among neonates, UTI secondary to group B streptococci is more common than in older populations [21]. In immunocompromised children and children with indwelling catheters, *Candida* may be isolated from the urine [22]. Nosocomial infections are typically more difficult to treat and are caused by various organisms, including *E. coli*, *Candida*, *Enterococcus*, *Enterobacter*, and *Pseudomonas* [23].

Pathogenesis

Bacterial clonal studies strongly support entry into the urinary tract by the fecal-perineal-urethral route with subsequent retrograde ascent into the bladder [10]. Because of differences in anatomy, girls are at a higher risk of UTI than boys beyond the first year of life. In girls, the moist periurethral and vaginal areas promote the growth of uropathogens. The shorter urethral length increases the chance for ascending infection into the urinary tract. Once the uropathogen reaches the bladder, it may ascend to the ureters and then to the kidneys by some as-yet undefined mechanism. Additional pathways of infection include nosocomial infection through instrumentation, hematogenous seeding in the setting of systemic infection or a compromised immune system, and direct extension caused by the presence of fistulae from the bowel or vagina.

The urinary tract (ie, kidney, ureter, bladder, and urethra) is a closed, normally sterile space lined with mucosa composed of epithelium known as transitional cells. The main defense mechanism against UTI is constant antegrade flow of urine from the kidneys to the bladder with intermittent complete emptying of the bladder via the urethra. This washout effect of the urinary flow usually clears the

Box 2. Urinary pathogens

Gram-negative rods

E coli
Pseudomonas aeruginosa
Klebsiella spp
Citrobacter spp
Enterobacter cloacae
Morganella morganii
Proteus mirabilis
Providencia stuartii
Serratia spp

Gram-negative cocci

Neisseria gonorrhea

Gram-positive cocci

Enterococcus spp
Streptococcus group B
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus group D
Streptococcus faecalis

Other pathogens

Candida spp
Chlamydia trachomatis
Adenovirus

Data from Chon C, Lai F, Shortliffe LM. Pediatric urinary tract infections. Pediatr Clin N Am 2001;48(6):1443.

urinary tract of pathogens [24]. The urine itself also has specific antimicrobial characteristics, including low urine pH, polymorphonuclear cells, and Tamm-Horsfall glycoprotein, which inhibits bacterial adherence to the bladder mucosal wall [25].

UTI occurs when the introduction of pathogens into this space is associated with adherence to the mucosa of the urinary tract. If uropathogens are cleared

inadequately by the washout effect of voiding, then microbial colonization potentially develops. Colonization may be followed by microbial multiplication and an associated inflammatory response.

Bacteria that cause UTI in otherwise healthy hosts often exhibit distinctive properties—known as virulence factors—to overcome the normal defenses of the urinary system [26–28]. In serotypes of *E coli* frequently isolated in UTI, bacterial adherence to the uroepithelium is enhanced by adhesins, often fimbriae (pili), which bind to specific receptors of the uroepithelium [27–29]. The interaction of fimbriae with the mucosal receptor triggers internalization of the bacterium into the epithelial cell, which leads to apoptosis, hyperinfection, and invasion into surrounding epithelial cells or establishment of a bacterial focus for recurrent UTI [28,30]. Uropathogenic strains of *E coli* have been recognized to release toxins, including cytolethal distending toxin, alpha hemolysin, cytotoxic necrotizing factor-1, secreted autotransporter toxin that causes cellular lysis, cause cell cycle arrest, and promote changes in cellular morphology and function [31–33]. To promote survival, various uropathogens possess siderophore systems capable of acquiring iron, an essential bacterial micronutrient, from heme [34]. Uropathogenic strains of *E coli* have a defensive mechanism that consists of a glycosylated polysaccharide capsule that interferes with phagocytosis and complement-mediated destruction [35].

Risk factors

Although all individuals are susceptible to UTI, most remain infection free during childhood because of the aforementioned innate ability to resist uropathogen attachment. There are specific subpopulations with an increased susceptibility to UTI, however (Box 3).

Box 3. Risk factors for pediatric urinary tract infections

Neonate/infant
Gender
Foreskin
Fecal and perineal colonization
Urinary tract anomalies
Functional abnormalities
Immunocompromised states
Sexual activity

Data from Chon C, Lai F, Shortliffe LM. Pediatric urinary tract infections. Pediatr Clin N Am 2001;48(6):1445.

Neonates and infants

Neonates and infants in their first few months of life are at a higher risk for UTI. This susceptibility has been attributed to an incompletely developed immune system [36]. Breastfeeding has been proposed as a means of supplementing the immature neonatal immune system via the passage of maternal IgA to the child [37], providing the presence of lactoferrin [38], and providing the effect of anti-adhesive oligosaccharides [39]. Several recent studies have demonstrated the protective effect of breastfeeding against UTI in the first 7 months of life [37,40].

Uncircumcised infant boys

Since the 1980s, studies have shown an increased frequency of UTI in uncircumcised boys during the first year of life [9,41–43]. Boys with foreskin have been demonstrated to harbor significantly higher concentrations of uropathogenic microbes that potentially may ascend into the urinary tract and lead to UTI [9,16]. Bacteriuria is 10- to 12-fold more common during the first 6 months of life for uncircumcised boys [9,16]. Although the available data associate a medical benefit and economic benefit [9] to neonatal circumcision, previously conducted clinical studies have been criticized for potential selection and sampling bias [44]. As a result, the American Academy of Pediatrics (AAP) Task Force on Circumcision reports that the existing scientific evidence does not support a recommendation for routine neonatal circumcision at this time [45].

Fecal and perineal colonization

Because most UTIs result from fecal-perineal-urethral retrograde ascent of uropathogens, fecal and perineal flora are important factors in the development of a UTI [10]. The flora of the colon and urogenital region is a result of native host immunity, existing microbial ecology, and the presence of microbe-altering drugs and foods. A recent investigation by Schlager and colleagues [12] supported the theory that a subset of the colonic microflora expressing particular virulence factors is most likely to infect the urinary tract. The selection for microbes resistant to antimicrobial agents is well recognized. As a result, the inappropriate use of antibiotics in the treatment of active nonurinary infections and in the prophylactic setting may place children at a higher risk for developing uropathogenic strains of microbe that may develop into symptomatic UTI [46,47].

Anatomic abnormalities

Anatomic abnormalities of the urinary tract predispose children to UTI because of inadequate clearance of uropathogens. Infections associated with urinary tract malformation generally appear in children younger than 5 years of age. It is essential to identify these abnormalities early because if uncorrected,

they may serve as a reservoir for bacterial persistence and result in recurrent UTI. Surgical intervention may be required to correct the anatomic abnormality (see Box 1). In contrast, congenital anatomic anomalies, such as posterior urethral valves and vesicoureteral reflux (VUR), do not predispose children to colonization but perhaps increase the likelihood of inadequate washout in the routine ways. These urinary tract malformations increase the likelihood that infections of the lower urinary tract (ie, bladder and urethra) will ascend to the upper tracts with possible pyelonephritis and potential renal deterioration [48]. Importantly, children with known urinary malformation may be on chronic antimicrobial prophylaxis. Consequently, this patient population is associated with a higher incidence of multidrug-resistant uropathogens [49] and non–*E coli* uropathogens, particularly *Pseudomonas* [50] and *Enterococcus* [51].

Functional abnormalities

Children with a functional abnormality of the urinary tract are also at a higher risk of developing a UTI. Inability to empty the bladder, as in the case of neurogenic bladders, frequently results in urinary retention, urinary stasis, and suboptimal clearance of bacteria from the urinary tract. Clean intermittent catheterization is helpful for emptying the neurogenic bladder, but catheterization itself may introduce bacteria to this normally sterile space. Chronically elevated bladder pressure secondary to poor emptying also may cause secondary VUR, in which the elevated pressure increases the potential renal damage of pyelonephritis.

Sexual activity

Sexual activity has been recognized as a risk factor for the development of UTI in young women [52–54]. A similar risk has not been demonstrated in men. Hooton and colleagues [55] reported a high association between UTI and recent sexual intercourse and the use of a diaphragm with spermicide. Virtually all women become bacteriuric after sexual intercourse [56]. Uropathogenic strains of *E coli* also are more likely to be shared during sexual intercourse than commensal *E coli* [57]. Although the exact relationship between sexual activity and UTI in young woman is currently unclear, the proposed mechanism is direct transfer of bacterial from the bowel or vagina to the urethral meatus during sexual intercourse [58]. Urogenital colonization and selection for uropathogenic microbes secondary to the use of spermicides are also suspected risk factors for UTI and currently are undergoing investigation [52]. Some researchers have suggested that adolescent UTI be seen as a marker of sexual activity [54].

Clinical presentation

Children who have UTI often do not necessarily present with the characteristic signs and symptoms seen in the adult population. The physical examination is

also frequently of limited value because costovertebral angle and suprapubic tenderness are not reliable signs in the pediatric population. There are various clinical presentations for children with UTI based on age. Infants younger than 60 to 90 days may have vague and nonspecific symptoms of illness that are difficult to interpret, such as failure to thrive, diarrhea, irritability, lethargy, malodorous urine, fever, asymptomatic jaundice, and oliguria or polyuria [59–61]. In fact, it has been recommended that testing for UTI be part of the evaluation of asymptomatic jaundice in infants younger than 8 weeks [61].

In older children younger than 2 years, the most common symptoms include fever, vomiting, anorexia, and failure to thrive [60]. Abdominal pain and fever were the most common presenting symptoms in children between 2 and 5 years of age [62]. After 5 years, the classic lower urinary tract symptoms, including dysuria, urgency, urinary frequency, and costovertebral angle tenderness, are more common [62].

Regardless of age, all children should have their sacral region examined for dimples, pits, or a sacral fat pad, because the presence of these signs is associated with neurogenic bladder. In all boys, a scrotal examination should be performed to evaluate for epididymitis or epididymo-orchitis. The signs and symptoms compatible with gastrointestinal and respiratory infections are often present in children with UTI [63]. As a result, UTI must be considered in all children with serious illness even if there is strong evidence of infection outside the urinary system.

Diagnosis

The definitive diagnosis of a UTI requires the isolation of at least one uropathogen from a urine culture [64,65]. Urine, which should be obtained before the initiation of antimicrobial therapy, can be collected by various methods. The simplest and least traumatic method is via a bagged specimen, which involves attaching a plastic bag to the perineum. Clinicians, however, are discouraged from obtaining a urine specimen in this fashion because there is an unacceptably high false-positive rate of 85% or higher [60]. The bagged specimen is useful in ruling out a UTI, but it has little use in accurately documenting a UTI. Older children can provide a clean-catch midstream urine specimen. Unfortunately, this type of specimen is often contaminated with periurethral and preputial organisms, which make a positive urine culture difficult to interpret; in children most susceptible to UTI, the periurethral colonization is the highest.

The most commonly used technique in young children is urethral catheterization. The catheterized specimen is considered reliable provided that the initial portion of urine that may be contaminated by periurethral organisms is discarded. The disadvantage of urethral catheterization is that it is invasive and periurethral organisms may be introduced into an otherwise sterile urinary tract. Suprapubic aspiration is considered the gold standard for accurately identifying bacteria within the bladder. Although the probability of a true infection with a positive

culture obtained via suprapubic aspiration is approximately 99%, this method is the most technically challenging and is associated with the lowest rate of success (23%–99%) [60]. The AAP recommends suprapubic aspiration or urethral catheterization to establish a diagnosis of UTI in neonates and young children [60]. A clean-catch specimen may be obtained from older children and young adults.

According the AAP, a diagnosis of UTI is established when a quantitative culture of urine obtained via catheterization or suprapubic aspiration demonstrates 105 cfu (colony-forming units)/mL of a single uropathogen [60]. It is unclear what result on urine culture truly defines a significant UTI. The technique by which the urine specimen is obtained alters the criterion value for establishing a UTI. The presence of bacteria in the urine may not necessarily demonstrate a UTI but rather might simply represent benign bacteriuria. The culture information should be interpreted in the context of the clinical scenario when determining the appropriate therapy.

Because urine culture typically requires at least 24 hours of incubation, urinalysis and urine microscopy are often used to guide initial empiric therapy. Under high-power magnification, the presence of bacteria represents approximately 3×10^4 bacteria/mL [48]. Urine microscopy, however, cannot distinguish a uropathogen from contaminating bacteria. Hoberman and Wald [66] reported that the positive predictive value of pyuria (10 white blood cells/mm^3) and bacteriuria is as high as 84.6%. Because of the low sensitivity, negative urine microscopy does not rule out UTI.

Although not as sensitive as urine microscopy, chemical screening for markers of infection in urinalysis can be used to provide additional evidence for a UTI. Certain bacteria, particularly gram-negative bacteria, reduce nitrates to nitrites. This test may produce false-negative results if it does not contain the first voided specimen, the bacteria are gram-positive organisms, or there has not been enough time for bacterial metabolism to produce nitrites. Leukocyte esterase is produced by activated leukocytes. This chemical, however, depends on white blood cells, which may not always be present during a UTI. The presence of nitrites and leukocyte esterase serves as indirect evidence of a UTI, although it is not a replacement for urine culture. Although urinalysis can help in directing therapy, clinicians are cautioned against establishing or ruling out a diagnosis of UTI without urine culture.

If the clinical picture and urinalysis are equivocal, additional tests, such as a complete blood count, erythrocyte sedimentation rate, and C-reactive protein, may help to determine the presence of a UTI and whether presumptive treatment should be initiated. Other laboratory tests, such as a basic metabolic panel, may be obtained to assess a child's overall health.

Diagnostic imaging studies

In the acute setting of a UTI, diagnostic imaging tests are generally not indicated unless the diagnosis of UTI is equivocal. Recently, Hoberman and

colleagues [67] demonstrated that a renal bladder ultrasound and renal scan obtained within 72 hours of the febrile UTI in young children is of limited value. The authors argued that the use of ultrasound to identify a urinary tract malformation is minimal given the prevalence of prenatal ultrasonography in the United States. If, however, the signs and symptoms of UTI continue to persist after 2 days despite appropriate antimicrobial therapy, then either ultrasound or CT scanning can be used to rule out disease states that may require invasive therapy, including a renal abscess, pyonephrosis, urinary calculi, or surgically correctable anatomic abnormalities [60,68].

Imaging studies generally can be pursued after the resolution of the acute infection because immediate management typically is based on clinical signs and symptoms. Infants and young children who have responded appropriately to antimicrobial therapy after their initial febrile UTI should be evaluated at the earliest convenient time with a renal bladder ultrasound and reflux studies, including voiding cystourethrography, to rule out urinary tract anomalies [60]. Evaluation of renal scarring may be conducted with ^{99m}Tc-labeled dimercaptosuccinic acid scintigraphy scan [69]. Alternatively, there is growing evidence that MRI is a rapid and accurate study for renal scarring that does not use ionizing radiation [70,71].

In children with an initial diagnosis of UTI, investigators revealed sonographic abnormalities in 12% of the study population [67]. VUR is diagnosed in approximately 50% of children with UTI who are younger than 1 year [60]. Although all children with UTI may develop pyelonephritis, children with reflux are at an increased risk for upper tract infection and renal scarring. The risk of renal damage increases with the severity of VUR [72,73]. Children with high-grade VUR have a four- to sixfold greater risk of renal scarring compared with children with low-grade VUR and an eight- to tenfold greater risk than children without evidence of VUR [60].

Management

Because treatment for a suspected UTI generally starts when the causative agent is identified, empiric treatment of UTI is based on the clinical status of the child, the predominant uropathogens for the patient's age group coupled with the antimicrobial sensitivities in the community, and patient compliance and ability for follow-up.

A generally healthy young child with a presumed uncomplicated UTI who is nontoxic, is taking in fluids, has reliable caretakers, and is able to follow-up on a daily basis may be managed as an outpatient with oral antibiotics [48]. Antimicrobial therapy should be initiated promptly after a proper urine culture is obtained. In these patients, a broad-spectrum antibiotic is recommended for empiric coverage (Table 2). First-line agents include amoxicillin, trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin, and cephalosporins (eg, cefixime) [74,75]. In young children older than 2 years, a short course (ie, 3–5 days) is

Table 2
Oral antimicrobial drugs for pediatric urinary tract infection

Drug	Daily dosage (mg/kg/d)	Frequency
Penicillin		
Ampicillin	50–100	q 6 h
Amoxicillin	20–40	q 8 h
Augmentin	20–40	q 8 h
Sulfonamide		
Trimethoprim-sulfamethoxazole	8[a]	q 6 h
Cephalosporin		
Cephalexin	25–50	q 6 h
Cefaclor	20	q 8 h
Cefixime	8	q 12–24 h
Cefadroxil	30[a]	q 12–24 h
Fluoroquinolone		
Ciprofloxacin	20–40[a]	q 12 h
Nalidixic acid	55 mg/kg/day	q 6 h
Other		
Nitrofurantoin	5–7	q 6 h

[a] Dose adjustment required with azotemia.

adequate because longer courses of oral antibiotics have not been shown to be more efficacious [76]. *E coli* is the causative uropathogen in most cases of UTI in infants and young children without underlying urinary tract abnormalities. Over the past 20 years, however, there has been increasing resistance to ampicillin, augmentin, and TMP-SMX among *E coli* associated with UTI [77–79]. It is important to consider the prevailing antimicrobial resistance patterns when selecting a drug for treatment of a presumed UTI.

In contrast, an acutely ill child, immunocompromised patient, or infant younger than 2 months of age is assumed to have acute pyelonephritis or a complicated UTI. These patients should be managed with hospital admission, rehydration, and parenteral broad-spectrum antimicrobial therapy immediately after urine culture is obtained (Table 3). Of note, infants younger than 60 to 90 days are more likely to have their course of disease change rapidly because of their physiology and incompletely developed immune system [36,80]. A sepsis evaluation that includes a suprapubic aspirate and blood cultures should be initiated upon evaluation. Any patient with questionable compliance or difficulty with follow-up should be considered for inpatient management. In general, the combination of ampicillin or cephalosporin (eg, cefazolin) plus an aminoglycoside (eg, gentamicin) is adequate coverage for most uropathogens. Because of changing resistance patterns of uropathogens and a concern for nephrotoxicity, a single third-generation cephalosporin (eg, ceftriaxone or ceftazidime) is increasingly being used as an alternative initial regimen [50]. The antimicrobial armamentarium continues to grow as several recent studies have demonstrated the efficacy of fourth-generation cephalosporins (eg, cefepime) in the parenteral treatment of pediatric UTI [81,82].

Table 3
Parenteral antimicrobial drugs for pediatric urinary tract infection

Drug	Daily dosage (mg/kg/d)	Frequency
Aminoglycoside		
Gentamicin	7.5[a]	q 8 h
Tobramycin	7.5[a]	q 8 h
Penicillin		
Ampicillin	50–100	q 6 h
Ticarcillin	50–200	q 4–8 h
Cephalosporin		
Cefazolin	25–50[a]	q 6–8 h
Cefotaxime	50–180[a]	q 4–6 h
Ceftriaxone	50–75	q 12–24 h
Cetriazidime	90–150[a]	q 8–12 h
Cefepime	100	q 12 h
Fluoroquinolone		
Ciprofloxacin	18–30[a]	q 8 h

[a] Dose adjustment required with azotemia.

The promptness of therapy for suspected acute pyelonephritis is of paramount importance, because a delay in therapy has been associated with more severe infections and worse renal damage [75,83]. Parenteral treatment is maintained until a patient is clinically stable and afebrile, generally 48 to 72 hours. At that point, the antimicrobial regimen may be changed to an oral agent based on the sensitivities of the urine culture. For children aged 2 months to 2 years, the guidelines established by the AAP suggest completion of a 7- to 14-day course [60]. For older children, the optimal total duration of treatment remains debatable. Numerous published studies, however, have shown resolution of symptoms and eradication of the causative agent with a 7- to 14-day course of antibiotics [53,75,84].

Alternative options for ambulatory management include outpatient parenteral therapy for patients with clinical presentations consistent with acute pyelonephritis. Several studies have demonstrated that once-daily parenteral administration of gentamicin or ceftriaxone in a day treatment center is safe, effective, and cost-effective in children with UTI [84–86]. Once the uropathogen is isolated in the urine culture and the antimicrobial sensitivities are finalized, children can be switched to an oral agent to complete a 10-day treatment course. A 14-day course of oral cefixime has been shown to be an efficacious and cost-effective therapeutic option in children with UTI who can tolerate fluids [75]. Intravenous and oral formulations of fluoroquinolones have been shown to have excellent coverage of gram-negative and -positive organisms in the urinary tract [87]. Although fluoroquinolones are widely used in the management of adult UTI, the use of these drugs historically has been discouraged in children because of the concern for drug-induced arthrotoxicity shown in animal models [88]. The available scientific data, however, fail to demonstrate an unequivocal association with arthropathy in the pediatric population [89,90]. Fluoroquinolones, such as ciprofloxacin, may be considered in the management of pediatric UTI.

Management of fungal urinary tract infections

Although fungus in the urinary tract is rare among healthy children, the incidence of fungal UTI is increased in hospitalized patients. In large tertiary care neonatal intensive care units, Bryant and colleagues [91] found the overall incidence of candiduria to be 0.5%, whereas Phillips and Karlowicz [22] reported *Candida* sp in 42% of patients with UTI. Risk factors for the development of funguria include long-term antibiotic treatment, use of urinary drainage catheters, parenteral nutrition, and immunosuppression [92]. The overwhelming majority of fungal UTIs are caused by *Candida* sp followed by *Aspergillos* spp, *Cryptococcus* spp, and *Coccidioides* spp [93]. The clinical presentation of patients with funguria ranges from an absence of symptoms to fulminant sepsis. The urinary tract is most frequently the primary entry point but also may represent the site of disseminated infection. Consequently, the challenge for clinicians is to determine whether the presence of fungus in the urinary tract represents infection, colonization, or contaminant.

Similar to bacterial infections, a fungal UTI is ideally diagnosed with suprapubic aspiration or transurethral bladder catheterization. Urine cultures with more than 10^4 colonies/mL have been used as the criterion for therapy [94]. The presence of a positive urine culture result mandates an evaluation of the upper urinary tract with renal ultrasonography for additional foci of funguria. Renal fungal balls have been identified in 35% of patients with candidal UTI in the pediatric population [22,91].

Therapeutic options for fungal UTI currently remain a matter of controversy. Investigations conducted in adult populations have shown that treatment of asymptomatic bladder infections results in poor long-term eradication rates and essentially no clinical benefit [95,96]. The removal of indwelling catheters has not been shown to clear infections reliably [48]. Symptomatic patients can be treated with bladder irrigations of amphotericin B or oral fluconazole. Although there is no consensus on optimal treatment dose or duration, amphotericin bladder irrigations consist of daily irrigations of 50 mg/L for 7 days [97] or continuous irrigations (42 mL/h) for 72 hours [98].

Fungal bezoars in the collecting system may cause obstruction in children. Patients with these upper tract foci of funguria should be treated with systemic therapy that consists of amphotericin B or fluconazole. In cases of obstruction, percutaneous nephrostomy is then used for drainage and potential local irrigation. Surgical removal may be necessary should the fungal balls persist [48].

Antimicrobial prophylaxis

Because renal damage and scarring have been shown to occur only in the presence of infection, the goal of antimicrobial prophylaxis is to sterilize the urine [99]. The ideal prophylactic antimicrobial agent should be administered orally and achieve a therapeutic drug level in the urine while concomitantly maintaining low fecal concentrations (Table 4). By avoiding high drug concentrations

Table 4
Prophylactic antibiotics

Drug	Daily dosage (mg/kg/d)	Age limitation
Cephalexin	2–3	None
Nitrofurantoin	1–2	>1 mo
Trimethoprim-sulfamethoxazole	1–2[a]	>2 mo

[a] Dose adjustment required for azotemia.

in the bowels, the development of resistant bacterial strains can be prevented or limited in the fecal flora. Similar to the selection of an antibiotic for treatment, the agent chosen for prophylaxis should be based on local antimicrobial resistance patterns.

After the treatment course for a first infection, infants or neonates should be placed on a different antimicrobial agent for prophylaxis until a thorough evaluation for an anatomic urinary tract abnormality is completed [74]. Prophylaxis should be considered in patients with a history of VUR [100], immunosuppression, or partial urinary obstruction [48] to decrease the potential for developing UTI. Once prophylactic antibiotics are initiated, they generally are continued until the underlying predisposition to UTI is resolved.

Prophylactic antibiotics also may be considered for children with recurrent UTI with normal urinary function and anatomy [101]. In patients with a history of two UTIs in 6 months or three UTIs in 12 months, prophylactic antibiotics have been shown to be more effective than placebo in decreasing the number of recurrences [102–105]. Various antibiotics have been used for prophylaxis in these children, including nitrofurantoin, TMP-SMX, cephalosporins, and fluoroquinolones; however, no single antibiotic has been shown to be superior [106,107].

Asymptomatic bacteriuria

Bacteria may be present in the urinary tract without any associated symptoms. This situation may exist without any anatomic abnormalities [108,109]. For a 6-year period, Wettergren and colleagues [109] followed 37 infants who were found to have no symptoms associated with urine culture–proven bacteriuria. These children were untreated. Ultimately, there was one episode of pyelonephritis and no evidence of decreased renal function at the end of the study. Similarly, Schlager and colleagues [110] reported on asymptomatic bacteriuria in children undergoing clean intermittent catheterization. These investigators concluded that asymptomatic bacteriuria is not associated with renal damage and the incidence of actual symptoms is low. If a child is found to have asymptomatic bacteriuria without an associated urinary malformation, then clinicians are recommended to follow-up with patients periodically without concurrent antimicrobial therapy.

Complications

The interaction of the host, uropathogen, and environment is incompletely understood not only in the development of infections of the urinary tract but also the progression of pediatric UTI. As a result, it is difficult to determine whether an episode of cystitis will resolve without incident or result in more serious infection involving the kidney. A pediatric urology referral should be considered in children suspected of having serious sequelae of pyelonephritis, including renal abscess formation, pyonephrosis, emphysematous pyelonephritis or cystitis, and xanthogranulomatous pyelonephritis [74,111]. Prompt recognition and treatment of upper tract infection are crucial to preventing potential irreversible renal damage.

Long-term consequences of pediatric urinary tract infection

Children with upper UTI (ie, pyelonephritis) are at risk for irreversible renal parenchymal damage evidenced by renal scarring. Renal scarring is noted in 10% to 30% of children after UTI [112,113]. The most widely used method of detecting renal scarring is ^{99}Tc-labeled dimercaptosuccinic acid scintigraphy scan [69]. Although the exact mechanisms responsible for renal scarring secondary to UTI are currently unclear [114], risk factors include underlying VUR or obstructive urinary tract abnormalities and recurrent UTI and a delay in treatment of UTI. A recent study by Orellana and colleagues [115] found a significantly higher incidence of renal damage in children with non–*E coli* UTI. Smellie and colleagues [1] found renal scarring more commonly in infants and young children and less frequently in older children and young adults, which suggests that younger kidneys are more susceptible to damage.

Long-term studies have established the causal relationship between renal damage after pediatric UTI and the subsequent development of hypertension [1,116,117]. The incidence of hypertension in adulthood after urinary infection ranges from 7% to 17% [1,116,118]. The pathogenesis, however, remains unclear, although the renin-angiotensin system and atrial natriuretic peptide have been proposed as mechanisms. To date, no direct relationship among severity of hypertension, degree of renal scarring, and glomerular filtration rate have been established.

Although the incidence of end-stage renal disease associated with pediatric UTI is uncommon [119,120], it remains a recognized cause of dialysis and renal transplantation in certain parts of the world [121,122]. Wennerstrom and colleagues [120] showed that glomerular filtration rate was significantly reduced in scarred kidneys during a 20-year follow-up period. In another study by Jacobson and colleagues [116], 30 children with nonobstructive focal renal scarring were followed for 27 years. Ultimately, 3 patients with bilaterally scarred kidneys developed end-stage renal disease. These longitudinal studies emphasize the need for long-term follow-up in patients with pediatric UTI and renal scarring.

Summary

Infections of the urinary tract are among the most common infections in the pediatric population. If not treated promptly and appropriately, pediatric UTI may lead to significant acute morbidity and irreversible renal damage. Children, however, have a wide variety of clinical presentation, ranging from the asymptomatic presence of bacteria in the urine to potentially life-threatening infection of the kidney. A clinician's main goals are early diagnosis, appropriate antimicrobial therapy, identification of anatomic anomalies, and preservation of renal function. Treatment should be based on urine culture. Children noted to have renal scarring after an acute episode of UTI should be followed long-term for signs of hypertension and renal insufficiency.

References

[1] Smellie JM, Prescod NP, Shaw PJ, et al. Childhood reflux and urinary infection: a follow-up of 10–41 years in 226 adults. Pediatr Nephrol 1998;12(9):727–36.
[2] Benador D, Benador N, Slosman D, et al. Are younger children at highest risk of renal sequelae after pyelonephritis? Lancet 1997;349(9044):17–9.
[3] Pewitt EB, Schaeffer AJ. Urinary tract infection in urology, including acute and chronic prostatitis. Infect Dis Clin North Am 1997;11(3):623–46.
[4] Abrahams HM, Stoller ML. Infection and urinary stones. Curr Opin Urol 2003;13(1):63–7.
[5] Conrad S, Busch R, Huland H. Complicated urinary tract infections. Eur Urol 1991;19(Suppl 1): 16–22.
[6] Richter S, Ringel A, Shalev M, et al. The indwelling ureteric stent: a friendly procedure with unfriendly high morbidity. BJU Int 2000;85(4):408–11.
[7] Kehinde EO, Rotimi VO, Al-Hunayan A, et al. Bacteriology of urinary tract infection associated with indwelling J ureteral stents. J Endourol 2004;18(9):891–6.
[8] Schlager TA, Clark M, Anderson S. Effect of a single-use sterile catheter for each void on the frequency of bacteriuria in children with neurogenic bladder on intermittent catheterization for bladder emptying. Pediatrics 2001;108(4):71–4.
[9] Schoen EJ, Colby CJ, Ray GT. Newborn circumcision decreases incidence and costs of urinary tract infections during the first year of life. Pediatrics 2000;105(4 Pt 1):789–93.
[10] Yamamoto S, Tsukamoto T, Terai A, et al. Genetic evidence supporting the fecal-perineal-urethral hypothesis in cystitis caused by Escherichia coli. J Urol 1997;157(3):1127–9.
[11] Kiyan G, Dagli TE, Iskit SH, et al. Epididymitis in infants with anorectal malformation. Eur Urol 2003;43(5):576–9.
[12] Schlager TA, Hendley JO, Bell AL, et al. Clonal diversity of Escherichia coli colonizing stools and urinary tracts of young girls. Infect Immun 2002;70(3):1225–9.
[13] Anderson GG, Palermo JJ, Schilling JD, et al. Intracellular bacterial biofilm-like pods in urinary tract infections. Science 2003;301(5629):105–7.
[14] Freedman AL. Urologic diseases in North America Project: trends in resource utilization for urinary tract infections in children. J Urol 2005;173(3):949–54.
[15] Wettergren B, Jodal U, Jonasson G. Epidemiology of bacteriuria during the first year of life. Acta Paediatr Scand 1985;74(6):925–33.
[16] Wiswell TE. The prepuce, urinary tract infections, and the consequences. Pediatrics 2000; 105(4 Pt 1):860–2.
[17] Marild S, Jodal U. Incidence rate of first-time symptomatic urinary tract infection in children under 6 years of age. Acta Paediatr 1998;87(5):549–52.

[18] Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Dis Mon 2003;49(2):53–70.
[19] Griebling TL. Urologic diseases in America project: trends in resource use for urinary tract infections in men. J Urol 2005;173(4):1288–94.
[20] Foxman B, Barlow R, D'Arcy H, et al. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol 2000;10(8):509–15.
[21] Wu CS, Wang SM, Ko WC, et al. Group B streptococcal infections in children in a tertiary care hospital in southern Taiwan. J Microbiol Immunol Infect 2004;37(3):169–75.
[22] Phillips JR, Karlowicz MG. Prevalence of Candida species in hospital-acquired urinary tract infections in a neonatal intensive care unit. Pediatr Infect Dis J 1997;16(2):190–4.
[23] Langley JM, Hanakowski M, Leblanc JC. Unique epidemiology of nosocomial urinary tract infection in children. Am J Infect Control 2001;29(2):94–8.
[24] Cox CE, Hinman Jr F. Experiments with induced bacteriuria, vesical emptying and bacterial growth on the mechanism of bladder defense to infection. J Urol 1961;86:739–48.
[25] Sobel JD. Pathogenesis of urinary tract infection: role of host defenses. Infect Dis Clin North Am 1997;11(3):531–49.
[26] Johnson JR. Microbial virulence determinants and the pathogenesis of urinary tract infection. Infect Dis Clin North Am 2003;17(2):261–78.
[27] Sussman M, Gally DL. The biology of cystitis: host and bacterial factors. Annu Rev Med 1999;50:149–58.
[28] Bower JM, Eto DS, Mulvey MA. Covert operations of uropathogenic Escherichia coli within the urinary tract. Traffic 2005;6(1):18–31.
[29] Wullt B, Bergsten G, Connell H, et al. P fimbriae enhance the early establishment of Escherichia coli in the human urinary tract. Mol Microbiol 2000;38(3):456–64.
[30] Mulvey MA, Schilling JD, Martinez JJ, et al. Bad bugs and beleaguered bladders: interplay between uropathogenic Escherichia coli and innate host defenses. Proc Natl Acad Sci U S A 2000;97(16):8829–35.
[31] Uhlen P, Laestadius A, Jahnukainen T, et al. Alpha-haemolysin of uropathogenic E. coli induces Ca2 + oscillations in renal epithelial cells. Nature 2000;405(6787):694–7.
[32] Guyer DM, Radulovic S, Jones FE, et al. Sat, the secreted autotransporter toxin of uropathogenic Escherichia coli, is a vacuolating cytotoxin for bladder and kidney epithelial cells. Infect Immun 2002;70(8):4539–46.
[33] Toth I, Herault F, Beutin L, et al. Production of cytolethal distending toxins by pathogenic Escherichia coli strains isolated from human and animal sources: establishment of the existence of a new cdt variant (Type IV). J Clin Microbiol 2003;41(9):4285–91.
[34] Russo TA, Carlino UB, Johnson JR. Identification of a new iron-regulated virulence gene, ireA, in an extraintestinal pathogenic isolate of Escherichia coli. Infect Immun 2001;69(10): 6209–16.
[35] Russo T, Brown JJ, Jodush ST, et al. The O4 specific antigen moiety of lipopolysaccharide but not the K54 group 2 capsule is important for urovirulence of an extraintestinal isolate of Escherichia coli. Infect Immun 1996;64(6):2343–8.
[36] Hanson LA. Escherichia coli infections in childhood: significance of bacterial virulence and immune defence. Arch Dis Child 1976;51(10):737–42.
[37] Marild S, Hansson S, Jodal U, et al. Protective effect of breastfeeding against urinary tract infection. Acta Paediatr 2004;93(2):164–8.
[38] Haversen L, Ohlsson BG, Hahn-Zoric M, et al. Lactoferrin down-regulates the LPS-induced cytokine production in monocytic cells via NF-kappa B. Cell Immunol 2002;220(2):83–95.
[39] Coppa GV, Gabrielli O, Giorgi P, et al. Preliminary study of breastfeeding and bacterial adhesion to uroepithelial cells. Lancet 1990;335(8689):569–71.
[40] Hanson LA, Korotkova M, Haversen L, et al. Breast-feeding, a complex support system for the offspring. Pediatr Int 2002;44(4):347–52.
[41] Wiswell TE, Smith FR, Bass JW. Decreased incidence of urinary tract infections in circumcised male infants. Pediatrics 1985;75(5):901–3.

[42] Wiswell TE, Enzenauer RW, Holton ME, et al. Declining frequency of circumcision: implications for changes in the absolute incidence and male to female sex ratio of urinary tract infections in early infancy. Pediatrics 1987;79(3):338–42.
[43] Herzog LW. Urinary tract infections and circumcision: a case-control study. Am J Dis Child 1989;143(3):348–50.
[44] Van Howe RS. Effect of confounding in the association between circumcision status and urinary tract infection. J Infect 2005;51(1):59–68.
[45] American Academy of Pediatrics Task Force on Circumcision. Circumcision policy statement. Pediatrics 1999;103(3):686–93.
[46] Hansson S, Jodal U, Lincoln K, et al. Untreated asymptomatic bacteriuria in girls: II. Effect of phenoxymethylpenicillin and erythromycin given for intercurrent infections. BMJ 1989; 298(6677):856–9.
[47] Smith HS, Hughes JP, Hooton TM, et al. Antecedent antimicrobial use increases the risk of uncomplicated cystitis in young women. Clin Infect Dis 1997;25(1):63–8.
[48] Shortliffe LM. Urinary tract infection in infants and children. In: Walsh P, Retik AB, Vaughn ED, et al, editors. Campbell's urology. 8th edition. Philadelphia: WB Saunders; 2002. p. 1846–84.
[49] Ladhani S, Gransden W. Increasing antibiotic resistance among urinary tract isolates. Arch Dis Child 2003;88(5):444–5.
[50] Ashkenazi S, Even-Tov S, Samra Z, et al. Uropathogens of various childhood populations and their antibiotic susceptibility. Pediatr Infect Dis J 1991;10(10):742–6.
[51] Bitsori M, Maraki S, Raissaki M, et al. Community-acquired enterococcal urinary tract infections. Pediatr Nephrol 2005;20(11):1583–6.
[52] Finer G, Landau D. Pathogenesis of urinary tract infections with normal female anatomy. Lancet Infect Dis 2004;4(10):631–5.
[53] Weir M, Brien J. Adolescent urinary tract infections. Adolesc Med 2000;11(2):293–313.
[54] Nguyen H, Weir M. Urinary tract infection as a possible marker for teenage sex. South Med J 2002;95(8):867–9.
[55] Hooton TM, Scholes D, Hughes JP, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med 1996;335(7):468–74.
[56] Buckley Jr RM, McGuckin M, MacGregor RR. Urine bacterial counts after sexual intercourse. N Engl J Med 1978;298(6):321–4.
[57] Foxman B, Manning SD, Tallman P, et al. Uropathogenic Escherichia coli are more likely than commensal E. coli to be shared between heterosexual sex partners. Am J Epidemiol 2002;156(12):1133–40.
[58] Zhang L, Foxman B. Molecular epidemiology of Escherichia coli mediated urinary tract infections. Front Biosci 2003;8:e235–44.
[59] Honkinen O, Jahnukainen T, Mertsola J, et al. Bacteremic urinary tract infection in children. Pediatr Infect Dis J 2000;19(7):630–4.
[60] American Academy of Pediatrics Committee on Quality Improvement, Subcommittee on Urinary Tract Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Pediatrics 1999;103(4 Pt 1): 843–52.
[61] Garcia FJ, Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. Pediatrics 2002;109(5):846–51.
[62] Smellie JM, Hodson CJ, Edwards D, et al. Clinical and radiological features of urinary infection in childhood. BMJ 1964;5419:1222–6.
[63] Bauchner H, Philipp B, Dashefsky B, et al. Prevalence of bacteriuria in febrile children. Pediatr Infect Dis J 1987;6(3):239–42.
[64] Hellerstein S. Recurrent urinary tract infections in children. Pediatr Infect Dis 1982;1(4): 271–81.
[65] Cheng YW, Wong SN. Diagnosing symptomatic urinary tract infections in infants by catheter urine culture. J Paediatr Child Health 2005;41(8):437–40.
[66] Hoberman A, Wald ER. Urinary tract infections in young febrile children. Pediatr Infect Dis J 1997;16(1):11–7.

[67] Hoberman A, Charron M, Hickey RW, et al. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med 2003;348(3):195–202.
[68] Dacher JN, Hitzel A, Avni FE, et al. Imaging strategies in pediatric urinary tract infection. Eur Radiol 2005;15(7):1283–8.
[69] Paterson A. Urinary tract infection: an update on imaging strategies. Eur Radiol 2004; 14(Suppl 4):L89–100.
[70] Kavanagh EC, Ryan S, Awan A, et al. Can MRI replace DMSA in the detection of renal parenchymal defects in children with urinary tract infections? Pediatr Radiol 2005;35(3): 275–81.
[71] Rodriguez LV, Spielman D, Herfkens RJ, et al. Magnetic resonance imaging for the evaluation of hydronephrosis, reflux and renal scarring in children. J Urol 2001;166(3):1023–7.
[72] Jodal U. The natural history of bacteriuria in childhood. Infect Dis Clin North Am 1987; 1(4):713–29.
[73] Martinell J, Hansson S, Claesson I, et al. Detection of urographic scars in girls with pyelonephritis followed for 13–38 years. Pediatr Nephrol 2000;14(10–11):1006–10.
[74] Malhotra SM, Kennedy II WA. Urinary tract infections in children: treatment. Urol Clin North Am 2004;31(3):527–34.
[75] Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics 1999;104(1 Pt 1):79–86.
[76] Jojart G. Comparison of 3-day versus 14-day treatment of lower urinary tract infection in children. Int Urol Nephrol 1991;23(2):129–34.
[77] Fritzsche M, Ammann RA, Droz S, et al. Changes in antimicrobial resistance of Escherichia coli causing urinary tract infections in hospitalized children. Eur J Clin Microbiol Infect Dis 2005;24(3):233–5.
[78] Gupta K. Emerging antibiotic resistance in urinary tract pathogens. Infect Dis Clin North Am 2003;17(2):243–59.
[79] Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic Escherichia coli isolates in Michigan. Clin Infect Dis 2002;34(8):1061–6.
[80] Littlewood JM. 66 infants with urinary tract infection in first month of life. Arch Dis Child 1972;47(252):218–26.
[81] Arrieta AC, Bradley JS. Empiric use of cefepime in the treatment of serious urinary tract infections in children. Pediatr Infect Dis J 2001;20(3):350–5.
[82] Jones ME, Karlowsky JA, Draghi DC, et al. Rates of antimicrobial resistance among common bacterial pathogens causing respiratory, blood, urine, and skin and soft tissue infections in pediatric patients. Eur J Clin Microbiol Infect Dis 2004;23(6):445–55.
[83] Smellie JM, Ransley PG, Normand IC, et al. Development of new renal scars: a collaborative study. Br Med J (Clin Res Ed) 1985;290(6486):1957–60.
[84] Gauthier M, Chevalier I, Sterescu A, et al. Treatment of urinary tract infections among febrile young children with daily intravenous antibiotic therapy at a day treatment center. Pediatrics 2004;114(4):e469–76.
[85] Lieu TA, Baskin MN, Schwartz JS, et al. Clinical and cost-effectiveness of outpatient strategies for management of febrile infants. Pediatrics 1992;89(6 Pt 2):1135–44.
[86] Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. J Pediatr 1992;120(1):22–7.
[87] Koyle MA, Barqawi A, Wild J, et al. Pediatric urinary tract infections: the role of fluoroquinolones. Pediatr Infect Dis J 2003;22(12):1133–7.
[88] Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. Clin Infect Dis 1997;25(5):1196–204.
[89] Grady R. Safety profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis J 2003;22(12):1128–32.
[90] Jafri HS, McCracken Jr GH. Fluoroquinolones in paediatrics. Drugs 1999;58(Suppl 2):43–8.
[91] Bryant K, Maxfield C, Rabalais G. Renal candidiasis in neonates with candiduria. Pediatr Infect Dis J 1999;18(11):959–63.

[92] Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis 2000;30(1):14–8.
[93] Sobel JD, Vazquez JA. Fungal infections of the urinary tract. World J Urol 1999;17(6):410–4.
[94] Jacobs LG, Skidmore EA, Freeman K, et al. Oral fluconazole compared with bladder irrigation with amphotericin B for treatment of fungal urinary tract infections in elderly patients. Clin Infect Dis 1996;22(1):30–5.
[95] Sobel JD, Kauffman CA, McKinsey D, et al. Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis 2000;30(1):19–24.
[96] Simpson C, Blitz S, Shafran SD. The effect of current management on morbidity and mortality in hospitalised adults with funguria. J Infect 2004;49(3):248–52.
[97] Wise GJ, Talluri GS, Marella VK. Fungal infections of the genitourinary system: manifestations, diagnosis, and treatment. Urol Clin North Am 1999;26(4):701–18.
[98] Wise GJ, Kozinn PJ, Goldberg P. Amphotericin B as a urologic irrigant in the management of noninvasive candiduria. J Urol 1982;128(1):82–4.
[99] Ransley PG, Risdon RA. The pathogenesis of reflux nephropathy. Contrib Nephrol 1979; 16:90–7.
[100] Elder JS, Peters CA, Arant Jr BS, et al. Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol 1997;157(5):1846–51.
[101] Mangiarotti P, Pizzini C, Fanos V. Antibiotic prophylaxis in children with relapsing urinary tract infections: review. J Chemother 2000;12(2):115–23.
[102] Lohr JA, Nunley DH, Howards SS, et al. Prevention of recurrent urinary tract infections in girls. Pediatrics 1977;59(4):562–5.
[103] Smellie JM, Katz G, Gruneberg RN. Controlled trial of prophylactic treatment in childhood urinary-tract infection. Lancet 1978;2(8082):175–8.
[104] Stamm WE, Counts GW, Wagner KF, et al. Antimicrobial prophylaxis of recurrent urinary tract infections: a double-blind, placebo-controlled trial. Ann Intern Med 1980;92(6):770–5.
[105] Schaeffer AJ, Jones JM, Flynn SS. Prophylactic efficacy of cinoxacin in recurrent urinary tract infection: biologic effects on the vaginal and fecal flora. J Urol 1982;127(6):1128–31.
[106] Albert X, Huertas I, Pereiro I, et al. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev 2004;4:1–56.
[107] Williams G, Lee A, Craig J. Antibiotics for the prevention of urinary tract infection in children: a systematic review of randomized controlled trials. J Pediatr 2001;138(6):868–74.
[108] Aggarwal VK, Verrier Jones K, Asscher AW, et al. Covert bacteriuria: long term follow up. Arch Dis Child 1991;66(11):1284–6.
[109] Wettergren B, Hellstrom M, Stokland E, et al. Six year follow up of infants with bacteriuria on screening. BMJ 1990;301(6756):845–8.
[110] Schlager TA, Dilks S, Trudell J, et al. Bacteriuria in children with neurogenic bladder treated with intermittent catheterization: natural history. J Pediatr 1995;126(3):490–6.
[111] Ma JF, Shortliffe LM. Urinary tract infection in children: etiology and epidemiology. Urol Clin North Am 2004;31(3):517–26.
[112] Pylkkanen J, Vilska J, Koskimies O. The value of level diagnosis of childhood urinary tract infection in predicting renal injury. Acta Paediatr Scand 1981;70(6):879–83.
[113] Stokland E, Hellstrom M, Jacobsson B, et al. Renal damage one year after first urinary tract infection: role of dimercaptosuccinic acid scintigraphy. J Pediatr 1996;129(6):815–20.
[114] Jahnukainen T, Chen M, Celsi G. Mechanisms of renal damage owing to infection. Pediatr Nephrol 2005;20(8):1043–53.
[115] Orellana P, Baquedano P, Rangarajan V, et al. Relationship between acute pyelonephritis, renal scarring, and vesicoureteral reflux: results of a coordinated research project. Pediatr Nephrol 2004;19(10):1122–6.
[116] Jacobson SH, Eklof O, Eriksson CG, et al. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. BMJ 1989;299(6701):703–6.

[117] Gill DG, Mendes de Costa B, Cameron JS, et al. Analysis of 100 children with severe and persistent hypertension. Arch Dis Child 1976;51(12):951–6.
[118] Wennerstrom M, Hansson S, Hedner T, et al. Ambulatory blood pressure 16–26 years after the first urinary tract infection in childhood. J Hypertens 2000;18(4):485–91.
[119] Sreenarasimhaiah S, Hellerstein S. Urinary tract infections per se do not cause end-stage kidney disease. Pediatr Nephrol 1998;12(3):210–3.
[120] Wennerstrom M, Hansson S, Jodal U, et al. Renal function 16 to 26 years after the first urinary tract infection in childhood. Arch Pediatr Adolesc Med 2000;154(4):339–45.
[121] Risdon RA, Yeung CK, Ransley PG. Reflux nephropathy in children submitted to unilateral nephrectomy: a clinicopathological study. Clin Nephrol 1993;40(6):308–14.
[122] Al-Eisa AA, Samhan M, Naseef M. End-stage renal disease in Kuwaiti children: an 8-year experience. Transplant Proc 2004;36(6):1788–91.