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ARTICLES

PEDIATRIC URINARY TRACT INFECTIONS

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Urinary tract infection (UTI) is common and results in significant morbidity in infants and children. In the past few decades,

a better understanding of the pathogenesis and the natural history of pediatric UTI, together with the identification of risk factors that predispose to subsequent renal parenchymal damage, have led to the recognition that prompt, appropriate, and thorough evaluation is essential for minimizing the acute morbidity and the long-term sequelae of UTIs, such as renal scarring, hypertension, and renal failure. This article describes a rational and practical approach toward evaluation and management of pediatric UTI for pediatricians, with additional emphasis on the appropriate use of acute and prophylactic antimicrobial agents.

CLASSIFICATION OF URINARY TRACT INFECTION

For practical purposes, pediatric UTIs can be classified based on the natural history and subsequent evaluation and

management (see box on following page). They can be categorized as first infection or recurrent infection. Recurrent infections can be subcategorized as unresolved bacteriuria, bacterial persistence, and reinfection.[29] Clinical classification of UTI, such as complicated versus uncomplicated, upper versus lower, or cystitis versus pyelonephritis, imply severity of infection when, in fact, this cannot be documented clinically nor may "lesser" infections require less rigorous evaluation.

Classification of Pediatric Urinary Tract Infection

First infection

Recurrent infection

Unresolved bacteriuria

Bacterial persistence

Reinfection

First infection is simply the initial UTI that is diagnosed. In infants and children, first infections are considered complicated

because of the high prevalence of urinary tract abnormalities that predispose to renal damage.

Unresolved infection is frequently a result of inadequate therapy. Most often, this is caused by resistance to the selected antimicrobial agent. In patients with renal failure, intestinal malabsorption, or giant staghorn calculi, unresolved infection also may be secondary to the inability to achieve adequate urinary levels of the therapeutic agent. Less frequently, infection involving multiple organisms with differing antimicrobial susceptibilities is the cause for unresolved infection. Fortunately, unresolved infections usually are treated easily once proper culture and antimicrobial sensitivities are known.

Bacterial persistence and reinfections are infections that occur after documented sterilization of urine. Reinfection differs from bacterial persistence in that the periodic infections can be caused by a variety of infecting organisms, whereas in bacterial persistence, the same infecting organism is always isolated. Reinfection most frequently occurs by the fecal-perineal-urethral route in girls and periurethral colonization in boys. In contrast, bacterial persistence most frequently occurs when there is an underlying abnormality in the urinary tract that allows the infecting organism to be shielded from an adequate antibiotic treatment. Clinically, bacterial persistence often suggests underlying abnormality in the urinary tract (e.g., infected calculus or necrotic papillus), and the identification of these abnormalities is important because these may be surgically correctable.

EPIDEMIOLOGY

Prevalence of UTI is sex and age dependent. Regardless of age, girls are more prone to UTIs than are boys. Among children

aged less than 1 year, the prevalence of UTI in girls is 6.5% compared with 3.3% in boys. After age 1 year, the prevalence of UTI in boys decreases to 1.9%, whereas in girls it increases slightly, to 8.1%.[2] The risk for UTI in uncircumcised boys is 5- to 20-fold higher than in circumcised boys, with the greatest risk being in boys aged less than 1 year.[1] Not surprisingly, prevalence of UTI in females further increases with the onset of sexual activity.

BACTERIA

The most commonly isolated urinary pathogens are enteric, gram-negative bacteria, especially *Escherichia coli*. Other

common community-acquired pathogens include *Enterobacter*, *Klebsiella*, and *Proteus* spp. In neonates, group B streptococci are more common. Nosocomial UTIs are caused by a greater variety of organisms and can be more difficult to treat; an example of such an organism is *Pseudomonas aeruginosa*. *Candida* sp may be present in immunocompromised or catheterized patients. In an otherwise healthy child, the presence of *Lactobacillus*, coagulase-negative staphylococci, and *Corynebacterium* are rarely clinically significant. A comprehensive list of community and nosocomial uropathogens is given in the box below.

Bacteria Causing Urinary Tract Infections

Gram-negative rods

Citrobacter

Escherichia coli

Enterobacter sp

Gardnerella vaginalis

Klebsiella sp

Morganella morganii

Proteus sp

Providencia stuartii

Pseudomonas aeruginosa

Serratia sp

Other pathogens

Chlamydia (*Chlamydia trachomatis*)

Mycoplasma (*Ureaplasma urealyticum*)

Gram-negative cocci

Neisseria gonorrhoea

Gram-positive cocci

Staphylococcus aureus

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus, Group D

Streptococcus faecalis

Streptococcus bovis

Streptococcus Group B

BACTERIAL VIRULENCE FACTORS

There are more than 150 strains of *E. coli*; however, fewer than 10 serotypes of *E. coli* account for most UTI cases (01, 02,

04, 06, 07, and 075).[17] [24] [30] The increased uropathogenicity in these strains of *E. coli* relates to the virulence properties they possess. *E. coli* strains associated with infection more commonly exhibit bacterial products, such as alpha-hemolysin, a cytolytic protein that disrupts cell plasma membrane; siderophores, iron-chelating protein that enhances bacterial survival; and capsular polysaccharides, which attenuate the activation of alternate complement pathway. Bacterial virulence also can be enhanced if the bacteria can adhere efficiently to the urothelium. Bacterial adherence to host vaginal epithelium and uroepithelium is mediated by long, hairlike, proteinaceous, cell-surface structures called pili or fimbriae. Strains of p-pili expressing *E. coli*, classified by their resistance to mannose hemagglutination and their ability to bind to glycolipid receptors, are associated with a higher degree of virulence because of their ability to bind glycolipid receptor found on the host uroepithelium. In fact, 91% of *E. coli* causing pyelonephritis, 19% of *E. coli* causing acute cystitis, and 14% of *E. coli* causing asymptomatic bacteriuria are found to express p-pili compared with 7% of *E. coli* from feces of healthy controls. [17] Recently, reports demonstrating prolonged febrile reactions with p-pili *E. coli* have led some to suggest that infections with p-pili expressing *E. coli* should be treated with a longer course of antibiotics.[30]

PATHOGENESIS

Bacteriuria occurs when bacteria gain access to the normally sterile urinary tract. Bacteria can enter the genitourinary tract by

four major pathways: (1) ascending, (2) hematogenous, (3) lymphatic, and (4) direct extension. Ascending infection from the urethra to the bladder and up toward the kidney is by far the most common. Hematogenous spread may occur in children who are immunocompromised or in neonates who have yet to develop a mature immune system and may involve *Staphylococcus aureus*, *Candida* sp, and tuberculosis. Lymphatic spread to the urinary tract from rectal, colonic, and periuterine lymphatics is hard to document. Direct extension can occur in the presence of fistulas from the vagina or intestines to any part of the urinary tract.

Host Susceptibility Factors

The ability for the host to resist infection is also an important determinant in the pathogenesis of UTI in children. The host factors that have been identified to increase susceptibility to UTIs are listed in the box on the opposite page. In infancy (i.e., first few months of life) there is a specific increased UTI incidence. This increase may be explained

Host Factors Affecting Bacteriuria

Age

Colonization

Fecal

Periurethral

Preputial

Gender

Genetics (uroepithelial receptors)

Genitourinary abnormalities

Neurogenic bladder

Pregnancy

Vesicoureteral reflux

Iatrogenic factors

Antibiotic use

Catheterization

Native immunity

Sexual activity

partially by the immaturity of a neonate's immune system and the higher periurethral bacterial colonization in the first year of life. This immaturity of the immune system has led some investigators to suggest that breastfeeding may convey a protective effect not only against infections in the urinary tract but also other infections during the first 6 months of life.

Circumcision status and its association with UTI, especially neonatal UTI, has been a source of immense controversy. Convincing prospective, randomized data on the subject are lacking; however, all studies from older retrospective to newer cohort and case-controlled studies have shown an increased risk for UTI in uncircumcised boys.[2] [27] [35] This risk may be as high as 10-fold in infants aged less than 1 year, although the absolute risk for UTI in uncircumcised neonates is still low, at approximately 1%.[2] In a recent American Academy of Pediatrics position paper, it is stated that, although scientific evidence shows medical benefits of neonatal circumcision, the data still are insufficient to support routine neonatal circumcision.

Because most UTIs occur by ascending infections, the importance of fecal colonization cannot be overlooked. Fecal bacterial flora depend on the surrounding microbial ecology, host native immunity, and microbe-altering drugs. For this reason, the importance of using appropriate antibiotics in the treatment of active infection and in the prophylactic setting cannot be overemphasized. The development of multidrug-resistant organisms in the gastrointestinal tract by antibiotics is well documented. In one study, treatment of school-aged girls with phenoxymethylpenicillin for infections, usually otitis media, resulted in fecal recolonization and bacteriuria with strains that are frequently more virulent.[10]

As mentioned previously, UTIs in infants and children warrant special attention because they often serve as a marker for anatomic abnormalities in the genitourinary tract. These abnormalities are important to identify early on because, if uncorrected, they may predispose a child to recurrent infections and possible renal parenchymal loss. Some surgically correctable genitourinary abnormalities are listed in the box above. Even though vesicoureteral reflux (VUR) and posterior urethral valves do not necessarily

predispose a child to bacteriuria, they do allow bladder bacteria rapid access to the kidney, with resulting pyelonephritis and possible subsequent renal damage. For this reason, imaging of the urinary tract is recommended strongly for all children presenting with a first UTI.[2]

Surgically Correctable Causes of Bacterial Persistence

Foreign bodies

Infected necrotic papillae in papillary necrosis

Infected poorly or nonfunctioning kidneys or renal segments

Infected calculus

Infected urachal cysts

Infected urethral stumps following nephrectomy

Infected urethral diverticulum or periurethral gland

Unilateral medullary sponge kidney

Urethral duplication or ectopic ureters

Vesicointestinal or urethrorectal fistula

Vesicovaginal fistula

Functional abnormalities in the genitourinary tract are also important to identify. Children with neurogenic bladders are at a

much greater risk for renal deterioration from UTIs because of elevated urinary tract pressures, incomplete bladder emptying, and increased frequency of instrumentation. Voiding dysfunction in an otherwise neurologically healthy child also may influence the frequency and severity of UTIs. These dysfunctions include bladder instability, infrequent voiding, the Hinman syndrome, and constipation. The exact mechanism by which voiding dysfunction predisposes to UTI is not known, but presumably, it is a combination of incomplete bladder emptying, urinary stasis, and abnormally high urinary tract pressures. Clinically, treatment of constipation or voiding disturbances alone or in combination has resulted in decreased frequency of UTIs.

NATURAL HISTORY OF URINARY TRACT INFECTIONS

Cystitis and Pyelonephritis

The natural history of pediatric UTI is unpredictable and incompletely understood. Part of the frustration lies in the fact that

there is no clear way to anticipate whether a given child will manifest localized symptoms of cystitis or progress to outright pyelonephritis. Although a child's host risk

factors and the virulence of specific bacterial strains may predict the course of a UTI partially, these factors alone have not been useful in predicting which individuals will develop pyelonephritis, renal scarring, or parenchymal damage that may lead to irreversible loss of renal function.

Prior studies have shown that clinical symptoms, such as fever and flank pain, correlate poorly with upper tract localization of bacteria, as demonstrated using the Fairley ureteral catheterization technique.[29] In fact, fewer than half of patients with fever and flank pain have upper tract involvement, whereas almost 20% of those who are asymptomatic have presence of upper tract bacteria.[6A] In its most recent practice guidelines, the American Academy of Pediatrics recommended that UTI be ruled out for any young children aged 2 months to 2 years with unexplained fever.[2] This guideline is especially pertinent given that classic symptoms of infection, including dysuria, hesitancy, and frequency, are unreliable in this age group. The use of nonspecific tests of inflammation (i.e., leukocyte count, C-reactive protein) and indirect evidence of bacterial localization (i.e., elevated levels of antibody titer to the infectious strains of *E. coli*) do not provide confirmatory evidence that the patient truly has pyelonephritis.

More recently, the widespread use of technetium-99m dimercaptosuccinic acid (DMSA) nuclear scanning has advanced the understanding of the natural history of UTIs. Animal models have confirmed that the lesions observed on DMSA scans correlate with areas of acute renal inflammation. When DMSA lesions are used as the standard, approximately 50% to 86% of children with febrile UTIs and other clinical signs were found to have pyelonephritis.[6] [14] Approximately half of these lesions persist on DMSA scans performed 2 months to 2 years later, which suggests that as many as 40% to 50% of young children who have febrile UTIs may develop renal scarring.

Complications

Recurrent Urinary Tract Infections

Considering the common occurrence of UTIs, pediatricians and other primary care physicians should be well aware of the risk for recurrent infections. The natural history of recurrent UTIs has been well documented by Winberg et al.[33] Among boys who become infected before age 1 year, 18% develop recurrent infections, with most recurrences occurring within the first year of initial infection. In contrast, approximately 32% become reinfected if the initial infection happens at an older age. Among girls, approximately 26% who have an initial neonatal infection develop recurrent infections. Similar to their male counterparts, recurrences tend to happen within the first year after the initial event. Girls who have their first UTI at an older age have a higher incidence of recurrence (40%), although most of these events occur within a year of initial infection.[33] As expected, the incidence of infections decreases with each infection-free year thereafter; however, these patients require close follow-up, given that a small, but significant, minority (8%) developed recurrent UTIs more than 4 years after the original infection in this study. The data presented by Winberg et al demonstrate, moreover, that the relative risk for recurrent infection depends on the number of prior infections.[33] For

example, one prior infection increased the risk for recurrence by 25%; this figure increased proportionately with the number of infections (50% and 75% with two and three infections, respectively). Importantly, this trend did not change, regardless of whether the initial infection was asymptomatic or symptomatic, cystitis, or pyelonephritis.

Renal Scarring

Before the advent of broad spectrum antibiotics, childhood UTIs often were associated with permanent renal changes. Clinical and animal studies have shed much light as to the pathogenesis and significance of UTI-induced renal scarring. Although it still is not clear why children's kidneys are prone to scarring whereas adults' kidneys are not, it is clear that VUR alone does not result in renal scars. Pig studies have shown that VUR alone without bacteriuria resulted in renal scarring only if the urethra was partially obstructed, causing abnormally high voiding pressures.[23] Renal infection stimulates humoral and cellular immune responses. During this acute process, aggregation of granulocytes may cause vascular occlusion and ischemia, with elevation in renin levels. The resulting release of enzymes, superoxide, and oxygen-free radicals is believed to be the main cause of renal tubular damage.

In prior clinical studies performed without the benefit of DMSA scans, approximately 17% of schoolchildren with screening bacteriuria (i.e., bacteriuria found on cultures performed for screening rather than for symptoms) had renal scarring.[3] In most children with UTI in whom renal scars are found, the scars are found on the first set of imaging studies and remain unchanged irrespective of the child's future clinical course. It is believed that the initial insult in the neonate or young child (age, < 5 years) causes whatever renal damage will occur and that this response determines the kidney's future course. Although older children may have less risk for scarring from infection than those aged less than 5 years, they are not completely free from risk until puberty. This possibility seems especially true in the setting of persistent or recurrent infection and VUR. For example, Filly et al[8] found that, in girls aged less than 10 years who had recurrent UTIs and VUR, renal scars progressed in 43% of kidneys, and 2 of 16 normal kidneys developed new scars. In this series, some of the scars took more than 2 years to develop fully.

Hypertension

Of significant concern to most physicians is the consequence of having a scarred kidney, specifically the potential for hypertension. Although the childhood prevalence in the US and in Europe of hypertension is estimated to be between 1% and 11%, depending on age and sex, pyelonephritic scarring remains the most common cause.[7] The cause of pyelonephritogenic hypertension is poorly understood. Current clinical literature, however, has associated the involvement of the renin-angiotensin mechanism with its pathogenesis. No direct relationship between blood pressure, degree of scarring, plasma renin activity, or creatinine can be made, however. Regardless, the successful treatment of patients with agents specifically designed to work on the renin-angiotensin system

lends further credence to the possible role of renin in hypertension associated with pyelonephritic nephropathy.

As for the risk for clinically significant hypertension, Wallace et al[31] studied a total of 141 patients with UTIs who underwent surgical correction of their VUR. Of these 141 patients, 12.8% developed hypertension in the first 10 years of follow-up. In another series, by Smellie and Normand,[28] 30% of children with clinical evidence of renal scars subsequently developed infection-related hypertension. In both studies, the prevalence of hypertension was found to be independent of the degree of scarring.

DIAGNOSIS

Clinical Features

There are no specific signs for UTIs in infants and young children. The most common signs of UTI in this age group are

nonspecific and include fever, irritability, poor feeding, vomiting, failure to thrive, and diarrhea. If present, crying on urination or malodorous urine may increase the likelihood of UTI. The prevalence of UTI in infants and young children with fever that is not localizable by history or physical examination is high, at approximately 5%.[2] This rate may be doubled in infants aged less than 8 weeks.[19] In seriously ill infants or young children, UTI still must be considered even if signs point to other sources of infection because, in this population, those not suspected to have a UTI are just as likely to have a urinary source as are those who are suspected to have a urinary source (5.1% versus 5.9%).[13] In older children, the classic symptoms of UTI are more commonly present and include dysuria, frequency, suprapubic or flank discomfort, intermittent voiding dysfunction, and incontinence.

Physical findings are frequently nonspecific. Occasionally, an abdominal mass may be palpated secondary to an infected hydronephrotic or xanthogranulomatous kidney. Examination of the perineum in girls rarely reveals an ectopic ureteral opening, ureterocele, or urethral discharge. In boys, testicular examination may reveal signs consistent with epididymitis or epididymo-orchitis. In older children, palpation of the flank or abdomen may illicit discomfort. Furthermore, a thorough examination of the back for evidence of scars, sacral fat pads, dimples, or pits is crucial because their existence is associated with the presence of a neurogenic bladder.

Collection of Urine

Diagnosis of UTI requires a urine culture. Urine can be obtained routinely in four ways, listed in the order from the least to the most reliable for diagnosis of urinary infection[11]

:

"Bagged specimen": Plastic bag attached to the perineum

Clean-catch midstream specimen

Urethral catheterized specimen

Suprapubic aspirate

Bagged specimen is the most convenient and least traumatic. Unfortunately, even with thorough cleaning of the prepuce or the perineum, the false-positive rate is still extremely high, on the order of 85% to 99% depending on the prevalence of UTI (5% overall to 0.2% in circumcised boys).[2] For this reason, bagged urine is effective in ruling out UTI but not useful in documenting a UTI. Similarly, clean-catch midstream specimens from older girls and circumcised boys often yield periurethral and preputial colonization, making a positive culture difficult to interpret. An urethral catheterized specimen is reliable if the initial portion of the urine contaminated by periurethral organisms is discarded. Drawbacks of this method are its invasiveness and its potential to introduce urethral organisms into an otherwise sterile urinary tract.[21] The gold standard for diagnosing UTI is a urine culture obtained from a suprapubic aspirate. The advantage of this method is its theoretic zero rate of contamination, such that the organisms from a suprapubic aspirate are pathognomonic of bacteriuria. Technically, aspiration can be performed safely and painlessly by applying topical and local anesthesia before percutaneously aspirating the bladder with a 21- or 22-gauge needle 1 to 2 cm above the pubic symphysis.[4] In clinical practice, if UTI is suspected in children who are not toilet trained and empiric therapy is entertained, a catheterized or needle aspirate specimen should be obtained. In older children, a clean-catch midstream specimen may be acceptable.

Urinalysis

Although quantitative urine culture is the gold standard for the diagnosis of UTI, urinalysis is a useful initial study because the results are immediately available. Presence of bacteria under high-power (450-750 \times magnification) represents approximately 30,000 bacteria per milliliter; however, the presence of bacteria alone may reflect contamination. Positive predictive value of urinalysis can be increased to 84.6% in a catheterized specimen if bacteriuria is associated with pyuria, defined as more than 10 WBC per high-power field.[13] The sensitivity of microscopy is so low, however, that a negative result alone does not rule out UTI.

Chemical screening of urine for markers of infections is less sensitive than is microscopy but can provide additional information. Nitrates are reduced to nitrites by certain bacteria. Activated leukocytes produce leukocyte esterase. The presence of urinary nitrites and leukocyte esterase, therefore, serves as indirect evidence for bacteriuria. Drawbacks of urine nitrites are:

It may take several hours for bacteria to reduce nitrates in vivo

The test is most useful on first voided morning specimen

Most gram-positive bacteria cannot be detected by this method

A major drawback of urine leukocyte esterase is that leukocytes may not always be present in an infection. In addition, both

chemical tests may be unreliable when bacterial count is less than 100,000 cells per milliliter. Nevertheless, in the general population, if microscopic and chemical tests are negative, the negative predictive value approaches 100%. [22] [32] In short, although urinalysis does not replace urine culture for diagnosis of UTI, in otherwise healthy and nontoxic children, urinalysis may be helpful in determining who may be at higher risk for UTI and thus benefit from prompt initiation of antibiotic therapy from those who are at lower risk for UTI and perhaps benefit from observation until the urine culture returns. Table 1 (Table Not Available) summarizes the sensitivity and specificity of each component of the urinalysis.

TABLE 1 -- SENSITIVITY AND SPECIFICITY OF COMPONENTS OF URINALYSIS

(Not Available)

From 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* 103:843-852, 1999; with permission.

Urine Culture

As mentioned previously, properly collected quantitative urine culture is the gold standard for diagnosing UTI. All urine specimens should be collected in a sterile container and processed as soon as possible. If a delay is likely, the specimen can be refrigerated up to 24 hours before plating. Pathogenic bacteria are identified based on species and colony forming units per milliliter (CFU/mL). What colony count constitutes a significant UTI is not absolute and varies

based on the method of urine collection. Table 2 (Table Not Available) is a guideline for probability of infection-based collection method and colony count. Occasionally, low numbers of bacteria may indicate significant UTI, especially when the specimen is obtained by suprapubic aspiration.

TABLE 2 -- CULTURE CRITERIA FOR DIAGNOSIS OF URINARY TRACT INFECTION

(Not Available)

From Hellerstein S: Recurrent urinary tract infections in children. *Pediatr Infect Dis* 1:271-281, 1982; with permission.

Other Laboratory Tests

Although not always necessary, complete blood counts and C-reactive protein may give further support for presence of infection when the clinical picture is vague. In an otherwise healthy patient with appropriate response to treatment, obtaining a baseline renal panel is probably prudent. In a toxic, ill-appearing, dehydrated child, additional studies, such as basic electrolytes and creatinine clearance, may provide a more complete clinical picture.

Diagnostic Imaging Studies

The ultimate goal of radiologic evaluation is to reduce the risk for renal damage in the acute setting and also in the future. To that end, radiologic imaging can be used to:

Localize acute UTI

Detect renal damage

Identify abnormal genitourinary anatomy

Evaluate change in urinary tract over time

In the acute setting, radiologic studies are occasionally necessary, especially when the source of infection is unclear and the

urine culture is indeterminate. In this setting, an acute DMSA scan may be helpful in documenting acute renal inflammation. Other indications for radiologic evaluation in the acute setting include:

Poor response to appropriate antimicrobial drugs after 4 days

Presence of unusual infecting organisms, such as tuberculosis, or urea-splitting organisms, such as *Proteus*

Known urinary tract abnormality

History of papillary necrosis

Neurogenic bladder

Evidence of renal deterioration or failure

In such cases, urologic consultation is likely appropriate and additional imaging studies, such as renal bladder sonography,

voiding cystourethrography (VCUG), or CT scanning, may be necessary. In terms of follow-up imaging studies, it is recommended that all infants and children presenting with first documented UTI undergo lower and upper urinary tract imaging studies,

usually consisting of a VCUG and renal bladder sonography. This recommendation is based on multiple studies that have shown that the prevalence of obstructive lesions can be as high as 5% to 10%, whereas the prevalence of VUR is higher, at 21% to 57%.[3] Younger children tend to have higher prevalence and grade of VUR compared with older children.

MANAGEMENT OF PEDIATRIC URINARY TRACT INFECTIONS

Treatment of Acute Urinary Tract Infection

As discussed previously, a delay in treatment of UTI leads to a greater risk for renal scarring, making prompt diagnosis and

treatment imperative. The therapeutic strategy depends on the child's age and the severity of illness. If the child is aged less than 2 or 3 months and is unable to tolerate adequate oral intake, systemically ill, or immunocompromised, the patient should be considered for hospitalization and treated with broad-spectrum, parenteral antibiotics. Although the choice of antibiotics should be tailored to each individual (depending on the patient's history of prior antibiotic use, allergies, and resistance rates in a given population or geographic region), a combination of aminoglycosides and ampicillin or cephalosporins or third- generation cephalosporins (Table 3) provides adequate coverage for most of the commonly encountered uropathogens. Alternatively, outpatient parenteral treatment may be a viable option for children with reliable parents capable of maintaining a rigid follow-up regimen with frequent contact between the health professional and the parents. For this purpose, a third- generation cephalosporin, such as ceftriaxone, provides broad coverage and the convenience of a once-a-day dosing schedule.[5] Again, even the newest generation of antibiotics may not treat certain species of *Enterococcus* or *Pseudomonas* adequately, emphasizing the importance of obtaining urine culture with sensitivities in choosing the appropriate medication. Parenteral treatment usually is continued for 48 to 72 hours until the child is afebrile and clinically stable. At this point, therapy may be switched to an oral antibiotic to which the organism is sensitive. The duration of treatment is somewhat debatable; however, most studies advocate treating febrile UTIs in young children for a total of 7 to 10 days.

TABLE 3 -- COMMONLY USED ANTIBIOTICS FOR TREATING PEDIATRIC URINARY TRACT INFECTIONS

Route
Drug
Dose (mg/kg/d)
Frequency (q hours)

Parenteral
Aminoglycosides

Gentamicin
7.5
8

Tobramycin
7.5
8

Penicillins

Ampicillin
50-100
6

Ticarcillin
50-200
4-8

Cephalosporins

Cefazolin
25-50
6-8

Ceftriaxone
50-75
12-24

Ceftazidime
90-150
8-12

Oral
Penicillins

Ampicillin
50-100
6

Amoxicillin
20-40
8

Augmentin
20-40
8

Sulfonamides

Trimethoprim-

sulfamethoxazole

8

12

Cephalosporins

Cephalexin

25-50

6

Cefaclor

20

8

Cefixime

8

12-24

Cefadroxil

30

12-24

Other

Nitrofurantoin

5-7

In clinically stable children, an oral, broad-spectrum antibiotic is recommended. Prior emphasis on potential bacterial

resistance to antibiotic treatment seems especially pertinent in such cases, given the fact that even the latest generation of cephalosporins may be ineffective against certain virulent strains of gram-negative bacteria. The recent advent of oral quinolones has provided physicians with a valuable weapon against gram-negative infection, especially in the case of *Pseudomonas aeruginosa*. Its use has been somewhat limited in the pediatric population because of its reported adverse effects on cartilage development in various animal studies.[26] These antibiotics have been used in limited complicated situations, and further examination of this use is warranted. UTI in an otherwise healthy child who has a normal genitourinary tract can be treated adequately with oral agents in a course of 3 to 5 days. A longer duration of antibiotic therapy has not been shown to be any more efficacious.[9] [16]

Antibiotic prophylaxis should be considered in any child with a history of UTI until a full evaluation for anatomic abnormality is complete. Prophylaxis may be recommended in infants aged less than 3 to 6 months with a history of recurrent UTIs and in children with VUR, partial obstruction, or immunosuppression. Prophylactic antibiotics also may be considered in children with history of recurrent UTI without any underlying anatomic abnormalities. Ideally, a prophylactic agent should provide high urinary antibiotic excretion with low serum and fecal levels (Table 4), which tends to minimize the development of resistant bacterial strains in the fecal flora. Inappropriately high doses may facilitate bacterial resistance. In addition, because urinary prophylaxis usually is started after a full course of treatment-dose antibiotics, the fecal flora already may be resistant to the previously used medication; hence, the prophylactic antibiotic, in most cases, should be different than the one used for treatment of the acute infection. In fact, the period of greatest risk for recurrent infection is usually the first few weeks after any full-dose treatment. In initial and prophylactic antimicrobial selection, local community and hospital bacterial ecology of sensitivities should be considered because of growing challenges of antimicrobial resistance patterns.

TABLE 4 -- PROPHYLACTIC ANTIBIOTIC AGENTS

Drug

Dose (mg/kg/d)

Age Limitations

Nitrofurantoin

1-2

>1 mo

Trimethoprim-sulfamethoxazole

1-2

>2 mo

Cephalexin

2-3

Treatment of Asymptomatic Bacteriuria

How to best manage asymptomatic bacteriuria, defined as an infection detected on a screening urine culture found during

evaluation for reasons unrelated to UTI, is controversial. Studies have shown that most of these patients do have symptoms related to the lower UTI when carefully interviewed. In addition, in one study,[25] approximately 50% of children were found to have normal anatomy when studied with a VCUG or an intravenous pyelogram (IVP). Although some investigators have suggested that most of these infections clear without difficulty, others have found that only approximately 30% of school-aged girls eradicate their infections without treatment.[20] Regardless of whether these patients are treated, investigators have found that most girls have or will experience persistent infections or reinfections.

For this reason, as with acute symptomatic UTIs, all first asymptomatic bacteriuria should be evaluated; however, once upper and lower urinary tracts have been deemed anatomically normal, further treatment is debatable. Several studies have established that treatment of infection alone rarely improves any accompanying symptoms of voiding dysfunction and does not affect the rate of future infections.[15] Furthermore, bacterial species responsible for asymptomatic bacteriuria may be less pathogenic; based on this finding, some have proposed that these organisms provide a somewhat protective role in preventing infection with more virulent strains associated with symptomatic UTI. Given

these reasons, most investigators currently recommend following up patients with asymptomatic bacteriuria without antibiotic treatment.

Treatment of Recurrent Urinary Tract Infections

Recurrent UTI is relatively common and should be familiar to pediatricians and urologists. The likelihood of a recurrent UTI is believed to be independent of whether the patient has a preexisting anatomic abnormality, such as VUR, and related to the child's biologic predisposition to UTI. Routine urine cultures and other testing methods do not allow clinicians to predict which patients have a biologic predisposition for UTI accurately. Hence, the management of recurrent UTIs depends on the child's age and the severity of symptoms. For those with frequent infections (defined as two or more infections in a 6-month period), a urinary prophylactic antimicrobial treatment over a limited period may be indicated, given that the child has been established as being biologically predisposed to UTIs. The use of prophylactic antibiotics may decrease the rate of infection; however, most patients eventually return to their increased baseline susceptibility once the prophylaxis is discontinued.[18]

Treatment of Fungal Urinary Tract Infections

As the incidence of fungal UTIs continues to increase, rapid diagnosis and treatment have become crucial. Predisposing factors for fungal UTIs include long-term antibiotic therapy, intravenous catheters, parenteral alimentation, and immunosuppression related to AIDS and other disease states. *Candida albicans* accounts for more than half of these infections, although *Aspergillus*, *Cryptococcus*, and *Coccidiomycosis* also have been implicated. As in bacterial infections, fungal cystitis can be diagnosed on a routine urine culture, although the colony count that defines clinically significant infection remains controversial. Current literature recommends treatment when repeat cultures show more than 10,000 colonies. For upper tract fungal infections, diagnosis depends on urine and blood cultures; however, urine cultures can be negative in as many as 24% of cases involving renal abscesses, reinforcing the importance of having a high suspicion for these cases when clinically indicated. Treatment of localized bladder infections should always start with the removal of indwelling catheters and stopping any unnecessary antibiotic therapy. Intravesical instillation of amphotericin B (50 mg/L) as a continuous or intermittent irrigation for 24 to 48 hours has been found to be effective.[34] For systemic infections, parenterally delivered amphotericin B remains the gold standard, although fluconazole also has been found to be equally efficacious with, perhaps, fewer nephrotoxic side effects.

INDICATIONS FOR REFERRAL

Children with abnormal voiding function, neurogenic bladder, abnormal genitourinary tract anatomy, recurrent UTI, or poor

response to appropriate antibiotics may need further evaluation and management; in these individuals, referral to a pediatric urologist should be considered.

SUMMARY

Urinary tract infection in the pediatric population can lead to significant morbidity if not treated promptly and appropriately.

All first infections may signify possible underlying anatomic or functional abnormality and require imaging of the lower and upper tracts. Accurate diagnosis of UTIs requires a properly collected quantitative urine culture. Treatment should be tailored to the pathogen as dictated by the urine culture sensitivities to minimize the development of multidrug-resistant organisms. Prophylactic agents should differ from the antibiotic used in the acute setting and preferably concentrated in the urinary tract, with minimal effects on the normal fecal flora. In the long term, patients with documented evidence of renal scarring should be followed up for signs of renal deterioration and hypertension.

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