Conferences and Reviews

Urinary Tract Infections in Children
An Update

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Urinary tract infection is a common and frequently recurring condition in children. The susceptibility of the host, the presence of urinary tract abnormalities, and the virulence of the urinary pathogens are of primary importance in the development of the infection. Renal parenchymal scarring, hypertension, and renal insufficiency are well-established complications of the infection in children. To reduce the risk of renal damage, diagnosis and treatment must be prompt. The diagnosis demands radiologic evaluation of the urinary tract in all boys, all children younger than 5 years, all patients with voiding dysfunction, and school-aged girls with recurrent infection to identify those patients with vesicoureteral reflux, obstruction, or other urinary tract abnormalities. Both voiding cystourethrography and renal ultrasonography are the initial examinations to use to determine the next appropriate study. Children with vesicoureteral reflux or with recurrent urinary tract infections should receive prophylactic antibiotic therapy and should be observed closely to prevent renal scarring.

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Urinary tract infection (UTI) occurs in as many as 5% of female and 1% to 2% of male children.[1-3] Although most children respond to therapy without having significant sequelae, severe infection may result in renal scarring, hypertension, or compromised renal function.[2,4] In this review we describe various aspects of this condition in children. Special emphasis is given to current concepts in the pathophysiology of UTI and to the diagnostic evaluation, management, and prognosis of children with UTI or asymptomatic bacteriuria.

Description and Definitions

The diagnosis of asymptomatic (covert) bacteriuria is made when an asymptomatic child has cultures of two properly obtained, clean-voided, midstream urine specimens growing 10^5 colonies or more per milliliter of a single organism, a catheterized specimen growing more than 10^3 colonies per milliliter, or a specimen obtained by suprapubic aspiration growing any number of colonies. Urinary tract infection is diagnosed when a symptomatic child has a culture of one properly obtained, clean-voided, midstream urine specimen growing 10^5 colonies or more per milliliter of a single organism, a catheterized specimen growing more than 10^3 colonies per milliliter, or a specimen obtained by suprapubic tap growing any number of colonies.

Urinary tract infection is generally subdivided into two categories: uncomplicated (lower tract infection or cystitis) and complicated (upper tract infection or pyelonephritis).[5,6] Some conditions associated with complicated UTI in children are vesicoureteral reflux, obstructive uropathy, neurogenic bladder, voiding dysfunction, renal calculi, systemic diseases such as diabetes mellitus, diseases associated with immunologic defects, and the presence of an indwelling catheter or nephrostomy tube.

Etiology

Gram-negative enteric bacteria are the most common organisms causing UTI[5-7]; *Escherichia coli* accounts for 80% of the cases. Other important organisms, especially in neonates and in complicated cases, are *Proteus mirabilis* (common in boys), *Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter* species, *Staphylococcus aureus* (especially in older children), *Streptococcus viridans,* enterococci, and *Candida albicans.*[5-7] Uncomplicated UTI is usually caused by a single organism, whereas in patients with complicated UTI, many organisms may be present. Urinary tract infections by urease-producing organisms such as *P mirabilis, K pneumoniae,* and *P aeruginosa,* which alkalinize the urine, predispose to calculous (struvite) formation.[8] Acute hemorrhagic cystitis may be caused by bacteria or an adenovirus. Urethritis (reviewed in detail by Parrott[9]) is diagnosed by the presence of urethral symptoms and low colony counts of less than 10^4 per ml. Gonococci, chlamydia, and *Ureaplasma urealyticum* are common etiologic agents.

Pathophysiology

The susceptibility of the host and the virulence of the invading bacteria are of primary importance in the development of UTI.[1,10,11] Young age, female sex, abnormal defense mechanisms, the presence of urinary tract abnormalities, sexual activity, and instrumentation are the main host-related factors that contribute to the development of UTI.[1,10,11]

In most cases bacteria ascend the urinary tract following perineal colonization. In neonates UTI is often presumed to be hematogenous,[6] although a bacteremia due to upper tract infection often cannot be excluded. The short female urethra and its proximity to fecal flora may, in part, explain the predominance of UTI in girls after the neonatal period. Uncircumcised male infants have an increased incidence of UTI

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ABBREVIATIONS USED IN TEXT
UTI = urinary tract infection
VCUG = voiding cystourethrogra[phy/m]

when compared with circumcised infants.[12,13] An increased periurethral carriage of uropathic organisms such as *E coli* and *P mirabilis* in association with higher bacterial colony counts has been noted in uncircumcised boys.[14,15] It has been hypothesized that circumcision reduces meatal contamination, thereby decreasing bacterial ascent into the bladder. The benefits of neonatal circumcision, however, are the subject of much debate,[16,17] and further prospective studies are needed both to confirm these observations and to assist in recommendations regarding circumcision. Sexual intercourse increases the risk of UTI in adolescent girls.[6,9]

Defense mechanisms protecting against bacterial growth in the urinary tract include complete bladder emptying, phagocytosis, secretory immunoglobulin IgA secretion by the bladder mucosa, and serum antibody production (which may reduce the severity of upper tract infection).[6,11]

Obstruction and urinary stasis, whether anatomic or functional, predispose to infection.[2,10] Posterior urethral valves, obstruction at the ureteropelvic junction or ureterovesical junction, and ectopic ureterocele are the main causes of anatomic obstruction in children.[2,10] Neurogenic bladder is an important cause of recurrent UTI. Incomplete bladder emptying plays a role in the pathogenesis of UTI in patients with neurogenic bladder, voiding dysfunction in those who are otherwise neurologically normal (bladder-sphincter dyssynergia), and in patients with vesicoureteral reflux or large bladder diverticula (aberrant micturition).[10,18,19] An association of constipation with uninhibited bladder contractions and UTI has also been described in children.[20]

Vesicoureteral reflux is found in 30% to 50% of children with UTI[2,21,22] but is rare in normal children.[23] Intrarenal reflux may be the mechanism by which bacteria enter the renal cortex and cause parenchymal infection and scarring. Intrarenal reflux is more common in compound calyces where a concave central portion of the papilla eliminates the obliquity of papillary duct entry.[22,24] Autopsy studies have shown an increased frequency of compound calyces in the upper and lower poles of the kidney. This distribution, in conjunction with the increased likelihood of intrarenal reflux in papillae serving these compound calyces, is thought to explain the bipolar distribution of reflux nephropathy. The likelihood of parenchymal scarring is related to the severity of vesicoureteral reflux.[23,24] The reflux of sterile urine may inhibit renal growth, but it is unlikely to cause parenchymal scarring in the absence of obstruction or dyssynergia.[25,26]

Instrumentation of the urinary tract, prolonged catheter drainage, and indwelling nephrostomy tubes bypass a person's natural defense mechanisms and predispose to asymptomatic bacteriuria or UTI.

The virulence characteristics of the bacteria causing UTI play a major role in the pathogenesis of the infection. Several excellent reviews of this subject have been published.[27-31] A correlation between elevated antibody titer to capsular O and K antigens of *E coli* and renal involvement has been demonstrated.[2] Bacterial adherence is of great importance in the genesis and severity of UTI[11,32] and has been extensively investigated.[28-31,33] Bacteria bind to uroepithelial mucosa by a process called attachment, the result of an interaction between bacterial surface ligands called adhesins and epithelial cell receptors. Adhesins are frequently associated with pili or fimbriae located on the bacterial surface.[28] Most attaching uropathogenic bacteria recognize the globoseries of glycolipid epithelial cell receptors with the common disaccharide galactose α-1-4 galactose-β (Gal-Gal). The pretreatment of bacteria with receptor analogues such as globotetraosylceramide inhibits attachment and aborts the inflammatory response.[33]

There is, furthermore, a relationship between the intensity of inflammatory response to a uropathogenic organism, as measured by temperature, the extent of pyuria, the concentrating ability and elevation of circulating acute-phase reactants, and attachment to Gal-Gal receptors.[29] This may relate to enhancement by attachment of the action of lipid A, the moiety of endotoxin that triggers inflammation. Fimbriated strains of *E coli* are present in 94% of children with pyelonephritis versus 14% to 19% of children with lower UTI.[32] Of interest, in patients with vesicoureteral reflux, pyelonephritic scars have been reported to be more often associated with nonattaching bacteria, suggesting reduced host resistance due to reflux as a contributing factor.[34] Human milk may have a preventive effect on UTI in infants as evidenced by increased concentrations of secretory IgA[35] and neutral oligosaccharides that inhibit bacterial adhesion[36] in the urine of breast-fed infants. Recently immunization with Gal-Gal pili vaccine has been shown to protect against pyelonephritis induced by fimbriated *E coli* in mice.[37]

Epidemiology

The occurrence of UTI varies with age and sex. The prevalence of asymptomatic bacteriuria in neonates ranges from 1% in full-term infants to 3% in premature infants.[1] Symptomatic UTI in the neonatal period has a prevalence of 0.14%. In the neonatal age group there is a male predominance whereas female predominance occurs afterwards.[38] The prevalence of asymptomatic bacteriuria is 1% of preschool children, 1.2% to 1.8% of schoolgirls, and 0.03% of schoolboys.[5] Symptomatic UTI will develop in about 1.5% to 2% of children ranging in age from 1 year to 5 years.[39] The risk of bacteriuria developing in girls is 5% to 10% during the school years.[5]

Risk Groups

The children who are at increased risk to have bacteriuria or symptomatic UTI with subsequent renal damage are premature infants discharged from neonatal intensive care units and children with systemic or immunologic disease; urinary tract abnormalities or renal calculi; neurogenic bladder, voiding dysfunction, or constipation; a family history of UTI or anomalies such as reflux; and girls younger than 5 years with a previous history of UTI.

Signs and Symptoms

Neonates with UTI often have bacteremia and may show signs of septicemia including fever, hypothermia, apneic spells, poor skin perfusion, abdominal distention, diarrhea, vomiting, lethargy, irritability, and convulsions. Poor weight gain, palpable kidneys, jaundice, acidemia, and electrolyte imbalance are common. Older infants with UTI may present with feeding problems, a failure to thrive, diarrhea, vomiting, fever, and malodorous urine. A careful history often discloses dribbling, a weak urinary stream, or prolonged

voiding. Abdominal and suprapubic tenderness, pallor, lethargy, and irritability are common physical signs. In older children the classic manifestations of UTI are more commonly observed: enuresis, frequency, dysuria, hesitancy, and suprapubic discomfort in patients with clinical cystitis; malaise, fever, chills, nausea, vomiting, and flank pain occur in those with clinical pyelonephritis.

Physical examination of a child with a possible UTI should always exclude hypertension, an abdominal or flank mass, a palpable bladder, neurologic deficits, abnormal genitalia, and abnormal urinary stream.

The presence of urinary symptoms in the absence of bacteriuria in repeated urine specimens suggests vaginitis, urethritis, masturbation, sexual molestation, the use of bubble baths, pinworms, hypercalciuria, viral cystitis, or, in a patient with hematuria, hemorrhagic cystitis. In adolescent girls, a history of dysuria and vaginal discharge or irritation makes vaginitis or vulvitis more probable.[40]

Sequelae

Urinary Tract Infection

As many as 80% of children with uncomplicated UTI will have recurrences.[1,2] Renal parenchymal infection and renal scarring are well-established complications of UTI in children.[2,11] Parenchymal scarring is found in 10% to 15% of children with this infection.[2] It has been estimated that of these, about 10% will have hypertension and a smaller number renal insufficiency.[2,21] Recently, however, a 27-year follow-up study from Sweden showed that focal renal scarring due to pyelonephritis in a child carried a 23% risk for hypertension, a 10% risk for end-stage renal disease, and a 13% risk for toxemia during pregnancy.[4] Further studies are needed to confirm these alarming findings. Neonatal and infantile UTI, particularly if associated with anatomic defects, results in a high incidence of renal scarring, renal atrophy, and renal insufficiency.[11,41] To reduce the risk of renal damage, the diagnosis and treatment of UTI, particularly in neonates and infants, must be prompt. A high incidence (15% to 50%) of structural urinary tract abnormalities is found in male children with UTI at any age.[42]

Vesicoureteral reflux is found in 30% to 50% of children with UTI but is less common in African Americans.[22] It facilitates the ascent of infected urine to the kidneys.[22] Children with reflux have a much higher incidence (30% to 60%) of pyelonephritic scarring than those without reflux, and more than 90% of children with renal parenchymal scarring have or have had vesicoureteral reflux and a history of UTI.[2] Pyelonephritis and scarring, however, can also occur without vesicoureteral reflux, with transient reflux or with functional ureteral obstruction due to atonic ureters or ureteritis due to infection.[11] Most of the damage to the kidney caused by reflux occurs during infancy and early childhood,[2,21,23] although the development of new scars later in childhood has also been documented.[43] Renal scarring after infantile pyelonephritis is often associated with impaired renal growth with the contralateral kidney showing compensatory hypertrophy.[11] Mild to moderate vesicoureteral reflux (grades 1 to 3) usually decreases or disappears with increasing age [21,44] whereas severe reflux (grades 4 and 5) often persists.[21,22] Vesicoureteral reflux may be familial, and a high prevalence (as much as 45%) is found in asymptomatic siblings of children with reflux.[45,46]

Asymptomatic Bacteriuria

Asymptomatic bacteriuria in children is associated with an increased risk of recurrent symptomatic infections that may result in renal scarring.[2,11] Hypertension or renal insufficiency, however, is unusual.[47] In 20% to 30% of school-aged girls with asymptomatic bacteriuria, radiologic investigation will reveal upper urinary tract damage, vesicoureteral reflux, or both.[47,48] Most of the kidney damage occurs before 5 years of age, however.[48] Most prospective studies of schoolgirls older than 5 years with asymptomatic bacteriuria have failed to demonstrate decreased glomerular filtration rates, impaired renal growth, or progressive parenchymal damage in kidneys that are normal at the start, even if bacteriuria is left untreated.[48-50] Bacteriuria in neonates and infants[5,39] and in boys beyond infancy,[42] however, is associated with a high incidence of urinary tract anatomic abnormalities and necessitates prompt diagnosis and early treatment.

Diagnosis

Proteinuria, hematuria, and pyuria may occur with urinary tract infection but are not diagnostic. Conversely, UTI can occur without pyuria. A positive culture in a urine specimen that is properly obtained is essential for the diagnosis. A positive culture in a specimen obtained by midstream clean catch has 80% diagnostic reliability in a female child and 95% reliability in a male child (less contamination). Two positive cultures in a female patient carry 95% diagnostic reliability.[5,6] In infants and toddlers the confidence level for a single positive culture from a specimen collected in a plastic bag is low.[51,52] Negative cultures of bag specimens are useful, however. Suprapubic aspiration or bladder catheterization is necessary in infants for the prompt and precise diagnosis of infection. In older and cooperative children, a clean, voided midstream specimen is satisfactory. The urine should be processed by a laboratory within 15 minutes after collection or refrigerated at 4°C until plating. The presence of bacteria in unspun or spun urine examined under high-power microscopy or a positive Gram's stain correlates highly with notable bacteriuria.[6]

Several simple and inexpensive techniques have been used for the screening and detection of UTI.[52-54] The Chemstrip Urine Test (Boehringer Mannheim Corporation) is an inexpensive, rapid chemical test that combines the determinations of leukocyte esterase and nitrite concentrations. The leukocyte esterase test detects esterases released from leukocytes that have broken down. The nitrite test detects nitrites that have been produced from dietary nitrates by urinary bacteria. These tests, however, alone or in combination, are not sufficiently sensitive to determine the need for urine culture. False-negative and -positive tests are common, occurring in 15% to 30% of cases, and both tests are characterized by a low positive predictive value.[53-55] A recommended screening method is the "dipslide," which is a slide coated with agar that represents a sensitive and specific alternative to the standard culture.[52,56] The dipslide test can be performed in the office or in a patient's home and used in conjunction with microscopy for the initial diagnosis of UTI, the assessment of antimicrobial effectiveness, and follow-up after treatment.[52]

Contaminated collection of urine specimens, the storage of urine specimens at room temperature, and the presence of

vaginitis are the most common reasons for false-positive urine cultures. False-negative cultures or cultures yielding low colony counts may be caused by diluted urine (afternoon specimen or after taking diuretics), partial treatment with antibiotics, low urinary pH, contamination of the collection container with disinfectants, and complete ureteral obstruction. The growth of mixed bacteria in a urine culture in the absence of a structural urinary tract abnormality usually, though not invariably, indicates a contaminated specimen.

The evaluation, treatment, and prognosis of UTI are related to the site of infection—upper tract versus lower tract. In older children, cystitis is often diagnosed in the presence of dysuria, frequency, and urgency and in the absence of fever or other systemic manifestations, whereas pyelonephritis is diagnosed in the presence of fever—temperature above 38°C—abdominal or flank pain, and systemic upset including pallor, lethargy, irritability, anorexia, and vomiting. Nonspecific tests such as the erythrocyte sedimentation rate and C-reactive protein level in serum have also been used in an attempt to locate the site of infection.[3] Unfortunately, symptoms and tests correlate poorly with the infection site.[10] Other methods used to determine the level of infection have included indirect techniques, such as urinary enzyme activities, serum antibody titers, urinary concentration ability, and antibody-coated bacteria; and direct methods, including ureteral catheterization, bladder washout, or renal biopsy cultures.[1,10,57] Although localizing the level of infection is important, these methods have been used predominantly as tools of research. In clinical practice we do not usually use these tests, with the possible exception of acute-phase reactants. Recently increases in the renal volume of more than 30%, as determined by ultrasonography, were found to indicate upper tract disease.[58,59] Normal ultrasonograms did not exclude upper tract involvement, however. Parenchyma-avid radionuclides such as succimer (formerly dimercaptosuccinic acid [DMSA]) labeled with technetium 99m and technetium Tc 99m gluceptate reveal diminished uptake in areas of focal pyelonephritis,[60-63] and their use appears to be a sensitive and specific approach to determining the level of infection. Further studies are needed to assess the clinical application of ultrasonography and radionuclides in locating infection.

Diagnostic Studies

A radiologic evaluation of the urinary tract in children with UTI is indicated to identify vesicoureteral reflux, obstruction, or other urinary tract abnormalities. In about 50% of children with their first proven case of symptomatic UTI, a structural abnormality will be found.[2,64] Most renal injuries appear to occur in young children,[41,48] and the incidence of structural abnormalities is high in boys,[42] so radiologic evaluation is indicated for the following: a first incident of asymptomatic bacteriuria or UTI in a child younger than 5 years, a first incident of asymptomatic bacteriuria or UTI in any male child, and the recurrence of either of these in any female child. Extensive evaluation, however, is not indicated in a sexually active adolescent girl with recurrent lower tract infections. A family history of UTI or urinary tract abnormalities, an abnormal voiding pattern, poor growth, or hypertension also should prompt a radiologic evaluation of the first incident of UTI.

Voiding cystourethrography (VCUG) and intravenous urography are the time-honored examinations of choice for the initial radiologic evaluation of childhood UTI.[65] The VCUG detects vesicoureteral reflux, affords resolution adequate to grade the severity of the reflux, and provides both anatomic and functional information pertaining to the lower urinary tract. The intravenous urogram is a powerful imaging technique for the upper urinary tract, providing both structural and functional information. The quality of images is related to the adequacy of renal function; thus, neonates with immature renal function and older children with diminished renal function are difficult to evaluate with this tool.

New methods for evaluating renal morphology and function used in recent clinical studies have suggested alternative approaches to the investigation of UTI in childhood.[19,59-61,64,66] The experience, skill, and interest of the interpreting radiologist are important factors in the quality and reliability of the diagnostic evaluation.[19] Although the VCUG provides both direct detection of vesicoureteral reflux and anatomy related to the lower urinary tract, reflux alone can be detected using direct radionuclide voiding cystography. This results in a 50- to 100-fold decrease in gonadal radiation exposure when compared with the conventional VCUG, affords monitoring over a longer period of time, and allows the quantitation of voiding and refluxing events.[67] Anatomic detail, however, is not yet sufficient to grade reflux accurately or to detect anatomic abnormalities that might influence management.

Although the intravenous urogram may remain the single best test for evaluating upper tracts, sonography and radionuclide scintigraphy can be used to evaluate particular aspects of the upper tracts. Sonography is noninvasive, free of ionizing radiation, and capable of providing excellent information regarding renal size, parenchymal texture, size of the collecting system, and anatomy of the bladder.[58,68] Calculi in the urinary tract can also be detected by this tool. Sonography, however, does not detect small focal renal scars and provides only indirect functional information. Thus, abnormal sonograms must often be supplemented by a functional study.

Various radionuclides have been used in the evaluation of the urinary tract.[60,69,70] Parenterally administered technetium Tc99m pentetate (diethylenetriamine-pentaacetic acid [DTPA]) is cleared by glomerular filtration (like inulin) and results in a dynamic radionuclide "intravenous urogram equivalent."[60] The particular strength of this test is in the evaluation of excretory function, which can be quantitated and performed as a "diuretic renogram" when combined with the administration of furosemide. Renal blood flow, closely paralleling global renal function, can be evaluated with iodohippurate sodium I 123 or I 131, which is secreted by the kidney. Again, excretory function is evaluated to a greater extent than is renal parenchyma. Technetium succimer accumulates in functional renal cortex and provides exquisite renal images. It is particularly useful in demonstrating acute pyelonephritis, evaluating focal parenchymal scarring, and assessing solid renal masses versus hypertrophied columns of Bertin.[60,62,70] Technetium succimer, however, delivers a substantial radiation dose to the renal parenchyma and provides no excretory information. Technetium gluceptate is a hybrid agent in that early images using this radionuclide provide information regarding excretion and delayed images show parenchymal detail.

Figure 1 summarizes a reasonable protocol for the radiologic evaluation of UTI in children. The choice of a particular examination, however, depends on the clinical findings, the

facilities available, and the experience and skills of the radiologist. Both VCUG and renal sonography are the initial studies used to determine the next appropriate tests (although some consider the combination of plain abdominal film and renal sonography adequate in children older than 7 years).[64,66] If both tests are normal, no further radiologic evaluation is indicated. In the absence of vesicoureteral reflux, small focal renal scars that may be undetected by ultrasonography are probably of little practical importance in the management of UTI.[68] If reflux is detected, the evaluation of both upper tract structure and function is recommended. If morphologic changes are identified by ultrasonography in the absence of reflux, a search for urinary tract abnormalities such as anatomic obstruction, ureterocele, ectopic kidney, or duplicated system should be carried out. The intravenous urogram serves these purposes well in most instances,

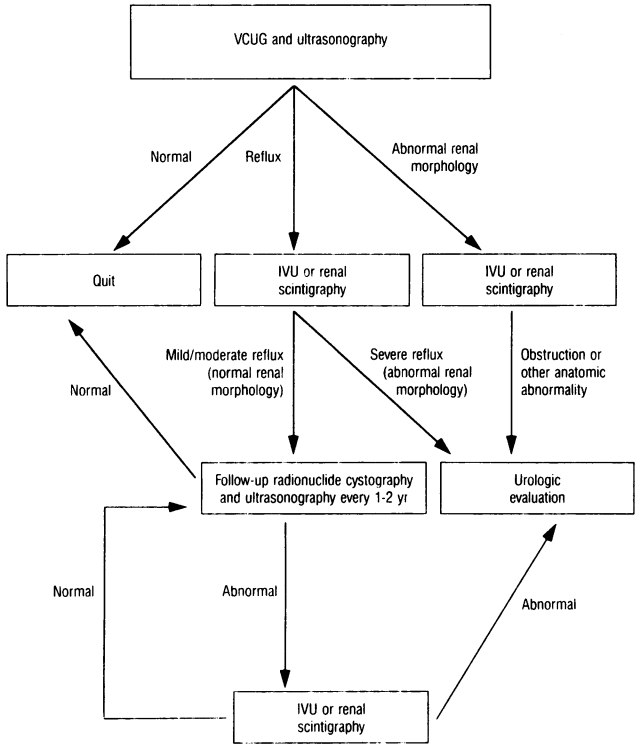

Figure 1.—The diagram shows the protocol for the radiologic evaluation of urinary tract infection in children. IVU = intravenous urography, VCUG = voiding cystourethrography

but quantitative scintigraphy with ^{99m}Tc-succimer, ^{99m}Tc-pentetate, ^{99m}Tc-gluceptate, or ^{123}I- or ^{131}I-iodohippurate is preferable for neonates and patients in whom poor renal function is anticipated. Moreover, recent studies have suggested that the ^{99m}Tc-succimer scan may be superior to intravenous urography in detecting early renal scars, especially in young children.[71,72] Others, however, think that intravenous urography is still essential for detecting scars.[73] In the presence of moderate or severe vesicoureteral reflux (grades 3 to 5), it is recommended that upper tract evaluations be carried out with a catheter in the bladder because reflux can either simulate or mask renal function.[74]

Follow-up studies of vesicoureteral reflux should be done with radionuclide VCUG to minimize radiation exposure because anatomic detail is not necessary. In cooperative children, a radionuclide VCUG may be obtained without catheterization following intravenous scintigraphy studies. Renal sonography should be done every year or two during follow-up to document normal renal growth.

Transient reflux can be masked or overestimated during an acute UTI, and, thus, the ideal time of the VCUG is four to six weeks after the completion of antimicrobial therapy,[19] although some have suggested such a wait is unnecessary. Certainly if the information is required urgently, the study can be done safely as long as the child is receiving appropriate antibiotics. Similarly, ureteral dilatation on an intravenous urogram (suggesting reflux) is a common transient finding in patients with acute febrile tract infection even in the absence of reflux.[75] Immediate sonography is helpful in an acutely ill child to exclude the combination of infection plus obstruction.

Pelvic radiographs (intravenous urogram or VCUG) taken during the evaluation of UTI should be examined for the presence of lower spine abnormalities. Children with a history suggestive of voiding dysfunction should have a urodynamic evaluation to exclude bladder sphincter dyssynergia.[10] Recently it has been recommended that siblings of patients with known vesicoureteral reflux should have a screening radionuclide VCUG for the early detection of reflux,[45] which is found in as many as 45% of these children[46]; others have argued that such screening is not cost effective.

Screening for Asymptomatic Bacteriuria

Screening for asymptomatic bacteriuria in children is controversial.[76] Although hypertension or renal insufficiency is a rare sequela, bacteriuria in schoolgirls is not an entirely benign condition and may signify an underlying structural abnormality or result in recurrent symptomatic urinary tract infections.[47] The main drawbacks, however, to screening schoolgirls for bacteriuria are as follows:

- A large population must be screened to detect the 1% to 2% with persistent bacteriuria;
- In girls with radiologically demonstrable anatomic abnormalities—0.2% to 0.5% of the school-age population—most of the kidney damage has already occurred before age 5 and may not progress afterwards; and
- There is controversy about the need to treat asymptomatic bacteriuria in schoolgirls.[48,50]

On the other hand, bacteriuria in infancy is often associated with a urinary tract abnormality and may result in intrarenal damage.[3,8] Screening neonates and infants for this disorder is not practical, however, mainly because of the difficulties in obtaining a clean urine specimen in this age group. The only group of children who definitely should be screened—with a semiannual to annual dipslide test or a standard urine culture—are the children at increased risk for bacteriuria and subsequent renal damage (see Risk Groups). The mass screening of children for bacteriuria is not recommended at this time.

Management

The approach to the treatment of UTI in children is based on clinical severity, site of infection, age, the presence of structural abnormalities, and the patient's compliance.[3,5,77] Immediate treatment, especially in infants and young children with vesicoureteral reflux or other urinary tract abnormalities, is important because delay increases the risk of renal parenchymal scarring.[11] The antibiotics used in the treatment of UTI in children are listed in Table 1.

Symptomatic UTI in neonates is frequently associated with sepsis and substantial mortality and, therefore, after complete studies for sepsis, should be treated with parenteral antibiotics for seven to ten days, usually using a combination of ampicillin and an aminoglycoside.[3]

Young infants with UTI, children with clinical evidence of acute pyelonephritis, and children with upper tract infection associated with urologic abnormalities or surgical procedures often require hospital admission and intravenous antibiotic therapy. Therapy can be initiated with a combination of an aminoglycoside and ampicillin or an aminoglycoside and cephalosporin.[3,5] The extended-spectrum penicillins such as piperacillin or azlocillin are especially active against *Pseudomonas* species and have been used successfully as single-agent therapy for severe and complicated UTI.[5] The recently introduced aminoquinolones are not generally recommended for children and should be reserved for infections with multiply resistant *P aeruginosa*.[77] In the presence of renal insufficiency, dosages of antibiotics excreted in the urine must be modified.

TABLE 1.—*Antibiotics Used in the Treatment of Urinary Tract Infection in Children*

Antibiotic	Route of Administration	Dosage, mg/kg/day
Amikacin	Parenteral	15 every 8 hr 7.5 every 12 hr (neonate)
Amoxicillin	Oral, parenteral	20-50 every 8 hr
Ampicillin	Oral, parenteral	50-100 every 6 hr
Cefaclor	Oral	20-40 every 8 hr
Cefazolin sodium	Parenteral	100-150 every 6-8 hr
Cefotaxime sodium	Parenteral	150 every 6-8 hr
Ceftazidime	Parenteral	150 every 8 hr
Ceftriaxone sodium	Parenteral	100 every 12-24 hr
Cephalexin	Oral	50 every 8 hr
Mezlocillin	Parenteral	100-150 every 4-6 hr
Nitrofurantoin	Oral	5-7 every 6 hr
Piperacillin sodium	Parenteral	100-150 every 4-6 hr
Sulfisoxazole acetyl	Oral	120-150 every 6 hr
Ticarcillin	Parenteral	200-300 every 6 hr
Tobramycin, gentamicin sulfate	Parenteral	5-7.5 every 8 hr
Trimethoprim (TMP) and sulfamethoxazole (SMZ)	Oral	8-10 TMP, 40-50 SMZ every 12 hr

In children with symptomatic lower UTI with or without reflux, oral therapy may be initiated with amoxicillin, ampicillin, sulfisoxazole acetyl, a combination drug containing trimethoprim and sulfamethoxazole, nitrofurantoin, or cephalosporins.

Controversy exists about the need for antibiotic treatment of asymptomatic bacteriuria.[76,77] The following objections have been raised:

- Treatment only reduces the duration of bacteriuria but has no effect on the emergence of symptoms, the clearance of vesicoureteral reflux, kidney function, kidney growth, or the progression of kidney scars[48,50];
- Short-term therapy may eradicate organisms of low virulence, but may precipitate acute pyelonephritis following recolonization by virulent organisms[78,79]; and
- Side effects may be associated with long-term antibiotic administration.

We treat children with asymptomatic bacteriuria if they are younger than 5 years, have a urinary tract structural abnormality, or if symptomatic UTI develops. Uncomplicated UTI and asymptomatic bacteriuria usually respond to treatment within 24 to 48 hours as evidenced by clinical improvement, a negative Gram's stain of the urine specimen, and sterile urine. If the patient responds to therapy adequately, in vitro susceptibility reports can be ignored because urinary antibiotic levels often markedly exceed the serum levels simulated by disc antibiotic sensitivity testing. A failure of response suggests noncompliance, poor absorption of the drug, bacterial resistance, improper dosage, or an underlying structural defect indicating the need for prompt radiologic evaluation.

Uncomplicated UTI or asymptomatic bacteriuria is usually treated for seven to ten days. The successful treatment of uncomplicated UTI in children has been reported with a three-day course of various antibiotics,[80] a single dose of oral amoxicillin (50 mg per kg),[81,82] or a single parenteral dose of gentamicin sulfate (5 mg per kg) or netilmicin sulfate (4.5 mg per kg).[83,84] Cure and recurrence rates in children treated with short-course therapy were comparable in some studies to those achieved with conventional seven- to ten-day treatment. The advantages of short-term therapy are better compliance, fewer side effects, cost savings, and less likelihood of altering fecal flora or selecting for bacterial resistance. The use of short-course therapy for UTI in children is still controversial, however.[85,86] Moffat and co-workers critically reviewed 14 published trials of short-course (<4 days) versus conventional (7 to 10 days) therapy and found that there was insufficient evidence to support the use of short-course therapy because of inadequate sample size and study methods. Until further data are available, this method of treatment should be reserved for selected patients with asymptomatic bacteriuria and girls older than 5 with clinical findings of lower tract infection, a documented normal genitourinary tract, and poor compliance.

A urine culture by dipslide or calibrated loop should be done three to seven days after the completion of therapy to exclude relapse. The importance of a follow-up culture cannot be overemphasized. Relapses usually occur within a week of completing therapy, are caused by the same bacteria, and often signify upper tract infection.[6] In contrast, the recurrence of UTI occurs from weeks to months after an infection and is commonly caused by different species of bacteria.[6] In every child with documented bacteriuria or UTI, two to three urine cultures per year should be obtained to detect recurrences. Usually three documented infections in a year indicate the need for prophylactic therapy. Both trimethoprim-sulfamethoxazole (10 mg per kg per day of sulfamethoxazole) given nightly or on alternate nights and nitrofurantoin (1 to 2 mg per kg per day) given nightly are highly effective in preventing recurrences and have few side effects.[3,77,87] Antibiotic prophylaxis may be continued for six months to two years. In selected patients with persistent vesicoureteral reflux, prophylaxis may need to be extended for several years because of the potential risk of new scar formation.[43] Prophylaxis is recommended for all children younger than 5 with vesicoureteral reflux or other urinary tract abnormalities. Some recommend that children who undergo catheterization of the urethra for any reason should receive full-dose prophylactic antibiotic therapy for 48 hours from the time of catheterization.[77]

Mild to moderate reflux (grades 1 to 3) usually disappears

with increasing age. Surgical intervention is not indicated if urine cultures are repeatedly sterile, long-term prophylactic therapy can be maintained, and sonograms every one to two years document adequate renal growth.[2,44] Double voiding and the avoidance of constipation are recommended preventive measures against infection. Patients should be referred to an experienced urologist for possible ureteral reimplantation if there is severe vesicoureteral reflux, increased reflux, uncontrolled infection, breakthrough infections, progressive scarring, renal growth arrest, or medical noncompliance. Surgical intervention may not decrease the incidence of UTI, but may reduce upper tract involvement.[1] Controversy exists whether reimplantation has a beneficial effect in preserving renal function, improving renal growth, and altering the course of chronic renal deterioration, especially when renal function is already decreased.[21,23] A recent five-year follow-up study of surgical versus medical treatment of severe vesicoureteral reflux in children reported no difference in the incidence of breakthrough urinary infections, renal tubular function, renal growth, the progression of existing renal scars, or new scar formation.[88] The submucosal administration of various substances (Teflon, bovine collagen) has been used recently as an alternative to ureteral reimplantation.[89] Concern remains, however, about the biocompatibility of these materials and about their suitability for the long-term prevention of vesicoureteral reflux.[89] Patients with obstruction or voiding dysfunction, such as neurogenic bladder or dyssynergia, should also be referred to a urologist.

There is no evidence that urethral dilatation, meatotomy, or urethrostomy reduces the incidence of UTI. Good hygiene including front-to-back wiping of the anus has been recommended. The use of shampoos, bubble bath, or other chemical irritants should be avoided. Constipation, often diagnosed only after a careful history, should be corrected.

Urinary tract infection complicated by neurogenic bladder, obstruction, or indwelling catheters responds poorly to antibiotic therapy unless the complication is corrected. Intermittent bladder catheterization has dramatically reduced infectious complications of neurogenic bladder.[90]

Summary

The early diagnosis and prompt treatment of urinary tract infection, especially in infants and young children, are of crucial importance. One must be aware of the nonspecific manifestations of UTI early in life when most of the kidney damage due to infection occurs. The diagnosis of UTI in questionable cases, especially in infants, should be verified by suprapubic aspiration or sterile bladder catheterization. The diagnosis demands prompt radiologic evaluation of the urinary tract in all male children, all children younger than 5 years, all patients with voiding dysfunction, and school-aged girls with recurrent UTI. The VCUG coupled with renal sonography remains the essential initial examination in children with UTI; the results of these tests determine whether intravenous urography or renal scintigraphy is the next appropriate test. Children with vesicoureteral reflux or with recurrent UTIs should receive prophylactic antibiotics and should be followed closely to prevent the development of renal parenchymal scars. In certain high-risk groups, asymptomatic bacteriuria may signify an underlying urinary tract abnormality and should be evaluated and treated accordingly. Further studies are needed to investigate the role of short-course antibiotic therapy in the management of UTI in children.

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