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Urinary Tract Infections in Children Younger Than 5 Years of Age

Epidemiology, Diagnosis, Treatment, Outcomes and Prevention

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Contents

Abstract

Although the true incidence of urinary tract infections (UTIs) in children is difficult to estimate, they are one of the most common bacterial infections seen by clinicians who care for young children. Except for the first 8 to 12 weeks of life, when infection of the urinary tact may be secondary to a haematogenous source, UTI is believed to arise by the ascending route after entry of bacteria via the urethra. Enterobacteriaceae are the most common organisms isolated from uncomplicated UTI. Infection with *Staphylococcus aureus* is rare in children without in-dwelling catheters or other sources of infection, and coagulase-negative staphylococci and *Candida* spp. are associated with infections after instrumentation of the urinary tract.

The diagnosis of UTI in young children is important as it is a marker for urinary tract abnormalities and, in the newborn, may be associated with bacteraemia. Early diagnosis is critical to preserve renal function of the growing kidney. A urine specimen for culture is necessary to document a UTI in a young child. Prior to culture, urinalysis may be useful to detect findings supporting a presumptive diagnosis of UTI.

The goals of the management of UTI in a young child are: (i) prompt diagnosis of concomitant bacteraemia or meningitis, particularly in the infant; (ii) prevention of progressive renal disease by prompt eradication of the bacterial pathogen, identification of abnormalities of the urinary tract and prevention of recurrent infections; and (iii) resolution of the acute symptoms of the infection. Delay in initiation of the antibacterial therapy is associated with an increased risk of renal scarring. The initial choice of antibacterial therapy is based on the knowledge of

the predominant pathogens in the patient's age group, antibacterial sensitivity patterns in the practice area, the clinical status of the patient and the opportunity for close follow-up. Imaging studies to detect congenital or acquired abnormalities are recommended following the first UTI in all children aged <6 years. Patients with significant urinary tract abnormalities and/or frequent symptomatic UTI may benefit from prophylactic antibacterials.

The main long term consequence of UTI is renal scarring which may lead to hypertension and end-stage renal disease. Prevention of recurrent UTI focuses on detection, and correction if possible, of urinary tract abnormalities. Interventions that have been associated with a decrease in symptomatic UTI in children with a history of recurrent UTI include relief of constipation and voiding dysfunction.

Urinary tract infections (UTIs) are one of the most common bacterial infections seen by the clinician who cares for young children. UTI is important for the clinician to diagnose as it is a marker for a urinary tract abnormality, and in the newborn may be associated with bacteraemia. In addition, recurrent UTI may lead to decreased renal function and hypertension.[1]

1. Epidemiology

The true incidence of UTI in children is difficult to estimate, particularly since young children with UTI may only have fever and no specific urinary tract symptoms (dysuria, urgency, urinary frequency) or signs (costovertebral angle tenderness).[2] The reported prevalence of UTI is influenced by patient selection, method of urine collection and definition of infection. Falsely high rates of infection are reported if urine samples are collected by application of a bag to the periurethral skin, a method known to have a substantial rate of bacterial contamination. The most important variables influencing prevalence are age and gender. In newborns, the rate for premature infants (2.9%) exceeds that for full term infants (0.7%),[3] and boys are 5 to 8 times more likely than girls to be infected.[4,5] Male predominance persists for the first 3 months of life, after which the prevalence among females exceeds that in males.[6] The prevalence reported in girls aged 1 to 5 years is 1 to 3%, whereas few infections occur in males of that age.[7-11] This is the age range in which children are most likely to experience a first symptomatic infection. Symptomatic infections occur 10 to 20 times more commonly in preschool girls than in boys.[12]

Febrile infants and children commonly have UTI. Urinary tract infections accounted for 7.5% of 442 febrile episodes in infants <8 weeks of age;[13] 5.3% of 945 episodes in those <1 year of age;[14] 4.1% of 501 episodes in children <2 years of age;[15] and 1.7% of 664 episodes among children <5 years of age.[16] Thus, the likelihood of UTI among febrile children decreases with increasing age.

Recurrence rate for UTI in girls is substantial regardless of the presence or absence of a urinary tract abnormality. The greatest risk of recurrence is during the first few months after an infection.[11] Approximately 75 to 80% of White and 50% of Black American schoolgirls will have a recurrence within 3 years of the first infection, with the greatest risk during the first 2 years. Recurrences tended to be less frequent the longer they remained free of infection but they are still at higher risk of ascquiring bacteriuria than the general population.[11,17] Most recurrent infections in girls represent reinfection from bowel flora rather than relapse with the same organism isolated at the initial infection.[11] Although recurrences are less frequent in males, approximately one-third have recurrent infection.[11]

Except for the first 8 to 12 weeks of life, when infection of the urinary tract may be secondary to a haematogenous source, UTI is believed to arise by the ascending route following entry of bacteria via the urethra.[18] The sequence of events leading to an ascending infection of the urinary tract is thought to begin when bacteria residing in the gas-

trointestinal tract colonise the periurethral mucosa. Periurethral bacteria may then ascend into the bladder and from there to the kidneys via the ureters by some undefined mechanism, establishing a risk of subsequent bladder urine or renal parenchymal infection. Thus, in order to acquire infection it is thought that at least small numbers of *Escherichia coli* or other uropathogens must colonise the urethra and gain entry into the bladder. To explain these observations, Stamey et al.[19] proposed the 'host susceptibility theory', which hypothesises that enteric bacteria tend to colonise the vaginal vestibule and urethra of females with recurrent UTI more frequently and in higher numbers than in otherwise healthy females. In contrast, Cattell et al.[20] proposed the 'chance colonisation theory' that all females with normal urinary tracts are at the same risk of developing a first episode of UTI. Once established, each infection sets the stage for the next infection. The theory by Stamey et al.[19] is supported by data on blood group antigens (ABO, P, Lewis and secretor)[21,22] and risk of infection. The theory by Cattell et al.[20] may be supported by work on virulence factors expressed by *E. coli* that may increase risk of UTI in healthy females.[23]

Enterobacteriaceae are the most common organisms isolated from uncomplicated UTI. Of these, *E. coli* accounts for 70 to 90% of infections.[24,25] *Pseudomonas aeruginosa* is the most prevalent of the nonenteric Gram-negative pathogens. *Enterococcus* spp. are the most common Gram-positive pathogens in young children. Group B streptococci are unusual urinary tract pathogens, but are occasionally isolated from the infected urine in neonates.[26] *Staphylococcus aureus* rarely causes pyelonephritis or cystitis in children without in-dwelling catheters; recovery of this organism from the urine suggests an additional site of infection such as renal abscess, osteomyelitis or bacterial endocarditis. *Proteus mirabilis* is prominent in young boys >1 year of age.[27] Coagulase-negative staphylococci and *Candida* spp. are associated with infections following instrumentation of the urinary tract. Adenovirus, a cause of acute haemorrhagic cystitis, is the only viral agent likely to be encountered as a urinary tract pathogen.[28]

2. Diagnosis

The clinician's major goal for the young child with a UTI is early diagnosis in order to allow identification of urinary tract abnormalities and preservation of renal function in the growing kidney. A urine specimen for culture is necessary to document a UTI in a young child.[29,30] Urine specimens may be obtained by suprapubic bladder aspiration, urethral catheterisation or by the bag technique in the non–toilet-trained child. Use of a urethral catheter provides a reliable method for culture. The urethral technique is simple but the catheter must be inserted carefully past the curved portion of the posterior urethra in boys to avoid mucosal trauma in that area. The low contamination rates of urine collected by suprapubic aspiration or catheterisation prevent the misinterpretation of culture results. Cumulative experience with the suprapubic aspiration technique indicates that it is a well tolerated and simple technique to use.[31,32] The morbidity associated with this procedure is minimal. Transient gross haematuria has been reported in 0.6% of 654 infants.[32] Bowel perforation, haematoma of the anterior bladder wall, peritonitis and anaerobic infection have been published as case reports because these complications are rare.[33-38] Although a culture-negative urine bag sample is reliable, this technique has a high rate of false positive cultures owing to contamination by periurethral flora.[39] Thus, urethral catheterisation or suprapubic aspiration is recommended following a positive urinalysis or culture result from a urine bag specimen to distinguish contamination from UTI prior to the initiation of antimicrobials. In the toilet-trained child, a voided midstream urine specimen is the preferred technique. Cleansing of the urethral meatus prior to collection of the voided specimen appears to have no significant effect on the rate of urine specimen contamination.[40-42]

Ideally, the collected urine specimen should be processed immediately. If that is not possible, the specimen should be refrigerated at 4°C and pro-

cessed within 24 hours. Quantitative aerobic culture of a properly collected urine specimen constitutes the most reliable method for documentation of a UTI. In order to quantify bacteria present in infected urine, a calibrated loop which delivers 10 or 1μl should be used to streak urine onto agar plates. After incubating the plates at 37°C for 24 hours, the number of colony forming units (CFU) should be counted. The number of organisms in 1ml of the urine specimen is estimated by multiplying the CFU count by the appropriate factor.

In 1957, Kass[43] demonstrated that women with a clinical diagnosis of pyelonephritis had 10^5 bacteria/ml of urine, whereas asymptomatic patients had smaller counts of bacteria, which were considered contaminants. Although no comparable studies have been conducted in children, the presence of $\geq 10^5$ CFU of a urinary tract pathogen per ml of urine is a widely accepted standard for documenting a UTI. Hellerstein[44] has defined the criteria for paediatric patients and included collection technique and gender as important variables. For suprapubic aspiration, if any gram-negative bacilli or >1000 gram-positive colonies are detected on the culture plate the probability of infection is >99%. For urine collected by catheterisation, if $>10^5$ colonies are detected, the probability of infection is 95%; if 10^4 to 10^5 colonies are detected, infection is likely; if 10^3 to 10^4 colonies are detected, one should treat as suspicious and repeat the test. If $<10^3$ colonies are detected, infection is unlikely. For clean-voided urine collected from a boy, infection is likely if $>10^4$ colonies are detected. For clean-voided urine from a girl, the probability of infection is 95% if $>10^5$ colonies are detected from 3 specimens, 90% if $>10^5$ colonies are detected from 2 specimens, and 80% if $>10^5$ colonies are detected in one specimen. Infection should be suspected (and test repeated) if 5×10^4 to 10^5 colonies are detected; infection should also be suspected if colony counts are 10^4 to 5×10^4 and child is symptomatic; however, if child is asymptomatic, infection is unlikely. Infection is also unlikely if $<10^4$ counts are detected.

Prior to culture, a urinalysis may be performed to detect findings supporting a presumptive diagnosis of UTI. Microscopic examination of the urine, in which a counting chamber determines white cell counts and a Gram stain classifies bacteria, has a high sensitivity and specificity for detecting UTI.[45] However, in clinical practice this technique of urine microscopy is not available. Instead, microscopy is performed using a 'standard' technique in which urine sediment is examined under a light microscope for bacteria and white cells. Standard microscopy is not reliable for excluding UTI in a young child (sensitivity of 60 to 70% for UTI when compared with culture) [Schlager, TA et al. unpublished data].[46-48] A dipstick analysis which can be performed at the bedside for nitrite and leucocyte esterase has a sensitivity of 80%. A recent study by Shaw et al.[47] demonstrated that standard microscopy was not accurate for predicting culture results and added little to the dipstick analysis for the presumptive diagnosis of UTI. These authors recommend that a urine culture be obtained when a physician wishes to exclude a UTI in a young child.

3. Localisation of Urinary Tract Infections

Despite extensive descriptions of signs and symptoms distinguishing upper and lower UTIs, these characteristics are often not useful for reliably localising UTIs. Invasive localisation studies (renal culture, ureteral catheterisation[49] or bladder washout test[50]) indicate that 30 to 50% of patients who present with cystitis may have upper tract disease.[51,52] False positive results suggesting upper tract disease can be seen if the child has a bladder infection and vesicoureteral reflux. Renal cortical scintigraphy using technetium-99m dimercaptosuccinic acid can suggest the presence of acute pyelonephritis, associated with focal or diffuse areas of decreased cortical uptake of tracer without any loss of volume or renal scarring, associated with areas of decreased uptake accompanied by loss of volume. Renal cortical scintigraphy, however, is not available to most physicians when a child presents with UTI to an office practice. In our practice setting, a child with fever and UTI is assumed to have upper tract disease until renal cortical scintigraphy is available.

4. Treatment and Workup

The goals of management are: (i) prompt diagnosis of concomitant bacteraemia or meningitis, particularly in the infant; (ii) prevention of progressive renal disease by prompt eradication of the bacterial pathogen, identification of abnormalities of the urinary tract and prevention of recurrent infections; and (iii) resolution of the acute symptoms of the infection. Delay in initiation of antimicrobial therapy is associated with an increased risk of renal scarring.[53] Hospitalisation should be considered for any child aged <5 years who is suspected of having a UTI and appears systemically ill. All infants at risk for bacteraemia and meningitis should be hospitalised for initial management. Children who are not so ill can be managed as outpatients as long as the child can orally ingest the antibacterial without vomiting and follow-up is guaranteed.

The initial choice of antibacterial therapy is based on the knowledge of the predominant pathogens in the patient's age group, antibacterial sensitivity patterns in the practice area, the clinical status of the patient and the opportunity for close follow-up. Broad coverage for group B streptococci and Enterobacteriaceae using the intravenous route is required during the first 8 weeks of life pending results of blood and cerebrospinal fluid cultures. Once blood and cerebrospinal fluid cultures are confirmed as definitely negative and the patient is afebrile, antimicrobial therapy may be completed using the oral route. Current studies on the duration of therapy for UTI suggest that single dose to 3-day therapy is not as effective as therapy of 7 to 14 days.[54-59]

A variety of effective oral antibacterials are available for treating outpatients. Sulfonamides or nitrofurantoin are comparable in effectiveness to cotrimoxazole (trimethoprim-sulfamethoxazole) for treating uncomplicated infections caused by susceptible agents. The Urinary Tract Subcommittee of the American Academy of Paediatrics reported that intramuscular ceftriaxone or gentamicin is effective in resolving UTI in children in whom oral therapy has failed.[60,61] Intravenous therapy should also be considered.

UTI in young children is a marker for abnormalities of the urinary tract. Imaging studies will detect congenital or acquired abnormalities of the urinary tract and are recommended following the first UTI in all boys and girls aged <6 years.[62-64] Currently the standard workup of the urinary tract in a child consists of renal ultrasound to define renal structure and detect dilatation of the collecting system, and cystography (voiding cystourethrogram or radionuclide cystogram) to define the presence and grade of reflux.[65] If either study is abnormal, consultation with a paediatric urologist will assist in determining the need for additional workup or treatment.

Patients with significant urinary tract abnormalities and/or frequent symptomatic UTI may benefit from prophylactic antibacterials.[66] The drugs of choice are nitrofurantoin and cotrimoxazole. This practice is based on a study conducted by Smellie et al.[67] who examined the effect of antimicrobial prophylaxis in children with recurrent UTI and structurally normal urinary tracts. In this study, 45 children (47 episodes of UTI) with radiologically normal urinary tracts were given prophylactic doses of cotrimoxazole or nitrofurantoin, or no prophylaxis, after treatment of a symptomatic UTI. During the initial 10 months of study, the 25 children on prophylaxis had significantly fewer episodes of bacteriuria than the 22 children not on prophylaxis; however, the number of symptomatic and asymptomatic episodes was not defined. During the 12 months follow-up after prophylaxis was stopped, there was no difference in the incidence of bacteriuria between the 2 groups. Further studies have indicated that nitrofurantoin, sulfonamides and cotrimoxazole are effective in reducing the recurrence rate of infection in patients with normal urinary tracts as long as the drug is given.[68,69]

Caldamone[70] in a recent letter has considered antimicrobial prophylaxis for infants with significant hydronephrosis diagnosed on prenatal ultrasound. During the neonatal period, amoxicillin at one-third the normal dosage is recommended. After 3 months, sulfamethoxazole or nitrofurantoin may be substituted.

Physicians need to be aware of resistance patterns of *E. coli* in their area of practice. Increasing resistance of *E. coli* to amoxicillin nationwide limits its use in symptomatic UTI.[71]

5. Outcome

Our evolving knowledge of the long term consequences of UTI centres on the pathogenesis of renal scarring. Renal scarring in childhood may lead to hypertension and endstage renal disease. Of particular interest is the role of vesicoureteral reflux (VUR) in renal scarring.[72] VUR is considered a congenital anomaly of the ureterovesical junction in which there is a shortened submucosal tunnel with lateral placement of the ureteral orifice in the bladder.[73] The high familial incidence of VUR, especially in HLA-identical twins, suggest a genetic anomaly. As a result of this deficiency, the ureter enters the bladder laterally without adequate submucosal length. The longitudinal muscle is not able to adequately constrict the submucosal ureter, so the valve mechanism is defective and urine backflows into the ureter.

VUR is identified in 30 to 50% of children who are evaluated after their first UTI.[73] It is graded according to degree of reflux, from reflux limited to the ureter to severe reflux associated with massive dilatation of ureter, pelvis and calyces. As the child grows, the submucosal tunnel elongates and the ratio between the submucosal tunnel length and the ureteral diameter increases. Therefore, the natural course of mild reflux is to resolve or improve with time. Patients with more severe reflux are less likely to have spontaneous resolution. The increased use of ultrasonography during pregnancy has identified infants with hydronephrosis.[74] Urological workup suggests that VUR and renal scarring is congenital in these infants and not a result of parenchymal infection.[75-77] In contrast, urological imaging in older children with UTIs, with and without VUR, suggests that infection of the renal parenchyma, not VUR, is the prerequisite for acquired renal scarring.[77-80]

Wennerstrom et al.[81] further characterised renal scarring in children in a prospective study where children were followed after their first symptomatic UTI. Boys usually had scarring noted during their first UTI (assumed to be congenital) with associated reflux. Girls, however, had acquired scarring related to recurrent febrile UTI. In a longitudinal study[82] in which 226 children with UTI and VUR were followed for 10 to 35 years, 17 patients (7.5%) as adults developed hypertension, impaired renal function or complications of pregnancy. Sixteen out of 17 had renal scarring on presentation; in 8 the scarring was severe. Deterioration in kidney function developed only in those patients who had renal damage at initial presentation.

In summary, children with renal injury present on prenatal examination are most likely to develop hypertension and end-stage renal disease. 'Acquired renal injury as a cause of hypertension and impaired renal function is less common today than earlier in this century; probably as a result of improved healthcare.'[83]

6. Prevention

Prevention of recurrent UTI focuses on detection, and correction if possible, of urinary tract abnormalities such as posterior urethral valves or ureterovesical obstruction. Interventions that have been associated with a decrease in symptomatic UTI in children with a history of recurrent UTI include relief of constipation[84] and voiding dysfunction.[85] In a study by Loening-Baucke,[84] the frequency of UTI in children with chronic constipation was evaluated and resolution of UTI was reported when constipation was treated. In this study, 176 boys and 8 girls (aged 5 to 18 years) with functional constipation were evaluated; 25 of the 176 children had recurrent UTI. Twenty out of 25 had structurally normal urinary tract by renal ultrasound and voiding cystourethrogram. Nineteen out of 20 had constipation relieved and none of the 19 had recurrence of UTI during the study period.

Voiding dysfunction related to incomplete bladder emptying, leading to increased bladder capacity and the presence of residual bladder urine, has been described in a group of girls with recurrent UTI.[85] Residual urine enhances the growth of col-

onising bacteria which may lead to a symptomatic infection. Establishing regular periods where the patient can completely empty her bladder (patient urinates, waits a few minutes, then urinates again) has been associated with a decrease in the number of symptomatic infections.

Circumcision as an intervention aimed at decreasing the frequency of UTI in male infants is controversial.[86,87] There are no randomised controlled trials examining circumcision in male infants and the frequency of UTI. Studies examining the association of UTI and circumcision have not controlled for urine collection methods, diagnostic criteria for UTI or asymptomatic bacteriuria. In addition, the epidemiological data on UTI in countries such as Denmark and Sweden, where few males are circumcised, report that 1% of male newborns have a UTI. In contrast, Wiswell et al.[88] reported a 4% rate of UTI in uncircumcised infants in the US compared with a 0.2% rate in circumcised infants. The American Academy of Paediatrics Task Force on Circumcision reported that 'in the absence of well designed prospective studies, conclusions regarding the relationship of UTI to circumcision are tentative.'[89]

Improved hygiene, particularly in young girls with recurrent UTI, has never been shown to decrease UTI. Bolgren and Winberg[90] demonstrated that although 75 to 80% of 200 infants of both genders were heavily colonised on the periurethra with aerobic Gram-negative rods, only 1 to 2% developed a UTI. The authors concluded that the fact that periurethral bacteria occur in abundance in infants and toddlers without causing infection must mean that neither soiling nor contamination of their perineum is sufficient to cause a UTI.

7. Conclusions

The clinician's major goal for the young child with UTI is early diagnosis in order to eradicate infection in the growing kidney and to allow identification of urinary tract abnormalities before the deterioration of renal function.

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