Urinary tract infections in infants and children: a comprehensive overview
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Purpose of review
Urinary tract infections are the most common serious bacterial infections in infants and young children. This review focuses on new additions to the literature for the period August 22, 2002, to August 21, 2003.

Recent findings
There is still considerable interest in determining which test is best to predict the likelihood of a positive urine culture in children at risk for urinary tract infection. One new analysis and several older analyses suggest that the finding of pyuria, as measured by at least 10 leukocytes/mm³ on unspun urine is a very valuable cutoff for identifying infants for whom urine culture is warranted. Several new investigations have studied the value of various imaging studies in children with urinary tract infections. It has been shown that the finding of vesicoureteral reflux is variable and that single studies may underestimate or overestimate the degree of reflux. The natural history for lower grades of reflux (grades 1, 2, and 3) is spontaneous resolution at a rate of 13% per year. The rationale for the determination of the degree of reflux by voiding cystourethrogram is to guide the institution of antimicrobial prophylaxis or surgical intervention until the reflux resolves. This is based on the assumption, as yet unproven, that these interventions will prevent or decrease reinfection and thereby prevent the development of renal scarizing. Data are presented indicating that there is still no evidence that this assumption is correct.

Summary
Continued attention to the need for and benefit of imaging procedures in children with urinary tract infection mandates that there be a randomized, controlled prospective trial of antimicrobial prophylaxis versus no treatment for children with various degrees of reflux.

Keywords
urinary tract infection, vesicoureteral reflux, voiding cystourethrogram

Introduction
Urinary tract infections (UTIs) are the most common serious bacterial infections in infants and young children. They are more common than bacterial meningitis, bacterial pneumonia, or bacteremia. Infection of the urinary tract may be limited to the bladder, one or both kidneys, or both sites. In general, infections of the bladder (cystitis), although they cause substantial morbidity, are not regarded as serious bacterial infections. By contrast, infections that involve the kidney (pyelonephritis) may cause both acute morbidity and lead to scarring with the consequences of hypertension, preeclampsia, and chronic renal disease. Accordingly, differentiation of the site of infection has received considerable attention.

Diagnosis of urinary tract infection
The diagnosis of UTI may be suggested by certain signs and symptoms, but culture of the urine is the gold standard. Because culture results are not available for at least 24 hours, there has been considerable interest in evaluating tests that may predict the results of the urine culture so that appropriate therapy can be initiated at the first encounter with the symptomatic patient. The tests that have received the most attention are urine microscopy for leukocytes (WBC) and bacteria, and biochemical analyses for leukocyte esterase and nitrite that can be assessed rapidly by dipstick.

Huicho et al. [1] performed a meta-analysis of urine screening tests to determine the risk of UTI in children. Their study updated the results of Gorelick and Shaw [2], which were reported in 1999. The latter study concluded that both the presence of any bacteria on a Gram stain of an uncentrifuged urine specimen and the result of dipstick analysis (for leukocyte esterase and nitrite) perform similarly in children from birth through 12 years of age and are superior to microscopic detection of pyuria. The newer study concluded differently; that pyuria of at least 10 WBC/hpf or at least 10 WBC/mm³ and bacteriuria (any) are best suited for assessing the risk of UTI in children. Other recent studies in both young
infants (<2 months of age) and older infants and children (<12 months and 1–24 months of age) have concluded that hemocytometer WBC counts (cell counts ≥10 WBC/mm³) provide the most valuable cutoff point for identifying infants for whom urine culture is warranted [3–5].

**Determining the site of infection**

Urinalysis is very useful for detecting infection but not for determining the location of the infection within the urinary tract (ie upper tract vs lower tract). To determine the site of infection (ie kidney vs bladder), there have been many investigations of the discriminatory ability of C-reactive protein (CRP), erythrocyte sedimentation rate, and total peripheral WBC.

Recently there has been enthusiasm for using levels of serum procalcitonin (PCT) to predict the level of infection in children with UTI [6•]. PCT is a prohormone of calcitonin that was initially described as a marker of bacterial disease. In normal individuals, the level of PCT is very low (<0.5 µg/L). A single measurement can be made with as little as 20 µl of serum, with test results that can be available within 2.5 to 3 hours. Smolkin et al. [6•] evaluated 64 patients from 2 weeks to 3 years of age with febrile UTI. On admission and before treatment was started, blood was sampled for routine laboratory investigations, including blood culture, CRP, and WBC counts. PCT levels were determined by immunoluminometric assay. The diagnosis of acute pyelonephritis was confirmed in patients who had abnormal technetium-99m-labeled dimercaptosuccinic acid (DMSA) scintigrams at the time of admission that showed partial or complete improvement 6 months later. For the prediction of acute pyelonephritis, the sensitivity and specificity of PCT were 94.1% and 89.7%, respectively, whereas CRP had a sensitivity of 100% and a specificity of 18.5%. Prat et al. [7•] also evaluated and compared PCT with CRP in 77 patients with UTI. PCT at the initial examination showed a significant correlation with the presence of renal scars in children with UTI. Using a cutoff point of 1 ng/mL for PCT and 20 mg/L for CRP, the sensitivity and specificity in distinguishing between UTI with and without renal damage were 92.3% and 61.9%, respectively, for PCT and 92.3% and 34.4%, respectively, for CRP. The positive and negative predictive values were 32% and 97.5%, respectively, for PCT and 23% and 95%, respectively, for CRP. Both groups of authors concluded that PCT may be an accurate marker for the early diagnosis of acute pyelonephritis [6•,7•].

**Imaging**

Imaging studies are the standard of care for young children with a first UTI. Hoberman et al. [8••] assessed the value of routine imaging studies after the diagnosis of a first febrile UTI in 309 children 1 to 24 months of age. Renal ultrasonography, DMSA, and contrast voiding cystourethrogram (VCUG) were performed in almost all of the children. Of the 309 ultrasonograms, 272 (88%) were abnormal and 12 showed modest abnormalities that did not alter treatment. The initial DMSA scans demonstrated that 61% (190 of 309) had findings compatible with acute pyelonephritis. VCUGs, which were performed in 98% of the children 1 month after diagnosis, showed that 39% (117 of 302) had evidence of vesicoureteral reflux (VUR), most of which (96%) was Grades 1, 2, and 3. The authors suggested that renal ultrasonography and DMSA scans at the time of the acute illness are of limited value because they do not provide information that modifies management. They noted that the usefulness of the VCUG rests on the unproved assumption that continuous prophylactic antimicrobial therapy, given if reflux is established, is effective in reducing the incidence of reinfection and renal scarring. Until a definitive study is undertaken to dispel this assumption, most clinicians will perform VCUGs and prescribe prophylaxis for children with any degree of reflux.

Grmek and Fettich [9••] recently demonstrated that reflux occurs intermittently. They performed follow-up radionuclide VCUGs in a group of children who had previously received diagnoses of either no reflux or Grade 1 reflux. Children were referred for imaging studies after their first UTI. The mean interval between studies was 465 days (SD 258 days). Of 31 children who did not have reflux on the initial exam, 52% were found to have reflux on the repeat study, including Grade 1 (29%), Grade 2 (16%), and Grade 3 (7%). For 275 children with Grade 1 reflux on the initial study, 61% had reflux on the second study, including Grade 1 (41%), Grade 2 (17%), and Grade 3 (3%). Their conclusion was that VUR in children tends to occur intermittently and may be either undergraded or even missed by currently recommended studies. These results prompt us to question whether our decisions to provide prophylaxis on the basis of a single VCUG are sensible. Should we instead have a high degree of suspicion for recurrences of UTI in any child who previously had a UTI rather than to subscribe to a daily prophylactic regimen in many children whose VUR may be intermittent and transient?

Wheeler et al. [10••] also raised the issue of the value of identification of children with reflux after a symptomatic UTI. They conducted a systematic review of randomized controlled trials of the effects of various interventions in patients with VUR on the development of subsequent UTI and renal parenchymal injury. The aims were to evaluate whether any intervention for reflux is better than no treatment and to evaluate the benefits and harms of the different treatment options that are currently used. Eight trials involving 859 evaluable children were reviewed. Seven trials compared antimicrobials alone with surgery plus antimicrobial prophylaxis. Only one small study, which showed no differences in the risk for UTI or renal damage, compared intermittent prophy-
laxis with continuous prophylaxis and no treatment. In the remaining studies, the risk of UTI by 1 or 2 and 5 years was not significantly different between the surgical and medical groups. Combined treatment (surgery plus antimicrobial prophylaxis) resulted in a 60% reduction in episodes of febrile UTI by 5 years, but, importantly, there was no significant reduction in the risk of new or progressive renal damage at 5 years. The additional benefit of surgery over antibiotics alone is small at best. Therefore, this study does not provide substantial support for the practice of routine identification and treatment of children with VUR.

Does the VCUG have predictive value in identifying children who are likely to have evidence of acute pyelonephritis when assessed by DMSA? This question was approached by Gordon et al. [11•]. A systematic literature review and meta-analysis were performed to determine how often the findings of primary VUR documented on VCUG in children hospitalized with UTI predicted renal parenchymal disease on DMSA scintigraphy. The meta-analysis showed that a positive VCUG increases the risk of renal damage in hospitalized UTI patients by approximately 20%, whereas a negative VCUG increased the chance of no renal involvement by just 8%. VUR is a weak predictor of renal damage in children hospitalized with UTI. The VCUG is not an effective tool to exclude renal damage in such patients.

What is the natural history of reflux? Schwab et al. [12•] determined the resolution rate by patient for 179 girls and 35 boys with UTI and diagnoses of primary VUR between 1981 and 1984. In this study, 107 patients (50%) had bilateral reflux, and 60 (28%) had dysfunctional voiding. Reflux spontaneously resolved in 146 patients (68%) during the study. Patients were categorized by the worst grade of reflux, received maintenance antibiotics, and underwent VCUG annually until reflux resolved. Kaplan-Meier curves were constructed to define the resolution rate. The study showed that Grades 1 to 3 reflux resolved at a rate of 13% per year for the first 5 years of follow-up and then at a rate of 3.5% per year during subsequent follow-up. Grades 4 and 5 reflux resolved at a rate of 5% per year. Bilateral reflux resolved more slowly than unilateral reflux and more rapidly in boys than in girls. Dysfunctional voiding had no effect on overall resolution.

Treatment

There are many choices for the antibiotic treatment of UTI in children. If a child has a toxic appearance or is vomiting, admission to the hospital for parenteral therapy is appropriate. Otherwise, children—even those with presumed pyelonephritis—generally do well with oral therapy [13]. For oral therapy, the choices are amoxicillin potassium clavulanate, second- or third-generation cephalosporins, or sulfamethoxazole-trimethoprim. Unfortunately, there has been a tendency during the past several years for the prevalence of antimicrobial resistance to increase. To assess the changing susceptibility of urinary pathogens to oral antibiotics in children with community-acquired UTI, Prais et al. [14•] reviewed the antimicrobial susceptibility of 142 children whose conditions were evaluated in 1991 and 124 children whose conditions were evaluated in 1999. The pathogens recovered during the two time periods were very similar. Most isolates were Escherichia coli. Approximately 8 to 13% were Klebsiella pneumoniae, and other gram-negative rods accounted for the remaining 5 to 8%. The study showed a slight but generalized decrease in bacterial susceptibility to common oral antibiotics over the decade. The overall resistance to antibiotics in 1999 was as follows: ampicillin 70%, cephalaxin 37%, sulfamethoxazole-trimethoprim 31%, amoxicillin-clavulanate 24%, nitrofurantoin 8%, cefuroxime-axetil 5%, and nalidixic acid 3%. As a consequence, ampicillin, cephalaxin, sulfamethoxazole-trimethoprim, or amoxicillin-clavulanate cannot be prescribed in Israel as empiric therapy for UTIs.

The optimal duration of therapy for children with UTI has been somewhat controversial. When pyelonephritis is confirmed or suspected, therapy for 10 to 14 days is conventional. Shorter courses of therapy have been successful in adult women with lower UTI. A recent meta-analysis conducted by the Cochrane Database of Systematic Reviews evaluated 10 trials in 652 children with lower tract UTI [15••]. There was no significant difference in the frequency of positive urine cultures between the short (2–4 days) and standard-duration (7–14 days) oral antibiotic therapy for UTI in children either early after treatment or at 1 to 15 months after treatment. Furthermore, there was no increase in the development of resistant organisms in UTI at the end of treatment or in recurrent UTIs between groups. In children with clear evidence of cystitis without pyelonephritis, short-course therapy may be acceptable.

Prophylaxis

It is generally recommended that children who are considered to be at risk for recurrent UTIs and potential scarring receive prophylactic treatment with either sulfamethoxazole-trimethoprim or nitrofurantoin. They include children with VUR, frequent and closely spaced UTIs without reflux, and occasionally children with urologic abnormalities or those who have just sustained an episode of acute pyelonephritis. Relatively few studies have systematically examined the benefits of prophylaxis. Hellerstein and Nickell [16•] described the outcome of using prophylactic antibiotics in children considered at risk for a UTI. They examined both breakthroughs that occurred during prophylaxis and recurrences that were observed when prophylaxis was discontinued. There was a significant risk of breakthrough infection among children with voiding dysfunction and abnormal kidneys during prophylaxis, and an increased
risk of infection among those with voiding dysfunction and VUR of at least Grade 3. Lesser grades of VUR and constipation did not significantly increase the risk of UTI.

The latest Cochrane Review [17••] of the effectiveness of long-term antibiotics for preventing recurrent UTI in children indicated that most published studies to date have been poorly designed without proper blinding. There is no question of the biologic plausibility of prophylactic antimicrobials in preventing recurrent UTI; however, the adverse effects of antimicrobials and difficulties with long-term adherence to prophylactic strategies are barriers to effectiveness.

**Voiding dysfunction**

Voiding dysfunction is a broad term indicating a voiding pattern that is abnormal for the child’s age. This condition should be considered in all children with a diagnosis of UTI. Hellerstein and Linebarger [18••] reviewed the records of 226 patients whose conditions were evaluated at the Children’s Kidney Center from October 1996 to July 2000. These children were referred by generalists and specialists because of suspected voiding dysfunction or UTI or both. The most common abnormality, which was present in 76.4% of children, was detrusor instability. This diagnosis was based on urinary urgency, with or without frequency, in the absence of local irritation. A total of 79% of the children had urge incontinence, and 45% had a history of recurrent UTIs. The occurrence of UTI in a child with detrusor instability was strongly influenced by the use of pelvic withholding maneuvers. UTI occurred in 72% of children in whom pelvic withholding maneuvers were observed, compared with 23% without such manerisms. The remaining problems were extraordinary daytime urinary frequency (8.7%), infrquent voiding (5.7%), daytime wetting (4.4%), transient voiding dysfunction (2.2%), dysfunctional voiding (0.9%), and unexplained dysuria. Constipation played a significant role in some children with detrusor instability. Attention to this comorbidity resulted in resolution of the UTI in some children.

**Conclusion**

Recent literature has focused on the value of imaging procedures for children with UTI and has questioned the necessity for antimicrobial prophylaxis in children with reflux. It is imperative that a randomized, prospective, placebo-controlled study be performed to determine whether antimicrobial prophylaxis is effective in preventing renal scarring in children with VUR.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


15. Hodson MM, Craig EM, Martin S, et al.: Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. Cochrane Database of Systematic Reviews, 2003. A 2- to 4-day course of oral antibiotics appears to be as effective as 7 to 14 days in eradicating lower tract UTI in children.


This study describes the pattern of voiding disorders in children and highlights the importance of detrusor instability with various posturing maneuvers as a risk for recurrent UTI.