CLINICAL MICROBIOLOGY REVIEWS, Apr. 2005, p. 417–422 Vol. 18, No. 2
0893-8512/05/$08.00+0 doi:10.1128/CMR.18.2.417–422.2005

Diagnosis and Management of Pediatric Urinary Tract Infections

Joseph J. Zorc,[1]* Darcie A. Kiddoo,[2] and Kathy N. Shaw[1]

Division of Pediatric Emergency Medicine, Department of Pediatrics, University of Pennsylvania School of Medicine,[1] and Department of Urology, Children's Hospital of Philadelphia,[2] Philadelphia, Pennsylvania

INTRODUCTION 417
EPIDEMIOLOGY AND IMPORTANCE OF UTI 417
DEFINITION AND PATHOPHYSIOLOGY 417
CLINICAL DIAGNOSIS 418
TREATMENT OF UTI 419
EVALUATION AFTER UTI 419
AGE DIFFERENCES 420
GENDER 420
VOIDING HABITS 420
STANDARD RADIOLOGICAL STUDIES 420
NUCLEAR MEDICINE 421
CONCLUSION 421
REFERENCES 421

INTRODUCTION

Urinary tract infection (UTI) is a problem that is frequently encountered by pediatric healthcare providers. Over recent decades, the importance of UTI has been increasingly recognized, in particular the role of UTI as an occult cause of febrile illness in young children. The evolving state of knowledge about pediatric UTI leaves many questions and controversies. This article reviews recent evidence regarding the epidemiology, diagnosis, management, and evaluation of children with UTI.

EPIDEMIOLOGY AND IMPORTANCE OF UTI

The epidemiology of UTI during childhood varies by age, gender, and other factors. The incidence of UTI is highest in the first year of life for all children (1%) but decreases substantially among boys after infancy (37). Estimates of UTI incidence among infant boys have varied in different populations, likely due to factors such as circumcision, which has been associated with a reduction in risk of UTI as discussed below (5, 13, 20, 78). Another issue affecting estimates of incidence is the increased recognition of UTI as a potential source of febrile illness in young children. Screening studies in emergency departments suggest that up to 5% of children under the age of 2 presenting with fever have UTI, and over half of these would have been given alternative diagnoses such as otitis media had the urine not been screened as part of the study (29, 60). A recent population-based study from Scandinavia reported a cumulative UTI incidence rate of 7.8% for girls (26) by the age of 7 years, more than twice the estimate of 3% reported by Winberg in the 1960s (76).

The clinical significance of UTI has been controversial. In the preantibiotic era, UTI had a mortality rate as high as 20% although acute complications in healthy children are now uncommon except in young infants, who may progress to systemic infection (14, 25) Long-term complications of UTI have been associated with renal scarring and include hypertension, chronic renal failure, and toxemia in pregnancy. Long-term follow-up data are limited, although one Swedish study found that children diagnosed with renal scarring due to pyelonephritis during the 1950s and 1960s developed high rates of hypertension (23%) and end-stage renal disease (10%) (36). More recent studies question the association between pyelonephritis and end-stage renal disease (18, 66). Although the individual risks associated with UTI remain unclear, the high prevalence of UTI and potential morbidity associated with complications require careful attention to diagnosis and management.

DEFINITION AND PATHOPHYSIOLOGY

UTI is defined by the presence of organisms in the urinary tract, which is usually sterile. However, since asymptomatic colonization of the urinary tract can occur, other features such as the presence of inflammatory markers or follow-up cultures may be needed to definitively diagnose a UTI. Clinically important infections usually occur due to bacteria, although viruses, fungi, and parasites can also cause infection. Common nonbacterial causes of UTI include hemorrhagic cystitis from adenovirus and *Candida* infection in immunocompromised individuals. Common bacterial pathogens include gram-negative species such as *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, and *Serratia* spp. and gram-positive organisms, including group B streptococci, *Enterococcus* sp., and *Staphylococcus aureus*. In general, bacteria infect the urinary tract by ascending from the urethra, although hematogenous infection may occur in rare instances among young infants.

UTI can be further subdivided into infection localized to the bladder and urethra (cystitis and urethritis) versus upper tract infection of the ureter, collecting system, and renal parenchyma (pyelonephritis). Ascending infection of the urinary

* Corresponding author. Mailing address: Division of Emergency Medicine, Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399. Phone: (215) 590-1944. Fax: (215) 590-4454. E-mail: zorc@email.chop.edu.

tract is a complex process that has been associated with bacterial adhesion, virulence, and motility properties as well as host anatomic, humoral, and genetic factors (69). The presence of fever, chills, and flank pain has usually been considered clinical evidence of upper tract infection. New technologies to identify the presence of upper tract infection, such as technetium 99m-labeled dimercaptosuccinic acid (DMSA) scans have demonstrated a wide range of estimates (34 to 70%) for the prevalence of pyelonephritis in children with febrile UTI (7, 9, 16, 17, 32, 44, 48).

The gold standard for diagnosis of UTI is growth of pathogenic bacteria in a urine culture. However, diagnosis is complicated by contamination from fecal bacteria that colonize the perineal area and distal urethra. In the 1950s, Kass studied adult women and established a threshold of ≥100,000 CFU per ml in a voided specimen as the standard to define a positive urine culture (40). In young children, urine is frequently obtained by catheter, and 10,000 CFU/ml has often been considered the cutoff for defining UTI (2). However, in a recent study of febrile children, Hoberman et al. noted that a high proportion (65%) of cultures with colony counts between 10,000 and 49,000 grew mixed or gram-positive organisms suggestive of contamination (31). Distinguishing true infection from contamination in cultures with this level of growth may be aided by a repeat culture if the patient has not been treated or by signs of acute infection such as the presence of pyuria.

Growth of any number of bacteria from urine obtained by suprapubic aspiration is considered a significant finding. However, even in these cases, diagnosis of an acute UTI is not certain due to the issue of colonization of the urinary tract known as asymptomatic bacteriuria. The definition and significance of asymptomatic bacteriuria has been a controversial topic since its identification in the 1950s and description by Kunin and colleagues (43).

Several long-term screening studies of infants and school-aged girls from Scandinavia have better defined this entity and reveal some of the complexities of the host-pathogen relationship in UTI (25). Among a group of 3,581 infants, asymptomatic bacteriuria was identified and confirmed by suprapubic aspiration in 2.5% of boys and 0.9% of girls (72). The majority of these cases cleared without treatment within a few months; only 2 of 45 infants went on to develop symptomatic infection. Among another 42 infants in the cohort who developed symptomatic UTI during the first year of life, none had been found to have asymptomatic bacteriuria at initial screening. This suggests that asymptomatic bacteriuria is a separate entity rather than a precursor to symptomatic infection. A long-term follow-up study of 116 school-aged girls with asymptomatic bacteriuria also found no difference in renal growth and function between those randomized to treatment or observation (45). Furthermore, treatment with prophylactic antibiotics appeared to lead to an increased likelihood of pyelonephritis, usually with different strains of bacteria than were originally present (25). None of the girls with asymptomatic bacteriuria who were left untreated went on to develop symptomatic infection. This suggests that some individuals may be persistently colonized with nonvirulent bacteria in the urinary tract.

TABLE 1. Clinical factors to determine risk of UTI and need for further screening in girls 2 to 24 months of age with fever[a]

Parameter	Relative risk of UTI (95% confidence interval)
Age less than 1 yr	2.8 (1.6–5.1)
Fever for 2 days or more	1.5 (0.9–2.6)
White race	6.0 (3.7–9.5)
Absence of a source for fever	1.9 (1.1–3.2)
Temperature ≥39°C	1.7 (0.9–3.1)

[a] Data from reference 23. Urine screening is recommended if two or more factors are present.

CLINICAL DIAGNOSIS

The question of when to screen for UTI has been evaluated in a number of studies and addressed by a subcommittee of the American Academy of Pediatrics (2). The presence of specific symptoms for UTI, including dysuria, frequency, urgency, suprapubic discomfort, and flank pain, should lead to screening. However, young children with UTI may present with nonspecific symptoms, such as poor feeding, vomiting, irritability, jaundice (in newborns), or fever alone, and a broader approach to screening may be appropriate.

Two recent studies of the prevalence of UTI among children presenting to an emergency department with fever found rates ranging from 3.5 to 5.5% (29, 60). Girls were more than twice as likely as boys to have UTI, and among boys, uncircumcised infants had an eightfold higher risk. This finding compares well with population-based studies of UTI which document a 4- to 10-fold increase in risk of UTI among uncircumcised males during the first year of life, likely due to colonization of the mucosal surface of the foreskin with bacteria (1). White children were significantly more likely to have UTI than black children in both prevalence studies, with rates as high as 16 to 17% among white girls (60). The reason for this increase associated with race is unclear, and referral bias may be a factor for these emergency department-based studies. However, some studies of white females suggest that there may be genetic tendencies for UTI, such as lack of secretion of carbohydrates that protect against bacterial adherence in the urinary tract (39, 61).

Other risk factors for UTI among children less than 2 years of age included young age, absence of another source of fever, height of fever, ill appearance, history of UTI, presence of urinary symptoms, and tenderness in the suprapubic area (60). The authors of one of these papers developed and validated a predictive model for girls 2 to 24 months of age with fever (Table 1) (23). They recommended screening for UTI if two or more of these factors were present based on a 95% sensitivity to detect UTI with this strategy.

Once the decision to obtain urine has been made, several collection options are available. Older children can provide a voided specimen, which should be obtained midstream after cleansing of the urethral meatus. Girls should be positioned backwards on the toilet seat to help spread the labia. For young children, suprapubic aspiration is the most specific technique but has a low rate of success unless aided by ultrasound visualization of urine in the bladder. Catheterization is the most commonly used technique in young children. The use of urine

TABLE 2. Predictive value of laboratory tests in the diagnosis of UTI in young children[a]

Test	Sensitivity, % (range)	Specificity, % (range)	Negative likelihood ratio
Dipstick tests			
Nitrites	50 (16–72)	98 (95–100)	0.51
Leukocyte esterase	83 (64–89)	84 (71–95)	0.20
Either leukocyte esterase or nitrites	88 (71–100)	93 (76–98)	0.13
Standard UA micro (≥5 wbcs/hpf)	67 (55–88)	79 (77–84)	0.42
Hemacytometer cell count (≥10/mm^3)	77 (57–92)	89 (37–95)	0.26
Gram stain (any organisms)	93 (80–98)	95 (87–100)	0.07
Enhanced UA (cell count *and* GS$^+$)	85 (75–88)	99 (99)	0.15
Enhanced UA (cell count *or* GS$^+$)	95 (94–96)	89 (84–93)	0.06

[a] Summary estimates are provided in addition to the range reported among studies reviewed in a meta-analysis. UA micro, microscopic urinalysis; wbcs/hpf, white blood cells per high-powered field; GS, Gram stain. Data from Gorelick et al. (24).

bags results in a high rate of false-positive cultures and is not recommended for this purpose (2).

Although urine culture is the gold standard for diagnosis of UTI, results are not available for 24 to 48 h. Rapid techniques to predict UTI include urine dipstick tests for leukocyte esterase and nitrites and various forms of urinalysis, including standard microscopy on a centrifuged specimen, high-powered microscopy with a hemacytometer, and Gram stain of unspun urine for organisms. Multiple studies have compared the performance of these tests, and the results have been combined in a recent meta-analysis (see Table 2) (24). As in all clinical tests, the choice of test may lead to a trade-off between false positives and false negatives. The most sensitive approach which yields the fewest missed diagnoses is "enhanced urinalysis," using a combination of a positive result on either hemacytometer cell count or Gram stain, which has been estimated to have a sensitivity of 95%. This approach has been recommended for situations in which a missed diagnosis is unacceptable, such as the febrile young infant (27). Gram stain alone performed nearly as well, with a lower false-positive rate.

A further meta-analysis by Huicho et al. determined that the combination of cell count and Gram stain (both being positive) had the overall best performance (taking into account both sensitivity and specificity) (34). However, other approaches may be more appropriate in typical outpatient settings based on practical considerations related to resources available at the time of evaluation, availability of follow-up, and the relative importance of either a false-positive or false-negative test. Urine dipstick combining the presence of either leukocyte esterase or nitrites had good overall performance and may be the most practical approach in an outpatient setting. However, back-up urine culture should be sent to detect the approximately 12% of UTIs that will be missed by the dipstick test.

TREATMENT OF UTI

The appropriate treatment for UTI has been a subject of recent research. Traditionally, young children with a clinical diagnosis of pyelonephritis were admitted to the hospital for intravenous antibiotics. Recently, a clinical trial by Hoberman et al. compared intravenous cefotaxime with oral cefoxime in a group of children with febrile UTI (30). Clinical outcomes, including detection of scarring by DMSA scan at 6 months, were similar between the two groups. The power to detect small differences in outcomes was limited, particularly among subgroups who may be at increased risk, such as younger children. However, this study suggests that outpatient therapy of pyelonephritis may be appropriate in selected children. The American Academy of Pediatrics committee reviewing this topic recommended oral or parenteral antibiotics unless the child appeared "toxic, dehydrated or unable to take oral intake," in which case parenteral therapy is indicated (2). Some clinicians routinely administer an initial dose of antibiotics parenterally at the time of evaluation. However, a recent small study assessing the efficacy of an initial intramuscular dose of ceftriaxone found no benefit compared to a 10-day course of oral antibiotics alone (4).

The choice of antibiotic may be affected by local resistance patterns and other considerations. Amoxicillin was traditionally the first-line therapy for outpatient treatment of UTI in children. However, increased rates of *Escherichia coli* resistance have made amoxicillin a less acceptable choice, and studies have found higher cure rates for trimethoprim-sulfamethoxazole (2). Other choices include amoxicillin-clavulanate or cephalosporins such as cefixime, cephalexin, cefprozil, or cefpodixime. Fluoroquinolones are widely used in adult patients, although concerns about potential effects on musculoskeletal joint development based on animal data have restricted their use in young children. A recent review of the use of fluoroquinolones for pediatric UTI noted a high rate of efficacy among patients with complex medical conditions or multidrug resistance, although data on the safety of these agents are limited (42). Inpatient treatment regimens may include the combination of ampicillin and gentamicin or third-generation cephalosporins. Urine should always be obtained for culture in children so that sensitivities can be determined to guide antibiotic therapy.

The length of antibiotic therapy for UTI in children has also been an area of controversy. In adults with uncomplicated cystitis, short courses of 1 to 3 days have been shown to be effective, but in children, several reviews have demonstrated better outcomes with 7 to 14 days (2, 41). The American Academy of Pediatrics parameter recommends a 7- to 14-day course for all children 2 months to 2 years of age with UTI (2). Additional antibiotics as prophylaxis are recommended until imaging studies to assess reflux are completed. The topic of long-term prophylaxis for vesicoureteral reflux is beyond the scope of this discussion, although a recent meta-analysis by the Cochrane Collaboration has found limited evidence to support efficacy (75).

EVALUATION AFTER UTI

The evaluation of children after a UTI was once thought to be quite straightforward and focused primarily on detecting

and treating vesicoureteral reflux in order to prevent end-stage renal disease from reflux nephropathy. Hutch in 1958 (35) and Hodson in 1960 (33) were among the first to describe a relationship between reflux and renal scarring. Subsequently, a relationship was established between reflux and chronic pyelonephritis (62, 73). Until recently, further evaluation of UTI has centered on the search for reflux with anatomic studies, including ultrasound and voiding cysto-urethrogram (VCUG). As newer radiological tests have become available, this routine work-up has been challenged, and in their recent review, the American Academy of Pediatrics subcommittee recognized the evolving nature of this area, although continuing to recommend a VCUG and ultrasound for all children under the age of 2 presenting with a febrile urinary tract infection (3).

AGE DIFFERENCES

Infants and young children presenting with urinary tract infections have traditionally been investigated extensively due to a concern that developing kidneys are more susceptible to damage from pyelonephritis and that the risk of identifying associated urinary tract abnormalities is statistically higher in this group. Originally there appeared to be a difference in outcomes with infection occurring under the ages of 3 to 5 based on studies which found a higher incidence of renal scarring in this age group (8, 21, 50, 77). However numerous studies have found that scarring can and does occur later (7, 22, 38, 57, 64, 68). In fact some studies have shown that neonates and infants may actually have a decreased incidence of scarring and abnormalities compared to older children (6, 10, 14). Certainly children with genitourinary tract abnormalities tend to present with infections earlier in life (58); Spencer et al. estimated the overall incidence of obstruction and reflux to range from 2.1 to 21.7% and 18 to 57%, respectively (65). The American Academy of Pediatrics guidelines focus on children under the age of 2 years, stating that those over 2 years old are less likely to have factors predisposing them to renal damage and are at lower risk (3). In older children, the decision to perform further investigations should be individualized based on other clinical factors.

GENDER

Under the age of 1 year, the incidence of UTI in boys is higher than in girls; however, after 1 year, girls are much more likely to develop a UTI than boys (26). Based on this observation, physicians generally treat children younger than 1 year similarly but then favor a more extensive evaluation in boys over 1 year to search for an anatomic cause for the UTI. Interestingly, boys and girls appear to have differences in timing and extent of scarring due to differences in underlying pathophysiology. Boys tend to present earlier with more extensive scarring and high-grade reflux which does not change over time due to a congenital abnormality (12, 49, 63, 71). In these children, the injury is not reversible, and extensive investigation may not change their ultimate renal status. The same studies show that girls with recurrent UTI present later with renal scarring and should be followed closely as further injury may be preventable. Girls with recurrent UTIs also tend to display symptoms of dysfunctional elimination, which can be modified (11). Guidelines such as the American Academy of Pediatrics committee's do not differentiate between the genders with regard to investigation; however, understanding the differences in presentation and possible etiology may be helpful to direct prognosis and management.

VOIDING HABITS

Hinman described the "non-neurogenic, neurogenic bladder syndrome" in the 1970s as a disorder of functional obstruction resulting in urinary retention, altered bladder anatomy, and upper urinary tract dilation and scarring (28). Since then, it has become accepted that children with "normal" anatomy may present with infections and renal damage as a result of abnormal voiding habits. Neumann, as early as 1973, described a decrease in recurrent UTI by correcting constipation (53). Girls with recurrent UTIs have a particularly high incidence of dysfunctional elimination (11, 52, 67) and should be screened with a thorough history, voiding diary, and appropriate clinical evaluation to rule out constipation. In children who demonstrate a high likelihood for this diagnosis, it may be appropriate to address these issues before proceeding to more invasive tests such as a VCUG.

STANDARD RADIOLOGICAL STUDIES

The standard imaging studies for children presenting with UTIs initially included an intravenous urogram and VCUG. Over time, the relatively noninvasive ultrasound has gradually supplanted the IVP as the anatomical study of choice. However, the ultrasound is neither sensitive nor specific for diagnosing vesicoureteral reflux (46). Although some studies suggest that it is of limited value (32), most physicians believe that it is an appropriate screening test to rule out major abnormalities. High-quality ultrasounds, often performed in the last trimester of pregnancy, identify significant congenital abnormalities, and the yield of a further ultrasound may be low if prenatal results were normal.

The VCUG has been used consistently since the 1960s and can be performed as a standard contrast study or with a radionuclide. Typically, the contrast study is chosen for the first study due to its greater anatomic detail, although the radionuclide cystogram has been shown in some studies to have a higher sensitivity (55). While debate exists regarding the timing of a VCUG study, it is generally accepted that it can be performed once the child is afebrile and has a negative urine culture (47). Compliance also appears to be better when the VCUG is performed early after a UTI (51). While no test is perfect, there is little question about the VCUG's ability to detect reflux. However, questions have been raised about whether routine work-up with VCUG is the best strategy to improve long-term outcomes, given a lack of evidence to support the benefit of prophylactic antibiotics once reflux is diagnosed (15, 74, 75). In addition, newer research has demonstrated the presence of renal scarring in the absence of reflux, which has led to interest in newer imaging modalities.

NUCLEAR MEDICINE

Renal scans have been used to evaluate children with UTIs since the 1980s (77), and their sensitivity and specificity for pyelonephritis have been well documented in animal models (56). A substantial number of defects on DMSA scans occur in the absence of reflux (62 to 82%) (7, 9, 16, 17, 44, 48, 68). This has led some to recommend that if renal scarring is to be avoided, a renal scan should be the initial investigation in a child with a UTI to detect those at greatest risk for a persistent scar. However, there is a lack of evidence documenting what the presence of a scar on a renal scan means for a child long-term, although at least one study showed a strong correlation between the absence of nocturnal blood pressure drop (a risk factor for hypertension in adults) and the severity of renal scarring following UTI (54).

Recent studies reporting on investigation during a febrile UTI document initial defect and subsequent scarring in 34 to 70% and 9.5 to 38%, respectively (7, 9, 16, 17, 32, 44, 48). Unfortunately, many studies do not have complete enough follow-up to determine the true incidence of scarring, as it has been shown that defects will change up to 6 months later (17, 70). There is also the potential for interobserver variability in renal scans, with differences ranging from small to notable (19, 59). As discussed earlier, the ramifications of renal scarring for the risk of long-term morbidity such as hypertension and renal failure are also unclear. Perhaps the most definite clinical situation is one in which a renal scan is done at the time of an acute UTI and no defect is found; these children appear not to be at risk for further scarring, and omitting further anatomic work-up may be appropriate in this situation (9, 57). However, further research with long-term follow-up will be necessary before physicians feel comfortable using a DMSA scan as the primary study to determine further management in a child with a first UTI.

CONCLUSION

UTI is a common pediatric problem with the potential to produce long-term morbidity. Young children presenting with fever may have nonspecific symptoms of UTI, and a high index of suspicion is appropriate in this setting, as bacteriuria would indicate a high probability of upper tract infection. The most reliable rapid test to diagnose UTI is the enhanced urinalysis, a combination of hemacytometer cell count and Gram stain of an unspun specimen. Urine dipstick tests also perform well, although urine culture should always be performed to detect false-negatives and to determine drug sensitivities to guide treatment. Treatment of febrile UTI in young children should last for 7 to 14 days. The appropriate work-up after a UTI in a young child or infant currently includes a renal ultrasound with a VCUG. Further research may define whether routine performance of these tests improves outcomes or whether more selective use or other tests such as DMSA may be a more effective approach.

REFERENCES

1. 1999. Circumcision policy statement. American Academy of Pediatrics Task Force on Circumcision. Pediatrics **103:**686–693.
2. 1999. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Pediatrics **103:**843–852.
3. **Anonymous.** 1999. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Pediatrics **103:**843–852.
4. **Baker, P. C., D. S. Nelson, and J. E. Schunk.** 2001. The addition of ceftriaxone to oral therapy does not improve outcome in febrile children with urinary tract infections. Arch. Pediatr. Adolesc. Med. **155:**135–139.
5. **Bauchner, H., B. Philipp, B. Dashefsky, and J. O. Klein.** 1987. Prevalence of bacteriuria in febrile children. Pediatr. Infect. Dis. J. **6:**239–242.
6. **Bauer, S., A. Eliakim, A. Pomeranz, R. Regev, I. Litmanovits, S. Arnon, H. Huri, and T. Dolfin.** 2003. Urinary tract infection in very low birth weight preterm infants. Pediatr. Infect. Dis. J. **22:**426–430.
7. **Benador, D., N. Benador, D. Slosman, B. Mermillod, and E. Girardin.** 1997. Are younger children at highest risk of renal sequelae after pyelonephritis? Lancet **349:**17–19.
8. **Berg, U. B., and S. B. Johansson.** 1983. Age as a main determinant of renal functional damage in urinary tract infection. Arch. Dis. Child. **58:**963–969.
9. **Biggi, A., L. Dardanelli, G. Pomero, P. Cussino, C. Noello, O. Sernia, A. Spada, and G. Camuzzini.** 2001. Acute renal cortical scintigraphy in children with a first urinary tract infection. Pediatr. Nephrol. **16:**733–738.
10. **Biyikli, N. K., H. Alpay, E. Ozek, I. Akman, and H. Bilgen.** 2004. Neonatal urinary tract infections: analysis of the patients and recurrences. Pediatr. Int. **46:**21–25.
11. **Chen, J. J., W. Mao, K. Homayoon, and G. F. Steinhardt.** 2004. A multivariate analysis of dysfunctional elimination syndrome, and its relationships with gender, urinary tract infection and vesicoureteral reflux in children. J. Urol. **171:**1907–1910.
12. **Clarke, S. E., J. M. Smellie, N. Prescod, S. Gurney, and D. J. West.** 1996. Technetium-99m-DMSA studies in pediatric urinary infection. J. Nuclear Med. **37:**823–828.
13. **Crain, E. F., and J. C. Gershel.** 1990. Urinary tract infections in febrile infants younger than 8 weeks of age. Pediatrics **86:**363–367.
14. **Dayan, P. S., E. Hanson, J. E. Bennett, D. Langsam, and S. Z. Miller.** 2004. Clinical course of urinary tract infections in infants younger than 60 days of age. Pediatr. Emerg. Care **20:**85–88.
15. **Dick, P. T., and W. Feldman.** 1996. Routine diagnostic imaging for childhood urinary tract infections: a systematic overview. J. Pediatr. **128:**15–22.
16. **Ditchfield, M. R., and H. R. Nadel.** 1998. The DMSA scan in paediatric urinary tract infection. Australasian Radiol. **42:**318–320.
17. **Ditchfield, M. R., S. D., Grimwood, K., Cook, D. J., Powell, H. R., Sloane, R., Nolan, T. M., de Campo, J. F.** 2002. Time course of transient cortical scintigraphic defects associated with acute pyelonephritis. Pediatr. Radiol. **32:**849–852.
18. **Esbjorner, E., U. Berg, and S. Hansson.** 1997. Epidemiology of chronic renal failure in children: a report from Sweden 1986–1994. Swedish Pediatric Nephrology Association. Pediatr. Nephrol. **11:**438–442.
19. **Gacinovic, S., J. Buscombe, D. C. Costa, A. Hilson, J. Bomanji, and P. J. Ell.** 1996. Inter-observer agreement in the reporting of 99Tcm-DMSA renal studies. Nuclear Med. Commun. **17:**596–602.
20. **Ginsburg, C. M., and G. H. McCracken, Jr.** 1982. Urinary tract infections in young infants. Pediatrics **69:**409–412.
21. **Gleeson, F. V., and I. Gordon.** 1991. Imaging in urinary tract infection. Arch. Dis. Child. **66:**1282–1283.
22. **Gordon, I.** July 1990. Urinary tract infection in paediatrics: the role of diagnostic imaging. Br. J. Radiol. **63:**507–511.
23. **Gorelick, M. H., and K. N. Shaw.** 2000. Clinical decision rule to identify febrile young girls at risk for urinary tract infection. Arch. Pediatr. Adolesc. Med. **154:**386–390.
24. **Gorelick, M. H., and K. N. Shaw.** 1999. Screening tests for urinary tract infection in children: a meta-analysis. Pediatrics **104:**e54.
25. **Hansson, S., J. Martinell, E. Stokland, and U. Jodal.** 1997. The natural history of bacteriuria in childhood. Infect. Dis. Clin. North Am. **11:**499–512.
26. **Hellstrom, A., E. Hanson, S. Hansson, K. Hjalmas, and U. Jodal.** 1991. Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch. Dis. Child. **66:**232–234.
27. **Herr, S. M., E. R. Wald, R. D. Pitetti, and S. S. Choi.** 2001. Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. Pediatrics **108:**866–871.
28. **Hinman, F.** 1974. Urinary tract damage in children who wet. Pediatrics **54:** 143–150.
29. **Hoberman, A., H. P. Chao, D. M. Keller, R. Hickey, H. W. Davis, and D. Ellis.** 1993. Prevalence of urinary tract infection in febrile infants. J. Pediatr. **123:**17–23.
30. **Hoberman, A., E. R. Wald, R. W. Hickey, M. Baskin, M. Charron, M. Majd, D. H. Kearney, E. A. Reynolds, J. Ruley, and J. E. Janosky.** 1999. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics **104:**79–86.
31. **Hoberman, A., E. R. Wald, E. A. Reynolds, L. Penchansky, and M. Charron.** 1994. Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. J. Pediatr. **124:**513–519.

32. **Hoberman, A., C. M., Hickey, R. W., Baskin, M., Kearney, D. H., Wald, E. R.** 2003. Imaging studies after a first febrile urinary tract infection in young children. N. Engl. J. Med. **348:**195–202.
33. **Hodson, C. J., and D. Edwards.** 1960. Chronic pyelonephritis and vesico-ureteric reflex. Clin. Radiol. **11:**219–231.
34. **Huicho, L., M. Campos-Sanchez, and C. Alamo.** 2002. Metaanalysis of urine screening tests for determining the risk of urinary tract infection in children. Pediatr. Infect. Dis. J. **21:**1–88.
35. **Hutch, J. A.** 1958. The ureterovesical junction. University of California Press, Berkeley, Calif.
36. **Jacobson, S. H., O. Eklof, C. G. Eriksson, L. E. Lins, B. Tidgren, and J. Winberg.** 1989. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. Br. Med. J. **299:**703–706.
37. **Jakobsson, B., S. H. Jacobson, and K. Hjalmas.** 1999. Vesico-ureteric reflux and other risk factors for renal damage: identification of high- and low-risk children. Acta Paediatr. Supp. **88:**31–39.
38. **Jakobsson, B., U. Berg, and L. Svensson.** 1994. Renal scarring after acute pyelonephritis. Arch. Dis. Child. **70:**111–115.
39. **Jantausch, B. A., V. R. Criss, R. O'Donnell, B. L. Wiedermann, M. Majd, H. G. Rushton, R. S. Shirey, and N. L. Luban.** 1994. Association of Lewis blood group phenotypes with urinary tract infection in children. J. Pediatr. **124:**863–868.
40. **Kass, E. H.** 1956. Asymptomatic infections of the urinary tract. Trans. Assoc. Am. Physicians **69:**56–64.
41. **Keren, R., and E. Chan.** 2002. A meta-analysis of randomized, controlled trials comparing short- and long-course antibiotic therapy for urinary tract infections in children. Pediatrics **109:**E70–80.
42. **Koyle, M. A., A. Barqawi, J. Wild, M. Passamaneck, and P. D. Furness, 3rd.** 2003. Pediatric urinary tract infections: the role of fluoroquinolones. Pediatr. Infect. Dis. J **22:**1133–1137.
43. **Kunin, C. M.** 1970. A ten-year study of bacteriuria in schoolgirls: final report of bacteriologic, urologic, and epidemiologic findings. J. Infect. Dis. **122:** 382–393.
44. **Lin, K. Y., N. T. Chiu, M. J. Chen, C. H. Lai, J. J. Huang, Y. T. Wang, and Y. Y. Chiou.** 2003. Acute pyelonephritis and sequelae of renal scar in pediatric first febrile urinary tract infection. Pediatr. Nephrol. **18:**362–365.
45. **Lindberg, U., I. Claesson, L. A. Hanson, and U. Jodal.** 1978. Asymptomatic bacteriuria in schoolgirls. VIII. Clinical course during a 3-year follow-up. J. Pediatr. **92:**194–199.
46. **Mahant, S., J. Friedman, and C. MacArthur.** 2002. Renal ultrasound findings and vesicoureteral reflux in children hospitalised with urinary tract infection. Arch. Dis. Child. **86:**419–420.
47. **Mahant, S., T. To, and J. Friedman.** 2001. Timing of voiding cystourethrogram in the investigation of urinary tract infections in children. J. Pediatr. **139:**568–571.
48. **Majd, M., and H. G. Rushton.** 1992. Renal cortical scintigraphy in the diagnosis of acute pyelonephritis. Semin. Nuclear Med. **22:**98–111.
49. **Marra, G., C. Oppezzo, G. Ardissino, V. Dacco, S. Testa, L. Avolio, E. Taioli, F. Sereni, and P. ItalKid.** 2004. Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ItalKid Project. J. Pediatr. **144:**677–681.
50. **Martinell, J., I. Claesson, G. Lidin-Janson, and U. Jodal.** 1995. Urinary infection, reflux and renal scarring in females continuously followed for 13–38 years. Pediatr. Nephrol. **9:**131–136.
51. **McDonald, A., M. Scranton, R. Gillespie, V. Mahajan, and G. A. Edwards.** 2000. Voiding cystourethrograms and urinary tract infections: how long to wait? Pediatrics **105:**E50.
52. **Mingin, G. C., A. Hinds, H. T. Nguyen, and L. S. Baskin.** 2004. Children with a febrile urinary tract infection and a negative radiologic workup: factors predictive of recurrence. Urology **63:**562–565.
53. **Neumann, P. Z., I. J. DeDomenico, and M. B. Nogrady.** 1973. Constipation and urinary tract infection. Pediatrics **52:**241–245.
54. **Patzer, L., T. Seeman, C. Luck, E. Wuhl, J. Janda, and J. Misselwitz.** 2003. Day- and night-time blood pressure elevation in children with higher grades of renal scarring. J. Pediatr. **142:**117–122.
55. **Polito, C., P. F. Rambaldi, A. La Manna, L. Mansi, and R. Di Toro.** 2000. Enhanced detection of vesicoureteric reflux with isotopic cystography. Pediatr. Nephrol. **14:**827–830.
56. **Rushton, H. G., M. Majd, R. Chandra, and D. Yim.** 1988. Evaluation of 99mtechnetium-dimercapto-succinic acid renal scans in experimental acute pyelonephritis in piglets. J. Urol. **140:**1169–1174.
57. **Rushton, H. G., M. Majd, B. Jantausch, B. L. Wiedermann, and A. B. Belman.** 1992. Renal scarring following reflux and nonreflux pyelonephritis in children: evaluation with 99mtechnetium-dimercaptosuccinic acid scintigraphy. J. Urol. **147:**1327–1332.
58. **Saxena, S. R., B. M. Laurance, and D. G. Shaw.** 1975. The justification for early radiological investigations of urinary-tract infection in children. Lancet **ii:**403–404.
59. **Shanon, A., W. Feldman, P. McDonald, D. J. Martin, M. A. Matzinger, J. F. Shillinger, P. N. McLaine, and N. Wolfish.** 1992. Evaluation of renal scars by technetium-labeled dimercaptosuccinic acid scan, intravenous urography, and ultrasonography: a comparative study. J. Pediatr. **120:**399–403.
60. **Shaw, K. N., M. Gorelick, K. L. McGowan, N. M. Yakscoe, and J. S. Schwartz.** 1998. Prevalence of urinary tract infection in febrile young children in the emergency department. Pediatrics **102:**e16.
61. **Sheinfeld, J., A. J. Schaeffer, C. Cordon-Cardo, A. Rogatko, and W. R. Fair.** 1989. Association of the Lewis blood-group phenotype with recurrent urinary tract infections in women. N. Engl. J. Med. **320:**773–777.
62. **Smellie, J. M., C. J. Hodson, D. Edwards, and I. C. Normand.** 1964. Clinical and radiological features of urinary infection in childhood. Br. Med. J. **1:** 1222–1226.
63. **Smellie, J. M., N. P. Prescod, P. J. Shaw, R. A. Risdon, and T. N. Bryant.** 1998. Childhood reflux and urinary infection: a follow-up of 10–41 years in 226 adults. Pediatr. Nephrol. **12:**727–736.
64. **Smellie, J. M., P. G. Ransley, I. C. Normand, N. Prescod, and D. Edwards.** 1985. Development of new renal scars: a collaborative study. Br. Med. J. Clin. Res. Ed. **290:**1957–1960.
65. **Spencer, J. R., and A. J. Schaeffer.** 1986. Pediatric urinary tract infections. Urol. Clin. North Am. **13:**661–672.
66. **Sreenarasimhaiah, S., and S. Hellerstein.** 1998. Urinary tract infections per se do not cause end-stage kidney disease. Pediatr. Nephrol. **12:**210–213.
67. **Stauffer, C. M., B. van der Weg, R. Donadini, G. P. Ramelli, S. Marchand, and M. G. Bianchetti.** 2004. Family history and behavioral abnormalities in girls with recurrent urinary tract infections: a controlled study. J. Urol. **171:** 1663–1665.
68. **Stokland, E., M. Hellstrom, B. Jacobsson, U. Jodal, P. Lundgren, and R. Sixt.** 1996. Early 99mTc dimercaptosuccinic acid (DMSA) scintigraphy in symptomatic first-time urinary tract infection. Acta Paediatr. **85:**430–436.
69. **Svanborg, C., and G. Godaly.** 1997. Bacterial virulence in urinary tract infection. Infect. Dis. Clin. North Am. **11:**513–529.
70. **Wallin, L., I. Helin, and M. Bajc.** 2001. Follow-up of acute pyelonephritis in children by Tc-99m DMSA scintigraphy: quantitative and qualitative assessment. Clin. Nuclear Med. **26:**423–432.
71. **Wennerstrom, M., S. Hansson, U. Jodal, and E. Stokland.** 2000. Primary and acquired renal scarring in boys and girls with urinary tract infection. J. Pediatr. **136:**30–34.
72. **Wettergren, B., U. Jodal, and G. Jonasson.** 1985. Epidemiology of bacteriuria during the first year of life. Acta Paediatr. Scand. **74:**925–933.
73. **Williams, D. I., and H. B. Eckstein.** 1965. Surgical treatment of reflux in children. Br. J. Urol. **37:**13–24.
74. **Williams, G., A. Lee, and J. Craig.** 2001. Antibiotics for the prevention of urinary tract infection in children: a systematic review of randomized controlled trials. J. Pediatr. **138:**868–874.
75. **Williams, G. J., A. Lee, and J. C. Craig.** 2001. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst. Rev. CD001534. [Online.] http://www.cochrane.org/cochrane/revabstr/ab001534.htm
76. **Winberg, J., H. J. Andersen, T. Bergstrom, B. Jacobsson, H. Larson, and K. Lincoln.** 1974. Epidemiology of symptomatic urinary tract infection in childhood. Acta Paediatr. Scand. Suppl. **252:**1–20.
77. **Winberg, J., I. Bollgren, G. Kallenius, R. Mollby, and S. B. Svenson.** 1982. Clinical pyelonephritis and focal renal scarring. A selected review of pathogenesis, prevention, and prognosis. Pediatr. Clin. North Am. **29:**801–814.
78. **Wiswell, T. E., and J. D. Roscelli.** 1986. Corroborative evidence for the decreased incidence of urinary tract infections in circumcised male infants. Pediatrics **78:**96–99.