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...
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.

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 increased association 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. Catherization is the most commonly used technique in young children. The use of urine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative risk of UTI (95% confidence interval)</th>
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<tbody>
<tr>
<td>Age less than 1 yr</td>
<td>2.8 (1.6–5.1)</td>
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<tr>
<td>Fever for 2 days or more</td>
<td>1.5 (0.9–2.6)</td>
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<tr>
<td>White race</td>
<td>6.0 (3.7–9.5)</td>
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<tr>
<td>Absence of a source for fever</td>
<td>1.9 (1.1–3.2)</td>
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<tr>
<td>Temperature ≥39°C</td>
<td>1.7 (0.9–3.1)</td>
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*Data from reference 23. Urine screening is recommended if two or more factors are present.*
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-sulfa- methoxazole (2). Other choices include amoxicillin-clavulanate or cephalsporins such as cefixime, cephalexin, cefprozil, or cefpodoxime. 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 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, which is a reliable rapid test to diagnose UTI. The appropriate work-up after a UTI in an unspun specimen. Urine dipstick tests also perform well, and a young child or infant currently includes a renal ultrasound (54). 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.

REFERENCES
