AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

MINIREVIEW

Diagnosis of Urinary Tract Infections in Children

Christopher D. Doern,[a] Susan E. Richardson[b]

Department of Pathology, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA[a]; Department of Paediatric Laboratory Medicine, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada[b]

Urinary tract infections (UTIs) are a common occurrence in children. The management and laboratory diagnosis of these infections pose unique challenges that are not encountered in adults. Important factors, such as specimen collection, urinalysis interpretation, culture thresholds, and antimicrobial susceptibility testing, require special consideration in children and will be discussed in detail in the following review.

Urinary tract infections (UTIs) are frequent in childhood and may have significant adverse consequences, especially for young children. The importance of UTIs is reflected not only by their frequency but also by the range of clinical severity that may occur, from asymptomatic to mild or moderate symptomatic lower UTI to bacteremia and septic shock. In addition, it has been shown that UTIs with fever in young children increase the probability of kidney involvement and are associated with an increased risk of underlying nephrourologic abnormalities and consequent renal scarring (1). Kidney scarring is considered to cause long-term morbidity (hypertension, chronic renal disease, preeclampsia), though much of this has now been shown to be caused by preexisting intrinsic renal disease (1).

Thus, it is clear that an accurate, reliable diagnosis of UTI in children is critical. Underdiagnosis may cause immediate or long-term harm while overdiagnosis subjects healthy children to unnecessary treatment and potentially invasive diagnostic testing. We know that in children less than 2 years of age, the clinical presentation may be nonspecific and also that the threshold established in adults for a clinically significant concentration of bacteria in the urine is not appropriate for this age group (2).

In this review, we will present a discussion of issues relevant to the diagnosis of UTIs in children, particularly as they differ from those in adults. We will review the literature to provide a framework for determining optimal laboratory testing for UTIs in children, from birth to adulthood, and will use the available evidence to explore controversial areas in diagnostic testing.

EPIDEMIOLOGY AND ETIOLOGY

Febrile UTIs are most common among boys and girls who are 2 to 24 months of age and occur in about 5% of children (3). Neonates (≤2 months of age) appear to have similar or higher rates of UTI with fever (4.6% to 7.5%) compared to older infants, with even higher rates of up to 20% in infants with low birth weights, predominantly males (2, 4). In a study of pediatric oncology patients with fever and neutropenia, the rate of UTI was 8.6%. None of the children with UTIs had symptoms referable to the urinary tract, despite a median age of 8 years, or concomitant bacteremia. UTI occurred as frequently as bacteremia in this population (5). UTIs occur at a higher rate in girls than in boys over the first 8 years of life (7% to 8% versus 2%, respectively), but nonfebrile UTIs are most frequent in girls who are older than 3 years of age (1).

With respect to the evaluation of young children with fever, Shaw et al. observed that 64% of young children with UTIs who were assessed in the emergency department were thought by the examining physician to have other sources of fever, i.e., upper respiratory tract (including otitis media) or gastrointestinal infection (6). Thus, until the age of about 5 years, the nonspecificity of symptoms in children dictates that front-line laboratory testing to diagnose UTI, i.e., urinalysis (UA) and urine culture, should provide the highest possible negative predictive value (NPV) and positive predictive value (PPV).

The most common cause of UTI in all age groups is *Escherichia coli* (65% to 75%). Other agents include *Klebsiella* species, usually *Klebsiella pneumoniae* (23%), *Proteus mirabilis* (7%), other *Enterobacteriaceae*, *Enterococcus* species, *Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus* (1% to 4%) (7, 8). *S. saprophyticus* is known to be an important cause of UTIs in adolescent, sexually active females but has also been shown to cause symptomatic UTIs in younger boys and girls. A prospective study by Abrahamsson et al. showed that of 59 *S. saprophyticus* infections in children under 16 years of age, 25% occurred in boys, 64% of whom were less than 13 years of age (9). *Candida* species most commonly cause UTIs in preterm neonates but may also, on occasion, be responsible for infection in otherwise healthy older children.

SPECIMEN TYPES

Febrile infants, children who present in shock, and all children who have urgent clinical indications to start antibiotics should be catheterized if they cannot provide a voided specimen unless there is gross infection of the genital area, labial adhesions in females, or failure to visualize the urethral opening in uncircumcised males. A midstream or clean catch sample is the optimal specimen for toilet-trained and older children without any obvious infection or abnormality of the external genitalia. In school-aged children, cleansing is not required unless there is gross contamination of the genitalia (10). Suprapubic aspirate (SPA) is carried out rarely but is reserved for diapered, uncircumcised boys whose urethral opening cannot be visualized and those infants/children who cannot be catheterized or who cannot produce an uncontaminated midstream sample (11). A recent systematic review and meta-

Accepted manuscript posted online 6 April 2016

Citation Doern CD, Richardson SE. 2016. Diagnosis of urinary tract infections in children. J Clin Microbiol 54:2233–2242. doi:10.1128/JCM.00189-16.

Editor: C. S. Kraft, Emory University

Address correspondence to Christopher D. Doern, christopher.doern@vcuhealth.org.

analysis of preanalytic practices affecting the contamination and accuracy of urine cultures concluded that, for children, the methodologic difficulties related to small sample size and heterogeneity in positivity thresholds and the inability to generate hierarchical summary receiver operating characteristic (HSROC) curves made it impossible to determine the method of noninvasive urine collection that is most accurate for the diagnosis of urinary tract infection in children using this methodology. However, multiple studies over many years support the use of straight catheterization for infants and midstream or clean catch urine without cleansing for older children as the best methods for obtaining a good urine specimen for culture.

Bag urine samples, though easy to obtain, are unsatisfactory specimens, and their use is strongly discouraged due to their very high false positivity rate (63%) compared to catheter (9%) and the unnecessary and potentially harmful treatment and investigations that may ensue. Al-Orifi et al. observed that 2% of contaminated urine samples obtained by bag culture resulted in one or more adverse clinical outcomes (compared to specimens obtained by catheter), including unnecessary recall (adjusted odds ratio [OR], 4.9), delayed diagnosis and treatment (infinite OR), unnecessary treatment (OR, 4.8), unnecessary prolonged treatment (OR, 15.6), unnecessary radiologic investigation (OR, 4.1), and unnecessary hospital admission (OR, 12.4) (12). The only utility of this method is that a negative bag urine sample tested by dipstick and culture effectively rules out UTI. The problem is that clinicians find it hard to ignore a "positive" culture when it returns, thus initiating a treatment and investigation cycle that is usually unwarranted.

URINALYSIS

Urinalysis has been shown to be an important addition to urine culture in the detection of UTI in children and adults, as the assessment of inflammation by way of pyuria can aid in the determination of contamination/colonization or asymptomatic bacteriuria versus infection. Fairley and Barraclough showed that the use of leukocyte excretion rate was a highly reproducible, though impractical, method that clearly distinguished clinically infected patients from uninfected patients or those with asymptomatic bacteriuria (13). The only method of assessment of pyuria that correlates tightly with the gold standard leukocyte excretion rate is the presence of >10 white blood cells (WBCs)/mm^3 as detected by hemocytometer analysis of an uncentrifuged urine specimen (14). The "standard" method using a centrifuged urine sample (with a threshold of 5 WBCs per high-power field [HPF] or approximately 25 WBCs/μl) is not standardized with respect to the centrifugation parameters or the pellet and resuspension volumes and, therefore, shows poorer correlation with the leukocyte excretion rate and a poor predictive value. Applying the hemocytometer WBC method to the evaluation of screening tests for the diagnosis of UTI in children 2 to 24 months of age, Hoberman found that an enhanced urinalysis, combining >10 WBC/mm^3 or Gram stain detection of any bacteria per 10 oil immersion fields on uncentrifuged urine, gave a sensitivity of 96% and a specificity of 93% (47). This method showed better performance characteristics than the standard microscopic urinalysis (83% sensitivity and 87% specificity) or the dipstick analysis (leukocyte esterase [LE] or nitrite positive, 67% and 79% specificity, respectively) (15).

Although it has been shown that pyuria can occur in the absence of UTI, as in fever from other infections and conditions such as Kawasaki disease or after vigorous exercise, it is rare that it is absent in true UTIs (3). The American Academy of Pediatrics (AAP) clinical guideline suggests that when pyuria is absent in a true UTI, it is usually either the method or the definition of pyuria that is at fault (3).

An exception to the value of the detection of pyuria in the diagnosis of UTI is in febrile neutropenic children. Sandoval et al. found a sensitivity of only 40% for the detection of pyuria by microscopy in 5/45 febrile neutropenic children with a positive urine culture ($\geq 10^4$ CFU/ml of a known urinary pathogen) (5). Klaassen et al. determined that only 4% of 54 episodes of UTI in febrile neutropenic children with UTI ($\geq 10^5$ CFU/ml) had detectable pyuria as determined by urine microscopy (16). Urinary nitrite testing may be useful in this population in addition to the microscopic detection of bacteria, as neither would be affected by the absence of pyuria.

The urinary nitrite test requires about 4 h for an uropathogen to convert dietary nitrates into nitrites in the bladder to yield a positive test. With the rapid bladder emptying found in infants and children, especially those with inflammation associated with UTIs, this test may be falsely negative. Other causes of false-negative tests include uropathogens that do not reduce nitrate to nitrite, i.e., *Enterococcus* spp., *Staphylococcus saprophyticus*, *Pseudomonas aeruginosa*, and *Candida* spp.; antibiotics that inhibit bacterial metabolism; and the competitive effect of ascorbic acid in the urine. Thus, although it has high specificity for UTIs, as a single test, the sensitivity is low.

According to the AAP 2011 clinical practice guideline, once a clinician has decided that the pretest likelihood of the risk of UTI merits obtaining a urine culture, establishing the diagnosis of UTI in this age group requires "both urinalysis results that suggest infection (pyuria and/or bacteriuria) and the presence of at least 5×10^4 CFU/ml of a single uropathogen cultured from a urine specimen obtained through catheterization or suprapubic aspirate" (sensitivity, 91.2%; PPV, 96.5%) (2). It is important to note that SI units (le Système international d'unités, which is an enhanced version of the metric system) are used for clinical laboratory reporting in most major countries except the United States. The SI requires the reporting of volume in CFU per liter; thus, the AAP threshold for significant bacteriuria in SI units would be 50×10^6 CFU/liter, which has the unfortunate effect of appearing very high to clinicians who read American UTI literature (reported in CFU/ml). Given the additional resources required for either a Gram stain or a hemocytometer WBC count in addition to culture, most microbiology laboratories do not perform either as part of routine UTI diagnostics, even in dedicated pediatric laboratories (Table 1) (S. E. Richardson, unpublished data). As a compromise, if it is not possible for a laboratory to include a Gram stain or hemocytometer WBC count, some laboratories move the reporting threshold for a significant bacterial countdown to $\geq 10^4$ CFU/ml ($\geq 10^7$ CFU/liter in SI units) or even lower. This practice is supported by a recent study (17) showing that, in infants with bacteremic UTI (not neutropenic), which by definition excludes infants with contaminated urine cultures or asymptomatic bacteriuria, either the leukocyte esterase (LE) test or the nitrite test had a sensitivity of 97.6% and a specificity of 93.9% in detecting UTI, which is much higher than those values previously reported in this population. Standard microscopic detection of pyuria showed a similar sensitivity, but the specificity was considerably lower (around 65%), which probably reflects the fact that various sub-

TABLE 1 Survey of pediatric urine culture practices in North America

Institution	Country	Culture threshold by specimen type (CFU/ml)				Reflex testing?	Microscopic analysis performed by microbiology?	Microscopic analysis affect testing/reporting?
		Clean catch	Catheter	Suprapubic	Bag urine			
1	USA	$>10^5$	$>10^3$	$>10^3$	Not accepted	No	No	No
2	USA	$>10^4$	$>10^3$	$>10^3$	$>10^4$	No	No	Yes if automated IRIS in hematology lab indicates infection No for urine samples submitted directly to microbiology for culture
3	Canada	$>10^5$	$>10^5$	$>10^4$	$>10^5$	No	On request only	No
4	USA	$>10^4$	$>10^4$	Any count	$>5 \times 10^4$	No	On request only	No
5	USA	$>10^3$	$>10^2$	Any count	Not accepted	No	No	No
6	USA	$>5 \times 10^4$	$>10^4$	Any count single uropathogen (UP) (broth), $>10^3$ 2 UP	Not accepted	No	No	Yes if microscopic analysis in core lab indicates infection
7	USA	$>10^5$	$>10^5$	$>10^2$	$>10^5$	No	On request only (Gram on unspun)	No
8	USA	$>10^5$	$>10^5$	$>10^2$	$>10^5$	No	No	No
9	Canada	$>5 \times 10^4 \pm >10$ WBC/mm^3, $>10^4$ to 5×10^4 with >10 WBC/mm^3	$>5 \times 10^4$ CFU/ml $\pm >10$ WBC/mm^3, $>10^4$ to 5×10^4 with >10 WBC/mm^3	$>10^3$	$>10^5$ with >10 WBC/mm^3	No	Yes	Yes. Extent of ID/AST[a] determined according to $<$ or >10 WBC/mm^3, i.e., positive pyuria determines ID/AST for probable pathogens 10^4 to 5×10^4 CFU/ml.
10	USA	$>10^4$	$>10^4$	Any count	$>10^4$	No	No	No
11	Canada	$>10^4$	$>10^4$	$>10^2$	$>10^4$	No	No	No

[a] ID/AST, identification and antimicrobial susceptibility testing.

optimal definitions using centrifuged urine samples were used. If validated in other age groups of children, the microscopic detection of pyuria might be rendered unnecessary by the much simpler dipstick test. This would be a boon to laboratories, as it is time-consuming and its interpretation continues to suffer from the lack of a standardized methodology (spun versus unspun, number of cells/mm^3 versus number of cells/HPF, centrifuge speed and time). Evidence to support the detection of the inflammatory component of a UTI by dipstick or automated detection of pyuria across all age groups would be very helpful, as it would provide a quick confirmation of the clinical significance of positive urine culture results in most cases.

Automated urine screening for UTI, with determinations of quantitative bacteriuria and pyuria, is becoming more common in laboratories that serve predominantly adult populations. The advantage of this approach is that if negative urine cultures can be reliably identified by rapid screening, urine culture may theoretically be eliminated in up to 80% of specimens. However, the difference between the commonly employed thresholds for significant bacteriuria in adults compared to children, i.e., $\geq 10^5$ CFU/ml versus $\geq 50 \times 10^4$ CFU/ml or lower, respectively, means that the available technologies must be evaluated for children at a lower threshold. Currently available systems use flow cytometry followed by fluorescent staining or digital imagery analysis for recognition of bacteria, WBCs, red blood cells (RBCs), and other particles (18, 19). Most published studies to date are in predominantly adult populations, and some have reported good negative predictive values for the diagnosis of UTI.

Data regarding the utility of these systems in diagnosing UTI or in ruling out UTI in children are limited at present (20–22). Two of these studies used the Iris iQ200 Elite or Iris iQ Elite systems (digital imagery followed by Auto-Particle Recognition software analysis; Iris Diagnostics) (19, 20). In the study by Shah et al. (20), automated urinalysis (UA) for pyuria and bacteriuria was compared to "enhanced UA" ($\geq$10 WBCs/mm^3 and any bacteria per 10 oil immersion fields on Gram stain) using a threshold of $\geq 5 \times 10^4$ CFU/ml of a single uropathogen as a positive urine culture (20). Although the sensitivity and the positive predictive value (PPV) of automated pyuria detection (79.5% and 37.5%, respectively) were lower than those for the microscopic detection of pyuria ($\geq$10 WBCs/mm^3, 83.6% and 59.4%, respectively) when either method was combined with urine Gram stain (not automated detection of bacteriuria), the sensitivity and PPV were comparable for the detection of a positive urine culture (77.5% and 84.4% for enhanced UA versus 75.5% and 84% for automated pyuria detection and Gram stain). Note that the retention of the resource-intensive Gram stain was necessary for acceptable sensitivity and PPV, as the automated detection of bacteriuria did not provide the same discrimination, even when coupled with automatic pyuria detection.

Cantey et al. compared the results of automated UA (positive = nitrite or leukocyte esterase positive or $\geq$10 WBCs per oil immersion field [note that microscopy was performed from spun urine if automated UA was positive]) and Gram stain (any organisms detected) to the growth of $\geq 5 \times 10^4$ CFU/ml of a uropathogen by conventional culture (21). They found that automated UA alone had a sensitivity, PPV, and NPV of 97.4%, 49.4%, and 99.6%, respectively, compared to those of Gram stain alone (97.3%, 33.6%, and 99.5%, respectively). Combining automated UA with Gram stain produced a sensitivity of 97.5%, a PPV of 50.6%, and a NPV of 99.6%. The authors concluded that automated UA does not need to be supplemented with Gram stain; however, they stop short of stating that urine specimens with negative automated UA can be reported as negative without conventional culture.

A third pediatric study (22) used the Sysmex UF-1000i automated urine particle analyzer (Sysmex America), which uses flow cytometry to determine cell counts, and the Siemens Clinitek 500 urine chemistry analyzer (Bayer Corporation) for analyzing UA test strips against manual dipsticks (Siemens Multistix 10 SG; Siemens Corporation), using $\geq 5 \times 10^4$ CFU/ml as the definition of a positive urine culture (22). They found that the manual dipstick (LE or nitrite positive) showed a sensitivity of 95%, a specificity of 98%, a positive likelihood ratio (LR+) of 57.1, and a negative likelihood ratio (LR−) of 0.05; the automated UA for WBCs ($\geq$100 cells/μl) had a sensitivity of 81%, a specificity of 98%, a LR+ of 42.9, and a LR− of 0.15; and the automated UA for bacteria ($\geq$250 cells/μl) had a sensitivity and specificity of 98%, a LR+ of 48.8, and a LR− of 0.02. The authors concluded that automated bacterial counts showed the best ability to diagnose UTIs but that both automated WBC counts and manual dipstick testing showed good and comparable diagnostic performance and could probably be used instead of automated bacterial counts. They also found that combinations of automated WBC and bacterial counts did not outperform bacterial counts alone.

Thus, the limited experience of automated urinalysis in pediatric UTIs to date indicates that there is variability in the predictive value of the detection of automated WBCs and bacteria, depending on the system used. Furthermore, combined with the data from Schroeder et al. (17), which showed the excellent performance of the dipstick in predicting bacteremic UTIs in infants less than 3 months of age, these studies suggest that microscopic methods, such as Gram stain and hemocytometer WBC counts, may be supplanted by either manual or automated methods for the detection of pyuria or bacteriuria in children. Whether these findings hold true if a lower threshold for significant bacteriuria is used in children, i.e., 10^4 CFU/ml, and how different automated testing systems compare to one another at different bacterial thresholds remain to be studied. The results of these studies will determine whether it will be possible to rule out UTI in children using a nonmicroscopic screening test and will, therefore, eliminate the need to culture every urine sample from a child with a suspected UTI.

CULTURE-BASED DIAGNOSIS

Accurate culture-based diagnosis of UTIs is dependent on the utilization of appropriate growth thresholds to distinguish infection from colonization. Culture-based definitions are complicated by asymptomatic bacteriuria, which can result in quantities of growth that resemble infection. A number of factors may influence where a threshold should be set, including specimen type, patient age, and perhaps even organism type. As mentioned above, most laboratories that provide services to adult-only populations use a threshold of $\geq 10^5$ CFU/ml to define significance (23). Although outside the scope of this review, it is worth noting that there is good evidence to suggest that the commonly used adult threshold ($\geq 10^5$ CFU/ml) is too high, particularly in women with urethritis and cystitis (24). Conversely, there is no consensus as to what threshold should be used to diagnose UTIs in various pediatric populations. This is reflected in the variation seen across

currently existing recommendations (3, 15, 25–27). Interestingly, the European Association of Urology/European Society for Pediatric Urology guidelines state that any amount of growth from SPA specimens is suggestive of a UTI. This is contrary to what was demonstrated by Pryles et al., who showed that SPA-collected urine may yield low-level contamination (2/42, 4.8%) (28). These findings are supported by those of Karacan et al., who identified contamination in 1 of 11 (9.1%) SPA urine cultures (29).

A recent informal survey of microbiology laboratory directors of North American laboratories serving pediatric populations showed that no two laboratories were using the same urine culture interpretive criteria (Table 1) (Richardson, unpublished data). Responses were elicited from 24 pediatric microbiologists at individual institutions via the ASM ClinMicroNet listserv (17 American and 7 Canadian), resulting in 11/24 (46%) responses (7 American and 4 Canadian). Not only do institutions differ with respect to the thresholds used for catheter, clean catch, and suprapubic urine specimens, but laboratories also differ as to the acceptability of bag urine samples for culture. Most pediatric laboratories use a threshold varying from 10^4 to 10^5 CFU/ml for clean catch/midstream urine samples and catheter urine samples. However, some laboratories use a threshold as low as 10^2 or 10^3 CFU/ml for clean catch and catheter specimens, for which there is little evidence as will be discussed. The approach to suprapubic urine samples is quite diverse, with thresholds varying from "any count" to $\geq 10^2$, 10^3, or 10^4 CFU/ml. This lack of consensus is due in part to the fact that the peer-reviewed literature varies considerably in what it suggests the correct threshold should be. A number of independent studies have attempted to identify the bacterial counts that most accurately define urinary tract infection in children. However, these studies use heterogeneous gold standards, culture methods, and patient populations, making it difficult to confidently establish thresholds. Nonetheless, semiquantitative urine culture is the standard of practice in pediatric microbiology, and as a result, laboratories must choose a threshold to guide their practice. The following review will discuss the most relevant literature with respect to establishing urine culture thresholds in pediatric patients.

Before discussing the literature regarding pediatric urine culture thresholds, we want to briefly address the limitations of semiquantitative culture. The standard practice in clinical microbiology is to interpret urine culture results in terms of absolute organism concentration (i.e., 50,000 CFU/ml), which correlates with a threshold that defines clinical significance. However, it has been shown that the inherent inaccuracy of the sampling loop (10 μl or 1 μl) may result in more than a +/−50% error rate, and inoculation angle can also have a significant impact on the reported bacterial count. Despite these methodological limitations, laboratories must select absolute thresholds with which to interpret their urine culture results, though clinicians should be aware of the existing inexactitude of the measurement. Accordingly, there is no rationale for reporting urine culture results in multiples of 10,000, for instance, between 10^4 and 10^5 CFU/ml. Although we also recognize the effect this inherent variability has had on reported thresholds in the published literature, we feel that combining results from multiple studies provides stronger evidence for a specific threshold and minimizes the error rate. For the purpose of this review, we will consider the values in each study to be absolute and comparable, as a detailed discussion of individual study methodologies is outside the scope.

Several variables should be considered when evaluating urine culture thresholds; these include patient age, patient status, specimen type, and causative organism. The diagnosis of UTI in children aged 2 to 24 months was addressed by the 2011 AAP clinical practice guideline (3). Although it is important for laboratory protocols to consider distinct age ranges, the reality is that most laboratories apply a single threshold to all age groups. Therefore, it is likely that the AAP recommendation for 2- to 24-month-old children (or any age-specific recommendation) will be extended to all age groups. The AAP document recommends a urine culture threshold of 5×10^4 CFU/ml based largely on a 1994 study published by Hoberman and colleagues (2). Of 2,181 catheter-obtained urine specimens from febrile children who were less than 2 years of age (including neonates), there were 110 patients with $\geq 10^4$ CFU/ml uropathogens detected; the majority of specimens (84%) had $\geq 10^5$ CFU/ml, another 9% had 5×10^4 to 9.9×10^4 CFU/ml, and 7% had 10^4 to 4.9×10^4 CFU/ml. Ninety-three of 102 patients (91%) with $\geq 5 \times 10^4$ CFU/ml had significant pyuria (≥ 10 leukocytes/mm^3 in uncentrifuged urine). In contrast, cultures with 10^4 to 4.9×10^4 CFU/ml were more likely to grow mixed or nonpathogenic Gram-positive cocci, and were less likely to have significant pyuria (33%). Although it is clear that a number of true UTIs occur between 10^4 and 4.9×10^4 CFU/ml in children, the authors conclude that $\geq 5 \times 10^4$ CFU/ml is the threshold that will capture the majority of true infections while minimizing false-positive results.

The threshold recommended by the AAP was based on a requirement to also include a valid method for detecting pyuria in the clinical determination of probable UTI, and, as such, they chose a higher threshold than a number of other studies presented below. Some of the earliest work was performed by Pryles et al., who published two elegant 1959 studies that demonstrated near-perfect diagnostic correlation between SPA, catheter-obtained specimens (COS), and clean-voided urine (CVU) (11, 28). In their December 1959 study, patients undergoing elective surgery without symptoms of UTI were enrolled and had both SPA and COS cultured (28). Within this low-risk population for UTI, they found that nearly all growth was below a 10^4 CFU/ml threshold; in fact, most cultures were negative (40/41, 98%) or grew $\leq 10^3$ CFU/ml. In their March 1959 publication, they compared growth from COS to CVU samples in girls aged 2 to 12 years with and without UTI and found a 98% diagnostic correlation between specimens (11). In the same study, they found that urine culture fell into two categories: those without UTI symptoms were negative or showed growth of $<10^3$ CFU/ml, and those with UTIs grew $>10^4$ CFU/ml. Of the 17 infected patients in this study, three had colony counts that were between 10^3 and 10^5 CFU/ml. However, on repeat culturing, all three patient specimens grew $>10^5$ CFU/ml, leading the authors to conclude that colony counts between 10^3 and 10^5 CFU/ml represent an intermediate result that should be confirmed with a second culture. They concluded that monomicrobic growth of $\geq 10^5$ CFU/ml from patients with UTI symptoms should be considered highly suggestive of UTI.

A number of other studies suggest using a lower threshold for defining pediatric UTI at $\geq 10^4$ CFU/ml. One of the more recent publications to arrive at this conclusion was that of Swerkersson and colleagues, who conducted a population-based retrospective investigation of 430 children who were <1 year of age without urogenital anomalies and who had symptoms of UTI (30). In the study, they correlated clinical and laboratory results as well as

findings on cystourethrography and ^{99m}technetium dimercaptosuccinic acid scintigraphy with urine bacterial counts at the initial presentation. Over the 10 year study, they found that 19% (n = 83) of patients had UTIs with colony counts of $<10^5$ CFU/ml. Importantly, they found that there was no difference in vesicoureteral reflux, kidney damage, or recurrence in those who presented with $>10^5$ or $<10^5$ CFU/ml. They also found that non-*E. coli* pathogens were more likely to be present at $<10^5$ CFU/ml and were associated with a low inflammatory response. Similarly, Kanellopoulos et al. found that in children who were <4.5 years of age, 14.1% of UTIs would be missed using a threshold of $\geq 10^5$ CFU/ml. They also showed that there are no differences in the clinical and laboratory findings of patients with low bacterial counts (defined as $<5 \times 10^4$ CFU/ml) and high bacterial counts (31). In their subanalysis though, they found that children who were <24 months old were more likely to have low bacterial counts and non-*E. coli* bacteria associated with UTI.

Hansson et al. also evaluated 366 infants who were <1 year of age with UTIs and found that approximately 20% of children with UTIs yielded $<10^5$ CFU/ml of a single uropathogen, with ~7% growing $<10^4$ CFU/ml (32). Although 89% of UTIs with $\geq 10^5$ CFU/ml had significant pyuria (hemocytometer count on uncentrifuged urine of ≥10 WBC/mm^3), 69% of the low-count UTIs were also accompanied by significant pyuria, supporting their clinical relevance. Hansson et al. also found that there was no statistically significant difference between patients with high and low organism burden and the rate of vesicoureteral reflux. Although not statistically significant, reflux was actually more common in patients with low-organism-burden infections (38%) than those with high-burden infections (30%).

In a recent report by Schroeder et al. that looked at children <3 months of age with bacteremic UTI, 19/283 (6.7%) children had $<5 \times 10^4$ CFU/ml in their urine sample of the same bacterium isolated from the blood (17). However, only those which were due to *E. coli* (12/19, 63%) had evidence of significant pyuria. Comparing urinalysis to culture, LE was the most sensitive test (100%), followed by microscopic pyuria (>3 WBC/HPF, centrifugation not stated, 92%), any bacteria on microscopy (91%), or any nitrite positive (17%). Only one of the seven low-count urine samples due to group B *Streptococcus* (GBS) (5), *Enterococcus faecalis* (1), or *Streptococcus pyogenes* had significant urinalysis results (1 case of GBS had microscopic pyuria and all 7 were LE negative). This probably reflects the fact that the urinary tract was not the initial or main site of infection in these children but exhibited spillover into the urine from the bacteremia. This study clearly supports the clinical significance of uropathogens isolated at low counts ($<5 \times 10^4$ CFU/ml) from urine samples in infants, especially for *E. coli*.

Combining the results from four studies (Hoberman et al., Swerkersson et al., Hansson et al., and Kanellopoulos et al.), the rate of missed UTIs using a threshold of $\geq 10^5$ CFU/ml in children is remarkably consistent at 16%, 19%, 20%, and 14.1%, respectively (30–32). Similarly, rates of missed UTIs using a threshold of $\geq 5 \times 10^4$ CFU/ml (7%, 10.5%, and 6.7%) are also consistent across the literature (2, 30, 31). Using either threshold, these are unacceptable false-negative rates for UTI in children.

In contrast to studies recommending lower thresholds for bacterial counts in UTIs, Coulthard and colleagues recommend a threshold higher than 10^5 CFU/ml (33). They studied 203 children (2 weeks to 17.7 years old) with diagnoses of suspected UTI in whom a second urine culture was obtained within 2 h of the first. Using the first culture only, they found 100% sensitivity and 93% specificity in diagnosing UTI, and concluded that the 7% false-positive rate resulting from using this threshold was unacceptably high. They recommend instead a threshold of $\geq 10^6$ CFU/ml, to increase the specificity to 95%, while still maintaining a sensitivity of 100% (33). Importantly, they also show that $\geq 10^5$ CFU/ml of heavy mixed growth was never indicative of infection and should be considered contamination. A significant problem with this study is that urine samples that cultured $<10^5$ CFU/ml of a single uropathogen were considered insignificant and excluded from the analysis. This represented 21/69 or 30.4% of urine samples with pure growth of a uropathogen. There was no attempt to determine whether or not these were clinically significant, i.e., by urinalysis or clinical chart review. Excluding low-count urine samples without further study may have resulted in a cleaner analysis but probably also resulted in significant underdiagnosis, which should be as great a concern as overdiagnosis.

There are a number of studies that can be referenced to support thresholds of $\geq 10^4$, $\geq 5 \times 10^4$, $\geq 10^5$, and $\geq 10^6$ CFU/ml. Of course, diagnostic specificity will be maximized with the higher thresholds but at the expense of sensitivity. As laboratories establish their own protocols, they should balance these two important criteria and consider that following thresholds of $\geq 5 \times 10^4$ CFU/ml may miss from 7% to 20% of UTIs, depending on the threshold used. Thus, it is our opinion that the body of literature supports a threshold of $\geq 10^4$ CFU/ml, which is more conservative than that recommended by the AAP ($\geq 5 \times 10^4$ CFU/ml). The evidence is not strong enough to suggest using a threshold of $<10^4$ CFU/ml.

In addition, this review of the literature did not identify enough evidence to support generating age-specific thresholds, although some studies did show that low-burden infection was particularly prevalent in those <24 months of age. A limitation of this review, and of the literature, is that only a small number of cases from the adolescent population were captured for analysis, making it difficult to know whether thresholds for this group ought to be different than for younger children.

It is clear that pediatric UTI is a complex disease with a spectrum of presentations. For example, conditions such as reduced bladder incubation time, dilution due to hyperhydration, antibiotic therapy, and organism type can all lead to true urinary tract infection presenting as low-burden infection. In most patients, the presence of pyuria should be considered in conjunction with colony counts in order to establish the clinical significance of culture results and to reduce the possibility of a false-positive diagnosis. The presence of significant pyuria may be particularly valuable in distinguishing asymptomatic bacteriuria from infection or in distinguishing contamination from infection, especially in those cultures with lower counts, i.e., 10^4 to 10^5 CFU/ml. Although the hemocytometer WBC counting method is regarded as the most reliable, standard microscopy may also be helpful. Given the recent evidence for the utility of the LE test in infants (17), it may not be necessary for the pediatric microbiology laboratory to perform microscopy for pyuria and bacteriuria (especially the resource-intensive hemocytometer WBC count). Adjunctive rapid urinalysis testing for LE and nitrites at point of care or in the core or microbiology laboratory (manual or automated) may be the only necessary additional test to urine culture in determining the clinical significance of urine culture results with high degrees of

sensitivity and specificity. It is important to keep in mind, however, that neutropenic patients are unable to mount a significant polymorphonuclear response to infection, and thus, in this setting, a threshold of $\geq 10^4$ CFU/ml will be the main criterion for infection. The addition of a nitrite test and microscopic detection of bacteria may aid in determining the significance of a low colony count in this population.

SUSCEPTIBILITY TESTING IN PEDIATRIC URINARY TRACT INFECTION

It is generally accepted that the successful management of an acute UTI requires the initiation of antibiotic treatment before culture and antimicrobial susceptibility results are available (34). As such, the AAP recommends the empirical use of amoxicillin-clavulanate, trimethoprim-sulfamethoxazole (TMP-SMX), cephalexin, and cefixime among other oral cephalosporins, though clinicians should be guided by their local antibiogram profiles for uropathogens, as agents like TMP-SMX are becoming less acceptable for empirical therapy (3). These recommendations are similar to those of the European Association of Urology (25). In fact, many antibiotic prescriptions are ordered even before urinalysis results have been completed (21). It is therefore critical that health care providers understand the probability of isolating a given pathogen as well as the likely antibiotic susceptibility profile of that pathogen. As in adult UTIs, *E. coli* is the most common cause of infection in children (34). However, children with underlying renal disease are at greater risk for non-*E. coli* infections as are hospitalized patients (34). The antibiogram of urinary tract pathogens varies by patient population and by institution. Beetz and Westenfelder surveyed the resistance rates of *E. coli* isolates that were collected from children with UTIs from several European regions (34). As an example, rates of resistance to amoxicillin-clavulanic acid (AMC) ranged from 7% (France) to 43% (Turkey). Similarly, 0.9% of isolates from London were resistant to cefuroxime while 19% were reported to be resistant in Turkey (34).

The type and duration of empirical antimicrobial treatment a patient receives are dictated, not only by the likely organism and its antibiogram, but also by patient characteristics (age, underlying condition, history of UTI, and the type of infection [cystitis versus pyelonephritis]). It has been shown that oral antibiotics are as effective as parenteral therapy in the treatment of children 0 to 18 years of age (2, 35). Certain clinical circumstances warrant the admission of parenteral therapy, including the presence of sepsis syndrome, immune-compromising conditions, the inability to take oral medication, underlying urological abnormality, infection due to antibiotic resistant bacteria, and family psychosocial issues. Antimicrobial susceptibility testing (AST) may play an important role in guiding antibiotic selection for the treatment of these infections, whether it is for initial drug selection or for the alteration of empirical therapy. Surprisingly though, there is little literature demonstrating the clinical relevance of AST in children with uncomplicated UTI. The Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and other organizations provide guidance documents for AST, but the majority of their recommendations focus on systemic infections (relevant to complicated UTI) and not uncomplicated UTI (36–38). Because many commonly used UTI antibiotics achieve high concentrations in the urine, it is unlikely that breakpoints derived for systemic infections would accurately predict clinical outcome in uncomplicated UTI. For some specific antibiotics, CLSI and EUCAST provide guidance specifically for uncomplicated UTI due to *Enterobacteriaceae*.

The CLSI approach utilizes cephalothin or preferably cefazolin to predict results for oral cephalosporins (cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef). However, there is evidence that some AST systems overestimate cephalothin resistance and, therefore, eliminate important antibiotics for the treatment of pediatric UTI (39). CLSI does not indicate UTI-specific breakpoints for amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, or ciprofloxacin, commonly recommended as oral agents for UTI treatment in children, although it does for nalidixic acid, fosfomycin, and amdinocillin, which are uncommonly used antibiotics for pediatric UTI (3).

In contrast, EUCAST provides UTI-specific breakpoints for a broader range of individual drugs, including amoxicillin-clavulanic acid, amdinocillin, individual cephalosporins (cefadroxil, cephalexin, cefixime, cefpodoxime, ceftibuten, and cefuroxime), fosfomycin, nitrofurantoin, and trimethoprim alone. Despite the loss of activity of ampicillin and TMP-SMX as first-line agents for UTI, amoxicillin-clavulanic acid (AMC) remains a commonly recommended and used antibiotic in the treatment of uncomplicated pediatric UTI and, thus, clinically relevant testing remains important to guide its use (21). A large U.S. study of outpatient urinary isolates of *E. coli* ($n = 759{,}749$, largely adults) showed a rise in resistance to amoxicillin-clavulanate of only 0.3% between 2000 and 2010 (40). Similarly, a large Irish study showed a 0.06% reduction in *E. coli* susceptibility to AMC in community UTIs (including children) between 1999 and 2009 (41).

It is important to remember that CLSI amoxicillin/clavulanic acid breakpoints for *Enterobacteriaceae* (susceptible [S] $\leq$ 8/4; intermediate [I] = 16/8; resistant [R] $\geq$ 32/16) have been developed for systemic infections compared to the uncomplicated UTI-specific EUCAST breakpoints (S $\leq$ 32; R $>$ 32), which take into account the high concentration of this drug in urine. Thus, laboratories using CLSI breakpoints for AMC are likely overcalling resistance, resulting in the loss of an important, inexpensive, well-tolerated drug for use in children (and adults). This is illustrated by examining the data from a large multicenter European study of uncomplicated UTI in women, which shows that by using the systemic breakpoint for the susceptibility of AMC against *E. coli* (S $\leq$ 8), 82.5% of isolates are susceptible, whereas if the UTI-specific EUCAST breakpoints are applied, 99% of isolates would be considered susceptible (42).

In terms of susceptibility testing in patients with uncomplicated UTIs, there are few data to suggest that AST provides clinically relevant information in any patient population, including children. McNulty et al. performed a prospective study in adult women with uncomplicated UTIs that assessed the clinical relevance of *in vitro* trimethoprim resistance (43). They found that patients with resistant isolates had worse outcomes as defined by longer symptom duration, higher rates of reconsultation, more subsequent antibiotic usage, and higher rates of significant bacteriuria at 1 month. Although one would expect that a UTI due to an extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* would result in treatment failure using noncarbapenem β-lactam agents, this was refuted in several studies (44–46) in which children with UTIs due to ESBL-producing strains all had

favorable clinical and microbiological outcomes despite being treated with β-lactam agents that were categorized as resistant by *in vitro* AST.

Given the frequency with which UTIs occur in children and the vast amount of AST that is performed on urine culture isolates, there is a surprisingly small body of literature supporting its routine use. A review of the literature only identified three studies that evaluated the clinical relevance of AST in children with UTIs, and all three concluded that *in vitro* testing did not accurately predict outcome. One might conclude from this that routine AST is not useful and therefore should not be done. However, the trend toward developing UTI-specific breakpoints (EUCAST and CLSI) will hopefully play a role in establishing more robust interpretive AST criteria for uncomplicated UTIs in children and adults. Despite the apparent inability of AST to predict outcome in uncomplicated UTI, there are a few reasons that laboratories continue to perform such testing. First, routine testing allows laboratories to assess ongoing changes in susceptibility, which aids in the development of antibiograms as well as in public health monitoring for the emergence of antibiotic resistance. Second, although the literature suggests that recurrence in the setting of inappropriately treated infection is rare, situations will undoubtedly arise where patients fail to respond, and the selection of additional therapeutic options will be guided by AST. Lastly, it is often difficult for the laboratory to identify those patients who have an uncomplicated UTI (and may not require AST) from those patients with underlying disease or pyelonephritis who may benefit from AST.

CONCLUSIONS AND RECOMMENDATIONS

Optimal diagnosis of urinary tract infection in children hinges around the determination of an appropriate threshold of bacterial growth that correlates with clinical disease, which is a balance between the increased sensitivity of lower thresholds versus the increased specificity of higher thresholds. In our opinion, the body of evidence suggests that a threshold of 10^4 CFU/ml optimizes sensitivity while providing acceptable specificity. The addition of pyuria detection by one of several methods (hemocytometer WBC count or LE test, in particular) can aid in the interpretation of the clinical significance of urine samples with lower bacterial counts, especially those between 10^4 and 5×10^4 CFU/ml, and even at higher counts. The detection of significant pyuria thereby increases the specificity of the threshold-based culture method. This balance is reflected in the 2011 AAP guidelines, which suggest that UTIs in 2- to 24-month-old children should only be diagnosed in the presence of pyuria and a culture yielding $\geq 5 \times 10^4$ CFU/ml of a uropathogen.

In contrast to the AAP guidelines, we feel that there is good evidence from multiple studies providing compelling evidence for the significance of counts between 10^4 and 5×10^4 CFU/ml in a significant proportion of children with UTIs (7% to 10%) (2, 11, 17, 30–32). To capture these true UTIs and manage them appropriately without compensatory overdiagnosis, it is necessary to lower the diagnostic threshold to $\geq 10^4$ CFU/ml and to accompany this analysis with a rapid, simple, and reliable detector of significant pyuria. Recent evidence suggests that the LE test is more reliable in infants than has been previously suggested (17). This test can be done at point of care and would obviate microscopy in the microbiology or core laboratory. This would be an important adjunct to establishing the clinical significance of urine culture because of its utility in distinguishing true infection with an inflammatory response from contamination or asymptomatic bacteriuria. Lowering the diagnostic threshold for children to $\geq 10^4$ CFU/ml in a well-collected urine specimen that is promptly transported to the laboratory or refrigerated until delivery will produce clinically valuable results with optimal sensitivity and specificity, especially when combined with a reliable test of inflammation in the urine.

ACKNOWLEDGMENTS

No funding was provided in support of the manuscript.

S.E.R. declares the following conflicts of interest: research support from Altona Diagnostics and Luminex Molecular Diagnostics Inc. C.D.D. declares the following conflicts of interest: research support from Cepheid and personal fees from Nanosphere and Thermo Fisher Scientific.

REFERENCES

1. **Montini G, Tullus K, Hewitt I.** 2011. Febrile urinary tract infections in children. N Engl J Med **365:**239–250. http://dx.doi.org/10.1056/NEJMra1007755.
2. **Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M.** 1994. Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. J Pediatr **124:**513–519. http://dx.doi.org/10.1016/S0022-3476(05)83127-0.
3. **Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB.** 2011. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics **128:**595–610. http://dx.doi.org/10.1542/peds.2011-1330.
4. **Cataldi L, Zaffanello M, Gnarra M, Fanos V, Neonatal Nephrology Study Group, Italian Society of Neonatology.** 2010. Urinary tract infection in the newborn and the infant: state of the art. J Matern Fetal Neonatal Med **23**(Suppl):S90–S93.
5. **Sandoval C, Sinaki B, Weiss R, Munoz J, Ozkaynak MF, Tugal O, Jayabose S.** 2012. Urinary tract infections in pediatric oncology patients with fever and neutropenia. Pediatr Hematol Oncol **29:**68–72. http://dx.doi.org/10.3109/08880018.2011.617809.
6. **Shaw KN, Gorelick M, McGowan KL, Yakscoe NM, Schwartz JS.** 1998. Prevalence of urinary tract infection in febrile young children in the emergency department. Pediatrics **102:**e16. http://dx.doi.org/10.1542/peds.102.2.e16.
7. **Spahiu L, Hasbahta V.** 2010. Most frequent causes of urinary tract infections in children. Med Arh **64:**88–90.
8. **Lo DS, Shieh HH, Ragazzi SL, Koch VH, Martinez MB, Gilio AE.** 2013. Community-acquired urinary tract infection: age and gender-dependent etiology. J Bras Nefrol **35:**93–98. http://dx.doi.org/10.5935/0101-2800.20130016.
9. **Abrahamsson K, Hansson S, Jodal U, Lincoln K.** 1993. *Staphylococcus saprophyticus* urinary tract infections in children. Eur J Pediatr **152:**69–71. http://dx.doi.org/10.1007/BF02072520.
10. **Lohr JA, Donowitz LG, Sadler JE, III.** 1989. Hospital-acquired urinary tract infection. Pediatrics **83:**193–199.
11. **Pryles CV, Steg NL.** 1959. Specimens of urine obtained from young girls by catheter versus voiding; a comparative study of bacterial cultures, Gram stains and bacterial counts in paired specimens. Pediatrics **23:**441–452.
12. **Al-Orifi F, McGillivray D, Tange S, Kramer MS.** 2000. Urine culture from bag specimens in young children: are the risks too high? J Pediatr **137:**221–226. http://dx.doi.org/10.1067/mpd.2000.107466.
13. **Fairley KF, Barraclough M.** 1967. Leucocyte-excretion rate as a screening test for bacteriuria. Lancet **i:**420–421.
14. **Brumfitt W.** 1965. Urinary cell counts and their value. J Clin Pathol **18:**550–555.
15. **Finnell SM, Carroll AE, Downs SM, Subcommittee on Urinary Tract Infection.** 2011. Technical report—diagnosis and management of an initial UTI in febrile infants and young children. Pediatrics **128:**e749–e770. http://dx.doi.org/10.1542/peds.2011-1332.
16. **Klaassen IL, de Haas V, van Wijk JA, Kaspers GJ, Bijlsma M, Bokenkamp A.** 2011. Pyuria is absent during urinary tract infections in neutropenic patients. Pediatr Blood Cancer **56:**868–870. http://dx.doi.org/10.1002/pbc.22799.
17. **Schroeder AR, Chang PW, Shen MW, Biondi EA, Greenhow TL.** 2015.

Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. Pediatrics **135:**965–971. http://dx.doi.org/10.1542/peds.2015-0012.
18. **Gutierrez-Fernandez J, Lara A, Bautista MF, de Dios Luna J, Polo P, Miranda C, Navarro JM.** 2012. Performance of the Sysmex UF1000i system in screening for significant bacteriuria before quantitative culture of aerobic/facultative fast-growth bacteria in a reference hospital. J Appl Microbiol **113:**609–614. http://dx.doi.org/10.1111/j.1365-2672.2012.05369.x.
19. **Sturenburg E, Kramer J, Schon G, Cachovan G, Sobottka I.** 2014. Detection of significant bacteriuria by use of the iQ200 automated urine microscope. J Clin Microbiol **52:**2855–2860. http://dx.doi.org/10.1128/JCM.00112-14.
20. **Shah AP, Cobb BT, Lower DR, Shaikh N, Rasmussen J, Hoberman A, Wald ER, Rosendorff A, Hickey RW.** 2014. Enhanced versus automated urinalysis for screening of urinary tract infections in children in the emergency department. Pediatr Infect Dis J **33:**272–275. http://dx.doi.org/10.1097/INF.0000000000000215.
21. **Cantey JB, Gaviria-Agudelo C, McElvania TeKippe E, Doern CD.** 2015. Lack of clinical utility of urine Gram stain for suspected urinary tract infection in pediatric patients. J Clin Microbiol **53:**1282–1285. http://dx.doi.org/10.1128/JCM.00045-15.
22. **Kanegaye JT, Jacob JM, Malicki D.** 2014. Automated urinalysis and urine dipstick in the emergency evaluation of young febrile children. Pediatrics **134:**523–529. http://dx.doi.org/10.1542/peds.2013-4222.
23. **Kass EH.** 2002. Asymptomatic infections of the urinary tract. 1956. J Urol **167:**1016–1019; discussion 1019–1021. http://dx.doi.org/10.1016/S0022-5347(02)80328-7.
24. **Hooton TM, Roberts PL, Cox ME, Stapleton AE.** 2013. Voided midstream urine culture and acute cystitis in premenopausal women. N Engl J Med **369:**1883–1891. http://dx.doi.org/10.1056/NEJMoa1302186.
25. **Stein R, Dogan HS, Hoebeke P, Kocvara R, Nijman RJ, Radmayr C, Tekgul S, European Association of Urology, European Society for Pediatric Urology.** 2015. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol **67:**546–558. http://dx.doi.org/10.1016/j.eururo.2014.11.007.
26. **McTaggart S, Danchin M, Ditchfield M, Hewitt I, Kausman J, Kennedy S, Trnka P, Williams G, Kidney Health Australia-Caring for Australasians with Renal Impairment.** 2015. KHA-CARI guideline: diagnosis and treatment of urinary tract infection in children. Nephrology (Carlton) **20:**55–60. http://dx.doi.org/10.1111/nep.12349.
27. **Deader R, Tiboni SG, Malone PS, Fairhurst J.** 2012. Will the implementation of the 2007 National Institute for Health and Clinical Excellence (NICE) guidelines on childhood urinary tract infection (UTI) in the UK miss significant urinary tract pathology? BJU Int **110:**454–458. http://dx.doi.org/10.1111/j.1464-410X.2011.10801.x.
28. **Pryles CV, Atkin MD, Morse TS, Welch KJ.** 1959. Comparative bacteriologic study of urine obtained from children by percutaneous suprapubic aspiration of the bladder and by catheter. Pediatrics **24:**983–991.
29. **Karacan C, Erkek N, Senel S, Akin Gunduz S, Catli G, Tavil B.** 2010. Evaluation of urine collection methods for the diagnosis of urinary tract infection in children. Med Princ Pract **19:**188–191. http://dx.doi.org/10.1159/000273068.
30. **Swerkersson S, Jodal U, Ahren C, Sixt R, Stokland E, Hansson S.** 2016. Urinary tract infection in infants: the significance of low bacterial count. Pediatr Nephrol **31:**239–245. http://dx.doi.org/10.1007/s00467-015-3199-y.
31. **Kanellopoulos TA, Vassilakos PJ, Kantzis M, Ellina A, Kolonitsiou F, Papanastasiou DA.** 2005. Low bacterial count urinary tract infections in infants and young children. Eur J Pediatr **164:**355–361. http://dx.doi.org/10.1007/s00431-005-1632-0.
32. **Hansson S, Brandstrom P, Jodal U, Larsson P.** 1998. Low bacterial counts in infants with urinary tract infection. J Pediatr **132:**180–182. http://dx.doi.org/10.1016/S0022-3476(98)70512-8.
33. **Coulthard MG, Kalra M, Lambert HJ, Nelson A, Smith T, Perry JD.** 2010. Redefining urinary tract infections by bacterial colony counts. Pediatrics **125:**335–341. http://dx.doi.org/10.1542/peds.2008-1455.
34. **Beetz R, Westenfelder M.** 2011. Antimicrobial therapy of urinary tract infections in children. Int J Antimicrob Agents **38**(Suppl)**:**42–50. http://dx.doi.org/10.1016/j.ijantimicag.2011.09.006.
35. **Hodson EM, Willis NS, Craig JC.** 2007. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev **4:**CD003772. http://dx.doi.org/10.1002/14651858.CD003772.pub3.
36. **Clinical and Laboratory Standards Institute.** 2015. Performance standards for antimicrobial susceptibility testing; 25th informational supplement. CLSI M100–S25. Clinical and Laboratory Standards Institute, Wayne, PA.
37. **EUCAST.** 2015. Breakpoint tables for interpretation of MICs and zone diameters. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf.
38. **Kahlmeter G, Poulsen HO.** 2012. Antimicrobial susceptibility of *Escherichia coli* from community-acquired urinary tract infections in Europe: the ECO·SENS study revisited. Int J Antimicrob Agents **39:**45–51. http://dx.doi.org/10.1016/j.ijantimicag.2011.09.013.
39. **Zhang SX, Parisian F, Yau Y, Fuller JD, Poutanen SM, Richardson SE.** 2007. Narrow-spectrum cephalosporin susceptibility testing of *Escherichia coli* with the BD Phoenix automated system: questionable utility of cephalothin as a predictor of cephalexin susceptibility. J Clin Microbiol **45:**3762–3763. http://dx.doi.org/10.1128/JCM.00968-07.
40. **Sanchez GV, Master RN, Karlowsky JA, Bordon JM.** 2012. *In vitro* antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. Antimicrob Agents Chemother **56:**2181–2183. http://dx.doi.org/10.1128/AAC.06060-11.
41. **Cullen IM, Manecksha RP, McCullagh E, Ahmad S, O'Kelly F, Flynn RJ, McDermott T, Murphy P, Grainger R, Fennell JP, Thornhill JA.** 2012. The changing pattern of antimicrobial resistance within 42,033 *Escherichia coli* isolates from nosocomial, community and urology patient-specific urinary tract infections, Dublin, 1999-2009. BJU Int **109:**1198–1206. http://dx.doi.org/10.1111/j.1464-410X.2011.10528.x.
42. **Schito GC, Gualco L, Naber KG, Botto H, Palou J, Mazzei T, Marchese A.** 2010. Do different susceptibility breakpoints affect the selection of antimicrobials for treatment of uncomplicated cystitis? J Chemother **22:**345–354. http://dx.doi.org/10.1179/joc.2010.22.5.345.
43. **McNulty CA, Richards J, Livermore DM, Little P, Charlett A, Freeman E, Harvey I, Thomas M.** 2006. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. J Antimicrob Chemother **58:**1000–1008. http://dx.doi.org/10.1093/jac/dkl368.
44. **Han SB, Lee SC, Lee SY, Jeong DC, Kang JH.** 2015. Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. BMC Infect Dis **15:**414. http://dx.doi.org/10.1186/s12879-015-1153-z.
45. **Lee B, Kang SY, Kang HM, Yang NR, Kang HG, Ha IS, Cheong HI, Lee HJ, Choi EH.** 2013. Outcome of antimicrobial therapy of pediatric urinary tract infections caused by extended-spectrum β-lactamase-producing *Enterobacteriaceae*. Infect Chemother **45:**415–421. http://dx.doi.org/10.3947/ic.2013.45.4.415.
46. **Tratselas A, Iosifidis E, Ioannidou M, Saoulidis S, Kollios K, Antachopoulos C, Sofianou D, Roilides EJ.** 2011. Outcome of urinary tract infections caused by extended spectrum β-lactamase-producing *Enterobacteriaceae* in children. Pediatr Infect Dis J **30:**707–710. http://dx.doi.org/10.1097/INF.0b013e31820eae6a.
47. **Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M.** 1996. Is urine culture necessary to rule out urinary tract infection in young febrile children? Pediatr Infect Dis J **15:**304–309.

Continued next page

Christopher D. Doern graduated with a B.S. from Wake Forest University in Winston-Salem, North Carolina, in 2003. He then went on to earn his Ph.D. in Microbiology and Immunology from the Wake Forest University School of Medicine in 2008. In 2010, he completed a fellowship in Medical and Public Health Microbiology at the Washington University School of Medicine in St. Louis under the direction of Dr. W. Michael Dunne, Jr., Ph.D. In 2010, Dr. Doern also passed the American Board of Medical Microbiology exam. Dr. Doern's first position was as an Assistant Professor of Pathology at the University of Texas Southwestern Medical Center serving as the Director of Clinical Microbiology at Children's Medical Center of Dallas. In 2014, Dr. Doern left Dallas to become an Assistant Professor of Pathology and the Associate Director of Clinical Microbiology at Virginia Commonwealth University Medical Center on the Medical College of Virginia Campus.

Dr. Susan Richardson is a medical microbiologist and infectious diseases physician. She obtained her M.D. from McGill University and fellowships in Internal Medicine, Infectious Diseases, and Medical Microbiology. She is a Senior Associate Scientist in the Research Institute at The Hospital for Sick Children and a Professor in the Department of Pathobiology and Laboratory Medicine at the University of Toronto. Dr. Richardson is Head of the Division of Microbiology at The Hospital for Sick Children and an Adjunct Scientist in Mycology at the Public Health Ontario Laboratory, Toronto. Her research interests are in the areas of fungal infections, optimization of pediatric diagnostic microbiology, the rapid diagnosis of viral respiratory infections, and molecular diagnostics as applied to pediatric infectious diseases.