UTI and Faulty Gold Standards

I read with interest the article by Shaikh et al[1] on the association between pyuria and uropathogen type in children being evaluated for urinary tract infection (UTI). Their conclusion differs from our related investigation[2] in *Pediatrics*, in which we concluded that the sensitivity of the urinalysis (UA) has been previously underestimated due to a faulty gold standard, namely, urine cultures that are falsely positive because of contamination and asymptomatic bacteruria (AB). In our sample of young infants with bacteremic UTI, a condition that cannot be explained by contamination or AB, 99.5% of subjects had a UA that was positive for either leukocyte esterase or pyuria (≥3 white blood cells per high-power field).[2] The accompanying commentary to our article concluded that "the absence of pyuria should create great doubt about the presence of a UTI."[3]

In this recent investigation, Shaikh et al[1] present data consistent with previous reports that pyuria on the UA is imperfectly sensitive, and provide new information suggesting that the sensitivity might differ by uropathogen. They report that the sensitivity of pyuria of only 90% cannot be explained by AB, because the prevalence of AB is "too low (<1%)." The actual prevalence of AB (detected via suprapubic aspirate) in the study by Wettergren et al,[4] which the authors cite in making this claim, is 1.4%: 0.9% in girls and 2.5% in boys. Nonetheless, even a prevalence of AB as low as 1% could have a substantial impact on the apparent sensitivity of the UA. In the Shaikh et al[1] study, for example, the estimated prevalence of UTI was ~5% (1394/26 151). If the population prevalence of AB is 1% in children, then an estimated 1 of 5 positive cultures in their sample will be falsely positive (ie, a positive urine culture with a negative UA). Therefore, if this population were similar to the population of Wettergren et al,[4] the sensitivity of even a perfect screening test applied to this population would theoretically be ~80%. As long as urine cultures alone are used as a gold standard to define UTI, we are unlikely to ever see UA sensitivities that approach 100%. The fact that sensitivities in this study appear to differ by pathogen also could be explained by the varying likelihoods of certain organisms to colonize the genitourinary tract and/or contaminate a urine sample.

Shaikh et al[1] also reiterate concerns that a delay in the diagnosis of UTI (as might occur if a physician is misled by a negative UA) may increase the risk of renal scarring. However, this concern is belied by data from their own meta-analysis demonstrating that fever >24 hours before diagnosis of UTI is not associated with renal scarring (odds ratio 1.11, 95% confidence interval 0.72–1.71).[5]

Alan R. Schroeder, MD
Stanford University School of Medicine
E-mail: aschroe@stanford.edu

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REFERENCES

1. Shaikh N, Shope TR, Hoberman A, Vigliotti A, Kurs-Lasky M, Martin JM. Association between uropathogen and pyuria. *Pediatrics*. 2016;138(1): e20160087
2. Schroeder AR, Chang PW, Shen MW, Biondi EA, Greenhow TL. Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. *Pediatrics*. 2015; 135(6):965–971
3. Roberts KB. The diagnosis of UTI: liquid gold and the problem of gold standards. *Pediatrics*. 2015;135(6):1126–1127
4. Wettergren B, Jodal U, Jonasson G. Epidemiology of bacteriuria during the first year of life. *Acta Paediatr Scand*. 1985;74(6): 925–933
5. Shaikh N, Craig JC, Rovers MM, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. *JAMA Pediatr*. 2014; 168(10):893–900

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Should We Believe the Urinalysis?

In the post–Haemophilus influenzae type b, postpneumococcal immunization era, urinary tract infections (UTIs) are the most common serious bacterial infection in infants and young children. The diagnosis of UTI is challenging in this population and has received much attention, including a 2011 American Academy of Pediatrics clinical practice guideline (CPG) on diagnosis and management of UTI in febrile infants and young children.[1] The recent article by Shaikh et al[2] in *Pediatrics* on the association between uropathogens and pyuria and the accompanying commentary by Aaron Friedman[3] support the importance of a urine culture even in the absence of a negative urinalysis (UA). On the other hand, Schroeder et al[4] find that in infants <3 months with a true UTI, UA sensitivity is higher than previously reported for UTI, suggesting that the UA is reliable even in young infants. What is a clinician to do?

As Dr Lewis First suggests in his commentary, let's look at the context.[5] The discrepancy regarding the utility of a UA as a screening test for UTI may be due to the different populations that these studies are addressing. Shaikh et al[2] evaluated children with "symptoms consistent with a diagnosis of a UTI" in whom it would make sense to have a high index of suspicion even with a negative UA and perhaps have a lower threshold for starting antibiotics pending urine culture results, which always should be obtained. Such an approach may be too conservative in a well-appearing (likely not bacteremic) patient with fever without localizing source with a low

suspicion of UTI (based on low assessment of UTI risk), in whom a negative urinalysis is likely to be reassuring by itself. The 2011 American Academy of Pediatrics CPG has it spot on in recommending that a negative UA may be sufficient if antibiotics are not planned in a well-appearing patient with fever without source. However, if ill-appearing and/or if antibiotics are planned, a reliable urine culture must be obtained. Finally, the CPG recommends that to establish a diagnosis of UTI, both a UA and urine culture are required. This CPG addresses a common clinical scenario in pediatrics (evaluation of the most common serious bacterial infection in children with fever), and continues to be a helpful resource for pediatric clinicians.

Shabnam Jain
Emory University
E-mail: sjain@emory.edu

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REFERENCES

1. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. 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*. 2011;128(3):595–610
2. Shaikh N, Shope TR, Hoberman A, Vigliotti A, Kurs-Lasky M, Martin JM. Association between uropathogen and pyuria. *Pediatrics*. 2016;138(1):e20160087
3. Friedman A. Management of UTI in children: murky waters. *Pediatrics*. 2016; 138(1):e20161247
4. Schroeder AR, Chang PW, Shen MW, Biondi EA, Greenhow TL. Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. *Pediatrics*. 2015;135(6):965–971
5. First L. *Now You See It—But What If You Don't! Can a UTI Occur in the Absence of Pyuria?* Pediatrics Journals Blog; 2016

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Author's Response
Response to Comments by Drs Schroeder and Jain

We thank Dr Schroeder for his comments on our article. We agree with Dr Schroeder that some children may have bacteriuria even when they are asymptomatic. We disagree, however, on the prevalence and clinical implications of this finding.

Schroeder states that 1.4% of children have asymptomatic bacteriuria, and because the prevalence of urinary tract infection (UTI) among those tested is low (~5%), a large proportion of children with apparent UTIs actually may have asymptomatic bacteriuria and are therefore being misdiagnosed. However, closer reading of the original articles describing the asymptomatic bacteriuria (by using a method of urine collection less prone to contamination, such as suprapubic aspiration), show that the 1.4% number is the period prevalence of asymptomatic bacteriuria (cumulative over the 12-month follow-up period).[1] At any 1 point in time after 1 month of age, only 0% to 0.4% (see Fig 3 in the article by Wettergren et al[1]) of children tested had asymptomatic bacteriuria (ie, the point prevalence of asymptomatic bacteriuria was ≤0.4%, and most often 0). Point prevalence represents the value that best reflects the probability of asymptomatic bacteriuria among children presenting to a clinician at 1 point in time. Furthermore, some children with asymptomatic bacteriuria go on to develop symptoms of UTI, making the number of truly misdiagnosed children even smaller. For these reasons, the magnitude of potentially misdiagnosed cases is much smaller than that portrayed by Dr Schroeder. Of note, the percentage of asymptomatic carriage pales in comparison with its frequency in other pediatric conditions (eg, 20% rate of asymptomatic carriage for Group A *Streptococcus*).

Even if some children diagnosed with UTI actually have asymptomatic bacteriuria, with currently available bedside tests, there is no way for the clinician to know this. In our opinion, this reinforces the need for new test(s) to supplement the urine culture. The leukocyte esterase test (or pyuria on urinalysis) is ill-suited to serve this role because (1) a significant proportion of children with asymptomatic bacteriuria have pyuria (56% in the study by Wettergren et al[1]), (2) ~10% to 20% of children with UTI do not have pyuria,[2] and (3) in our study,[3] and in a subsequent study by Lubell et al,[4] the likelihood of observing pyuria varied by the type of uropathogen present. Although a study conducted by Schroeder et al[5] seems to suggest that the sensitivity of pyuria is much higher than previously reported, as we have discussed elsewhere,[6] there are several issues with the design of that study that limit its generalizability. Accordingly, the bulk of available data suggests that the inflammatory response to a UTI is complex (dependent on the interaction between pathogen and host), and that the presence or absence of pyuria alone, albeit informative in a large number of cases, is not always an accurate indication of the presence or absence of UTI. Accordingly, we currently do not believe that pyuria, albeit present in most instances, should be required for a diagnosis of UTI in symptomatic children; this requirement will result in missed cases of true UTI and will slow down the search for better biomarkers for UTI.

Although our previous meta-analysis did not show that delayed treatment leads to scarring, this could have been due to the limitations in the way data on delayed treatment were

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