5. Glauser MP, Meylan P, Bille J. The inflammatory response and tissue damage. The example of renal scars following acute renal infection. Pediatr Nephrol 1987;1:615-22.
6. Kemper K, Avner E. The case against screening for asymptomatic bacteriuria in children. Am J Dis Child 1992;146:343-6.

Reply

To the Editor:

We thank Drs Roberts and Wald for their interest in our article. However, the calculations presented in the first paragraph of their letter are misleading because they assume the "best case scenario" in favor of the authors' argument. Only when both prevalence of urinary tract infection (UTI) and false positive rate of on currently-available point-of-care tests for pyuria are 5% would the prevalence of true missed UTI without pyuria (ie, 0.25%) approach that of asymptomatic bacteriuria without pyuria (0.21%, the overall rate of asymptomatic bacteriuria without pyuria from our study). A more balanced calculation is presented in the Appendix to our report, in which we show, using mean values from meta-analyses of the literature (which support higher values for prevalence of UTI and lower values for sensitivity of pyuria), that the prevalence UTI without pyuria is approximately 10 fold higher than the prevalence of asymptomatic bacteriuria without pyuria. Moreover, the calculations presented in their letter support the conclusions in our manuscript. If the prevalence of true UTI without pyuria and asymptomatic bacteriuria are similar, requiring pyuria to diagnose UTI, while sparing one child with asymptomatic bacteriuria from unnecessary antibiotics, would result in harm to another. In both the Guidelines[1] and their letter, the authors use asymptomatic bacteriuria to justify changes to the definition of UTI. What our report adds is an unbiased estimate of the prevalence of asymptomatic bacteriuria without pyuria, which can then be compared with the prevalence of true UTI without pyuria. From the available data, it is clear that asymptomatic bacteriuria, because of its low prevalence, cannot be used to justify the changes that were made to the definition of UTI.

In response to their second paragraph, our intent in mentioning contamination was not to dismiss it. Clearly contamination of urine samples is an issue that clinicians encounter on a regular basis. We simply wanted to point out that contamination was also an issue in some of the studies that we pooled in our study and that this might have led us to overestimate the prevalence of asymptomatic bacteriuria.

Their third paragraph conflates absence of pyuria on currently-available point-of-care tests with the absence of inflammation; these tests quickly screen for UTI (with only modest sensitivity) and were not designed as a definitive tests for inflammation. For example, in a study of 260 febrile infants being evaluated for UTI by bladder catheterization,[2] 9 of the 35 children with likely UTI had a negative leukocyte esterase test. However, all but one had elevated levels of another largely neutrophil-derived protein (neutrophil gelatinase-associated lipocalin). We would be remiss telling parents of these 9 febrile children, all of whom had significant bacteriuria, that their child does not have a UTI simply because a quick screening test performed on their child's urine was negative. This is especially important knowing that no more than 1 of such 9 children likely has asymptomatic bacteriuria (ie, $260 \times 0.21\%$, rounded up, with 0.21% being the prevalence of asymptomatic bacteriuria without pyuria from our report), and knowing that 8 likely would have clear evidence of inflammation if we had used more sensitive tests. Of note, the prevalence of UTI in the above referenced article[3] is higher and the sensitivity of the leukocyte esterase test is lower than the values we used in the Appendix to our study, which suggests the values we used represent a reasonable point between best and worst case scenarios. We are not suggesting at this point that neutrophil gelatinase-associated lipocalin should replace pyuria in the definition of UTI; large studies are needed before screening tests that are capable of reliably replacing the urine culture as the gold standard of UTI can be identified. Rather, we are suggesting that pyuria, based on years of study, is certainly the wrong test for the task it was assigned. The likelihood of renal scarring is not relevant here because prevention of renal scarring is not the only reason children with UTIs are treated with antimicrobials.

In summary, our data suggest that a definition of UTI that requires presence of pyuria will not capture every case. The definition of UTI endorsed by the American Academy of Pediatrics, that has elevated a quick and rather inaccurate screening test for UTI to the position of the gold standard for the disease, may do more harm than good; many children with true UTI may be left untreated to reduce unnecessary antibiotic use in a fraction. The public health ramifications of this definition, which can be seen in hospitals doing away with the urine culture without the clinician's consent ("reflex urine culture"[3] only if pyuria present) and the increasing use of quick urine collection methods (eg, "2-step process"[4]), all in the name of antimicrobial stewardship, are even more concerning. We are hopeful that this letter clarifies the implications of our manuscript and leads to further discussion.

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References

1. Subcommittee on Urinary Tract Infection SCoQI, Management, Roberts KB. 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;128:595-610.
2. Lubell TR, Barasch JM, Xu K, Ieni M, Cabrera KI, Dayan PS. Urinary neutrophil gelatinase-associated lipocalin for the diagnosis of urinary tract infections. Pediatrics 2017;140:e20171090.

3. Humphries RM, Dien Bard J. Point-counterpoint: reflex cultures reduce laboratory workload and improve antimicrobial stewardship in patients suspected of having urinary tract infections. J Clin Microbiol 2016;54:254-8.
4. Lavelle JM, Blackstone MM, Funari MK, Roper C, Lopez P, Schast A, et al. Two-step process for ED UTI screening in febrile young children: reducing catheterization rates. Pediatrics 2016;138:e20153023.

Editors' Response

We take this opportunity to comment on the letter to the editor from Drs Roberts and Wald, questioning the validity of the analysis and conclusion of the manuscript by Shaikh et al, and the authors' response. We believe that the analysis performed by Shaikh et al is sound and stand by the decision of *The Journal* to publish their study. We also choose to publish the letter and response to further enrich the deliberations of our readers.

The crux of the writers' argument about the meaning of bacteriuria in the absence of pyuria is an example of the utility of Bayes' Theorem in clinical decision making. The positive (or negative) predictive value of any test for a condition depends on the pretest probability of that condition in the patient being tested. The pretest probability of urinary tract infection in a febrile infant with no apparent clinical focus of infection is considerably higher than the probability in an asymptomatic child undergoing a "screening" test. The interpretation of finding bacteriuria in the absence of pyuria in the 2 situations also would be expected to be different. Although pyuria is a typical finding in urinary tract infections, we agree with Shaikh et al that the absence of pyuria does not necessarily exclude that diagnosis or the need for timely antibiotic therapy.

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Associate Editor

Sarah S. Long, MD
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