Yetimakman et al also draw attention to our interpretation of stability in older patients who were already ventilated and who were more likely to remain stable. We do acknowledge that the interpretation of these data is difficult, because natural history data reporting possible changes in hours or modalities of ventilation are scanty and often depend on compliance with standards of care, availability of resources, or, in the past, different approaches to proactive respiratory care. Although we agree completely that these data should be interpreted with caution, we have had feedback from the families that many older ventilated patients were not always stable and had to change parameters over time, often in the setting of infections. Infections or other adverse events often triggered an increased need for ventilation that often persisted after the infection subsided. Furthermore, from our personal experience during continuous interviews with parents and families, most parents report that stability represents one of their targets when choosing treatment for their children.

We also fully agree on the need for better surrogates for respiratory function in which proactive care and type and approach to ventilatory care should play a minor part. This may prove to be challenging in our children with type 1 SMA. Vital capacity, as suggested, is definitely a good measure, but not applicable to children younger than 6 years of age or in very weak older patients. More longitudinal data over longer periods will hopefully help to define what is the best measure to monitor ventilatory progression in the treated patients who are developing new phenotypes, compared with those classically identified in the different forms of SMA.

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E.M. and V.S. serve as scientific consultants in Biogen's Advisory Boards.

Reconsidering asymptomatic bacteriuria and contamination as causes of bacteriuria without pyuria

To the Editor:

Shaikh et al performed a meta-analysis to determine the prevalence of asymptomatic bacteriuria in children.[1] The clinical issue is whether a positive urine culture with a negative urinalysis represents a urinary tract infection (UTI) or asymptomatic bacteriuria. The authors calculate the rate of bacteriuria without pyuria (the working definition of asymptomatic bacteriuria) to be 0.18% in boys and 0.38% in girls. They compare these rates with the 5% rate of what they call "UTIs," determine the rate of asymptomatic bacteriuria to be "at least an order of magnitude less than the prevalence of UTI," and conclude that "the current definition of UTI should be revisited."[1] However, the majority of the 5% have both bacteriuria and pyuria and clearly have a UTI, not asymptomatic bacteriuria. It is the remainder of the 5%—the 5%-15% with bacteriuria without pyuria—that should be compared with the prevalence of asymptomatic bacteriuria. Because 5%-15% of 5% is 0.25-0.75%, the rate in febrile children is similar to the prevalence of asymptomatic bacteriuria calculated by Shaikh et al.

The authors not only dismiss asymptomatic bacteriuria as an explanation for bacteriuria without pyuria but contamination as well. There are ample data to refute their position, including specimens obtained by catheterization.[2-4]

Fortunately, the combination of bacteriuria without inflammation (positive culture-negative urinalysis) occurs in only about 0.5% of febrile infants. Accordingly, the rate of missed bacteriuria is low when screened by urinalysis; moreover, the significance of bacteriuria without inflammation is not clear because inflammation appears to be required to cause renal scars.[5] There is harm in presuming that bacteriuria without inflammation represents a UTI: treatment of asymptomatic bacteriuria increases the likelihood of a symptomatic UTI,[6] which would be mistaken as a recurrent UTI and trigger imaging, increasing cost, radiation, and discomfort.

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References

1. Shaikh N, Osio VA, Wessel CB, Jeong JH. Prevalence of asymptomatic bacteriuria in children: a meta-analysis. J Pediatr 2020;217:110-7.e4.
2. Lau AY, Wong SN, Yip KT, Fong KW, Li SP, Que TL. A comparative study on bacterial cultures of urine samples obtained by clean-void technique versus urethral catheterization. Acta Pediatrica 2007;96:432-6.
3. Wingerter S, Bachur R. Rick Factors for contamination of catheterized urine specimens in febrile children. Ped Emerg Care 2011;27:1-4.
4. Eliacik K, Kanik A, Yavascan O, Alparslan C, Kocyigit C, Aksu N, et al. A comparison of bladder catheterization and suprapubic aspiration methods for urine sample collection from infants with a suspected urinary tract infection. Clin Pediatr 2016;55:819-24.

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.