Determining the Best Definition for a Positive Urine Culture in Young Children

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In this issue of *Pediatrics*, Shaikh and colleagues propose a new lower bound to define a positive urine culture.[1] Addressing what defines a positive urine culture is essential, as urinary tract infections (UTIs) are common in young infants and children; prompt accurate diagnosis is necessary to avoid short-and long-term complications.[2–4]

In this study, Shaikh and colleagues evaluated the diagnostic properties of conventional urine culture at various cutoffs to identify UTI cases using 16S ribosomal RNA (rRNA) sequencing as the reference standard. One advantage of 16S sequencing over conventional culture is that it can indicate the presence of organisms difficult to culture conventionally. There is also the exciting future promise of rapid turnaround times for 16S sequencing and the potential for determining the presence of antibiotic-resistant organisms.[5] This method could provide a more comprehensive picture of the microorganisms in urine than is possible with culture. However, the challenge is not only determining what is in urine, but judging whether it reflects infection or contamination.

Traditionally, significant bacteriuria, a level indicative of infection, has been defined according to the method of urine collection.[6] The concept of significant bacteriuria adjusts for the possibility that there may be contamination of urine that traverses the distal urethra. The more likely that contamination may occur, the more permissive the definition. For samples that are midstream clean catch, the definition of significant bacteriuria is ≥100 000 colony-forming units (cfu)/mL; for samples obtained by urethral catheterization, the definition has varied between 10 000 and 50 000 cfu/mL, whereas for samples obtained by suprapubic aspiration (SPA), a method bypassing the urethra, any colony count has been considered significant.

However, urine, long-considered to be normally sterile, has now been shown to harbor a low level of bacterial colonization at all times.[7–11] This is not surprising since the distal urethra is almost always colonized with perirectal and in females with vaginal flora.[8] The pathogenesis of most UTIs, excluding the immediate neonatal period, is by the ascending route. Bacteria from the periurethral area adhere to uroepithelial cells of the urethra and may consistently and continually ascend to the bladder and begin to multiply. In general, when the individual voids, the colony count is diminished or eliminated. The factors that influence whether bacteria initiate an inflammatory response instigating infection or are merely present without an inflammatory response, thereby creating the constituents of the urobiome or the elements of asymptomatic bacteriuria, are complex and incompletely understood.

In this study by Shaikh and colleagues, an infection was considered present if at least 80% of sequences belonged to a single taxon (a like population of organisms) and if there was evidence of a host inflammatory response in the urine. All 341 of the subjects were febrile without another obvious site of infection. When using a cutoff of ≥10 000 cfu/mL to define a positive urine culture,

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45 of 46 children with UTI were correctly identified by conventional culture (sensitivity 98%, 95% confidence interval: 93% to 100%). In contrast, when a cutoff of 50 000 or 100 000 cfu/mL was used, 20% and 30%, respectively, of cases of UTI were missed without observing changes in specificity (97% to 99%). These findings provide strong endorsement for the lower cutoff value as long as there is evidence of an inflammatory response in the urine.

Although obtaining urine via catheterization reduces the likelihood of contamination compared with clean voided samples, there is strong evidence that contamination of catheterized samples is common.[12–15] Lowering the cutoff value of significant bacteriuria from 50 000 to 10 000 cfu/mL for samples obtained by catheter could result in a higher number of false positives from contamination outside the urinary tract. This may lead to unnecessary antibiotics, unnecessary imaging procedures, and will likely temporarily alter the urobiome negatively, potentially predisposing to future UTIs with more resistant organisms.[16,17]

There is other convincing evidence that UTIs may occur with colony counts between 10 000 and 50 000 cfu/mL. Perhaps the strongest data are provided by urine samples obtained by SPA. If 10 000 colonies of *Escherichia coli* are evidence of infection in a urine obtained by SPA, conceptually, we acknowledge that 10 000 cfu/mL may cause bona fide infection. Furthermore, it has been shown that there may be diurnal variation in urinary colony counts attributable to states of hydration and urinary frequency.[18] Therefore, these same 10 000 cfu/mL of *E. coli* can be evidence of infection in urine retrieved by catheter if there is definite evidence of inflammation.

Other studies[19,20] analyzed the number of cfu/mL in urine obtained by SPA in large numbers of symptomatic infants with UTI and then grouped their results according to colony count. About 20% of infants in each study had colony counts $\leq$100 000 cfu/mL; children in both high and low groups were shown to have similar degrees of vesicoureteral reflux, including those considered high grade, and in the Swerkersson study,[20] similar rates of renal scarring, providing evidence that low colony counts are common and clinically important.

Although SPAs are virtually free of contamination, they may uncover children with asymptomatic bacteriuria whose fever is from another source. Traditionally, children with asymptomatic bacteriuria are distinguished from those with true infection by the absence of host response, ie, no pyuria. The confounder here is the recognition that a few uropathogens (accounting for $<$5% of first UTIs) are less likely to lead to pyuria than *E. coli*, namely *Enterococcus* species, *Pseudomonas* and *Klebsiella*.[21]

The results of this study affirm the strength of current culture techniques, provide a step forward in helping to capture important symptomatic UTIs that may occur with low colony counts (a threshold of 10 000 cfu/mL is reasonable) but with evidence of urinary inflammation, and endorse continued exploration of 16S rRNA sequencing as a diagnostic aid in UTI.

ABBREVIATIONS

cfu: colony-forming units
SPA: suprapubic aspiration
UTI: urinary tract infection

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