

The Diagnosis of UTI: Colony Count Criteria Revisited

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Urinalysis (UA) is valuable in allowing clinicians to make a presumptive diagnosis of urinary tract infection (UTI) and initiate appropriate empirical antimicrobial treatment.¹ The American Academy of Pediatrics (AAP) UTI Clinical Practice Guideline for infants and children 2 months to 2 years of age advocates a definition of significant bacteriuria as $\geq 50\,000$ colony-forming units (CFU) per milliliter and endorses the finding of inflammation on UA as a necessary component of the diagnosis of UTI.^{2,3} However, reports of the accuracy and application of UA in the diagnosis of UTI in infants <2 months of age have been somewhat variable. In this issue of *Pediatrics*, Tzimenatos et al⁴ (for the Pediatric Emergency Care Applied Research Network) substantiate the excellent sensitivity and high specificity of the aggregate UA for diagnosing UTIs in febrile infants 60 days and younger with and without concurrent bacteremia, extending the use of this laboratory test to those younger than the age addressed in the AAP guideline. Along with UA, the authors applied the criterion of $\geq 50\,000$ CFU/mL for the diagnosis of UTI but also evaluated $\geq 10\,000$ CFU/mL, raising the important issue of what threshold should be used to define significant bacteriuria.

Before the 1950s, the number of bacteria associated with UTIs was described in vague terms, such as “numerous.”⁵ In his 1956 landmark study of adult women, Kass⁶ proposed that $100\,000$ CFU/mL be considered the diagnostic threshold, a criterion that was accepted quickly and

widely. Fifteen years later, Pryles and Lustik,⁷ while acknowledging that data in children were still limited, considered the studies in adults sufficient to conclude the following: “urine specimens containing <1000 CFU/mL are indicative of contamination; specimens containing between 1000 and 100 000 CFU/mL are to be suspected of infection and the studies repeated; and urine specimens containing >100 000 CFU/mL are indicative of infection.” This view went unchallenged until 1994, when Hoberman et al⁸ proposed the colony count criterion be decreased to $\geq 50\,000$ CFU/mL in catheterized specimens, a view that was supported by Hellerstein⁹ but with the following proviso: “Febrile infants or children usually have $\geq 50 \times 10^3$ CFU/mL of a single urinary pathogen, but infection may be present with counts from 10×10^3 to 50×10^3 CFU/mL.”¹⁰ The proposed standard of $\geq 50\,000$ CFU/mL was recommended in the 2011 AAP UTI guideline² and applied in the Randomized Intervention for Children with Vesicoureteral Reflux Trial.¹¹ In 2012, however, the Italian Society of Pediatric Nephrology issued guidelines recommending the threshold be $\geq 10\,000$ CFU/mL for specimens collected by catheterization.¹² Accordingly, the issue raised by Tzimenatos et al⁴ is an appropriate one: what is the correct criterion? The reason for uncertainty is the lack of a valid gold standard for a UTI. Specimens other than those obtained by suprapubic aspiration (SPA) (including urethral catheterization)^{13,14} may contain organisms, generally in small numbers, that do not

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constitute true infection but reflect a contamination of the specimen. The other confounder in the interpretation of urine cultures is the entity of asymptomatic bacteriuria, which is distinguished from true UTI by the absence of an inflammatory response represented by pyuria. The importance of ensuring that the diagnosis of UTI is accurate is to avoid overtreatment and possible additional procedures, such as imaging. In attempts to distinguish true UTI from the confounders of contamination and asymptomatic bacteriuria, 6 strategies have been applied:

1. Clinicians' assessment: This was the approach used by Kass,⁶ who obtained urine specimens by catheterization from women who were diagnosed with pyelonephritis and 3 groups of asymptomatic women. The colony counts in patients with clinical pyelonephritis began to increase from between 10 000 and 100 000 CFU/mL, reaching upward of 1 000 000 CFU/mL. The author concluded that $\geq 100\,000$ CFU/mL be used as the criterion for survey purposes but acknowledged that lower counts could be considered for clinical purposes. The criterion of $>100\,000$ CFU/mL was accepted quickly and was unquestioned as the standard cutoff for both survey and clinical uses.
2. Association with pyuria: Kass⁶ also related colony counts to the presence of pyuria and noted that the latter was not always present when the colony count exceeded the proposed threshold. The previous year, Sanford et al¹⁴ related pyuria and colony counts in catheterized specimens from 164 adults with clinical symptoms or signs of urogenital infection.¹⁵ They noted that more of the urine samples with $\geq 10\,000$ CFU/mL had pyuria but provided no further details about the colony

count to help identify whether the cutoff should be 10 000 CFU/mL or higher.

Pryles and Eliot¹⁵ obtained 275 clean-voided samples from 136 infants and children (22 boys and 114 girls) and concluded that "in general, the proportion having a higher leukocyte count is greater in urine [samples] with high bacterial counts."¹⁶ Only 7 of the 275 specimens had colony counts of 10 000 to 100 000 CFU/mL; so again, this approach lacked sufficient detail to challenge the threshold of 100 000 CFU/mL.

At the time of these studies, asymptomatic bacteriuria had not yet been accepted as an entity, and all high colony counts in asymptomatic individuals were considered true UTIs. Pyuria was not considered to be a key component of the diagnosis of UTI until investigators recognized that the host response to bacteriuria was valuable in the documentation of true UTI⁸ and is the mechanism by which renal scarring occurs.¹⁷

3. Single versus multiple or Gram-positive organisms: Hoberman et al's⁸ approach was to compare urine cultures with the growth of a single organism to those with multiple or Gram-positive organisms. Specimens were obtained by catheterization from 2181 febrile children <2 years old. The authors again noted the preponderance of urine cultures with $\geq 100\,000$ CFU/mL (84% of the cultures with single organisms) but recognized that an additional 9% were between 50 000 and 100 000 CFU/mL. Thus, 93% of the cultures with single organisms contained $\geq 50\,000$ CFU/mL, warranting a reduction in the threshold. This study also illustrated the significance of pyuria in distinguishing true UTI from asymptomatic bacteriuria. Of the 70 patients with cultures containing $\geq 50\,000$ CFU/mL

who had dimercaptosuccinic acid scans performed acutely, 77% of the 65 with pyuria had evidence of pyelonephritis, whereas all of the 5 without pyuria had normal scans.

4. Bacteremic UTI: Schroeder et al¹⁸ reasoned that if a blood culture result revealed the same organism as the urine culture, the UTI was a true UTI rather than being affected by contamination or asymptomatic bacteriuria. The authors assembled a multicenter database of 276 infants <3 months old with bacteremic UTIs and confirmed the significance of pyuria. Regarding the distribution of colony counts, the authors found, like Hoberman et al,⁸ that 93% of the urine cultures contained $\geq 50\,000$ CFU/mL. An additional 6.8% contained 10 000 to 50 000 CFU/mL, suggesting that 10 000 CFU/mL might be an appropriate, highly sensitive threshold, at least in patients who are bacteremic.
5. SPA, inflammation, and imaging abnormalities: Swerkersson et al¹⁹ assessed the results of specimens obtained by SPA from 430 febrile infants <1 year old with symptomatic UTIs. Of the 430 specimens, 81% contained $\geq 100\,000$ CFU/mL, and 83% contained $\geq 50\,000$ CFU/mL; but an additional 12% had 10 000 to 50 000 CFU/mL, bringing the total to 95%. Any growth in urine obtained by SPA is considered significant,⁵ but it stands to reason that the number of bacteria present in the bladder is also present in urine obtained by other means, such as catheterization. The reason for accepting a lower threshold for urine obtained by SPA is that urine obtained by that means should be sterile and, unlike other collection methods, unaffected by contamination. Although SPA presumably eliminates

contamination as a confounder, it does not eliminate asymptomatic bacteriuria.^{9,20} As noted above, what distinguishes UTI from asymptomatic bacteriuria is the presence of pyuria in the former. In Swerkersson's¹⁹ study, the rate of pyuria was lower in the group with <100 000 CFU/mL than in those with ≥100 000 CFU/mL (77.5% vs 92.1%), suggesting that some of the infants had asymptomatic bacteriuria. The rates of vesicoureteral reflux or scarring in infants with <100 000 CFU/mL and those with >100 000 CFU/mL were not statistically significantly different but were virtually identical when only infants with pyuria in the 2 groups were considered (S. Swerkersson, personal communication, 2016). If 10 000 CFU/mL with pyuria in febrile infants constitutes a UTI when the urine is obtained by SPA, consideration should be given to the triad (fever, pyuria, and 10 000 CFU/mL) in other specimens. The concern is that this might open the door to reduced specificity (ie, a large number of UTI diagnoses that are false-positives).

6. Combination of fever and/or symptoms, pyuria, and colony count: Primack et al²¹ recently provided evidence that the criteria of fever, pyuria, and a colony count of ≥10 000 CFU/mL could be applied to specimens obtained by means other than SPA

without decreasing specificity. The authors evaluated the colony count distribution of specimens from children 2 months to 6 years old in the Randomized Intervention for Children with Vesicoureteral Reflux Trial who were suspected of having a recurrent UTI during the study. The colony count criterion was ≥100 000 CFU/mL if the urine was obtained by clean catch or ≥50 000 CFU/mL if obtained by catheterization. If the diagnostic criterion had been reduced to ≥10 000 CFU/mL in those with both pyuria and fever and/or symptoms, 2 additional children would have been diagnosed with a recurrence; of particular note, specificity was unaffected. If either pyuria or fever and/or symptoms was not present, however, the number of cultures with 10 000 to 50 000 CFU/mL increased considerably, which is a reminder that a threshold of ≥10 000 CFU/mL should only be considered in appropriate clinical situations (fever and/or symptoms) and when pyuria is present.

The AAP UTI guideline, published in 2011² and reaffirmed in 2016,³ recommends both pyuria and 50 000 CFU/mL be present in febrile infants 2 to 24 months old to diagnose a UTI. This may appear to identify 2 criteria (pyuria and colony count) but, in fact, includes 3 because they are applied to infants and young children

with fever. When pyuria and fever are both present, there are limited data to suggest that 10 000 CFU/mL may be an acceptable colony count threshold for a UTI in a specimen obtained by catheterization, which is now supported by Tzimenatos et al.⁴ In addition to the modest increase in true UTIs identified, there is a practical advantage of reducing the colony count criterion to 10 000 CFU/mL, namely that it helps clinicians whose laboratories do not report gradations between 10 000 and 100 000 CFU/mL and who, therefore, cannot apply the recommended ≥50 000 CFU/mL criterion. Tzimenatos et al⁴ demonstrate that this difficulty associated with trying to apply ≥50 000 CFU/mL is frequent and overcome by applying the lower threshold to infants with fever and a positive UA result without sacrificing specificity. The criterion of ≥50 000 CFU/mL remains the current standard,^{2,3} but clinicians may want to consider ≥10 000 CFU/mL in catheterized specimens from young infants who are at risk for UTI and have both fever and pyuria.

ABBREVIATIONS

AAP: American Academy of Pediatrics
 CFU: colony-forming unit
 SPA: suprapubic aspiration
 UA: urinalysis
 UTI: urinary tract infection

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