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COMMENTARY

Complicated Urinary Tract Infections: What's a Lab To Do?

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The article by Price et al. in this issue (T. K. Price et al., J Clin Microbiol 54:1216–1222, 2016, http://dx.doi.org/10.1128/JCM.00044-16) advocates for the use of a larger inoculum when culturing urine obtained by "in-and-out" catheterization in a selected female population. Their findings and the resulting challenges will afford clinical microbiologists and specialty physicians an opportunity to review what will or should be done with the additional microbiological culture data.

The guideline for diagnosing urinary tract infections (UTIs) was established in the 1950s by Kass (1). Normal urine was assumed to be sterile, and patients diagnosed with UTIs had urine with bacterial counts of $>10^5$ CFU/ml. While this is still common practice today, Stamm et al. reported documented UTIs in women with colony counts between 10^2 and 10^5 in 1982 (2), and more recently, the interpretation of urine culture results has been further complicated by reports that urine is not necessarily sterile (3, 4). Moreover, diagnosis is even further complicated by the fact that urine samples are often contaminated with normal indigenous bacteria during the collection process. Finally, microbiology laboratories do not routinely work up (e.g., identification and antibiotic susceptibility testing) organisms grown from midstream urine when they are present at concentrations below 10^4 CFU/ml. Most laboratories have complex protocols guiding what types and how many different organisms to work up when there are between 10^4 and 10^5 CFU/ml. Some uropathogens, as noted, above, can cause urinary tract infections at significantly lower numbers (10^2 CFU/ml) while contaminants can be present at higher numbers (10^3 to 10^5 CFU/ml). What's a lab to do?

The American Society for Microbiology Cumitech 2C recommends two different protocols for processing urine specimens for culture (5). For specimens obtained noninvasively, 0.001 ml of clean voided midstream urine is cultured. However, for specimens collected by straight "in-and-out" catheterization or similar methods such as cystoscopy, 0.01 ml of urine is cultured. For these specimens, identification and antibiotic susceptibility testing are recommended for up to 2 isolates with colony counts of $>10^3$/ml.

In this issue of the *Journal of Clinical Microbiology*, Price and colleagues (6) studied urine cultures from a defined group of female patients who were being seen at a pelvic medicine and reproductive clinic and who answered either "yes" or "no" to the subjective question "Do you feel you have a UTI?" Those who said "yes" were enrolled in one group, and those who said "no" were enrolled in the control group.

Their working hypothesis was that even small numbers of bacteria could be pathogenic in the bladder of these selected patients. To test this hypothesis, urine was collected directly from the bladder by catheterization, and 0.1 ml, 0.01 ml, and 0.001 ml were plated on multiple agar plates under multiple incubation conditions (ambient air, CO_2, anaerobically). These expanded-spectrum enhanced quantitative urine culture (EQUC) results were compared to the standard urine culture results. Standard urine culture changed during the study but always included plating 0.001 ml on a blood agar plate and a MacConkey agar plate. Initial samples were cultured for 24 h without CO_2, while later samples were cultured with 5% CO_2 for 24 (MacConkey agar) or 48 (blood agar) hours. Not surprisingly, catheterized urine from women with self-reported urinary symptoms, with as few as 10^2 CFU/ml of certain bacteria, had documented UTIs and these responded to appropriate antibiotic therapy. Many of these infections would have been missed had an inoculum smaller than 0.1 ml been used. However, with a 0.1-ml inoculum, some women in the control group had colony counts of $>10^2$ CFU/ml of suspected "uropathogens." For example, a woman in the control group had a urine culture with close to 10^5 CFU/ml of *Escherichia coli*, another had a culture with $>10^3$ CFU/ml of *Enterobacter aerogenes*, and another had a culture with $>10^3$ CFU/ml of *Actinobaculum schaalii*. Should these be considered true infections, or are they representative of asymptomatic colonization? On the other hand, four women with self-reported UTIs had 10^1 to 10^2 CFU/ml of *Serratia marcescens*, *Morganella morganii*, *Aerococcus sanguinicola*, or *Oligella urethralis*. Another important uropathogen, *Enterococcus faecalis*, did not elicit subjective symptoms at 10^2 CFU/ml but did at 10^4 CFU/ml. Similar findings have been reported in older men with complicated UTIs (7). Given these data, there are two main questions that need to be resolved for women with complicated UTIs. First, what is the cutoff CFU per milliliter that determines a true infection and the need for antibiotic treatment? Second, is the cutoff CFU per milliliter different for different uropathogens? Clearly, further studies are needed to ensure that persons with infections are properly treated and those without infections are not given antibiotics.

This study raises an important issue. Should we change the protocol for routine bacteriological cultures of urine? It seems clear that urine obtained by straight in-and-out catheterization should be processed by a more sensitive protocol. After comparing multiple culturing and plating methods, the authors pro-

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posed, for simplicity and ease of use, a streamlined EQUC (0.1 ml of catheterized urine plated on a sheep blood agar plate, a MacConkey agar plate, and a colistin-nalidixic acid [CNA] agar plate, all incubated in 5% CO_2 at 35°C). The streamlined EQUC captured all significant UTIs in the self-reporting group. The downside is that the streamlined EQUC also captured asymptomatic bacteriuria in the control group, and that could result in unnecessary antibiotic treatment.

The work as presented in this article has some limitations. Self-reporting as the enrollment criterion may be biased by subjective symptoms. Organisms from the control group were not treated but would have been treated in the self-reported infected group. Of importance was that the urine was collected via catheterization, and so specimen quality was less compromised than that of midstream urine. However, some in-and-out catheterized urine cultures yielded organisms associated with vaginal flora, and this suggests that even carefully obtained catheterized specimens may be contaminated. In this paper, all organisms were referred to as "uropathogens." Since there can be bacteria in urine in patients without urinary tract infections, we will need a different term for organisms that constitute the urobiome (S. M. Brecher, newly created word for bacteria and other types of organisms found in normal urine). Also, this was a single-center study, which limits patient diversity (8).

These results strongly support changes in the way that we approach urine cultures. Clearly, not all urine samples need to be processed by the enhanced streamlined protocol. However, urine collected by catheterization should be cultured differently than midstream clean-catch urine. The significant recommended changes are culturing more urine (0.1 ml rather than 0.01 ml) and incubation in CO_2. The real trick is what to do with the results. In this study, some women in the non-UTI control group had significant numbers of potential uropathogens in their urine (6). How will the microbiologist communicate this information for appropriate utilization by the physician? While the interpretation of the results will ultimately be the responsibility of the treating physician, the microbiology laboratory will need guidelines on how to proceed. Clinical microbiologists do not want to be responsible for missing significant UTIs, but at the same time, we do not want our results to be responsible for unnecessary antibiotic use in these important times of antibiotic stewardship. That said, it will be very important for clinical microbiologists, infectious disease physicians, urologists, women's health specialists, other specialists, and pharmacists to work together to define reporting and treatment guidelines for patients with urinary tract infections. This paper is a step in the right direction.

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