Journal of Clinical Microbiology

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J. Clin. Microbiol. **2011, 49(9 Supplement):S34. DOI: 10.1128/JCM.00788-11.**

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2011, p. S34–S38 VOL. 49, NO. 9 SUPPL.
0095-1137/11/$12.00 doi:10.1128/JCM.00788-11

A Critical Appraisal of the Role of the Clinical Microbiology Laboratory in the Diagnosis of Urinary Tract Infections

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Urinary tract infections (UTI) are a common health problem in both outpatient and inpatient settings, and urine cultures occupy much of the workload in many clinical microbiology laboratories. Appropriate utilization of urine cultures by health care providers and generation of meaningful results by the laboratory are important for optimal care of patients as well as efficient operation of laboratories. The following discussions focus on some potential opportunities for generation of meaningful test results and improving laboratory utilization.

SHOULD MIDSTREAM CLEAN-CATCH URINE SPECIMENS FROM OUTPATIENTS WITH ACUTE, FIRST-EPISODE CYSTITIS BE ORDERED AND PROCESSED ROUTINELY?

Acute uncomplicated cystitis generally refers to infection in premenopausal, nonpregnant women with no known urological abnormalities or comorbidities. Postmenopausal women or women with well-controlled diabetes with no urological sequelae are also included in the definition by some experts. Most cases of UTI in outpatients are uncomplicated. The bacteria associated with acute uncomplicated cystitis are reasonably predictable, with *Escherichia coli* causing 70 to 95% of cases, *Staphylococcus saprophyticus* causing 5 to 10%, and other *Enterobacteriaceae*, *Enterococcus*, or group B *Streptococcus* strains causing the remainder. The diagnostic sensitivity for uncomplicated UTI based on typical symptoms and risk factors is 50 to 90% (20). The concern in treating these infections is antimicrobial resistance. Increased resistance of *E. coli* to amoxicillin and trimethoprim-sulfamethoxazole (TMP-SXT) (as high as 30%) has been reported in some populations.

Several factors support the premises that routine urine cultures are not necessary in cases of acute uncomplicated cystitis and that treatment can be initiated based on symptoms alone. These factors include predictable microbiology limited to a few pathogens, reliable clinical diagnosis, and low morbidity. Typically a 24- to 72-h time span exists before final culture results are available, and culture results thus may have little impact on antibiotic therapy of 72 h in duration. Arguments against treatment based on symptoms alone include the facts that cultures provide greater diagnostic reliability and that susceptibility results can be used to refine specific antibiotic therapy.

There are published practice guidelines for the diagnosis and treatment of uncomplicated UTI from several groups, including the American College of Obstetricians and Gynecologists (ACOG) (2008), the Scottish Intercollegiate Guidelines Network (SIGN) (2006), the University of Michigan Health System (UMHS) (2005), and the Infectious Disease Society of America (IDSA) (2011). These guidelines vary regarding choice and duration of antibiotic therapy, treatment instruction by telephone, etc., but there is an overall consensus that urine culture is not needed in the vast majority of initial uncomplicated cystitis cases and that empirical treatment can be initiated based on symptoms alone (1, 7, 16, 17). The guidelines further agree that culture should be performed in all cases of upper or complicated UTI, since diagnosis can be difficult, the microbial etiology is different, antimicrobial resistance is more common, and complications are more frequent. Culture may also be indicated if there is no clinical improvement within 48 h, in cases of recurrence, or if there are other complicating factors. It is recommended that practitioners review local community (preferred) or hospital surveillance data, if available. If rates of resistance of *E. coli* to TMP-SXT are greater than 20%, an alternative antibiotic should be used for empirical therapy (7).

Several reports have documented that many physicians practice independently of published guidelines and that physicians continue to obtain cultures, do not use trimethoprim-sulfamethoxazole as a first-line agent, and continue treatment for longer than the recommended 3 days. These practices occur because physicians either are not aware of the guidelines or choose not to follow the recommended practices. Educational interventions in addition to other measures are needed to support changes in practice.

Discussion. The discussants agreed with the existing guidelines that recommend that urine cultures are no longer recommended as part of the routine workup for young women with first-episode acute, uncomplicated cystitis, since in most cases culture and susceptibility testing add little to the diagnosis or choice of antibiotic used for treatment. The group discussed several ways that the laboratory could potentially participate to ensure that only appropriate specimens are submitted for culture. One opportunity would be for laboratory directors to take an active role in educating ordering physicians about the existing guidelines. This could be done by having direct conversations with clinicians, publishing guidelines in the Laboratory User's Manual, giving in-service presentations, etc. Education is a needed component of a utilization plan, but even if providers are educated, this does not ensure that they will comply. Achieving compliance may be somewhat easier in closed-practice systems where care plans and utilization guidelines exist.

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Another approach would be for laboratories to develop rejection criteria for outpatient urine specimens, since the risks associated with rejection are low, the number of patients who do not respond to therapy is low, and guidelines suggest that these cultures are not necessary. The problem is the accurate identification of specimens that belong to patients with first-episode acute cystitis and should be rejected. There is not an easy answer. One suggestion was to hold urine samples and perform culture only when the laboratory is notified that the patient did not respond to therapy. Checkboxes on an order form, whether electronic or manual, indicating that the specimen is from first-episode acute cystitis could be used to identify these specimens. The majority of suggestions involved using technology and modifying electronic orders so that diagnostic codes are attached to each culture to allow the laboratory to know which specimens to reject. Electronic medical records can be used to warn against or restrict the ordering of urine cultures for patients without an appropriate diagnosis. Regardless of the mechanism of rejection, it would be important that large reference laboratories, as well as hospital/clinic laboratories, adopt similar rejection policies so that testing practices would be consistent across the discipline.

To optimize utilization of urine cultures, publication of data regarding the costs associated with performance of cultures and susceptibility testing and the number of women treated without culture would be helpful to educate providers about the health care cost benefits associated with appropriate limited utilization of urine cultures. Such data would also give support to laboratories to adopt utilization restrictions, since the enforcement of rejection policies could result in a large cost savings for many clinical laboratories. This would allow laboratories to redirect resources to other areas. Large health care organizations may already have these data, and we encourage publication. Microbiology laboratories would also be supported in these efforts by the development of comprehensive practice guidelines that come from the microbiology community and parallel those of the clinical groups. The discussants were aware that the American Society for Microbiology (ASM) and the Centers for Disease Control and Prevention (CDC) Best Practices Committee are in the process of developing evidence-based practice guidelines. These guidelines are important to all of the medical community as well as clinical microbiology laboratories, and the group offered any support needed by that committee when the topic of urine cultures is addressed. The group felt that it is essential that any practice guidelines that are developed be available in easily accessible literature not only to laboratorians but also to clinical practitioners. It is important to have urology specialists contribute to, or at least review, any proposed guidelines to ensure consistency with clinical need. The discussants also expressed that payers could have the largest impact by not paying for poor practices. Such denials would be motivation for the appropriate utilization of urine cultures within accepted guidelines.

A potential drawback to limiting cultures is the loss of local antimicrobial susceptibility data for the population of women with community-acquired uncomplicated urinary tract infections to determine empirical treatment decisions. Prospective and unbiased surveillance data would be required.

SHOULD URINE SPECIMENS BE SCREENED FOR PYURIA AS A CRITERION FOR PERFORMING CULTURE?

Some laboratories have adopted the practice of screening urine for the presence of pyuria and performing cultures only when it has been detected. However, published data supporting this practice are lacking. Pyuria is found in most women with acute uncomplicated cystitis. However, pyuria is also present in other infectious diseases (e.g., *Chlamydia* infection, *Trichomonas* infection, pneumonia, sepsis, etc.) as well as noninfectious clinical conditions (e.g., stones, organ enlargement, etc.). There are several laboratory methods to evaluate urine for the presence of pyuria, with variable sensitivity and specificity. These include a dipstick test to screen for leukocyte esterase, manual microscopy (wet mount examination of spun or unspun urine or cell-counting chamber technique), and automated microscopy.

The dipstick leukocyte esterase test is a rapid and inexpensive test that detects esterase, an enzyme released by white blood cells (WBC). The dipstick leukocyte esterase test is reported to have a sensitivity of 72 to 96% and a specificity of 9 to 98% for detection of UTI when using >10 leukocytes per high-power field (hpf) or $\geq 10^5$ CFU per ml of urine as the reference standard. False-positive tests are usually caused by contamination, often by vaginal secretions. False-negative tests can be caused by glycosuria, urobilinogen, and high specific gravity. Because of low sensitivity, a negative result does not exclude infection, and it is recommended that symptomatic patients with a negative leukocyte esterase test receive antibiotic treatment and/or further workup (1, 7, 17).

A microscopic urinalysis exam is used to look for formed cellular elements, casts, bacteria, yeast, parasites, and crystals, using either unspun urine or centrifuged urine sediment, examined directly or in a 1-mm-deep chamber. In centrifuged urine, generally a level of fewer than 5 WBC per hpf is considered normal, but cutoff values of ≥3 and ≥10 WBC per hpf have also been used. In unspun urine, normal values of ≥10 WBC/mm^3 and ≥100 WBC/mm^3 have been used. Manual microscopy results correlate well with automated microscopy if unspun urine is used, but correlation is poorer with spun urine. In many laboratories it is a standard practice to exclude the microscopic exam if all chemical testing yields negative or normal results. Automated urine microscopy is generally done using flow cytometry. Newer-generation urine flow cytometers use fluorescent dyes and analytical channels that allow detection and enumeration of white blood cells as well as bacteria. Cutoffs used in the literature include ≥ 25, 30, 45, and 150 WBC/μl. Reported sensitivities of automated methods for detection of UTI range from 71 to 98%, with specificities of 55 to 92% (3, 4, 5, 9).

Recent guidelines regarding acute uncomplicated UTI agree that pyuria is consistent with but not diagnostic of UTI (17). The guidelines further suggest that clinical diagnosis may be a more reliable predictor than pyuria alone and that absence of pyuria does not exclude the diagnosis of UTI in patients with consistent symptoms. Routine measurement of pyuria is not consistently recommended or necessary for management of patients, and it may be appropriate to simply treat a patient with classic UTI symptoms without any diagnostic testing. Doc-

umentation of pyuria may be useful for evaluation of women who present with atypical symptoms.

Practice guidelines for catheterized patients suggest that pyuria is not diagnostic of either asymptomatic bacteriuria or UTI (8). The presence, absence, or degree of pyuria should not be used to differentiate asymptomatic bacteriuria from UTI in catheterized patients. Further, pyuria accompanying bacteriuria should not be interpreted as an indication for antimicrobial treatment in asymptomatic patients. The absence of pyuria in a symptomatic catheterized patient suggests a diagnosis other than UTI.

Recent literature suggests that assessing pyuria and bacteriuria together markedly increases the probability of a diagnosis of UTI but that this still may not exceed the probability of a clinical diagnosis (1, 3, 4, 11). Quantitative thresholds for both parameters have not been unequivocally established. Assessing bacteriuria alone may be relevant in special situations such as with renal tuberculosis patients, neutropenic patients, and cancer patients, in whom pyuria is typically absent or minimal even in the presence of true infection.

Discussion. The group agreed that the practice of using urinalysis to reflex to culture warranted review since there are no published data supporting that practice. The data surrounding pyuria detection were reviewed, and the group concluded that sensitivity and specificity data for dipstick pyuria were sufficiently poor to suggest that the test should probably not be used at all. Sensitivity and specificity data for the newer automated systems seem better, since both pyuria and bacteriuria are assessed simultaneously. There may be a role for triaging specimens to be sent for culture using these newer automated instruments, but the studies correlating results with UTI are in development and are not sufficient to support routine use yet. Once clearly defined cutoffs are established, this technology may be useful to triage specimens. A manufacturer-specific FDA-cleared indication for this triage-to-culture practice would also justify this practice.

A CRITICAL APPRAISAL OF QUANTITATIVE BACTERURIA CUTOFF VALUES FOR CULTURES OF CLEAN-CATCH SPECIMENS, STRAIGHT CATHETER SPECIMENS, CYSTOSCOPIC ASPIRATES, AND SUPRAPUBIC NEEDLE ASPIRATES

In the past, the diagnosis of UTI was based on a quantitative urine culture yielding greater than 100,000 CFU of a single bacterial isolate per milliliter of urine. This definition of significant bacteriuria was established 5 decades ago and was chosen because of its high specificity for the diagnosis of true infection, even in asymptomatic patients. This cutoff value, however, is felt to have poor sensitivity (about 50%), and subsequent data have established that lower bacterial counts, usually in the range of 10^3 to 10^5 CFU/ml, are significant when there is strong clinical evidence of UTI and the pretest probability is high (18). However, not all clinical laboratories report counts of less than 10,000 CFU per ml of urine, and low-pathogen-count urinary tract infections may be underdiagnosed.

The best information that clinical microbiologists have to guide the determination of significant colony counts and extent of workup is based on method of urine collection and is published in Table 1 of *Cumitech 2C* (13). Recently published guidelines from IDSA state that a colony count of $\geq 10^3$ CFU/ml of a single bacterial species is indicative of UTI in patients with indwelling (urethral or suprapubic) catheters (8). To accommodate this guideline, Table 1 in Cumitech 2C would need to be modified so that indwelling catheters are moved to the invasive category with qualifying comments. A recently published report has also critically reexamined UTI in children and recommends raising the colony counts that determine significant bacteriuria from the previously recommended $\geq 10^5$ to $\geq 10^6$ CFU/ml (2). Colony counts of 10^4 to 10^5/ml may not be significant if there is mixed growth but may warrant repeat culture if associated with a single pathogen. For critically ill children, thresholds of $\geq 5 \times 10^4$ CFU/ml in catheterized patients and $\geq 10^5$ CFU/ml of not more than 2 species in uncatheterized patients may be appropriate (10).

Discussion. The discussion focused largely on the significant colony count guidelines presented in Table 1 of *Cumitech 2C*, since that information is widely used by clinical laboratories for urine culture procedures. The group discussed the IDSA recommendation to consider colony counts of $\geq 10^3$ CFU/ml of a single bacterial species as significant in catheterized patients. The group reiterated that indwelling catheter cultures with more than 3 bacterial species should not be worked up, since indwelling catheters, especially if they are in place long terminal repeat term, are readily colonized by organisms that are not present in the bladder.

The group also discussed the fact that pedibags tend to be highly contaminated and that cultures from pedibags have poor specificity and yield results that are difficult to interpret. It was felt that pedibags are not an acceptable specimen for urine culture, and a recommendation was made that pedibags be removed from Table 1 of *Cumitech 2C* as a noninvasive collection method and be considered an unacceptable specimen. It was further discussed that quantitative criteria for urine cultures in children should be added to Table 1 of *Cumitech 2C*.

There are no clear quantitative diagnostic criteria for fungal UTI. Studies that will help laboratories establish quantitative guidelines for workup of yeast in urine cultures need to be performed and published.

WHAT IS THE VALUE, IF ANY, OF ANTIMICROBIAL SUSCEPTIBILITY TESTING OF ISOLATES FROM URINE CULTURES?

The management of UTI has become more difficult due to increasing antimicrobial resistance. Existing guidelines suggest that if bacteria are detected in urine in quantities associated with a particular condition, antibiotic susceptibility testing should be performed. Many antibiotics are excreted partially or completely by glomerular filtration. In addition, a number of antimicrobial agents (e.g., TMP-SXT and ciprofloxacin) reach the urinary space by tubular secretion and produce high concentrations in urine even if the glomerular filtration rate is diminished. The result is that many antibiotics achieve a concentration in urine that is 100 to 1000 times higher than that achieved in serum. However, routine susceptibility test interpretation is based on achievable serum concentrations that are anticipated to occur in response to bloodstream infections.

There is poor correlation between the disappearance of bacteria from urine and the level of antibiotic in blood (21). As expected, there is good correlation between the disappearance of bacteria from urine and the level of antibiotic achieved in the urine. Therefore, the clinical significance of the interpretation of resistance based on serum concentration is not completely known. To better predict responses in patients with UTI, susceptibility test results may need to be interpreted based on urine concentrations.

Several studies have addressed the impact of antimicrobial resistance on treatment outcomes in uncomplicated UTI in women. These studies have involved relatively small numbers of women with resistant organisms. In one study, symptoms resolved without further treatment in the majority (11/18 = 61%) of patients with resistant organisms (6). On the other hand, one group reported that patients with resistant isolates (n = 44) had a longer median time to symptom resolution (7 versus 4 days), greater rates of returning to the practice for further care (39% versus 6%), a greater need for subsequent antibiotics (36% versus 4%), and higher rates of significant bacteriuria at 1 month (42% versus 20%) (15). Similar studies showed that 42 to 50% of women had bacteriological failure and 40% had clinical failure if the causative pathogen was resistant to TMP-SMX *in vitro* (12, 14, 19).

There is less information available regarding complicated UTI. Many comparative clinical trials have been reported, but these trials are generally designed to compare the efficacy of a new antibiotic with that of a currently prescribed antibiotic. Patients with resistant isolates are generally excluded from these evaluations. Since evidence from clinical trials is lacking, the role of resistance is not really known. Current guidelines recommend treatment with empirical therapy and reassessing when culture and susceptibility results are available (1, 7, 17).

Discussion. Although current guidelines recommend the performance of susceptibility testing whenever cultures are performed, the discussants acknowledged that there is uncertainty as to how relevant antibiotic susceptibility interpretations are for urinary tract isolates. The group expressed that it would be helpful to have separate MIC breakpoints and interpretations for isolates from the urinary tract. There are already some antibiotics, e.g., nitrofurantoin and fosfomycin, that appear in the CLSI M100 tables and are used to treat urinary tract infections only.

Clinical data to determine urine-specific breakpoints need to be generated, and there are few existing references that correlate *in vitro* susceptibility results for urinary tract isolates with therapeutic responses. Since existing published studies address uncomplicated UTI and pyelonephritis, it is not known whether the existing breakpoints based on systemic MICs are more relevant in patients with complicated UTI. The group anticipated that if the criteria for culturing urine were refined to eliminate tests on patients with first-episode acute, uncomplicated cystitis and if the quantitative cutoffs for significance were standardized, then susceptibility test interpretations may be more relevant.

SUMMARY

The discussants recommended a number of areas for change in practice and called for new clinical studies and cooperative new recommendations. The needed action items are highlighted below.

- Microbiology laboratories need to develop methods to help clinicians adhere to guidelines recommending that urine cultures not be performed for patients with first-episode acute, uncomplicated cystitis.
- The publication of data regarding the reduction in laboratory costs associated with treating women with acute first-episode cystitis based on symptoms alone would be helpful to educate providers and give support to laboratories to adopt utilization restrictions.
- Microbiologists need to develop comprehensive practice guidelines for the diagnosis of UTI that parallel those of existing societies but come from the microbiology community. The guidelines need to include methods for obtaining susceptibility data to guide empirical therapy for acute, uncomplicated UTI if cultures are not performed.
- The microbiology community needs to interface with payers to educate and encourage payment for laboratory testing that is consistent with evidence-based best practices.
- Dipstick leukocyte esterase tests are insensitive and nonspecific and should not be used.
- There are few published data to support the practice of urinalysis with reflex to culture only if the urinalysis is positive (criteria vary among laboratories). Outcome studies based on currently accepted culture criteria, excluding women with first-episode cystitis, are needed. The application of this practice to complex patient populations (e.g., immunosuppressed, etc.) is also needed.
- Studies are needed to establish quantitative guidelines for yeast in urine and correlation to urinary tract infection.
- The colony count guidelines presented in Table 1 of *Cumitech 2C* can be updated to include new recommendations for catheterized patients and children.
- Well-designed studies are needed to help determine how relevant current antibiotic susceptibility interpretations are for urinary tract isolates.

Session discussants: Ellen Jo Baron, Lynn Boyer, Stephen M. Brecher, Joseph Campos, Kimberle Chapin, Richard L. Hodinka, Markus Kostrzewa, Mark LaRocco, Mary Ann Silvius, Michael L. Towns, Markita Weaver, and Donna M. Wolk.

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