Laboratory Diagnosis of Urinary Tract Infections in Adult Patients

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Urinary tract infections (UTIs) are among the most common bacterial infections and account for a significant part of the workload in clinical microbiology laboratories. Enteric bacteria (in particular, Escherichia coli) remain the most frequent cause of UTIs, although the distribution of pathogens that cause UTIs is changing. More important is the increase in resistance to some antimicrobial agents, particularly the resistance to trimethoprim-sulfamethoxazole seen in E. coli. Physicians distinguish UTIs from other diseases that have similar clinical presentations with use of a small number of tests, none of which, if used individually, have adequate sensitivity and specificity. Among the diagnostic tests, urinalysis is useful mainly for excluding bacteriuria. Urine culture may not be necessary as part of the evaluation of outpatients with uncomplicated UTIs, but it is necessary for outpatients who have recurrent UTIs, experience treatment failures, or have complicated UTIs, as well as for inpatients who develop UTIs.

Urinary tract infections (UTIs) are among the most common bacterial infections. It has been estimated that symptomatic UTIs result in as many as 7 million visits to outpatient clinics, 1 million visits to emergency departments, and 100,000 hospitalizations annually [1]. UTIs have become the most common hospital-acquired infection, accounting for as many as 35% of nosocomial infections, and they are the second most common cause of bacteremia in hospitalized patients [2, 3]. The annual cost to the health care system of the United States attributable to community-acquired UTI alone is estimated to be approximately $1.6 billion [4].

UTIs are challenging, not only because of the large number of infections that occur each year, but also because the diagnosis of UTI is not always straightforward. Physicians must distinguish UTI from other diseases that have a similar clinical presentation, some UTIs are asymptomatic or present with atypical signs and symptoms, and the diagnosis of UTIs in neutropenic patients (who do not typically have pyuria) may require different diagnostic criteria than those used for the general patient population. Because of these factors, physicians frequently rely on a small number of imperfect laboratory tests to augment clinical impressions; even when clinical diagnoses are unequivocal, physicians may order laboratory tests to identify the cause of the infection and/or to provide isolates for antimicrobial susceptibility testing. It therefore comes as no surprise that the laboratory examination of urine specimens accounts for a large part of the workload in many hospital-based laboratories. In fact, in many clinical laboratories, urine cultures are the most common type of culture, accounting for 24%–40% of submitted cultures; as many as 80% of these urine cultures are submitted from the outpatient setting.

The purpose of this review is to summarize the laboratory diagnosis of routine UTI using current diagnostic methods. The review will not cover the diagnosis of UTI in special patient populations, a topic that merits a separate review.

CAUSES OF UTIs

The etiological agents of community-acquired and hospital-acquired UTIs differ (table 1) [5–14]. Only a limited amount of data has been published regarding changes in the frequency of causative agents among outpatients. Enteric bacteria (in particular, Escherichia coli) have been and remain the most frequent
cause of UTI, although there is some evidence that the percentage of UTIs caused by *E. coli* is decreasing [6, 15]. In contrast, significant changes in the causes of nosocomial UTI have been reported since 1980. Bronsema et al. [13] reported that, from 1980 through 1991, the percentage of UTIs caused by *E. coli*, *Proteus* species, and *Pseudomonas* species decreased, whereas the percentage of UTIs caused by yeasts, group B streptococci, and *Klebsiella pneumoniae* increased. Weber et al. [6] reported different changes in the causative agents of UTI, with a decrease in the percentage of UTIs caused by *Enterobacter* species, but with an increase in the percentage of UTIs caused by *Acinetobacter* species and *Pseudomonas aeruginosa*. *Candida albicans* is the most common cause of funguria, followed by *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and other yeasts [16].

**SPECIMEN COLLECTION, TRANSPORTATION, AND PROCESSING**

**Specimen collection.** Suprapubic aspiration is the best method to avoid contamination of specimens with bacteria in the distal urethra. This collection method is used infrequently because it is not indicated clinically (except in rare circumstances), it is invasive and uncomfortable, and it requires too much time and too many resources to be practical. Collection of urine by use of a single catheter (straight catheter technique) is the next-best technique for obtaining urine specimens with minimal contamination, but, again, it is not indicated clinically for most patients because it is too labor intensive and costly for routine use and it is invasive. It has added disadvantages, because the process of inserting a catheter through the urethra can introduce bacteria into the bladder (and thereby cause UTI), and rare complications have been reported.

Most urine specimens are obtained from adult patients via the clean-catch midstream technique. This technique has the following advantages: it is neither invasive nor uncomfortable, it is simple and inexpensive, it can be performed in almost any clinical setting, there is no risk of introducing bacteria into the bladder by catheterization, and there is no risk of complications. Colony counts from urine specimens collected by this method correlate reasonably well with those of specimens collected via suprapubic aspiration or straight catheterization [15]. The obvious disadvantage of this technique is that the urine sample passes through the distal urethra and can become contaminated with commensal bacteria. Simple procedures that have been developed to decrease the contamination rate include cleansing of skin and mucous membranes adjacent to the urethral orifice before micturition, allowing the first part of the urine stream to pass into the toilet, and collecting urine for culture from the midstream [17]. Although the clean-catch midstream method is accepted and used widely, the available evidence suggests that the cleansing procedures may not decrease urine contamination rates significantly and, therefore, may be unnecessary as a routine [18–23]. There may be difficulties with proper collection of samples from elderly patients, as well as from those patients who have physical or other types of impairments, which adds to the importance of collecting specimens properly to avoid contamination.

As discussed below, correct processing and handling of urine specimens, as well as correct interpretation of test results, is dependent on the method used to collect the specimen. It is, therefore, of obvious importance for clinicians to specify the method of collection on the test requisition slip. Other information that should be included on the test requisition slip includes the date and time of specimen collection, patient demographic information, and any clinically relevant information (e.g., whether the patient was treated with antimicrobial agents or whether anatomic abnormalities, stones, or an indwelling urinary catheter were present).

**Specimen transportation.** Several studies have demonstrated the adverse effect of delays in transportation or processing of urine specimens on their quality [24–26]. In each study, urine specimens were plated within 2 h after collection and then were plated again after delays of up to 24 h; results were compared to determine whether delays in plating resulted in an increase in colony counts. In each of the studies, some of the cultures that were delayed showed increases in the number of colony forming units (cfu) per mL to $>10^5$ cfu/mL, thereby leading to false-positive results. It should be noted that these studies were performed before the publication of current criteria for interpreting quantitative urine cultures and that the effect on interpretation would have been even greater if colony counts of $10^5$ or $10^6$ cfu/mL were used to define probable infection in specific patients [15]. On the basis of the results of these and other similar studies, it is currently recommended that urine specimens be plated within 2 h after collection unless specimens have been refrigerated or kept in a preservative [17].

**Specimen processing.** Routine urine cultures should be plated using calibrated loops for the semiquantitative method. This method has the advantage of providing information regarding the number of cfu/mL, as well as providing isolated colonies for identification and susceptibility testing. The types of media used for routine cultures should be limited to blood agar and MacConkey’s agar. For urine specimens obtained from outpatients, it is not necessary to routinely inoculate a medium that is selective for gram-positive bacteria, because nearly all UTIs in outpatients are caused by aerobic and facultative gram-negative bacteria (table 1) [27, 28]. Even in patient populations in which *Staphylococcus saprophyticus* is a common cause of UTIs, it is not necessary to use selective media. In contrast, urine specimens obtained from hospitalized patients are likely to contain enterococci, which have emerged as the second most
common cause of nosocomial infections. Laboratories may want to consider inoculating urine specimens obtained from hospitalized patients, or from patients in whom gram-positive bacterial infection is suspected but not documented, to a medium that is selective for gram-positive cocci. A medium such as phenylethyl alcohol suppresses the growth of swarming *Proteus* species and other gram-negative bacilli that can overgrow gram-positive cocci in the specimen. Urine cultures should be incubated overnight at 35°C–37°C in ambient air before being read. There is no added benefit to incubating routine urine cultures for 48 h, provided that specimens are incubated for a full 24 h and that urine specimens containing <10^5 uropathogens or specimens from patients with suspected funguria are incubated for 48 h [29–31].

Most pathogenic yeasts grow well on blood agar plates, so it is unnecessary to use selective fungal media for urine cultures, even for samples obtained from patients with suspected funguria. Selective fungal media can be used in those rare instances in which there is a high clinical probability that a UTI is caused by a more fastidious yeast or mold. Urine specimens obtained from patients with suspected mycobacterial UTIs should be processed and plated to the appropriate mycobacterial media [32].

**NONCULTURE METHODS FOR THE LABORATORY DIAGNOSIS OF UTI**

**Detection of bacteriuria by urine microscopy.** Bacteriuria can be detected microscopically using Gram staining of uncentrifuged urine specimens, Gram staining of centrifuged specimens, or direct observation of bacteria in urine specimens. Gram stain of uncentrifuged urine specimens is a simple method. A volume of urine is applied to a glass microscope slide, allowed to air dry, stained with Gram stain, and examined microscopically. The performance characteristics of the test are not well-defined, because different criteria have been used to define a positive test result. In one study, the test was found to be sensitive for the detection of ≥10^5 cfu/mL but insensitive for the detection of lower numbers of bacteria (table 2) [28]. Other investigators have found the test to be of low sensitivity for the detection of UTI [33–42].

The urine Gram stain test has the important advantage of providing immediate information as to the nature of the infecting bacterium or yeast (rarely infectious agents such as microsporidia) and thereby guiding the physician in selecting empiric antimicrobial therapy. This is of importance in some settings, but the Gram stain test has 3 disadvantages that limit its usefulness in most clinical settings. First, it is an insensitive test, being reliably positive only if the concentration of bacteria in the urine is ≥10^5 cfu/mL; infections with bacterial concentrations of 10^2–10^3 cfu/mL may not be detected by this test. Second, the test is too labor intensive for it to be practical for most clinical microbiology laboratories to offer it on more than a select basis. Last, because it may not detect bacteria at concentrations of 10^2–10^3 cfu/mL, it should not be used in the outpatient setting for patients with uncomplicated UTIs. Because of these limitations, its use should be limited to patients with cases of acute pyelonephritis, patients with invasive UTIs, or other patients for whom it is important to have immediate information as to the nature of the infecting pathogen.

**Detection of bacteriuria by nitrite test.** Bacteriuria can be detected chemically when bacteria produce nitrite from nitrate.
The biochemical reaction that is detected by the nitrite test is associated with members of the family Enterobacteriaceae (the pathogens most commonly responsible for UTIs), but the usefulness of the test is limited because nitrite production is not associated with urinary-tract pathogens such as S. saprophyticus, Pseudomonas species, or enterococci [43]. Another limitation to the test is that it requires testing a specimen of the first urine produced in the morning, as >4 h are required for bacteria to convert nitrate to nitrite at levels that are reliably detectable.

**Detection of pyuria by urine microscopy.** Pyuria can be detected and quantified microscopically by measuring the urinary leukocyte excretion rate, counting leukocytes with a hemocytometer, counting leukocytes in urine specimens using Gram staining, or counting leukocytes in a centrifuged specimen. The advantages to urine microscopy are that leukocytes, leukocyte casts, and other cellular elements are observed directly. One disadvantage to urine microscopy is that leukocytes deteriorate quickly in urine that is not fresh or that has not been adequately preserved. In addition, each of these methods has disadvantages that limit its usefulness as a routine test [28]. Because of these disadvantages, urine microscopy should be limited to patients in whom pyelonephritis or other more serious infections are suspected.

The most accurate microscopic method for quantitating pyuria is to measure the urinary leukocyte excretion rate [43]. Patients with symptomatic UTIs have urinary leukocyte excretion rates of ≥400,000 leukocytes/h [43]. The test is impractical for clinical use, however, making it necessary for laboratories to use other methods. A simple and inexpensive alternative is to count urine leukocytes with a hemocytometer. Comparison of hemocytometer counts with urinary leukocyte excretion rates has shown that a hemocytometer count of ≥10 leukocytes/mm³ correlates with a urinary leukocyte excretion rate of ≥400,000 leukocytes/h [43]. Moreover, the correlation of hemocytometer counts with urine colony counts has shown that patients with symptomatic UTIs and bacterial concentrations of >10⁵ cfu/mL have urine leukocyte counts of ≥10 leukocytes/mm³ [43]. The correlation of hemocytometer cell counts for patients with bacterial concentrations of <10⁵ cfu/mL was studied by Stamm et al. [15], who found that urine leukocyte counts of ≥8 cells/mm³ correlated with bacterial concentrations of <10⁵ cfu/mL in specimens obtained by suprapubic aspiration or straight catheterization from acutely dysuric female subjects. Although using a hemocytometer to count leukocytes is easier than measuring urinary leukocyte excretion rates, it is impractical for clinical laboratories to use a hemocytometer to count leukocytes on a routine basis. The most practical microscopic method involves counting the number of leukocytes in the sediment of centrifuged urine specimens. As reviewed by Pappas [43], this method is inaccurate because of inadequate standardization of the method. For these reasons, and to facilitate the processing of large numbers of specimens, most laboratories use rapid tests for leukocyte esterase as a surrogate for microscopic leukocyte counts.

**Detection of pyuria by leukocyte esterase tests.** Leukocyte esterase tests are based on the hydrolysis of ester substrates by proteins with esterolytic activity [44]. Human neutrophils produce as many as 10 proteins with esterolytic activity. These proteins react with ester substrates to produce alcohols and acids that then react with other chemicals to produce a color change that is proportional to the amount of esterase in the specimen [44]. These tests have the advantage of detecting both esterases in intact leukocytes and esterases released after cell lysis; therefore, even specimens that have not been preserved...
Table 3. Performance characteristics of leukocyte esterase and nitrite tests, alone or in combination, for detection of bacteriuria and/or pyuria.

<table>
<thead>
<tr>
<th>Test, colony count</th>
<th>Performance characteristics</th>
<th>Predictive values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10^5 cfu/mL</td>
<td>68–98</td>
<td>59–96</td>
</tr>
<tr>
<td>&gt;10^4 cfu/mL</td>
<td>64–77</td>
<td>59–83</td>
</tr>
<tr>
<td>&gt;10^3 cfu/mL</td>
<td>62–79</td>
<td>56–84</td>
</tr>
<tr>
<td>Nitrite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10^5 cfu/mL</td>
<td>19–45</td>
<td>95–98</td>
</tr>
<tr>
<td>&gt;10^4 cfu/mL</td>
<td>8–39</td>
<td>97–98</td>
</tr>
<tr>
<td>&gt;10^3 cfu/mL</td>
<td>0–50</td>
<td>48–98</td>
</tr>
<tr>
<td>Leukocyte esterase and nitrite</td>
<td>35–84</td>
<td>98–100</td>
</tr>
<tr>
<td>&gt;10^4 cfu/mL</td>
<td>0–45</td>
<td>62–98</td>
</tr>
<tr>
<td>Leukocyte esterase and/or nitrite</td>
<td>67–100</td>
<td>67–98</td>
</tr>
<tr>
<td>&gt;10^3 cfu/mL</td>
<td>74–79</td>
<td>66–82</td>
</tr>
<tr>
<td>&gt;10^2 cfu/mL</td>
<td>71–84</td>
<td>41–83</td>
</tr>
</tbody>
</table>

NOTE. The criteria used to assess the clinical importance of isolates and the laboratory methods used varied between studies; the data are presented only as an overview of reported performance characteristics of the tests. All numbers are rounded to the nearest whole number. cfu, colony-forming units.
Table 4. Interpreting culture results for urine specimens yielding common urinary tract pathogens.

<table>
<thead>
<tr>
<th>Probability of contamination, no. of microorganisms isolated</th>
<th>Quantitation, cfu/mL</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low probability</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;10^2</td>
<td>Probable contaminant</td>
</tr>
<tr>
<td>1</td>
<td>≥10^2</td>
<td>Significant isolate</td>
</tr>
<tr>
<td>2</td>
<td>&lt;10^4 for each</td>
<td>Probable contaminants</td>
</tr>
<tr>
<td>2</td>
<td>≥10^4 for each</td>
<td>Significant isolates</td>
</tr>
<tr>
<td>2</td>
<td>≥10^2 for 1</td>
<td>Significant isolate and contaminant</td>
</tr>
<tr>
<td>&gt;3</td>
<td>≥10^4 for 1</td>
<td>Significant isolate and contaminants</td>
</tr>
<tr>
<td>&gt;3</td>
<td>≥10^6 for each</td>
<td>Probable contaminants</td>
</tr>
<tr>
<td><strong>High probability</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;10^2</td>
<td>Probable contaminant</td>
</tr>
<tr>
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<td>≥10^2</td>
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<td>2</td>
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<td>&gt;3</td>
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<td>Significant isolate and contaminants</td>
</tr>
<tr>
<td>&gt;3</td>
<td>≥10^6 for each</td>
<td>Probable contaminants</td>
</tr>
</tbody>
</table>

**NOTE.** cfu, colony-forming units.

<sup>a</sup> Urine specimens obtained via aspiration (suprapubic, bladder, ureter, renal pelvis, kidney) or single (straight) catheterization, specimens obtained in the operating room, and urine specimens obtained from patients receiving antimicrobial therapy.

<sup>b</sup> Urine specimens obtained via clean catch technique, from indwelling catheters (urinary or suprapubic), or from nephrostomy tubes, ureterostomy tubes, or ileal loops.

necessary for determination of the identity of the infecting microorganism(s) and for antimicrobial susceptibility testing. This is particularly true because of the increased incidence of antimicrobial resistance.

The most commonly used criterion for defining significant bacteriuria is the presence of ≥10^5 cfu per milliliter of urine [15, 57, 58]. This criterion was established only for women with acute pyelonephritis or women who were asymptomatic but had multiple urine cultures that yielded this number of bacteria; however, the criterion is often applied to other patient populations [15]. Most patients with UTIs, however, do not fall into either category, and 30%-50% of patients with acute urethral syndrome will have colony counts of <10^5 cfu/mL [15]. For this reason, many laboratories have opted to use lower colony counts as a criterion for interpreting and reporting results. One common criterion is a colony count of 10^4 cfu/mL, which would be expected to increase the sensitivity of the test without making the test impractical for clinicians and laboratories to use.

Catheterized patients (who may have low concentrations of bacteria that can progress to higher concentrations) and many patients with infections of the lower urinary tract have colony counts much lower than 10^5 cfu/mL if the specimens are obtained via suprapubic aspirate or catheterization [59]. Accordingly, the most appropriate diagnostic criterion for urine culture specimens obtained via suprapubic aspirate or catheterization is a bacterial concentration of ≥10^5 cfu/mL [15, 59].

Routine follow-up cultures for test-of-cure are not recommended for patients who have been treated for asymptomatic bacteriuria, acute uncomplicated cystitis, or acute uncomplicated pyelonephritis [60] and for whom there is evidence of an appropriate clinical response to therapy [2]. Follow-up cultures are, however, recommended for patients with infections that do not respond to therapy, patients who have recurrent UTIs, patients who have anatomic or functional abnormalities of the urinary tract, or patients who continue to have unexplained abnormal urinalysis findings.

**Anaerobic bacterial urine cultures.** The normal flora of the large intestine, vagina, and skin contain large numbers of anaerobic bacteria. Because anaerobic bacteria cause UTIs only in rare circumstances, however, recovery of anaerobic bacteria from urine by culture is of no clinical relevance for most patients with UTIs. Urine cultures for anaerobic bacteria should be limited to patients with anatomic abnormalities (e.g., enterovesical fistulae) that increase the likelihood of infection with anaerobic bacteria.

**Fungal urine cultures.** As stated previously, microbiologic detection of almost all cases of funguria can be achieved using...
routine bacterial media. There are limited data regarding the use of tests other than culture to detect funguria. Huang et al. [61] reported that pyuria did not correlate with funguria, regardless of whether patients had concomitant bacteriuria or an indwelling urinary catheter. Kauffman et al. [16] reported that, of 648 patients with funguria whose urine specimens underwent urinalysis, 354 (54.6%) had pyuria and 230 (35.5%) had hematuria. Of the 648 patients, only 410 had urine specimen reports that included a comment as to the presence or absence of yeasts; 247 (60.2%) of these 410 patients had urine specimens that were positive for yeasts [16]. On the basis of these observations, and because the nitrite test would be of no use in the detection of funguria, there appears to be limited value in using urinalysis in the detection of funguria at this time. This conclusion may change as further information is published regarding the clinical outcomes of patients with funguria, the results of laboratory testing of urine specimens, and the effects of chemotherapy.

**Mycobacterial urine cultures.** Although it is an uncommon finding in the United States, extrapulmonary tuberculosis may involve the genitourinary tract. The traditional laboratory diagnosis of mycobacterial UTI is by use of acid-fast smears and mycobacterial cultures [62], but more recent data suggests that the diagnosis can also be made by use of nucleic acid amplification tests [63, 64]. There are, however, only limited data about the use of such assays for the diagnosis of genitourinary tuberculosis, and none of these assays have been cleared or approved by the US Food and Drug Administration for this indication. Until better data are available, the authors recommend against the routine use of nucleic acid amplification tests, particularly with patients for whom there is low clinical suspicion of genitourinary tuberculosis.

Because nontuberculous mycobacteria, such as *Mycobacterium smegmatis*, may be present as colonizing flora (and to reduce the number of contaminating bacteria), the external genitalia should be washed before specimens are obtained [64]. The best specimen for mycobacterial urine cultures is the first voided urine. Multiple specimens may be needed, because mycobacterial culture results are positive for 25%–95% of patients and smears are positive for 50%–70% of patients with tuberculous genitourinary tract infections [62].

**Interpretation of urine culture results.** Microbiologists need to interpret the microbiologic relevance of growth on culture plates to determine whether further identification and antimicrobial susceptibility testing are necessary. Most culture results can be interpreted readily; no growth and gross contamination are both unambiguous results, as are pure cultures of common pathogens growing in a quantity of >10^9 cfu per milliliter of urine. The interpretation of cultures that yield pure growth in lower quantities is also clear for specimens obtained via suprapubic aspiration or straight catheterization. On the other hand, interpretation of urine cultures that yield mixed flora in varying quantities can be difficult. Although a number of algorithms have been developed to guide the interpretation of urine cultures, the large number of potential combinations of microorganisms—in varying quantities—and the need to correlate these results with different types of UTIs limits the usefulness of any algorithm. One algorithm is presented in table 4.

Irrespective of the algorithm used to guide interpretation, laboratories should report culture results with interpretive guidelines to help the ordering physician assess the clinical relevance of the results. Cultures that yield unambiguous culture results should be interpreted and reported as such. Test results for cultures that yield mixed flora in varying quantities should specify the microorganisms that were recovered, the quantity of each microorganism, and the probable clinical importance of each isolate.

**Antimicrobial susceptibility testing.** Each laboratory should have guidelines by which pathogens are tested for antimicrobial susceptibility. These guidelines should be developed and antimicrobial susceptibility tests should be performed and reported according to the most recent version of the NCCLS guidelines. Bacterial or fungal isolates of uncertain clinical importance should not be tested for antimicrobial susceptibility for purposes of routine patient care.

**CONCLUSION**

Most patients with uncomplicated acute cystitis have cases that are clinically straightforward, and they may not require any laboratory testing beyond urinalysis. For a significant number of patients, however, the clinical history and physical findings alone may be insufficient to make a definitive diagnosis of UTI. For those patients and for patients with complicated UTIs, laboratory tests are necessary to make the diagnosis and to provide specific information regarding the identity and the antimicrobial susceptibility pattern of pathogens. Both the laboratory diagnosis and the clinical diagnosis of laboratory test results must be made in light of the method of collection used; clinicians should specify the method of collection on test requisition forms. Of the available laboratory tests, urinalysis is helpful primarily as a means of excluding bacteriuria, but it is not a surrogate for culture. Although cultures identify pathogens, the accurate interpretation of culture results requires clinical information that is usually available only to the clinician. We hope that infectious diseases physicians, in particular, will understand both the strengths and the limitations of the laboratory-based diagnostic studies for UTIs that have been reviewed in this article, and we hope that they will incorporate this understanding with current treatment guidelines [65] to optimize patient care.
References


