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Point-Counterpoint: Reflex Cultures Reduce Laboratory Workload and Improve Antimicrobial Stewardship in Patients Suspected of Having Urinary Tract Infections

Romney M. Humphries,[a] Jennifer Dien Bard[b,c]

Department of Pathology and Laboratory Medicine, UCLA David Geffen School of Medicine, Los Angeles, California, USA[a]; Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, Los Angeles, California, USA[b]; Keck School of Medicine, University of Southern California, Los Angeles, California, USA[c]

Urinary tract infections (UTIs) are frequent and lead to a large number of clinical encounters. A common management strategy for patients suspected of having a urinary tract infection is to test for pyuria and bacteria by urine analysis (UA) of midstream urine, with initiation of antibiotic therapy and urine culture if one or both tests are positive. Although this practice was first used in an outpatient setting with midstream urine samples, some institutions allow its use in the management of catheterized patients. The ideas behind the reflex urine culture are to limit laboratory workload by not performing culture on negative specimens and to improve antimicrobial stewardship by not giving antimicrobials to patients with negative UA results. The questions are, first, whether reflex urine culture reduces workloads significantly and, second, whether it improves antimicrobial stewardship in the era of increasing numbers of urinary tract infections due to extensively drug-resistant Gram-negative bacilli. Romney Humphries from UCLA supports the idea that reflex urine cultures are of value and describes what reflex parameters are most useful, while Jennifer Dien Bard of Children's Hospital Los Angeles discusses their limitations.

POINT

> **How often misused tests generate misleading thoughts: an argument for the appropriate use of the urinalysis to rule out urinary tract infections.**
> —Adapted from Herbert Spencer

Optimum use of laboratory testing requires that providers order tests only for patients with an appropriate indication; urine cultures are no exception to this rule. Guidelines published by the Infectious Diseases Society of American support urine testing and sterilization in the absence of symptoms for only two groups: pregnant women and those about to undergo urologic surgery (1). For the remainder of patients, such testing should be done only in the context of symptoms consistent with a urinary tract infection (UTI): fever, urgency, frequency, dysuria, suprapubic tenderness, altered mental status, or hypotension. And yet, up to half of patients for whom a urine test is ordered in the emergency department (ED) or general medicine services (2) do not have symptoms consistent with a UTI. Unfortunately, several studies have demonstrated that these test results, and not the patient's symptoms, drive antibiotic utilization (2–4). Such overuse of testing is problematic on several fronts, including potential misdiagnosis (i.e., early case closing and failure to evaluate for other causes of symptoms by the physician), overuse of antimicrobials and their associated risks, and a high burden of testing for the laboratory. A rapid diagnostic strategy to diagnose UTI is therefore desirable but does not exist at present. However, UA (performed either with a dipstick or an automated instrument) is thought by many to be a useful screen by which to rule out UTI in a symptomatic patient. I will demonstrate that the detection of pyuria or bacteria by UA is a screening test that, when used appropriately, is associated with a high negative predictive value (NPV) that should impart confidence to the physician that a urine culture will not yield additional, clinically relevant information (i.e., the culture will be negative), and that a UTI is unlikely to be the cause of their patient's symptoms. However, it should be emphasized that the appropriate use of UA to rule out UTI is in the context of a patient with symptoms consistent with a UTI.

The absence of pyuria upon UA is an excellent predictor of a negative urine culture. One of the challenges associated with implementing a UA reflex-to-culture algorithm is the absence of evidence-based guidance on which UA parameters best predict urine culture results. Several studies have evaluated the predictive values of both indirect markers of infection: a positive result for nitrite (a marker for the presence of *Enterobacteriaceae* in the urine) or leukocyte esterase (LE; a marker for the presence of leukocytes) or direct observation of white blood cells (i.e., pyuria) or bacteria in the urine by microscopy. When evaluated in a population with a low prevalence of positive bacterial cultures, such as outpatients suspected of having a UTI, the NPV of any of these factors individually is excellent. For instance, a large study performed in Turkey retrospectively reviewed 32,998 patients in community clinics or the emergency department (ED) who had been diagnosed preliminarily with a UTI and for whom both UA and culture were ordered. Only 2.3% of patients in this study were positive by urine culture, and the NPV for LE, nitrite, bacteria, and

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Address correspondence to Romney M. Humphries, rhumphries@mednet.ucla.edu, or Jennifer Dien Bard, jdienbard@chla.usc.edu.

>5 white blood cells (WBC) per high-power field (HPF) were all individually more than 98% (5). Similarly, when evaluating a population with a high incidence of positive urine cultures, the combined criteria of the presence of all four markers was associated with an NPV of 98.2% in a study of 1,546 patients who were >5 years of age and evaluated in the ED of a single hospital. In this study, 20% of the patients had positive urine culture results (6). When analyzed individually, the NPV of pyuria (evaluated by the presence of >10 WBC/HPF) was 92%, and the NPV for the presence of bacteria was 96%, the presence of LE was 93%, and the presence of nitrite was 86%. Similar results were found in a study of 874 men among whom the prevalence of a positive urine culture was also 20%. Pyuria (defined as >5 WBC/HPF) had an NPV of 97% (7). From these studies, it is evident that pyuria (at either >5 or >10 WBC/HPF) and the presence of bacteria are excellent markers by which to rule out bacteriuria in populations with a prevalence of bacteriuria of ≤20%. The few cases (2 to 6%) missed by these criteria may be caught if the presence of a positive nitrite result is incorporated into the algorithm. Instituting a policy by which urine specimens that were negative for pyuria are not cultured would have resulted in a 39 to 69% reduction in the number of urine specimens submitted to the laboratory for culture, a significant cost avoidance (6, 7).

Performance of UA for catheterized patients. The performance of a UA is less well studied in patients with indwelling urinary catheters. However, the NPV of pyuria was 90.5% in a study of 761 patients (8) and 92% in a study of 300 urine specimens from 106 catheterized patients in a surgical intensive-care unit (ICU) (9). Both these studies used a cutoff of >10 WBC/HPF to define pyuria, and the former study demonstrated that the mean urine WBC count was significantly higher in patients with catheter-associated (CA) UTI than in those without infection (71 versus 4 WBC/μl; $P = 0.006$). As such, as is the case for uncatheterized patients, the absence of pyuria in a symptomatic catheterized patient suggests a diagnosis other than CA UTI (10), and cancellation of urine cultures ordered for these patients may be appropriate.

Can UA be used to support antimicrobial stewardship? UA is often described as a disappointing test for the diagnosis of UTI due to the poor positive predictive value (PPV) for a positive urine culture. The PPV for pyuria, for example, ranged from 4 to 32% in the studies discussed above. This, combined with both the fact that culture results are not available for 18 to 24 h and the common occurrence of pyuria in hospitalized patients (2), in particular those with acute nephrolithiasis or an indwelling urinary catheter (10), begs the question of whether a UA reflex algorithm reduces the number of unnecessarily treated patients. Unfortunately, data demonstrate that both catheterized and noncatheterized patients with pyuria are more likely to be treated if they are asymptomatic than are those without pyuria documented by UA (4), even though treatment guidelines clearly advise against this practice (10). In one study of 484 cases of bacteriuria in hospitalized patients, 219 cases were classified as asymptomatic, among which 70 were inappropriately treated. Factors in this study associated with inappropriate treatment included pyuria or positive nitrite results upon UA (3). However, if we apply UA appropriately as a rule-out test, the absence of pyuria should be associated with appropriate withholding of antimicrobials. This holds true only for populations with a low incidence of pyuria; this is not often the case for hospitalized/catheterized patients (2). In outpatients, in contrast, use of UA has been demonstrated to yield a reduction in inappropriate prescribing of antimicrobials. A study in the Netherlands of 1993 nonpregnant women with symptoms consistent with a UTI demonstrated that 94% with a nitrite-positive specimen and 71% with a positive LE result received antimicrobial therapy but that only 20% of those with negative results for these tests were prescribed antibiotics (11). Similarly, a Canadian study of 231 women with symptoms of a UTI demonstrated that evaluation for pyuria would reduce the frequency of unnecessary antimicrobial prescription by one-third (12).

Conclusions. The diagnostic reference standard for UTI is quantitative urine culture, a labor-intensive test associated with a minimum delay or an 18- to 20-h delay before a negative result is available. From the data discussed above, UA and, in particular, evaluation for pyuria by either LE or WBC testing are an efficient means by which to mitigate both inappropriate testing and antimicrobial prescription. However, careful evaluation of the patient's symptoms before ordering such testing is imperative, as this testing module is associated with high rates of false-positive results.

Romney M. Humphries

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COUNTERPOINT

Whatever is only almost true is quite false and among the most dangerous of errors, because being so near truth, it is the more likely to lead astray.
—Henry Ward Beecher

The diagnosis of urinary tract infection (UTI) is not straightforward, as providers must be able to distinguish UTIs from other syndromes with a similar clinical presentation and to recognize UTIs that present with unusual manifestations. The practice of using UA results to reflex to culture continues to be debated. Supporters of reflex testing suggest that if a majority of urine cultures are negative, why not streamline the process by using UA to eliminate unnecessary cultures, avoid treatment in patients who have a negative UA result, and initiate early therapy in patients who have a positive UA result. This sounds like a clear-cut approach, no? On the contrary, UA testing is complex and institution specific, consisting of a variety of methods and criteria to define a positive UA (i.e., the presence of WBC, leukocyte esterase [LE], nitrite, and bacteria). Moreover, the absence of data to support the practice and the overall lack of consensus for reflex testing in laboratories indicates that the decision is multifaceted.

Patients asymptomatic for bacteriuria can have a positive UA result. The issue is not whether we can conserve laboratory resources by enforcing a reflex testing algorithm. Rather, the issue is whether UA and/or urine culture orders are justified. Emphasis must be placed on optimizing providers' ordering practices through the adoption of guidelines to ensure that urine testing is ordered only when clearly indicated.

Asymptomatic bacteriuria (ASB) is common, particularly with advancing age or certain underlying conditions. Guidelines provided by the Infectious Diseases Society of America (IDSA) state that pyuria (i.e., the detection of LE or the presence of WBC) is not diagnostic of ASB, catheter-associated (CA) UTI, or non-CA UTI, as pyuria is prevalent in other infectious and noninfectious conditions. Similarly, the presence of bacteriuria (i.e., the detection of nitrites and the presence of bacteria) does not rule out contamination or ASB and is a poor predictor of UTI (1, 2).

Pyuria is present with ASB in 32% of young women, 90% of elderly patients in long-term care facilities, and 90% of hemodialysis patients (1), rendering UA useless in determining when a urine culture should be done. Thus, screening and antibiotic treatment is not indicated for patients with ASB, except pregnant women or individuals undergoing urologic procedures (1, 2). Despite these guidelines, inappropriate treatment of ASB is widespread, and only 53% of providers were reported to be practicing in accordance with these guidelines when diagnosing bacteriuria; the bulk of discordant signs/symptoms were associated with the presence of pyuria in urine (3).

How reliable is UA as a screening test for UTI? For the majority of patients, a negative UA result is a good predictor of a negative urine culture. However, in a certain subset of patients, screening with UA is insufficient, and missing a UTI due to a negative UA result may be detrimental in cases of complicated UTIs and urosepsis. For example, a Canadian study demonstrated this in an elderly population, finding the sensitivity of a positive urine culture to be 73.7% in symptomatic patients. Five patients with negative UA (defined by the absence of LE or nitrite) had urosepsis proven by both positive urine culture and positive blood culture (4). In addition, it must be emphasized that a positive UA result is a poor predictor of a positive urine culture and UTI. Multiple studies have confirmed the inadequate performance of UA in predicting true-positive UTI cases, with positive predictive values (PPVs) ranging from 31 to 46% (5-7). These findings corroborate the finding that UA results are a poor predictor of the presence UTIs.

Contradictory impact on antimicrobial stewardship. A major argument for urine reflex testing is that it will streamline testing and avoid the use of antibiotics in patients with negative UA results. However, as indicated by the high incidences of pyuria and bacteriuria in patients with ASB, screening by UA is not a sufficient gatekeeper to prevent unnecessary urine culture and inappropriate antibiotic administration. Rather, abnormal UA results may trigger initiation of antibiotics prior to the availability of urine culture results. This is particularly concerning, since the specificity of UA has been reported to be 54% of that of urine culture, meaning that more patients may potentially be prescribed antibiotics when positive UA results are available without culture results (6).

A retrospective study evaluating urine testing and antibiotic prescribing practice for 676 patients who were ≥12 years old and had a positive urine culture reported that 60% of urine tests were ordered without indication. One hundred eighty-four of 676 (27%) patients had ASB, and 37/184 (20%) were treated with antibiotics. Importantly, of the patients with ASB that were treated with antibiotics, 89% were given antibiotics based on positive UA results (8). The injudicious use of antibiotics in this setting was further evident in a prospective study of 343 adult women seen in the emergency department. That study reported overtreatment of 47% of patients when UA was positive for LE, nitrite, or trace blood but urine culture was negative. Using these UA criteria, 13% of patients with true signs and symptoms of UTIs (and positive urine culture) would not have been treated due to negative UA results (9). This study also demonstrated that UA performance characteristics are highly dependent on the cutoffs that are adopted; had a more stringent UA cutoff been used (e.g., an LE of >2 and positivity for nitrite), the overtreatment rate would have decreased to 13%, but the undertreatment rate would have escalated to 48%.

The biggest potential impact on appropriate antimicrobial usage is to adopt the mantra that "less is more" to mitigate unnecessary urine testing and/or reporting (10). This was demonstrated in a recent prospective pre- and postintervention comparison study conducted on adult patients with urinary catheters who were admitted to acute-medicine and long-term care wards (11). At the intervention site, extensive educational programs were introduced and included case-based audits, direct feedback, and interactive presentations to train clinicians to use a streamlined diagnostic algorithm based on IDSA guidelines for CA UTI and ASB. In contrast, the comparison site received traditional education methods and an email with the full text of the IDSA guidelines. The intervention site demonstrated a significant reduction in urine culture orders from 41.2 to 23.3 per 1,000 bed days. In

addition, the rate of ASB overtreatment decreased by 1.6 per 1,000 bed days to 0.6 per 1,000 bed days, and the overall likelihood of ASB overtreatment decreased by 50%. In contrast, urine culture order rates and treatment of ASB were comparable to baselines at the comparison site. A proof-of-concept study conducted at an acute-care hospital in Canada demonstrated that intervention at the time of laboratory reporting can significantly decrease unnecessary antimicrobial usage. During the intervention period, rather than routinely reporting positive urine cultures from noncatheterized inpatients, technicians appended a comment to electronic medical records to request clinicians to call the laboratory for culture results if UTI is strongly suspected. Of the 37 modified reports, results were requested for only 5 (14%) patients, decreasing the rate of antibiotic therapy from 48% to 12% in noncatheterized patients with ASB (12).

Reflex urine culture and laboratory resources. There are limited data on the impact of reflex culture on laboratory utilization. Depending on the institution, UA may be rather complex, consisting of one or more of the following: dipstick, urine microscopy, and urine Gram staining. A study found that performing dipstick analysis and culture on samples from all pediatric patients was the most cost-effective compared to performing microscopy UA and urine Gram staining on all urine specimens with reflex to culture ($3.70 versus $6.66/patient). Performing only microscopic UA with reflex to culture was found to reduce costs to $3.48/patient, but 18% of patients with UTIs would be missed due to the absence of culture (13). The cost reduction stated in this study is rather insignificant when you take into account the number of samples where testing was likely not warranted. Hence, the biggest impact on laboratory resources would be to restrict urine studies to only those from patients with clinical indications for testing.

Reflex to culture based on symptoms rather than urinalysis. As discussed, it is not uncommon for providers to test and treat patients based on positive UA results, even in the absence of signs and symptoms of UTI. The Canadian study described above reported treatment of 71.4% of culture-positive elderly patients, despite the absence of symptoms compatible with UTI (4). A contributor to excessive testing and treating is the incorrect association of certain clinical features, namely, pyuria and bacteriuria, with UTI, resulting in poor diagnostic accuracy and reliability. Providers must identify correct signs and symptoms of UTIs prior to ordering UA or urine culture and be conscious of the high prevalence of ASB when interpreting a positive result.

How can these evidence-discordant norms of practice and biases be shifted to allow for evidence-based decision-making practices that use signs and symptoms associated with UTI to guide testing? One approach is asymmetric paternalism, defined as assisting individuals who are more inclined to make irrational decisions without actually limiting their freedom of choice (14). This has been applied in recent studies to assist providers in achieving their goals (i.e., correctly diagnosing and treating UTIs) in the presence of biases (discordant signs and symptoms of UTI). A common intervention strategy used by advocates of asymmetric paternalism is to exploit the same biases that would normally result in harmful behavior to instead promote healthy behavior (14). Trautner et al. (3) conducted a two-part study that first confirmed the inaccuracies of the "providers' mental models" in diagnosing CA UTIs. This was followed by the redirection of the providers' mental model through creation of a valid diagnostic "kicking CA UTI" algorithm that began with ordering only urine culture for patients who presented with symptoms of CA UTIs. The use of the diagnostic algorithm enhanced the reliability of differentiating between CA UTI and CA ASB diagnosis (3), and its success was demonstrated in the study described above (11). A large U.S. study of 1,469 females of <2 years of age presenting to the ED applied a similar approach. A clinical-prediction model was derived to identify children at high risk for UTIs, using clinical factors highly associated with positive urine cultures. Clinical factors that were associated with UTIs in females of <2 years of age included <12 months of age, white race, urinary symptoms, and the absence of gastrointestinal symptoms. Of note, a history of UTIs was not included in the prediction model, as clinicians may be influenced to obtain urine culture for these patients, even in the absence of other indications. Using this model, 95% of the patients with UTIs were identified and 30% of unnecessary urine cultures would have been eliminated (15).

If the correct diagnostic paradigm is utilized, then reflex culture may be limited to certain patient populations. In fact, there is consensus among multiple practice guidelines that culture should be limited to infection of the upper urinary tract or complicated UTIs, that culture is unnecessary in the vast majority of uncomplicated cystitis cases, and that treatment may be initiated based on symptoms alone. This typically includes premenopausal, nonpregnant women in the absence of urological abnormalities or comorbidities (16, 17). In contrast, culture may be warranted for other patient groups, including elderly patients in long-term care facilities and patients with hematologic malignancies or urological abnormalities.

Conclusions. Reflexing urine culture from UA results does not directly improve antimicrobial stewardship or conserve laboratory resources. Rather, reeducating providers on the appropriate diagnostic algorithm associated with potential UTI signs and symptoms and adopting utilization restrictions are imperative. This will in turn reduce UA and culture orders, thereby decreasing the utilization of laboratory resources, reducing unnecessary antimicrobial therapy, and improving overall health care costs.

Jennifer Dien Bard

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SUMMARY

Points of agreement

- Reflex urine cultures are frequently ordered for patients who do not have symptoms of urinary tract infections. This may result in inappropriate antimicrobial use.
- A negative pyuria/nitrate screen has a high negative predictive value for urine culture; a positive pyuria/nitrate screen does not have as high a positive predictive value for infection, particularly for catheterized patients. The value of reflex urine culture is primarily in detecting patients who do not need and should not have a urine culture done.
- Positive urinalysis is not useful in differentiating catheterized patients with asymptomatic bacteriuria from those with urinary tract infections. Additionally, a positive urinalysis result in this setting frequently results in inappropriate antimicrobial therapy.

Points requiring further consideration

- The clinical effectiveness of reflex urine culture has been documented primarily for women with cystitis in the outpatient setting. Its value in other patient populations is either less certain or has not been established.
- The most accurate urinalysis parameters, particularly white blood cell numbers, to determine the likelihood of a positive urine culture are not known.
- With CA UTI being used by the Centers for Medicare & Medicaid Services (CMS) and the National Healthcare Safety Network (NHSN) as important metrics of quality of care, are there laboratory approaches that can be used to differentiate patients with asymptomatic bacteriuria from those with urinary tract infections? In addition, what role should the laboratory play in assisting the antimicrobial stewardship committee to reduce the inappropriate use of antimicrobials in catheterized patients?

Peter H. Gilligan, Editor, *Journal of Clinical Microbiology*