

Lack of Clinical Utility of Urine Gram Stain for Suspected Urinary Tract Infection in Pediatric Patients

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Urinary tract infection (UTI) is one of the most common infections in children. Urine culture remains the gold standard for diagnosis, but the utility of urine Gram stain relative to urinalysis (UA) is unclear. We reviewed 312 pediatric patients with suspected UTI who had urine culture, UA, and urine Gram stain performed from a single urine specimen. UA was considered positive if ≥ 10 leukocytes per oil immersion field were seen or if either nitrates or leukocyte esterase testing was positive. Urine Gram stain was considered positive if any organisms were seen. Sensitivity, specificity, and positive and negative predictive values were calculated using urine culture as the gold standard. Thirty-seven (12%) patients had a culture-proven UTI. Compared to urine Gram stain, UA had equal sensitivity (97.3% versus 97.5%) and higher specificity (85% versus 74%). Empirical therapy was prescribed before the Gram stain result was known in 40 (49%) patients and after in 42 (51%) patients. The antibiotics chosen did not differ between the two groups ($P = 0.81$), nor did they differ for patients with Gram-negative rods on urine Gram stain compared to those with Gram-positive cocci ($P = 0.67$). From these data, we conclude that UA has excellent negative predictive value that is not enhanced by urine Gram stain and that antibiotic selection did not vary based on the urine Gram stain result. In conclusion, the clinical utility of urine Gram stain does not warrant the time or cost it requires.

Urinary tract infection (UTI) is one of the most common infections in children, accounting for up to 2% of pediatric hospital admissions at an annual cost of more than half a billion dollars (1). Timely diagnosis and antibiotic therapy are necessary to reduce the risk of serious complications from UTI (2). However, due to nonspecific manifestations, UTI requires a high degree of suspicion, which in turn has contributed to both under- and overdiagnosis (3, 4). The need for timely antibiotic therapy necessitates the use of rapid diagnostic tests in addition to urine culture, notably, urinalysis (UA) and urine Gram stain. However, the utility of urine Gram stain relative to UA remains controversial. Previous studies have supported the use of urine Gram stain, urinalysis, or both as a screening test (5–8). However, the most recent American Academy of Pediatrics guidelines for the management of UTI in children 2 to 24 months of age does not include Gram stain as part of the diagnosis (9). Furthermore, significant resources are required to perform urine Gram stain in a timely manner, including microbiology technician time. The objectives of our study were to identify the sensitivity and specificity of UA and urine Gram stain and to determine whether urine Gram stain has utility in diagnosis or optimal antimicrobial prescribing for pediatric UTI.

MATERIALS AND METHODS

Patient cohort. We retrospectively included all patients aged ≤ 19 years of age who had a urine culture, urinalysis, and urine Gram stain ordered on a single urine specimen between 28 September and 19 November 2011 at Children's Medical Center, Dallas, TX. Immunocompromised patients, including patients with malignancy undergoing chemotherapy, were excluded. Patients with structural or functional urologic defects requiring routine catheterization were also excluded.

Patient data collection. Medical records were reviewed for pertinent demographic, clinical, and laboratory information and, specifically, the time from urine collection to reporting of results. Data on diagnosis of UTI, any prescribed antimicrobial therapy, and the time that those orders were placed in the computerized physician order entry system were re-

corded. The urine collection method was documented; our local practice recommends clean-catch urine samples for children 2 years of age or older and catheterized specimens for children younger than 2 years of age. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board (082011-059).

Laboratory testing. Urinalysis and automated microscopy were performed from unspun urine on the Iris iQelite urine chemistry system (Iris Diagnostics Division, Chatsworth, CA). Urine culture was considered positive if $\geq 50,000$ CFU of a uropathogen were identified (9). UA was considered positive if ≥ 10 leukocytes per oil immersion field were seen or if either nitrate or leukocyte esterase testing was positive. Gram stain was considered positive if any organisms were seen. Urine culture results were used as the gold standard for comparison.

Statistical methods. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were calculated for each testing method. Demographic variables were summarized using descriptive statistics. Comparisons between the categorical variables were performed using a chi-square or Fisher's exact test, as appropriate. Paired continuous variables were compared with a paired t test (normally distributed) or McNemar test of paired proportions (if not normally distributed). The

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TABLE 1 Efficacy of rapid diagnostic testing for pediatric urinary tract infection

Test ^a	Result	No. with urine culture	
		Positive	Negative
UA	Positive	38	39
	Negative	1	230
Gram stain	Positive	36	71
	Negative	1	200
UA and Gram stain	Positive	39	38
	Negative	1	230

^a UA rapid diagnostic testing alone had sensitivity of 97.4%, specificity of 85.5%, PPV of 49.4%, and NPV of 99.6% in our patient cohort. Urine Gram stain rapid diagnostic testing alone had sensitivity of 97.3%, specificity of 73.8%, PPV of 33.6%, and NPV of 99.5%. Performing both UA and urine Gram stain resulted in sensitivity of 97.5%, specificity of 85.8%, PPV of 50.6%, and NPV of 99.6%. Urine culture was used as the gold standard for comparison.

data were analyzed using SigmaPlot statistical software, version 12.5 (Systat Software, San Jose, CA).

RESULTS

Three hundred twelve patients had urine culture, UA, and urine Gram stain performed from a single urine specimen during the study period. Four patients had bag urine samples submitted and were excluded. Of the remaining 308 patients, 63% were female, and the median age was 4 years (interquartile range [IQR], 10 months to 10 years). All had their samples obtained in the outpatient setting, through either the emergency department (82%) or a clinic (18%). Urine samples were obtained by catheterization (55.2%) or clean catch (44.8%). Thirty-seven patients (12%) had a pathogen identified in urine culture. Using urine culture as a gold standard for comparison, the sensitivity and specificity of UA and Gram stain were calculated (Table 1). The sensitivity and specificity of UA were 97.4% and 85.5%, and the PPV and NPV were 49.4% and 99.6%, respectively. Urine Gram stain had a sensitivity and specificity of 97.3% and 73.8%, and the PPV and NPV were 33.6% and 99.5%. Of the 231 patients who had a negative UA, only 8 had a positive Gram stain. There was no difference between the proportion of clean-catch ($n = 4$) and catheterized ($n = 4$) samples when comparing discordant UA and Gram stain results. All eight of these patients received antibiotics, but only one had a positive urine culture. Of the 199 patients with a negative Gram stain, 15 had a positive UA and 7 received antibiotics, but only 1 had a positive urine culture.

One hundred thirty-seven (44%) patients were prescribed antibiotic therapy for presumptive UTI before the urine culture results were known. Empirical therapy was prescribed before any rapid urine test results were known in 55 (40%) patients, after the UA but before the Gram stain result in 40 (29%) patients, and after the Gram stain results were known in 42 (31%). Patients who were prescribed antibiotics before any results were known were younger (median, 2 months [IQR, 3 weeks to 4 months] versus 5 years [IQR, 4 months to 10 years]; $P < 0.001$) and less likely to have a UTI (18% versus 45%; $P < 0.001$). The class of antibiotic prescribed did not differ depending on whether the Gram stain showed any organisms ($P = 0.81$) (Table 2) or whether the result was Gram-negative rods ($n = 45$) versus Gram-positive cocci ($n =$

TABLE 2 Antibiotic-prescribing patterns^a

Antibiotic class	% prescribed		
	Group 1 (before any rapid test results)	Group 2 (before Gram stain result)	Group 3 (after Gram stain result)
Aminopenicillin (± aminoglycoside)	80 ^b	25	14
3rd-generation cephalosporin	18	70	69
Trimethoprim-sulfamethoxazole	2	5	10
Other	0	0	7

^a Antibiotic-prescribing patterns for patients with suspected urinary tract infection based on available information at time of prescription.

^b Group 1 was more likely than group 2 or 3 to receive aminopenicillin-based therapy ($P < 0.001$). There were no differences in antibiotics prescribed between group 2 and group 3.

27; $P = 0.67$). Once prescribed, no course of antibiotic was subsequently discontinued based on additional results.

The resource utilization to perform these 308 urine Gram stains was calculated. Each urine Gram stain took approximately 15 min to perform once the sample reached the clinical microbiology laboratory. The median turnaround time from urine collection to a reported Gram stain result in the electronic medical record was 91 min (IQR, 67 to 118 min) for Gram stain compared to only 38 min (IQR, 22 to 59 min) for UA. The Gram stain results were available before the UA results in 18 patients (5.8%). Based on our volume, the burden of urine Gram stains resulted in approximately 40 h of technologist time per month. The patient costs of UA and urine Gram stain testing were similar at our institution, approximately \$100.

DISCUSSION

Evaluation of the use of rapid tests in combination with urine culture to improve the speed and accuracy of diagnosis in pediatric UTI has not led to clarity (8). Ideally, management of suspected UTI would include high-sensitivity rapid testing and culture or reflexive culture if the rapid test did not exclude UTI. If the rapid test could also help guide the selection of empirical antimicrobial therapy, its usefulness would increase. However, if a rapid test does not improve the diagnosis of UTI or the selection of therapy, then it is inefficient, not cost-effective, and ultimately unnecessary. Previous studies have proposed UA, urine Gram stain, or a combination of both as the optimal approach to rapid screening for UTI (5–7, 10–12). Therefore, the aim of our study was to determine whether urine Gram stain either improved the diagnosis of UTI at our medical center or altered the selection of antibiotics when UTI was suspected.

Previous trials, as well as meta-analyses, have supported the relatively high sensitivity and NPV of both UA and urine Gram stain. Williams et al. (8) found in their 2010 meta-analysis that the sensitivity of leukocyte esterase on UA was 79% (95% confidence interval [CI], 73 to 84%) and the sensitivity of nitrites was 49% (95% CI, 41 to 57%). The sensitivity of both analytes together was 88% (85% CI, 82 to 91%), which was virtually identical to the sensitivity of urine Gram stain (91% [95% CI, 80 to 96%]). Hoberman et al. (13) demonstrated that pyuria, defined as the presence of >10 white blood cells per high-power field, has excellent NPV either alone (98.4%) or in combination with bacteriuria

on Gram stain (99.3%). Our study supports these findings. A positive UA alone had a sensitivity of 97.4% and an NPV of 99.6%, which were similar to those of urine Gram stain (sensitivity, 97.3%; NPV, 99.5%). The use of UA in combination with Gram stain did not improve these values, as only 1 patient out of 231 had a negative UA, a positive Gram stain, and a subsequent proven UTI (0.4%). If all patients with suspected UTI had a UA obtained, our data show that the number of urine Gram stains that would need to be performed to identify one additional UTI (the number needing to be screened) is approximately 1,200 (14). The poor specificity (~74%) of urine Gram stain prevents its utilization as a trigger for antibiotics. This poor specificity may be due to asymptomatic bacteriuria or collection technique, particularly when clean-catch specimens are ordered for young children (15, 16). UA and urine Gram stain testing are billed at similar costs to the patient at our institution, so performing both rapid tests doubles the patient cost of rapid UTI screening with no additional impact on UTI diagnosis. Furthermore, the turnaround time of UA was 53 min faster than that for Gram stain, an important difference, as outpatient clinics and emergency departments focus on throughput efficiency (17, 18). The results of our study suggest that routine Gram stain does not add to the diagnosis of suspected UTI in children.

Even if urine Gram stain does not enhance the diagnosis of pediatric UTI, it could theoretically improve antibiotic-prescribing practices if clinicians used the results of the Gram stain to guide appropriate empirical therapy. The results of the Gram stain have been shown to affect prescribing patterns for adult patients with pneumonia or UTI (19). However, antibiotic selection for UTI in pediatrics has historically been driven by local resistance patterns and institutional prescribing guidelines rather than the results of urine Gram stain (20, 21). Additionally, antibacterials used in the management of UTI generally achieve very high urinary concentrations, making precise empirical pathogen targeting unnecessary (22). We stratified our cohort into patients prescribed an antibiotic before the Gram stain was available and those prescribed an antibiotic after the Gram stain had a result. We found no difference in the selection of antibiotics, which were predominantly 3rd-generation cephalosporins, followed by aminopenicillins (e.g., amoxicillin or amoxicillin-clavulanate). A large proportion ($n = 55$; 40%) of children were treated immediately after the cultures were obtained and before any test results were back. These were primarily young infants with suspected serious bacterial infections, who received ampicillin plus gentamicin or ampicillin plus cefotaxime according to our institutional practice. For this reason, these patients were excluded from the antibiotic analysis (Table 2). For the group of children who had their antibiotic selected after the Gram stain showed a result, children with Gram-positive cocci were prescribed antibiotics similar to those prescribed for children with Gram-negative rods identified ($P = 0.67$). Our results suggest that at our medical center, the results of the urine Gram stain are not driving antibiotic selection, and in the majority of cases, antibiotics are prescribed before the Gram stain even has a result.

The lack of utility of urine Gram stain at our center is compounded by the relatively high resource utilization it commands. Each urine Gram stain takes approximately 15 min to perform and analyze, utilizing resources in the microbiology laboratory that could be better spent elsewhere. The cost to the patient for a urine Gram stain is equal to that of performing a UA at our institution,

so performing both rapid tests doubles the cost to patients without any additional aid in UTI diagnosis. Given the number needing to be screened (1,200), this equates to an additional 300 h of technician time and an additional \$120,000 in patient costs to identify a single additional UTI.

The limitations of our study include those inherent to retrospective chart reviews. Neither urine Gram stains nor urinalyses are ordered systematically (i.e., in an electronic order set) at our center; rather, certain providers prefer to order both rapid tests when evaluating suspected UTI. This may translate into a selection bias for the patients tested. Although the sensitivities and NPV of UA and Gram stain in our cohort are consistent with those in previously published meta-analyses, it should be noted that NPV is dependent on local prevalence. Areas with higher rates of UTI will have lower NPVs than reported here, which will in turn improve the clinical utility (and lower the number needing to be screened) of urine Gram stain. Furthermore, our study excluded immunocompromised children. The sensitivity of UA in patients with impaired neutrophil response is somewhat decreased (23, 24), and it is possible that urine Gram stain may have a diagnostic role in that population.

In conclusion, our findings demonstrate that urine Gram stain does not enhance the diagnosis or antibiotic prescribing for UTI in immunocompetent children when UA is also performed. Furthermore, urine Gram stain accounts for significant costs in both technician time and cost to the patient. In the absence of clinical utility, we recommend that urine Gram stain not be included in the routine evaluation of suspected pediatric UTI. Instead, it should be reserved for rare cases in which UA may not be optimal (i.e., immunocompromised hosts) or when the provider is clear as to how the result will impact antibiotic selection for suspected UTI. Such an approach will maximize the clinical impact of rapid diagnostic testing for UTI while minimizing costs for both the clinical microbiology laboratory and the patient.

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