

Can Urine Clarity Exclude the Diagnosis of Urinary Tract Infection?

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ABSTRACT. *Objectives.* To determine the association of clear urine by visual inspection with the absence of significant bacteruria, and to compare it with standard urinalysis.

Methods. The study was performed in the emergency department of Children's Hospital Medical Center, Cincinnati, Ohio. It was a prospective, convenience sample of children <21 years of age who had catheterized or midstream clean-catch urine specimen collected for culture. Clinical findings including the presence or absence of fever, abdominal pain, dysuria, frequency, and urgency were collected for each patient. Urine was visually assessed for clarity by 2 independent observers using a standardized technique. Standard laboratory urinalysis and microscopy were also performed on all specimens. A positive urine culture was defined as $\geq 10^4$ colony-forming unit (CFU)/mL of a urinary pathogen if obtained by catheterization and $\geq 10^5$ CFU/mL if obtained by midstream.

Results. Samples were obtained from 159 patients ranging in age from 4 weeks to 19 years. Females comprised 77% of the patients. One hundred ten of the samples (69%) were clear to visual inspection. There were a total of 29 positive cultures; however, 3 were in children with clear urine. The finding of clear urine on visual inspection had a negative predictive value of 97.3%. These results were similar to those obtained with standard urinalysis.

Conclusion. Clear urine on visual inspection cannot completely eliminate the possibility that a child has a urinary tract infection. However, it is a reproducible test that offers the advantages of being simple, fast, and inexpensive. The finding of clear urine should be considered a reasonable and relatively effective bedside screen for the presence of a urinary tract infection. *Pediatrics* 2000;106(5). URL: <http://www.pediatrics.org/cgi/content/full/106/5/e60>; urinary tract infection, child, urine clarity, urinalysis, diagnosis.

ABBREVIATIONS. UTI, urinary tract infection; NPV, negative predictive value; ED, emergency department; LE, leukocyte esterase; WBC, white blood cell count; hpf, high-power field; CFU, colony-forming unit; MSU, midstream specimen.

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Urine specimens for urinalysis and culture are frequently obtained on pediatric patients suspected of having a urinary tract infection (UTI). A culture result of an appropriately obtained urine specimen is considered the gold standard for diagnosis of a UTI; however, these results require up to 24 hours to obtain. Investigators have tried using the urine dipstick, Gram stain, microscopy, and enhanced urinalysis for more rapid diagnosis, but none of these methods were capable of detecting all UTIs.¹⁻⁶ Because no rapid method can exclude a UTI with 100% certainty, most clinicians send all urine specimens for culture, irrespective of the findings on routine urinalysis.

There are 2 studies that have examined the association of crystal clear urine with the absence of a UTI.^{7,8} In the first study, the presence of clear urine had a negative predictive value (NPV) for the absence of UTI of 100%. However, in the second study, the NPV was only 96%. These studies never explained the exact methods by which urine was determined to be clear, and they used a large number of bag specimens, which have a high rate of contamination.

The purpose of this study was to determine the association of clear urine by visual inspection with the absence of significant bacteruria and to compare it with standard urinalysis.

METHODS

All previously healthy patients <21 years of age presenting to the emergency department (ED) of Children's Hospital Medical Center in Cincinnati, Ohio, who had either a catheterized or midstream, clean-catch urine specimen collected for urine culture were eligible for the study. This study used a convenience sample, with patients being enrolled when one of the investigators was in the ED. Patients were excluded if they were: 1) referred to the ED for evaluation of an abnormal urinalysis or positive urine culture; 2) currently on antibiotics; 3) had an underlying medical problem requiring repeat catheterization, eg, neurogenic bladder; 4) unable to obtain an adequate volume of urine (ie, 3 mL of urine in excess of that required by the laboratory); or 5) known to have an underlying renal and/or genitourinary abnormality.

The decision to obtain a urine culture and the method of urine collection were made by the evaluating physician. No attempt was made to change current physician practice. The required quantity of urine was sent to the laboratory in a sterile container for routine urinalysis and culture. Urine in excess of this amount was used for the study.

Three milliliters of urine was poured into a standard 7-mL red-topped blood tube (Vacutainer, Becton Dickinson, Franklin Lakes, NJ) using universal precautions. This specimen was held 1 cm from a standard white background with black printed 11-font text and was viewed under normal fluorescent lighting conditions. As a control for the observer, another tube with water was viewed under the same conditions. To be considered a clear urine specimen, the printed text had to be as legible through the urine as

through the water. One of the study investigators, blinded to the clinical information, determined whether the urine was clear. If the urine was not clear, .1 mL of a .1-mol/L acetic acid solution was added to dissolve any phosphates and the visual inspection described above was repeated. A second observer, blinded to the clinical information and to the results of the first observer, performed the same visual inspection. If there was a discrepancy in determination of clarity between these 2 individuals, the specimen was considered cloudy.

Pertinent clinical information was collected from the patient and recorded. This included the age, gender, presence and duration of fever, presence or absence of urinary symptoms (ie, dysuria, frequency, and urgency), abdominal or flank pain, and method of urine collection. Information recorded from the urinalysis included the presence of nitrites, leukocyte esterase (LE), bacteria on microscopy, and white blood cells/high-powered field.

Laboratory Methods

Standard laboratory methods and techniques were used as follows: urine specimens were collected in sterile containers and transported on ice to the microbiology laboratory. A trained laboratory technician tested the unspun sample with the dipstick (Clinitek 200, Ames, Tarrytown, NJ) and recorded the results of the LE and nitrite. LE was recorded as negative, trace, small (+1), moderate (+2), or large (+3) at 2 minutes. For the purposes of the study, LE was recorded as positive if the reading was small or more. Nitrite was recorded as positive or negative at 1 minute. The urine was then spun in a centrifuge for 5 minutes at 2200 rpm and microscopy was performed. The number of leukocytes and organisms per high-powered field ($\times 400$) were recorded. A volume of .5 mL was used for resuspension of the urinary sediment, and pyuria was defined as ≥ 5 white blood cell count (WBC)/high-power field (hpf). Bacteria on microscopy was defined as any bacteria/hpf. Urine was plated onto MacConkey agar plates and sheep-blood agar plates with a .01-mL calibrated loop. The cultures were incubated for 48 hours at 35°C and examined daily for growth. Cultures were considered positive if on a catheterized specimen there were $>10^4$ colony-forming unit (CFU)/mL, and on a mid-stream if there were $\geq 10^5$ CFU/mL. Cultures were considered contaminated if >3 organisms were isolated.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL). Analysis involved χ^2 statistics with 95% confidence intervals. Likelihood ratios were also calculated for each variable. The κ coefficient was calculated to measure agreement beyond chance for assessment of urine clarity.

RESULTS

Samples were obtained from 159 patients ranging in age from 4 weeks to 19 years (mean: 5.8 years).

TABLE 1. Comparison of Urine Clarity With Standard Urinalysis Along With 95% Confidence Intervals

| Test | Sensitivity | Specificity | Positive Predictive Value | NPV | Positive Likelihood Ratio | Negative Likelihood Ratio |
|--|-------------------|-------------------|---------------------------|-------------------|---------------------------|---------------------------|
| Urine clarity (overall) | 89.7% (72.7–97.8) | 82.3% (75.7–88.9) | 53% (38.3–67.5) | 97.3% (92.2–99.4) | 5.07 | .13 |
| Urine clarity (catheterized specimens only) | 83.3% (51.6–97.9) | 86.2% (74.6–93.9) | 55.6% (30.8–78.5) | 96.2% (86.8–99.5) | 6.04 | .19 |
| Urine clarity (MSU only) | 94.1% (71.3–99.8) | 79.2% (68.0–87.8) | 51.6% (33.1–69.8) | 98.3% (90.8–100) | 4.52 | .07 |
| LE (\geq small) | 82.8% (64.2–94.2) | 95.4% (90.2–98.3) | 80.0% (61.4–92.3) | 96.1% (91.2–98.7) | 18 | .18 |
| Nitrite | 27.6% (12.7–47.2) | 97.7% (93.4–99.5) | 72.7% (39.0–94.0) | 85.8% (80.2–91.4) | 12.0 | .74 |
| ≥ 5 WBC/hpf | 86.2% (68.3–96.1) | 78.5% (71.4–85.5) | 47.2% (33.3–61.4) | 96.2% (90.6–99.0) | 4.01 | .18 |
| Bacteria on microscopy | 93.1% (77.2–99.2) | 40.0% (31.6–48.4) | 25.7% (17.4–34.1) | 96.3% (87.2–99.5) | 1.55 | .17 |
| \geq Small LE or positive nitrite (abnormal dipstick) | 82.8% (64.2–94.2) | 93.8% (88.2–97.3) | 75.0% (56.6–88.5) | 96.1% (91.0–98.7) | 13.40 | .18 |
| ≥ 5 WBC/hpf or bacteria on microscopy (abnormal microscopy) | 100% (88.1–100) | 32.3% (24.3–40.3) | 24.8% (17.0–32.6) | 100% (91.6–100) | 1.48 | — |
| Abnormal dipstick or abnormal microscopy | 100% (88.1–100) | 33.1% (25.0–41.2) | 25% (17.1–32.9) | 100% (91.8–100) | 1.49 | — |

Females made up 77% of the patients ($n = 122$). Seventy of the specimens (44%) were collected by catheterization, while 89 (56%) were clean-catch mid-stream specimens (MSU). Of the 51 children <2 years of age, 49 (96%) had catheterized specimens vs 21 of the children >2 years (19%). All of the children 2 years of age and younger were being evaluated for a fever without focus.

Of the 159 samples, 49 were cloudy (31%) and the remaining 110 were clear (69%) on visual inspection. The addition of acetic acid to urine samples that were not clear did not change any assessment of clarity. There were 29 positive cultures giving a prevalence of UTI in our sample of 18%. Females accounted for 24 of the positive cultures (83%). All positive cultures grew only 1 pathogen: *Escherichia coli* ($n = 22$), *Klebsiella pneumoniae* ($n = 2$), *Proteus mirabilis* ($n = 2$), *Pseudomonas aeruginosa* ($n = 1$), group B β -hemolytic streptococcus ($n = 1$), and *Staphylococcus epidermidis* ($n = 1$). Positive cultures were obtained by catheterization in 12 of the 29 cases and by MSU in the remaining 17.

One hundred thirty urine specimens were culture-negative, and of these 107 were clear on visual inspection giving a specificity of 82.3%. Of the 110 clear urine specimens, 107 were culture negative (ie, an NPV of 97.3%). The likelihood ratio for clear urine was .13 ($1 - \text{sensitivity} \div \text{specificity}$).

Comparison of urine clarity with standard urinalysis is shown in Table 1 along with 95% confidence intervals and likelihood ratios.

Of the 159 urine specimens obtained, there were disagreements about the clarity in 8. The κ value calculated for agreement between the 2 different clinical observers for assessment of urine clarity was .876.

There were 3 patients with clear urine who had a UTI (Table 2). Two were nontoxic-appearing infants <12 months of age being evaluated for fever without source. These 2 infants had negative urine dipsticks and <5 WBC/hpf, but they both had some bacteria on microscopy. One grew *E coli* and the other *K pneumoniae*. The third patient with clear urine was a

TABLE 2. Characteristics of Three Children With UTI Who Had Clear Urine on Visual Inspection

| Age and Gender | Entrance Complaint | History and/or Physical Examination Findings | Method of Collection | Dipstick Urinalysis* | Pyuria | Bacteria on Microscopy | Organism (CFU/mL) |
|----------------|--------------------|--|----------------------|----------------------|-------------|------------------------|---|
| 2 mo, male | Fever | No focus of infection and negative blood culture | Catheterization | Negative | <5 WBC/hpf | +1 | <i>E coli</i> (>10 ⁴) |
| 7 mo, female | Fever | No focus of infection and negative blood culture | Catheterization | Negative | <5 WBC/hpf | +1 | <i>K pneumoniae</i> (>10 ⁵) |
| 19 y, female | Abdominal pain | Dysuria | Midstream | Negative | >15 WBC/hpf | +3 | <i>E coli</i> (>10 ⁵) |

*Negative dipstick includes both negative findings for LE and nitrites.

19-year-old female with abdominal pain and dysuria. She had a negative urine dipstick but >15 WBC/hpf and large bacteruria on microscopy and grew *E coli*.

DISCUSSION

Up to 45% of children diagnosed with a UTI will have a genitourinary abnormality requiring treatment.^{9,10} A missed diagnosis of UTI could result in the failure to appropriately treat a patient and possibly lead to renal damage.^{5,10} Many previous studies have examined the utility of urine dipsticks and microscopy in the rapid detection of UTIs in children.¹⁻⁶ None of these tests have produced a screening study with 100% sensitivity. Therefore, urine cultures are routinely obtained on all specimens.

There are anecdotal observations that urine, which is clear on visual inspection, will not result in growth of a urinary pathogen. There are 2 studies that examined the association of crystal clear urine with the absence of a UTI.^{7,8} In the first study, 376 urine samples were obtained from patients 6 weeks to 17 years of age. Eighty-five percent of these specimens were midstream clean-catch, 13% bag specimens, and 2% suprapubic aspirations. The presence of clear urine had an NPV for the absence of a UTI of 100%. In the second study, 500 samples from children 6 weeks to 18 years of age were examined.⁸ Fifty-seven percent were obtained by midstream clean-catch, 42% from bag specimens, and 1% were obtained by catheterization. Three hundred eighty-six of the urine samples were clear (77%) and 114 were cloudy (23%). Three hundred twenty-two of the clear specimens had either a negative culture or a culture with <10 000 CFU/mL. Forty-six of the clear specimens grew 10 000 to 100 000 CFU/mL and 18 grew >100 000 CFU/mL. UTI was diagnosed in 15 of these patients; the others were considered contaminants. The NPV was 96%. This study used a large number of bag urine specimens (42%), which have a high rate of contamination. In our study, we used only catheterized and MSU specimens to decrease the possibility of contamination commonly found in bag specimens.¹⁰ The method by which a urine sample is obtained does seem to change the sensitivity of the test (Table 1).

The clinical usefulness of a diagnostic test is primarily determined by the accuracy, with which it either identifies or excludes its target disorder. In this study, the purpose was to determine whether clear urine by visual inspection was predictive of a nega-

tive urine culture. The NPV for children with clear urine was 97.3%, which was better than that for LE, nitrites, WBC/hpf, and the presence of bacteria on microscopy (Table 1). Only abnormal microscopy (ie, \geq WBC/hpf or bacteria on microscopy) performed better.

As can be seen in Table 1, LE has the best combination of sensitivity and specificity. The value of 95.4% for its specificity is much higher than in previously reported literature. It is not clear to us why it achieved such a high specificity in our population. This high specificity is the reason that LE has such a high likelihood ratio because the calculation is: sensitivity \div 1 - specificity.

The problem with NPV and PPV is that they are dependent on the prevalence of disease in the population. If prevalence decreases, PPV will decrease with it and the NPV will increase. The prevalence of UTI in our sample of 18% is higher than most quoted prevalence rates in populations of children having a fever without source. An average age of 5.8 years in our group of children likely accounts for this increased prevalence.

Likelihood ratios measure the accuracy of a diagnostic test and are not dependent on the prevalence of the disease in the population.^{11,12} They indicate how much a test result will raise or lower the posttest probability of disease. A likelihood ratio of 1 indicates that the posttest probability is the same as the pretest probability and, therefore, the test in question is of no clinical benefit. If the pretest probability of a UTI is 5%, the pretest odds are .053 (probability \div 1 - probability). If the urine sample is clear, the posttest odds are .0068 (pretest odds \times likelihood ratio). This gives a posttest probability of .7% (posttest odds \div 1 + post test odds). Similarly, if the urine is not clear, then the posttest probability of a UTI is 21%.

Comparisons of the likelihood ratios of urine clarity with items on the standard urinalysis and microscopic examination of urinary sediment for WBCs and bacteria in our specimens are displayed in Table 1. Patients with insignificant bacteruria can be identified with significant accuracy by finding: 1) clear urine on visual inspection, 2) absence of LE on urinalysis, 3) finding <5 WBC/hpf, or 4) the absence of bacteria on microscopy. However, assessment of urine clarity is simple, can quickly be performed at the bedside, and is inexpensive.

Recently, there has been considerable interest in clinical prediction rules. If properly derived and val-

idated, clinical rules can greatly increase or decrease the probability that a patient has the disease of interest. As a result, a set of methodological standards for their development and validation has been formulated.¹³ It seems reasonable that a combination of several findings, including an assessment of urine clarity, may determine the necessity to perform a urine culture in children being assessed for the possibility of a UTI. This remains to be seen.

There are several limitations to this study. First, using urine clarity as a screening tool requires accuracy in performing visual inspection. We used 2 independent observers and achieved a κ value of .876. A high κ value indicates that different examiners may reliably assess a variable. Based on guidelines suggested by Landis and Koch,¹⁴ this is considered nearly perfect. However, considering that we had only 3 patients with positive cultures and clear urine a disagreement on 8 of 159 specimens may be significant and warrants further evaluation. Second, it is a preliminary study attempting to define a method that may reveal the absence of significant bacteruria. A larger, prospective study needs to be performed to confirm these findings and to potentially derive a useful clinical prediction rule.

CONCLUSION

Finding clear urine on visual inspection cannot eliminate the possibility that a child has a UTI. If the pretest probability of a UTI in a certain child is 5%, the finding of a clear urine specimen lowers this probability to <1%. Assessment of urine clarity is a reproducible test that offers the advantages of being simple, fast, and inexpensive. The finding of clear

urine should be considered a reasonable and relatively effective bedside screen for the presence of a UTI.

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