Urine Specific Gravity and the Accuracy of Urinalysis

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abstract

BACKGROUND: A recent study in young infants found that different cutoffs maximized the accuracy of the urine white blood cell count in dilute versus concentrated urine samples. We aimed to confirm this finding and to determine its impact on clinical care.

METHODS: We conducted a retrospective analysis of data gathered on consecutive children <24 months of age with visits to the emergency department during a 5-year period. We evaluated the accuracy of screening tests for urinary tract infection (UTI) in dilute and concentrated urine samples. We also calculated the number of children who would have been treated differently in a hypothetical cohort of 1000 children presenting with fever had urine specific gravity (SG) been taken into consideration.

RESULTS: We included 10 078 children. The ability to rule in UTI (as measured by the positive likelihood ratio [LR]) was similar in dilute and concentrated urine for the leukocyte esterase test (11.76 vs 10.71, respectively). The positive LR for urine white blood cell count per high-powered field was higher in dilute urine (9.83 vs 6.12). In contrast, the positive LR for the nitrite test was lower in dilute urine (20.54 vs 47.44). Despite these differences, we found little change in the number of children treated with antibiotics in predictive models that took urine SG into consideration.

CONCLUSIONS: Although we found that urine SG influences the accuracy of some components of the urinalysis, its inclusion in the decision-making process had negligible effect on the clinical care of children with UTI.

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Dr Shaikh designed the work, was involved in data acquisition, analysis, and interpretation, and helped draft the manuscript; Ms Shope contributed to data analysis, interpretation of data, and drafting and revising the manuscript; Ms Kurs-Lasky was involved in data cleaning and analysis, interpretation of data, and revising the manuscript critically for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

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WHAT'S KNOWN ON THIS SUBJECT: A recent study found that different cutoffs maximized the accuracy of the urine white blood cell count test in dilute versus concentrated urine samples, suggesting that urine specific gravity should be considered when interpreting urinalysis results.

WHAT THIS STUDY ADDS: Although urine specific gravity influences the accuracy of some components of the urinalysis, its inclusion in the decision-making process did not appreciably change the number of children receiving inappropriate treatment for urinary tract infection.

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Clinicians rely on the urinalysis to make a presumptive diagnosis of urinary tract infection (UTI) in children. An important part of the urinalysis is quantification of the degree of pyuria by enumerating urinary white blood cells (WBCs). Clinicians have been concerned that the WBC counts obtained may be influenced by the specific gravity (SG) of the urine sample. Indeed, a recent study by Chaudhari et al[1] in children <3 months of age suggested that urine SG should be considered when interpreting results of a urine WBC count. This recommendation was based on their observation that different cutoffs maximized the accuracy of the WBC test in dilute versus concentrated urine samples, suggesting the use of distinct diagnostic cutoffs for WBC count when dealing with dilute versus concentrated urine.

We performed this study to assess the reproducibility of this finding in a larger cohort that included older children and to explore how the incorporation of SG into the clinical decision-making process affects the number of children receiving inappropriate treatment (ie, children with UTIs who are misdiagnosed as not having a UTI and therefore not treated and children without a UTI who are or inappropriately treated with antimicrobial agents).

METHODS

We conducted a retrospective analysis of data gathered in consecutive visits to the emergency department at the Children's Hospital of Pittsburgh between 2007 and 2013. We included children <24 months of age who underwent bladder catheterization and who had both an automated urinalysis performed (using the Iris iQ200 Elite urine microscopic analyzer) and a urine culture obtained within a 3-hour window of each other. We excluded children with major genitourinary anomalies (as defined by billing codes) and children with a missing result for the leukocyte esterase (LE) test. In children with multiple visits, 1 visit was randomly selected (Supplemental Fig 1). Each child either had a standard automated urinalysis, measuring LE, nitrites, white blood cell count per high-powered field (WBC/hpf), and bacteria per high-powered field (hpf), or an "enhanced" urinalysis,[2] measuring LE, nitrites, protein, blood, WBC per mm^3, and bacteria on Gram-stain (with the last 2 components performed manually by a laboratory technician). The test ordered was at the discretion of the provider. We considered the LE result to be positive if the reading was 1+, 2+, or 3+ (0 or trace was considered a negative result). We defined UTI as the growth of at least 100 000 colony-forming units per milliliter of a uropathogen from specimens obtained by using the clean catch method and the growth of 50 000 colony-forming units per mL from specimens obtained via catheterization.[3] Cultures not meeting these criteria were categorized as having a negative result. Because 1 of our goals was to evaluate the accuracy of pyuria according to urine SG, we did not require pyuria for the diagnosis of UTI.

We evaluated the accuracy of screening tests frequently used for the diagnosis of UTI by comparing the sensitivity, specificity, and likelihood ratios (LRs) in dilute versus concentrated urine samples. We defined dilute and concentrated as having SG of <1.015 and ≥1.015, respectively.

To give clinicians a better understanding of the implications of including SG in their diagnostic process, we calculated, for each component of the urinalysis alone and then for combinations of components, the number of children who would have been overtreated or missed with and without SG being considered in the decision-making process. To do this, we constructed, for each component of the urinalysis, 2 logistic models, 1 with SG and a second without it. For example, for the nitrite test, we constructed 1 model that included nitrite and SG as predictors and a second model that included only the nitrite test. We arrived at β coefficients for each predictor in these models using the data set described above. After obtaining these coefficients, we calculated, for each child in the database, the probability of UTI. Because clinicians ultimately will need to make a dichotomous (yes versus no) decision regarding the use of antibiotics, we dichotomized the obtained probabilities using a cutoff of 5% (ie, we assumed that children with a calculated probability of UTI of ≥5% are diagnosed with a UTI and treated with antibiotics). The 5% treatment threshold was based on previous studies,[4,5] which found that clinicians would likely treat a child for a UTI if the probability of UTI was between 5% and 25%. We then tallied the number of children in our database with true UTI who did not receive antibiotics (hereinafter referred to as "missed") and, likewise, the number of children without UTI who were inappropriately treated with antibiotics. Because the total number of children with each test varied in our database, instead of presenting results for our cohort, we present results for a hypothetical cohort of 1000 children presenting with fever, of whom 70 were assumed to have a UTI (prevalence of UTI in such a cohort is ∼7%).[6] For each model, we used the proportion of children with UTI who did not receive antibiotics to calculate how many of the 70 children with UTI in our hypothetical cohort would have been missed. Similarly, we used the proportion of children without UTI who received antibiotics to calculate how many of the 730 children without UTI in our hypothetical cohort would have received

antimicrobial agents inappropriately. We performed the analyses above using SG first as a dichotomous variable then as a continuous variable. As a sensitivity analysis, we repeated the above analysis using a treatment threshold of 25%.

RESULTS

Table 1 describes the demographic characteristics of our sample. Of 10 078 children included, 3966 (39.4%) had concentrated urine (defined as SG ≥1.015).

The prevalence of UTI was lower in concentrated urine than in dilute urine (4.8% in concentrated urine versus 7.0% in dilute urine); the SG test by itself had a positive LR of 0.77 (confidence interval [CI] 0.68–0.87) and a negative LR of 1.15 (CI 1.09–1.22). The area under the receiver operating characteristic (ROC) curve for the SG test was 0.55.

Table 2 shows accuracy of the various screening tests, as measured by the LR, according to whether the urine was dilute (SG <1.015) or concentrated (SG ≥1.015) for the cutoff most frequently used in practice. Data for other cutoffs are shown in Supplemental Tables 4–9. For some tests (ie, LE), the ability to rule in UTI (as measured by the positive LR) was similar in dilute and concentrated urine. Other tests were either less useful (ie, WBC/hpf and WBC per mm^3) or more useful (ie, nitrite) in ruling in UTI when the urine sample was concentrated. For WBC per mm^3, the cutoff that resulted in a positive LR of 10 (suggested by Chaudhari et al[1] as the ideal cutoff for the test) was 10 in dilute and 15 in concentrated urine (Supplemental Table 6). The corresponding numbers for WBC/hpf were 5 and 8, respectively (Supplemental Table 5). The percentages of children with concentrated urine and values between these cutoffs (ie, the number of children affected by having 2 cutoffs) were 1.7% and 2.5% for the WBC per mm^3 and WBC/hpf tests, respectively. The negative LRs, which measure the ability of a test to rule out disease, were similar for all tests regardless of urine SG.

Table 3 shows the clinical implications of considering SG in the diagnosis and treatment of UTIs when using a treatment threshold of 5%. We found no change in treatment with or without the inclusion of SG in predictive models for the components of the urinalysis considered in isolation or for the urine dipstick. For the urinalysis as a whole, when SG was included, an additional 1.2% (11 of 930) of children without UTI received antibiotics. Results were similar with a treatment threshold of 25% (Supplemental Table 9); although differences were noted for specific components of the urinalysis, the number of children receiving inappropriate treatment was similar when examining the dipstick or urinalysis test as a whole regardless of whether SG was considered. Results of our models were similar when SG was entered in as a continuous variable (data not shown).

DISCUSSION

Although we included older children in our study, like Chaudhari et al,[1] we found that SG influences the accuracy of some components of the urinalysis (WBC/hpf, WBC per mm^3, and nitrite). However, by investigating the likely clinical ramifications of the noted changes in accuracy on clinical decision-making, we found that the inclusion of SG in the decision-making process would likely not result in appreciable changes to clinical practice; regardless of whether SG was

TABLE 1 Characteristics of the Study Population

	UTI (*n* = 617; 6.1%)	No UTI (*n* = 9461; 93.9%)
Age, mo, median (IQR)	6.0 (3.0–11.0)	7.0 (2.0–13.0)
Girls, *n* (%)	544 (88.2)	6199 (65.5)
Race, *n* (%)		
African American	88 (14.3)	2650 (28.0)
White	500 (81.0)	6135 (64.8)
Other	25 (4.0)	425 (4.5)
Multiracial	0	9 (0.1)
Missing	4 (0.6)	242 (2.6)
Ethnicity, *n* (%)		
Hispanic	2 (0.3)	80 (0.8)
Not Hispanic	607 (98.4)	9153 (96.7)
Missing	8 (1.3)	228 (2.4)
Temperature, °C, median (IQR)	39.4 (38.9–40.0)	38.8 (38.2–39.4)
SG, *n* (%)		
<1.015	427 (69.2)	5685 (60.1)
≥1.015	190 (30.8)	3776 (39.9)

IQR, interquartile range.

TABLE 2 LRs (With 95% CIs) of Screening Tests for the Diagnosis of UTI According to SG

Test Cutoff, Sample Size	Positive LR (95% CI)		Negative LR (95% CI)	
	SG <1.015	SG ≥1.015	SG <1.015	SG ≥1.015
LE test ≥1+ (n = 10 078)	11.76 (10.65–12.99)	10.71 (9.38–12.23)	0.14 (0.11–0.18)	0.22 (0.16–0.29)
Nitrite test positive result (n = 10 076)	20.54 (16.11–26.20)	47.44 (32.02–70.29)	0.68 (0.63–0.73)	0.62 (0.55–0.69)
WBC/hpf ≥5 (n = 2163)	9.83 (8.01–12.06)	6.12 (4.95–7.57)	0.18 (0.12–0.28)	0.15 (0.06–0.36)
WBC per mm^3 ≥10 (n = 7797)	10.61 (9.47–11.89)	7.16 (6.36–8.07)	0.19 (0.15–0.24)	0.17 (0.12–0.25)
Bacteria per hpf ≥ few (n = 1240)	3.62 (3.04–4.32)	3.55 (2.79–4.53)	0.24 (0.16–0.37)	0.24 (0.11–0.53)
Bacteria on Gram-stain ≥ any (n = 7781)	18.11 (15.65–20.97)	33.38 (25.67–43.41)	0.20 (0.16–0.25)	0.28 (0.22–0.36)

considered, the number of children with a UTI who would have been missed and the number of children without a UTI who would have inappropriately received antimicrobial treatment were almost equivalent. Furthermore, when changes were observed, they were in most cases detrimental (ie, increase in antimicrobial overuse without a decrease in missed UTI or a decrease in antibiotic overuse at the expense of a large number of missed UTIs). There are several explanations for this apparent paradox. First, as reflected by its poor test characteristics (area under the ROC curve of 0.55), SG alone was a poor predictor of UTI; adding it to the mix of tests in the urinalysis would add much "noise" and little "signal." Second, as an effect modifier, the influence of SG on various components of the urinalysis were in opposing directions; although some tests performed worse in concentrated urine, others performed better. Taken together, these resulted in little change in the accuracy of the urinalysis. Third, because many components of the urinalysis (eg, LE and bacteria per hpf) were not affected by SG, its overall influence on the accuracy of the urinalysis as a whole was negligible. This is especially important because in many settings, the LE test serves as the main test used for decision-making, and this test was not influenced by urine SG. Fourth, even when SG was influential as an effect modifier (ie; for WBC per mm, WBC/hpf, and nitrite), its influence was minor; this is apparent by looking at the largely overlapping ROC curves with and without SG for these urine WBC counts (Supplemental Fig 2) and by the relatively small difference in the LRs in dilute and concentrated urine for these tests (Table 2). Finally, the identical numbers of children who would have been missed or overtreated if SG was considered (Table 3) for the 3 components of the urinalysis that were influenced by SG reflects the fact that minor differences in the LR are unlikely to influence clinicians' actions. For example, although large differences in the positive LR were observed for the nitrite test in dilute versus concentrated urine (21 vs 47, respectively), a positive test result would have likely led to the same clinical action (ie, the clinician would likely diagnose a UTI regardless of whether the urine was dilute or concentrated). This largely held true whether using 5% or 25% probability of UTI as the clinical threshold for treatment or whether SG was dichotomized or continuous.

Intuitively, one could posit that if the urine sample is dilute, a lower cutoff (fewer cells per hpf or mm^3) should be used. This principle (ie, lower

TABLE 3 Influence of SG on the Treatment of UTI by Using a Treatment Threshold of 5% in a Hypothetical Cohort of 1000 Children, 70 of Whom Have a UTI

Test (Cutoff)	Without SG in Model		With SG in Model[a]	
	Of 70 With UTI, No. Missed[b]	Of 930 Without UTI, No. Treated With Antibiotics[b]	Of 70 With UTI, No. Missed[b]	Of 930 Without UTI, No. Treated With Antibiotics[b]
LE ≥1+	10	68	10	68
Nitrite test positive result	45	12	45	12
WBC per mm^3 ≥10	11	87	11	87
WBC/hpf ≥5[c]	10	100	10	100
Bacteria per hpf ≥ few	13	210	13	210
Bacteria on Gram-stain ≥ any	15	33	15	33
Dipstick[c]	8	75	8	75
Urinalysis[d]	6	95	6	106

[a] SG was dichotomized by using a cutoff of 1.015.
[b] Missed indicates that the patient had a UTI but was not treated with antibiotics.
[c] Dipstick consisted of LE and nitrite tests using the cutoffs provided above for each of the components.
[d] Urinalysis includes the dipstick, WBC/hpf, and bacteria per hpf using the cutoffs provided above for each of the components.

cutoffs are needed in dilute samples to achieve same positive LR) seems to be borne out by the results we observed for the WBC counts but not for the number of bacteria. The reasons for this discrepancy are unclear. It is also unclear why the accuracy of the nitrite test varies according to the concentration of the urine sample. Perhaps children who are relatively dehydrated (ie, children with a higher urine SG) urinate relatively less frequently, increasing the likelihood of conversion of nitrates to nitrites by urine bacteria.[7]

This study has some limitations. Children on antibiotics or immunosuppressants were not excluded, which may have caused inaccurate results for a small number of subjects. Furthermore, the number of subjects with high SG who had a UTI was small (n = 190) relative to the number of subjects in other groups. Strengths of our study included the relatively large sample size and analysis of the clinical ramifications of including SG in the decision-making process.

CONCLUSION

Although urine SG influences the accuracy of some components of the urinalysis, its inclusion in the decision-making process had little effect on the clinical care of children with UTI.

ABBREVIATIONS

hpf: high-powered field
LE: leukocyte esterase
LR: likelihood ratio
ROC: receiver operating characteristic
SG: specific gravity
UTI: urinary tract infection
WBC: white blood cell
WBC/hpf: white blood cell count per high-powered field

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