Diagnostic Accuracy of the Urinalysis for Urinary Tract Infection in Infants <3 Months of Age

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abstract

BACKGROUND: The 2011 American Academy of Pediatrics urinary tract infection (UTI) guideline suggests incorporation of a positive urinalysis (UA) into the definition of UTI. However, concerns linger over UA sensitivity in young infants. Infants with the same pathogenic organism in the blood and urine (bacteremic UTI) have true infections and represent a desirable population for examination of UA sensitivity.

METHODS: We collected UA results on a cross-sectional sample of 276 infants <3 months of age with bacteremic UTI from 11 hospital systems. Sensitivity was calculated on infants who had at least a partial UA performed and had ≥50 000 colony-forming units per milliliter from the urine culture. Specificity was determined by using a random sample of infants from the central study site with negative urine cultures.

RESULTS: The final sample included 245 infants with bacteremic UTI and 115 infants with negative urine cultures. The sensitivity of leukocyte esterase was 97.6% (95% confidence interval [CI] 94.5%–99.2%) and of pyuria (>3 white blood cells/high-power field) was 96% (95% CI 92.5%–98.1%). Only 1 infant with bacteremic UTI (Group B *Streptococcus*) and a complete UA had an entirely negative UA. In infants with negative urine cultures, leukocyte esterase specificity was 93.9% (95% CI 87.9 – 97.5) and of pyuria was 91.3% (84.6%–95.6%).

CONCLUSIONS: In young infants with bacteremic UTI, UA sensitivity is higher than previous reports in infants with UTI in general. This finding can be explained by spectrum bias or by inclusion of faulty gold standards (contaminants or asymptomatic bacteriuria) in previous studies.

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WHAT'S KNOWN ON THIS SUBJECT: The sensitivity of the urinalysis (UA) traditionally has been considered suboptimal in young infants. Whether the finding of a negative UA and a positive urine culture represents a false-negative UA versus a false-positive urine culture remains unclear.

WHAT THIS STUDY ADDS: In infants <3 months with bacteremic urinary tract infection, a condition that represents true infection, the UA sensitivity is higher than previously reported for urinary tract infection in general, suggesting that the UA is reliable even in young infants.

The sensitivity of the urinalysis (UA) for the diagnosis of urinary tract infection (UTI) in children generally has been reported to be 75% to 85%.[1–6] Because of this suboptimal sensitivity, the urine culture is considered to be the gold standard for the diagnosis of UTI. However, the findings of a positive urine culture in a patient with a negative UA also may reflect a false-positive urine culture due to asymptomatic bacteriuria or contamination.[7–10] The 2011 American Academy of Pediatrics' (AAP) UTI guideline suggests that the diagnosis of UTI should require an abnormal UA in addition to a positive urine culture.[4] However, these guidelines do not include infants <2 months, and young infants with a negative UA and a positive urine culture are generally considered to have UTI.[11–13]

Bacteremic UTI represent a unique and desirable condition in which to assess the sensitivity of the UA. Infection with the same organism in the blood and urine renders contamination or asymptomatic bacteriuria extremely unlikely, thereby minimizing the probability that the urine culture represents a false positive.

The aim of this study was to calculate the sensitivity of the UA in a multicenter sample of infants <3 months with bacteremic UTI. UA specificity was calculated by using a separate sample of similar-aged infants with negative urine cultures.

METHODS

Setting

A multicenter database of infants <3 months with bacteremic UTI was assembled to analyze management and outcomes for this condition. This investigation included 276 infants from 20 hospitals at 11 hospital systems (see Acknowledgments) between 1998 and 2013. The central site for the study was Santa Clara Valley Medical Center, in San Jose, CA. All sites had existing databases that included infants with bacteremic UTI. Each site obtained additional independent institutional review board approval for this study. Informed consent was waived.

Subjects

Infants were included if they were <3 months of age and had the same pathogenic organism isolated from blood and urine. The primary aim of the initial investigation was to examine parenteral antibiotic duration and outcomes. Therefore, infants were excluded if they had major comorbidities (defined as neuromuscular conditions such as spina bifida, previous urologic surgery other than circumcision, or immunodeficiency), if they were managed in the ICU, or if they had indwelling urinary or central venous catheters at the time the cultures were drawn. For this secondary analysis, infants were excluded if no UA was performed or if the urine culture grew <50 000 colony-forming units/milliliter (CFU/mL), the AAP threshold for UTI.[4] However, UA findings from this subgroup are presented.

Data Collection and Variables

Bacteremic UTIs at each site were originally identified by using existing microbiology databases. Site investigators reviewed charts by using a protocol specifically designed for this study. Data on specific components of the UA (white blood cells/high-power field [WBC/HPF], bacteria, nitrites, leukocyte esterase [LE]) were collected for each infant. To avoid verification bias, infants with partial UA results were included. Given that the terminology of UA results varied by hospital, we created a uniform categorization for the purposes of this study. For urinary WBC/HPF, the categories (0–3, 4–10, 11–20, 21–50, and >50 WBC/HPF) reflect an amalgamation of categories used at the participating hospitals. If a UA WBC/HPF result category differed from that used in this study, placement was determined by the middle value in the reported range. For example, 11–25 WBC/HPF was placed in the 11–20 category and 3–5 WBC/HPF was placed in the 4–10 category. The exceptions were 5 patients with a result of 2–5 WBC/HPF, which represented the second lowest category for the reporting laboratory (0–1 WBC/HPF was the lowest). These results were placed in the 4–10 WBC/HPF category. Categories were also created for urine culture CFU/mL (<10 000, 10–25 000, 25–50 000, 50–100 000 and >100 000). Three infants had culture reports of 10 000–100 000 CFU/mL. These results were placed in the 50 000–100 000 category.

The AAP recommendation to include the UA to establish the diagnosis of UTI suggests using pyuria and/or bacteriuria. The suggested threshold for pyuria is 5 WBC/HPF, but there is no quantitative recommendation for bacteriuria. We therefore created 2 definitions of a positive UA by using AAP criteria: (1) pyuria (>3 WBC/HPF) and/or any bacteriuria on the UA and (2) pyuria (>10 WBC/HPF) and/or any bacteriuria on the UA.

The primary objective of the study was to assess the sensitivity of the UA in this sample of infants with bacteremic UTI. However, to better interpret the sensitivity of differing thresholds of the various components of the UA, we also assembled a sample of 115 similarly aged infants with negative urine cultures to calculate UA specificity. These infants were randomly selected (1 in every 10 infants) from a microbiology database at the central site of ~1200 infants <90 days who underwent a workup for serious bacterial infection between 2005 and 2010.[14]

Statistical calculations were performed by using Stata 13 (Stata Corp, College Station, TX). To compare characteristics of the 2 samples, the Fisher's exact test or χ^2 test were used, as appropriate, to

compare proportions, and the Wilcoxon rank sum test was used to compare age. Given that the sensitivity and specificity of the UA were calculated in 2 separate samples of patients, likelihood ratios and predictive values would be misleading and were not calculated, and receiver operator characteristics curves were not created.

RESULTS

A total of 276 infants with bacteremic UTI were identified, from which 31 (11%) were excluded: 12 infants had no UA performed and 19 infants had urine cultures with <50 000 CFU/mL. Baseline characteristics of the remaining 245 infants and the 115 infants with negative urine cultures are depicted in Table 1. For the 245 included infants with bacteremic UTI, 35 had missing results for LE, 2 for nitrites, 22 for WBC microscopy (although WBC dipstick results were available for 13 of these infants) and 45 for bacteria. Complete UA results were available for 178 infants.

Table 2 lists the results for the various components of the UA in infants with bacteremic UTI and infants with negative urine cultures. Of the various individual UA components, LE had the highest sensitivity (97.6%, 95% confidence interval [CI] 94.5%–99.2%) and nitrites had the highest specificity (100%, 95% CI 96.8%–100%). Four infants with bacteremic UTI and 4 infants with negative urine cultures had "trace" LE. Categorizing "trace" results as negative reduced the LE sensitivity to 95.7% and increased the specificity to 97.4%. For the 4 infants with bacteremic UTI with "trace" LE, all 4 had bacteriuria on the UA, 3 had 4 to 10 WBC/HPF and 1 had 0 to 3 WBC/HPF.

Table 3 reports the sensitivity and specificity of individual and aggregate UA components. Selecting an aggregate definition of a positive UA that includes pyuria (>3 WBC/HPF) and/or any LE, the sensitivity (99.5%, 95% CI 98.5% –100%) and specificity (87.8%, 95% CI 80.4%–93.2%) were both higher than those calculated by using the AAP definition of a positive UA (pyuria >3 WBC/HPF or bacteriuria), where sensitivity was 98.3% (95% CI 95.2%–99.7%) but specificity was only 63.5% (54%–72.3%). An aggregate definition that included any positive UA component was highly sensitive (99.4% in infants with complete UAs, 98.4% in infants with incomplete UAs) but was less specific (60%, 95% CI 50.4% –69%) than the aggregate of pyuria and/or LE. There was 1 infant in the bacteremic group with a complete UA that was entirely negative. This infant was a 64-day old girl who had Group B *Streptococcus* (GBS) in the blood and urine (>100 000 CFU/mL).

UA performance did not differ significantly between infants ≤ or >30 days of age (Table 3). For infants ≤30 days of age, all 82 who had both LE and microscopy for WBC/HPF performed were positive for 1 or both of these tests. UA performance did not change significantly if infants with bag specimens were excluded: the UA sensitivity changed by <0.5% and the UA specificity changed by <1% for each component of the UA.

TABLE 1 Characteristics of Infants With Bacteremic UTI and Infants With Negative Urine Cultures

Variable	Bacteremic UTI, *n* = 245	Negative Urine Culture, *n* = 115	*P*
Age, d, median (IQR)	37 (18–59)	37 (16–59)	.48
Age ≤30 d, %	41.2	42.6	.80
Age ≤14 d, %	19.2	22.6	.45
Boys, %	60	50.4	.09
Urine collection method documented, %	75	96.5	<.001
Urine collection method, if documented, %			.003
Catheterization	98.1	91	
Bag/clean catch	1.9	9	
Organism		—	—
E coli	91.0		
Enterobacter spp	3.7		
Klebsiella spp	2.5		
Klebsiella+Pseudomonas	0.8		
Enterococcus spp	0.8		
Group B Streptococcus	0.4		
Staphylococcus aureus	0.4		
Citrobacter	0.4		

IQR, interquartile range; —, non-applicable.

Urine culture and UA results for the 19 infants with bacteremia and urine culture growth <50 000 CFU/mL are depicted in Table 4. All infants with *Escherichia coli* had a positive UA but only 1 infant with a non–*E coli* organism had a positive UA.

DISCUSSION

This study sheds new light on the diagnostic characteristics of the UA in young infants. A definition of a positive UA that includes pyuria and/or positive LE was highly sensitive and specific. All but 1 of 203 infants with bacteremic UTI and recorded UA results for both LE and WBC/HPF were positive for 1 or both of these tests, and the one infant with negative results for these components was infected with an organism (GBS) not commonly described as a uropathogen. A negative LE and the absence of pyuria were also fairly specific (87.8%) in infants with negative urine cultures. UA bacteria, however, demonstrated poor specificity, suggesting that this component of the UA is not as useful as LE or pyuria for ruling in a UTI.

There are 2 possible explanations for the near-perfect sensitivity of the UA in infants with bacteremic UTI. One explanation is that the UA is in fact

TABLE 2 Urinalysis Results in Infants With Bacteremic UTI and Infants With Negative Urine Cultures

Urinalysis Component	Bacteremic UTI	Negative Urine Culture
Leukocyte esterase, total *n*	210	115
Negative	5 (2.4)	108 (93.9)
Trace, small, or 1+	18 (8.6)	6 (5.2)
Moderate, positive, or 2+	74 (35.2)	0 (0)
Large or 3+	113 (53.8)	1 (0.9)
Nitrites, total *n*	243	115
Negative	147 (60.5)	115 (100)
Positive	96 (39.5)	0 (0)
WBC/HPF, total *n*	223	115
0–3	9 (4)	105 (91.3)
4–10	34 (15.3)	7 (6.1)
11–20	34 (15.3)	1 (0.9)
21–50	35 (15.7)	2 (1.7)
>50	111 (49.8)	0 (0)
WBC, dip only, total *n*	13	—
Negative	1 (7.7)	
Small	1 (7.7)	
Moderate	6 (46.2)	
Large	5 (38.5)	
Bacteria, total *n*	200	115
None	16 (8)	76 (66.1)
Few, occasional, rare, small, trace, or 1+	58 (29)	31 (37)
Moderate, present, or 2+	60 (30)	7 (6.1)
Many or 3–4+	66 (33)	1 (0.9)

Unless otherwise noted, results are shown as *n* (%). —, non-applicable.

a highly sensitive test, and that previous reports of suboptimal UA sensitivity have been flawed by a faulty gold standard (urine cultures that are positive because of asymptomatic bacteriuria or contamination). The second explanation is spectrum bias: screening tests are more sensitive when disease is severe.[15]

Whether bacteremic UTI represents a severe form of UTI is controversial. Several previous investigations comparing clinical characteristics of infants with UTI with and without bacteremia have demonstrated only minor or no differences between these 2 groups at presentation. In a sample of 134 children (88 of whom were <3 months) with bacteremic UTI matched with 134 children with UTI and no bacteremia, Honkinen et al[16] demonstrated that bacteremic patients were more likely to have feeding problems (20% vs 10%, $P = .02$) and had higher C-reactive protein concentrations (115 vs 76 mg/mL, $P < .01$), but had no differences in highest temperature, duration of fever, irritability, or serum WBC values. Schnadower et al[17] demonstrated that infants 29 to 60 days of age with UTI and bacteremia were more likely to have ≥1250 peripheral bands per microliter (adjusted odds ratio 3.8, 95% CI 2.3–6.2) or an absolute neutrophil count of <1500 cells/μL (adjusted odds ratio 9.0, 95% CI 4.0–19.9) than infants with UTI and negative blood cultures, but were no more likely to appear clinically ill on presentation. Of note, the definition of UTI did not require a positive UA in either of these studies. Consequently, some of the patients with nonbacteremic UTI may not have had true UTI, which could account for these few reported differences. In a prospective study by Newman et al,[6] bacteremic and nonbacteremic infants <3 months with UTI did not differ in clinical appearance or maximum temperature. Finally, Hoberman et al[18] demonstrated that patients with bacteremic UTI were younger than those with nonbacteremic UTI, and had slightly higher serum WBC findings (24.9 vs 20.3, $P = .04$), but did not have significant differences in highest temperature, duration of fever before or after antibiotics, or C-reactive protein values. Even if bacteremic UTI is indeed a more severe form of disease, it is reassuring that the UA is highly reliable for severe UTIs.

TABLE 3 Sensitivity and Specificity of Individual and Aggregate Components of the Urinalysis

Urinalysis Component	Sensitivity[a] (95% CI)	Specificity (95% CI) *n* = 115
Individual components		
Any LE, "trace" included	97.6 (94.5–99.2)	93.9 (87.9–97.5)
Any LE, "trace" categorized as negative	95.7 (92.0–98.0)	97.4 (92.5–99.5)
+ for nitrites	39.5 (33.3–46)	100 (96.8–100)
Pyuria, >3 WBC/HPF	96 (92.5–98.1)	91.3 (84.6–95.6)
Pyuria, >10 WBC/HPF	80.7 (74.9–85.7)	97.4 (92.6–99.5)
Any bacteria	92 (87.3–95.4)	66.1 (56.7–74.7)
Aggregate components[a]		
Nitrites or LE, *n* = 209	97.6 (95.5–99.7)	93.9 (87.8–97.5)
Pyuria >3 WBC/HPF or any bacteriuria, *n* = 197	98.3 (95.2–99.7)	63.5 (54–72.3)
Pyuria >10 WBC/HPF or any bacteriuria, *n* = 197	97 (94.5–99.4)	65.2 (55.8–73.9)
Pyuria >3 WBC/HPF or any LE, *n* = 203	99.5 (98.5–100)	87.8 (80.4–93.2)
Any positive UA (pyuria ≥3 WBC/HPF), infants with complete UA results only, *n* = 178	99.4 (98.3–100)	60 (50.4–69)
Infants ≤30 d, *n* = 72	100 (95–199)	53.1 (38.3–67.5)
Infants 31–92 d, *n* = 106	99.1 (94.9–100)	65.2 (52.4–76.5)
Any positive UA (pyuria ≥3 WBC/HPF), entire sample, *n* = 245	98.4 (96.8–100)	60 (50.4–69)
Infants ≤ 30 d, *n* = 101	99 (94.6–100)	53.1 (38.3–67.5)
Infants 31–92 d, *n* = 144	97.9 (94–99.6)	65.2 (52.4–76.5)

[a] Analyses performed for infants in whom results for each component were reported. The "*n*'s" refer to the denominator for the sensitivity calculations.

TABLE 4 Urine Culture and UA Results in Infants With Bacteremia and Urine Culture Growth With <50 000 CFU/mL of the Same Organism

Organism	*n*	Urine Culture Growth, CFU/mL			UA Result			
		<10K	10–25K	25–50K	Pyuria >3 WBC/HPF	Any Bacteria	Any LE	Any Nitrites
E coli	12	1	7	4	11/12	10/11[a]	12/12	2/12
GBS	5	4	1	0	1/5	0/4[a]	0/5	0/5
Enterococcus faecalis	1	1	0	0	0	ND	0	0
GAS	1	1	0	0	ND	ND	0	0

GAS, Group A *Streptococcus*; ND, not done.

[a] Denominators reflect that not all infants had UA bacteria results.

The alternative explanation for our study findings (that the UA is indeed highly reliable for all forms of UTI, and that previous reports of suboptimal UA sensitivity are biased by use of a flawed gold standard) is supported by several previous studies on asymptomatic bacteriuria. Wettergren et al[8,9] performed screening bag urine cultures on 3581 asymptomatic infants at 3 separate intervals during the first year of life, beginning at 0.25 to 2 months. Infants with ≥50 000 CFU/mL from 2 successive bag cultures underwent suprapubic aspiration. Fifty (1.4%) of the original cohort of 3581 infants had growth from suprapubic aspiration (0.9% of girls and 2.5% of boys). Only 2 of the 45 untreated infants were diagnosed with pyelonephritis within 2 weeks of detection of the bacteriuria.[9] Follow-up tests for renal-concentrating capacity (a measure of renal function) were done in 47 of 50 children and were normal.[8] In a study by Hoberman et al,[7] of 212 children <2 years of age with positive urine cultures (>50 000 CFU/mL), 22 patients had <10 WBC/mm^3 from an enhanced UA (equivalent to ∼2 WBC/HPF from an automated UA[19]). Dimercaptosuccinic acid scans were performed on 15 of 22 of these patients and only 1 was positive, and that patient had elevated inflammatory markers and 8 WBC/mm^3 on the UA. The authors concluded that asymptomatic bacteriuria was the likely explanation for these positive cultures without pyuria.

Contaminated urine cultures are generally defined by growth of nonpathogens or multiple organisms, or growth of a pathogenic organism with a low colony count.[20] Given the challenges in obtaining a clean urine specimen from an infant, especially a girl or an uncircumcised boy, contaminated specimens are common. In 1 study, 14% of urine cultures were contaminated. Age <6 months, difficult catheterization, and lack of circumcision were independent risk factors for contamination.[20] Uncircumcised boys <6 months of age had a contamination rate of 43%.

Therefore, given that most estimates of UTI prevalence for a given condition (eg, febrile infant) rely exclusively on the urine culture, some of these estimates may be inflated due to asymptomatic bacteriuria or contamination, which in turn can affect the apparent diagnostic performance of the UA. For example, if the baseline prevalence of asymptomatic bacteriuria is 1% and the reported prevalence of UTI in a given population is 5%, then 20% of the patients in that population do not have true UTIs, in which case even a perfect screening test would not appear to have a sensitivity >80%.

In a recent study of 770 infants <90 days with UTI, the reported sensitivity of the UA dipstick (∼90%) and the combined dipstick + microscopic analysis (∼95%) were considerably higher than that reported from previous studies but still below the sensitivity found in our investigation.[12] Why the sensitivity exceeded previous estimates in this study is unclear. Like previous studies, however, the authors categorized infants with a negative UA and a positive urine culture as an initial "missed UTI."

We used the AAP-recommended threshold of 50 000 CFU/mL for the urine culture definition of UTI. However, there were 19 infants in our sample who had the same organism in the blood and urine but <50 000 CFU/mL on urine culture (Table 4). All 12 of the infants with <50 000 CFU/mL of *E coli* had a positive result for at least 1 component of the UA, indicating that some infants with low bacterial growth may have true UTIs. However, the 7 infants with <50 000 CFU/mL of non–*E coli* organisms had unremarkable UAs, indicating that these infants may have had a primary bacteremia with seeding into the urine.

The primary limitation of this study is that spectrum bias might account for the near-perfect sensitivity of the UA in infants with bacteremic UTI, as discussed previously. Spectrum bias also may inflate the UA specificity, given that the random sample had negative urine cultures, which may represent the far end of the spectrum of nondisease. In addition, the urine collection method was by bag in 4 infants and was not documented in approximately one-fourth of infants in the bacteremic UTI group. Most of these undocumented cases came from 1 site where collection method was not routinely noted in the laboratory reports, but where the standard of care is to obtain urine by catheterization. Although bag specimens have been demonstrated to have an increased risk of contamination, the fact that infants in the bacteremic UTI group had the same pathogenic organism in the blood and urine lessens this concern, and exclusion of infants with bag specimens did not affect UA sensitivity. In the negative urine

culture group, all of the specimens came from 1 site, which limits generalizability, and 9% of the specimens were obtained by bag. Several studies have compared UA sensitivity and specificity in specimens obtained by bag versus catheterization and have yielded mixed results, likely because of a lack of consistent and reliable gold standards.[13,21] Although UA specificity may be influenced slightly by inclusion of bag specimens, exclusion of infants with bag specimens had a very minimal impact (change of <1%) on the UA specificity in our sample.

Requiring a positive UA to make the diagnosis of UTI could have important clinical implications. In a study of infants with bronchiolitis and fever, the risk of UTI was 1.1% if a positive UA (using the 2011 AAP UTI guidelines criteria) was incorporated into the definition versus 6.1% if the definition relied on the urine culture alone.[22] In young, febrile infants, UTI is the most common serious bacterial infection. This diagnosis drives substantial interventions, including hospitalization for prolonged antibiotic therapy[23] and follow-up urinary imaging.[24] Our study highlights the need to further define the role of the UA in young infants with suspected UTI to minimize the possibility of harm and excessive costs from overtreatment.

CONCLUSIONS

The UA is highly sensitive in young infants with bacteremic UTI. Although this finding may reflect spectrum bias, it is also consistent with previous studies, suggesting that the suboptimal sensitivity of the UA may be explained by urine culture results that do not reflect true UTI.

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