Urine Concentration and Pyuria for Identifying UTI in Infants

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abstract

BACKGROUND: Varying urine white blood cell (WBC) thresholds have been recommended for the presumptive diagnosis of urinary tract infection (UTI) among young infants. These thresholds have not been studied with newer automated urinalysis systems that analyze uncentrifuged urine that might be influenced by urine concentration. Our objective was to determine the optimal urine WBC threshold for UTI in young infants by using an automated urinalysis system, stratified by urine concentration.

METHODS: Retrospective cross-sectional study of infants aged <3 months evaluated for UTI in the emergency department with paired urinalysis and urine culture. UTI was defined as ≥50 000 colony-forming units/mL from catheterized specimens. Test characteristics were calculated across a range of WBC and leukocyte esterase (LE) cut-points, dichotomized into specific gravity groups (dilute <1.015; concentrated ≥1.015).

RESULTS: Two-thousand seven hundred infants with a median age of 1.7 months were studied. UTI prevalence was 7.8%. Optimal WBC cut-points were 3 WBC/high-power field (HPF) in dilute urine (likelihood ratio positive [LR+] 9.9, likelihood ratio negative [LR–] 0.15) and 6 WBC/HPF (LR+ 10.1, LR– 0.17) in concentrated urine. For dipstick analysis, positive LE has excellent test characteristics regardless of urine concentration (LR+ 22.1, LR– 0.12 in dilute urine; LR+ 31.6, LR– 0.22 in concentrated urine).

CONCLUSIONS: Urine concentration should be incorporated into the interpretation of automated microscopic urinalysis in young infants. Pyuria thresholds of 3 WBC/HPF in dilute urine and 6 WBC/HPF in concentrated urine are recommended for the presumptive diagnosis of UTI. Without correction of specific gravity, positive LE by automated dipstick is a reliably strong indicator of UTI.

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WHAT'S KNOWN ON THIS SUBJECT: Previously recommended pyuria thresholds for the presumptive diagnosis of UTI in young infants were based on manual microscopy of centrifuged urine. Test performance has not been studied in newer automated systems that analyze uncentrifuged urine.

WHAT THIS STUDY ADDS: The optimal diagnostic threshold for microscopic pyuria varies by urine concentration. For young infants, urine concentration should be incorporated into the interpretation of uncentrifuged urine analyzed by automated microscopic urinalysis systems.

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Urinary tract infections (UTIs) are the most common bacterial infection identified in febrile infants aged younger than 3 months, with a reported prevalence of ~7%.[1] Accurate diagnosis is important to provide timely treatment of patients with UTI while avoiding unnecessary antibiotics when UTI is unlikely. Traditionally, urine culture has been the reference standard for the diagnosis of UTI. However, urine cultures are not reported for 24 to 48 hours, necessitating the use of screening urinalyses for the presumptive diagnosis of UTI while awaiting culture results. Previously well studied strategies for the standard evaluation and management of febrile infants included urinalysis by manual microscopy.[2–4]

Microscopic urinalyses historically depended on centrifuged urine, standardly reported as cells per high-power field (HPF), although manual hemocytometer counts on uncentrifuged urine have also been described in the "enhanced" urinalysis (reported as cells per cubic millimeter [mm^3]).[5–7] Many hospital laboratories currently use automated urinalysis systems to analyze uncentrifuged urine. The 2 most common systems analyze uncentrifuged urine on the basis of either fluorescence flow cytometry or digital imaging with computer-based recognition of cellular elements.[8–12] As automated urinalysis systems are becoming more ubiquitous, determining accurate thresholds for pyuria for the presumptive treatment of UTI on the basis of these automated systems is important.[6,13,14]

Microscopic pyuria and dipstick leukocyte esterase (LE) and nitrite are the most diagnostically relevant results for the presumptive diagnosis of UTI as defined by positive urine culture.[15,16] Generally, higher levels of pyuria or larger amounts of LE are more predictive of UTI.[6,14,16,17] The concentration of white blood cells (WBCs) reflects the balance between the migration of WBCs into the urinary system as related to the degree of inflammation and the volume of urine as determined by both the rate of urine production and urine clearance. Intuitively, a few WBCs in low-flow concentrated urine may be less indicative of UTI as compared with a few WBCs in high-flow, dilute urine. To account for the potential effect, pyuria thresholds may need to be adjusted based on urine concentration, as measured by specific gravity.

Our objective was to determine the optimal urine WBC threshold for the presumptive diagnosis of UTI in young infants aged <3 months by using an automated urinalysis system stratified by urine concentration.

METHODS

We conducted a retrospective study of infants aged <3 months evaluated for UTI at a major pediatric academic hospital with ~60 000 emergency department (ED) visits annually. The hospital serves as a major referral center for New England with ~26% of ED visits referred by primary care offices or other regional EDs.

All infants aged <3 months who presented to the ED between May 2009 and December 2014 and had paired urinalysis and urine culture were identified by the hospital's electronic medical record. The local implementation of the automated urinalysis systems in May 2009 was selected at the beginning of the study period. Data including age, sex, temperature in the ED, and laboratory study results were extracted directly from the hospital's data warehouse. The institutional review board approved this study with a waiver of informed consent. Standard procedures were instituted for patient confidentiality.

To characterize the study population, 5% of the patient sample was randomly selected for manual record review. For this audit, clinical information that might influence the performance or interpretation of the urinalysis and urine culture was recorded: history of fever (≥38°C) before the ED, previous UTI, presence of preexisting genitourinary abnormalities that may predispose a patient to UTI or bacterial colonization, exposure to antibiotics 48 hours before their ED visit, or significant comorbidity such as severe neurologic disability or underlying immunodeficiency. No patients were excluded from analysis on the basis of this descriptive review.

At the study institution, it is standard of care for urine culture specimens from infants to be obtained by urethral catheterization, although in rare instances urine may be obtained by using a bag or by suprapubic aspiration. Dipstick urinalyses included specific gravity measurements and were performed in the clinical laboratory by using the CLINITEK Atlas Automated Urine Chemistry Analyzer (Siemens Medical Solutions USA, Inc, Malvern, PA). The Atlas system analyzes urine dipsticks by automated colorimetric interpretation. Dipstick tests with positive results for LE, nitrite, or blood automatically trigger a microscopic urinalysis, which is performed by the IRIS iQ200 Series Automated Urine Microscopy Analyzer (Beckman Coulter, Inc, Brea, CA). The iQ200 measures cell counts on uncentrifuged urine by using Flow Cell Digital Imaging. Microscopic digital imaging captures a collection of images that are analyzed by Auto-Particle Recognition software, which classifies particles with a reported sensitivity of 0.86 to 0.97 for cellular elements[12,18] and a high correlation with manual microscopy for WBCs,[10–12,18,19] reported as WBC/HPF. At the discretion of the ordering provider, a microscopic urinalysis may be ordered independent of the

dipstick test result. At the study institution, if dipstick testing is negative, microscopic urinalysis is not routinely performed. In cases when a microscopic urinalysis was not separately performed, a negative dipstick result for LE was considered equivalent to a negative microscopic urinalysis consistent with previous literature.[20]

The primary outcome was a positive urine culture, defined as ≥50 000 colony-forming units (CFUs)/mL of a single urinary pathogen from catheterized specimens and any pathogen growth from suprapubic aspiration, based on previously established guidelines for UTIs.[6,13,21] Organisms considered pathogenic genitourinary organisms included *Escherichia coli*, *Proteus* species, *Enterococcus* species, *Klebsiella* species, *Serratia marcescens*, *Citrobacter* species, *Enterobacter* species, *Streptococcus agalactiae*, and *Pseudomonas* species. Cultures yielding nonpathogenic organisms or reported by the laboratory as "mixed organisms," "multiple organisms," or "urogenital flora" were considered contaminated. To avoid potential misclassification of the primary outcome, contaminated cultures were excluded from analysis rather than being classified as negative. Cultures yielding pathogenic organisms at <50 000 CFU/mL were considered negative. Cultures collected from a bag specimen, clean void, or indwelling catheters were excluded.

All statistical analyses were performed by using Stata/SE version 13.1 (Stata Corp, College Station, TX). Standard test performance characteristics were calculated with 95% confidence intervals (CIs) for a range of cut-points for microscopic pyuria and dipstick LE (+/− nitrite). For dipstick, "trace" LE was considered negative. A cut-point of "small" or "any" LE was considered positive. As clinicians generally use screening urinalyses to determine the need for empirical treatment, analysis was focused on likelihood ratios (LRs) as being most relevant to clinical decision-making.[22] Sensitivity, specificity, and predictive values for microscopic urinalysis and dipstick were also calculated across the range of cut-points. Secondary analysis of standard test performance characteristics on the subgroup of patients who had fever (≥38°C) measured in the ED was performed.

To keep analysis simple for future application of the findings, urine sample results were a priori dichotomized on the basis of specific gravity into relative terms of dilute and concentrated urine. Without a strict medical definition of these terms, a threshold to dichotomize was identified by graphing LR+ across urine specific gravity groups defined by increasing increments of 0.005 in specific gravity at a WBC cut-point of 5 WBC/HPF. We then visually inspected the graph for a logical threshold (Supplemental Fig 3). A value of 1.015 was chosen, which conveniently also represents a near-midway point in the continuum of specific gravity and a cognitively natural breakpoint for clinicians to remember.

Receiver operating characteristic (ROC) curves were generated to measure the overall diagnostic value of pyuria for UTI when stratified by urine concentration for both the primary analysis group and the subgroup of infants with fever documented in the ED. A priori an optimal threshold was determined to be the best combination of LR+ near 10 and LR− near 0.1, considering the importance of conservative management in this age group.

RESULTS

There were 3077 infants with paired urinalysis and urine culture identified. Three hundred seventy-seven patients (12%) were excluded from analysis for the following reasons: urine culture grew mixed urogenital organisms (n = 42) or nonpathogenic organisms (n = 15); urine culture was obtained from a bag (n = 7), clean void sample (n = 145), or indwelling catheter (n = 10); the urine source was missing (n = 2); or the specific gravity was missing (n = 156). There were no urine specimens obtained by suprapubic aspiration. The remaining 2700 children constituted the study group, of which 211 (7.8%) had a positive urine culture.

The median (interquartile range [IQR]) age of the sample was 1.7 (1.0–2.3) months and 45% (1200) of patients were girls. Forty-nine percent had fever ≥38°C documented in the ED. Median (IQR) body temperature measured in the ED was 37.9°C (37.4–38.4). Self-identified race and ethnicity were 43% white, 14% African American, 13% Hispanic, 4% Asian, 21% other, and 5% not identified. Fifty-seven percent (1529) of patients were admitted to the hospital (Table 1). Common uropathogens were *E coli* (84%), *Klebsiella* species (7%), *Enterobacter* species (4%), *Enterococci* species (2%), and *S agalactiae* (2%). There were 2200 (81.5%) cases in the dilute (<1.015) specific gravity group and 500 (18.5%) in the concentrated (≥1.015) group.

Our manual audit of 5% (135) of the study sample revealed fever either before the ED or during the ED course in 112 (83%), previous UTI in 1 (0.7%), presence of genitourinary abnormalities that may predispose a patient to UTI or bacterial colonization in 6 (4%), antibiotic exposure within 48 hours of the ED visit in 2 (1%), or significant comorbidity in 6 (4%).

LRs, sensitivity, specificity, and predictive values at various microscopic pyuria thresholds are presented in Tables 2 and 3, stratified by urine concentration. Of patients with positive urine cultures, 12 (5.7%) had a negative urinalysis.

TABLE 1 Characteristics of Study Population

	No UTI (*n* = 2489)	UTI (*n* = 211, 7.8%)	All (*n* = 2700)
Median age (IQR), mo	1.7 (1.0–2.3)	1.8 (1.0–2.4)	1.7 (1.0–2.3)
Girls, *n* (%)	1112 (44.7)	89 (42.2)	1201 (44.5)
Race/ethnicity, *n* (%)			
White	1074 (43.1)	86 (40.8)	1160 (43.0)
Black	355 (14.3)	17 (8.1)	372 (14.0)
Hispanic	309 (12.4)	36 (17.1)	345 (13.0)
Asian	94 (3.8)	19 (9.0)	113 (4.0)
Race: other	527 (21.2)	45 (21.3)	572 (21.0)
Not identified	130 (5.2)	8 (3.8)	138 (5.0)
Temperature, °C			
Maximum temperature in ED, median (IQR), °C	37.9 (37.4–38.3)	38.3 (37.8–38.9)	37.9 (37.4–38.4)
≥38°C, *n* (%)	1178 (47.3)	137 (64.9)	1315 (48.7)
≥39°C, *n* (%)	157 (6.3)	47 (22.3)	204 (7.6)
Specific gravity, *n* (%)			
<1.015	2008 (80.7)	192 (91.0)	2200 (81.5)
≥1.015	481 (19.3)	19 (9.0)	500 (18.5)
Disposition: admitted, *n* (%)	1359 (54.6)	170 (80.6)	1529 (56.6)

Results represent numbers of patients or samples unless otherwise specifically identified by row title. Percentages based on column totals.

TABLE 2 LR+ and LR– of Microscopic Pyuria Across the 2 Groups of Specific Gravity (<1.015, *n* = 2200 and ≥1.015, *n* = 500)

WBC Cut-Point Cells/HPF	LR+ (95% CI)		LR– (95% CI)	
	<1.015	≥1.015	<1.015	≥1.015
1	3.0 (2.8–3.3)	2.1 (1.9–2.4)	0.09 (0.05–0.16)	0
2	6.9 (6.1–7.8)	3.2 (2.6–3.9)	0.13 (0.08–0.19)	0.15 (0.04–0.54)
3	9.9 (8.5–11.5)	4.4 (3.3–5.7)	0.15 (0.10–0.21)	0.20 (0.07–0.55)
4	12.2 (10.3–14.5)	5.9 (4.4–7.9)	0.18 (0.13–0.25)	0.18 (0.07–0.52)
5	14.8 (12.2–17.9)	7.0 (5.1–9.5)	0.19 (0.14–0.26)	0.18 (0.06–0.51)
6	19.0 (15.2–23.8)	10.1 (7.1–14.4)	0.23 (0.18–0.30)	0.17 (0.06–0.49)
7	23.2 (18.0–29.8)	12.3 (8.4–18.0)	0.26 (0.20–0.33)	0.17 (0.06–0.48)
8	27.7 (21.0–36.4)	14.6 (9.4–22.6)	0.26 (0.21–0.33)	0.22 (0.09–0.53)
9	31.6 (23.5–42.4)	16.5 (10.4–26.1)	0.27 (0.21–0.34)	0.22 (0.09–0.53)
10	37.4 (27.2–51.8)	18.1 (11.2–29.1)	0.28 (0.22–0.35)	0.22 (0.09–0.53)

Microscopic Urinalysis

A cut-point of 3 WBC/HPF in dilute urine resulted in LR+ 9.9 (CI, 8.5–11.5) and LR– 0.15 (CI, 0.10–0.21), whereas a cut-point of 6 WBC/HPF resulted in LR+ 10.1 (CI, 7.1–14.4) and LR– 0.17 (CI, 0.06–0.49) in concentrated urine. The effect of specific gravity on LR+ for microscopic pyuria is graphically depicted in Fig 1. ROC curves for both dilute and concentrated urine groups were generated for a range of cut-points for microscopic pyuria (Fig 2). In both figures, the cut-points of 3 and 6 WBC/HPF are highlighted. The area under the curve (AUC) for both specific gravity groups are equal (0.93).

Dipstick

Test characteristics for LE (+/– nitrite) are presented in Tables 4 and 5. A cut-point of any (positive) LE (small or 1+) resulted in LR+ 22.1 (CI, 17.7–27.6) and LR– 0.12 (0.09–0.18) in dilute urine, and LR+ 31.6 (CI, 17.2–57.8) and LR– 0.22 (CI, 0.09–0.52) in concentrated urine.

Febrile Infant Subgroup Analysis

Test characteristics of the subgroup analysis of patients with fevers (≥38°C) documented in the ED were similar to the entire cohort (Supplemental Table 6). A cut-point of 3 WBC/HPF in dilute urine resulted in LR+ 10.3 (CI, 8.3–12.8) and LR– 0.12 (CI, 0.07–0.2), whereas a threshold of 6 WBC/HPF resulted in LR+ 14.4 (CI, 8.7–23.8) and LR– 0.09 (CI, 0.01–0.58) in concentrated urine. A cut-point of 5 WBC/HPF in concentrated urine from febrile infants was similar to a cut-point of 6 WBC/HPF in concentrated urine in the entire cohort [LR+ 9.6 (CI, 6.3–14.6), LR– 0.09 (CI, 0.01–0.6)]. The presence of any LE (≥1+) resulted in LR+ 24.2 (CI, 17.3–33.9) and LR– 0.12 (0.07–0.19) in dilute urine, and LR+ 93.8 (CI, 22.8–388.8) and LR– 0.25 (CI, 0.09–0.67) in concentrated urine. The AUC of ROC curves for both specific gravity groups was again 0.93 among the febrile infants.

DISCUSSION

In a large hospital-based data set of 2700 infants aged younger than 3 months with paired urinalyses and urine cultures, we found that the test characteristics of the automated microscopic urinalysis in young

TABLE 3 Sensitivity, Specificity, PPV, and NPV of Microscopic Pyuria Across the 2 Groups of Specific Gravity (<1.015, n = 2200 and ≥1.015, n = 500)

WBC Cut-Point Cells/HPF	Sensitivity (95% CI)		Specificity (95% CI)		PPV (95% CI)		NPV (95% CI)	
	<1.015	≥1.015	<1.015	≥1.015	<1.015	≥1.015	<1.015	≥1.015
1	93.8 (89.3–96.7)	100.0 (82.4–100.0)	69.1 (67.0–71.1)	53.1 (48.6–57.7)	22.5 (19.7–25.6)	7.8 (4.8–11.9)	99.1 (98.5–99.6)	100.0 (98.6–100.0)
2	89.1 (83.8–93.1)	89.5 (66.9–98.7)	87.1 (85.6–88.6)	71.9 (67.6–75.9)	39.9 (35.2–44.7)	11.2 (6.7–17.3)	98.8 (98.2–99.3)	99.4 (97.9–99.9)
3	86.5 (80.8–91.0)	84.2 (60.4–96.6)	91.3 (90.0–92.5)	80.6 (76.8–84.1)	48.7 (43.3–54.1)	14.7 (8.6–22.7)	98.6 (98.0–99.1)	99.2 (97.8–99.8)
4	83.3 (77.3–88.3)	84.2 (60.4–96.6)	93.2 (92.0–94.2)	85.6 (82.2–88.6)	53.9 (48.0–59.7)	18.8 (11.2–28.8)	98.3 (97.6–98.9)	99.3 (97.9–99.9)
5	81.8 (75.6–87.0)	84.2 (60.4–96.6)	94.5 (93.4–95.4)	87.9 (84.7–90.7)	58.6 (52.4–64.5)	21.6 (12.9–32.7)	98.2 (97.5–98.7)	99.3 (98.0–99.9)
6	77.6 (71.0–83.3)	84.2 (60.4–96.6)	95.9 (95.0–96.7)	91.7 (88.8–94.0)	64.5 (58.0–70.7)	28.6 (17.3–42.2)	97.8 (97.1–98.4)	99.3 (98.0–99.9)
7	75.0 (68.3–81.0)	84.2 (60.4–96.6)	96.8 (95.9–97.5)	93.1 (90.5–95.2)	68.9 (62.2–75.1)	32.7 (20.0–47.5)	97.6 (96.8–98.2)	99.3 (98.1–99.9)
8	74.5 (67.7–80.5)	79.0 (54.4–94.0)	97.3 (96.5–98.0)	94.6 (92.2–96.4)	72.6 (65.8–78.7)	36.6 (22.1–53.1)	97.6 (96.8–98.2)	99.1 (97.8–99.8)
9	74.0 (67.2–80.0)	79.0 (54.4–94.0)	97.7 (96.9–98.3)	95.2 (92.9–96.9)	75.1 (68.3–81.1)	39.5 (24.0–56.6)	97.5 (96.7–98.2)	99.1 (97.8–99.8)
10	72.9 (66.1–79.1)	79.0 (54.4–94.0)	98.1 (97.4–98.6)	95.6 (93.4–97.3)	78.2 (71.4–84.0)	41.7 (25.5–59.2)	97.4 (96.6–98.1)	99.1 (97.8–99.8)

FIGURE 1
Effect of specific gravity on LR+ of select cut-points of pyuria.

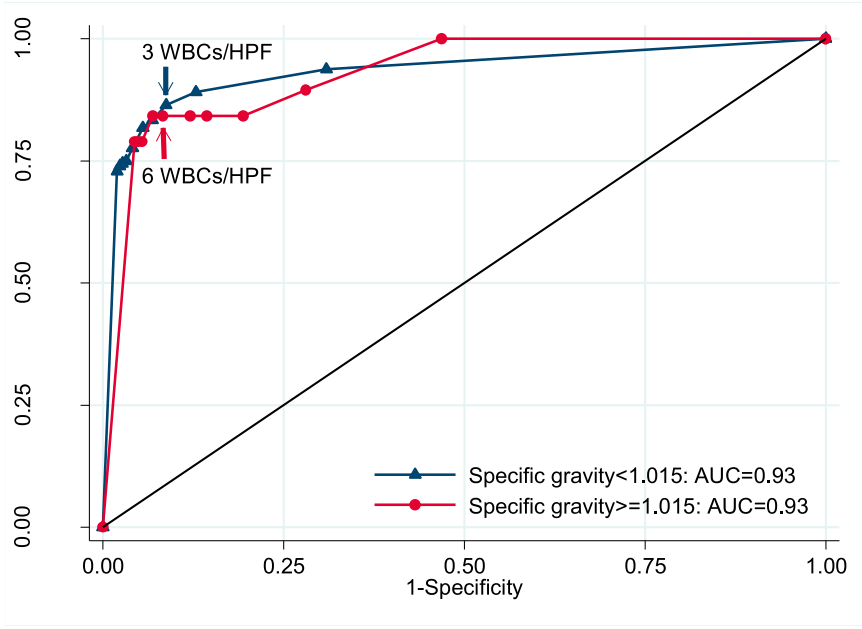

FIGURE 2
ROC curves for pyuria.

infants varies by urine concentration. Overall diagnostic performance of microscopic pyuria over a range of WBC thresholds was similar in dilute and concentrated urine (both AUC 0.93); however, a threshold of 3 WBC/HPF in dilute urine and 6 WBC/HPF in concentrated urine provided the optimal thresholds for the presumptive diagnosis of UTI as defined by a positive urine culture of ≥50 000 CFU/mL. Any LE by dipstick has strong diagnostic performance regardless of urine concentration. Secondary analysis of patients who had a documented fever (≥38°C) in the ED revealed similar test characteristics.

TABLE 4 LR+ and LR− of LE (+/− Nitrite) Across the 2 Groups of Specific Gravity (<1.015, $n = 2200$ and ≥1.015, $n = 500$)

	LR+ (95% CI)		LR− (95% CI)	
	<1.015	≥1.015	<1.015	≥1.015
Small LE	22.1 (17.7–27.6)	31.6 (17.2–57.8)	0.12 (0.09–0.18)	0.22 (0.09–0.52)
Moderate LE	32.1 (23.9–43.0)	50.5 (21.3–120.1)	0.26 (0.20–0.33)	0.37 (0.21–0.67)
Large LE	49.4 (32.4–75.8)	62.7 (13.1–304.9)	0.44 (0.37–0.51)	0.74 (0.57–0.97)
Any LE + Nitrite	328.1 (81.2–1335.8)	62.7 (13.1–304.9)	0.67 (0.61–0.74)	0.74 (0.57–0.97)

Much of the literature on UTI in young infants is embedded in investigations and reviews on the approach to the febrile infant. Management strategies have been established to identify febrile infants with serious bacterial infection while avoiding unnecessary admission or antibiotics in patients who can be considered low risk.[2–4] Three of the most commonly cited "criteria" published in the early 1990s were the "Philadelphia," "Rochester," and "Boston" criteria. All 3 protocols included the microscopic urinalysis as part of their laboratory determinants of low risk, with a pyuria threshold of <10 WBC/HPF; the Philadelphia criteria also included a negative urine Gram stain and the Rochester criteria also included the absence of bacteria by microscopy.[2–4] Since the publication of these protocols, techniques for the analysis of urine and definitions of clinically significant pyuria have evolved. In subsequent studies, the pyuria threshold used for the presumptive diagnosis of UTI ranged from ≥5 to 10 WBC/HPF by manual microscopy and ≥10 WBC/mm^3 by hemocytometer.[15,16] For automated systems, thresholds may be lower at 2 WBC/HPF for digital imaging[6] and 25 to 50 WBC per microliter for flow cytometry.[14]

As hospitals transition from manual microscopy to automated systems, use of previously established pyuria thresholds for the presumptive diagnosis of UTI should also be reevaluated. In 2014, Shah et al[6] studied 703 urine samples to compare automated and enhanced urinalysis. They found that ≥2 WBC/HPF on the automated IRIS iQ200 microscopic urinalysis system was comparable to ≥10 WBC/mm^3 on the "enhanced" urinalysis.[6] Of note, this 2 WBC/HPF threshold on the automated urinalysis is lower than the 5 to 10 WBC/HPF commonly used for centrifuged manual microscopy. Shah et al[6] suggested that this difference was potentially from using uncentrifuged urine in the automated system. Given the variability of centrifuged specimens, the automated urinalysis with uncentrifuged urine with urine concentration correction should be an upgrade over the manual process of spinning urine with suspension of sediment.

Our analysis indicated that the diagnostic value of WBC concentration varies by urine concentration. Both the measured WBC and urine concentration are reported on a continuous scale, which we chose to categorize to improve clinical utility; however, as a possible future application of our findings, automated systems may need to mathematically adjust their pyuria measurements by normalizing to a "standard" specific gravity. Advanced decision support for clinicians could not only adjust the pyuria for urine concentration, but also provide the test characteristics for each potential threshold.

Interestingly, automated dipstick LE has superior diagnostic value to the microscopic evaluation of pyuria. This diagnostic value of dipstick analysis in infants has previously been noted by Glissmeyer et al[17] who studied 6394 infants and found the combination of LE and nitrite have a positive predictive value (PPV) of 66.8% and a negative predictive value (NPV) of 98.7%.

Our investigation has several important limitations. First, the study sample included infants who had a paired urinalysis with urine culture and is not restricted to febrile infants alone, which is the basis for much of the previous UTI literature in this age group. In our limited audit of medical records, 83% of infants had either a history of fever or a documented fever in the ED. Importantly, our prevalence of UTI was similar to previously published prevalence of UTI in infants younger than 3 months.[1] Furthermore, our estimates of test performance for components of the urinalysis are similar to previous studies of microscopic urinalyses and dipsticks, including newer automated systems.[6,15–17] Almost half of our sample had a fever (≥38°C) documented while in the ED, and analysis of test characteristics in this subgroup revealed similar test characteristics as the larger cohort.

Second, we analyzed the performance of 1 of the 2 most common hospital-based automated urinalysis systems, the IRIS iQ200 Series Automated Urine Microscopy Analyzer. Our findings should be investigated with the other major automated

TABLE 5 Sensitivity, Specificity, PPV, and NPV of LE (+/− Nitrite) Across the 2 Groups of Specific Gravity (<1.015, n = 2200 and ≥1.015, n = 500)

	Sensitivity		Specificity		PPV		NPV	
	<1.015	≥1.015	<1.015	≥1.015	<1.015	≥1.015	<1.015	≥1.015
Small LE	88.0 (82.6–92.3)	79.0 (54.4–94.0)	96.0 (95.1–96.8)	97.5 (95.7–98.7)	67.9 (61.7–73.6)	55.6 (35.3–74.5)	98.8 (98.2–99.3)	99.2 (97.8–99.8)
Moderate LE	75.0 (68.3–81.0)	63.2 (38.4–83.7)	97.7 (96.9–98.3)	98.8 (97.3–99.5)	75.4 (68.7–81.3)	66.7 (41.0–86.7)	97.6 (96.8–98.2)	98.5 (97.0–99.4)
Large LE	56.8 (49.4–63.9)	26.3 (9.2–51.2)	98.9 (98.3–99.3)	99.6 (98.5–100.0)	82.6 (75.0–88.6)	71.4 (29.0–96.3)	96.0 (95.1–96.8)	97.2 (95.3–98.4)
Any LE + Nitrite	32.8 (26.2–39.9)	26.3 (9.2–51.2)	99.9 (99.6–100.0)	99.6 (98.5–100.0)	96.9 (89.3–99.6)	71.4 (29.0–96.3)	94.0 (92.9–94.9)	97.2 (95.3–98.4)

microscopy system that also analyzes uncentrifuged urine.

Furthermore, we decided to conservatively define and exclude contaminated cultures to avoid misclassifying a limited number of cases as potentially false-negative or false-positive cultures. Theoretically, dehydrated infants may be at higher risk of having contaminated cultures as urogenital flora are introduced into a more concentrated lower volume urine sample; if this is true, more infants with dehydration would have been excluded from the analysis creating a bias toward the null and a less pronounced difference between the concentrated and dilute urine groups. Interestingly, patients with UTI were more likely to have dilute urines than patients without UTI (91% vs 81%), but we do not have detailed clinical data to surmise the cause.

Finally, the definition of UTI is a common limitation in studies assessing performance of urinalysis. We used a standard colony count definition of bacterial concentration of ≥50 000 CFU/mL to define UTI in catheterized specimens, which is in agreement with previous studies.[6,13,21] However, lower colony count definitions have been described in the literature.[15,16] In the 2011 updated American Academy of Pediatrics (AAP) clinical practice guideline for diagnosing UTI in febrile patients 2 to 24 months, the definition of UTI was updated to include both a positive urine culture with ≥50 000 CFU/mL of a single urinary pathogen, and a positive urinalysis with pyuria and/or bacteriuria from a specimen obtained by catheterization.[13] The requirement of pyuria for defining infection was deliberate to discriminate UTI from asymptomatic bacteriuria.[21] However, to study the diagnostic value of pyuria and LE, we used strict urine culture criteria to define UTI in alignment with previous studies on urinalysis performance.[6,13,15,16] By not including pyuria into our definition of UTI, patients with simple bacteriuria may have been included. Despite the American Academy of Pediatrics' definition of UTI that includes pyuria, the occurrence of positive urine cultures without pyuria is reported in the literature.[23] However, in patients with bacteremic UTI, this occurrence is very uncommon,[24] highlighting the challenges with the reference standard definition of UTI.

CONCLUSIONS

Urine concentration should be incorporated into the interpretation of the automated microscopic urinalysis in young infants. Using the automated system with uncentrifuged urine, pyuria thresholds 3 WBC/HPF in dilute urine (specific gravity <1.015) and 6 WBC/HPF in concentrated urine (specific gravity ≥1.015) are recommended for the presumptive diagnosis of UTI. Without correction of specific gravity, positive LE by automated dipstick is a reliably strong indicator of UTI in this age group.

ABBREVIATIONS

AUC: area under the curve
CFU: colony-forming unit
CI: confidence interval
ED: emergency department
HPF: high-power field
IQR: interquartile range
LE: leukocyte esterase
LR: likelihood ratio
NPV: negative predictive value
PPV: positive predictive value
ROC: receiver operating characteristic
UTI: urinary tract infection
WBC: white blood cell

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