Urine Dipstick for the Diagnosis of Urinary Tract Infection in Febrile Infants Aged 2 to 6 Months

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abstract

OBJECTIVE: Urine dipsticks can be performed at the point of care, whereas urinalysis requires laboratory analysis. We compared the accuracy of urine dipstick with urinalysis for the diagnosis of urinary tract infection (UTI) in febrile infants aged 2 to 6 months.

METHODS: We performed a cross-sectional study of previously healthy infants aged 2 to 6 months who presented to one of 5 emergency departments with a temperature greater than or equal to 38.0 °C and had a catheterized urine culture obtained. We defined a UTI with a urine culture growing greater than or equal to 50 000 colony-forming units (CFUs) per milliliter of a single bacterial uropathogen. Using receiver operator characteristic (ROC) curve analysis to select the optimal urine white blood cell (WBC) cut point, we compared positive urine dipstick (≥1+ leukocyte esterase or positive nitrite) to dichotomized urine WBC count for the diagnosis of UTI.

RESULTS: Of 9387 febrile infants who had a urine culture performed, 1044 (11%) had a UTI. *Escherichia coli* was the most common pathogen identified (923; 88.4%). The optimal urine WBC cut point was greater than or equal to 7 cells per high-power field (HPF). When compared with urine WBC count of greater than or equal to 7 cells per HPF, urine dipstick had a higher sensitivity (831/921 [90.2%] dipstick vs 738/880 [83.9%] urine WBC; difference 6.4%, 95% CI 3.8%–8.9%) and specificity (6352/6862 [92.6%] dipstick vs 3679/4231 [87.0%] urine WBC; difference 5.6%, 95% CI 4.7%–6.6%).

CONCLUSION: Urine dipstick is an accurate diagnostic test for UTI in febrile infants aged 2 to 6 months. Laboratory urinalysis may not be required to guide initial treatment decisions.

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Dr Hunt conceptualized and designed the study, conducted the primary data analysis, drafted the initial manuscript, and reviewed and revised the final manuscript. Dr Green supervised and performed data abstraction, helped conceptualize and design the study, and revised the final manuscript critically for important intellectual content. Dr Nigrovic supervised data abstraction, helped conceptualize and design the study, conducted the primary data analysis, helped draft the initial manuscript, and reviewed and revised the final manuscript. Drs Sartori, Aronson, Chamberlain, and Florin supervised data abstraction, contributed to study design, (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Urinary tract infection (UTI) is the most common serious bacterial infection in infants. Initial antibiotics are prescribed based on urine diagnostic tests. Urine dipstick can be performed at point of care, yet its diagnostic accuracy is not well characterized in older febrile infants.

WHAT THIS STUDY ADDS: In this multicenter study of more than 9000 febrile infants aged 2 to 6 months, urine dipstick was a highly sensitive and specific test for diagnosing UTI. Point-of-care testing may be adequate to guide initial antibiotic decision-making for older febrile infants.

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BACKGROUND

Infants with urinary tract infections (UTIs) often present with nonspecific symptoms, particularly fever. Prompt antibiotic treatment can hasten recovery and prevent long-term sequelae such as renal scarring.[1,2] The challenge for clinicians is to identify and empirically treat infants at the highest risk for UTI, while minimizing overtesting and treating low-risk infants.

Currently available urine diagnostic tests (ie, urine dipstick and microscopy) guide empirical antibiotic treatment decisions while awaiting definitive culture results. Urine dipstick can be performed at the point of care, providing rapid and low-cost results. In contrast, urine microscopy requires specialized equipment and a trained laboratory technician, resulting in longer turnaround times for results. Infants younger than 6 months have impaired urine concentrating ability, which may impact the accuracy of urine diagnostic tests.[3] With this context, the accuracy of urine dipstick vs microscopy as a diagnostic test for UTI in older (aged 2 to 6 months) febrile infants has not been rigorously evaluated.[4–7]

We assembled a 5-center retrospective cohort of infants aged 2 to 6 months who presented to the emergency department (ED) for evaluation of fever. The primary goal of our analysis was to compare the accuracy of a point-of-care diagnostic (urine dipstick) with a laboratory diagnostic (urine microscopy) for the diagnosis of UTI in this age group.

METHODS

Study Design and Setting

We conducted a planned secondary analysis of a previously assembled cross-sectional sample of febrile infants presenting to the ED at one of the following 5 participating pediatric centers: Boston Children's Hospital (Boston, MA), Children's Hospital of Philadelphia (Philadelphia, PA), Children's National Hospital (Washington, DC), Lurie Children's Hospital of Chicago (Chicago, IL), and Yale New Haven Children's Hospital (New Haven, CT). The institutional review board at each participating site approved the study protocol with permission for data sharing. Details of the study procedures have been previously described.[8] Our study adhered to STROBE guidelines for observational studies.[9]

Study Population

The parent cohort included infants aged 60 to 180 days (ie 2 to 6 months) presenting between January 1, 2011, and December 31, 2019, with a documented temperature of greater than or equal to 38.0 °C in the ED. The study start date varied across sites based on electronic record availability. Fevers measured at any point during the ED encounter and by any route were included. For infants with more than 1 eligible ED encounter during the study period, only the first encounter was included. We excluded infants with any complex chronic condition including congenital urogenital abnormalities using previously assigned diagnosis codes.[10] For this planned secondary analysis, we selected infants who had a urine culture obtained during the ED encounter.

Data Collection

The following data elements were abstracted through an automated query from each study institution's electronic medical record: demographics (age, sex, participating center), vital signs (temperature), urine test results (leukocyte esterase, nitrite, white blood cell [WBC] count per high-power field [HPF], specific gravity [SG]), and microbiology results (urine culture).

Urine Diagnostic Tests

We defined a positive urine dipstick as positive leukocyte esterase (≥1+ or small) and/or positive nitrite. Urine dipsticks were performed either at the point of care by trained ED staff or in the hospital laboratory, and these data were aggregated. For urinalysis, we used the reported number of WBCs per HPF on an unspun urine sample. When laboratories reported a range for the urine WBC count (eg, 5 to 10 cells per HPF), we selected the midpoint of the range for analysis as a proxy for what might be the average WBC count across these samples.

Outcome Measure

Our primary outcome was a UTI defined by a urine culture growing greater than or equal to 50 000 CFUs/mL of a single bacterial pathogen obtained by catheterization.[11] When the source of the urine culture was not recorded, we assumed urine was obtained by catheterization based on standard clinical practice at the participating centers. We classified the following bacterial species as pathogenic: *Escherichia coli*, *Proteus* species, *Enterococcus* species, *Klebsiella* species, *Serratia marcescens*, *Citrobacter* species, *Enterobacter* species, *Streptococcus agalactiae*, *Pseudomonas* species, and *Staphylococcal aureus*.[12,13] Cultures were classified as negative if the organism was nonpathogenic or if the laboratory reported "mixed/multiple organisms" or "urogenital flora." Because recent guidelines have suggested that urine cultures with lower bacterial counts may also represent infection, we performed a secondary analysis for UTI defined by a urine culture growing greater than or equal to 10 000 CFUs/mL of a single bacterial pathogen.[14]

Statistical Analysis

We described the prevalence of urine testing and UTI by study site and by patient age and sex using frequencies and percentages. For the infants who had a urine culture obtained, we compared baseline characteristics of infants

with and without a UTI using median and percent differences with 95% CIs.

Next, we used receiver operator characteristic (ROC) curve analysis with the Liu method to select the optimal urine WBC cut point to discriminate between infants with and without a UTI.[15] Given prior research suggesting that the optimal urine WBC cut point for diagnosing UTI varies by urine concentration, we next stratified our analysis by urine concentration (dilute specific gravity <1.015 vs concentrated specific gravity ≥1.015) and again selected optimal cut points.[13] Recognizing the challenges of interpreting urine WBC ranges, we calculated these cut points with and without the samples that reported ranges included. Finally, we calculated test characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) for urine dipstick and urine WBC count. Positive urine culture was used as the reference standard for calculating test characteristics.

To compare 2 diagnostic tests (urine dipstick and urine WBC count) within the same sample (ie, paired data), we estimated 2 intercept-only generalized linear models with the binomial family and the identity link, using the primary UTI outcome as the dependent variable. We obtained an estimate of sensitivity (among infants with a UTI) and specificity (among infants without a UTI) for each diagnostic test and combined all estimates into a single parameter vector with a simultaneous sandwich/robust covariance matrix to compare dipstick with urine WBC count for diagnosis of UTI.[16]

We analyzed data using SPSS Statistics version 27.0 (IBM Corp) and Stata version 16.1 (StataCorp). Figures were produced in R version 4.3.2 (R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

Of 21 150 febrile infants, 9387 (44.4% of parent study population) had a urine culture obtained (Figure 1), with the number of cultures sent ranging from 343 to 3175 across sites. The proportion of infants who had a urine culture obtained varied by site (range 31.8% to 63.2%; Figure 2). Infants who had a urine culture obtained were younger (median 107 days, IQR 79–142 tested vs 137 days, IQR 108–161 not tested; median difference 30, 95% CI 28.4–31.6) and more likely to be female (50.1% tested vs 39.8% not tested; percent difference 10.4; 95% CI 9.1–11.8). Of the 9387 infants with a urine culture, 7738 (82.4%) had a urine dipstick with both nitrite and leukocyte esterase, 5111 (54.4%) a urine WBC count, 4533 (48.3%) both diagnostic tests, and 1026 (10.9%) neither test. Of those patients with urine culture obtained and either a positive dipstick (≥1+ leukocyte esterase OR positive nitrite) or negative dipstick (negative leukocyte esterase AND negative nitrite), 1308 (16.8%) had dipstick performed at the point of care, 5995 (77%) had a dipstick performed in the laboratory, and 480 (6.2%) had both point-of-care and laboratory dipstick performed. Of the 5111 urine microcopy results, 1352 (26.6%) reported a WBC range, although only 105 (2.1%) reported a range with 5 to 10 cells per HPF.

UTI Frequency

Overall, 1044 infants (11.1%) had a UTI defined by greater than or equal to 50 000 CFUs/mL (primary outcome; Figure 1) and 1319 infants (14.1%) had a UTI using the greater than or equal to 10 000 CFUs/mL definition (secondary outcome). Using the primary outcome, infants with a UTI were older, were more likely to be female, and had a higher peak temperature than those without a UTI (Table 1). The frequency of UTI varied by participating site (range 10.2% to 16.9%; $P = .004$; Figure 2). The following uropathogens were identified: *E coli* (n = 923; 88.4%), *Klebsiella* species (n = 54; 5.2%), *Enterobacter* species (n = 18; 1.7%), *Proteus mirabilis* (n = 13; 1.2%), *Citrobacter* species (n = 12; 1.2%), *Enterococcus faecalis* (n = 11; 1.1%),

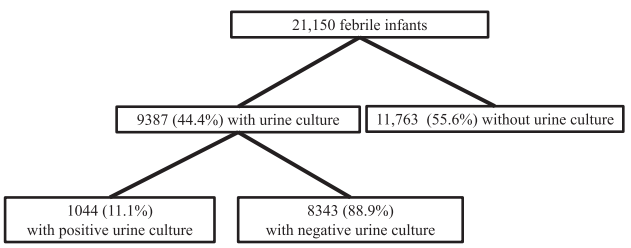

FIGURE 1.
Study patients with positive urine culture defined by greater than or equal to 50 000 CFUs/mL of a single uropathogen. CFU, colony-forming unit.

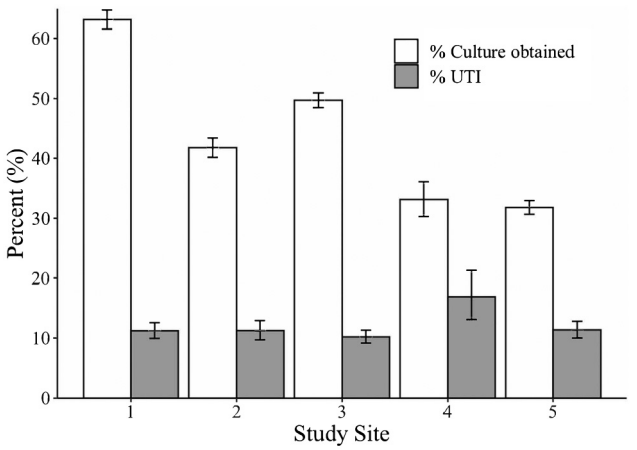

FIGURE 2.
Variation in percentage of febrile infants with urine culture obtained and UTI rates with 95% CIs for point estimate. UTI, urinary tract infection.

TABLE 1. Baseline Characteristics of Enrolled Patients With and Without Urinary Tract Infection			
	Positive Urine Culture n (%)	Negative Urine Culture n (%)	Percent difference (95% CI)
Age, days			
60–90	357 (34.2)	3205 (38.4)	−4.2 (−7.3 to −1.2)
91–120	232 (22.2)	1888 (22.6)	−0.4 (−3.1 to 2.3)
121–150	216 (20.7)	1711 (20.5)	0.2 (−2.4 to 2.8)
151–180	239 (22.9)	1539 (18.5)	4.4 (1.8 to 7.1)
Sex			
Female	665 (63.7)	4042 (48.4)	15.2 (12.1 to 18.4)
Maximum measured temperature, °C			
38.0–38.9	511 (48.9)	5396 (64.7)	−15.7 (−18.9 to −12.5)
39.0–39.9	422 (40.4)	2514 (30.1)	10.3 (7.2 to 13.4)
≥40	111 (10.7)	433 (5.2)	5.4 (3.5 to 7.4)

Streptococcus agalactiae (n = 7; 0.7%), *Pseudomonas aeruginosa* (n = 3; 0.3%), *Staphylococcus aureus* (n = 2; 0.2%), and *Serratia marcescens* (n = 1; 0.1%). Overall, 32 (3.1%) of infants with a UTI had a positive blood culture with the same bacterial pathogen.

Accuracy of Urine Tests for Primary Outcome

For those infants with a urine WBC count obtained, we displayed ROC curves for urine WBC count overall and for both dilute and concentrated urine (Figure 3). The optimal urine WBC cut point overall was greater than or equal to 7 cells per HPF (≥6 cells per HPF in dilute urine and ≥11 cells per HPF in concentrated urine). We calculated the accuracy of urine dipstick and urine microscopy across a range of cut points for our primary UTI outcome (Table 2). Combining nitrite and leukocyte esterase optimized sensitivity and specificity of the dipstick. Increasing the urine WBC cut point decreased sensitivity and increased specificity. A positive urine dipstick had a higher sensitivity (90.2%, 95% CI 88.1%–92.1%; difference 6.4%, 95% CI 3.8%–8.9%) and specificity (92.6%, 95% CI 91.9%–93.2%; difference 5.6%, 95% CI 4.7%–6.6%) when compared with urine WBC count greater than or equal to 7 cells per HPF (sensitivity 83.9%, 95% CI 81.3%–86.2%; specificity 87.0%, 95% CI 85.9%–88.0%). Adjusting urine WBC cut point for urine concentration did not improve accuracy. When microscopy samples with ranges were excluded, optimal WBC counts were greater than or equal to 9 cells per HPF overall, greater than or equal to 9 cells per HPF in dilute urine, and greater than or equal to 13 cells per HPF in concentrated urine.

Of the 6442 infants with a negative urine dipstick (both negative nitrite and <1+ leukocyte esterase), 90 (1.4%) had a UTI (negative predictive value [NPV] 98.6%; Table 2). Of the 3821 infants who had negative urine microscopy (WBC <7 cells per HPF), 142 (3.7%) had a UTI (NPV 96.3%; Table 2). Of the infants with a UTI, those with a negative urine dipstick were less likely to have an *E coli* UTI (53.3% negative dipstick vs 92.2% positive dipstick; difference 38.8%, 95% CI 28.6%–49.2%). Of those patients who had urine dipstick who did not have urine microscopy performed (n = 3250), 232 (7.1%) had a positive dipstick. Of those patients who had both dipstick and microscopy performed (n = 4533), 1109 (24.5%) had a positive dipstick.

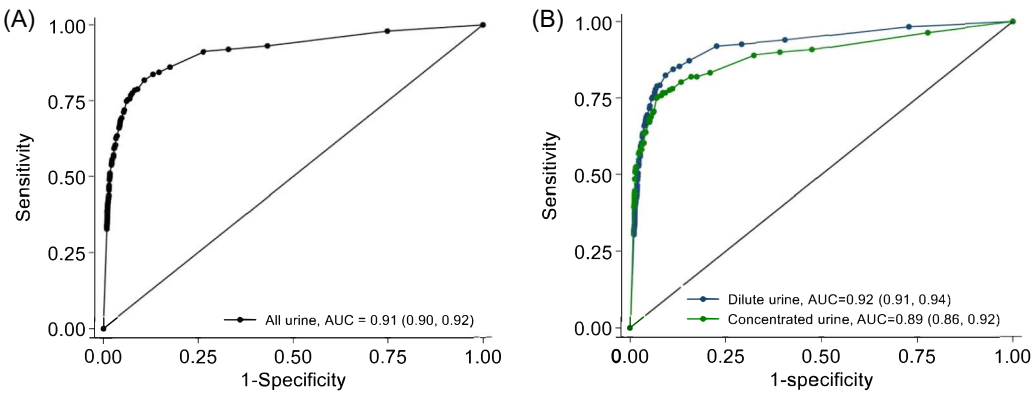

FIGURE 3.
Receiver operator characteristic curves for urine white blood cell count overall (A) and for dilute and concentrated urine (B) with AUC and 95% CIs. AUC, area under the curve.

TABLE 2. Test Characteristics for Urine Dipstick vs Urinalysis

	Sensitivity n/N (%) [95% CI]	Specificity n/N (%) [95% CI]	Positive Predictive Value n/N (%) [95% CI]	Negative Predictive Value n/N (%) [95% CI]
Urine dipstick				
≥Trace leukocyte esterase[a]	810/888 (91.2) [89.2–93.0]	6217/6872 (90.5) [89.8–91.2]	810/1465 (55.3) [52.7–57.9]	6217/6295 (98.8) [98.5–99.0]
≥1+ Leukocyte esterase	775/888 (87.2) [84.9–89.4]	6398/6872 (93.1) [92.5–93.7]	775/1249 (62.1) [59.9–64.2]	6398/6511 (98.3) [97.9–98.5]
≥2+ Leukocyte esterase	692/888 (77.9) [75.1–80.6]	6560/6872 (95.5) [94.9–95.9]	692/1004 (68.9) [66.0–71.8]	6560/6756 (97.1) [96.7–97.5]
≥3+ Leukocyte esterase	465/888 (52.4) [49.0–55.7]	6749/6872 (98.2) [97.9–98.5]	465/588 (79.1) [75.6–82.3]	6749/7172 (94.1) [93.5–94.6]
Positive nitrite[b]	373/1018 (36.6) [33.7–39.6]	7950/8039 (98.9) [98.6–99.1]	373/462 (80.7) [76.9–84.1]	7950/8595 (92.5) [91.9–93.0]
≥1+ Leukocyte esterase OR positive nitrite[c]	831/921 (90.2) [88.1–92.1]	6352/6862 (92.6) [91.9–93.2]	831/1341 (62.0) [59.9–64.0]	6352/6442 (98.6) [98.3–98.9]
Urine microscopy				
WBC ≥ 5	759/880 (86.3) [83.8–88.5]	3489/4231 (82.5) [81.3–83.6]	759/1501 (50.6) [48.0–53.1]	3489/3610 (96.6) [96.0–97.2]
WBC ≥ 7	738/880 (83.9) [81.3–86.2]	3679/4231 (87.0) [85.9–88.0]	738/1290 (57.2) [54.5–59.9]	3679/3821 (96.3) [95.6–96.9]
WBC ≥10	692/880 (78.6) [75.8–81.3]	3882/4231 (91.8) [90.9–92.6]	692/1041 (66.5) [63.5–69.3]	3882/4070 (95.4) [94.7–96.0]
Pyuria by specific gravity[d]	730/877 (83.2) [80.6–85.6]	3728/4207 (88.6) [87.6–89.5]	730/1209 (60.4) [57.6–63.1]	3728/3875 (96.2) [95.6–96.8]

Abbreviations: HPF, high-power field; WBC, white blood cell.
[a] 7760 had dipstick leukocyte esterase results.
[b] 9057 had dipstick nitrite results.
[c] 7783 had either a positive dipstick (≥1+ leukocyte esterase OR positive nitrite) or negative dipstick (negative leukocyte esterase AND negative nitrite).
[d] Urine WBC count greater than or equal to 6 cells per HPF in dilute urine (specific gravity < 1.015) and greater than or equal to 11 cells per HPF in concentrated urine (specific gravity ≥1.015)

Accuracy of Urine Tests for Secondary Outcome

Last, we assessed the accuracy of urine diagnostic tests for our UTI outcome defined by greater than or equal to 10 000 CFUs/mL. When compared with urine WBC count greater than or equal to 7 cells per HPF, dipstick had higher sensitivity (85.0%, 95% CI 82.8%–87.0% dipstick vs 80.4%, 95% CI 77.9%–82.7% urine WBC; difference 4.6%, 95% CI 2.1%–7.1%) and higher specificity (94.7%, 95% CI 94.1%–95.2% dipstick vs 89.7%, 95% CI 88.7%–90.6% urine WBC; difference 5.0%, 95% CI 4.1%–6.0%).

DISCUSSION

In this 5-center retrospective cohort of febrile infants aged 2 to 6 months, urine dipstick (leukocyte esterase combined with nitrite) was more sensitive and specific than urine microscopy WBC count for identifying UTI. Our results suggest that clinical decisions about empirical antibiotics for UTI in older febrile infants could be made based on urine dipstick, although culture obtained by catheterization is still required to confirm a UTI diagnosis and guide definitive antibiotic treatment.

The accuracy of urine dipstick for diagnosing UTI is not well studied in infants aged 2 to 6 months who may have impaired urine concentrating ability. In older children, significant data support the accuracy of urine dipstick. In a large meta-analysis including data from 95 studies in 95 703 children younger than 18 years, urine WBC count had a sensitivity of 74% (95% CI 67%–80%) and a specificity of 86% (95% CI 82%–90%), whereas dipstick (positive leukocyte esterase or nitrite) had a sensitivity of 88% (95% CI 82%–91%) and a specificity of 79% (95% CI 69- 87%).[4] However, selected urine WBC cut points were not uniform across studies and results were not stratified by age. Smaller studies have targeted children younger than 2 years. For example, in a prospective convenience sample of 342 febrile children younger than 2 years, of whom 42 had a UTI, a positive urine dipstick had a sensitivity of 95% and a specificity of 98%.[17] In a single-center study of 50 infants younger than 6 months with UTI, point-of-care urine leukocyte esterase had a sensitivity of 92% and nitrite 38% for UTI.[18] In contrast to older children, young infants empty their bladders frequently, potentially impacting the accuracy of urine testing. However, urine dipstick has still been shown to be an effective diagnostic test in febrile infants younger than 90 days.[5–7] In a study of 6394 infants aged 1 to 90 days, of whom 770 had a UTI, urine dipstick had a sensitivity of 91%, comparable to our study.[6] However, to our knowledge, our study is the first large, multicenter study to investigate urine diagnostic test accuracy in the 2- to 6-month age group.

Although validated clinical prediction rules and national practice guidelines are often used to guide care of febrile neonates, the optimal approach for febrile infants aged 2 to 6 months has not been delineated. We observed considerable variability in the workup for potential UTI across our participating institutions.[3] Older infants are at lower risk for invasive bacterial infections, yet UTI remains a concern in this age group.[19] Although prospective validation studies are still needed, our findings suggest that for well-appearing febrile infants aged 2 to 6 months, urine dipstick can be used to guide empirical antibiotic decisions for potential UTIs without the need for urine microscopy. Point-of-care testing can be done in a variety of clinical settings, including primary care clinics and urgent care centers, which often lack real-time access to diagnostic laboratories. Even in

clinical settings with laboratory access, urine dipstick can reduce testing costs, as well as associated laboratory workloads.[20,21] Urine dipstick use may increase the speed at which clinicians can make clinical decisions, thus potentially decreasing length of stay, alleviating overcrowding, strengthening quality of care, and increasing patient satisfaction.[22–26]

Prior work has demonstrated that the optimal urine WBC cut point for diagnosing UTI in infants varies by urine concentration.[12,27,28] In a retrospective cross-sectional study of children younger than 2 years, optimal WBC cutoffs were 3, 6, and 8 at low, moderate, and high urine concentrations, respectively.[15] In another study of infants younger than 3 months, optimal WBC cut points were 3 WBCs per HPF in dilute urine (SG <1.015) and 6 WBCs per HPF in concentrated urine (SG ≥1.015). Similarly, we similarly found a higher urine WBC cut point in concentrated urine as compared with dilute urine. However, stratifying urine WBC cut point by urine concentration did not improve overall diagnostic test accuracy, which may reflect the inability of the youngest infants to concentrate their urine. Therefore, we posit that, in a busy clinical setting, clinicians are more likely to use a single cut point (ie, urine WBC ≥7 cells per HPF) when interpreting the urinalysis, regardless of the urine concentration.[29]

Our study has several limitations. First, we only included infants who had a urine culture obtained. This selection bias could theoretically inflate test sensitivity, as providers may defer sending a urine culture for those infants with negative diagnostic tests. Second, not all infants had both a urine dipstick and urinalysis obtained; however, we made appropriate statistical adjustments to compare test accuracy. Importantly, the results of the dipstick may have influenced the provider's decision to also obtain urinalysis. Third, because the source of urine was not reported for all cultures and urine diagnostic tests, we assumed all samples were obtained by catheterization unless otherwise noted, based on standard practice at the participating institutions. Urine bag samples are rarely sent for bacterial cultures given the risk of contamination, and suprapubic taps are rarely performed. However, we cannot account for potential small differences in urine dipstick performance by method of specimen collection. Fourth, we combined results of point-of-care and laboratory-performed urine dipstick test results, as this assay performs similarly in different clinical settings.[20] Fifth, a minority of microscopy results were reported as a WBC count range rather than a single cell count. To account for this in analysis, we first took the midpoint and then excluded these results when selecting the optimal WBC cut points, which did not substantially impact the selected cut points. Importantly, automated urine analyzers, which report the actual urine WBC count, are now used broadly, eliminating this issue. Sixth, although we were able to exclude infants with chronic conditions using previously assigned diagnostic codes, we did not have access to other clinically important UTI risk factors including history of previous UTI, circumcision status, and alternate sources of fever, which could impact the interpretation of urine testing. Finally, although American Academy of Pediatrics (AAP) guidelines include pyuria in the UTI case definition, we defined UTI by positive urine culture alone, consistent with other studies that have examined the accuracy of urine diagnostic tests.[13,27] Although pyuria is included in the AAP definition in part to avoid misconstruing asymptomatic bacteriuria as UTI, all of the study infants had a fever documented in the ED and would be classified as symptomatic. Additionally, certain uropathogens may not elicit a strong host inflammatory response, leading to a positive culture without pyuria.[30]

CONCLUSION

Urine dipstick is an accurate diagnostic test for UTI in older febrile infants, with important clinical implications for increasing the speed of diagnostic decision-making and reducing health care costs. Clinicians can use urine dipstick results (combining leukocyte esterase and nitrite) to guide initial antibiotic decisions while awaiting urine culture results. Future prospective studies are needed to confirm these findings and to quantify the potential cost-saving benefit of dipstick use prior to widespread implementation of these practices.

and revised the final manuscript critically for important intellectual content. Drs Michelson and Chaudhari contributed to study design and revised the final manuscript critically for important intellectual content. Dr Monuteaux helped conduct the primary data analysis, provided data interpretation, and revised the final manuscript critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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