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# Urinary Predictors of Bacteremia in Febrile Infants with Urinary Tract Infection

RESEARCH

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## ABSTRACT

**Background:** Predicting the risk of bacteremia in febrile infants with urinary tract infection (UTI) remains a diagnostic challenge. Prior studies have focused on the utility of blood biomarkers in predicting the risk of bacteremia in febrile infants, the role of urinary components in predicting bacteremia remain unexplored. This study aims to evaluate the utility of components of urinalysis (UA) in predicting bacteremia in febrile infants < 3 and 3–24 months with UTI.

**Methods:** We reviewed records of 2000 febrile children 0–24 months with UTI, seen over a 6-year-period in the pediatric emergency department. We defined UTI as positive urine culture, based on the 2016 AAP thresholds. Descriptive, chi-square ($\chi^2$), and logistic regression analyses were performed as appropriate, including test probabilities (sensitivity [Sn], specificity [Sp], and negative predictive value [NPV]) to evaluate the bacteremia predictive probabilities of components of UA using SAS-9.4®.

**Results:** Of 813 febrile infants with UTI who had blood cultures, 82 (10.1%) had bacteremia. There was no statistically significant difference between compared groups in terms of sex, ethnicity, or urine collection method. Infants < 3 months had significantly higher prevalence of bacteremia compared to infants 3–24 months (14.3% vs. 4.3%, p < 0.0001). Urinary predictors of bacteremia in infants < 3 months include bacteriuria-(pOR:2.3, p = 0.010, Sn-80.0%, NPV-91.8%, Sp-36.8%), pyuria-(pOR-6.7, p = 0.031, Sn-98.4%, NPV-97.4%, Sp-10.0%), and growth of *E. coli* in urine culture-(pOR-9.8, p = 0.0006, Sn-98.5%, NPV-98.1%, Sp-12.9%). There were no UA predictors of bacteremia among infants 3–24 months.

**Conclusion:** Components of UA may be useful in predicting bacteremia in febrile infants < 3 months with UTI. Among infants < 3 months with UTI, potential predictors of bacteremia were bacteriuria, pyuria, and growth of *E. coli* on urine culture. Urinary components did not predict bacteremia in infants 3–24-months.

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## INTRODUCTION

Serious bacterial infections (SBI), including urinary tract infection (UTI), bacteremia, and bacterial meningitis, are a significant cause of morbidity in febrile infants [1–3]. Of these, UTI is by far the most common cause of SBI, accounting for the majority (85%) of SBI in febrile infants < 90 days, compared to bacteremia and bacterial meningitis, which together account for ~10–15% of SBI in febrile infants < 90 days [1–6].

The risk of invasive bacterial infection (bacteremia and bacterial meningitis) is even higher among febrile infants with UTI compared to those without UTI. Depending on patient cohort and demographic differences, 5–31% of febrile infants with UTI have concomitant bacteremia [7–9]. Therefore, prompt identification of bacteremia in the setting of UTI and targeted treatment is necessary to prevent significant morbidity, long-term complications, and prolonged exposure to broad-spectrum antibiotics.

Unfortunately, predicting the likelihood of bacteremia in febrile children with UTI remains a diagnostic challenge. Clinical appearance, signs and symptoms, and blood biomarkers do not reliably identify febrile infants at higher risk of invasive bacterial infection [2, 4–10]. Prior studies have focused on the utility and diagnostic accuracy of serum/blood biomarkers in predicting the likelihood of bacteremia in febrile infants. These studies have shown the diagnostic accuracy of peripheral blood biomarkers including white cell count (WBC), absolute neutrophil count (ANC), band count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), serum creatinine, albumin, and procalcitonin, to be either variable or discordant, providing limited utility in predicting bacteremia in febrile infants [2, 11–14].

Urinalysis (UA) is a readily available, highly sensitive, and non-invasive screening test for UTI [12]. Typically, UA results are available and finalized before blood biomarkers and culture. Components of UA may be useful in predicting bacteremia in febrile young children with culture positive-UTI. If this is true, it may potentially expedite medical decision making, helping the clinician better determine the utility of further testing, as well as institute early intervention and treatment to prevent complications in febrile young children. Furthermore, it may also improve the care of febrile young children in settings where simultaneous blood biomarker or culture evaluation for bacteremia is not feasible.

Although, components of UA have been shown to predict UTI with a high degree of accuracy and reliability [12, 15]; their bacteremia-predictive value in febrile young children remains largely unknown. We have not identified any study that specifically investigated the utility or role of components of UA in predicting the likelihood of bacteremia in febrile infants with UTI. We hypothesize that components of UA may be useful in predicting bacteremia in febrile infants with culture positive UTI. The objective of this study was to identify components of UA that may have predictive value for bacteremia in febrile young children with UTI. This may be of value since a significant proportion of febrile infants do not get blood biomarker or culture evaluation during their visit to a provider [9]. Secondarily, we evaluated and compared pathogens isolated in patients with concomitant bacteremic UTI.

## METHODS

### STUDY DESIGN, SETTING, AND POPULATION

This is a retrospective cross-sectional study of febrile children ≤ 24 months of age with positive urine culture, who had urinalysis, urine culture, and blood culture evaluation during their emergency department (ED) visit at a quaternary children's hospital from January 2012 to December 2017. The study was approved by the Institutional Review Board under waiver of consent.

### ELIGIBILITY CRITERIA

Children ≤ 24 months of age with documented evidence of fever and a positive urine culture, who had urinalysis, urine culture, and blood culture evaluation during their ED visit were eligible. We excluded afebrile patients with positive urine culture, patients without blood culture evaluation, patients with unknown urine collection method, indwelling catheter, bag urine specimen, growth of mixed uropathogens, multiple organisms or normal urogenital flora, and missing urine culture colony count. See Figure 1 for the study population and number excluded.

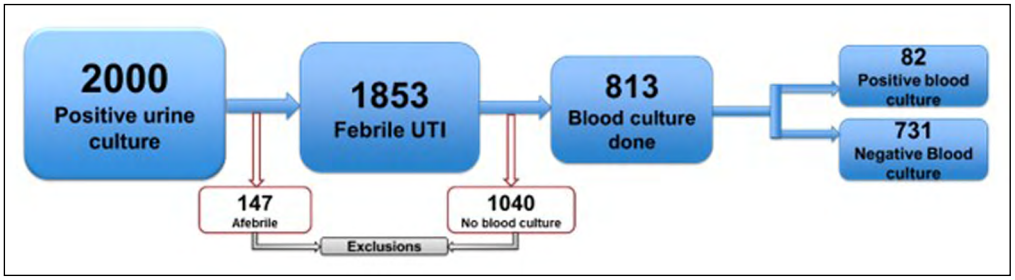


**Figure 1** Study population.

## DEFINITIONS

Fever was defined as a temperature ≥38.0°C measured in the ED, by a referring provider, or at home within a few hours of arrival. All patients in this study had verifiable evidence of fever in the ED. Given the need to evaluate pyuria independent of UTI diagnosis for this study, we used positive urine culture, alone, as a surrogate to define 'UTI'. Positive urine culture was defined based on the 2016 American Academy of Pediatrics (AAP) clinical practice guideline (CPG), as growth of ≥ 50,000 colony forming units (CFU)/mL of a single uropathogen from a transurethral catheter urine specimen [16–18]. Standard midstream urine specimen was considered positive if growth of ≥ 100,000 CFU/mL of a single uropathogen.

Pyuria was defined as ≥5 white blood cells per high power field (WBC/hpf) and microscopic bacteriuria was defined as ≥1+ bacteria on microscopic urinalysis. Leucocyte esterase (LE) was considered positive if small or more on dipstick urinalysis. Urine specific gravity (USG) was arbitrarily categorized into ≤1.015 and >1.015 based on prior studies [19]. Bacteremia was defined as growth of a single bacterial pathogen on blood culture, not considered *a priori* as a contaminant [2, 20]. Concomitant bacteremic UTI was defined as isolation of the same bacterium in both urine and blood cultures [8, 14].

Dipstick urinalysis was performed using the Clinitek Atlas Automated Urine Chemistry Analyzer (Siemens Medical Solutions USA, Inc.; Malvern, PA). Microscopic urinalysis was performed by the Iris iQ200 Series Automated Urine Microscopy Analyzer (Beckman Coulter, Inc., Brea, CA) on all specimens with a positive dipstick result for leukocyte esterase, nitrite, protein, or blood. For urine culture, 1µL of urine specimen was inoculated to tryptic soy agar with 5% sheep's blood, MacConkey agar, and Columbia agar with 5% sheep blood with colistin and nalidixic acid (Remel, San Diego, CA) and incubated at 35–37°C, 5% $CO_2$ for at least 40 hours. For bacterial blood culture, appropriate volume of blood specimen was incubated in the BACT/ALERT (bioMerieux, Durham, NC, USA) or BD BACTEC FX instrument (Franklin Lakes, NJ, USA) for up to 5 days. Positive samples were inoculated to chocolate agar, tryptic soy agar with 5% sheep's blood, MacConkey agar, and Columbia agar with 5% sheep blood with colistin and nalidixic acid (Remel, San Diego, CA, USA). Upon visible colony growth for both urine and blood cultures, organisms were identified using the matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI Biotyper, Bruker, Billerica, MA, USA) or Microscan Gram negative and Gram-positive biochemical identification panels (Beckman Coulter, Brea, CA, USA), as appropriate.

## DATA COLLECTION

The electronic health record (Epic, Verona, WI) was used to gather demographic and clinical data, including, age, biological sex, ethnicity, temperature, urine collection method, UA and urine culture results, blood culture result, and ED disposition.

## OBJECTIVES AND OUTCOME MEASURES

The primary study objective was to identify components of urinalysis that predict bacteremia in febrile young infants with UTI, comparing infants < 3 months to those 3–24 months of age. Secondarily, we aimed to evaluate test characteristics of each, or a combination of, urinary component(s) that predict bacteremia; and to describe pathogens isolated in patients with concomitant bacteremic UTI.

## STATISTICAL ANALYSES

Descriptive statistics as appropriate for continuous and categorical variables were used to summarize demographic, clinical, and laboratory data. Continuous variables like age,

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temperature, and urine specific gravity (USG) were categorized and summarized as proportions. We performed Chi-square, Fisher Exact, and Logistic regression analyses as appropriate, at alpha 0.05 statistical significance to identify urinary predictors of bacteremia in children <3 months and those 3–24 months of age. Furthermore, we performed test probabilities to evaluate the predictive value of each urinary components. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC).

## RESULTS

We identified 2000 pediatric patients ≤ 24 months of age with UTI defined as positive urine culture. Of these, 1853 (92.7%) had fever and 813 (43.9%) had paired urine and blood culture evaluation done during their ED visit. We excluded 147 afebrile infants with UTI and 1040 febrile infants without blood culture evaluation during their visit (Figure 1). Of the 813 febrile infants with UTI, 409 (50.3%) were male, 469 (57.7%) were <3 months of age, 497 (61.3%) were identified as Hispanic/Latinx, and 804 (99.0%) had urine specimen collection by in-and-out transurethral catheterization (Tables 1 and 2). There were no statistically significant differences between the bacteremic and non-bacteremic groups in terms of sex, ethnicity, year of visit, temperature, or urine collection method. However, febrile infants with concomitant bacteremic UTI were more likely to be younger than 3 months and be admitted compared to non-bacteremic febrile infants ($p < 0.0001$).

**Table 1** Demographic data.

| | SUBGROUP | ALL (n = 813) | NO BACTEREMIA (n = 731) | BACTEREMIA (n = 82) | p-VALUE |
|---|---|---|---|---|---|
| Age (month) | 0 < 3 | 469 (57.7%) | 403 (55.1%) | 67 (81.7%) | <0.0001 |
| | 3–24 | 344 (42.3%) | 328 (44.9%) | 15 (18.3%) | |
| Sex | Female | 404 (49.7%) | 368 (50.3%) | 36 (43.9%) | 0.269 |
| | Male | 409 (50.3%) | 363 (49.7%) | 46 (56.1%) | |
| Ethnicity | Hispanic | 497 (61.3%) | 448 (61.3%) | 49 (59.8%) | 0.846 |
| | Non-Hisp | 310 (38.1%) | 278 (38.0%) | 32 (39.0%) | |
| | Unknown | 6 (0.74%) | 5 (0.7%) | 1 (1.2%) | |
| Fever | <102°F | 497 (61.1%) | 450 (61.6%) | 47 (57.3%) | 0.455 |
| | ≥102°F | 316 (38.9%) | 281 (38.4%) | 35 (42.7%) | |
| Disposition | Discharged | 280 (34.5%) | 269 (36.9%) | 11 (13.4%) | <0.0001 |
| | Admitted | 532 (65.5%) | 461 (63.2%) | 71 (86.6%) | |

**Table 2** Urine analysis and culture results.

SG: specific gravity; UA, urinalysis; WBC, white blood count; LE, leucocyte esterase; CFU, colony forming unit.

| | DESCRIPTION | ALL (n = 813) | NO BACTEREMIA (n = 731) | BACTEREMIA (n = 82) | p-VALUE |
|---|---|---|---|---|---|
| Urine collection | Catheter | 804 (98.9%) | 723 (98.9%) | 81 (98.8%) | 0.918 |
| | Clean catch | 9 (1.1%) | 8 (1.1%) | 1 (1.2%) | |
| Urine SG | ≤1.015 | 653 (80.3%) | 576 (78.9%) | 77 (93.9%) | 0.001 |
| | >1.015 | 159 (19.7%) | 154 (21.1%) | 5 (6.1%) | |
| UA bacteria | Yes (1–4+) | 545 (67.0%) | 480 (65.7%) | 65 (79.3%) | 0.013 |
| | None | 268 (33.0%) | 251 (34.3%) | 17 (20.7%) | |
| UA WBC | 0 < 5 | 82 (10.4%) | 78 (11.0%) | 4 (5.1%) | 0.101 |
| | ≥5 | 704 (89.6%) | 629 (89.0%) | 75 (94.9%) | |
| UA LE | Positive | 721(88.7%) | 642 (87.7%) | 79 (96.3%) | 0.020 |
| | None or trace | 92 (11.3%) | 89 (12.3%) | 3 (3.7%) | |
| Nitrite | Positive | 309 (38.0%) | 281 (38.4%) | 28 (34.2%) | 0.448 |
| | Negative | 504 (62.0%) | 450 (61.6%) | 54 (68.9%) | |
| Colony count (CFU) | 50000 – 100000 | 143 (17.6%) | 134 (18.3%) | 9 (11.0%) | 0.097 |
| | >100000 | 670 (82.4%) | 597 (81.7%) | 73 (89.0%) | |
| Uropathogen | *Escherichia coli* | 713 (87.7%) | 633 (86.6%) | 80 (97.6%) | 0.004 |
| | Non-*E. coli* | 100 (12.3%) | 98 (13.4%) | 2 (2.4%) | |
| | *Klebsiella sp.* | 39 (4.8%) | 37 (5.1%) | 2 (2.4%) | |
| | *Enterococcus sp.* | 22 (2.7%) | 22 (3.0%) | 0 (0.0%) | |
| | *Enterobacter sp.* | 17 (2.1%) | 17 (2.3%) | 0 (0.0%) | |
| | *Proteus sp.* | 7 (0.9%) | 7 (1.0%) | 0 (0.0%) | |
| | *Citrobacter sp.* | 4 (0.5%) | 4 (0.5%) | 0 (0.0%) | |
| | *Pseudomonas sp.* | 4 (0.5%) | 4 (0.5%) | 0 (0.0%) | |
| | Serratia sp. | 4 (0.5%) | 4 (0.5%) | 0 (0.0%) | |
| | Streptococcus sp. | 3 (0.4%) | 3 (0.4%) | 0 (0.0%) | |

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Of the 813 febrile infants with UTI, 89.6% had pyuria (≥ 5 WBC/HPF), 88.7% had positive LE, 67.0% had microscopic bacteriuria, and 38.0% had positive nitrite. See Table 2 for all urine culture and analysis findings. *Escherichia coli* was the predominant uropathogen (87.7%) followed by *Klebsiella* species (4.8%), *Enterococcus* species (2.7%), *Enterobacter* species (2.1%), and *Proteus* species (0.9%).

Among all febrile infants with UTI, the prevalence of bacteremia was 10.1%. The prevalence of bacteremia in febrile infants with UTI did not differ by sex (p = 0.983), but significantly differed with age (p < 0.0001). After stratifying our study population into infants <3, and 3–24 months (Table 3), we observed that the prevalence of bacteremia was significantly higher in infants < 3 months compared to those 3–24 months (14.3% vs. 4.3%, p < 0.0001). Among infants < 3 months of age with positive urine and blood cultures, 99% had the same pathogen isolated in both urine and blood cultures, thus meeting our definition of concomitant bacteremic UTI, compared to 74% of infants 3–24 months of age. Of note, preliminary blood culture result of 18 patients showed growth of *a priori* contaminants and repeat blood cultures were all negative. These patients were classified as non-bacteremic.

**Table 3** Blood culture results.

*mo:* Months, *E. Coli*: *Escherichia Coli*, Sp: Species, MRSA: Methicillin Resistant *Staphylococcus Aureus*.

| | DESCRIPTION | 0–24 MO. (n = 813) | 0 < 3 MO. (n = 469) | 3–24 MO. (n = 344) | p-VALUE |
|---|---|---|---|---|---|
| Result | Bacteremic | 82 (10.1%) | 67 (14.3%) | 15 (4.3%) | <0.0001 |
| | No bacteremia | 731 (89.9%) | 402 (85.7%) | 329 (95.6%) | |
| Organisms | *E. coli* | 75 (91.5%) | 65 (97.0%) | 10 (66.7%) | 0.002 |
| | *Streptococcus sp* | 4 (4.9%) | 1 (1.5%) | 3 (20.0%) | |
| | *Klebsiella sp* | 2 (2.4%) | 1 (1.5%) | 1 (6.7%) | |
| | *MRSA* | 1(1.2%) | 0 (0%) | 1 (6.7%) | |

Components on urinalysis associated with bacteremia among febrile infants < 3 months included microscopic bacteriuria (pOR, 2.3, p = 0.010) and pyuria (pOR, 6.7, p = 0.031). The growth of *E. coli* in urine culture was also associated with bacteremia (pOR, 9.8, p = 0.006) (Table 4). In infants < 3 months, pyuria predicted bacteremia with a sensitivity of 98.4% and negative predictive value (NPV) of 97.4%, while microscopic bacteriuria demonstrated a sensitivity of 80.0% and NPV of 91.8%. Growth of *E. coli* in urine predicted bacteremia with a sensitivity and NPV of 98.5% and 98.1%, respectively. In general, specificities for all three urinary components were poor (bacteriuria-36.8%, pyuria-10.0%, and *E. coli* growth in urine-12.9%). See supplemental data.

**Table 4** Urinary predictors of bacteremia.

OR: prevalence OR, CI: confidence interval, UTI: urinary tract infection.

| | FEBRILE CHILDREN 0 < 3 MONTHS WITH UTI | | OR (95 CI) | p-VALUE |
|---|---|---|---|---|
| | NO BACTEREMIA (n = 402) | BACTEREMIA (n = 67) | | |
| USG ≤ 1.015 | 343 (85.3%) | 63 (94.0%) | 2.7 (1.0–9.2) | 0.054 |
| Leuk esterase | 370 (92.0%) | 65 (97.0%) | 2.8 (0.8–17.6) | 0.203 |
| Bacteriuria | 257 (63.9%) | 54 (80.6%) | 2.3 (1.2–4.5) | 0.010 |
| Nitrite | 139 (34.6%) | 22 (32.8%) | 0.9 (0.5–1.6) | 0.781 |
| Pyuria | 355 (88.3%) | 63 (94.0%) | 6.7 (1.4–50.0) | 0.031 |
| *E. coli* UTI | 350 (87.1%) | 66 (98.5%) | 9.8 (2.1–72.1) | 0.006 |
| | **FEBRILE CHILDREN 3–24 MONTHS WITH UTI** | | **OR (95 CI)** | **p-VALUE** |
| | **NO BACTEREMIA (n = 329)** | **BACTEREMIA (n = 15)** | | |
| USG ≤ 1.015 | 233 (71.0%) | 14 (93.3%) | 5.7 (0.7–44.0) | 0.076 |
| Leuk esterase | 271 (82.4%) | 14 (93.3%) | 3.0 (0.6–54.8) | 0.482 |
| Bacteriuria | 223 (67.8%) | 11 (73.3%) | 1.1 (0.4–4.1) | 0.782 |
| Nitrite | 142 (41.2%) | 6 (40.0%) | 1.2 (0.4–3.3) | 0.990 |
| Pyuria | 274 (87.3%) | 12 (80.0%) | 0.6 (0.2–2.6) | 0.427 |
| *E. coli* UTI | 283 (86.0%) | 14 (93.3%) | 2.3 (0.4–41.7) | 0.703 |

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Among febrile infants 3–24 months of age with UTI, there were no significant urinary predictors of bacteremia (Table 4). In both age strata, urine specific gravity (USG), leucocyte esterase (LE), nitrites, and uropathogen colony count were not predictors of bacteremia. Of note, LE and USG <1.015 did not retain statistical significance (Table 2 and 4) following age stratification.

Across all age categories, *E. coli* was the most common pathogen in concomitant bacteremic UTI (Table 3). Among infants < 3 months of age, *E. coli* was isolated in 97.0% of positive blood culture, compared to 66.7% of infants 3–24 months with UTI. Other pathogens isolated from blood culture include *Streptococcus* species (not viridans or a priori contaminant), *Klebsiella* sp., and methicillin resistant *Staphylococcus aureus* (MRSA).

## DISCUSSION

In this single center study of febrile children ≤ 24 months with positive urine culture, the prevalence of bacteremia was 10.1%. After stratifying by age (<3 and 3–24 months), we observed that the prevalence of bacteremia in febrile infants <3 months was significantly higher compared to infants 3–24 months. Approximately 82% (~4 of 5) febrile young infants with concurrent bacteremic UTI were <3 months of age. Among febrile infants < 3 months with UTI, significant predictors of bacteremia were pyuria, bacteriuria, and growth of *E. coli* on urine culture. No component of urinalysis predicted bacteremia in infants 3–24 months.

Ninety-nine percent (99%) of bacteremic febrile infants < 3 months of age had concomitant bacteremic UTI, compared to 74% of febrile infants 3–24 months of age. *E. coli* was the most common uropathogen cultured from blood, accounting for 97% of bacteremia in febrile infants < 3 months with UTI and 67% of bacteremia in febrile young children 3- 24 months. This data is consistent with prior reports on pathogens involved in bacteremic UTI [8, 13, 21]. Averbuch [13] noting that among febrile infants 0–2 months of age with UTI, *E.coli* was the only uropathogen associated with bacteremia. The increased risk of bacteremia may be related to the virulence of pathogenic *E. coli* strains in destroying renal parenchyma with hematogenous spread to the blood and CSF [22].

Younger age (age < 3 months) has previously been shown to be a significant predictor of bacteremia in febrile children with UTI and our study corroborates these finding [12–14, 22]. The prevalence of bacteremia,— 7.3% [8], and 9.3% [12, 14] reported by Yoon, Tzimenatos, and Megged, respectively, in infants < 3 months were lower than what we observed. However, similar or much higher prevalence also have been reported—11.3% [7], 22.7% [22], and 17.3% [13]. Cohort and demographic differences may account for these variances in prevalence of bacteremia among febrile young infants.

Since young age is a significant predictor of bacteremia in febrile children with UTI, stratification into clinically meaningful age categories (0 < 3 and 3–24 months) was necessary to minimize possible confounding of our prediction model by age spectrum. Following stratification, we observed that pyuria, bacteriuria, and *E. coli* UTI remained as significant urinary predictors of bacteremia in febrile infants <3 months. Pyuria had a sensitivity of 98.4% and NPV of 97.5%; while microscopic bacteriuria demonstrated a sensitivity of 80.0% and NPV of 91.8%. Specificities for both urinary components were low.

Nitrite, USG, LE, and uropathogen colony counts were not significant predictors of bacteremia in both age strata. Although, urine specific gravity and leucocyte esterase had shown statistical significance in the combined population of children 0–24 months, they did not retain their significance after stratifying our study population into clinically meaningful age categories (Tables 2 and 4). These initial results were probably confounded by age spectrum. Although prior studies have demonstrated that urinary components like leukocyte esterase, nitrite, and pyuria predict UTI [12, 15, 16], our study only identified pyuria as a significant predictor of bacteremia in febrile young infants < 3 months with UTI.

A prior study showed that positive UA defined as presence of LE, nitrite, or pyuria in urine had a near perfect sensitivity and negative predictive value for UTI with bacteremia in febrile infants < 60 days of age [12]; however, this study did not specifically evaluate the bacteremia predictive value of each urinary component independently. In another study looking at diagnostic accuracy of UA for UTI in infants < 3 months, Schroeder [15] noted that in four infants with

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bacteremic UTI, all had bacteriuria and three had significant pyuria. This report closely reflects the significance of microscopic bacteriuria and pyuria in predicting bacteremia in febrile infants < 3 months with UTI we noted. The near perfect sensitivity and NPV reported by Tzimenatos et al., and Schroeder et al., were probably due to differences in UTI definition based on positive UA and cohort-specific age spectrum bias.

It is not clear why pyuria and bacteriuria were the only urinary components to be significantly associated with bacteremia in febrile young infants with UTI. This may be due to the relative predominance of *E. coli* uropathogen in the bacteremic subgroup. Shaikh et al. looking at the association between uropathogens and pyuria showed that the odds of pyuria was much higher with *E.coli* compared to non-*E.coli* uropathogens [23]. Magruder et al. also reported that a 1% relative gut abundance of *E.coli* was an independent risk factor for bacteriuria [24].

Although *E.coli* has also been associated with increased likelihood of leucocyte esterase and nitrite on urine dipstick [25], interestingly these urinary components were not significant predictors of bacteremia in our population. The relatively short incubation period of urine in the bladder of infants ≤ 24 months may explain why nitrite is not a sensitive predictor of UTI or bacteremia, but the non-significance of leucocyte esterase at predicting bacteremia remains unclear. Urine specific gravity < 1.015 was not significant in predicting bacteremia. The cut-off of 1.015 was set based on prior studies [19].

Although we found statistically significant associations between pyuria, bacteriuria, and growth of *E. coli* in urine culture, with bacteremia; the positive predictive values of each or a combination of these urinary components based on the test probabilities were moderate. Our findings may not be sufficient evidence to change practice guidelines but may be useful for clinicians evaluating febrile young infants < 3 months with positive urine culture who demonstrate pyuria and/or bacteriuria on UA microscopy. Future prospective studies may consider evaluating the utility of a combination of urine and blood biomarkers in predicting the likelihood of bacteremia in febrile infants.

This single institutional study specifically evaluated the utility of urinary components in predicting the likelihood of bacteremia in febrile young children with a relatively large sample size. The definition of UTI and bacteremia based on positive urine and blood cultures, and verifiable ED temperatures for fever significantly improved our case ascertainment and minimized the likelihood of misclassification. Stratification of our study population by age also reduced the likelihood of confounding by age spectrum.

However, there are several limitations. First, a non-differential selection bias by severity is likely, since we only looked at febrile patients who had concurrent or paired urine and blood culture evaluation during their ED visit. It is likely that children who had paired urine and blood culture evaluations were clinically different from those who had urine evaluation without blood culture. Theoretically, this should not create a difference between the bacteremic and non-bacteremic subgroups since the same inclusion criteria was applied to both subgroups. However, it is likely that the slightly higher prevalence of bacteremia seen on our population may be related to disease severity and the relative predominance of a younger age in this population. Second, we did not exclude immunocompromised patients and patients with background urologic anomalies, which may constitute a different risk category compared to previously well febrile infants. Third, we were also not able to perform stratified analyses looking at the bacteremia predictive value of different degrees of pyuria, bacteremia, or LE. While this may be of value, it is beyond the scope of our stated objectives. Fourth, our prediction model may not be applicable to patients with non-urinary source of bacteremia, since the majority of febrile infants < 3 months had same bacteria isolated in both urine and blood. Finally, the retrospective single center design despite stringent case ascertainment criteria may limit generalizability.

## CONCLUSIONS

Components of urinalysis may be useful in predicting bacteremia in febrile infants < 3 months with positive urine culture UTI. Among febrile infants < 3 months of age with UTI, significant urinary predictors of bacteremia were bacteriuria, pyuria, and growth of *E. coli* in urine culture. These urinary components were not significant predictors of bacteremia in children 3–24 months. Prospective studies are needed to validate these findings.

## COMPETING INTERESTS

The authors have no competing interests to declare.

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