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Serious Bacterial Infections in Young Febrile Infants With Positive Urinalysis Results

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abstract

OBJECTIVE: To determine the prevalence of bacteremia and/or bacterial meningitis in febrile infants ≤60 days of age with positive urinalysis (UA) results.

METHODS: Secondary analysis of a prospective observational study of noncritical febrile infants ≤60 days between 2011 and 2019 conducted in the Pediatric Emergency Care Applied Research Network emergency departments. Participants had temperatures ≥38°C and were evaluated with blood cultures and had UAs available for analysis. We report the prevalence of bacteremia and bacterial meningitis in those with and without positive UA results.

RESULTS: Among 7180 infants, 1090 (15.2%) had positive UA results. The risk of bacteremia was higher in those with positive versus negative UA results (63/1090 [5.8%] vs 69/6090 [1.1%], difference 4.7% [3.3% to 6.1%]). There was no difference in the prevalence of bacterial meningitis in infants ≤28 days of age with positive versus negative UA results (~1% in both groups). However, among 697 infants aged 29 to 60 days with positive UA results, there were no cases of bacterial meningitis in comparison to 9 of 4153 with negative UA results (0.2%, difference -0.2% [-0.4% to -0.1%]). In addition, there were no cases of bacteremia and/or bacterial meningitis in the 148 infants ≤60 days of age with positive UA results who had the Pediatric Emergency Care Applied Research Network low-risk blood thresholds of absolute neutrophil count $<4\times10^3$ cells/mm^3 and procalcitonin <0.5 ng/mL.

CONCLUSIONS: Among noncritical febrile infants ≤60 days of age with positive UA results, there were no cases of bacterial meningitis in those aged 29 to 60 days and no cases of bacteremia and/or bacterial meningitis in any low-risk infants based on low-risk blood thresholds in both months of life. These findings can guide lumbar puncture use and other clinical decision making.

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WHAT'S KNOWN ON THIS SUBJECT: Studies regarding the risk of concomitant bacteremia and/or bacterial meningitis(ie, invasive bacterial infections) in febrile infants ≤60 days old with urinary tract infections are limited because of their small cohort size, retrospective design, and variable inclusion/exclusion criteria.

WHAT THIS STUDY ADDS: Among low-risk febrile infants ≤60 days old with positive urinalysis results, there were no cases of bacterial meningitis in those 29 to 60 days old and no cases of invasive bacterial infections in infants with normal absolute neutrophil counts and serum procalcitonin levels.

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~10% of febrile infants ≤60 days old have serious bacterial infections (SBIs), including 8% with urinary tract infections (UTIs), 1.8% with bacteremia, and 0.5% with bacterial meningitis (the latter 2 categorized as invasive bacterial infections [IBIs]).[1–5] Although the prevalence of IBIs is low, there are little data on the precise risk of bacteremia and bacterial meningitis in febrile infants with UTIs. The implications are important as clinicians must decide whether infants with positive screening urinalysis (UA) results should undergo lumbar punctures (LPs) at the time of evaluation.

Parents of young febrile infants are often reluctant to have LPs performed on their children,[6] given the discomfort involved. In addition, other potential risks include secondary infection, bleeding, unnecessary antibiotic administration, and unnecessary hospitalization.[7–9] In addition, there is substantial practice pattern variation in the performance of LPs among clinicians.[4,10,11] Authors of previous studies regarding the prevalence of bacterial meningitis and bacteremia in the presence of UTIs or positive UA results have mostly used retrospective data, often with small sample sizes with small numbers of IBIs.[12–17] In addition, several publications, including a recent meta-analysis, have questioned the need for performing LPs in febrile infants with positive UA results, especially in the second month of life.[12,13,18] It is now possible to further risk stratify febrile infants for SBIs using a simple prediction rule derived from the Pediatric Emergency Care Applied Research Network (PECARN) that uses UA, absolute neutrophil count (ANC), and serum procalcitonin (PCT) values with high accuracy.[19,20]

We sought to determine the prevalence of concomitant bacteremia and/or bacterial meningitis in febrile infants ≤60 days old with positive UA results. We also analyzed the subgroup of febrile infants 22 to 28 days old recently recognized by the American Academy of Pediatrics.[21]

METHODS

Setting

We conducted a secondary analysis of a large prospective observational study to identify SBIs in febrile infants ≤60 days old who had at least a blood culture obtained.[22] The parent study enrolled a convenience sample of febrile infants presenting to 26 emergency departments (EDs) in PECARN between March 2011 and April 2019. The institutional review board for each participating hospital approved this study and informed consent from the parent or legally authorized representative was obtained.

Patient Eligibility

In the parent study, we enrolled 7407 febrile infants (temperatures ≥38°C in ED, from a referring facility or by history) and excluded infants with histories of prematurity (<37 weeks' gestation), significant comorbid conditions, antibiotic use in the preceding 48 hours, and those with critical illnesses requiring endotracheal intubation or vasoactive medication. Infants were eligible for the current analysis if they had UAs performed. We excluded infants from this analysis if a UA was not performed and cerebrospinal fluid was not obtained at the ED visit and we were unable to contact the parents at a 7 day follow-up telephone call.

Study Definitions

UAs were completed according to standard procedures at the participating hospitals' clinical laboratories. We defined a positive UA result by the presence of nitrites, any leukocyte esterase, or >5 white blood cells per high-power field.[2] We evaluated both the individual components of the UA and the UA in aggregate. We defined UTI as the growth of ≥50 000 colony-forming units [CFU]/mL of a known urinary pathogen from a culture obtained via catheterization or ≥10 000 CFU/mL from a catheterized specimen in association with an abnormal UA result or ≥1000 CFU/mL from a culture obtained via suprapubic aspiration. We defined a negative urine culture result as one with no growth, growth of a contaminant in the absence of a pathogen, or growth of a pathogen that did not reach the CFU/mL threshold. We defined bacteremia and bacterial meningitis by the growth of a known pathogen. All culture results were reviewed and assigned as positive or negative by consensus of the 3 Principal investigators, 1 of whom is a pediatric infectious disease specialist.

Statistical Analysis

We described the study population in 2 age cohorts (28 days old and younger and 29 to 60 days old) using counts and percentages for categorical variables and means and standard deviations or medians and interquartile ranges for continuous variables. We compared the demographic and clinical characteristics of infants with positive and negative UA results using risk differences and 95% confidence intervals (CI). We performed a separate analysis for infants 22 to 28 days of age. As predictor variables for IBI in multivariable models, we included age, qualifying temperature, Yale Observation Scale score,[1] white blood cell count, ANC, and 1 model with and another without serum PCT level. We also performed multivariable analysis to identify factors associated with IBIs in febrile infants with UTIs. Finally, we determined the prevalence of IBIs in

the cohort of febrile infants with positive UA results using low-risk cutoffs of ANC ($<4 \times 10^3$ cells/mm^3) and PCT (<0.5 ng/mL) according to the PECARN Febrile Infant Prediction rule.[19] All analyses were performed in SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Among the 7407 febrile infants enrolled in the parent study, 7180 (96.9%) infants were eligible for analysis, of whom 1090 (15.2%) had positive UA results (Fig 1). Patients with positive UA results had higher levels of blood inflammatory markers and were more likely to be hospitalized than those with negative UA results (Table 1).

Of the patients with positive UA results, nearly one-half had UTIs (Table 2). In contrast, few patients with negative UA results had UTIs. The overall risk of IBI was significantly higher in infants with positive versus negative UA results (Table 2). This increased risk was greatly driven by the higher prevalence of bacteremia in infants with positive UAs in both the first and second months of life. There was no difference in the prevalence of bacterial meningitis between the 2 groups in the first month of life. Importantly, however, of 697 infants 29 to 60 days old with positive UA results, there were no cases of bacterial meningitis (Table 2). A description of the bacterial pathogens involved in each of the IBIs is provided in Supplemental Table 4. Notably, *E. coli* was the most common bacterial cause of concomitant UTIs and bacteremia although Group B *Streptococcus* caused most cases of bacterial meningitis with few cases of concomitant UTIs. The characteristics and rates of IBIs of patients who were enrolled in the original cohort, but who were excluded from the current analysis because the UA and/or bacterial meningitis status were missing ($n = 227$) were similar to patients included in this analysis (Supplemental Table 5).

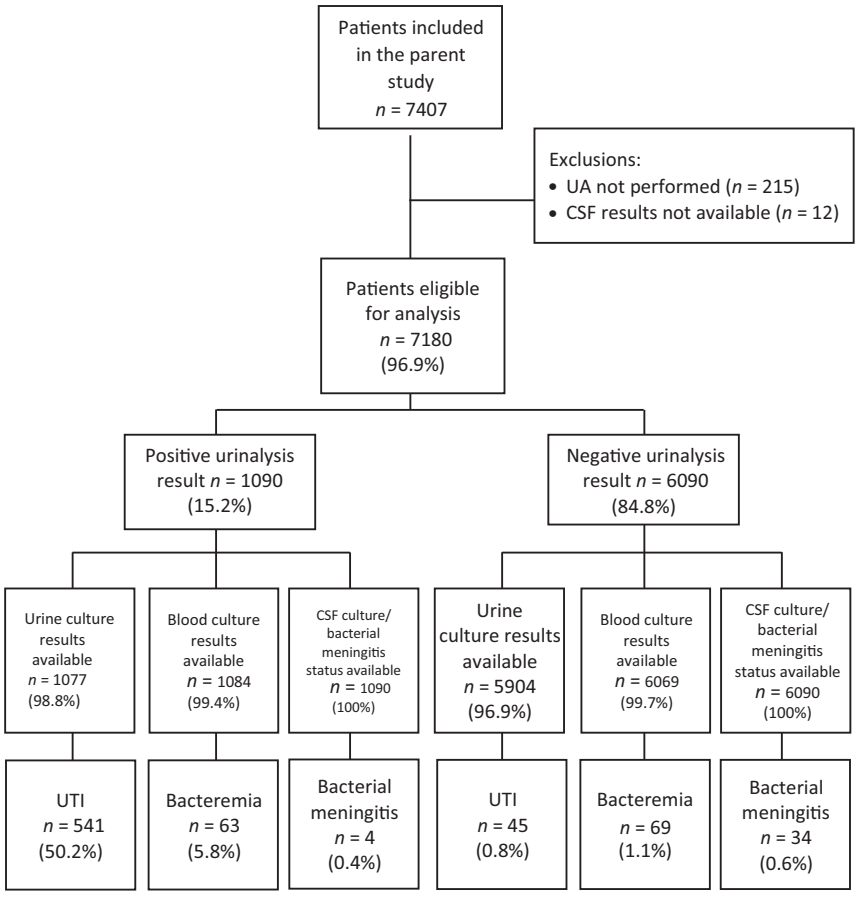

FIGURE 1
Patient enrollment.

The univariable and multivariable analyses evaluating the associations with IBI among infants with positive UA results are shown in Supplemental Tables 6 and 7. Because PCT was not obtained in the entire analytic cohort, we developed 2 separate multivariable models with ($n = 470$) and without PCT ($n = 1047$) results available to identify factors independently associated with IBIs in febrile infants with positive UA results. Among febrile infants who had PCT results available, only age and serum PCT were independently associated with IBI among those with positive UA results. When PCT was not included in the model, younger age, higher temperature, and higher ANC were identified as independent predictors of IBI (Supplemental Table 7). In an analysis of those with positive UA results and low-risk blood biomarkers per the PECARN febrile infant SBI prediction rule (ie, ANC $<4 \times 10^3$ cells/mm^3 and PCT <0.5 ng/mL),[19,20] there were no cases of bacteremia or bacterial meningitis in the first or second month of life (Table 3). Of those with PCT <0.5 ng/mL, none of the 283 had bacterial meningitis.

TABLE 1 Demographics of the Study Population

	Urinalysis		
	Positive (n = 1090)	Negative (n = 6090)	Difference (95% CI)
Sex			
Male	632 (58.0%)	3451 (56.7%)	1.31% (−1.9% to 4.5%)
Female	458 (42.0%)	2639 (43.3%)	−1.3% (−4.5% to 1.9%)
Age, ≤28 d vs >28 d			
≤28 d	393 (36.1%)	1937 (31.8%)	4.2% (1.2% to 7.3%)
22–28 d	119 (10.9%)	749 (12.3%)	−1.4% (−3.4% to 0.6%)
>28 d	697 (63.9%)	4153 (68.2%)	−4.2% (−7.3% to −1.2%)
Qualifying elevated temperature in Celsius			
Mean (SD)	38.6 (0.49)	38.5 (0.44)	0.1 (0.1 to 0.15
Duration of fever			
<12 h	603 (55.3%)	3501 (57.5%)	−2.2% (−5.4% to 1.0%)
12–24 h	248 (22.8%)	1285 (21.1%)	1.7% (−1.0% to 4.3%)
>24 h	83 (7.6%)	381 (6.3%)	1.4% (−0.3% to 3.0%)
Unknown	156 (14.3%)	923 (15.2%)	−0.8% (−3.1% to 1.4%)
After physical examination, but before laboratory testing, clinical assessment of risk of SBI			
<1% (minimal)	315 (28.9%)	2254 (37.0%)	−8.1% (−11.1% to −5.2%)
1%–5% (slight)	453 (41.6%)	2571 (42.2%)	−0.7% (−3.8% to 2.5%)
6%–10% (somewhat)	192 (17.6%)	885 (14.5%)	3.1% (0.7% to 5.5%)
11%–50% (likely)	89 (8.2%)	260 (4.3%)	3.9% (2.2% to 5.6%)
>50% (very likely)	17 (1.6%)	46 (0.8%)	0.8% (0.0% to 1.6%)
Unknown	24 (2.2%)	74 (1.2%)	1.0% (0.1% to 1.9%)
Yale observation scale			
Median (IQR)	6.0 (6.0 to 8.0)	6.0 (6.0 to 8.0)	0.0 (−0.2 to 0.2)
White blood cell count × 1000 cells/mm^3			
Mean (SD)	13.0 (5.80)	10.1 (4.33)	2.9 (2.5 to 3.2)
Absolute neutrophil count × 1000 cells/mm^3			
Mean (SD)	6.1 (4.37)	3.8 (2.75)	2.3 (2.1 to 2.6)
Viral status			
Not tested	435 (39.9%)	2090 (34.3%)	5.6% (2.4% to 8.7%)
Negative or inconclusive	468 (42.9%)	2148 (35.3%)	7.7% (4.5% to 10.8%)
Positive	187 (17.2%)	1852 (30.4%)	−13.3% (−15.8% to −10.7%)
Procalcitonin result (ng/mL)			
n	477	2738	—
Mean (SD)	2.9 (10.39)	0.7 (3.89)	2.2 (1.3 to 3.2)
Disposition			
Discharged	139 (12.8%)	1901 (31.2%)	−18.5% (−20.8% to −16.2%)
Admitted	950 (87.2%)	4181 (68.7%)	18.5% (16.2% to 20.8%)
Other	1 (0.1%)	8 (0.1%)	−0.0% (−0.2% to 0.2%)

IQR< interquartile range; SD, standard deviation; —, not applicable.
Differences and 95% CI are calculated as risk differences for categorical variables and mean differences for continuous variables.

Finally, we describe the demographics of febrile infants with UTIs in Supplemental Table 8. In univariable and multivariable analyses, we found that, when available, PCT was the only independent predictor for IBI among patients with UTIs. When PCT was not included as a predictor, only age ≤28 days was an independent predictor (Supplemental Tables 9 and 10).

DISCUSSION

In this analysis of a large, prospectively enrolled cohort of noncritically ill febrile infants ≤60 days old, we found that the rate of bacteremia was higher but the rate of bacterial meningitis was lower in infants with positive UA results. The rate of bacterial meningitis was similar in the first month of life regardless of UA results. However, there were no cases of bacterial meningitis in the second month of life among those with positive UA results. In addition, there were no cases of bacterial meningitis in any infants with positive UA results who had low serum PCT levels, and no cases of bacteremia among any infants who had both normal ANC and serum PCT levels according to a recently published prediction rule but here applied specifically to febrile infants with positive UA results.[19,20]

Several previous studies have investigated the prevalence of IBIs in young febrile infants with positive UA results.[12–14] Some were conducted retrospectively and others prospectively. A retrospective analysis of a cohort of 833 febrile

TABLE 2 SBI Status Distributed by Urinalysis Results: Patients Who Have UA Results and Meningitis Results Available

	UA Positive (n = 1090)	UA Negative (n = 6090)	Difference (95% CI)
Serious bacterial infection	547/1090 (50.2%)	130/6090 (2.1%)	48.7% (45.7% to 51.7%)
Age ≤28 d	221/393 (56.2%)	63/1937 (3.3%)	53.8% (48.8% to 58.8%)
Age 22–28 d	57/119 (47.9%)	18/749 (2.4%)	46.2% (37.1% to 55.4%)
Age >28 d	326/697 (46.8%)	67/4153 (1.6%)	45.8% (42.0% to 49.5%)
Invasive bacterial infections	64/1090 (5.9%)	87/6090 (1.4%)	4.5% (3.0% to 5.9%)
Age ≤28 d	36/393 (9.2%)	50/1937 (2.6%)	6.6% (3.7% to 9.6%)
Age 22–28 d	4/119 (3.4%)	10/749 (1.3%)	2.1% (−1.3% to 5.5%)
Age >28 d	28/697 (4.0%)	37/4153 (0.9%)	3.1% (1.6% to 4.6%)
Bacteremia status	63/1090 (5.8%)	69/6090 (1.1%)	4.7% (3.3% to 6.1%)
Age ≤28 d	35/393 (8.9%)	36/1937 (1.9%)	7.1% (4.2% to 10.0%)
Age 22–28 d	3/119 (2.5%)	7/749 (0.9%)	1.7% (−1.3% to 4.6%)
Age >28 d	28/697 (4.0%)	33/4153 (0.8%)	3.2% (1.7% to 4.7%)
Bacterial meningitis status	4/1090 (0.4%)	34/6090 (0.6%)	−0.2% (−0.6% to 0.2%)
Age ≤28 d	4/393 (1.0%)	25/1937 (1.3%)	−0.3% (−1.4% to 0.8%)
Age 22–28 d	1/119 (0.8%)	4/749 (0.5%)	0.3% (−1.4% to 2.0%)
Age >28 d	0/697 (0.0%)	9/4153 (0.2%)	−0.2% (−0.4% to −0.1%)
UTI status	541/1090 (49.6%)	45/6090 (0.7%)	49.5% (46.5% to 52.5%)
Age ≤28 d	216/393 (55.0%)	13/1937 (0.7%)	55.0% (50.0% to 59.9%)
Age 22–28 d	57/119 (47.9%)	8/749 (1.1%)	47.2% (38.2% to 56.3%)
Age >28 d	325/697 (46.6%)	32/4153 (0.8%)	46.4% (42.6% to 50.1%)
UTI Positive			
Bacterial meningitis status	3/541 (0.6%)	0/45 (0.0%)	0.6% (−0.1% to 1.2%)
Age ≤28 d	3/216 (1.4%)	0/13 (0.0%)	1.4% (−0.2% to 2.9%)
Age 22–28 d	1/57 (1.8%)	0/8 (0.0%)	1.8% (−1.7% to 5.2%)
Age >28 d	0/325 (0.0%)	0/32 (0.0%)	—

—, risk difference not able to be computed.

infants aged 29 to 60 days in an outpatient ambulatory care setting did not reveal differences in the prevalence of bacterial meningitis among infants with positive UA results versus negative UA results.[13] Other investigators reviewed a large, multicenter cohort (n = 20 570) of well-appearing febrile infants 7 to 60 days old[12] and found no difference in the treatment rate for bacterial meningitis between febrile infants with positive versus negative UA results. A recent systematic review and meta-analysis that included pooled data from 48 studies in 2703 infants aged 29 to 60 days with positive UA results revealed no differences in the prevalence of bacterial meningitis when compared with those with negative UA results (n = 10 032).[18] Of note, a recent retrospective review of febrile infants ≤60 days with positive UA results and IBI revealed a substantially higher number (n = 14) of febrile infants with bacterial meningitis; 7 each in the first and second months of life.[23] The 3 high-risk criteria identified (high-risk past medical history, ill appearance, and/or abnormal white blood cell count) had a sensitivity of only 53.4% (95% CI: 45.0 to 61.6) for identifying IBI. Because patients were assessed retrospectively, it is difficult to know their clinical appearance and therefore whether they would qualify for our study.

In a prospective multicenter study in Spain to derive a prediction model for IBI among 766 febrile infants ≤90 days old with abnormal UA results on the dipstick, of whom 39 had IBIs, well appearance, age >21 days, normal C-reactive protein,

TABLE 3 Bacteremia Distribution Among UA Positive Patients Across ANC and PCT Levels

	ANC $<4 \times 10^3$ cells/mm^3		ANC $\geq 4 \times 10^3$ cells/mm^3	
	PCT <0.5 ng/mL	PCT ≥0.5 ng/mL	PCT <0.5 ng/mL	PCT ≥0.5 ng/mL
Bacteremia	0/148 (0.0%)	1/32 (3.1%)	3/135 (2.2%)	23/325 (7.1%)
≤28 d	0/37 (0.0%)	1/13 (7.7%)	1/40 (2.5%)	13/121 (10.7%)
>28 d	0/111 (0.0%)	0/19 (0.0%)	2/95 (2.1%)	10/204 (4.9%)
Bacterial meningitis	0/148 (0.0%)	0/32 (0.0%)	0/135 (0.0%)	1/158 (0.6%)
≤28 d	0/37 (0.0%)	0/13 (0.0%)	0/40 (0.0%)	1/68 (1.5%)
>28 d	0/111 (0.0%)	0/19 (0.0%)	0/95 (0.0%)	0/90 (0.0%)

and normal PCT values had 100% sensitivity and negative predictive values for identifying those with IBIs.[14] In a more recent study, the same investigators derived and validated a prediction model with excellent performance characteristics consisting of 3 criteria: age ≤15 days, PCT ≥0.6 ng/mL, and CRP ≥20 mg/L among 1111 febrile infants aged ≤90 days with positive UA results to identify those at high risk of IBI ($n = 57$).[24] Our results were similar to these 2 studies and, although we did not evaluate C-reactive protein in our cohort, both young age and elevated PCT were associated with IBIs in febrile infants with positive UA results. Our large prospective cohort study revealed that there were no cases of bacterial meningitis in the second month of life among 697 infants with positive UA results.

Our main analysis focused on the risk of IBIs in febrile infants with positive UA results because the results of this routinely performed test are available in near real-time in many clinical settings and can influence provider decision-making regarding the performance of LPs. Several studies have investigated the prevalence and risk for bacterial meningitis in febrile infants with UTIs and have revealed a higher prevalence of bacterial meningitis among infants <28 days old compared with 29 to 60 days old,[15] no cases of bacterial meningitis in infants <28 days,[16] and only 1 instance of possible bacterial meningitis in a 46-day-old febrile infant.[17] Our results were similar because young age and elevated serum PCT were associated with IBIs in febrile infants with confirmed UTIs. Despite similarities of our study results to most of the above-mentioned studies identifying prevalence and risk factors for IBIs using either abnormal UA or UTIs, there are some important differences that make direct comparisons difficult. These include varying definitions of UTI (defined by cultures vs abnormal UA result), retrospective versus prospective study designs, and differing age cutoffs (0–90 days vs ≤30 days vs 29–60 days).

There are several important implications of our study results. First, the pathogens causing bacterial meningitis (typically Group B *Streptococcus*) are different from those associated with UTIs (typically Gram-negative bacteria, most commonly *E. coli*); thus, the screening test for UTI (ie, the UA) is unlikely to be abnormal in infants with bacterial meningitis, although frequently positive in those with bacteremia. Second, there was an overall higher prevalence of IBIs in the first month of life. Although there were no instances of bacterial meningitis in febrile infants in the first month of life with positive UA results who had normal ANC and PCT levels, we concur with the American Academy of Pediatrics guidelines regarding the recommendation to perform LPs on all those 8 to 21 days old and those 22 to 28 days old with positive blood inflammatory markers. The risk of herpes simplex virus meningitis and bacterial meningitis in these age groups justifies this approach. In the second month of life, however, in the presence of a positive UA result, given the lack of bacterial meningitis, one could strongly consider not performing an LP. In addition, the ANC and serum PCT can further aid the clinician in decision-making regarding the risk of bacteremia and bacterial meningitis among infants ≤60 days with positive UA results and the need for more intensive therapy.

Additionally, opportunities exist for a patient-centered, shared decision making approach while evaluating the well-appearing febrile infant in the first 2 months of life. For instance, those with positive UA results in the second month of life and low-risk values of ANC and serum PCT could be considered for outpatient management with close follow-up as the risk of IBI is extremely low. In addition, less aggressive evaluation and management could be considered for 22- to 28-day-old infants, as well, with low-risk values of ANC and PCT.[21] One could consider a strategy of no LP, administering antibiotics with brief inpatient or ED observation, and close follow-up. Our study results can also help reduce practice pattern variation by providing clinicians with more precise estimates of risks of bacteremia and bacterial meningitis in the presence of a positive UA result.[6] By helping to mitigate the use of LPs, patient discomfort, parental anxiety, costs, and complications associated with this invasive procedure can be reduced.[9,11]

Our study has some limitations. We enrolled a convenience sample of febrile infants across PECARN on the basis of research staff availability at the time of patient enrollment. However, the prevalence of IBIs in the cohort of febrile infants that were eligible for enrollment but were missed was similar to the enrolled cohort. In addition, the prevalence of IBIs in the enrolled cohort was similar to the prevalence revealed by recent studies.[5,25,26] Additionally, the low prevalence of bacterial meningitis in our cohort, despite its large sample size, limits the power of our conclusions. However, this reflects the overall low prevalence of this disease in the general population. PECARN EDs are also specialized pediatric EDs, and our cohort may not represent the population of febrile infants evaluated in

community EDs; however, this is unlikely to limit the generalizability of our findings. Finally, the role of PCT in risk stratifying febrile infants with positive UA results who have IBIs is limited by the number of patients in whom PCT was measured.

CONCLUSIONS

The risk of bacterial meningitis is low in the second month of life in well-appearing febrile infants with positive UA results, regardless of inflammatory biomarker levels. Therefore, LPs are not typically needed in the evaluation of fever in these infants. However, in those infants with positive blood biomarkers, shared decision-making may be useful in LP decision making. Finally, because the prevalence of bacteremia is higher in well-appearing febrile infants ≤60 days old with positive UA results compared with those with negative UA results, blood tests for screening biomarkers and blood cultures should be strongly considered.

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ABBREVIATIONS

ANC: absolute neutrophil count
CI: confidence interval
ED: emergency department
IBI: invasive bacterial infection
LP: lumbar puncture
PCT: procalcitonin
PECARN: Pediatric Emergency Care Applied Research Network
SBI: serious bacterial infection
UA: urinalysis
UTI: urinary tract infection

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