BRIEF REPORT

Febrile Infants ≤60 Days Old With Positive Urinalysis Results and Invasive Bacterial Infections

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ABSTRACT

OBJECTIVES: We aimed to describe the clinical and laboratory characteristics of febrile infants ≤60 days old with positive urinalysis results and invasive bacterial infections (IBI).

METHODS: We performed a planned secondary analysis of a retrospective cohort study of febrile infants ≤60 days old with IBI who presented to 11 emergency departments from July 1, 2011, to June 30, 2016. For this subanalysis, we included infants with IBI and positive urinalysis results. We analyzed the sensitivity of high-risk past medical history (PMH) (prematurity, chronic medical condition, or recent antimicrobial receipt), ill appearance, and/or abnormal white blood cell (WBC) count (<5000 or >15 000 cells/μL) for identification of IBI.

RESULTS: Of 148 febrile infants with positive urinalysis results and IBI, 134 (90.5%) had bacteremia without meningitis and 14 (9.5%) had bacterial meningitis (11 with concomitant bacteremia). Thirty-five infants (23.6%) with positive urinalysis results and IBI did not have urinary tract infections. The presence of high-risk PMH, ill appearance, and/or abnormal WBC count had a sensitivity of 53.4% (95% confidence interval: 45.0–61.6) for identification of IBI. Of the 14 infants with positive urinalysis results and concomitant bacterial meningitis, 7 were 29 to 60 days old. Six of these 7 infants were ill-appearing or had an abnormal WBC count. The other infant had bacteremia with cerebrospinal fluid pleocytosis after antimicrobial pretreatment and was treated for meningitis.

CONCLUSIONS: The sensitivity of high-risk PMH, ill appearance, and/or abnormal WBC count is suboptimal for identifying febrile infants with positive urinalysis results at low risk for IBI. Most infants with positive urinalysis results and bacterial meningitis are ≤28 days old, ill-appearing, or have an abnormal WBC count.

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All risk-stratification criteria for febrile infants ≤60 days old include a positive urinalysis result as a criterion to classify infants as nonlow-risk for invasive bacterial infection (IBI) (ie, bacteremia and/or bacterial meningitis).[1] Consequently, many febrile infants with positive urinalysis results undergo lumbar puncture and are hospitalized with empirical intravenous antimicrobial therapy while awaiting culture results.[2,3] Although a positive urinalysis result alone may not increase the risk that an infant has bacterial meningitis,[3,4] the optimal strategy to stratify risk of IBI among febrile infants with positive urinalysis results remains uncertain. Identifying febrile infants with positive urinalysis results at low risk of having an IBI could assist clinical decision-making by recognizing a subset of patients in whom it is safe to avoid lumbar puncture and treat with oral antimicrobial therapy as an outpatient.[2] Our objective was to describe the clinical and laboratory characteristics of febrile infants ≤60 days old with positive urinalysis results and IBI.

METHODS

We performed a planned secondary analysis of a retrospective cohort study of infants ≤60 days old who presented to 11 emergency departments (EDs) between July 1, 2011, and June 30, 2016, and had a rectal temperature ≥38.0°C measured at home, in a clinic, or in the ED.[5] The study was approved by each site's institutional review board.

Infants with IBI were identified by query of microbiology laboratories or electronic health record systems at each site and were included if an a priori defined pathogen was identified in blood culture (bacteremia) and/or cerebrospinal fluid (CSF) culture (definite bacterial meningitis) and was treated as a pathogen clinically. Infants with bacteremia and CSF pleocytosis but negative CSF culture after antimicrobial pretreatment were classified as having possible bacterial meningitis if the infant was treated for meningitis.[6] We conducted medical record review for each infant to confirm eligibility and to extract demographic, clinical, and laboratory data. Additional details of the study have been described previously.[5,6]

We limited this secondary analysis to infants with IBI and a positive urinalysis result, which was defined per established criteria as positive leukocyte esterase (excluding trace), nitrite positivity, or >5 white blood cells (WBCs) per high powered field.[7,8] We defined urinary tract infection (UTI) as a catheterized urine culture with ≥10 000 colony-forming units (CFUs)/mL of a single pathogen or ≥100 000 CFUs/mL of a single pathogen from a bagged urine specimen or unknown method of collection only if the pathogen was also identified in the blood.[6] High-risk past medical history (PMH) was defined as gestational age <37 weeks, presence of a chronic medical condition,[9,10] or antimicrobial receipt in the past 72 hours.[11] Ill appearance was defined by any of the following documented in the ED physical examination: ill appearing, toxic, limp, unresponsive, gray, cyanotic, apnea, weak cry, poorly perfused, grunting, listless, lethargic, or irritable.[6,12] We defined an abnormal peripheral WBC count as <5000 or >15 000 cells/μL.[11]

We calculated the sensitivity of the following characteristics for identification of IBI among infants with positive urinalysis results, overall and stratified by age (≤28 days vs 29–60 days old) and type of infection (bacteremia without meningitis and bacterial meningitis): high-risk PMH, ill appearance, or abnormal peripheral WBC. We also described the clinical and laboratory characteristics of infants with definite or possible bacterial meningitis. Statistical analyses were performed by using Stata Data Analysis and Statistical Software version 15.0 (StataCorp, Inc, College Station, TX).

RESULTS

Of 350 febrile infants ≤60 days old with IBI, 148 had positive urinalysis results. Of these 148 infants, 134 (90.5%) had bacteremia without meningitis, and 14 (9.5%) had definite (11) or possible (3) bacterial meningitis (11 with concomitant bacteremia); 113 (76.4%) had UTIs, including 7 with a bagged or undocumented method of collection (all of whom had *Escherichia coli* bacteremia). Overall, 76 infants were ≤28 days (51.4%) and 72 (48.7%) were 29 to 60 days old. Seven of the 14 infants with bacterial meningitis (50%) were 29 to 60 days old.

TABLE 1 Clinical and Laboratory Characteristics of Febrile Infants ≤60 Days Old With Positive Urinalysis Results and IBIs

	High-Risk PMH[a] *n* (%)	Ill Appearing *n* (%)	Peripheral WBC <5000 or >15 000, *n* (%)	High-Risk PMH, Ill Appearing, or Abnormal WBC,[b] *n* (%; 95% CI)[c]
Age ≤28 d				
All infants with IBI, *n* = 76	17 (22.4)	14 (18.4)	29 (38.2)	43 (56.6; 44.7–67.9)
Bacteremia without meningitis, *n* = 69	17 (24.6)	12 (17.4)	26 (37.7)	39 (56.5; 44.0–68.4)
Bacterial meningitis, *n* = 7[c]	0 (0)	2 (28.6)	3 (42.9)	4 (57.1; 18.4–90.1)
Age 29–60 d				
All infants with IBI, *n* = 72	15 (20.8)	10 (13.9)	29 (40.3)	36 (50.0; 38.0–62.0)
Bacteremia without meningitis, *n* = 65	13 (20.0)	6 (9.2)	24 (36.9)	30 (46.2; 33.7–59.0)
Bacterial meningitis, *n* = 7[c]	2 (28.6)	4 (57.1)	5 (71.4)	6 (85.7; 42.1–99.6)

CI, confidence interval.

[a] Presence of gestational age <37 wk, chronic medical condition, or antimicrobial receipt in preceding 72 h.

[b] Abnormal WBC defined as peripheral WBC <5000 or >15 000 cells/μL.

[c] Definite (*n* = 11) or possible (*n* = 3) bacterial meningitis.

Among the 148 infants with positive urinalysis results and IBI, 58 (39.2%) had an abnormal peripheral WBC count. Overall, the presence of a high-risk PMH, ill appearance, or abnormal WBC count had a low sensitivity for IBI (53.4%; 95% confidence interval: 45.0–61.6), which was similar among infants ≤28 days and those 29 to 60 days of age (Table 1).

Thirty-five infants (23.6%) with positive urinalysis results and IBI did not have UTIs, including 25 infants with no bacterial growth on urine culture (Table 2). Thirteen of these infants (1 with possible meningitis) did not have a high-risk PMH, ill appearance, or abnormal WBC count; 5 had *E coli*, 4 had group B *Streptococcus* (GBS), 2 had *Enterococcus spp*, 1 had *Staphylococcus aureus*, and 1 had *Klebsiella oxytoca*.

Of the 14 infants with positive urinalysis results and concomitant bacterial meningitis, 7 were 29 to 60 days old (Table 3). Six of these infants (85.7%) were ill-appearing and/or had an abnormal WBC count. The other infant was a 39-day-old infant initially discharged from the ED on cefidinir for presumptive UTI, who had a return visit within 24 hours. The infant had *E coli* bacteremia and CSF pleocytosis (differential: 84% polymorphonuclear cells, 3% lymphocytes, 13% monocytes) but negative CSF culture after antimicrobial treatment and was treated for meningitis without reported adverse outcome.

TABLE 2 Characteristics of Febrile Infants ≤60 Days Old With Positive Urinalysis Results and IBIs but Without UTIs

Clinical and Laboratory Characteristics	Bacteremia and/or Bacterial Meningitis (n = 35), n (%)	Bacteremia Without Meningitis (n = 26), n (%)	Bacterial Meningitis (n = 9), n (%)
Age			
≤28 d	17 (48.6)	14 (53.9)	3 (33.3)
29–60 d	18 (51.4)	12 (46.2)	6 (66.7)
History and physical exam			
High-risk PMH[a]	11 (31.4)	9 (34.6)	2 (22.2)
Ill appearance	11 (31.4)	6 (23.1)	5 (55.6)
Urine dipstick			
Leukocyte esterase positive[b]	17 (48.6)	15 (57.7)	2 (22.2)
Nitrite positive	5 (14.3)	3 (11.5)	2 (22.2)
Urine WBC			
Not performed	1 (2.9)	1 (3.8)	0 (0)
0–5	7 (20.0)	6 (23.1)	1 (11.1)
6–10	11 (31.4)	6 (23.1)	5 (55.6)
11–20	7 (20.0)	5 (19.2)	2 (22.2)
>20	9 (25.7)	8 (30.8)	1 (11.1)
Peripheral WBC <5000 or >15 000 cells/μL	16 (45.7)	10 (38.5)	6 (66.7)
Urine culture			
Not performed	1 (2.9)	1 (3.8)	0 (0)
No growth	25 (71.4)	17 (65.4)	8 (88.9)
Mixed flora	2 (5.7)	2 (7.7)	0 (0)
<10 000 CFUs/mL	5 (14.3)	4 (15.4)	1 (11.1)
10 000–49 000 CFUs/mL[c]	1 (2.9)	1 (3.8)	0 (0)
50 000–100 000 CFUs/mL[d]	1 (2.9)	1 (3.8)	0 (0)
Blood and/or CSF pathogens			
GBS	11 (31.4)	8 (30.6)	3 (33.3)
E coli	10 (28.6)	8 (30.6)	2 (22.2)
S aureus	4 (11.4)	4 (15.4)	0 (0)
Enterococcus spp[e]	4 (11.4)	4 (15.4)	0 (0)
K oxytoca[e]	2 (5.7)	2 (7.7)	0 (0)
Pseudomonas aeruginosa	2 (5.7)	1 (3.8)	1 (11.1)
Listeria monocytogenes	1 (2.9)	0 (0)	1 (11.1)
Streptococcus pneumoniae	1 (2.9)	0 (0)	1 (11.1)
Neisseria meningitidis	1 (2.9)	0 (0)	1 (11.1)

[a] Presence of gestational age <37 wk, chronic medical condition, or antimicrobial receipt in preceding 72 h.
[b] Trace leukocyte esterase defined as negative.
[c] Unknown method of urine collection.
[d] Bag specimen.
[e] One infant had blood culture positive for both *Enterococcus* spp and *K oxytoca*.

DISCUSSION

In this multicenter descriptive study, high-risk PMH, ill appearance, and/or abnormal peripheral WBC count had low sensitivity for IBI among febrile infants ≤60 days old with positive urinalysis results. Most infants with positive urinalysis results and bacterial meningitis were ≤28 days old, ill-appearing, or had abnormal WBC counts.

Approximately 6.5% of febrile infants with positive urinalysis results have a concomitant IBI.[13,14] Existing risk stratification criteria classify infants with positive urinalysis results as nonlow-risk; consequently, these infants are often hospitalized and treated with empirical antimicrobial therapy pending culture results.[2] Criteria that identify febrile infants with positive urinalysis results at low risk for IBI could reduce unnecessary lumbar punctures and hospitalizations. With our data, we suggest that presence of high-risk PMH, ill appearance, or an abnormal peripheral WBC count have low sensitivity for determining which febrile infants with positive urinalysis results have concomitant IBI, overall and among infants 29 to 60 days old. Therefore, absence of a high-risk PMH, well appearance, and a normal WBC count should not be used to identify febrile

TABLE 3 Febrile Infants ≤60 Days Old With Positive Urinalysis Results and Bacterial Meningitis

Age, d	High-Risk PMH, Yes or No[a]	Ill Appearance, Yes or No	Peripheral WBC	CSF WBC[b]	Urine Culture	Blood Culture	CSF Culture
4	No	No	3950	Not done	*E coli*	*E coli*	*E coli*
11	No	No	10 400	473	*E coli*	*E coli*	*E coli*
11	No	No	15 350	2638	No growth	No growth	*L monocytogenes*
15	No	Yes	12 000	53	*S aureus*	*S aureus*	*S aureus*
21	No	Yes	1800	4008	No growth	No growth	GBS
25	No	No	9670	91	*Klebsiella pneumoniae*	*K pneumoniae*	No growth[c]
26	No	No	11 450	Not done	*E coli*[d]	No growth	*E coli*
31	No	No	17 800	71	*E coli*	*E coli*	No growth[c]
39	No	No	14 800[e]	102[e]	No growth	*E coli*	No growth[c]
40	No	Yes	6900	2908	No growth	No growth	GBS
43	Yes	Yes	4310	294	No growth	*S pneumoniae*	*S pneumoniae*
46	No	Yes	3300	33	No growth	GBS	GBS
53	Yes[f]	No	24 000	3811	No growth	No growth	*P aeruginosa*
54	No	Yes	4500	4680	No growth	No growth	*N meningitidis*

[a] Presence of gestational age <37 wk, chronic medical condition, or antimicrobial receipt in preceding 72 h.
[b] Uncorrected CSF WBC.
[c] CSF culture obtained >11 h after antibiotics administered; treated as bacterial meningitis.
[d] <10 000 CFUs/mL.
[e] Obtained on return visit to the ED within 24 h of initial visit; infant on cefdinir.
[f] Infant with ventriculo-peritoneal shunt.

infants with positive urinalysis results at low risk for bacteremia. Although a prediction model using age, C-reactive protein, and procalcitonin has higher sensitivity for IBI (93%) among febrile infants with positive urinalysis results,[14,15] prospective validation is needed.

Because infants with positive urinalysis results are routinely treated with empirical antimicrobial therapy for UTI,[13] most infants with bacteremic UTIs will likely be adequately treated regardless of risk stratification.[16,17] However, nearly 25% of infants with positive urinalysis results and IBI did not have UTIs, including 13 infants who had no high-risk PMH, were not ill appearing, and had normal peripheral WBC counts. This high proportion of infants with positive urinalysis results and IBIs but negative urine culture results may reflect a less-than-perfect sensitivity of urine culture for UTI, which has been shown in a small study of adult patients,[18] although this finding merits further study in febrile infants. Infants with positive urinalysis results discharged from the ED therefore require close follow-up in the uncommon scenario that only the blood or CSF culture is positive.

In previous investigations, researchers have demonstrated that a positive urinalysis result alone does not increase the risk of bacterial meningitis for infants 29 to 60 days old.[19] The vast majority of febrile infants with positive urinalysis results treated for UTI without CSF testing recover without complications.[3,19] This finding, combined with the overall low prevalence of bacterial meningitis in febrile infants with positive urinalysis results,[3,4] renders the question of which of these infants should undergo lumbar puncture. Although the small number of infants with bacterial meningitis in our sample introduces some uncertainty around the sensitivity of abnormal peripheral WBC count as a stand-alone characteristic of infants with bacterial meningitis, most infants 29 to 60 days old with meningitis will be ill appearing or have an abnormal WBC count. Although the 39-day-old "low-risk" infant treated for meningitis did not have a positive CSF culture (and so may have had bacteremia with sterile CSF pleocytosis), clinicians should arrange close follow-up for infants 29 to 60 days old with positive urinalysis results and normal WBC count if a lumbar puncture is not performed. Pending further study, clinicians should exercise caution in decisions about lumbar puncture for infants ≤28 days old with positive urinalysis results.

Our study has several limitations. First, as discussed above, our sample included only 14 infants with bacterial meningitis, although this low number highlights the rarity of bacterial meningitis among infants with positive urinalysis results.[19] Second, we used medical record review for data collection, and variables such as clinical appearance may not be accurately recorded. Third, few infants had a procalcitonin or C-reactive protein, which are components of newer risk stratification criteria.[20,21] Last, we chose to dichotomize the urinalysis result as positive or negative, which did not allow for assessment of urinalysis WBC count as a predictor of IBI.

CONCLUSIONS

The sensitivity of high-risk PMH, ill appearance, and/or abnormal WBC count is suboptimal for identification of febrile infants ≤60 days old with positive urinalysis results at low-risk for IBI. Although most infants 29 to 60 days old with positive urinalysis results and bacterial meningitis are ill-appearing or have abnormal WBC counts, researchers of future studies should evaluate novel criteria to determine which febrile infants with positive urinalysis results do not require lumbar puncture.

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