Testing for Meningitis in Febrile Well-Appearing Young Infants With a Positive Urinalysis

Marie E. Wang, MD, MPH,[a] Eric A. Biondi, MD, MSBA,[b] Russell J. McCulloh, MD,[c] Matthew D. Garber, MD,[d] Beth C. Natt, MD, MPH,[e] Brian P. Lucas, MD, MS,[f] Alan R. Schroeder, MD[a]

abstract

BACKGROUND AND OBJECTIVES: To determine factors associated with cerebrospinal fluid (CSF) testing in febrile young infants with a positive urinalysis and assess the probability of delayed diagnosis of bacterial meningitis in infants treated for urinary tract infection (UTI) without CSF testing.

METHODS: We performed a retrospective cohort study using data from the Reducing Excessive Variability in Infant Sepsis Evaluation quality improvement project. A total of 20 570 well-appearing febrile infants 7 to 60 days old presenting to 124 hospitals from 2015 to 2017 were included. A mixed-effects logistic regression was conducted to determine factors associated with CSF testing. Delayed meningitis was defined as a new diagnosis of bacterial meningitis within 7 days of discharge.

RESULTS: Overall, 3572 infants had a positive urinalysis; 2511 (70.3%) underwent CSF testing. There was wide variation by site, with CSF testing rates ranging from 64% to 100% for infants 7 to 30 days old and 10% to 100% for infants 31 to 60 days old. Factors associated with CSF testing included: age 7 to 30 days (adjusted odds ratio [aOR]: 4.6; 95% confidence interval [CI]: 3.8–5.5), abnormal inflammatory markers (aOR: 2.2; 95% CI: 1.8–2.5), and site volume >300 febrile infants per year (aOR: 1.8; 95% CI: 1.2–2.6). Among 505 infants treated for UTI without CSF testing, there were 0 (95% CI: 0%–0.6%) cases of delayed meningitis.

CONCLUSIONS: There was wide variation in CSF testing in febrile infants with a positive urinalysis. Among infants treated for UTI without CSF testing (mostly 31 to 60-day-old infants), there were no cases of delayed meningitis within 7 days of discharge, suggesting that routine CSF testing of infants 31 to 60 days old with a positive urinalysis may not be necessary.

[a]Division of Pediatric Hospital Medicine, Department of Pediatrics, Lucile Packard Children's Hospital Stanford and School of Medicine, Stanford University, Stanford, California; [b]Division of Pediatric Hospital Medicine, Johns Hopkins Children's Center and School of Medicine, Johns Hopkins University, Baltimore, Maryland; [c]Division of Pediatric Hospital Medicine, University of Nebraska Medical Center and Children's Hospital and Medical Center, Omaha, Nebraska; [d]Division of Hospital Pediatrics, Department of Pediatrics, College of Medicine, University of Florida, Jacksonville, Florida; [e]Department of Pediatrics, School of Medicine, University of Connecticut, Farmington, Connecticut; and [f]The Dartmouth Institute for Health Policy and Clinical Practice and Department of Medicine, School of Medicine, Dartmouth College, Hanover, New Hampshire

WHAT'S KNOWN ON THIS SUBJECT: A positive urinalysis places a febrile infant in the high-risk group in many risk stratification algorithms. Little is known about cerebrospinal fluid (CSF) testing practices and the risk of not performing CSF testing in infants with a positive urinalysis.

WHAT THIS STUDY ADDS: There is wide variation in CSF testing in febrile young infants with a positive urinalysis. Among infants with a positive urinalysis treated for urinary tract infection without CSF testing, none were diagnosed with meningitis within 7 days of discharge.

To cite: Wang ME, Biondi EA, McCulloh RJ, et al. Testing for Meningitis in Febrile Well-Appearing Young Infants With a Positive Urinalysis. *Pediatrics*. 2019;144(3): e20183979

Fever is a common presenting complaint in the young infant, with urinary tract infection (UTI) being the most common serious bacterial infection in this population.[1] Commonly used risk stratification criteria place infants with a positive urinalysis in the high-risk category, with cerebrospinal fluid (CSF) testing recommended in this group if not already part of routine evaluation.[2–4] Despite these criteria, there continues to be wide variation in the diagnostic workup performed for febrile infants,[5,6] although less is known specifically about CSF testing practices in infants with a positive urinalysis.

The need for CSF testing in infants in the second month of life who are diagnosed with UTI has been controversial. Authors of studies to date that have attempted to analyze this question have focused on the overall prevalence of concomitant meningitis in patients with UTI, under the assumption that this prevalence should drive decision-making. Recent estimates of prevalence have ranged from 0.8% to 1.2% in the first month of life to 0% to 0.3% in the second month of life.[7–11] The risk of not performing CSF testing in febrile young infants diagnosed with UTI is the potential for inadequate treatment of a concomitant meningitis because the recommended route, dosing, and duration of antibiotics is different for UTI than for meningitis.[12,13] The probability of delayed diagnosis of meningitis in febrile young infants treated for UTI who did not undergo initial CSF testing is largely unknown, with only 1 published study to date examining this question in a northern California population.[14] Therefore, our objectives in this study were to (1) determine factors associated with CSF testing in infants with a positive urinalysis and (2) assess the probability of delayed diagnosis of bacterial meningitis in infants treated for UTI who did not receive CSF testing.

METHODS

We conducted a secondary analysis of data collected by the Reducing Excessive Variability in Infant Sepsis Evaluation (REVISE) quality improvement project led by the American Academy of Pediatrics (AAP) Value in Inpatient Pediatrics Network, which has led many national quality improvement projects.[15,16] The goal of REVISE was to increase the rate of appropriate evaluation, hospitalization, and length of stay (LOS) for well-appearing febrile infants aged 7 to 60 days presenting to the emergency department (ED) or inpatient setting.[17] Of note, there were no specific recommendations on when to obtain CSF testing included as part of the intervention package for this project. A total of 124 university-affiliated and community hospitals participated, and deidentified data were collected retrospectively on eligible patients evaluated from September 2015 to November 2017. This study was considered exempt by the institutional review board of the AAP. Sites obtained institutional review board approval and data sharing agreements as required by their own site.

Inclusion and Exclusion Criteria

Well-appearing infants 7 to 60 days old were included if they were evaluated for fever without a source (temperature ≥38.0°C) in the site's ED or admitted to the site's inpatient setting and discharged from the site's ED or inpatient unit. Patients were excluded if they were not well-appearing on presentation (defined as having documented terms in the chart such as "toxic," "ill-appearing," "lethargic," "sick-appearing"), had comorbidities predisposing to severe or recurrent bacterial illness (including genetic, congenital, chromosomal, neuromuscular, or neurodevelopmental abnormalities), had a discharge diagnosis of bronchiolitis, or transferred to or from another inpatient setting. Eligible patients were identified by investigators at each site, and only patients who met inclusion criteria without any exclusion criteria based on manual chart review were entered into the database. The number of excluded patients and reasons for exclusion were not collected.

Variables and Definitions

Age was recorded dichotomously as either 7 to 30 days or 31 to 60 days. A positive urinalysis result was defined as the presence of a positive leukocyte esterase result (including trace), a positive nitrite result, or >5 white blood cells (WBCs) per high-power field. Presence of abnormal inflammatory markers was recorded as a dichotomous variable and defined as the presence of ≥1 of the following: (1) WBC count <5000 or >15 000/mm^3; (2) absolute band count ≥1500 cells per mm^3; (3) bands-to-total neutrophil ratio ≥0.2; (4) elevated C-reactive protein or procalcitonin as defined by the institutional range; or (5) CSF WBC count >8/mm^3 or positive Gram-stain result (if CSF obtained). Although these CSF studies do not necessarily constitute systemic inflammatory markers, these parameters were included to risk-stratify infants regarding appropriate hospitalization. Data on individual inflammatory marker results were not collected. Receipt of empiric antibiotics was defined as receipt of antibiotics within 24 hours of arrival to the ED or direct admission. LOS was defined as time between the first vital sign and placement of the discharge order (inclusive of the ED visit if at the same institution).

The REVISE data tool was designed to capture physician practice regarding treatment of infection; therefore, patients were categorized as receiving treatment for UTI if there

was a "yes" answer to the question, "Did the urine culture grow an organism that was treated as a pathogen with a full course of antibiotics?" Similarly, patients were categorized as receiving treatment for meningitis if there was a "yes" answer to the question, "Did the CSF culture grow an organism that was treated as a pathogen with a full course of antibiotics?" A full course of antibiotics was defined as the patient receiving an antibiotic treatment course for the specified infection as determined by physician chart review. Definitions of bacterial infection were based on definitions used in previous multisite observational studies in this age group.[18,19] A delayed diagnosis of meningitis was 1 of the balancing measures of the quality improvement project and was defined as a "yes" answer to the question, "Did the patient return to the ED or get readmitted to the hospital for new diagnosis of bacterial meningitis within 7 days of the date of treat and release or hospital discharge?" Determination of a new diagnosis of bacterial meningitis was made through physician chart review. Detailed data on infecting organism and treatment regimen were not collected. Information on hospital characteristics was collected through a survey completed by the site lead at the beginning of the project. Team members were trained on data definitions and data entry into a standardized online tool via webinars.

Statistical Analysis

We refer to cumulative incidence proportions as rates. When examining rates of CSF testing by individual hospital site, we limited the sample to sites with ≥10 patients with a positive urinalysis in the respective age groups. To determine the association between the receipt of CSF testing and patient and site characteristics, we included all patients who had a urinalysis performed before the decision to admit or discharge from the ED. We used multilevel mixed-effects logistic regression and included patient and site characteristics that were selected a priori. Hospital site was included as a random effect to adjust for clustering. We "marginalized" the estimated coefficients from our mixed-effects models so that our estimates reflected the average effect across hospitals rather than the effect for an average hospital.[20] The rate of delayed diagnosis of meningitis was calculated by using a Clopper-Pearson 1-sided exact 95% confidence interval (CI).[21] Data were analyzed using Stata version 15 (Stata Corp, College Station, TX).[22]

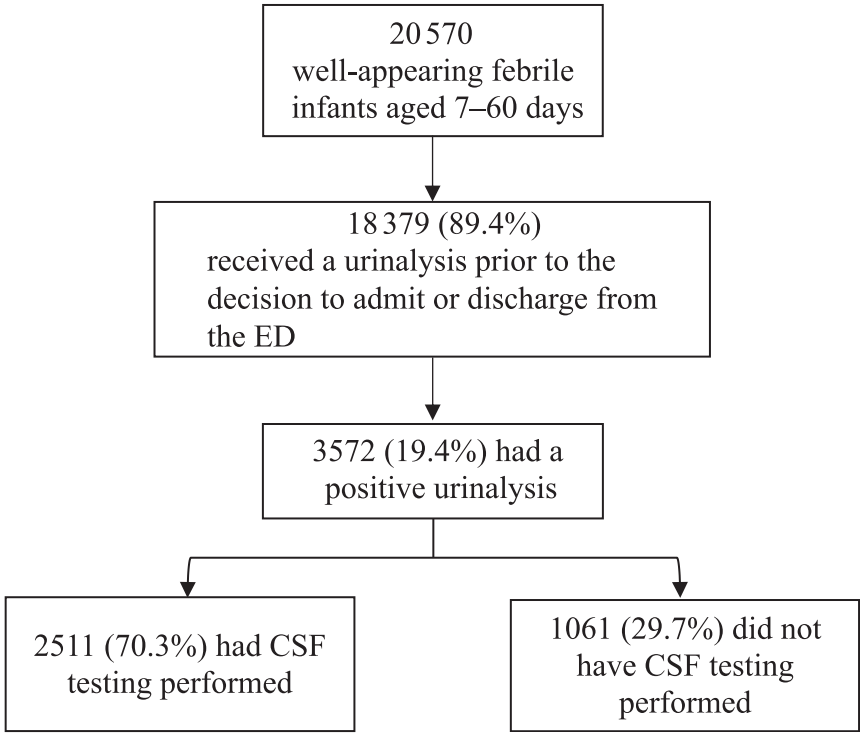

FIGURE 1
Cohort flow diagram.

RESULTS

Patient Population and CSF Testing by Urinalysis Results

There were 20 570 well-appearing febrile infants 7 to 60 days old included in the REVISE quality improvement project. The majority (18 379 of 20 570; 89.4%) underwent urinalysis before the decision to admit or discharge from the ED, and 3572 of 18 379 (19.4%) had a positive urinalysis (Fig 1). Urine cultures were obtained by straight catheterization and/or suprapubic aspirate in 89% and "other/unknown" method in 10% of 3572 infants (1% had missing data). Seventy percent of patients with a positive urinalysis had CSF testing performed, and the proportion of infants with CSF testing was higher in the group with a positive urinalysis when compared to the group with a negative urinalysis (70.0% vs 58.1%; $P < .001$). When comparing infants with a positive versus negative urinalysis who underwent CSF testing, there was no difference in the percentage of infants who received treatment for bacterial meningitis (0.7% vs 0.9%; $P = .37$; Supplemental Table 4). Among

infants with a positive urinalysis, the group that underwent CSF testing had a higher proportion of infants who were male, 7 to 30 days of age, and who had abnormal inflammatory markers when compared with the group who did not receive CSF testing (Table 1).

Variation in CSF Testing in Patients With a Positive Urinalysis by Hospital Site

There was substantial variation in the percentage of infants with a positive urinalysis who underwent CSF testing. Among the 62 hospital sites with ≥10 patients 7 to 30 days old with a positive urinalysis, the proportion of patients who underwent CSF testing ranged from 64% to 100% (Fig 2). Among the 77 hospital sites with ≥10 infants 31 to 60 days old with a positive urinalysis, CSF testing rates ranged from 10% to 100%.

Factors Associated With CSF Testing in Infants With a Positive Urinalysis

In multivariable analysis, infants with a positive urinalysis were more likely to undergo CSF testing if they were 7 to 30 days of age (adjusted odds ratio [aOR]: 4.6; 95% CI: 3.8–5.5) and had abnormal inflammatory markers (aOR: 2.2; 95% CI: 1.8–2.5) (Table 2). CSF testing was also more likely to be done in patients seen at hospitals with an annual volume of >300 febrile infants (aOR: 1.8; 95% CI: 1.2–2.6) when compared to hospitals with an annual volume of ≤100 febrile infants and less likely to be done in the Midwest region (aOR: 0.6; 95% CI: 0.4–0.8) when compared with the Northeast. Sex, university affiliation, and urban setting were not associated with CSF testing. After accounting for patient and hospital characteristics (Table 2), CSF testing in patients with a positive urinalysis was affected by hospital site ($P <$ .001) with an intraclass correlation coefficient of 11.2% (95% CI: 2.4%–16.9%).

TABLE 1 Characteristics of Infants With a Positive Urinalysis by Receipt of CSF Testing

	No CSF Testing Performed (n = 1061), n (%)	CSF Testing Performed (n = 2511), n (%)	P[a]
Subjects			
Age, d			<.001
7–30	187 (17.6)	1281 (51.0)	
31–60	874 (82.4)	1230 (49.0)	
Sex			<.001
Male	559 (52.7)	1546 (61.6)	
Female	502 (47.3)	965 (38.4)	
Abnormal inflammatory marker			<.001
Yes	426 (40.1)	1524 (60.7)	
No	556 (52.4)	934 (37.2)	
Not obtained[b]	79 (7.4)	53 (2.1)	
Hospitals			
University affiliated			.019
Yes	667 (62.9)	1681 (67.0)	
No	394 (37.1)	830 (33.1)	
Urban setting			.001
Yes	743 (70.0)	1898 (75.6)	
No	318 (30.0)	613 (24.4)	
Annual volume of febrile infants			<.001
<100	336 (31.7)	671 (26.7)	
101–300	383 (36.1)	849 (33.8)	
>300	342 (32.2)	991 (39.5)	
Region			<.001
Northeast	144 (13.6)	408 (16.3)	
Midwest	329 (31.0)	572 (22.8)	
South	322 (30.3)	936 (37.3)	
West	266 (25.7)	595 (23.7)	

[a] P value is calculated from the χ^2 test.
[b] This reflects the number of patients who did not receive a complete blood cell count, C-reactive protein, or procalcitonin.

Delayed Diagnosis of Meningitis in Patients Treated for UTI Who Did Not Receive CSF Testing

Of the 1061 infants with a positive urinalysis who did not undergo CSF testing, 734 (69.2%) received empiric antibiotics and 505 received a full course of treatment for UTI (Fig 3).

Among the 505 infants treated for UTI without CSF testing, most (407 of 505; 80.5%) were 31 to 60 days of age, and median LOS was 49 hours (interquartile range [IQR]: 29–65) (Table 3). Of the 483 infants (95.6%) discharged from the ED or hospitalized for <14 days, 13 (2.7%)

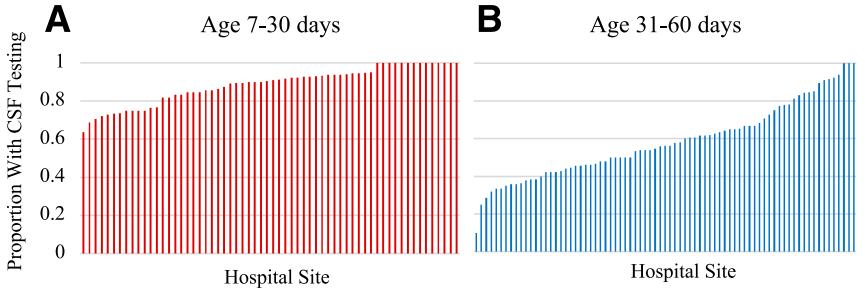

FIGURE 2
Proportion of infants with a positive urinalysis who underwent CSF testing by hospital site. Includes hospital sites with ≥10 patients with a positive urinalysis in the respective age groups. A, A total of 62 sites were included; median number of patients per site was 16 (IQR: 13–21). B, A total of 77 sites were included; median number of patients per site was 20 (IQR: 14–27).

TABLE 2 Factors Associated With CSF Testing in Infants With a Positive Urinalysis

	aOR[a] (95% CI)
Subjects	
Age, d	
7–30	4.6 (3.8–5.5)
31–60	Reference
Sex	
Male	1.1 (1.0–1.3)
Female	Reference
Abnormal inflammatory marker	
Yes	2.2 (1.8–2.5)
No	Reference
Hospitals	
University affiliated	
Yes	1.1 (0.8–1.4)
No	Reference
Urban setting	
Yes	1.0 (0.7–1.4)
No	Reference
Annual volume of febrile infants	
>300	1.8 (1.2–2.6)
101–300	1.3 (0.9–1.8)
≤100	Reference
Region	
Midwest	0.6 (0.4–0.8)
South	0.9 (0.6–1.4)
West	0.6 (0.4–1.0)
Northeast	Reference

Model excludes 132 of 3572 (3.7%) patients who did not have serum inflammatory markers done.

[a] Our single mixed-effects multilevel model included these 7 factors as fixed effects and hospital site as a random effect to adjust for clustering. Estimated coefficients from the mixed-effects models were marginalized to reflect the average effect across hospitals.

had bacteremia. Nine of the 505 infants treated for UTI (1.8%) had a LOS ≥14 days, and 6 of these infants had positive blood culture results and were treated for bacteremia. There were 0 of 505 cases of delayed diagnosis of meningitis (0%; 95% CI: 0%–0.6%) within 7 days of ED or hospital discharge. Infants 7 to 30 days old had 0 of 98 cases (0%; 95% CI: 0%–3.0%), and infants 31 to 60 days old had 0 of 407 cases (0%, 95% CI 0%–0.7%).

DISCUSSION

In a nationally representative cohort of >3500 well-appearing febrile infants ≤60 days of age with a positive urinalysis, nearly 30% did not receive CSF testing, although these patients are classified as high risk by multiple risk stratification algorithms in which CSF testing would be recommended. We demonstrate wide variation in CSF testing between hospital sites in this population. An age of 7 to 30 days, abnormal inflammatory markers, and high annual volume of febrile infants were associated with increased CSF testing. No cases of delayed bacterial meningitis within 7 days of discharge were documented in infants who were treated for UTI without CSF testing, most of whom were 31 to 60 days old.

Previous studies have reported that a substantial proportion of febrile infants in other high-risk groups (eg, ≤ age 28 days) often do not undergo CSF testing.[5,23] In our cohort of febrile infants with a positive urinalysis, both younger age and abnormal inflammatory markers were associated with increased CSF testing in our model, which would be consistent with criteria promoted by major risk stratification algorithms.[2–4,24] High institutional volume of febrile infants (>300 infants per year) was also associated with CSF testing, which could reflect institutional guidelines that incorporate published algorithms at larger centers. Previous work has revealed that children's hospitals with clinical practice guidelines were more likely to perform CSF testing in young febrile infants.[6]

Our finding of 0 of 505 cases of delayed meningitis within 7 days among infants who were treated for UTI without CSF testing is consistent with a recent study by Young et al[14] using data from Kaiser Permanente Northern California. They reported 0 of 345 cases of delayed diagnosis of meningitis within 30 days of initial evaluation among infants with a positive urinalysis in the second month of life treated empirically with antibiotics for UTI without CSF testing (213 had a positive urine culture result). Our study demonstrates similar results using a larger, nationally representative sample that includes university-affiliated and community sites. These findings suggest that there may be a subset of well-appearing febrile young infants with a positive urinalysis for whom the risks of CSF testing (procedural complications, family anxiety, traumatic taps, prolonged hospitalizations, or empiric treatment due to indeterminate results) outweigh the benefits (early diagnosis of bacterial meningitis and/or avoidance of the potential difficulty in interpretation of CSF pleocytosis in a pretreated child).

The absence of any reported cases of delayed meningitis within 7 days has several potential explanations. First, it could reflect the overall low rate of concomitant UTI and meningitis, reported to be from 0.8% to 1.2% in the first month of life and 0% to 0.3% in the second month of life.[7–11] Second, these results may also reflect the ability of practitioners to use clinical and laboratory data to select patients who they believed were at

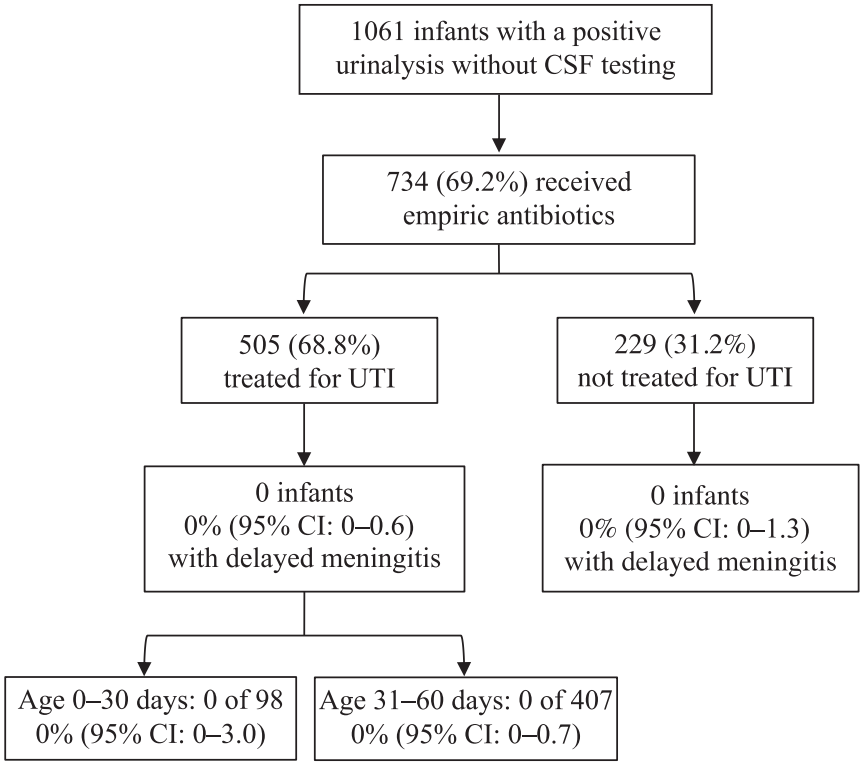

FIGURE 3
Delayed diagnosis of meningitis in febrile well-appearing infants treated for UTI without CSF testing.

higher risk of meningitis and required CSF testing.[25] Third, cases of delayed meningitis may not have been captured during the follow-up period if they presented to another institution. Fourth, a small percentage of patients may have been treated presumptively for meningitis despite not receiving CSF testing because of their clinical presentation, presence of bacteremia, or other factors. A lumbar puncture may have been unsuccessful or declined by the family. Nine infants (1.8%) treated for UTI without CSF testing had a LOS ≥14 days, and although detailed clinical information is not available, these infants likely received parenteral antibiotics during that time. Fifth, some infants who received several days of parenteral antibiotics may have had sufficient treatment for early, undiagnosed meningitis.

The strengths of this study are that it represents recent data from a large, nationally representative pediatric cohort including both university-affiliated and community hospitals. In addition, the diagnosis of fever without a source was confirmed by chart review, ensuring appropriate cohort identification and minimizing the probability of misclassification, which may be present in studies in which only administrative data were used.[26] Lastly, whereas most previous related studies were focused exclusively on the probability of meningitis in infants with UTI, to our knowledge, this study represents the largest study to date in which the probability of delayed diagnosis of meningitis in infants treated for UTI without initial CSF testing is reported.

There are several limitations to this study. First, the data were collected as part of a multisite quality improvement initiative; consequently, interrater reliability was not assessed, and automated quality checks were not able to be performed. However, sites received standard training on data definitions and data entry through multiple webinars and project materials.

Second, detailed data on symptoms, examination findings, laboratory studies, and treatment regimen were not collected. Thus, our regression model may not have all relevant patient-level characteristics that could influence the decision to perform CSF testing. Third, not all infants received inflammatory markers, and the measure of abnormal inflammatory markers combined tests with variable performance characteristics into a single surrogate, so we were unable to evaluate the relationship between the type of inflammatory marker used or the magnitude of the abnormality on CSF testing. In addition, inclusion of CSF parameters in the abnormal inflammatory marker variable may have overestimated the association of serum inflammatory markers with CSF testing if infants had pleocytosis without elevation of serum inflammatory markers. However, previous research in infants with UTIs has revealed that sterile pleocytosis is associated with higher

TABLE 3 LOS by Age Group of Infants Treated for UTI Without CSF Testing

	All Infants (*N* = 505)	Age 7–30 d (*n* = 98)	Age 31–60 d (*n* = 407)
LOS, h, median (IQR)	49 (29–65)	72 (49–162)	46 (19–61)
Disposition, *n* (%)			
Discharged from the ED	98 (19.4)	2 (2.0)	96 (23.6)
Admitted infants by LOS			
<48 h	143 (28.3)	18 (18.4)	125 (30.7)
2–6 d	228 (45.2)	56 (57.1)	172 (42.3)
7–13 d	27 (5.4)	15 (15.3)	12 (3.0)
≥14 d	9 (1.8)	7 (7.1)	2 (0.5)

WBC and band counts.[10] Our data captured a provider's clinical diagnosis rather than a disease diagnosis based solely on laboratory data, which might overestimate rates of infection because of potential misclassification. However, provider documentation of a treatment course for UTI (with or without laboratory confirmation) has been used as a "gold standard" reference for the accuracy of administrative codes to identify hospitalized infants with UTIs, with an 85% positive predictive value (in contrast to a positive predictive value of 50% for laboratory-confirmed UTI).[27] Therefore, our data reflect a higher proportion of provider-confirmed UTI (100%) when compared with the 85% that would be expected with studies using administrative codes.[28,29] Additionally, most of our cohort of infants treated for UTI without CSF testing were 31 to 60 days old, so the low rate of delayed meningitis may not apply to the 7 to 30 day age group. Lastly, it is possible that cases of delayed meningitis may have presented after the 7-day follow-up period. Data on timing of presentation of partially treated meningitis is limited; however, 1 retrospective study of 83 children ≤24 months of age pretreated with oral antibiotics before being diagnosed with bacterial meningitis indicated that they presented on average 2.4 days after initiation of antibiotics.[30] Those data suggest that most patients ≤24 months of age with delayed meningitis would present within the 7-day follow-up time period. Regardless, more data are likely needed to understand the time course of presentation of delayed meningitis in the ≤60-day age group.

CONCLUSIONS

There is significant variation in CSF testing among febrile infants ≤60 days of age with a positive urinalysis , and CSF testing is more likely in infants 7 to 30 days of age, those with abnormal inflammatory markers, and infants evaluated in sites with a high annual volume of febrile infants. There were no cases of delayed diagnosis of meningitis within 7 days of discharge in our large, multicenter cohort of well-appearing febrile young infants treated for UTI without CSF testing (most of whom were 31 to 60 days old), suggesting that CSF testing may not be needed for all infants with a positive urinalysis in the 31 to 60 day age group. Additional large studies are needed to further elucidate the risk/benefit profile for CSF testing in well-appearing febrile infants with a positive urinalysis.

ACKNOWLEDGMENTS

We thank all of the local teams who participated in the REVISE project and Brittany Jennings, Naji Hattar, Faiza Wasif, and Vanessa Shorte at the AAP for their valuable leadership and contributions.

ABBREVIATIONS

AAP: American Academy of Pediatrics
aOR: adjusted odds ratio
CI: confidence interval
CSF: cerebrospinal fluid
ED: emergency department
IQR: interquartile range
LOS: length of stay
REVISE: Reducing Excessive Variability in Infant Sepsis Evaluation
UTI: urinary tract infection
WBC: white blood cell

Dr Wang designed the study, collected local data, performed the data analyses, interpreted the data, and drafted the initial manuscript; Drs Biondi, McCulloh, Garber, and Natt designed the Reducing Excessive Variability in Infant Sepsis Evaluation quality improvement project, supervised collection of the data nationally, and interpreted the data; Dr Lucas contributed to the design of the study, performed the data analyses, and interpreted the data; Dr Schroeder designed the study and the Reducing Excessive Variability in Infant Sepsis Evaluation quality improvement project, supervised collection of the data nationally, and interpreted the data; and all authors reviewed and revised the manuscript critically for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2018-3979

Accepted for publication May 28, 2019

Address correspondence to Marie E. Wang, MD, MPH, Division of Pediatric Hospital Medicine, School of Medicine, Stanford University, 300 Pasteur Dr, MC 5776, Stanford, CA 94305. E-mail: marie.wang@stanford.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Dr Biondi provides consultation for McKesson; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Montini G, Tullus K, Hewitt I. Febrile urinary tract infections in children. *N Engl J Med*. 2011;365(3):239–250
2. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr*. 1992;120(1):22–27
3. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329(20):1437–1441
4. Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection–an appraisal of the Rochester criteria and implications for management. Febrile Infant Collaborative Study Group. *Pediatrics*. 1994;94(3): 390–396
5. Aronson PL, Thurm C, Alpern ER, et al; Febrile Young Infant Research Collaborative. Variation in care of the febrile young infant <90 days in US pediatric emergency departments [published correction appears in *Pediatrics* 2015;135(4):775]. *Pediatrics*. 2014;134(4):667–677
6. Chua KP, Neuman MI, McWilliams JM, Aronson PL; Febrile Young Infant Research Collaborative. Association between clinical outcomes and hospital guidelines for cerebrospinal fluid testing in febrile infants aged 29-56 days. *J Pediatr*. 2015;167(6):1340.e9-1346.e9
7. Tebruegge M, Pantazidou A, Clifford V, et al. The age-related risk of co-existing meningitis in children with urinary tract infection. *PLoS One*. 2011;6(11): e26576
8. Thomson J, Cruz AT, Nigrovic LE, et al; Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) HSV Study Group. Concomitant bacterial meningitis in infants with urinary tract infection. *Pediatr Infect Dis J*. 2017;36(9): 908–910
9. Wallace SS, Brown DN, Cruz AT. Prevalence of concomitant acute bacterial meningitis in neonates with febrile urinary tract infection: a retrospective cross-sectional study. *J Pediatr*. 2017;184:199–203
10. Schnadower D, Kuppermann N, Macias CG, et al; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Sterile cerebrospinal fluid pleocytosis in young febrile infants with urinary tract infections. *Arch Pediatr Adolesc Med*. 2011;165(7):635–641
11. Schnadower D, Kuppermann N, Macias CG, et al; American Academy of Pediatrics Pediatric Emergency Medicine Collaborative Research Committee. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics*. 2010;126(6):1074–1083
12. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3): 595–610
13. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39(9): 1267–1284
14. Young BR, Nguyen THP, Alabaster A, Greenhow TL. The prevalence of bacterial meningitis in febrile infants 29-60 days with positive urinalysis. *Hosp Pediatr*. 2018;8(8):450–457
15. Parikh K, Biondi E, Nazif J, et al; Value in Inpatient Pediatrics Network Quality Collaborative For Improving Care In Community Acquired Pneumonia. A multicenter collaborative to improve care of community acquired pneumonia in hospitalized children. *Pediatrics*. 2017;139(3):e20161411
16. Ralston SL, Garber MD, Rice-Conboy E, et al; Value in Inpatient Pediatrics Network Quality Collaborative for Improving Hospital Compliance with AAP Bronchiolitis Guideline (BQIP). A multicenter collaborative to reduce unnecessary care in inpatient bronchiolitis. *Pediatrics*. 2016; 137(1)
17. Biondi EA, McCulloh RJ, Staggs VS, et al. Reducing Variability in the Infant Sepsis Evaluation (REVISE): A National Quality Initiative. *Pediatrics*. 2019;144(3): e20182201
18. Biondi E, Evans R, Mischler M, et al. Epidemiology of bacteremia in febrile infants in the United States. *Pediatrics*. 2013;132(6):990–996
19. Biondi EA, Mischler M, Jerardi KE, et al; Pediatric Research in Inpatient Settings (PRIS) Network. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatr*. 2014;168(9): 844–849
20. Hedeker D, du Toit SHC, Demirtas H, Gibbons RD. A note on marginalization of regression parameters from mixed models of binary outcomes. *Biometrics*. 2018;74(1):354–361
21. McCracken CE, Looney SW. On finding the upper confidence limit for a binomial proportion when zero successes are observed. *J Biom Biostat*. 2017;8(2):338
22. Stata Corp. *Stata Statistical Software: Release 15 [computer program]*. College Station, TX: Stata Corp; 2017
23. Greenhow TL, Hung YY, Pantell RH. Management and outcomes of previously healthy, full-term, febrile infants ages 7 to 90 Days. *Pediatrics*. 2016;138(6):e20160270
24. Gomez B, Mintegi S, Bressan S, et al; European Group for Validation of the Step-by-Step Approach. Validation of the "step-by-step" approach in the management of young febrile infants. *Pediatrics*. 2016;138(2):e20154381
25. Pantell RH, Newman TB, Bernzweig J, et al. Management and outcomes of care of fever in early infancy. *JAMA*. 2004;291(10):1203–1212
26. Aronson PL, Williams DJ, Thurm C, et al; Febrile Young Infant Research Collaborative. Accuracy of diagnosis codes to identify febrile young infants using administrative data. *J Hosp Med*. 2015;10(12):787–793
27. Tieder JS, Hall M, Auger KA, et al. Accuracy of administrative billing codes to detect urinary tract infection hospitalizations. *Pediatrics*. 2011;128(2): 323–330
28. Brady PW, Conway PH, Goudie A. Length of intravenous antibiotic therapy and

treatment failure in infants with urinary tract infections. *Pediatrics*. 2010;126(2):196–203

29. Lewis-de Los Angeles WW, Thurm C, Hersh AL, et al. Trends in intravenous antibiotic duration for urinary tract infections in young infants. *Pediatrics*. 2017;140(6):e20171021
30. Rothrock SG, Green SM, Wren J, et al. Pediatric bacterial meningitis: is prior antibiotic therapy associated with an altered clinical presentation? *Ann Emerg Med*. 1992;21(2):146–152

Testing for Meningitis in Febrile Well-Appearing Young Infants With a Positive Urinalysis

Marie E. Wang, Eric A. Biondi, Russell J. McCulloh, Matthew D. Garber, Beth C. Natt, Brian P. Lucas and Alan R. Schroeder

Pediatrics 2019;144;
DOI: 10.1542/peds.2018-3979 originally published online August 8, 2019;

Testing for Meningitis in Febrile Well-Appearing Young Infants With a Positive Urinalysis

Marie E. Wang, Eric A. Biondi, Russell J. McCulloh, Matthew D. Garber, Beth C. Natt, Brian P. Lucas and Alan R. Schroeder

Pediatrics 2019;144;
DOI: 10.1542/peds.2018-3979 originally published online August 8, 2019;