

Management of Hospitalized Febrile Neonates Without CSF Analysis: A Study of US Pediatric Hospitals

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OBJECTIVE: Management of febrile neonates includes obtaining blood, urine, and cerebrospinal fluid (CSF) cultures with hospitalization for empiric parenteral antibiotic therapy. Outcomes and management for neonates were compared based on whether CSF was obtained.

METHODS: This multicenter retrospective review of the 2002 to 2012 Pediatric Health Information System database included hospitalized infants aged ≤ 28 days (neonates) admitted to an inpatient ward with a diagnosis code for fever or neonatal fever. Patients admitted to an ICU or with a complex chronic condition diagnosis code were excluded. Neonates were categorized as full septic workup (FSW; charge codes for blood, urine, and CSF culture or cell count) or as partial septic workup (PSW; charge codes for blood and urine cultures only), and their data were compared.

RESULTS: Of 27 480 neonates with a diagnosis code for fever, 14 774 underwent the FSW and 3254 had a PSW. Median length of stay was 2 days for both groups, with no significant difference in readmissions, disposition, or parenteral antibiotic administration. Neonates with a PSW had significantly greater odds of having charge codes for additional laboratory testing and imaging, and they were more likely to receive a diagnosis code for sepsis, meningitis, or bronchiolitis.

CONCLUSIONS: Neonates with PSW had lengths of stay and readmission rates similar to those with FSW but were more likely to undergo additional laboratory testing and imaging. Future studies including information about clinical severity and test results may provide additional insight into the variation in practice for this patient population.

ABSTRACT

www.hospitalpediatrics.org

DOI:10.1542/hpeds.2014-0175

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HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The 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.

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Algorithms have attempted to standardize the diagnostic evaluation of young infants presenting with fever.¹⁻³ The newborn infant aged ≤ 28 days is susceptible to serious bacterial infection due to immunologic immaturity, and most guidelines call for these infants, when febrile, to undergo evaluation for serious bacterial infection, such as bacteremia, urinary tract infection, and meningitis. The traditional management for febrile neonates includes collection of blood, urine, and cerebrospinal fluid (CSF) cultures, with additional evaluations based on symptoms. As standard practice, these patients often receive empiric antibiotic therapy in an inpatient setting because the clinical appearance of the newborn may not be sensitive enough to identify infants at risk for serious bacterial infection.⁴⁻⁹

The success rate of lumbar punctures to obtain CSF varies according to patient, provider, and procedural factors.¹⁰⁻¹³ In addition, the performance of lumbar punctures in the febrile neonate may vary based on demographic factors, such as hospital type and insurance.¹⁴ Whether due to the decision to forgo a lumbar puncture or due to the inability to obtain CSF samples, the absence of CSF analysis poses challenges because of the inability to assess the risk of meningitis in the febrile neonate.⁷

The purpose of the present study was to describe practice patterns when CSF is not obtained for a hospitalized febrile neonate. Our specific objectives were to: (1) determine how often neonates with fever do not have CSF analysis performed; (2) to identify the length of hospital stay, readmission rate, disposition, frequency of additional testing, imaging studies obtained, procedures performed, and diagnoses given to febrile neonates without CSF analysis; and (3) to compare these data with those of febrile neonates who underwent the full septic workup (FSW) with blood, urine, and CSF cultures.

METHODS

Data Source

Data for this study were obtained from the Pediatric Health Information System (PHIS), a comprehensive administrative database that contains data from 44 not-for-profit,

tertiary care pediatric hospitals affiliated with the Children's Hospital Association that are geographically distributed among all census regions and divisions in the United States. PHIS contains administrative and financial information, along with a unique patient identifier that allows for tracking across multiple, same-hospital admissions. Data are de-identified at the time of submission and are subjected to reliability and validity checks before being included.

Study Sample

Patients aged 0 through 28 days of any gestational age (hereafter termed neonates) admitted to a participating hospital between January 1, 2002, and December 31, 2012, with any admitting or discharge diagnosis code for fever (780.6 or 780.60) or neonatal fever (778.4) based on the *International Classification of Diseases, Ninth Revision, Clinical Modification*, were included. Patients cared for in any ICU or critical care unit setting or with a concomitant complex chronic condition diagnosis code demonstrating medical complexity¹⁵ were not included.

The study group included neonates with fever who had charge codes for both blood and urine cultures but did not have a charge code for either CSF culture or cell count at the participating hospital (partial septic workup [PSW]). They were compared with a control group with charge codes for blood, urine, and CSF cultures or cell count (FSW). Records without charge codes for either blood or urine cultures or both were excluded from the analysis because those represent a more significant departure from the standard evaluation for the febrile neonate.

Demographic and financial data were gathered, including: masked patient medical record number; admission and discharge date; date of birth; discharge disposition; charge codes for laboratory tests, imaging, parenteral antibiotics, and supplies (eg, central venous catheters); and *International Classification of Diseases, Ninth Revision, Clinical Modification*, diagnosis codes. Diagnoses given to patients by clinicians were abstracted from the medical record by coders; for infections, they reflect diagnoses named at any time during the

hospitalization. Length of stay and age at admission were appended by using the dates of admission, discharge, and birth. Laboratory testing and radiology results are not available in the PHIS system.

Data Analysis

Descriptive statistics were compiled by using SAS version 9.2 (SAS Institute, Inc, Cary, NC) for all variables. The χ^2 test or Fisher's exact test was performed to compare categorical variables in both cohorts. Post-hoc difference in proportions was used if the χ^2 or Fisher's exact tests revealed a statistically significant difference between the 2 samples. Readmissions were analyzed by matching the masked medical record number for subsequent hospital admissions within 7 days. The χ^2 tests were used to detect differences between readmissions in the 2 subgroups. Those variables with a detected difference ($P < .05$) were identified as possible influences of not having CSF collected. Those variables were included in a multivariate logistic regression model, dependent on their uncorrected level of significance ($P < .05$). Using an iterative model process in which variables are removed based on corrected significance, a final model was constructed that corrects all variables for possible covariability.¹⁶ The model estimates the impact of each variable on not having CSF collected.

The Children's National Health System institutional review board approved the study protocol.

RESULTS

A total of 27 480 neonates with any diagnosis code for fever were admitted to a PHIS participating hospital over the study period. Of these, 14 774 (53.8%) neonates were categorized as having an FSW and 3254 (11.8%) as having a PSW based on charge codes. The remaining 34.4% were missing either a blood or urine culture, or both, and were not included in the study (Fig 1).

The demographic spread according to region of the PSW group differed significantly from that of the FSW group ($P < .001$). In PHIS hospitals in the northeast region, 31.3% of febrile neonates did not

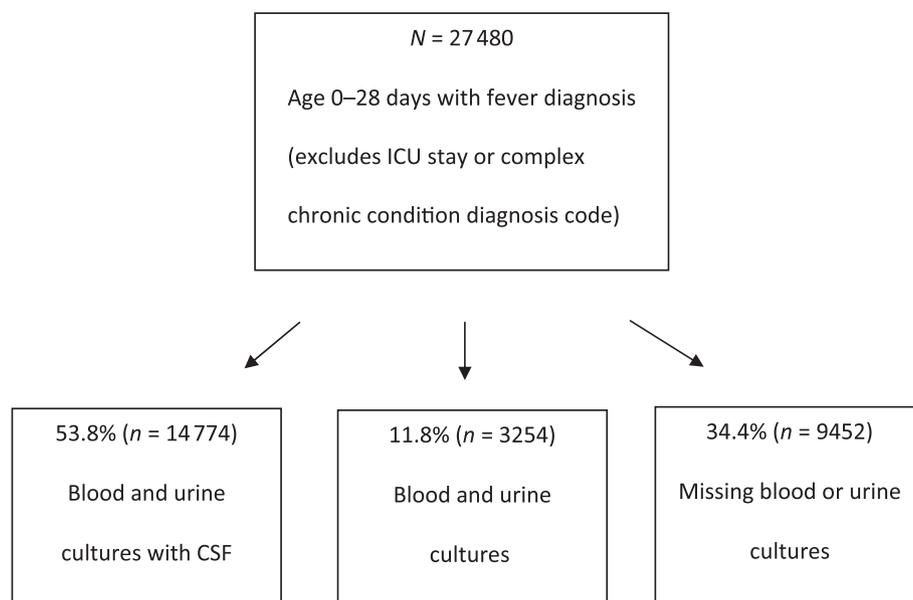


FIGURE 1 Study sample.

have charge codes for CSF analysis compared with 10.7% of febrile neonates in the southern region (Table 1).

Clinical Outcomes

For all neonates with fever, >99% of patients in both groups were discharged from the hospital, and 95.8% ($n = 17\,278$) were discharged within 5 days. The median length of stay for both FSW and PSW groups was 2 days (interquartile range: 2–3 [for both]). No deaths occurred in the PSW group, and there was 1 death in the FSW group. PSW did not differ from FSW with respect to readmissions within 7 days (odds ratio [OR]: 1.05 [95% confidence interval (CI): 0.71–1.55]; $P = .82$).

Laboratory Testing

Laboratory tests performed for inflammatory markers and respiratory and viral testing for both groups are shown in Table 2. Nearly all patients in

both groups had a charge code for complete blood cell counts, and nearly 20% of patients from both groups had a charge code for C-reactive protein; there was minimal use of procalcitonin. The PSW and FSW groups were similar with regard to laboratory testing for these inflammatory markers. Although testing for the erythrocyte sedimentation rate was infrequently performed, febrile neonates in the PSW group were at greater odds of having a charge code for this test (OR: 1.46 [95% CI: 1.04–2.04]; $P = .03$).

The odds of having a charge code for influenza testing were similar between the 2 groups, but neonates with a PSW were at greater odds of having a charge code for respiratory syncytial virus testing, hepatic enzyme tests, respiratory culture, and testing for herpes simplex virus compared with the FSW group (Table 2).

Imaging

Chest radiographs were performed in more than one-third of patients in both groups, but neonates in the PSW group were at significantly higher odds of having charge codes for a chest radiograph (OR: 1.19 [95% CI: 1.10–1.28]; $P < .001$). Neuroimaging using head computed tomography scans was rare in both groups, with no differences detected between groups. There was a significant association with charge codes for head ultrasound, head MRI, and spinal ultrasound in the PSW group compared with the FSW group (Table 2), although these tests were performed infrequently in both groups.

Intravenous Therapies

Neonates with a PSW were at no greater odds than those in the control group to receive a parenteral antibiotic (FSW: 11 245 [76.1%]; PSW: 2457 [75.5%]; OR: 0.97 [95% CI: 0.89–1.06]; $P = .46$). Rates of charge codes for central venous catheters and peripherally inserted central catheters in both groups were similar (Table 2).

Diagnoses

Rates of diagnosis codes for infections in both groups are shown in Table 3. Neonates with a PSW were at greater odds of having a diagnosis code for sepsis (OR: 1.34 [95%

TABLE 1 Febrile Neonates With FSW and PSW According to US Census Region

Region ^a	FSW ($n = 14\,774$)	PSW ($n = 3\,254$)
North-central ($n = 12$)	74.2% ($n = 2856$)	25.4% ($n = 991$)
Northeast ($n = 7$)	68.7% ($n = 1359$)	31.3% ($n = 619$)
South ($n = 15$)	89.3% ($n = 7586$)	10.7% ($n = 909$)
West ($n = 10$)	80.2% ($n = 2973$)	19.8% ($n = 735$)

^a Number of participating hospitals are given in parentheses.

TABLE 2 Laboratory Testing, Imaging, and Central Venous Line Placement Performed in Febrile Neonates Comparing FSW and PSW Groups

Variable	FSW (% of 14 774)	PSW (% of 3254)	OR (95% CI)	P
Laboratory test				
Complete blood count	14 424 (98%)	3160 (97%)	0.82 (0.65–1.03)	.08
C-reactive protein	2722 (18%)	581 (18%)	0.96 (0.87–1.06)	.44
Erythrocyte sedimentation rate	141 (1%)	45 (1.4%)	1.46 (1.04–2.04)	.03
Procalcitonin	14 (0.1%)	3 (0.1%)	0.97 (0.28–3.39)	.97
Influenza	2780 (19%)	629 (19%)	1.03 (0.94–1.14)	.50
Respiratory syncytial virus	4118 (28%)	1034 (32%)	1.21 (1.11–1.31)	<.001
Herpes simplex virus	572 (4%)	157 (5%)	1.26 (1.05–1.51)	<.001
Hepatic enzymes	3078 (21%)	929 (29%)	1.52 (1.39–1.65)	<.001
Respiratory culture	21 (0.1%)	18 (0.6%)	3.91 (2.08–7.34)	<.001
Imaging study				
Chest radiograph	5669 (38%)	1382 (42%)	1.19 (1.10–1.28)	<.001
Head computed tomography scan	306 (2%)	62 (1.9%)	0.92 (0.70–1.21)	.54
Head MRI	89 (0.6%)	31 (1%)	1.59 (1.05–2.39)	.03
Head ultrasound	150 (1%)	65 (2%)	1.99 (1.48–2.67)	<.001
Spine ultrasound	112 (0.8%)	115 (3.5%)	4.80 (3.69–6.24)	<.001
Central venous line placement				
Peripherally inserted central catheters	116 (0.8%)	30 (0.9%)	1.18 (0.79–1.78)	.43
Central venous catheters	117 (0.8%)	25 (0.8%)	0.97 (0.63–1.50)	.89

These findings are consistent with those of Aronson et al,⁶ who recently also noted variation in management of febrile infants aged <90 days. Although both of these studies focused on emergency department management, the focus of the present study was on subsequent inpatient management (including neonates not presenting initially to PHIS emergency departments with fever). According to our data, the frequency of the clinical scenario in which a hospitalized febrile neonate did not have CSF analysis is nearly 12%, with varied geographical distribution of occurrence. These similarities in findings strongly suggest that large variation in practice exists.

In our patient population, the median length of stay for both groups was 2 days, with no detectable differences in length of stay, disposition, or management plan as determined by using charge codes for parenteral antibiotic administration, or peripherally inserted central catheter or central venous catheter placement suggestive of long-term antibiotic therapy. We also found no difference in readmission rate at 7 days (readmissions to other hospitals would not be detected by our method).

Despite the reported utility of C-reactive protein and procalcitonin in predicting serious bacterial infection among young infants^{17–19} (the latter marker is often not routinely available in hospital laboratories), the use of these tests did not differ between groups and appeared less commonly used than the complete blood cell count as part of the evaluation for neonatal fever. This finding suggests that clinicians did not rely on these inflammatory markers to help diagnose meningitis in the absence of CSF analysis. However, patients in the PSW group were more likely to have charge codes for laboratory testing for respiratory syncytial virus, respiratory cultures, and hepatic enzyme tests. Although charge codes for chest radiographs were reported in more than one-third of patients in both groups, they were statistically more likely to occur in the PSW group, as was neuroimaging. Certain laboratory and imaging studies may be ordered by practitioners searching for additional sources of fever. Neuroimaging with MRI may provide some evidence of

CI: 1.02–1.76]; $P = .04$), meningitis (OR: 1.76 [95% CI: 1.13–2.74]; $P = .01$), and bronchiolitis (OR: 1.38 [95% CI: 1.17–1.64]; $P < .001$) compared with the FSW group. There were no differences in the rates of urinary tract infection, bacteremia, or pneumonia based on diagnosis codes.

Multivariate Analysis

When logistic regression analyses were performed to correct for covariability, neonates with a PSW were at significantly greater adjusted odds for having charge codes for respiratory syncytial virus testing, respiratory culture, and hepatic enzyme tests compared with those in the FSW group. The PSW group also had significantly greater adjusted odds for having charge

codes for chest radiographs, head ultrasound, and spine ultrasound compared with the FSW group. In addition, the diagnosis code for bronchiolitis was statistically more likely in neonates with a PSW compared with neonates with an FSW (Table 4).

DISCUSSION

Recent studies have described the variation in emergency department management of febrile neonates.^{5,6} The recent report by Jain et al⁵ identified that only 73% of febrile neonates presenting to PHIS-participating hospital emergency departments in 2010 received an FSW and that there was significant variation in treatment and management of these infants in this setting.

TABLE 3 Diagnoses Given to Febrile Neonates, Comparing Those With an FSW Versus Those With a PSW

Diagnosis	FSW (% of 14 774)	PSW (% of 3254)	OR (95% CI)	P
Urinary tract infection	465 (3%)	118 (3.6%)	1.16 (0.94–1.42)	.16
Bacteremia	122 (0.8%)	32 (1.0%)	1.19 (0.81–1.76)	.38
Meningitis	70 (0.5%)	27 (0.8%)	1.76 (1.13–2.74)	.012
Sepsis	232 (1.6%)	68 (2.1%)	1.34 (1.02–1.76)	.036
Pneumonia	59 (0.4%)	10 (0.3%)	0.77 (0.39–1.50)	.44
Bronchiolitis	611 (4%)	183 (5.6%)	1.38 (1.17–1.64)	<.001

TABLE 4 Adjusted ORs Calculated From a Multivariate Model Associated With Having a PSW

Variable	Adjusted OR	P
Respiratory syncytial virus testing	1.164	<.001
Respiratory culture	3.809	<.001
Hepatic enzyme tests	1.511	<.001
Chest radiograph	1.139	.001
Head ultrasound	1.704	<.001
Spine ultrasound	4.543	<.001
Diagnosis of bronchiolitis	1.318	.002

inflammation in the setting of meningitis for patients in the study group. Spinal ultrasound may have been ordered more commonly in the study group as part of a re-attempt for lumbar puncture to obtain CSF. Conversely, CSF testing may have been deliberately forgone in patients with diagnoses confirmed by using alternate studies. However, we are unable to draw inferences about the rationale for testing based on this study design.

Although not the intent of the present study, the rate of reported diagnosis codes were noted for urinary tract infections, meningitis, bacteremia, sepsis, and pneumonia for febrile neonates managed in the inpatient setting over the past decade. However, these rates reflect only the selection of codes as chosen by clinicians or hospitals; they may not be representative of the true prevalence of infection, especially due to the exclusion of neonates admitted to ICU settings or with complex chronic diagnoses and our study requirement for the presence of fever, as neonates with serious bacterial infection may present without fever. Exclusion of ICU patients also likely explains the very low mortality (1 death) and suggests an overall excellent prognosis in febrile neonates not requiring intensive care. In addition, those patients who were diagnosed with a bacterial infection who were not given a diagnosis code for fever were not included in this study.

Despite the absence of charge codes for CSF, neonates with a PSW were more likely to have a diagnosis code for meningitis. This finding may indicate that the diagnosis was made presumptively based on clinical appearance

of the infant without laboratory confirmation or because the patients were ultimately treated for meningitis. Bronchiolitis often associated as a diagnosis code for the patients in the PSW group, which may suggest that in neonates with respiratory symptoms, a CSF analysis may not have been attempted by clinicians. Indeed, several studies assessing rates of concomitant serious bacterial infection in the setting of bronchiolitis have reported negligible rates of meningitis and bacteremia.^{20–27}

Our study has several limitations. As in many cases when administrative databases are used, the data collected were dependent on diagnosis and charge codes selected by clinicians and reported by hospitals. For example, 34% of febrile neonates lacked charge codes for blood cultures, urine cultures, or both. Although this finding may reflect an actual absence of specific cultures, we speculate that variability in coding practices may have complicated this assessment; for example, some institutions may report charge codes for bacterial cultures but not specify the source of the specific bodily fluid sent for culture. In addition, based on the data available, we were unable to reliably distinguish whether those in the PSW group were missing CSF because of a failed attempt at lumbar puncture or because a lumbar puncture was never attempted. Furthermore, we were unable to determine whether an infant could have had a lumbar puncture performed at another facility and was then transferred to a PHIS-participating hospital. In addition, if “fever” was not included as a diagnosis, data would have been omitted. In addition, septic evaluations may also occur in nonfebrile neonates, such as patients with lethargy, hypothermia, or poor feeding, and these patients were not included in the analysis. Data were included from only the 44 participating children’s hospitals and did not include any previous testing from referring hospitals or from patients hospitalized at a nonparticipating facility. However, because CSF cultures are rarely obtained without an attempt at acquiring blood and urine cultures, it is unlikely that an infant would have charge codes for blood and urine cultures at the PHIS hospital and a CSF sample obtained

from the referring facility. Finally, no test results, clinical data, or information related to severity of illness for patients were available. The absence of this information makes it difficult to compare specific clinical outcomes related to risk stratification or patient morbidity in either group or to identify the rationale for diagnostic or management decisions.

Despite these limitations, use of the PHIS database enables access to comprehensive information for large populations of pediatric patients over lengthy time periods, and it serves to generate ideas for prospective studies on which more reliable inferences can be made. The results of the present study suggest that pediatric hospital medicine providers should be prepared to manage the febrile neonate admitted without CSF analysis. It may be beneficial to assess these patients jointly with first-contact clinicians (eg, in the emergency department), case by case, to determine whether to initiate antibiotic administration based on clinical appearance and available laboratory data because the decision to continue or stop antibiotic treatment may become more difficult with time. Given that outcomes for febrile neonates with PSW do not seem to differ significantly from those with an FSW, multiple subsequent attempts at lumbar punctures may not be warranted in neonates who remain well-appearing and have not received antibiotics. Clinicians may wish to investigate if the numbers of febrile neonates without CSF at their institution are due to failed attempts at lumbar puncture, parental refusal, or other reasons for variation in practice, and then direct interventions accordingly.

CONCLUSIONS

In the present study, the overall rate of hospitalized febrile neonates without charge codes for CSF analysis was 11.8%. It is unclear if this finding was due to failed attempts at lumbar puncture or other factors, such as parental refusal or physician determination. Neonates with a PSW seem more likely to undergo certain laboratory testing and imaging studies and were more likely to have diagnosis codes for meningitis, sepsis, and bronchiolitis

than those with an FSW. We found no differences in length of stay, readmissions, or parenteral antibiotic administration between febrile neonates with FSW and those with PSW. Future studies including information about clinical severity and test results may provide additional insight into the variation in practice for this patient population.

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Hospital Pediatrics 2015;5:528

DOI: 10.1542/hpeds.2014-0175

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