BRIEF REPORT

Cerebrospinal Fluid Profiles of Infants ≤60 Days of Age With Bacterial Meningitis

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ABSTRACT

OBJECTIVES: We aimed to describe the cerebrospinal fluid (CSF) profiles of infants ≤60 days old with bacterial meningitis and the characteristics of infants with bacterial meningitis who did not have CSF abnormalities.

METHODS: We included infants ≤60 days old with culture-positive bacterial meningitis who were evaluated in the emergency departments of 11 children's hospitals between July 1, 2011, and June 30, 2016. From medical records, we abstracted clinical and laboratory data. For infants with traumatic lumbar punctures (CSF red blood cell count of ≥10 000 cells per mm^3), we used a red blood cell count/white blood cell (WBC) count correction factor of 1000:1 to determine the corrected CSF WBC count. We calculated the sensitivity for bacterial meningitis of a CSF Gram-stain and corrected CSF pleocytosis (≥16 WBCs per mm^3 for infants ≤28 days old and ≥10 WBCs per mm^3 for infants 29–60 days old).

RESULTS: Among 66 infants with bacterial meningitis, the sensitivity of a CSF Gram-stain was 71.9% (95% confidence interval [CI]: 59.2–82.4), and the sensitivity of corrected CSF pleocytosis was 80.3% (95% CI: 68.7–89.1). The sensitivity of combining positive Gram-stain results with corrected CSF pleocytosis was 86.4% (95% CI: 75.7–93.6). Of 9 infants with meningitis who had a negative Gram-stain result and no corrected CSF pleocytosis, 8 (88.9%) had either an abnormal peripheral WBC count (>15 000 or <5000 cells per μL) or bandemia >10%.

CONCLUSIONS: Most infants ≤60 days old with bacterial meningitis have CSF pleocytosis or a positive Gram-stain result. Infants with no CSF pleocytosis and a negative Gram-stain result are unlikely to have bacterial meningitis in the absence of other laboratory abnormalities.

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Approximately 1% of infants ≤60 days of age who undergo cerebrospinal fluid (CSF) testing in the emergency department (ED) have bacterial meningitis.[1] While awaiting bacterial culture results, which can take up to 48 hours to return, clinicians need to make treatment decisions on the basis of the infant's CSF profile. Young infants with bacterial meningitis may have normal CSF white blood cell (WBC) counts and protein and glucose levels.[2–4] However, in previous studies, investigators frequently included neonates during birth hospitalizations or did not describe the characteristics of infants with normal CSF profiles.[2–4] An improved understanding of the clinical and laboratory features of infants with meningitis and normal CSF profiles could help guide management of young infants who undergo CSF testing. Our objectives were to describe the CSF profiles of infants ≤60 days of age with bacterial meningitis evaluated in the ED and to describe the characteristics of infants with bacterial meningitis who did not have CSF abnormalities.

METHODS

Study Design

We conducted a planned secondary analysis of a cross-sectional study of infants ≤60 days of age with bacteremia and/or bacterial meningitis evaluated in the EDs at 11 geographically diverse US children's hospitals between July 1, 2011, and June 30, 2016.[5] The current study was limited to infants with culture-positive bacterial meningitis. The study was approved by each site's institutional review board.

Study Sample

For the parent study, we queried each hospital's microbiology laboratory database or electronic medical record system for positive blood or CSF culture results obtained in the ED from infants ≤60 days of age.[5] For this secondary analysis, we selected infants with a positive CSF culture result for an a priori–defined bacterial pathogen[5] with both CSF WBC and red blood cell (RBC) counts available. We excluded infants with ventriculoperitoneal shunts. Given the diagnostic ambiguity, we also excluded infants with growth of a bacterial pathogen only from a CSF enrichment broth culture,[6] with the exception of 1 infant who had CSF pleocytosis and growth of *Listeria monocytogenes* from the CSF.

Data Collection

For each included infant, we abstracted demographic, historical, physical examination, and laboratory data, including results of a complete blood cell count, the CSF profile (ie, Gram-stain, WBC count and differential, RBC count, and protein and glucose levels), and bacterial cultures (ie, urine, blood, CSF).

Definitions

Bacterial meningitis was defined as a CSF culture that grew a pathogen. The result of the CSF Gram-stain was considered positive if bacteria were identified (eg, Gram-positive cocci, Gram-negative rods). We defined CSF pleocytosis as a CSF WBC count ≥16 cells per mm^3 for infants ≤28 days and ≥10 cells per mm^3 for infants 29 to 60 days of age.[7] For infants with traumatic lumbar punctures (ie, CSF RBC count ≥10 000 cells per mm^3), we used an RBC/WBC correction factor of 1000:1 to determine the corrected CSF WBC count.[8] An abnormal CSF profile was defined as a positive Gram-stain result, CSF pleocytosis, neutrophil predominance on the CSF WBC differential (>50% neutrophils), an elevated CSF protein level (≥128 mg/dL for infants ≤28 days and ≥100 mg/dL for infants 29–60 days of age),[7] or a low CSF glucose level (<25 mg/dL for infants ≤28 days and <27 mg/dL for infants 29–60 days of age).[7]

Statistical Analysis

We calculated the sensitivity for bacterial meningitis of the CSF Gram-stain and corrected CSF pleocytosis, alone and in combination. Proportions were compared by using the χ^2 test or Fisher's exact test. Statistical analyses were performed by using Stata version 15.0 (Stata Corp, College Station, TX).

RESULTS

Over the study period, 10 635 infants ≤60 days of age had CSF cultures obtained, and 76 (0.7%) had positive culture results. Ten of these 76 infants (13.2%) were excluded: 3 had ventriculoperitoneal shunts, and 7 did not have CSF cell counts performed. Of the remaining 66 study infants with bacterial meningitis, 44 (66.7%) were ≤28 days, and 22 (33.3%) were 29 to 60 days of age; 32 (48.5%) were not ill appearing. The most commonly isolated pathogens were Group B *Streptococcus* (GBS) (n = 41 [62.1%]), *Escherichia coli* (n = 8 [12.1%]), and *L monocytogenes* (n = 4 [6.1%]). The distribution of pathogens was slightly different between infants ≤28 days and those 29 to 60 days of age (P = .03) (Supplemental Table 3). Forty-eight infants (72.7%) had concomitant positive blood culture results with the same bacterial pathogen.

Overall, 62 of 66 infants with bacterial meningitis had an abnormal CSF parameter (93.9%; 95% confidence interval [CI]: 85.2–98.3) (Table 1). The sensitivity of the CSF Gram-stain for bacterial meningitis was 71.9% (95% CI: 59.2–82.4). After correction of CSF WBCs for CSF RBCs, the sensitivity of CSF pleocytosis for bacterial meningitis was 80.3% (95% CI: 68.7–89.1). The sensitivity of combining a positive Gram-stain result with corrected CSF pleocytosis was 86.4% (95% CI: 75.7–93.6). The proportion of infants with a positive Gram-stain result or corrected CSF pleocytosis was the same among infants ≤28 days and infants 29 to 60 days of age (86.4% vs 86.4%; P = 1.0) (Table 1). Among infants who were not ill appearing, the sensitivity of combining a positive Gram-stain result with corrected CSF pleocytosis was 81.3% (95% CI: 63.6–92.8).

A total of 9 infants with bacterial meningitis had a negative CSF Gram-stain result and no CSF pleocytosis (3 of whom had no pleocytosis only after correction of CSF WBCs for CSF RBCs). Six infants (66.7%) were ≤28 days, and 3 (33.3%) were 29 to 60 days of age. Pathogens isolated from the CSF of these infants were GBS (5 infants), *E coli* (2 infants), *Staphylococcus aureus* (1 infant), and *Klebsiella oxytoca* (1 infant). Five infants (55.6%) had concomitant bacteremia. No infants had low CSF glucose levels, whereas 5 (55.6%) had an elevated CSF protein level (Table 2).

Of the 9 infants, 8 (88.9%) had either an abnormal peripheral WBC count (>15 000 or <5000 cells per μL) or bandemia >10% (Table 2). The other infant was 42 days old and had *E coli* bacteremia and meningitis and no CSF pleocytosis after correction of CSF WBCs for RBCs. The infant was not ill appearing, had a normal

TABLE 1 CSF Parameters of Infants ≤60 Days of Age With Bacterial Meningitis

	Positive CSF Gram-stain Result, *n*/*N* (%)	CSF Pleocytosis (Corrected), *n* (%)	Neutrophil-Predominant CSF Among Infants With CSF Pleocytosis (Corrected), *n*/*N* (%)	Elevated CSF Protein Levels, *n*/*N* (%)	Low CSF Glucose Levels, *n*/*N* (%)	CSF Pleocytosis (Corrected) or Positive CSF Gram-stain Result, *n* (%)	Any Abnormal CSF Parameter, *n* (%)
Overall ($N = 66$)	46/64 (71.9)[a]	53 (80.3)	46/51 (90.2)[b]	46/63 (73.0)[c]	31/63 (49.2)[c]	57 (86.4)	62 (93.9)
By age group							
Age ≤28 d ($n = 44$)	29/43 (67.4)[a]	35 (79.6)	29/33 (87.9)[b]	28/42 (66.7)[c]	18/42 (42.9)[c]	38 (86.4)	41 (93.1)
Age 29–60 d ($n = 22$)	17/21 (81.0)[a]	18 (81.8)	17/18 (94.4)	18/21 (85.7)[c]	13/21 (61.9)[c]	19 (86.4)	21 (95.5)
P[d]	.38	1.0	.65	.14	.15	1.0	1.0

[a] Two infants had missing CSF Gram-stain results.
[b] Two infants with corrected CSF pleocytosis had no CSF WBC differential.
[c] Three infants did not have a CSF protein or glucose level measurement.
[d] *P* value for comparison of parameter by age group (≤28 vs 29–60 d).

peripheral WBC count, and had an absolute neutrophil count of 4599 neutrophils per mm^3, without a band count performed.

DISCUSSION

In this multicenter cross-sectional study, the majority of young infants with bacterial meningitis who were evaluated in the ED had either a positive Gram-stain result or corrected CSF pleocytosis. Of the few infants with bacterial meningitis without these laboratory markers, all but 1 had either an abnormal peripheral WBC count or bandemia.

We found that CSF pleocytosis had a sensitivity of 80.3%, which is higher than reported in some recent studies.[3,8] Our study builds on this previous work by revealing a higher sensitivity (86.4%) when CSF pleocytosis was combined with a positive CSF Gram-stain result.

The bacterial meningitis score combines clinical and laboratory features to accurately identify infants with CSF pleocytosis at low risk for bacterial meningitis.[9] However, although this validated score has 100% sensitivity in infants ≤60 days of age, it has a specificity of 1.6% and should not be applied clinically in this age group.[10] Therefore, these youngest infants with CSF pleocytosis are often treated presumptively for bacterial meningitis until the results of CSF bacterial cultures are available. Although a minority of infants with bacterial meningitis in our study had normal CSF profiles, they frequently had either an abnormal peripheral WBC count or bandemia. Our results, combined with the overall low prevalence of bacterial meningitis (1%) among infants who undergo CSF testing,[1] reveal that infants with no CSF pleocytosis and a negative Gram-stain result are unlikely to have bacterial meningitis in the absence of other laboratory abnormalities.

Traumatic lumbar punctures artificially elevate the CSF WBC count by introducing peripheral blood into the spinal space (which could have resulted in the positive CSF culture result for the infant with no CSF pleocytosis, a normal Gram-stain result, and growth of *E coli* in the blood and CSF). Correcting CSF WBCs for the presence of RBCs reduces the sensitivity for bacterial meningitis, whereas it increases the specificity.[8] In our study, applying a CSF

TABLE 2 Characteristics of the 9 Infants With Bacterial Meningitis Who Had a Negative Gram-Stain Result and No Corrected CSF Pleocytosis

Age, d	History of Prematurity, Yes or No[a]	Ill Appearing, Yes or No	WBC Count, Cells per μL	ANC, Cells per mm^3	Bands, %	CSF WBC Count, Corrected, Cells per mm^3	CSF RBC Count, Cells per mm^3	CSF Protein Level, mg/dL	CSF Glucose Level, mg/dL	Blood Culture Result	CSF Culture Result
10	No	No	23 900[b]	6955	0	8	2	684	58	No growth	*K oxytoca*
11	No	No	17 000[b]	9520	11[c]	4	2	73	52	GBS	GBS
15	No	Yes	12 000	4320	22[c]	0	53 805	199	51	*S aureus*	*S aureus*
19	No	No	3310[b]	1324	1	0	243 500	313	55	No growth	*E coli*
23	No	No	13 600	4216	20[c]	4	0	52	42	GBS	GBS
28	Yes	Yes	4870[b]	1768	0	0	3065	86	58	No growth	GBS
36	Yes	No	5630	1278	14[c]	3	225	197	52	GBS	GBS
42	No	No	10 950	4599	—[d]	0	62 778	589	41	*E coli*	*E coli*
43	Yes	Yes	21 500[b]	17 200	0	8	6	86	39	No growth	GBS

ANC, absolute neutrophil count;—, not applicable.
[a] Prematurity was defined as gestational age <37 wk.
[b] Abnormal values: WBC count >15 000 or <5000 cells per μL.
[c] Abnormal values: band percentage >10%.
[d] Band count not performed at this site.

RBC/WBC correction factor of 1000:1 classified 3 additional infants with bacterial meningitis as having no CSF pleocytosis. However, the peripheral WBC count, band count, or CSF protein level was abnormal in these infants. When applying a CSF RBC/WBC correction to young infants with traumatic lumbar punctures, clinicians should consider additional laboratory parameters when making management decisions.

Our study has several limitations. First, in contrast to the parent study, we only included infants with a positive CSF bacterial culture result. We excluded 13 infants with bacteremia and CSF pleocytosis but negative CSF culture results after antimicrobial pretreatment because of potential misclassification of these infants as having bacterial meningitis. Second, CSF pleocytosis and an abnormal peripheral WBC count or elevated band count are not specific for bacterial meningitis, and we do not know the overall number of infants with these laboratory abnormalities. Therefore, our findings are most applicable when clinicians have clinical concern for bacterial meningitis, but the infant has a normal CSF profile. Third, our study was conducted at pediatric EDs, and our findings may not be generalizable to other settings. Fourth, we could not assess abnormalities in newer biomarkers because only 4 infants had a procalcitonin level measured, and 12 had a C-reactive protein measurement obtained.

CONCLUSIONS

Most infants ≤60 days of age with bacterial meningitis have either CSF pleocytosis or a positive Gram-stain result. Among infants with normal CSF profiles, bacterial meningitis is rare, and clinicians should consider the results of additional laboratory parameters in making treatment decisions.

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REFERENCES

1. Biondi EA, Lee B, Ralston SL, et al. Prevalence of bacteremia and bacterial meningitis in febrile neonates and infants in the second month of life: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(3):e190874
2. van de Beek D, Cabellos C, Dzupova O, et al; ESCMID Study Group for Infections of the Brain (ESGIB). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect*. 2016;22(suppl 3):S37–S62
3. Leazer R, Erickson N, Paulson J, et al. Epidemiology of cerebrospinal fluid cultures and time to detection in term infants. *Pediatrics*. 2017;139(5): e20163268
4. Ouchenir L, Renaud C, Khan S, et al. The epidemiology, management, and outcomes of bacterial meningitis in infants. *Pediatrics*. 2017;140(1): e20170476
5. Woll C, Neuman MI, Pruitt CM, et al; Febrile Young Infant Research Collaborative. Epidemiology and etiology of invasive bacterial infection in infants ≤60 days old treated in emergency departments. *J Pediatr*. 2018;200: 210–217.e1
6. Shah SS, Hines EM, McGowan KL. Cerebrospinal fluid enrichment broth cultures rarely contribute to the diagnosis of bacterial meningitis. *Pediatr Infect Dis J*. 2012;31(3):318–320
7. Thomson J, Sucharew H, Cruz AT, et al; Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) HSV Study Group. Cerebrospinal fluid reference values for young infants undergoing lumbar puncture. *Pediatrics*. 2018;141(3):e20173405
8. Lyons TW, Cruz AT, Freedman SB, et al; Pediatric Emergency Medicine Clinical Research Network (PEM CRC) Herpes Simplex Virus Study Group. Interpretation of cerebrospinal fluid white blood cell counts in young infants with a traumatic lumbar puncture. *Ann Emerg Med*. 2017;69(5): 622–631
9. Nigrovic LE, Kuppermann N, Macias CG, et al; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. *JAMA*. 2007; 297(1):52–60
10. Rees CA, Cruz AT, Freedman SB, et al; HSV Study Group of the Pediatric Emergency Medicine Collaborative Research Committee. Application of the bacterial meningitis score for infants aged 0 to 60 days [published online ahead of print December 10, 2018]. *J Pediatric Infect Dis Soc*. doi:10.1093/jpids/piy126