Cerebrospinal Fluid Reference Values for Young Infants Undergoing Lumbar Puncture

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abstract

OBJECTIVES: To determine age-specific reference values and quantify age-related changes for cerebrospinal fluid (CSF) white blood cell (WBC) counts and protein and glucose concentrations in infants ≤60 days of age.

METHODS: This multicenter, cross-sectional study included infants ≤60 days old with CSF cultures and complete CSF profiles obtained within 24 hours of presentation. Those with conditions suspected or known to cause abnormal CSF parameters (eg, meningitis) and those with a hospital length of stay of >72 hours were excluded. Reference standards were determined for infants ≤28 days of age and 29 to 60 days of age by using the third quartile +1.5 interquartile range for WBC and protein and the first quartile −1.5 interquartile range for glucose. CSF parameter centile curves based on age were calculated by using the LMST method.

RESULTS: A total of 7766 patients were included. CSF WBC counts were higher in infants ≤28 days of age (upper bound: 15 cells/mm^3) than in infants 29 to 60 days of age (upper bound: 9 cells/mm^3; $P < .001$). CSF protein concentrations were higher in infants ≤28 days of age (upper bound: 127 mg/dL) than in infants 29 to 60 days of age (upper bound: 99 mg/dL; $P < .001$). CSF glucose concentrations were lower in infants ≤28 days of age (lower bound: 25 mg/dL) than in infants 29 to 60 days of age (lower bound: 27 mg/dL; $P < .001$).

CONCLUSIONS: The age-specific CSF WBC count, protein concentration, and glucose concentration reference values identified in this large, multicenter cohort of infants can be used to interpret the results of lumbar puncture in infants ≤60 days of age.

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Dr Thomson helped conceptualize and design the study, collected local data, performed data analysis and interpretation, drafted the initial manuscript, incorporated revisions, and takes responsibility for the manuscript as a whole; Dr Sucharew participated in the study design, performed data analysis, supervised the interpretation of the data, and reviewed and revised the manuscript; Dr Cruz participated in the study design, collected local data, coordinated data

WHAT'S KNOWN ON THIS SUBJECT: Previous studies in which researchers define cerebrospinal fluid (CSF) reference standards for infants have been limited by their single-center study designs and small sample sizes.

WHAT THIS STUDY ADDS: In this multicenter, cross-sectional study, we define age-specific CSF reference values and provide CSF parameter centile curves based on age. These values and curves can be used to interpret the results of lumbar puncture in infants ≤60 days of age.

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The examination of cerebrospinal fluid (CSF) is crucial for the diagnosis of bacterial meningitis, which causes significant morbidity and mortality in infants. Accurate reference ranges are required to facilitate the interpretation of CSF laboratory values, including white blood cell (WBC) counts and protein and glucose concentrations.[1] There are limitations on how these reference ranges can be determined because lumbar puncture (LP) cannot be ethically performed in a healthy infant without a medical indication. Researchers in several studies of neonates and young infants undergoing LP during emergency department (ED) evaluation of fever have attempted to define CSF reference standards.[2–9] They have demonstrated that CSF values change considerably within the first few weeks of life. However, the validity of these previous studies to serve as reference standards is limited by their single-center study designs and relatively small sample sizes, which have led to imprecise estimates.

We sought to develop age-specific reference standards for CSF WBC counts as well as CSF protein and glucose concentrations for infants ≤60 days of age by using multicenter data to improve the precision and generalizability of reference values.

METHODS

Study Design

This planned secondary analysis of a 23-center retrospective cross-sectional study was conducted by the Pediatric Emergency Medicine Collaborative Research Committee (PEMCRC) Herpes Simplex Virus (HSV) Study Group. All centers obtained institutional review board approval with a waiver of informed consent and permission for data sharing.

Study Population

The parent study included infants ≤60 days of age who presented to the ED between January 1, 2005, and December 31, 2013, who had a CSF culture obtained within 24 hours of ED presentation. For this study, 5 of the 23 participating PEMCRC sites had incomplete CSF profiles recorded for >80% of cases and were excluded from analysis; the remaining 18 sites were included. To determine reference ranges for other laboratories (eg, complete blood cell counts), specimens were collected from healthy volunteers and unaffected persons. It is not ethical to perform LP on infants without indication; therefore, our goal was to create a cohort of infants who were as near to normal as possible (ie, without disease or factors that may influence CSF culture results). To do this, subjects with conditions that were suspected or known to cause abnormal CSF parameters were excluded sequentially as follows: (1) missing any component of the CSF profile (ie, WBC count, red blood cell [RBC] count, protein, or glucose); (2) CSF RBC count >500/mm^3 because any amount of peripheral blood contamination may affect CSF parameters[10–12]; (3) invasive bacterial infection, which was defined as the growth of pathogenic bacteria from either CSF or blood; (4) urinary tract infection (UTI) because a minority of infants with a UTI will have associated sterile CSF pleocytosis[13–18]; (5) viral central nervous system (CNS) infection, which was defined as a positive CSF enteroviral polymerase chain reaction (PCR) test result, a positive CSF HSV PCR result, or a positive CSF viral culture result; and (6) non-CNS HSV disease, which was defined as an HSV PCR or viral culture result that was positive for HSV from blood or eye, skin, or oral mucosa. We also excluded children with a hospital length of stay of >72 hours because these children could have had other conditions (eg, osteomyelitis, seizures, or congenital infections) affecting CSF parameters.

Study Definitions

Invasive bacterial infection was defined as the growth of a pathogen (eg, group B *Streptococcus* and *Escherichia coli*; Supplemental Table 3) from a blood or CSF culture, the growth of any bacteria from >1 sterile site, or the identification of any bacteria on CSF Gram-stain. UTI was defined as the growth of a single pathogenic organism (Supplemental Table 3) from a catheterized specimen with either ≥50 000 colony-forming units/mL or 10 000 to 50 000 colony-forming units/mL with an abnormal urinalysis result (ie, positive for leukocyte esterase and/or nitrite and/or >5 WBCs per high-powered field).[19] A viral CNS infection was defined as the identification of any virus in the CSF by viral culture or a positive HSV or enterovirus PCR test result.

Data Collection

Eligible infants were identified by using electronic search strategies that were optimized for each study site as indicated previously.[11,18,20–22] Depending on the available data systems, data elements were electronically or manually abstracted from medical records. Data included age, sex, laboratory data (urinalysis, CSF cell counts, CSF glucose and protein concentrations, and CSF Gram-stain), and microbiologic test results (bacterial cultures [blood, urine, and CSF]). The period of data collection varied from site to site depending on the availability of electronic data sources.

Statistical Analysis

To facilitate the implementation of our results into clinical practice, we grouped infants as ≤28 days of age and 29 to 60 days of age. We considered different reference standard definitions, including mean,

SD, median, 90th and 95th percentile (for WBC count and protein) or 5th and 10th percentile (for glucose) values, and the upper bound (third quartile +1.5 interquartile range [IQR]) for WBC count and protein and the lower bound (first quartile −1.5 IQR) for glucose.[23–25] Although these definitions may be considered equally acceptable for upper and lower reference limits, the latter definition may better account for non-normally distributed data with extreme outliers.[26] The Wilcoxon rank test was used to compare CSF parameter distributions by age group. Because CSF testing for viruses was not routinely performed, we repeated the age-group analyses in the subset of infants with negative enterovirus test results.

CSF parameter reference curves were created by using the centiles estimation based on the 4 parameter Box-Cox t distribution to correct for skewness and kurtosis called the LMST method.[27] The LMST method is an extension of the LMS method, which models for skewness and not for kurtosis by estimating 3 parameters: L (λ: skewness), M (μ; median), and S (σ; coefficient of variation). The 4 parameters of the LMST method are μ (median; relating to location), σ (coefficient of variable; relating to scale), ν (power transformation to symmetry; relating to skewness), and τ (degrees of freedom; relating to kurtosis). This method models cross-sectional CSF parameter values as a smooth, nonparametric function of age. Models were implemented by using the Generalized Additive Models for Location Scale and Shape package in the R statistical program (R Foundation for Statistical Computing, Vienna, Austria).

To avoid the influence of potentially abnormal values, we excluded extreme outliers from the analysis, which were defined as any CSF parameter values >2 SDs and <2 SDs of the sample median. These were based on age-specific values through curves that were estimated continuously across the CSF parameter range by using the LMS method, fixing L = 1 to restrict the skewness of the distribution; extreme outliers have minimal impact on μ and σ but can affect the estimate of the λ parameter.[28] In total, only a small proportion of the observations were excluded in this step, most of which were in the upper end of the distribution.

Data were analyzed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC) and R, and figures were created by using R. Two-tailed *P* values <.05 were considered statistically significant.

RESULTS

Study Cohort

A total of 22 397 infants ≤60 days of age presented to the 18 participating EDs and had a CSF culture obtained within 24 hours of presentation. Of these, 7766 (33.7%) met sequential inclusion criteria. The median number of CSF specimens per site was 435 (IQR: 266–489; full range: 20–1149). The median patient age was 31 days (IQR: 18–44 days); 45.8% (*n* = 3557) were 28 days or younger. Overall, 54.7% (*n* = 4251) were boys, and 74.0% (*n* = 5743) were hospitalized. After exclusions based on parameter-specific outliers, 7496 were included in the analysis for CSF WBC count, 7738 were included in the analysis for CSF protein concentration, and 7761 were included in the analysis for CSF glucose concentration (Fig 1).

CSF WBC Count

The median CSF WBC count was 3 cells/mm^3 (IQR: 2–6). CSF WBC counts were higher for infants ≤28 days of age than for infants 29 to 60 days of age (*P* < .001). The median CSF WBC count was 4 cells/mm^3 (95th percentile value: 16 cells/mm^3; upper bound: 15 cells/mm^3) for infants ≤28 days of age and 2 cells/mm^3 (95th percentile value: 11 cells/mm^3; upper bound: 9 cells/mm^3) for infants 29 to 60 days of age (Table 1). Table 2 gives the estimated smoothed centile distribution by age in days for each of the CSF parameters. Figure 2A displays the estimated smoothed median, 90th and 95th percentile curves, and observed values for CSF WBC count. There was an age-related decline in CSF WBC counts (Table 2, Fig 2A). The median CSF WBC count declined from a high value of 8.0 cells/mm^3 to a low value of 2.3 cells/mm^3 at age 60 days.

CSF WBC differentials were performed on 2665 infants. The median polymorphonuclear leukocyte percentage was 2% (IQR: 0–6). The polymorphonuclear leukocyte percentage did not differ between infants ≤28 days of age (median: 2%; IQR: 0–5) and infants 29 to 60 days of age (median: 1%; IQR: 0–6; *P* = .1).

CSF Protein Concentration

The median CSF protein concentration was 57 mg/dL (IQR: 43–73). CSF protein concentrations were higher for infants ≤28 days of age than for infants 29 to 60 days of age (*P* < .001). The median CSF protein concentration was 66 mg/dL for infants ≤28 days of age (95th percentile value: 118 mg/dL; upper bound: 127 mg/dL) and 49 mg/dL for infants 29 to 60 days of age (95th percentile value: 91 mg/dL; upper bound: 99 mg/dL; Table 1). There was an age-related decline in CSF protein concentrations (Table 2, Fig 2B). The median CSF protein concentration declined from a high value of 91.6 to a low value of 41.9 mg/dL at age 60 days.

CSF Glucose Concentration

The median CSF glucose concentration was 46 mg/dL (IQR: 41–51). CSF glucose concentrations were lower for infants ≤28 days of age than for infants 29 to 60 days of age (*P* < .001).

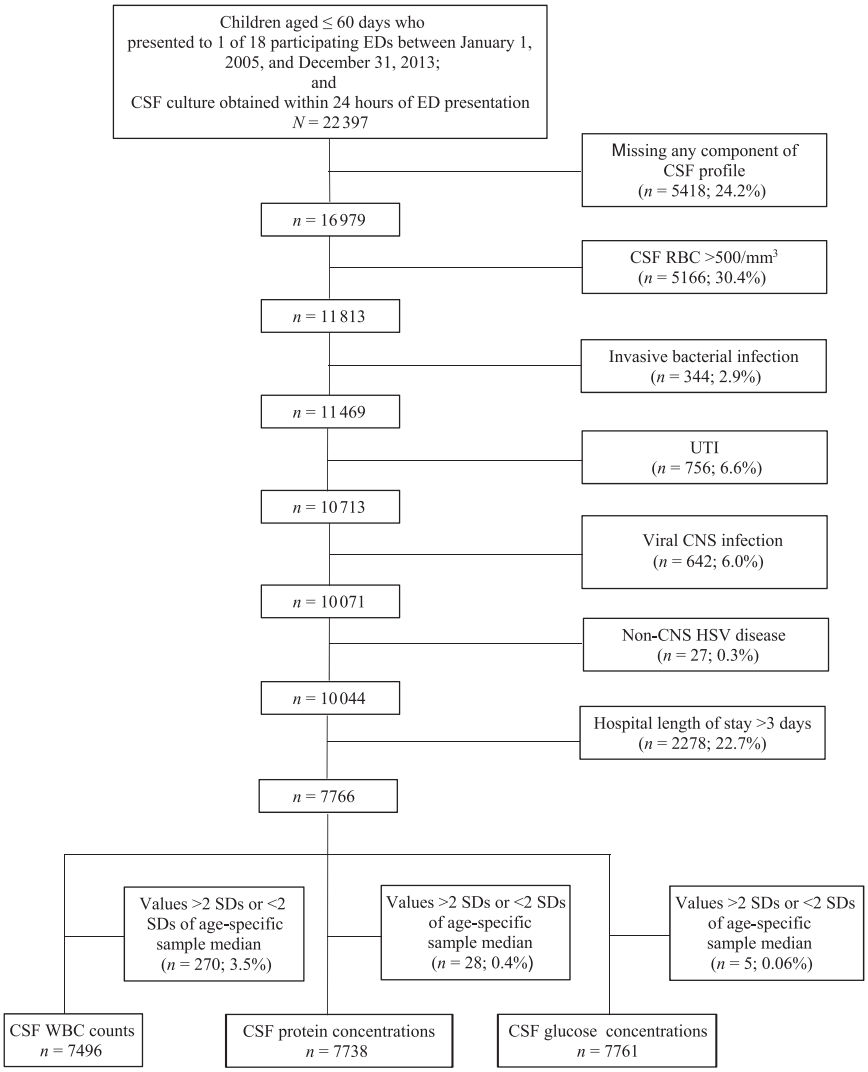

FIGURE 1
Cohort diagram. [medium]

The median CSF glucose concentration was 45 mg/dL for infants ≤28 days of age (5th percentile value: 35 mg/dL; lower bound: 25 mg/dL) and 47 mg/dL for infants 29 to 60 days of age (5th percentile value: 37 mg/dL; lower bound: 27 mg/dL; Table 1). There was an age-related increase in CSF glucose concentrations (Table 2, Fig 2C). The median CSF glucose concentration increased from a low value of 45.2 mg/dL to a high value of 50.0 mg/dL at age 60 days.

Values in Infants With Negative Enterovirus Testing Results

In a subanalysis that was limited to infants who had negative results in enterovirus PCR testing of the CSF (Table 2), CSF WBC values were slightly higher for infants ≤28 days of age (95th percentile value: 22 cells/mm^3; upper bound: 17 cells/mm^3) and infants 29 to 60 days of age (95th percentile value: 16 cells/mm^3; upper bound: 11 cells/mm^3), whereas CSF protein and glucose concentrations were similar to those of the entire cohort.

DISCUSSION

In this study, we establish age-specific reference values for CSF WBC counts, CSF protein concentrations, and CSF glucose concentrations in young infants. We determined that infants ≤28 days of age have higher CSF WBC counts, higher CSF protein concentrations, and lower CSF glucose concentrations than infants 29 to 60 days of age. We also illustrate the age-related decline in CSF WBC counts and protein concentrations and the age-related increase in CSF glucose concentrations over the first 2 months of life.

Various reference manuals and previous studies provide CSF reference values for young infants.[29–38] Although the authors of these references consistently report that values vary by age, reported age-specific values and rates of change over the first 2 months of life vary considerably. Previous studies have been limited by their single-center designs and relatively small sample sizes, with most including <100 patients and the largest including 600 infants <60 days of age.[2–9] Our large, multicenter study of >7000 infants represents the largest study to date. This large sample size allows us to define more precise reference intervals than what are seen in previous studies.

Our age-specific reference values were determined with CSF from presumptively uninfected infants by using sequential, stringent exclusion criteria. A direct comparison among studies is difficult given the variable inclusion (eg, age) and exclusion (eg, presence of certain diagnoses or test results) criteria as well as the lack of consistent reporting of results across studies.[2–9] We present the 90th percentile, 95th percentile, and upper bound values (for WBC and protein) or the 10th percentile, 5th percentile, and lower bound values (for glucose) to allow for more a broad comparison with previous studies.

The values provided in our study are generally comparable to previously published reference values. In a

TABLE 1 CSF Normative Values by Age Among All Infants and in the Subset of Infants Who Had Negative CSF Enterovirus Test Results

Parameter	All		Negative for CSF Enterovirus	
	0–28 d	29–60 d	0–28 d	29–60 d
CSF WBC count, cells/mm^3, *n*	3467	4029	480	563
Mean (SD)	5.5 (6.0)	3.6 (4.3)	6.3 (6.9)	4.6 (6.0)
Median	4	2	4	3
90th percentile	12	8	15	11
95th percentile	16	11	22	16
Upper bound	15	9	48	11
CSF protein concentration, mg/dL, *n*	3551	4187	499	608
Mean (SD)	69.9 (25.7)	53.2 (21.2)	68.2 (25.7)	53.7 (22.7)
Median	66	49	64	49
90th percentile	102	79	100	80
95th percentile	118	91	121	93
Upper bound	127	99	121	102
CSF glucose concentration, mg/dL, *n*	3556	4205	499	613
Mean (SD)	45.7 (8.0)	48.1 (8.0)	45.6 (8.3)	48.2 (7.5)
Median	45	47	45	48
10th percentile	37	39	37	39
5th percentile	35	37	34	37
Lower bound	25	27	25	28

TABLE 2 Smoothed Centile Distribution of CSF Parameters Based on Age in Days

Age, d	Percentile								
	5th	10th	15th	25th	50th	75th	85th	90th	95th
CSF WBC count, cells/mm^3									
7	0.7	1.3	1.7	2.6	5.0	8.7	11.6	14.2	19.1
14	0.6	1.0	1.4	2.1	4.0	7.0	9.5	11.6	16.0
21	0.4	0.8	1.1	1.8	3.4	5.9	8.0	9.9	13.7
28	0.3	0.7	1.0	1.6	3.0	5.2	7.0	8.6	11.9
35	0.2	0.6	0.9	1.4	2.8	4.7	6.3	7.7	10.7
42	0.2	0.5	0.8	1.6	2.6	4.4	5.8	7.1	10.0
48	0.2	0.5	0.8	1.3	2.5	4.2	5.5	6.8	9.7
56	0.2	0.5	0.8	1.3	2.4	3.9	5.3	6.6	9.7
CSF protein concentration, mg/dL									
7	47.0	52.9	57.2	64.0	78.4	96.0	107.4	116.0	130.7
14	39.6	44.8	48.5	54.3	66.9	82.4	92.4	100.1	113.1
21	34.9	39.6	43.0	48.4	60.0	74.3	83.7	90.9	103.1
28	32.1	36.6	39.8	45.0	56.2	70.2	79.3	86.3	98.4
35	29.8	34.1	37.2	42.2	53.1	66.7	75.7	82.7	94.6
42	27.5	31.6	34.6	39.4	49.9	63.2	72.0	78.9	90.6
48	25.6	29.6	32.4	37.1	47.3	60.3	69.0	75.7	87.4
56	23.2	26.9	29.6	34.0	43.8	56.4	64.8	71.4	82.9
CSF glucose concentration, mg/dL									
7	34.7	36.8	38.2	40.4	44.9	50.2	53.6	56.2	60.6
14	34.7	36.7	38.1	40.3	44.6	49.8	53.0	55.5	59.7
21	34.8	36.8	38.1	40.2	44.5	49.5	52.7	55.1	59.2
28	35.2	37.1	38.5	40.6	44.8	49.8	53.0	55.4	59.5
35	36.0	38.0	39.4	41.5	45.8	50.8	54.0	56.4	60.5
42	37.0	39.0	40.5	42.6	47.0	52.1	55.3	57.8	61.9
48	37.7	39.8	41.2	43.4	47.9	53.1	56.3	58.8	63.0
56	38.8	41.0	42.4	44.7	49.2	54.5	57.8	60.4	64.7

single-center study of 380 infants, Kestenbaum et al[6] defined the CSF WBC count upper bounds at 15 cells/mm^3 for infants ≤28 days of age and 4 cells/mm^3 for those 29 to 56 days of age. In a single-center study of 596 infants, Byington et al[4] presents CSF WBC count upper bounds of 18 cells/mm^3 for infants ≤28 days of age and 9 cells/mm^3 for those 29 to 60 days of age. These numbers are similar to the upper bound that we defined in our larger, multicenter study (≤28 days: 15 cells/mm^3; 29–60 days: 9 cells/mm^3).

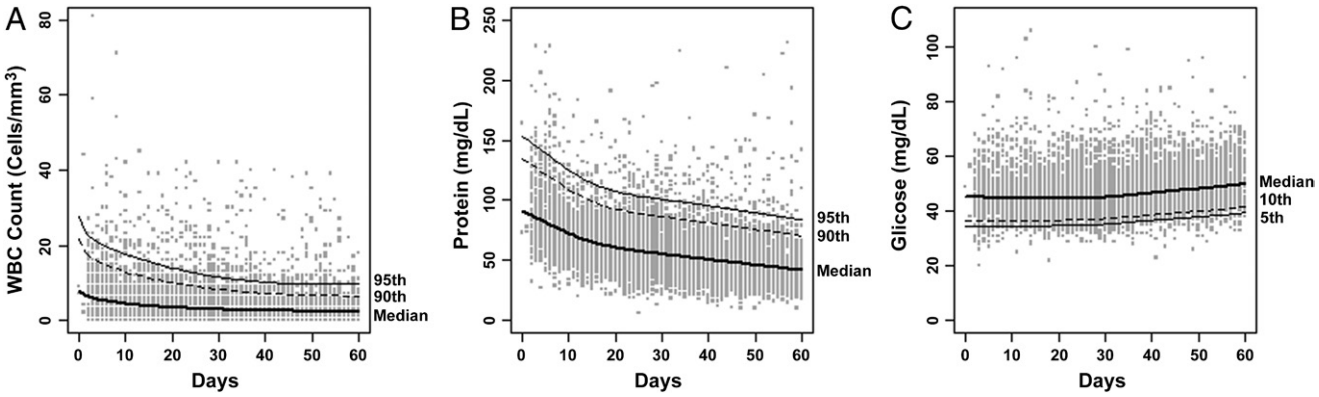

FIGURE 2

A, Scatter plot with smoothed centile curves of CSF WBC counts based on age. B, Scatter plot with smoothed centile curves of CSF protein concentrations based on age. C, Scatter plot with smoothed centile curves of CSF glucose concentrations based on age. Light-gray dots represent observed values from included infants, bolded black lines indicate age-specific median values, dashed black lines indicate the 90th percentile values for CSF WBC counts and protein concentrations and the 10th percentile values for CSF glucose concentrations, and solid light-black lines indicate the 95th percentile values for CSF WBC counts and protein concentrations and the 5th percentile values for CSF glucose concentrations.

For CSF protein concentration, Byington et al[4] defined the upper limits at 131 mg/dL for infants ≤28 days and 106 mg/dL for infants 29 to 60 days of age, which were marginally higher than our upper-limit values of 127 mg/dL and 99 mg/dL, respectively. In a single-center analysis of 375 infants, Shah et al[7] defined normative CSF protein concentrations using 95th percentile values (≤28 days: 115 mg/dL; 29–56 days: 89 mg/dL). Although we included infants up to 60 days of age, our 95th percentile values for CSF protein concentration are similar (≤28 days: 118 mg/dL; 29–60 days: 91 mg/dL).

Compared with the lower limits of normal defined by Byington et al[4] (≤28 days: 30 mg/dL; 29–60 days: 30.5 mg/dL), the CSF glucose concentration lower bounds defined in our study are marginally more liberal (≤28 days: 25 mg/dL; 29–60 days: 27 mg/dL).

We were further able to model the age-related decline in CSF WBC counts and protein concentrations and the age-related increase in CSF glucose concentrations in the centile estimation by using the LMST method. These age-related changes have previously been observed and described, but only the decline in CSF protein concentrations has previously been quantified. Shah et al[7] found a 6.8% decrease (95% confidence interval: 5.4%–8.1%) in CSF protein concentration for each 1-week increase in age. Our study shows that the weekly percentage decrease in median CSF protein concentrations depends on age, with a higher decrease during the first few weeks of life. The provided smoothed centile distribution by age for each CSF parameter can serve as a reference for evaluating WBC counts, protein concentrations, and glucose concentrations for infants. Given an infant's age and CSF WBC count, one can determine the approximate percentile of the value on the basis of this reference sample. For example, an infant aged 7 days with a WBC count of 5 cells/mm^3 would be at the median (or the 50th percentile), but a WBC count of 20 cells/mm^3 would be > 95th percentile, indicating a potential need for further workup and/or referral.

This study has several limitations. First, we may have included infants with viral meningitis. CSF testing for viruses was not routinely performed, and data regarding other viral testing or examination findings that are consistent with viral disease were not available. Additionally, higher CSF WBC counts may have prompted enteroviral testing, and those testing negative for enterovirus may have been infected with other viruses. To mitigate the potential impact of this limitation, we excluded infants with observations falling 2 SDs above or below our sample median. We also repeated analyses in the subset of infants who tested negative for enterovirus. Furthermore, the inadvertent inclusion of infants with enterovirus infection (ie, those who were not tested) may not meaningfully influence our findings because up to 41% of young infants with enterovirus infection lack CSF pleocytosis.[39] Second, data on the time of antibiotic administration relative to bacterial culture attainment were not available, which might have caused an inadvertent inclusion of infants with pretreated invasive bacterial infection and negative blood and CSF culture results. Furthermore, we could not identify children with certain concomitant invasive bacterial infections (eg, osteomyelitis with negative blood culture results) or congenital infections (eg, cytomegalovirus). We believe that these children would likely have been excluded on the basis of our exclusion of children with a length of stay >3 days. Third, the infants in this study received LP for a clinical indication (eg, fever or other

concern for infection). Therefore, our findings do not represent normal values per se but reasonable reference standards to facilitate the interpretation of CSF parameters for infants who require LP as part of initial evaluation in the ED. Caution should be taken when extrapolating our results into practice in the newborn nursery or NICU; our cohort only included 57 infants ≤2 days of age. Children with serious conditions, including bacterial meningitis, may have CSF parameters within the references standards presented. Finally, the linear relationship between the levels of serum and CSF glucose is well recognized.[40] We were unable to account for this relationship in our determination of reference CSF glucose concentrations because serum glucose was not reliably obtained within 60 minutes of CSF collection in our cohort.

CONCLUSIONS

The age-dependent reference values presented in this study will be used to provide guidance to clinicians when interpreting the CSF parameters of young infants.

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ABBREVIATIONS

CNS: central nervous system
CSF: cerebrospinal fluid
ED: emergency department
HSV: herpes simplex virus
IQR: interquartile range
LP: lumbar puncture
PCR: polymerase chain reaction
PEMCRC: Pediatric Emergency Medicine Collaborative Research Committee
RBC: red blood cell
UTI: urinary tract infection
WBC: white blood cell

transfer from other sites, and reviewed and revised the manuscript; Drs Nigrovic and Freedman contributed to the study design, supervised data collection locally and nationally, and reviewed and revised the manuscript; Drs Garro, Balamuth, Mistry, Arms, Ishimine, and Kulik collected data at their sites and reviewed and revised the manuscript; Dr Neuman helped conceptualize and design the study and reviewed and revised the manuscript; Dr Shah conceptualized and designed the study, supervised the interpretation of the data, and drafted the initial manuscript; and all authors approved the final manuscript as submitted.

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