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Cerebrospinal Fluid Reference Ranges in Term and Preterm Infants in the Neonatal Intensive Care Unit

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Abstract

Objective—To determine reference ranges of cerebrospinal fluid (CSF) laboratory findings in term and preterm infants in the neonatal intensive care unit.

Study design—Data were collected prospectively as part of a multisite study of infants aged <6 months undergoing lumbar puncture for evaluation of suspected sepsis. Infants with a red blood cell count >500 cells/ μ L or a known cause of CSF pleocytosis were excluded from the analysis.

Results—A total of 318 infants met the inclusion criteria. Of these, 148 infants (47%) were preterm, and 229 (72%) received antibiotics before undergoing lumbar puncture. The upper reference limit of the CSF white blood cell (WBC) count was 12 cells/ μ L in preterm infants and 14 cells/ μ L in term infants. CSF protein levels were significantly higher in preterm infants (upper reference limit, 209 mg/dL vs 159 mg/dL in term infants; $P < .001$), and declined with advancing postnatal age in both groups (preterm, $P = .008$; term, $P < .001$). CSF glucose levels did not differ in term and preterm infants. Antibiotic exposure did not significantly affect CSF WBC, protein, or glucose values.

Conclusions—CSF WBC counts are not significantly different in preterm and term infants. CSF protein levels are higher and decline more slowly with postnatal age in preterm infants compared with term infants. This study provides CSF reference ranges for hospitalized preterm and term infants, particularly in the first month of life.

Bacterial meningitis causes significant morbidity and mortality in infants.^{1,2} Examination of cerebrospinal fluid (CSF) is crucial for diagnosis, and accurate reference ranges are needed to facilitate correct interpretation of CSF laboratory findings, including white blood cell (WBC) count and protein and glucose concentrations. There are limitations on how these reference ranges can be obtained, however, given that lumbar puncture (LP) cannot be

ethically performed in a healthy infant without a medical indication. Previous studies have evaluated data obtained from infants and children who were evaluated for suspicion of sepsis and meningitis but were subsequently deemed healthy.^{3–16} Subjects' age ranges, inclusion and exclusion criteria, and sample sizes vary greatly among these studies, and most were retrospective in nature. Recent investigations evaluated reference ranges in infants presenting with a concern for sepsis in the emergency room setting, but included few preterm infants.^{12–15}

CSF culture is the gold standard method for diagnosing bacterial meningitis. However, in the neonatal intensive care unit (NICU), clinicians often initiate antibiotics before performing LP, citing a lack of cardiorespiratory stability at the time of concern for sepsis. Antibiotic treatment before LP reduces the yield of cultures, forcing clinicians to diagnose meningitis indirectly, based on interpretation of other CSF laboratory test results.^{3,4,16,17} Furthermore, previous studies of reference ranges in infants in NICUs relied on retrospective analyses of information from databases, which often had significant amounts of missing information.^{18–20} Most of those studies did not address the effects of antibiotic pretreatment on CSF reference ranges, however.

The objective of the present study was to characterize clinically relevant reference ranges of CSF laboratory findings in term infants and preterm infants hospitalized in the NICU, including in the setting of antibiotic pretreatment, using prospectively collected data.

Methods

Data for this study were obtained as part of a prospective study of CSF biomarkers in neonatal meningitis conducted at 3 sites: The Children's Hospital of Philadelphia, a quaternary center with inborn and out-born infants, and the Hospital of the University of Pennsylvania and Pennsylvania Hospital, tertiary centers with labor and delivery units and predominantly inborn infants. The study was approved by the Institutional Review Boards at the study sites. Written or verbal consent was obtained from parents, and data were collected and stored in an electronic database.

Infants aged <6 months undergoing LP for evaluation for sepsis in 1 of the 3 study NICUs between March 1, 2008, and December 31, 2010 were eligible for inclusion. We chose the 0–6 months as the age range representative of infants in the NICU, especially preterm infants with long hospital stays. Infants were excluded sequentially for reasons known or suspected to be associated with CSF pleocytosis (Table I). In infants undergoing multiple LPs that met the inclusion criteria, only results from the first LP were included in this analysis.

Preterm infants were defined as those born at gestational age <37 weeks. Culture-proven bacterial meningitis was defined by the identification of bacterial pathogens on CSF culture. Bacteremia was defined as a positive blood culture during the sepsis event for which the LP was performed. Seizure was defined based on clinician description or electroencephalography findings.

The 3 hospital laboratories used comparable testing methods for analyzing CSF. One laboratory (The Children's Hospital of Philadelphia) performed an additional enrichment step for detection of bacteria in CSF cultures. Given that this study deals primarily with uninfected infants, and potentially infected infants were diligently excluded, this difference should have only a minimal impact on the results.

Data were obtained prospectively from the medical records of enrolled subjects and stored in an electronic database. Information included demographic data, vital signs at the time of LP, history and physical examination findings leading to sepsis evaluation, results of laboratory tests and brain imaging studies, and antibiotic administration.

For statistical analysis, continuous variables were described using mean, median, SD, IQR, and 90th and 95th percentile values. Categorical data were described using proportions. CSF findings were compared in preterm and term infants, in infants aged ≤ 7 days and infants aged >7 days, and in infants on antibiotic therapy at the time of LP and others. The Wilcoxon rank-sum test was used to compare data across 2 categories, and the Kruskal-Wallis test to compare data across more than 2 categories. We created upper (or lower, when appropriate) limits for the reference range for each CSF measurement by applying two definitions: 95th (or 5th) percentile value,^{12,13} and 1.5 times the IQR ($1.5 \times \text{IQR}$) added to the upper bound of the IQR (or subtracted from the lower bound of the IQR).^{14,21,22} These definitions are considered equally acceptable methods for the development of reference ranges, and the latter definition may better account for nonnormal distributions and outlying results.^{14,21,22} Linear regression was performed to identify changes in CSF findings with increasing postnatal age and to develop predictive rules.

Antibiotic therapy before LP, as well as contamination of CSF with blood, can affect CSF WBC and protein values. Secondary analyses were carried out to assess the effect of intraventricular hemorrhage (IVH) and antibiotic therapy before LP on CSF characteristics. All statistical analyses were performed using Stata/IC 11 (StataCorp, College Station, Texas).

Results

Of the 677 infants enrolled in the study, 318 (47%) met the inclusion criteria (Table I). Overall, 47% of the 318 infants were preterm, 62% were ≤ 7 days old, 81% were ≤ 28 days old, and 72% were receiving antibiotics at the time of LP (Table II). A central venous catheter was present in 28% of the infants. Preterm infants underwent evaluation for sepsis later in the course of hospitalization, and were more likely than term infants to have a central venous catheter in place at the time of the LP (Table II). Infants exposed to antibiotics were more frequently preterm (50% vs 38%), and to have had LPs performed at an earlier postnatal age (3 days vs 7 days).

CSF WBC count did not differ between preterm and term infants during the first week of life and beyond (median, 3 cells/ μL ; IQR, 1–6 cells/ μL) (Table III). In all subgroups, the upper limits of CSF WBC counts were lower when defined using $1.5 \times \text{IQR}$ compared with the 95th percentile values. CSF WBC values did not decline significantly with increasing

postnatal age in either preterm infants (95% CI for weekly rate of change, -0.59 to 0.01 cells/ μ L/week; $P = .06$, $R^2 = 0.02$) or term infants (95% CI, -0.49 to 0.69 cells/ μ L/week; $P = .74$, $R^2 = 0.0007$) (Figure).

CSF protein values were significantly higher in the preterm infants compared with the term infants (median, 104 mg/dL vs 74 mg/dL; $P < .001$) (Table III). This difference persisted when analyzed during the first week of life and beyond ($P < .001$). CSF protein values also decreased significantly with increasing postnatal age in both preterm and term infants (Figure). The rate of decline was greater in term infants (4.8 mg/dL/week; 95% CI, 2.2 – 7.4 mg/dL/week; $P < .001$; $R^2 = 0.07$) compared with preterm infants (3.1 mg/dL/week; 95% CI, 0.8 – 5.5 mg/dL/week; $P = .008$; $R^2 = 0.05$).

CSF glucose values were similar in preterm and term infants both early and later in life. Because the lower limit is of interest in defining reference limits for CSF glucose, we present 5th percentile values and $1.5 \times$ IQR subtracted from the lower bound in Table III. CSF glucose level did not show significant decreases with increasing postnatal age in either preterm infants (95% CI: -1.3 to 0.4 mg/dL/week; $P = .32$; $R^2 = 0.007$) or term infants (95% CI, -0.38 to 1.5 mg/dL/week; $P = .24$; $R^2 = 0.008$) (Figure).

There were no significant differences in CSF findings between sites, supporting the pooling of data. We provide additional data on CSF findings in antibiotic-unexposed infants (Table III) to verify that the overall results are corroborated by the cohort of infants who were not receiving antibiotics at the time of LP. CSF protein values were significantly higher in infants receiving antibiotics compared with unexposed infants (median, 92 mg/dL [IQR, 65 – 122 mg/dL] vs 80 mg/dL [IQR, 59 – 102 mg/dL]; $P = .02$) (data not shown). However, these differences do not appear to be clinically relevant, with the values in both groups falling within currently accepted “normal” ranges. CSF WBC and glucose concentrations were not different among these subgroups. There were no significant associations between CSF findings and increasing days of antibiotic exposure before the LP. We do not present data on antibiotic-exposed infants in Table III, because summary statistics from that subgroup do not add information beyond that already presented.

Infants with a CSF red blood cell (RBC) count >500 cells/ μ L were excluded from analysis in this study. Among the 112 included infants with available head imaging results, no differences in CSF findings were seen between infants with IVH and those without IVH (data not shown).

Discussion

Here we have provided prospectively collected reference ranges for CSF laboratory findings in hospitalized term and preterm infants, including infants receiving antibiotic therapy. Our study is novel in that nearly half of the included infants were preterm, and a substantial proportion was receiving antibiotic therapy at the time of LP. We found that, contrary to popular teaching, CSF WBC counts do not differ between preterm and term infants. CSF protein levels were significantly higher in the preterm infants and declined with advancing postnatal age.

Although many previous studies have characterized reference ranges of CSF findings in infants, controversy persists, especially regarding appropriate values in hospitalized preterm infants and in the context of antibiotic pretreatment. Normative CSF values are of special importance to identify infants with central nervous system infection in settings in which CSF cultures may yield false-negative results. Most early studies attempting to establish reference ranges were retrospective and examined small populations of infants.^{3–8} Many did not have well-developed exclusion criteria; some included infants with traumatic LP, bacteremia, and seizures.^{6,8} Recent studies examining populations of infants evaluated in the emergency department used more stringent inclusion and exclusion criteria.^{12–14} Only a small proportion of the subjects included in these studies were born preterm, however. Retrospective analyses based on large databases have found significant amounts of missing data, as well as a lack of information on antibiotic pretreatment.^{18,19}

For the clinician, the most useful information from this study is the upper and lower limits of the reference range, depending on whether high or low values are considered abnormal. Previous studies have presented reference ranges in a number of different ways, and we have chosen 2 common formats.^{12–14} The use of the 95th or 5th percentile generally is acceptable for normally distributed data; however, in the presence of skewed data (such as our sample), reference ranges defined by the IQR are widely accepted as the best method of presentation.^{21,22} Depending on the degree of suspicion for infection, the clinician may choose to use one or the other as a cutoff.

We grouped infants as preterm and term, and further classified them into subgroups of postnatal age ≤ 7 days and >7 days, as recent retrospective analyses have reported the greatest differences in CSF findings using this demarcation.¹⁵ We found no difference in CSF WBC counts and glucose values between preterm and term infants, and no significant changes with advancing postnatal age. Of interest, the lower confidence limits of CSF glucose in our cohort were below the commonly used cutoff of 40 mg/dL; however, we did not record simultaneously measured serum glucose values in this study. CSF protein values were higher and declined more slowly with increasing postnatal age in preterm infants compared with term infants. We speculate that this might be related to the increased permeability of the blood-brain barrier in preterm infants.²³ Alternatively, increased amounts of growth factors and other proteins may be present in the CSF of preterm infants, with levels decreasing with advancing postnatal age.²⁴

Administration of antibiotic therapy before LP is common in many NICUs, most often related to concerns for cardiorespiratory instability at the time of the sepsis evaluation. Under these circumstances, culture results are often negative, and clinicians must rely on interpretation of CSF laboratory findings to determine whether or not the infant has presumed meningitis. These factors further impact decisions regarding duration of antibiotic therapy. There are scant data on the effect of antibiotic pretreatment on CSF findings in infants. A large proportion of our study population was exposed to antibiotics before undergoing LP, which provided us the opportunity to analyze this effect. Although we found a slight difference in CSF protein value between antibiotic-exposed infants and antibiotic-unexposed infants, both values fell well within currently accepted normal standards. No differences in CSF WBC count or glucose level due to short-term antibiotic exposure were

detected; however, the upper limit for CSF WBC counts was higher in term infants not exposed to antibiotics compared with in all term infants. Because most infants had received antibiotics before LP, the antibiotic-unexposed group was relatively small; thus, the estimates for this subgroup may be less stable and more susceptible to influence by outlying values.

The strengths of our study include the high enrollment rate, as well as the prospective nature of data collection, with few missing values. We included a wide clinical spectrum of infants as is encountered typically in both tertiary and quaternary NICUs. This permits generalizability of our findings to diverse NICU settings. Although recent studies have provided data on febrile infants presenting to the emergency department, our data provide an accurate representation of CSF findings in the evaluation of nosocomial infection in the NICU. We excluded infants with CSF RBC counts >500 cells/mm³, thereby eliminating confounding due to bloody CSF of any cause—IVH, birth trauma, or traumatic LP.

Our study also has several limitations. The data were obtained from infants evaluated for sepsis in the NICU and thus might not be applicable to febrile infants evaluated in the emergency department. The high proportion of antibiotic-pretreated infants could have led to the inclusion of infants with partially treated meningitis. Some study patients might have had viral central nervous system infections, although these infections are far less common in the emergency department than in the outpatient setting. In addition, only a small proportion of infants were aged >28 days, making it difficult to extrapolate the results of our study to older infants. IVH was another potential source of bias in our results, especially given the large number of preterm infants in the population. By excluding infants with a CSF RBC count >500 cells/ μ L, we likely eliminated the majority of infants with traumatic LP or acute IVH from further analysis; therefore, we cannot draw conclusions about such effects on CSF findings from our study. Finally, it is noteworthy that 30% of infants were excluded because of RBC counts. We have determined reference ranges from infants who underwent LP because of concern for sepsis; consequently, the reference ranges reported might not reflect a truly healthy patient population.

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Glossary

CSF	Cerebrospinal fluid
IVH	Intraventricular hemorrhage
LP	Lumbar puncture
NICU	Neonatal intensive care unit
RBC	Red blood cell

WBC White blood cell

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Figure.

Changes in **A** and **D**, CSF WBC count (**A** and **D**), CSF protein level **C** and **F**, and CSF glucose level with increasing postnatal age in preterm and term infants. The graphs exclude infants with unknown CSF WBC concentration ($n = 1$) or an extremely outlying value ($n = 1$; CSF WBC of 850), unknown CSF protein concentration ($n = 4$), and unknown CSF glucose concentration ($n = 2$). The *solid lines* represent the best linear fit for each laboratory test result; the *dashed lines* represent upper limits (for CSF WBC and protein) and lower limits (for CSF glucose) based on the addition or subtraction of $1.5 \times \text{IQR}$ to the upper or lower limit of the IQR, respectively; and the *dotted lines* represent upper limits (for CSF WBC and protein) and lower limits (for CSF glucose) based on the 95th and 5th percentile values, respectively. The *vertical line* represents a postnatal age of 7 days.

Table ISelection of infants eligible for inclusion in the study^{*}

Reason for exclusion	Number excluded
Postnatal age >6 months	2
Culture-proven bacterial meningitis	10
Unknown CSF culture results	6
Positive CSF herpes simplex virus/enterovirus PCR	2
Ventriculoperitoneal shunt	4
Seizure	34
Bacteremia	94
CSF RBC >500 cells/ μ L	197
Infants included in the final analysis [†]	318

PCR, polymerase chain reaction.^{*} Total number of infants enrolled in the study: 667.[†] Infants included in the final analysis, by site: The Children's Hospital of Philadelphia, 122; Hospital of the University of Pennsylvania, 73; Pennsylvania Hospital, 123.

Table II

Demographic data for all eligible infants, preterm infants, and term infants

Characteristic	All infants (n = 318)	Preterm (n = 148)	Term (n = 170)
Male sex, n (%)	191 (60)	87 (59)	104 (61)
White, n (%)	118 (37)	51 (34)	67 (39)
Non-Hispanic, n (%)	263 (83)	128 (86)	135 (79)
Birth weight, g, median (IQR)	2735 (1650–3326)	1580 (1005–2279)	3233 (2917–3635)
Gestational age, weeks, median (IQR)	37 (32–39)	31 (28–35)	39 (38–40)
Postnatal age, days, median (IQR)	3 (1–20)	12 (2–29)	2 (1–6)
Antibiotics at time of LP, n (%)	229 (72)	114 (77)	115 (68)
Days on antibiotics before LP, median (IQR)	1 (0–4)	2 (1–10)	1 (0–2)
Central line present, n (%)	89 (28)	66 (45)	23 (14)

Table III

CSF findings in preterm and term infants

Value	Preterm infants			Term infants		
	All (n = 148)	7 days (n = 66)	>7 days (n = 82)	All (n = 170)	7 days (n = 130)	>7 days (n = 40)
CSF WBC, cells/ μ L						
All infants						
Median (IQR)	3 (1–6)	3 (1–7)	3 (1–4)	3 (1–6)	3 (1–6)	2 (1–4)
95th percentile	16	18	12	26	23	32
Upper IQR bound + $1.5 \times$ IQR	14	16	9	14	14	9
Antibiotic-unexposed						
95th percentile	11	17	10	32	31	53
Upper IQR bound + $1.5 \times$ IQR	9	17	9	20	20	21
CSF protein, mg/dL *						
All infants						
Median (IQR)	104 (79–131)	116 (93–138)	93 (69–122)	74 (54–96)	78 (60–100)	57 (42–77)
95th percentile	203	213	203	137	137	158
Upper IQR bound + $1.5 \times$ IQR	209	206	202	159	160	130
Antibiotic-unexposed						
95th percentile	195	195	136	136	136	284
Upper IQR bound + $1.5 \times$ IQR	175	245	143	172	188	105
CSF glucose, mg/dL						
All infants						
Median (IQR)	49 (42–62)	53 (43–65)	47 (40–58)	51 (44–57)	50 (44–56)	52 (45–64)
5th percentile	33	33	33	36	35	38
Lower IQR bound – $1.5 \times$ IQR	12	10	13	24	26	17
Antibiotic-unexposed						
5th percentile	33	33	35	33	33	33
Lower IQR bound – $1.5 \times$ IQR	19	25	18	21	26	21

Eight infants were excluded from the analysis because of unknown CSF WBC (n = 1), extremely outlying value (n = 1; CSF WBC 850), unknown CSF protein concentration (n = 4), and unknown CSF glucose concentration (n = 2).

* CSF protein values: $P < .001$, term versus preterm, term age 7 days versus preterm age 7 days, and term age >7 days versus preterm age >7 days.