

Valores normales de líquido cefalorraquídeo en Neonatos: una revisión sistemática

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RESUMEN

Antecedentes: el diagnóstico de meningitis neonatal a menudo se basa en hallazgos microscópicos y bioquímicos en el líquido cefalorraquídeo (LCR). Existe una incertidumbre permanente sobre valores normales relacionados con la edad para los hallazgos del LCR en neonatos, y

Muchos estudios previos han incluido lactantes a los que se les administraron antibióticos antes de la punción lumbar o en quienes no se excluyó la meningitis viral.

Método: Se realizó una búsqueda sistemática en MEDLINE y EMBASE para identificar estudios originales que investigaron los valores normales del LCR en recién nacidos sanos o febriles en quienes la meningitis bacteriana y viral fueron excluidas de forma fiable.

Resultados: Se identificaron siete estudios que investigaron 270 y 96 recién nacidos prematuros.

Había diferencias mínimas entre prematuros y recién nacidos a término en la sangre blanca del LCR recuento de glóbulos blancos y concentración de glucosa. Por el contrario, el recuento de neutrófilos en el LCR y la concentración de proteínas se vieron influidos por la edad gestacional y cronológica.

En los cuatro estudios que informaron datos de pacientes individuales, en el 95% de los casos el recuento de leucocitos en LCR fue <12 células/ μL en prematuros y <10 células/ μL en recién nacidos a término, el recuento de neutrófilos fue <16 y 8 células/ μL , y la concentración de proteína fue <210 y 110 mg/dL, respectivamente.

Conclusión: El rango normal de los parámetros del LCR en los recién nacidos es diferente al de los lactantes mayores, y algunos parámetros están influenciados por la edad gestacional y cronológica.

Los parámetros del LCR por sí solos no son suficientemente fiables para descartar meningitis.

Normal Values for Cerebrospinal Fluid in Neonates: A Systematic Review

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Keywords

Meningitis · Cerebrospinal fluid · Cell count · White cells · White blood cell · Leucocytes · Lymphocytes · Neutrophils · Protein · Glucose · Lumbar puncture

Abstract

Background: The diagnosis of neonatal meningitis often rests on microscopic and biochemical findings in the cerebrospinal fluid (CSF). There is ongoing uncertainty about age-related normal values for CSF findings in neonates, and many previous studies have included infants in whom antibiotics were administered before lumbar puncture or in whom viral meningitis was not excluded. **Methods:** A systematic search was done using MEDLINE and EMBASE to identify original studies which investigated CSF normal values in either healthy neonates or febrile neonates in whom bacterial and viral meningitis were reliably excluded. **Results:** We identified seven studies investigating 270 term and 96 preterm neonates. There were minimal differences between preterm and term neonates in the CSF white blood cell (WBC) count and glucose concentration. In contrast, the CSF neutrophil count and protein concentration were influenced by gestational and chronological age. In the four studies that reported individual patient data, in 95% of cases the CSF WBC count was <12 cells/ μ L in preterm and <10 cells/ μ L in term neonates, the neutrophil count was <16 and 8 cells/ μ L, and the protein concentration was <210 and 110 mg/dL,

respectively. **Conclusion:** The normal range for CSF parameters in neonates is different to that in older infants, and some parameters are influenced by gestational and chronological age. CSF parameters alone are not sufficiently reliable to exclude meningitis.

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Introduction

The gold standard for diagnosing bacterial meningitis is the isolation of pathogens in the cerebrospinal fluid (CSF). However, the diagnosis often depends on the microscopic and biochemical findings in the CSF, including a Gram stain, white blood cell (WBC) count, and differential, together with protein and glucose concentrations. This is also the case when antibiotics are administered before lumbar puncture (LP). Even with all these parameters available, it is often difficult to diagnose meningitis and to differentiate bacterial from aseptic meningitis. Furthermore, there is ongoing uncertainty about age-related normal values of CSF parameters, especially in neonates. The blood-brain barrier in neonates differs to that in older children [1], and normal values in infants, particularly neonates, are therefore different from those in older children. Age-related normal values of CSF findings have previously been reviewed [2]. However, many studies included children in whom antibiotics were given be-

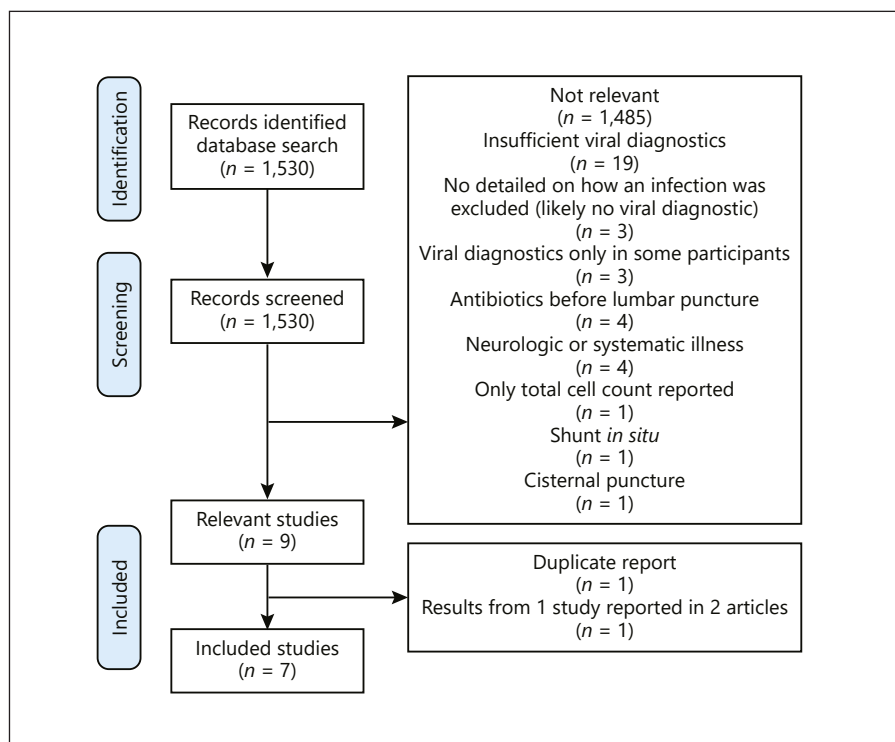


Fig. 1. Selection of studies. LP, lumbar puncture.

fore LP or in whom viral meningitis was not excluded reliably [3–7]. Also, additional studies have been published in recent years. In this systematic review, we summarize studies which investigated CSF parameters in healthy neonates, including those born preterm, using stringent inclusion criteria to define normal neonatal CSF values more reliably.

Systematic Review Methods

To identify studies which investigated CSF normal values in healthy neonates or febrile neonates in whom meningitis was reliably excluded, MEDLINE (1946 to present) and EMBASE (1947 to present) were searched in August 2020 using the Ovid interface with the following search terms: (cerebrospinal fluid [analysis, chemistry, cytology, diagnosis, microbiology] OR meningitis [cerebrospinal fluid, diagnosis] OR spinal puncture OR lumbar puncture) AND (infant OR neonat* OR newborn) without any language limitations. Exclusion criteria were studies that: (i) did not include molecular diagnostics to exclude enterovirus infection; (ii) included neonates in whom antibiotics were administered before LP; (iii) included neonates with underlying disease; (iv) included neonates with CSF shunts, and (v) included neonates in whom CSF was collected by a route other than LP. References of retrieved articles were hand-searched for additional publications.

The following variables were extracted from the included studies: year of study, country, study design, number, and characteris-

tics of participants and key findings including CSF WBC and CSF glucose and protein concentrations. Statistical analyses and graphs were done using R version 3.4.3. The Mann-Whitney U test was used to compare values between groups.

Systematic Review Results

Our search identified 1,530 studies. Of these, nine fulfilled the inclusion criteria (Fig. 1) [8–16]. No additional relevant studies were identified by hand searching of references. Two studies reported the same group of neonates, one the cell counts and the other the biochemical findings, considered hereon in as one study [8, 9]. Two other studies reported the same findings in different languages [10, 11]. Therefore, 7 studies were included in the review, all of which were case series. These reported the results from 270 term (in 5 studies) [12–16] and 96 preterm infants (in 2 cohorts) [8–11]. The number of participants in each study ranged from 19 to 108 (mean 52, median 43). The studies were done in Brazil 4, USA 2, and Spain 1. The results of the studies are summarized in Table 1.

WBC Count

The two studies that investigated the CSF WBC count in preterm neonates, reported a range from 0 to

Table 1. Summary of findings of studies investigating normal values of CSF parameters in preterm and term neonates

Author Country Publication year	Neonates, n Sex	Characteristics Inclusion criteria	WBC count in cells/ μ L Mean \pm SD 95% CI Range Median IQR	Neutrophil count in cells/ μ L Mean \pm SD 95% CI Range Median IQR	Protein concentration in mg/dL Mean \pm SD 95% CI Range Median IQR	Glucose concentration in mg/dL (CSF/blood glucose) Mean \pm SD 95% CI Range Median IQR	Other findings
<i>Preterm neonates</i>							
Diniz et al. [8], De Albuquerque et al. [9] Brazil, 1982	43 40% male	Asymptomatic preterm neonates <37 wk (mean 33.2 \pm 2.0)	Day 7 of life (n = 43) 7.6 \pm 5.0 ns 1.0–23.0 ns ns	Day 7 of life (n = 43) 2.1 \pm 4.7 ns ns ns	ns	Day 7 of life (n = 43) 57.5 \pm 14.3 ns 35.0–88.0 ns ns	
			Day 28 of life (n = 30) 3.9 \pm 2.4 ns 1.0–13.0 ns ns	Day 28 of life (n = 30) 1.9 \pm 2.45 ns ns ns	ns	Day 28 of life (n = 30) 54.2 \pm 10.3 ns 42.0–75.0 ns ns	
Vaz et al. [10, 11] Brazil, 1977	53 ¹ 43% male	Asymptomatic preterm neonates <37 wk (mean 33.8 \pm 2.3)	Day 2 of life 4.0 \pm 3.6 3.0–5.0 0–16.0 2.7 3.3	Day 2 of life 0.3 \pm 0.4 0.2–0.4 0–1.4 0.1 4.0	Day 2 of life 144.6 \pm 48.1 131.3–157.9 52.0–300.0 144.0 72.5	Day 2 of life 51.6 \pm 18.3 46.6–56.6 17.0–162.0 49.0 10.0	No correlation between RBC and protein concentration (<i>p</i> = 0.21) ³
<i>Term neonates</i>							
Martin-Ancel et al. [12] Spain, 2006	19 40% male	Asymptomatic neonates in whom toxoplasmosis was excluded Atraumatic LP (<1,000 RBC/ μ L)	Day 0 to 8 of life 1.5 \pm 1.7 0.6–2.3 0–5.0 1.0 2.0	ns	ns	ns	
Wong et al. [13] USA, 2000	43 ² Sex ns	Evaluation for neurological disease including meningitis Atraumatic LP (<200 RBC/ μ L) Viral and bacterial CSF cultures negative Enterovirus CSF PCR negative No neurological or system illness	ns	ns	ns	ns	

Table 1 (continued)

Author Country Publication year	Neonates, <i>n</i> Sex	Characteristics Inclusion criteria	WBC count in cells/ μ L Mean \pm SD 95% CI Range Median IQR	Neutrophil count in cells/ μ L Mean \pm SD 95% CI Range Median IQR	Protein concentration in mg/dL Mean \pm SD 95% CI Range Median IQR	Glucose concentration in mg/dL (CSF/blood glucose) Mean \pm SD 95% CI Range Median IQR	Other findings
Ahmed et al. [14] USA, 1996	108 56% male	Evaluation for possible meningitis Atraumatic LP (<1,000 RBC/ μ L) No AB before LP Blood, CSF, and urine cultures negative CSF viral culture negative CSF PCR for enteroviruses negative	Day 0 to 30 of life 7.3 \pm 13.9 6.6–8.0 0–130.0 4.0 ns	Day 0 to 30 of life 0.8 \pm 6.2 ns 0–65.0 0 ns	ns	Day 0 to 30 of life 51.2 \pm 12.9 (62%) ns ns ns ns	No difference in WBC or glucose concentration between week 1 and 4 ($p > 0.05$) Neutrophil counts and protein concentration were higher in weeks 1 and 2 than weeks 3 and 4 ($p < 0.05$)
Luz et al. [15] Brazil, 1975	79 67% male	Healthy term neonates	Day 2 of life (<i>n</i> = 79) 4.4 \pm 3.8 3.5–5.3 0–22.0 3.7 3.3	ns	ns	ns	No difference between means of WBC and protein concentration at day 2 and day 7 ($p = 0.96$, $p = 0.66$) ³ Mean RBC higher on day 2 than day 7 ($p = 0.01$) ³
Livramento et al. [16] Brazil, 1974	21 Sex ns	Healthy term neonates (screened for bilirubin concentration in CSF)	Day 2 to 7 of life 5.4 \pm 2.4 4.3–6.5 1.0–11.0 5.0 3.0	Day 2 to 7 of life 2.9 \pm 4.1 1.0–4.8 0–17.0 2.0 4.0	ns	ns	

AB, antibiotics; ns, not specified; CI, confidence interval; RBC, red blood cell; IQR, interquartile range; SD, standard deviation; LP, lumbar puncture; WBC, white blood cell; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; wk, week. ¹One neonate was excluded because RBC > 1,000/ μ L. ²Included neonates up to the age of 2 months. ³Calculated from reported data.

Table 2. Summary of findings from the 4 of 7 studies investigating normal CSF values that specified individual values

	WBC count, cells/ μ L			Neutrophil count, cells/ μ L			Protein concentration, mg/dL			Glucose concentration, mg/dL
	Preterm (<i>n</i> = 53)	Term (<i>n</i> = 119)	<i>p</i> value	Preterm (<i>n</i> = 45)	Term (<i>n</i> = 21)	<i>p</i> value	Preterm (<i>n</i> = 53)	Term (<i>n</i> = 79)	<i>p</i> value	Preterm (<i>n</i> = 53)
Median	2.7	3.7		3.0	2.0		144.0	74.0		49.0
Range	0.3–16.3	0–22.0		0–34.0	0–17.0		52.0–300.0	19.0–140.0		17.0–162.0
IQR	3.3	3.3		4.0	4.0		66.0	35.5		10.0
95th percentile	12.0	10.0		16.0	8.0		210.0	110.2		32.0*
Mean	4.0	4.2	0.35	5.0	2.9	0.04	144.6	71.4	<0.01	51.6
SD	3.6	3.6		6.6	4.1		48.1	24.2		18.3
95% CI	3.0–4.9	3.6–4.9		3.1–7.1	1.0–4.8		131.4–157.9	66.0–77.9		46.5–56.6

CI, confidence interval; IQR, interquartile range; SD, standard deviation; WBC, white blood cell; CSF, cerebrospinal fluid. *5th percentile.

23.0 cells/ μ L in the first week of life and from 1.0 to 13.0 cells/ μ L at 1 month of age [8, 10]. In one of the studies in preterm neonates, the CSF WBC count decreased from a mean of 7.6 (range 1.0–23.0) cells/ μ L on day 7 of life to a mean of 3.9 (range 1.0–13.0) cells/ μ L on day 28 of life [8]. The other study in preterm neonates reported a mean of 4.0 (range 0–16.0) cells/ μ L on day 2 of life [10].

Four studies reported the CSF WBC count in term infants. This ranged from 0 to 130.0 cells/ μ L (though this upper value was deemed potentially indicative of meningitis by the authors) with means ranging from 1.5 to 7.3 cells/ μ L [12, 14–16]. There was no difference between the CSF WBC count on day 2 and 7 ($p = 0.96$) [15]. In one study there were 2 term neonates with very high WBCs (130.0 and 62.0 cells/ μ L) [14]. Apart from these two neonates, the highest WBC count in a term neonate was 28.0 cells/ μ L [14].

Table 2 and Figure 2 summarize the CSF WBC count for individual neonates in the four studies in which these data were reported [10, 12, 15, 16]. The mean CSF WBC count was 4.0 cells/ μ L in preterm ($n = 53$) (standard deviation [SD] 3.6, median 2.7, interquartile range [IQR] 3.3, range 0.3–16.3) and 4.2 cells/ μ L in term ($n = 119$) neonates (3.6, 3.7, 3.3, 0–22.0) ($p = 0.35$). The 95th percentile for CSF WBC count was 12.0 cells/ μ L in preterm and 10.0 cells/ μ L in term neonates.

Neutrophil Count

Four studies (two in preterm neonates) reported the neutrophil count in CSF [8, 10, 14, 16]. In 96 preterm neonates [8, 10], the mean neutrophil count was 0.3 and 2.1 cells/ μ L, respectively (range 0–1.4 in 1 study, not specified in the other) and in 129 term neonates [14, 16] it was

0.8 and 2.9 (range 0–65.0) cells/ μ L. In term neonates, the CSF neutrophil count was higher in week 1 and 2 compared to week 3 and 4 ($p < 0.05$) [14]. The study which reported the value of 65 included the neonate with the WBC count of 130.0 cells/ μ L.

The two studies which reported individual neutrophil values are summarized in Table 2 and Figure 3 [10, 16]. The mean neutrophil count was 5.0 cells/ μ L in preterm neonates ($n = 45$) (SD 6.6, median 3.0, IQR 4.0, range 0–34.0) and 2.9 cells/ μ L in term neonates ($n = 21$) (4.1, 2.0, 4.0, and 0–17.0) ($p = 0.04$). The 95th percentile for the CSF neutrophil count was 16.0 cells/ μ L in preterm and 8.0 cells/ μ L in term neonates.

Protein Concentration

Four studies (one in preterm neonates) investigated the protein concentration in CSF [10, 13–15]. The protein concentration was higher in preterm ($n = 53$) compared with term neonates ($n = 79$) (mean 144.6 mg/dL, range 52.0–300.0 vs. mean 61.0–71.4 mg/dL, range 8.0–140.0). In term neonates, no difference was found between the protein concentration on day 2 and day 7 of life ($p = 0.66$) in one study [15], while another found a higher protein concentration in week 1 and 2 compared to week 3 and 4 ($p < 0.05$) [14]. In the study in preterm neonates, there was no correlation between the red blood cell (RBC) count and protein concentration; therefore, the observed increase in CSF protein cannot be attributed to a higher RBC count ($p = 0.21$) [10].

The two studies which reported individual values are summarized in Figure 4 [10, 15]. The mean protein concentration was higher in preterm neonates ($n = 53$) (mean 144.6, SD 48.1, median 144.0, IQR 66.0, range 52.0–300.0) compared with term neonates ($n = 79$) (71.4, 24.2, 74.0,

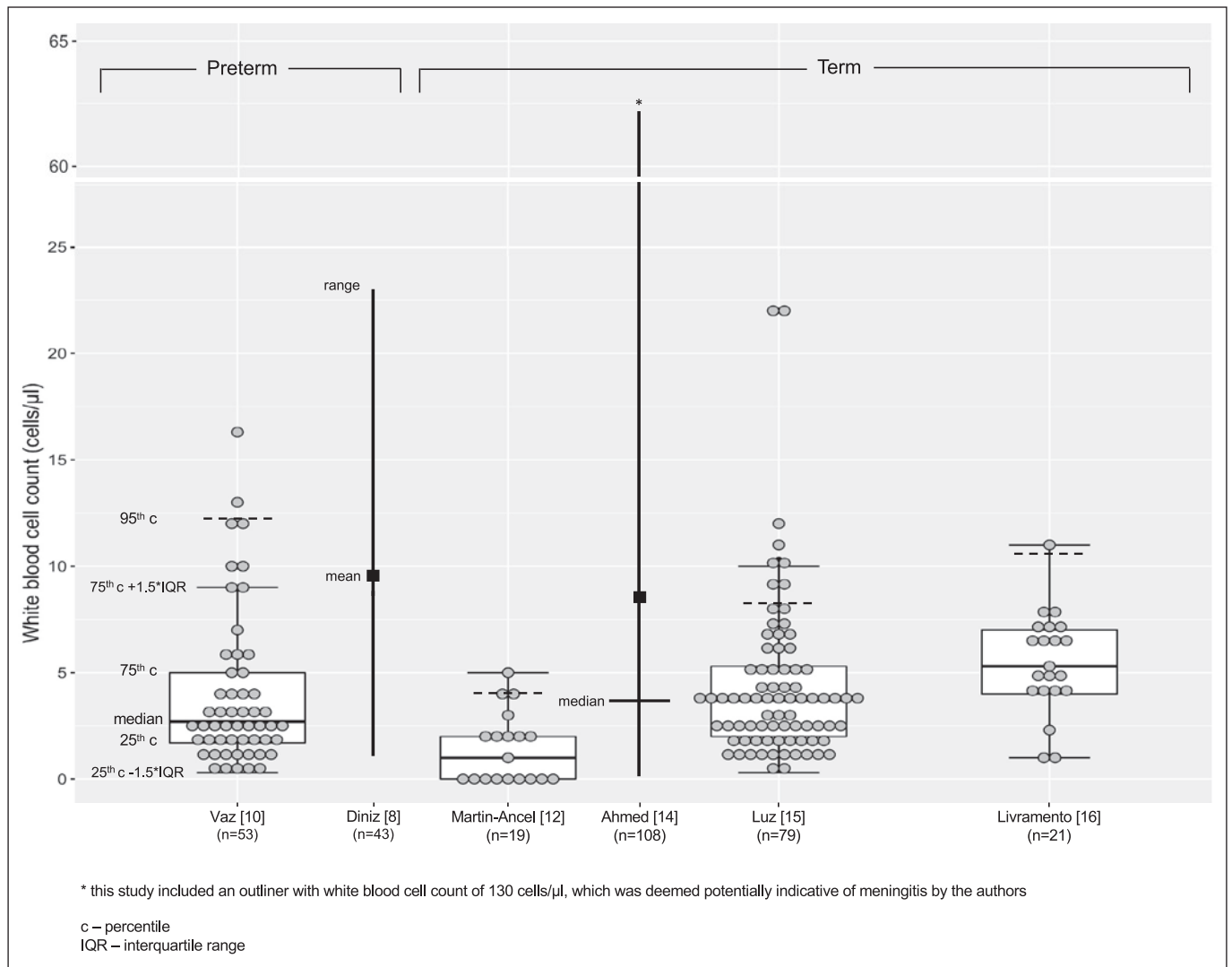


Fig. 2. The CSF WBC count in healthy preterm and term neonates. Boxplots show medians, interquartile ranges (IQR) with whiskers indicating 25th percentile minus 1.5*IQR and 75th percentile plus 1.5*IQR, and dotted lines indicating the 95th percentile. For studies which did not report individual values, the range (solid vertical line), mean (square) and median (solid horizontal line) are shown.

35.5, and 19.0–140.0) ($p < 0.01$). The 95th percentile for CSF protein was 210.0 mg/dL in preterm and 110.2 mg/dL in term neonates.

Glucose Concentration

Three studies (two in preterm neonates) reported glucose concentrations in CSF [9, 10, 14]. There was no difference in the mean glucose concentration between preterm (57.5 and 51.6 mg/dL, range 35.0–162.0) and term neonates (51.2 mg/dL, range not specified). In term neonates, no difference was found between the glucose concentration between week 1–4 ($p > 0.05$) [14]. Only one

study in 53 preterm neonates reported individual concentrations with a mean of 51.6 mg/dL, SD 18.3, median 49.0, IQR 10.0, range 17.0–162.0) [10]. The 5th percentile for CSF glucose was 32.0 mg/dL (Table 2).

Discussion

The incidence of bacterial meningitis is highest in neonates, where it causes substantial morbidity and mortality. Despite an extensive literature review, we only found seven studies (reported in nine articles) investigating normal

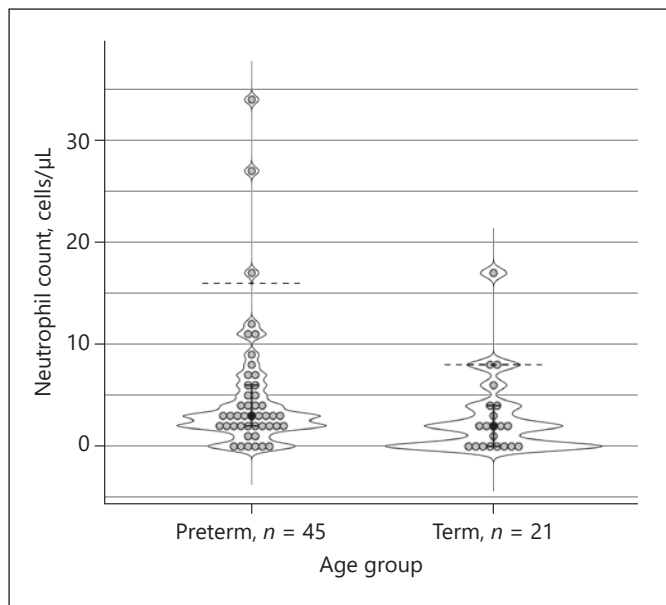


Fig. 3. The CSF neutrophil count in healthy preterm and term neonates showing the median (point), IQR (continuous line), and 95th percentile (dashed line). CSF, cerebrospinal fluid; IQR, interquartile range. Data shown only for the two studies which included individual values [10, 16].

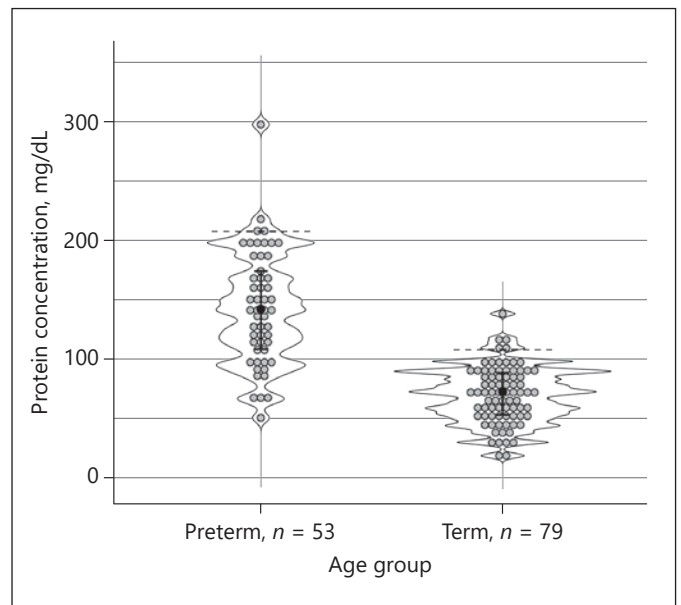


Fig. 4. Comparison between protein concentration in CSF in healthy preterm and term neonates showing the median (point), IQR (continuous line), and 95th percentile (dashed line). CSF, cerebrospinal fluid; IQR, interquartile range. Data shown only for the two studies which included individual values [10, 15].

CSF values that were of sufficient quality to be included in this systematic review. The main reason for exclusion of studies was the absence of viral diagnostics to exclude aseptic meningitis (see online suppl. Table 1; see www.karger.com/doi/10.1159/000517630 for all online suppl. material) [5–7, 17–38]. Even when viral culture is done, up to 35% of enteroviruses are not detected [39–42], and therefore polymerase chain reaction is necessary to reliably exclude viral meningitis. A further common exclusion reason was antibiotic administration before LP which can lead to false negative cultures and inclusion of neonates with meningitis [3, 4, 43, 44]. The degree to which antibiotic administration changes CSF parameters is still unknown. One study found that protein concentrations were significantly higher in neonates who had received antibiotics before LP than those who had not (median 92 vs. 80 mg/dL, $p = 0.02$) but CSF WBC and glucose concentration did not differ between the two groups [3]. Comparing our findings with studies which included neonates who had received antibiotics before LP, the values for CSF glucose and protein concentrations (median and 95th percentile) and the median CSF WBC count in preterm and term infants were similar. However, the 95th percentile for CSF WBC was lower (12 vs. 16 cells/ μ L in term infants and 9 vs. 12 cells/ μ L in preterm term infants, respectively;

and 16 and 78 cells/ μ L in the studies which did not specify separate values for preterm and term infants) [3, 43, 44].

Many guidelines or reviews recommend a cutoff value of 20–22 CSF WBCs/ μ L with a CSF neutrophil count of <2–8 cells/ μ L for the diagnosis of meningitis in neonates [2, 45–47]. However, these recommendations are based on studies that included a proportion of patients who had been administered antibiotics before LP [43, 44] or which did not reliably exclude viral meningitis [6, 7, 19, 26, 28]. Consistent with this, a large study of neonatal meningitis including 9,111 neonates reported that a CSF WBC count of >21 cells/ μ L has a sensitivity of 79% and specificity of 81% for bacterial meningitis [48] and another study, including 3,467 neonates, reported a 95th percentile of 16.0 cells/ μ L and protein 118 mg/dL [43] (both studies did not meet the criteria for our review). In our review, we found that in 95% of cases, the CSF WBC count was <12.0 cells/ μ L in preterm and <9.2 cells/ μ L in term neonates, and the CSF neutrophil count <16.0 and 8.0 cells/ μ L, respectively. However, these values are derived from only the 4 studies for which individual patient data were reported. Even though it has previously been claimed that the presence of even a single polymorphonuclear leucocyte in CSF is pathological, the data from the studies included in our review suggests this might not be the case in neonates.

CSF glucose and protein concentrations are highly variable in neonates [6, 7, 43, 48]. However, a CSF protein concentration of <150.0 mg/dL in preterm and <100.0 mg/dL in term neonates, and a CSF glucose concentration of >30.0–36.0 mg/dL is often considered as normal [45, 46]. In our review, in 95% of cases the protein concentration was <210.0 mg/dL in preterm neonates and 110.2 mg/dL in term neonates, respectively. In preterm neonates the 5th percentile for the CSF glucose concentration was 32.0 mg/dL, while there were not enough individual data to determine percentiles for term neonates. These values are also only derived from only the 3 studies for which individual patient data were reported.

We found minimal difference in the CSF WBC count or glucose concentration between preterm and term neonates [8–12, 14–16]. However, the CSF neutrophil count and protein concentration were higher in preterm neonates than in term neonates [8, 10, 11, 13–16]. Consistent with this, one of the studies done in term neonates which analysed consecutive samples reported that there was no difference in the WBC count and glucose concentration between the first and the fourth week of life, but the protein concentration was higher in the first than in the fourth week [14]. This is consistent with animal studies, which found increased concentration of growth factors and other proteins in the CSF of preterm compared to term animals [49]. However, it is often stated that this difference is due to increased permeability of the blood-brain barrier in preterm infants [50], this remains unproven. Animal studies suggest that the blood-CSF tight junctions are functionally mature from early life and that proteins are actively transferred transcellularly [51–53].

Even a small amount of blood or bilirubin in CSF can significantly alter the protein concentration [54, 55]. In neonates, it has been estimated that 1,000 RBCs/ μ L raises the protein concentration by 1.5–1.9 mg/dL [56, 57]. However, in the study included in this review, there was no correlation between the RBC count and protein concentrations [10]; therefore, the observed increase in CSF protein is not attributable to a higher RBC count.

Unfortunately, none of the studies included in this review measured CSF lactate. Lactate is produced by anaerobic bacteria and not influenced by blood lactate concentration, which is an advantage compared to the CSF glucose concentration. A meta-analysis summarizing results from 30 studies in children and adults suggested that a CSF lactate concentration of 35 mg/dL could be used as a cutoff value to discriminate between viral and bacterial meningitis [58].

As we have previously shown, it is important to note that an initial CSF with a normal WBC count does not definitively exclude bacterial meningitis [59]. On the other hand, pleocytosis can be found in neonates without central nervous system infection, but with other infections, such as gastroenteritis [12] or urinary tract infections [60, 61].

The main limitation of our review is that there were only a small number of studies of sufficient quality to include. However, the use of stringent inclusion criteria means the normal neonatal CSF values determined in our review are likely to be more reliable. Another potential limitation is that not all the studies included in our review used molecular diagnostics to exclude viruses other than enterovirus (e.g., parechovirus or herpes virus) as a cause of neonatal meningitis and that some studies included neonates with a high RBC count. The paradoxical finding in preterm infants of a higher upper limit of normal for CSF neutrophils than for WBC cells (16 vs. 12/ μ L) is a result of the small number of studies that provided differential CSF WBC counts. Furthermore, the small number of studies only enabled the influence of gestational age to be compared between preterm and term infants.

Conclusion

The interpretation of CSF in neonates can be challenging. The normal range for CSF parameters is different in neonates compared with older infants. Gestational and chronological age lead to only minor differences in CSF WBC and glucose concentrations, but have a greater influence on the CSF neutrophil count, RBC count, and protein concentration. CSF parameters alone are not sufficiently reliable to exclude meningitis. In clinical practice, CSF samples, regardless of cellularity and biochemistry, need to be subjected to culture and viral molecular diagnostics to reliably exclude meningitis.

Statement of Ethics

The paper is exempt from Ethical Committee approval as it is a review of previously published literature.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

P.Z. drafted the initial manuscript. N.C. critically revised the manuscript and both authors approved the final manuscript as submitted.

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