

## Research Article

# Prevalence of Meningitis in Patients with Late Neonatal Sepsis in a Reference Maternity

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## Keywords

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- Meningitis
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## Abstract

**Introduction:** Neonatal infections are responsible for high morbidity and mortality rates. Neonatal meningitis, meningeal infection occurring up to 28 days of life, can be confirmed by means of laboratory criteria, through the analysis of cerebrospinal fluid. In this period, it is an entity with many peculiarities, since the etiology and non-specific clinical presentation are indistinguishable from sepsis.

**Objectives:** To analyze the prevalence of meningitis in patients with late neonatal sepsis in reference maternity, in the year 2016; to demonstrate the epidemiological variables present in late neonatal sepsis with meningitis and to identify the prevalence of lumbar puncture and study of the cerebrospinal fluid in these newborns.

**Methodology:** This was a descriptive and retrospective study, in which patients with positive blood cultures in the neonatal period - based on a microbiology report from the institution - and met criteria for late sepsis were selected. Data were collected from the medical records regarding the diagnosis of meningitis, epidemiological and laboratory data.

**Results:** Of the 415 patients with late neonatal sepsis, 202 (48.7%) had a formal contraindication to lumbar puncture. Of the remaining 213, only 77 (36.1%) were submitted to CSF for the diagnosis of meningitis. Among the confirmed cases, 19% were identified through the culture of liquor, 23.8% by cytology/ biochemistry and 57.2% by the two methods together. The prevalence of meningitis among patients with late neonatal sepsis was 27.3% (21/77).

**Conclusion:** A prevalence of meningitis cases was found in children with late neonatal sepsis like the literature, predominantly male, full term and suitable for gestational age. It is extremely worrying to see the number of patients with late sepsis confirmed by blood culture who did not undergo CSF analysis.

## ABBREVIATIONS

CSF: Cerebrospinal fluid; UFPI: Federal University of Piauí; MDER: Dona Evangelina Rosa Maternity

## INTRODUCTION

Despite all the research and discoveries of perinatology in recent decades, neonatal infections are responsible for high morbidity and mortality rates [1]. In Brazil, it is estimated that 60% of infant mortality occurs during this period, with neonatal sepsis being one of the main causes [2].

Late neonatal sepsis is a syndrome that manifests itself with signs of infection and systemic inflammatory response and may be accompanied by bacteremia [3]. Clinical and / or laboratory criteria characterize it, occurring in the interval after the first 48 hours of life until the 28th day of life. The incidence is high, especially in preterm newborns, with a birth weight of less than 1,500 grams [4].

Neonatal meningitis, meningeal infection up to 28 days old, is characterized by clinical and / or laboratory criteria. Its occurrence in neonatal sepsis in Brazil is around 25%, although in recent years, in developed countries, a decrease has been observed for about 5 to 10% [5].

The clinical presentation usually non-specific and indistinguishable from these pathologies, similar etiologies, and the predilection of some pathogens by the central nervous system show the extreme importance of discarding meningitis in all neonates evaluated for neonatal sepsis, especially late sepsis [6].

Meningitis is more common in the first month of life than in any other age group. In this period, it is an entity with many peculiarities. The etiology, clinical status and morbidity and mortality are very different from those seen at higher ages. The nonspecific clinical presentation, indistinguishable from that caused by sepsis, especially late, makes it imperative to identify

early and to manage adequately for treatment success [4].

During the period of meningitis, treatment should be extended up to 21 days. The choice of the antibiotic should consider the penetration capacity in the blood-brain barrier, the integrity of this drug concentration in the cerebrospinal fluid and its intrinsic activity. It is also necessary to consider the high index (20-58%) of neurological sequelae resulting from the disease, such as: ossific labyrinthitis with hearing loss, hearing loss, deafness, amaurosis and retardation of neuropsychomotor development [6].

Thus, any investigation of late sepsis should include the investigation of cerebrospinal fluid (CSF) by lumbar puncture, an essential procedure for the early diagnosis of neonatal meningitis. The definitive diagnosis for neonatal meningitis is the positive CSF culture; however, for therapeutic purposes, changes in CSF cytochemical values, compatible with meningitis, indicate newborn impairment [7].

Considering the severity of the occurrence of meningitis in patients with neonatal sepsis, the interest for the development of this study emerged, with the primary objective of analyzing the prevalence of meningitis in patients with late neonatal sepsis in a reference maternity hospital in the city of Teresina / Piauí / Brazil, in the year 2016. As secondary objectives, we sought to demonstrate the epidemiological and laboratory variables present in late neonatal sepsis with meningitis; and to identify the prevalence of lumbar puncture and study in patients with late neonatal sepsis.

## MATERIALS AND METHODS

This is a descriptive and retrospective study developed by researchers from the Federal University of Piauí (UFPI) at the Maternity Hospital Dona Evangelina Rosa (MDER), Teresina / Brazil.

The research was analyzed and approved by the Research Ethics Committee of the UFPI, CAAE 73197717200005214 in accordance with Resolution 466/2012 of the Ministry of Health, National Health Council, which regulates the operational and ethical issues of scientific work involving human beings.

Data were collected from October 1, 2017 to November 30, 2017. Data collection was based on MDER's daily microbiology report for 2016, from which 482 positive blood cultures were identified.

The inclusion criterion for late neonatal sepsis was bacteremia (defined as bacterial growth in blood culture) initiated after 48 hours of life up to 28 days of life. By this criterion, 43 identifications of early sepsis were excluded from the total.

After defining the sample, the selected charts were reviewed and used to fill out a standardized questionnaire. We chose this mode of collection because of the inherent limitations of retrospective studies, with the intention of avoiding or reducing the bias resulting from a review of medical records, with incomplete or questionable reliability of information. It was impossible to access 5% (24) of the medical records.

The instrument of data collection was standardized with the following variables: epidemiological (gestational age at birth, gender, and birth weight); (CSF: culture and cellularity / biochemistry) and contraindications to CSF puncture (hemodynamic instability, thrombocytopenia <50,000, signs

of intracranial hypertension and focal neurological signal). The analysis of the cytological and biochemical changes of the CSF for the diagnosis of meningitis was carried out in accordance with the respective birth weight, according to Table (1).

The information collected through the printed questionnaires was tabulated in the Microsoft Windows Excel 2003 program and later exported to IBM SPSS Statistics 23. Descriptive statistics analyzed data, with quantitative data presented in absolute values and proportions. The existence of an association between the gender of the newborn and gestational age and birth weight was tested using the Fisher's test, where the Odds Ratio (OR) was calculated. The level of significance was set at  $p < 0.05$  and considered a 95% confidence interval.

## RESULTS

Lumbar puncture would be a formal indication for the group of 415 patients with late neonatal sepsis, but 202 (48.7%) newborns presented formal contraindication to the procedure: signs of intracranial hypertension, focal neurological sign, thrombocytopenia (<50,000), hemodynamic instability (Table 2).

Among the 213 newborns, 77 (36.1%) were submitted to lumbar puncture and in the other 136 (63.9%) the procedure was not performed despite the absence of contraindication (Table 3).

Thus, the prevalence of meningitis could only be calculated in those patients who performed the collection (77). Among these, 21 with a positive result: prevalence of 27.3% of meningitis in neonates with late neonatal sepsis.

Graph 1 presents the methods of CSF analysis for the diagnosis of meningitis in late-born sepsis. Of the 21 children, 4 (19%) were diagnosed through CSF culture; 5 (23.8%) through changes in cellularity / biochemistry; and 12 (57.2%) by both methods. There were 66.7% identification of *Enterobacter cloacae* and 33.3% of *Enterococcus faecalis*. Among the cases with cellular and biochemical alterations, maximum and minimum values, mean and median, are respectively: cellularity (15-270, 52; 30); proteins (163-444; 397; 468); glucose (20-51, 36, 41).

Table (4) shows the relationship between the gender of

**Table 1:** Normal values of csf in newborns.

	PT < 1000g	PT > 1000g	TERM
Leucocytes (mm <sup>3</sup> )	≤ 15	≤ 15	≤ 20
Protein (mg/dL)	≤ 200	≤ 150	≤ 150
Glycose (mg/dL)	> 30	> 30	> 30

SOURCE: UNIFESP/EPM, August 2006<sup>17</sup>.  
**Abbreviations:** CSF: cerebrospinal Fluid; PT : Preterm; mm3: Cubicmillimeter; mg: Milligram; dL: Deciliter

**Table 2:** Criteria for contraindication to lumbar puncture.

VARIABLES	Nº	%
Signals of ICH	11	5,5
Focal neurological signals	2	1,0
Thrombocytopenia (<50.000)	91	45,0
Hemodynamic instability	98	48,5
<b>TOTAL</b>	<b>202</b>	<b>100</b>

**Abbreviations:** CSF: Cerebrospinal Fluid; ICH: Intracranial Hypertension

newborns with meningitis and variables related to birth, such as gestational age and birth weight classifications. Among preterm infants, 7 (33.3%) were boys, while 2 (9.5%) were girls. In relation to newborns, the number of boys was 10 (47.6%) and girls were 2 (9.5%). As for the birth weight, the ones suitable for gestational age were predominant, being male 13 (61.9%) and girls 3 (14.2%). Among the SGA, the values were equal between the gender. And in very low birth weight infants, the value for boys was 2 (9.5%) and for girls 1 (4.7%). When looking for association between gender and birth weight and gestational age, no statistically significant difference was found.

When evaluating the relationship between the gender of meningitis patients and the methods of CSF analysis for the diagnosis of meningitis, there was no statistical difference between the groups. For the female genus, in 50% of the cases the diagnosis was performed by only one method (culture or biochemistry / cellularity), while in the other 50% the two methods were positive. For boys, in 60% of the cases the diagnosis was made by the association of the two methods, with 33% less chance of only one diagnostic method (OR 0.667, 95% CI 0.1 - 4.48, p = 1).

## DISCUSSION

There was a prevalence of full-term and suitable gestational-age males among preterm newborns with meningitis. Cruz et al., and Villega et al., in their studies demonstrated the occurrence of meningitis associated with bacteremia, premature labor, male gender, neural tube defects, and urinary tract abnormalities [8,9]. Mendoza et al also identified similar results regarding the age of newborns and the gender [10].

In this research, regarding gestational age, there was a 40% greater chance that the male gender would be of term and that there is a 2.8 times greater chance of the male newborn with meningitis to have weight within the normal range. In addition,

the male gender has a 17 times greater chance of presenting adequate weight for gestational age.

There are several factors that contribute to the apparent susceptibility to infection of preterm infants, especially those with very low birth weight (<1500 grams). The immaturity of the immune system, which consists of phagocytosis, opsonization by antibodies and deficient complement functions, also contributes to the severity of this infection [11].

Regarding the method of analysis of cerebrospinal fluid of newborns with late sepsis, in 57.2% of the patients the cellularity / biochemistry examination and the culture were suggestive of meningitis, whereas 23.8% positivized only the culture and in 19% there were only changes in biochemistry and cellularity. Although cerebrospinal fluid culture is considered the gold standard for the diagnosis of meningitis, changes in CSF cytochemical examination consistent with meningitis indicate impairment of the newborn, which should be promptly treated [7].

It is extremely worrying to observe the number of patients with late sepsis confirmed by blood culture (Table 3) who were not submitted to cerebrospinal fluid analysis, which is imperative in sepsis. And the question arises: why a formal indication procedure according to the literature was not properly applied in a reference maternity, as was evident after review and analysis of the data for the year 2016. This could justify several cases of under diagnosis, as well as some offshore data from the literature, such as birth weight and gestational age.

The prevalence of meningitis for neonates with late neonatal sepsis evaluated in the study period could only be calculated for those who performed lumbar puncture and was 27.3%, diverging from the results identified in the study by Mendoza et al., which showed a prevalence of 16.9%, more frequent in newborns with sepsis due to Group B *Streptococcus* (GBS) [10]. Approximately 25% chance rates of meningitis development in patients with sepsis according to the American Academy of Pediatrics are reported, with risk factors for these two outcomes being very similar [12].

Ansong et al., in a series of cases of sepsis due to GBS describe how meningitis occurred in 15% of neonates with early sepsis and 57% with late sepsis. Overlapping of the initial clinical presentation of the disease and late onset may occur [13,14].

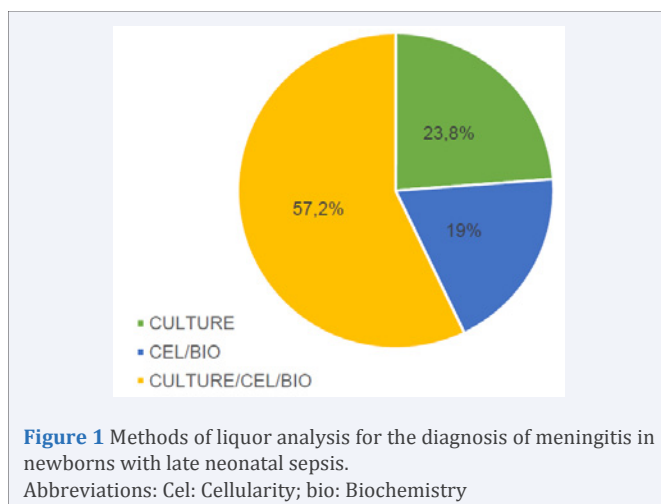
Studies point out that the determination of the etiologic agent of meningitis is often difficult, since there are many factors that interfere with its research, such as previous antibiotic therapy, inadequate collection and storage of the materials sent for examination, early diagnosis of meningitis when the number of meningitis is still very small, bacteria in the cerebrospinal fluid, among others. In addition, exams requiring more specialized techniques often have high operating costs and are not available in many centers [12,15,16].

Thus, the low number of patients with late sepsis submitted to lumbar puncture shows an unreliable result regarding the prevalence of meningitis in that group. Other limiting factors were the retrospective design of the study, which makes it difficult to collect the data and the adequate follow-up of the patients, and the restriction of data to only one maternity.

Since it is a disease with difficult clinical diagnosis and early

**Table 3:** Newborn lumbar puncture with late sepsis.

VARIABLES	Nº	%
Performed	77	18,6
Not performed/ no Contraindication	136	32,8
Not performed /Contraindication	202	48,7
<b>TOTAL</b>	415	100



**Table 4:** Relationship between the gender of the newborn with meningitis and gestational age and weight at birth.

		Gender				TOTAL		OR	CI 95%	p
		MALE		FEMALE						
		n	%	n	%	n	%			
GA	TNB	10	58,8	2	50	12	57,1	1,4	0,16 - 13	1
	PNB	7	41,2	2	50	9	42,9			
	<b>Total</b>	<b>17</b>	<b>100</b>	<b>4</b>	<b>100</b>	<b>21</b>	<b>100</b>			
WEIGHT	Normal	11	73,3	3	50	14	66,7	2,8	0,38 - 20	0,3544
	VLW	4	26,7	3	50	7	33,3			
	<b>Total</b>	<b>15</b>	<b>100</b>	<b>6</b>	<b>100</b>	<b>21</b>	<b>100</b>			
WEIGHT/GA	SGA	15	100	4	66,7	19	90,5	17	0,69 - 428	0,0714
	SMGA	0	0	2	33,3	2	9,5			
	<b>Total</b>	<b>15</b>	<b>100</b>	<b>6</b>	<b>100</b>	<b>21</b>	<b>100</b>			

**Abbreviations:** OR: Odds Ratio; CI: Confidence Interval; GA: Gestational Age; TNB: Term Newborn; PNB: Preterm Newborns; VLW: Very Low Weight; SGA: Suitable for Gestational Age; SMGA: Small for Gestational Age

management has a decisive influence on the prognosis, it is fundamental that we know and identify the risk factors present in the motherhood studied for the occurrence of meningitis in newborns with late sepsis [17,18].

## CONCLUSION

A prevalence of meningitis cases in children with late neonatal sepsis similar to the literature was found, with a predominance of term and suitable for gestational age patients. It is extremely worrying to observe the number of patients with late sepsis confirmed by blood culture who did not undergo cerebrospinal fluid analysis.

In view of the high public expenditures and the serious physical and psychological consequences of the disease, as opposed to the low rate of examinations for screening, it is expected that more effective protocols will be followed for earlier diagnosis and treatment.

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