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## **Research Article**

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# **Incidence of meningitis in late onset sepsis**

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### **ABSTRACT**

**Background:** Bacterial sepsis and meningitis continue to be major causes of morbidity and mortality in newborns, particularly in premature infants. The present study was undertaken to know the incidence of meningitis in neonates with late onset sepsis.

**Methods:** Hospital based observational study, conducted in the post graduate department of pediatrics, government medical college, Srinagar, conducted for a period of one year. 423 patients fulfilling the inclusion criteria were included and subjected to detailed history, clinical examination followed by investigations.

**Results:** The annual incidence of meningitis in LOS was 16. The majority of patients (46.1%) presented in the age group of 3-7 days. The mean weight of neonates was  $2.61 \pm 0.606$ ) kg. 60.3% of neonates with meningitis were of low birth weight (P <0.005). 61.7% of preterms with LOS had meningitis as against 38.2% for terms (P <0.005). 57.4% males had meningitis as against 42.6% females (P >0.005). In meningitis cases 100% cases were lethargic; seizures in 92.8%, fever in 50%. Blood culture was positive in 42.6% cases of meningitis. Meningitis was seen in 60.7% of proven gram negative sepsis as against 30.7% cases of proven gram positive sepsis (P <0.005). 94.5% of the exclusively breast fed neonates with meningitis recovered and 6.3% expired whereas for the other feeding group the corresponding figures were 77 % and 22.4 % respectively (P <0.005). 17.6% cases of meningitis had mortality as against 4.8% in those who had sepsis but no meningitis (P <0.005).

**Conclusions:** Meningitis is common in late onset sepsis, associated with high mortality, with a beneficial effect from exclusive breast feeding.

Keywords: Meningitis, Preterm, LBW, Lumber puncture, Breast feeding

### INTRODUCTION

Neonatal infections are important causes of mortality and morbidity in newborn infants all over the world including the industrialized countries with high hygienic standards, deliveries at hospitals, access to antimicrobial agents for prophylaxis, treatment and facilities for advanced intensive care. Most studies of incidence and etiology of neonatal sepsis and meningitis come from these countries, while there is a lack of data from the developing countries where the mortality and morbidity are probably immense.

Sepsis is responsible for about 30-50% of the total neonatal deaths in developing countries. Various community and hospital based studies report sepsis as a cause of neonatal death in 20-50% of cases. A Culture proven sepsis may occur in upto 20% of NICU admissions. The incidence of neonatal sepsis according to the data from National neonatal perinatal database is 30 per 1000 live births. The database comprising 18 tertiary care neonatal units across India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths. Septicemia was the commonest clinical category with an incidence of

23 per 1000 live births while the incidence of meningitis was reported to be 3 per 1000 live birth. <sup>6</sup>

Neonatal sepsis is a clinical syndrome characterised by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections.<sup>2,5,7</sup>

There is no consensus on how to classify neonatal sepsis and meningitis in periods after birth. Early and late onset sepsis has been reported as occurring before or after 48 hours of age, 72 hours of age, 9,10 or 96 hours of age. 11-13 The first week of life is often reported as early onset sepsis with a subgroup of infections that develop during the first 24 hours of life called very early onset infections. 14-17 Late onset infections occur during the second to fourth weeks of life while infections from day 28-30 to day 120-180 are called very late onset infections. 12

For all practical purposes in the subsequent discussion, neonatal septicemia is classified as:

- Early Onset Septicemia (EOS): It presents within 72 hours of life. 9.10,18-20
- Late onset septicemia: It usually presents after 72 hours of age. <sup>18-22</sup>

Any newborn with bacterial sepsis is also at risk of meningitis. As such the incidence of meningitis in neonatal sepsis has varied from 0.3-3% in various studies but late onset septicemia has been reported to be fairly associated with meningitis; with percentage ranging from 3 to 30%. <sup>18,23-25</sup>

In cases of LOS, LP should be done in all infants prior to starting antibiotics. LP could be postponed in a critically sick neonate but should be performed once the clinical condition stabilizes.<sup>7</sup>

This study is being done to estimate the incidence of meningitis in late onset sepsis so as to reduce mortality and morbidity.

# **METHODS**

The study was a hospital based observational study, conducted in the post graduate department of pediatrics, government medical college, in the G.B. Pant cantonment general hospital; Srinagar. The hospital is the referral hospital housing the department of Pediatrics.

The study was conducted on the neonates admitted in the division of neonatology, department of pediatrics, from 1<sup>st</sup> April, 2011 to 31<sup>st</sup> March 2012 for a period of one year.

#### Inclusion criteria

- Neonates older than 72 hours with signs and symptoms suggestive of sepsis viz:
- Clinical features of sepsis i.e. physical examination demonstrating either circulatory, respiratory, CNS dysfunction or other features of sepsis.
- CVS signs & symptoms as evident by the presence of tachycardia (heart rate more than 160/min) or bradycardia (heart rate less than 100/min) or capillary refill time more than 3 seconds.
- Respiratory signs & symptoms as evidenced by the presence of grunting, flaring, retractions, tachypnea (respiratory rate more than 60/min) or apnea lasting more than 20 seconds.
- CNS signs & symptoms as evidenced by the presence of excessive crying, high pitched cry, bulging fontanelle and/or occurrence of/or history of convulsions.
- ➤ Other symptoms/signs of sepsis included will be; Lethargy, reduced feeding ability, no spontaneous movement, temperature more than 38°C, hypothermia, cyanosis, abdominal distension, increased pre feed aspirates in pre terms/LBW's, pustular lesions, umbilical sepsis.
- Positive C-reactive protein.

### Exclusion criteria

- 1) Patients with spina bifida (e.g. meningocoele, myelomeningocoele, lipomeningocoele).
- 2) Anencephaly, other neural tube defects.
- 3) In very sick neonates, after initial stabilisation.

In each neonate with clinical features of sepsis, a detailed history and examination was done. Neonates with features of sepsis and positive CRP (was done as a qualitative estimation as positive/negative with the help of latex slide agglutination test) were subjected to the following investigations:

- 1) Blood culture (1 ml sample of blood was collected under all aseptic precautions by veni-puncture and placed in a pediatric blood culture bottle containing tryptic soya broth).
- 2) Lumber Puncture after informed consent taken from parents of neonate (Included CSF cytology, biochemistry and culture).
- 3) Complete blood count.

- 4) Blood sugar.
- 5) Serum bilirubin.
- 6) Renal function tests.
- 7) USG head was done in all patients with meningitis.
- 8) Chest X-ray.
- Meningitis was labelled in a neonate whose CSF findings satisfied all the following criteria (NNF Guidelines 2010):
- CSF glucose less than the plasma glucose (sample to be taken prior to LP) by ≥50%.
- 2) CSF white cell count >10/cumm.
- 3) CSF protein >80 mg/dl
- 4) With/without CSF culture positive.
- Other investigations like, Arterial blood gas analysis, CT/MRI brain was done when required.

### Plan of analysis

The data has been analysed with the help of computer software Epi-Info version 6.0.1 and SPSS 10.0 for Windows. Chi-square test was used to ascertain statistical significance among the proportions. Incidence along with 95% confidence limits was calculated to express magnitude. Odd's ratio with 95% confidence limits was estimated vis a vis the presence or absence of meningitis in late onset neonatal sepsis.

A P value of <0.05 was considered as statistically significant unless proved otherwise. Confounding factors were dealt with appropriate methods of adjustment.

### **RESULTS**

The total admissions in this period were 31328, total admissions in neonatology were 4390. Study group comprised of 423 cases. It included those neonates who satisfied the inclusion criteria and Incidence of meningitis was studied in them.

Table 1: Admission data from April 2011 to March 2012.

Admission data from April 2011 to Mar	ch 2012
Total admission	31328
Neonatal admission	4390
Total neonates with suspected late onset sepsis	960
Total neonates included in study	423

Table 2: Showing gender, gestation, weight distribution of cases.

Study group	423	%
Meningitis	68	
No meningitis	355	
Males	223	(52.7)
Term	159	(71.3)
Preterm	64	(28.6)
Females	200	(47.3)
Term	110	(55)
Preterm	90	(45)
Weight(kg)		
<1.5	30	7.09
1.5-2.499	178	42.08
>2.5	215	50.8

The annual incidence of meningitis in late onset was 16%

Table 3: Age of presentation of study group (n=423).

Age of presentation	Number (n)	Percentage (%)
3-7 days	198	46.1
8-12 days	71	16.7
13-17 days	65	15.3
18-22 days	68	16
23-27 days	21	4.96

The mean age of presentation was  $10.8 \pm 7.05$  days

Table 4: Table showing the signs/symptoms in cases with meningitis.

Symptom/sign	% age
Lethargy	100
Seizures	92.8
Fever	50
Refusal/dec feeding	46.4
Respiratory signs	25
Abdomen distention	21
Shock/sclerema	11

However the patients who were diagnosed with only septicaemia and no meningitis had lethargy and other general sign/symptoms like decreased/refusal of feed in 100% cases, respiratory signs in 58.5%, gastrointestinal signs/symptoms like loose motions/vomiting etc. in 31.7% cases, seizures in 13.4% cases and shock/sclerema in 1.2 cases.

Table 5: Showing the occurrence of meningitis in males vs. females, according to weight and according to gestation.

	Men		No n	No meningitis	
	No.	% age	No.	% age	value
Gender					
Males	39	57.4	184	51.8	0.609
Females	29	42.6	171	48.2	0.698 (NS)
Total	68		355		(145)
Weight					
<1.5 kg	2	2.9	28	7.9	0.002
1.5-2.499 kg	41	60.3	137	38.6	0.003 (SIG)
>2.5 kg	25	36.8	190	53.5	(310)
Total	68		355		
Gestation					
Preterm	42	61.7	112	31.5	0.000
Term	26	38.2	243	68.5	0.000 (NS)
Total	68		355		(149)

Table 6: Showing the microorganisms isolated from the blood cultures of septic neonates.

Organisms	No.	% age
Mrsa	24	44.4
Klebsiella	10	18.5
E.coli	9	16.6
Enterobacter	4	7.4
Acnitobacter	3	5.5
CoNS	2	3.7
Pseudomonas	2	3.7
Total	54	100

Table 7: Showing the microrganisms isolates in the study group.

	No.	% age					
Gram positive organisms							
MRSA	24	92.3					
CoNS	2	7.69					
Total	26	100					
Gram negative organisms							
Klebsiella	10	35.7					
E. coli	9	32.1					
Enterobacter	4	14.2					
Acinetobacter	3	10.71					
Pseudomonas	2	7.14					
Total	28	100					

The commonest isolate recovered was MRSA constituting 34.4%, followed by Klebsiella 27.5%, E. coli 20.6%, Enterobacter 6.8% and Acinetobacter and coagulase negative Staphylococcus 3.4% each (Table 8).

Table 8: Showing the microorganisms isolated from the blood cultures of meningitic neonates.

Organisms	No.	% age
Mrsa	10	34.4
Klebsiella	8	27.5
E. coli	6	20.6
Enterobacter	2	6.8
Acinetobacter	1	3.4
CoNS	1	3.4
Total	29	100

Table 9: Showing Blood culture positivity in meningitis and non-meningitis patient.

Blood	Men	ingitis	No m	eningitis	P value
culture	No.	% age	No.	% age	P value
Positive	29	42.6	25	7.04	0.0001
Negative	39	57.3	330	92.9	0.0001 (SIG)
Total	68	100	355	100	(310)

Above Table 9 shows blood culture was positive in 42.6% cases of meningitis vs. 7.04% cases who had sepsis only but no meningitis. P value <0.005 was being statistically significant.

Table 10: Showing the risk of meningitis in gram positive vs. gram negative sepsis.

	Gram negative sepsis		Gram positive sepsis		P value
	No.	% age	No.	% age	value
Meningitis	17	60.7	8	30.7	0.020
No meningitis	11	39.2	18	69.2	0.028 (SIG)
Total	28	100	26	100	(310)

The above Table 10 gives us the values of presence or absence of meningitis in the cases with proven gram positive versus gram negative septicaemia. Meningitis was seen in 60.7% (17/28) cases of proven gram negative sepsis and 30.7% (8/26) cases of proven gram positive sepsis. The Chi squared value for the above distribution of data is 4.793 with a P value of 0.0285 which is statistically significant.

Table 11: Showing the outcome in meningitis vis a vis the feeding given.

	Meni	Meningitis outcome				
	Reco	Recovered Death			value	
	No.	% age	No.	% age	value	
B/F exclusively	18	94.5	1	6.3	0.000	
Other feeding	38	77	11	22.4	(SIG)	

For statistical analysis the top fed and mixed fed group was clubbed together. The above Table 11 shows that 94.5% (18/19) of the breast fed cases with meningitis recovered and 6.3 (1/19) expired while for other feeding

group the corresponding figures were 77% (38/49) and 22.4% (11/49) respectively. The results were significant with P value 0.000.

Table 12: Showing the outcome of meningitis vs. non meningitis cases.

	Meningitis		No m	No meningitis	
	No.	% age	No.	% age	value
Expired	12	17.6	17	4.8	0.000
Recovered	56	82.4	338	95.2	(SIG)

The above Table 12 shows the outcome of meningitis versus no meningitis in LOS cases in the study group in terms of recovery and death of the case. The death in the meningitis cases were 17.6 % while the same figure for non-meningitis cases was 4.8%. On statistical analysis of the data the chi square value was 4.921 with a P value of 0.000 which is significant in statistical terms.

#### **DISCUSSION**

Neonatal sepsis is one of the commonest causes of neonatal morbidity and mortality. Near about 0.3-3% of neonates with sepsis do have meningitis but in case of LOS, the incidence of meningitis is higher, even upto 30%. The overlapping clinical manifestations of septicemia and meningitis make it very difficult to differentiate a neonate with meningitis from the one with septicemia alone as meningitis is associated with much more mortality and morbidity, it is always better to have a high suspicion for meningitis while treating neonates with septicemia

The incidence of meningitis in LOS in our study was 16%. Similar observation was reported by Visser et al. (1980)<sup>26</sup> where 24% septic neonates with LOS had meningitis. Laving et al. (2003),<sup>27</sup> Anjos De Silva et al. (2007)<sup>28</sup> and Tisukumara et al. (2009)<sup>29</sup> reported prevalence of meningitis in neonates with late onset sepsis as 17.9%, 17% and 17.2% respectively.

The LBW neonates with sepsis accounted for 49.2% and preterms with sepsis accounted for 36.4%. However meningitis was observed in 63.3 % of LBW neonates and 61.7% of preterm neonates. This high incidence of meningitis in LBW and especially preterm has also been reported by Longe et al. (1984), Moreno et al. (1994) and Anjos da Silva (2007). Jiang et al., (2004) beserved that LOS was significantly more common in VLBW and preterm neonates.

Male to female ratio in sepsis was 1.1:1, similar to observations made by Laving et al., (2003), <sup>27</sup> Jiang et al.,  $(2004)^{32}$  and Gheibi et al., (2008).

The neonates with meningitis in the present study had diverse signs and symptoms with lethargy predominating in 100% cases followed by seizures, fever, refusal/decreased feeding and respiratory sign/symptoms

in 92.8%, 50%, 46.4% and 25%, respectively. Abdominal distention and shock/sclerema was noticed in 21% and 11% cases respectively. Similar to these observations Laving et al., 2003<sup>27</sup> also reported feed intolerance and lethargy as most common clinical features in meningitis, present in 73.3% and 60% cases respectively, while Hoque et al.  $(2006)^{34}$  observed no difference in the clinical features in cases with meningitis and septicemia alone. The patients who were diagnosed with only septicemia and no meningitis had lethargy and other general symptom including refusal of feed/decreased feeding in 100%, respiratory signs, gastrointestinal sign/symptoms, seizures in 58.5%, 31.7% and 13.4% respectively while shock was observed in only 1.2%. Karthikeyan et al. (2001)<sup>35</sup> observed that in cases with culture proven sepsis, lethargy with refusal of feeds (28%), fever (28%) and respiratory distress (31.3%) were the major presenting features.

Blood culture was positive in 54 (12.7%) septic neonates with Gram positive organisms comprising 48.1% (26/54) and Gram negative organisms comprising 51.8% (28/54). In their study Moreno et al., 1994,<sup>31</sup> Greenberg et al., 1997<sup>36</sup> and Tisukumara et al., 2009<sup>29</sup> reported that Gram positive organisms contributed to the culture positive isolates in 39%, 41% and 53.4% respectively whereas Gram negative organisms contributed to the same in 61%, 59% and 46.6% respectively.

MRSA was the commonest gram positive isolate 92.3% (24/26) followed by coagulase negative Staphylococci viz. 7.69% (2/26) in our study. Moreno et al., 1994,<sup>31</sup> Karthikeyan et al., 2001,<sup>35</sup> and Sundaram et al., 2009<sup>37</sup> also reported S. aureus as the commonest gram positive isolate. Karthikeyan et al., 2001<sup>35</sup> reported 66% as MRSA of the all Staphylococcus aureus isolates whereas in our study 92.3 Staphylococcus aureus isolates were MRSA. Issacs et al., 1996, Berger et al., 1998, 22 Ronnestad et al., 1998,<sup>14</sup> Zhu et al., 2008<sup>38</sup> and Tisukumara et al., 2009<sup>29</sup> reported coagulase negative Staphylococcus as the commonest gram positive isolate, where as in our study coagulase negative Staphylococci was reported in 7.69% of gram positive isolates. Of the gram negative isolates in our study the commonest were Klebsiella comprising 35.71% (10/28), E. coli 32.1% (9/28), Enterobacter 14.2% (4/28) followed by Acinetobacter 10.71% (3/28) and Pseudomonas 7.14% (2/28). Moreno et al., 1994<sup>31</sup> observed that the commonest gram negative isolates were Klebsiella and E. coli whereas Kuruvilla et al., 1998, 39 Zhu et al., 2008, 38 Khassawneh et al., 2009, 40 Sundaram et al., 2009<sup>37</sup> and Tisukumara et al., 2009<sup>29</sup> reported Klebsiella as the most common Gram negative isolate were similar to the observations made in our study.

Among the meningitic group blood culture was positive in 29 (42.6%) cases. Meningitis was seen in 60.7% cases of proven gram negative sepsis and 30.7% cases of proven gram positive sepsis.

The overall mortality was 6.8% (29/423) which included preterms who accounted for 48.27% (14/29) of total deaths. However mortality in culture positive cases was 33.3%. Bhutta et al. (1991), Ahmed et al. (2002) observed a mortality rate of 43% and 40% in cases of culture positive LOS.

Out of the neonates having meningitis, 17.6% expired (12/68) in the present study which is similar to the observations made by Tisukumara et al. (2009)<sup>29</sup> who observed that meningitis was associated with a mortality of 20% in his study. A much higher mortality rate in the meningitis group i.e. 37.7% and 37.5% was reported by Longe et al. (1984)<sup>30</sup> and Hoque et al. (2006)<sup>34</sup> respectively but in both these studies EOS group was also included along with LOS group. Al Harithi et al. (2000) had observed a mortality of 48% in neonatal meningitis but they included EOS cases also and meningitis was documented only on CSF culture positivity.

Those neonates with meningitis who were exclusively breast fed had 94.7% recovery and those on other feeding (viz. fop fed or mixed fed) had 77% recovery in our study.

Incidence as high as 16 % of meningitis in neonates with LOS in the present study, endorses the need of doing a lumbar puncture in all the neonates with LOS, before starting antibiotics.

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institutional ethics committee

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