

## Original Research Article

# Incidence of meningitis in term neonates with sepsis and antibiotic sensitivity pattern: an observational study

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## ABSTRACT

**Background:** To find out the incidence of meningitis in neonatal sepsis and antibiotic sensitivity pattern in term neonates.

**Methods:** This prospective observational cohort study was done in a tertiary care hospital located in rural South India for a period of 2 years. Blood culture and lumbar puncture were performed for all term babies with clinically suspected sepsis. Growth, if detected was followed by antibiotic sensitivity testing.

**Results:** Of a total of 50 neonates investigated with blood culture, 32(64%) were found to be culture positive for neonatal septicemia, 16 were diagnosed to have meningitis. Meningitis was present in 4(25%) early onset sepsis cases and in 12(75%) late onset sepsis cases (p-value: 0.008). Blood culture showed growth in all of the 16 cases of meningitis, but Cerebro Spinal Fluid (CSF) culture was positive in 5 cases. The most common presenting features are lethargy, seizures, decreased acceptance of feeds, instability of temperature regulation, vomiting, respiratory distress, and apnea. The most common organism in blood culture was Coagulase Negative *Staphylococcus* (CONS) (20%) followed by *Klebsiella spp.* (16%). CONS was most sensitive to Linezolid (100%), Vancomycin (90%). Of the 8 cases of *Klebsiella*, 62.5% cases were sensitive to Colistin and Tigecycline, 50% to Cotrimoxazole. CSF culture was positive in 5(31.25%) cases. CONS and *Enterococci spp.* were the most common organisms isolated in CSF.

**Conclusions:** Clinical manifestations of meningitis overlap with those of sepsis and are nonspecific. Significant number of neonates with sepsis have meningitis. Hence, it is necessary to rule out meningitis in neonates presented with clinical features of sepsis. CONS was the most common agent isolated in both blood and CSF culture. Routine bacterial surveillance and study of their resistance patterns must be an essential component of neonatal care which helps in implementation of a rational empirical treatment strategy.

**Keywords:** Antibiotic sensitivity, Bacteriological profile, Meningitis, Neonatal septicemia

## INTRODUCTION

Neonatal sepsis is a significant cause of morbidity and mortality among neonates globally, contributing to one third of neonatal mortality.<sup>1,2</sup> It accounts for 30-50% of neonatal deaths in developing countries.<sup>3</sup> The Million Death Study captured 52,252 deaths in neonates during 2000 to 2015 in India.<sup>4</sup> The neonatal mortality rate from infection fell by 66% from 11.9 per 1000 live births in

2000 to 4 per 1000 live births in 2015.<sup>4</sup> Neonatal meningitis is the inflammation of the meninges during the first 28 days of life.<sup>5</sup> Meningitis and sepsis typically share a common cause and pathogens.<sup>6</sup>

Neonatal sepsis is classified into Early Onset Neonatal Sepsis (EONS) (within first 72 hours of life) and Late Onset Neonatal Sepsis (LONS) (occurs after 72 hours of life).<sup>7</sup> EONS is a commonly maternally acquired and

common organisms causing EONS are Group B *Streptococcus* (GBS), *Escherichia coli*, *Coagulase Negative Staphylococcus* species (CONS), *Haemophilus influenzae* and *Listeria monocytogenes*.<sup>8,9</sup> The organisms implicated in LONS include CONS, *Staphylococcus aureus*, *E.coli*, *Klebsiella spp.*, *Pseudomonas spp.*, *Enterobacter spp.*, *Candida spp.*, GBS, *Serratia spp.*, *Acinetobacter spp.* and anaerobes. The bacteriological profile for causative organisms of neonatal sepsis differs significantly between developed and developing countries.<sup>10-12</sup> *Klebsiella pneumoniae* is the most common bacterial agent causing neonatal sepsis in developing countries, while Group B *Streptococcus* and *Coagulase-negative staphylococci* (CONS) are the common agents in the developed.<sup>13</sup> Even among developing countries, regional variation in prevalence of the bacterial agents causing neonatal sepsis exists.<sup>14,15</sup> Not only the pathogenic agent but also the sensitivity pattern of the organism varies between the different neonatal units as well as in the same neonatal unit over time. Hence, the present study has been undertaken to assess the incidence of meningitis in neonatal sepsis and antibiotic sensitivity pattern of term neonates admitted with clinical suspicion of sepsis over a period of 2 years.

## METHODS

This prospective observational cohort study was done in a tertiary care hospital located in rural South India for a period of 2 years from December 2016 to December 2018. The study was approved by Institutional Ethics Committee and Institutional Review Board.

During the study period 1200 neonates were admitted in NICU, among them 876 were term babies, 117 term neonates met the criteria for "clinical sepsis". Neonatal septicemia was suspected if the neonate has symptoms and signs of sepsis like poor feeding, poor activity, lethargy, vomiting, loose stools, abdominal distension, fever, hypothermia, tachypnoea, chest retractions, nasal flaring, grunting, apnea, bulging fontanelle, seizures, loss of consciousness, periumbilical erythema, cyanosis, mottling, tachycardia, weak pulse, delayed capillary refill time. Among them 67 neonates were excluded from study. Our exclusion criteria include neonates with shock and severe cardiorespiratory instability, severe asphyxia, congenital malformations and neonates in whom Lumbar Puncture (LP) was contraindicated. Remaining 50 term neonates underwent LP.

Meningitis was diagnosed in neonates with clinical sepsis who met any of the following criteria on Cerebro Spinal Fluid (CSF) analysis:

- CSF cytology showing >30 cells with more than 60% polymorphs.<sup>16-18</sup>
- CSF glucose <50% of blood glucose (Blood glucose done simultaneously).
- CSF protein >150 mg/dl.<sup>19</sup>

Blood culture and sensitivity was performed on all the term neonates with clinical features of sepsis. Before starting empirical antibiotics, 1 ml of blood was collected from all neonates with aseptic precautions and added to pediatric fastidious plus (PF plus) blood culture bottles and loaded into the Bact alert automated (Biomérieux) blood culture instrument. Positive cultures were subcultured onto blood agar, chocolate agar and MacConkey's agar at 37°C for 24 hours. Isolated colonies were then processed for bacterial identification. Antibiotic sensitivity testing was done using automated VITEK 2 compact. (Biomérieux, VITEK 2GN, VITEK 2 AST-N281). Culture was reported as sterile if there was no growth for 7 days.

## Statistical analysis

Data will be analyzed by statistical software. Data will be summarized by Mean±SD for continuous data, Median +/- IQR for ordinal data and percentages for categorical data. The relation between variables will be correlation analysis for continuous data; the association between variables will be done for Chi square test.

## RESULTS

Of a total of 50 neonates with suspected neonatal sepsis, 30(60%) were males and 20(40%) were females and 39(78%) were out born and 11(22%) were inborn. Of 50 neonates, 26(52%) and 24(48%) were normal birth weight and Low Birth Weight (LBW) neonates, respectively. EOS and LOS were 26(52%) and 24(48%) neonates, respectively. The common clinical presentations were decreased acceptance of feeds (70%), decreased activity (56%), seizures (36%), jaundice (38%), respiratory distress (34%), fever (20%) apnea (16%) hypoglycemia (14%) and pustules (10%) (Table 1). Among the suspected neonatal sepsis cases, 32(64%) were found to be blood culture positive, 20(60%) males and 12(40%) females, 18(56.25%) were LBW neonates and 14(43.75%) were normal birth weight neonates.

**Table 1: Symptoms of neonatal sepsis.**

| Clinical features    | Number (%) |
|----------------------|------------|
| Decreased feeding    | 35(70%)    |
| Dull activity        | 28(56%)    |
| Seizures             | 18(36%)    |
| Jaundice             | 19(38%)    |
| Respiratory distress | 17(34%)    |
| Fever                | 10(20%)    |
| Apnoea               | 8(16%)     |
| Hypoglycemia         | 7(14%)     |
| Pustules             | 5(10%)     |

Among the 50 neonates presented with clinical sepsis, 16(32%) neonates had biochemical and cytological CSF findings suggestive of meningitis. In this study, blood cultures showed growth in all of the sixteen cases of

meningitis (p value :0.0001), but CSF culture was positive in only 5(31.2%) cases. Meningitis was present in 4(25%) early onset sepsis cases and in 12(75%) late onset sepsis cases. The mean age was 6.68 days and p-value: 0.008 (<0.05). 10(62.5%) were males and 6(37.5%) were female neonates and 12(75%) were outborn and 4(25%) were inborn neonates, 9(56.25%) were LBW neonates and 7(43.75%) were normal birth weight neonates. The common clinical presentations were decreased acceptance of feeds (62.5%), seizure (75%), decreased activity (50%), jaundice (31%), respiratory distress (18.25%), apnea (12%) hypoglycemia (6.25%), pustules (6.25%), and fever (18.25%) (Table 2,3).

**Table 2: Characteristics of neonates with meningitis.**

|                     |           | Number | %      | p value |
|---------------------|-----------|--------|--------|---------|
| Age at presentation | <72 hours | 4      | 25%    | 0.008   |
|                     | >72 hours | 12     | 75%    |         |
| Sex                 | Male      | 7      | 43.75% | 0.107   |
|                     | Female    | 9      | 56.25% |         |
| Birth Weight        | <2500 gm  | 9      | 56.25% | 0.107   |
|                     | >2500 gm  | 7      | 43.75% |         |
| Admission           | In born   | 4      | 25%    | 0.725   |
|                     | Out born  | 12     | 75%    |         |

**Table 3: Symptoms of meningitis.**

| Clinical features    | Number (%) |
|----------------------|------------|
| Decreased feeding    | 10(62.5%)  |
| Seizures             | 12(75%)    |
| Dull activity        | 8(50%)     |
| Jaundice             | 5(31.25%)  |
| Apnoea               | 2(12.5%)   |
| Pustules             | 1(6.25%)   |
| Hypoglycemia         | 1(6.25%)   |
| Respiratory distress | 3(18.75%)  |

Of the total of 32 blood culture positive cases, microorganisms isolated were CONS (10,31.2%), *Klebsiella spp.* (8,25%), *candida spp.* (6,18.7%), *pseudomonas spp.* (4,12.5%), *Acinetobacter spp.* (3,9.3%), and *enterococci spp.* (1,3.1%) (Table 4,5).

Of the 16 cases of meningitis, only 5(31.2%) were CSF culture positive. Microorganism yield of CSF were CONS (4, 80%) and enterococci (1, 20%) (Table 6).

**Table 4: Bacteriological profile of neonatal sepsis cases.**

| Organism in blood culture | Number(%) |
|---------------------------|-----------|
| CONS                      | 10(31.2%) |
| <i>Klebsiella</i>         | 8(25%)    |
| <i>Candida</i>            | 6(18.7%)  |
| <i>Pseudomonas</i>        | 4(12.5%)  |
| <i>Acinetobacter</i>      | 3(9.3%)   |
| <i>Enterococci</i>        | 1(3.1%)   |

**Table 5: Blood culture in neonates with and without meningitis.**

| Blood culture | Meningitis | No meningitis | p value |
|---------------|------------|---------------|---------|
| Positive      | 16         | 16            | 0.0001  |
| Negative      | 0          | 18            |         |

p<0.05 considered statistically significant. Fischer's exact test used

**Table 6: CSF culture positivity.**

| Organism in CSF culture | Number (%) |
|-------------------------|------------|
| CONS                    | 4(80%)     |
| <i>Enterococci</i>      | 1(20%)     |

Sensitivity patterns of CONS were as follows: Linezolid (100%), Vancomycin (90%), Amikacin, Gentamycin, Tigecycline (40%), Levofloxacin (40%) and Ciprofloxacin, Cotrimoxazole, Teicoplanin (10%).

Sensitivity pattern of *Klebsiella spp.* were Colistin and Tigecycline (62.5%), Cotrimoxazole (50%), Ciprofloxacin (37.5%), and Levofloxacin, Amikacin, Piperacillin-Tazobactam (25%).

## DISCUSSION

Neonatal sepsis is a significant cause of morbidity and mortality among neonates globally, particularly in developing countries, contributing to one third of neonatal mortality. Early suspicion and accurate identification of organisms and their antibiotic sensitivity patterns is essential for empirical and definitive treatment to improve the outcome.

In this study, incidence of meningitis is nearly two thirds of neonatal sepsis. Incidence of septicemia and meningitis is more common among Low Birth Weight (LBW) babies (56.25%), which is similar with findings of Hristeva L et al, Altayeb MH et al, Kavuncuoglu et al.<sup>20-22</sup> Incidence is more common in males with male: female ratio of 3:2. Similar findings were found by Hristeva L et al, Khalessi N et al.<sup>20,23</sup> Majority of the clinical manifestations of meningitis overlaps with those of sepsis and are nonspecific. The common presenting symptoms in this study were lethargy, poor feeding, temperature instability, vomiting, respiratory distress (respiratory rate >60/min, retractions, grunting, nasal flaring, cyanosis), apnea and seizures. Seizures are frequently observed and can be caused by either direct central nervous system inflammation or by metabolic abnormalities.<sup>24</sup> A bulging fontanel may be seen, but this is usually a late manifestation. In a study by Khalessi N et al, poor feeding and seizures were the common manifestations. While bulging of fontanel was noticed in only 5% patients.<sup>23,25</sup>

In the present study, the most common organism in blood culture was CONS (31.2%) which was most sensitive to Linezolid (100%), Vancomycin (90%). *Klebsiella spp.* was the second most common isolate (8, 25%); of which

62.5% cases were sensitive to Colistin and Tigecycline and 50% to Cotrimoxazole. Although there is a close relationship between bacterial sepsis and meningitis, it has been estimated that 15% to 30% of the infants with CSF-proven meningitis have negative blood cultures.<sup>26</sup> In our study, blood culture was positive in 100% of meningitis cases. CSF culture was positive in 31.25% meningitis cases. *CONS* and *Enterococci* were the most common isolates. In a study by Al-Harthi et al, *Klebsiella*, *CONS*, *Serratia spp.* were the commonest organisms isolated from CSF.<sup>27</sup> Prior use of antibiotics before the performance of the LP, the delay in the transport of the CSF to the laboratory and the low density of bacteria in CSF could be some of the reasons for low CSF culture positivity rate.<sup>28</sup>

## CONCLUSION

Common clinical manifestations of meningitis overlap with those of neonatal sepsis and are non-specific. This study concludes nearly one third of term neonates presenting with neonatal sepsis had meningitis. Hence, Author recommend ruling out meningitis in neonates presented with sepsis. Coagulase negative staphylococcus was the most common isolate from blood and CSF, which was sensitive to linezolid and vancomycin. Periodic bacterial surveillance and antibiotic sensitivity patterns is essential to identify bacterial resistance to routinely used empirical antibiotics and changing the empirical treatment strategy to improve the outcome.

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