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# The Clinical and Bacteriogical Spectrum of Neonatal Sepsis in a Tertiary Care Hospital, Deen Dayal Upadhyay Hospital, Harinagar New Delhi India

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***Abstract: Objective****: Sepsis is an important cause of neonatal morbidity and mortality especially in developing countries where identification of the organisms and treatment is often unsatisfactory. The aim of the study was to assess the clinical presentation, and bacteriological profile of neonatal infections.*

***Methods:*** *We carried out a prospective analytic study in the Pediatric Hospital in New Delhi over 1 year period from December 2009 to November 2010. On the basis of history and/or clinical findings and biochemical investigations, 560 neonates out of a total of 2240 admissions were investigated and managed for neonatal infection.*

***Results:*** *During the study period, out of total 2240 admissions, sepsis was diagnosed in 560 (25%) neonates. Among these 560 neonates 80 near term and term neonates with weight appropriate for gestational age had at least one episode of positive blood culture. Other 480 neonates had clinical features as well as biochemical evidences of sepsis but there blood cultures were persistently sterile.Out of 80 neonates, Gram positive sepsis occurred in 21/80 (26.25%), gram negative sepsis occurred in 54/80 (67.5%), and fungal sepsis was diagnosed in 5/80 (6.25%). Among gram negative sepsis klebsella sepsis was most common 40%, followed by Acenatobacter (15%), Ecoli (7.5%) and pseudomonas (5%). Staph aureus was most common organism isolated in 16.25% patients among gram positive sepsis followed by Enterococcus in 7.5% patients. Fungal sepsis was found in 6.25%.*

***Conclusion:*** *Sepsis is an important cause of morbidity and mortality in neonates especially in preterm babies. Throughout the world, 1.6 million neonates die even year from infection. Most of these deaths are in developing countries, where neonatal mortality from sepsis may be as high as 60%.*

***Keywords:*** *Neonatal sepsis, Bacteriological profile, Blood culture, Gram positive sepsis, Gram negative sepsis.*

## I. Introduction

Throughout the world, 1.6 million neonates die even year from infection [1]. Although most of these deaths are in developing countries, where neonatal mortality from sepsis may be as high as 60% [2], the incidence of infection in developed world is also very high at 2.2 to 8.6 per 1000 live births [3]. Neonatal deaths account for half of deaths of children less than 5 years of age and two thirds of infant deaths [4]. The Millennium Development Goal-4 includes a reduction of childhood mortality by two-thirds between 1995 and 2015 and a major component is reduction of neonatal mortality [5]. Sepsis is an important cause of morbidity and mortality in neonates especially in preterm babies. It is commonest in small and extremely premature infants in whom the clinical presentation can be subtle and nonspecific [6]. Immunological defense mechanisms in neonates are immature and/or deficient, which predispose them to serious and opportunistic infection [7]. Signs of sepsis in neonates are non-specific, subtle and inconspicuous but the clinical course may be alarmingly fulminant leading to septic shock disseminated intravascular coagulation (DIC) and death within hours of onset |8|.

In neonates sepsis is defined as isolation of an organism from either blood or CSF culture [9]. More than one fifth (20%) of all VLBW (birth weight <1500 gram) neonates who survive beyond 72 hours have at least one episode of blood culture confirmed sepsis [10]. These infected neonates have higher mortality than non-infected neonates [10] and are more likely to develop adverse neurodevelopmental complications [11]. Sepsis accounts for approximately half of all deaths beyond second week of life in VLBW babies [12].

Thus early diagnosis of sepsis in neonates is warranted to interrupt the cascade of events leading to septic shock and multiorgan failure.

## II. Material And Methods

The study was conducted over a period of one year from December 2009 to November 2010 in neonatal intensive care unit of Deen Dayal Upadhyay Hospital, a tertiary care hospital in North India. All babies who were admitted during this period were evaluated prospectively for evidence of sepsis. Sepsis was defined according to international sepsis definition conference [13] as "clinical syndrome characterized by presence of both infection and systemic inflammatory response syndrome". Systemic inflammatory response syndrome in case of neonates is defined as two or more of the following:-

1. Tachypnea (respiratory rate more than 60 bpm + grunting or retractions.
2. Temperature instability < 36°C or more than 37.9°C.
3. Capillary refill time more than 3 seconds.
4. White blood cell count < 5000/µl or more than 34000/µl.
5. CRP more than 10 mg/dl IL-6 more than 70 pg/ml.
6. Procalcitonin more than 8.1 mg/dl or more than 2 SD above normal values.

Sepsis is defined as one or more systemic inflammatory response syndrome criteria with signs of infection [14]. Only first episode of sepsis in a patient was included to avoid any confounding effect of earlier sepsis on platelets. Sepsis evaluation was based on clinical signs and symptoms and rapid screen tests for sepsis, including changes in complete blood counts and positive blood culture. In case of CONS sepsis repeat blood culture was taken to rule out contamination. Babies with congenital malformations, and chromosomal anomalies were excluded. Near term and term babies with weight appropriate for gestation ages were included in this study. This study was approved by ethics committee of Deen Dayal Upadhyay hospital.

Blood for culture (1 ml of blood) and complete blood counts was obtained by means of venipuncture. Nosocomial sepsis was defined as an infection that occurs 48 hours after admission in a baby who did not have any evidence of infection on admission characterized by growth of a pathogen not related to infection at another side from 1 blood culture in presence of clinical features of infection. Early onset sepsis was defined as infection during the 1st 72 hours of life and late onset sepsis as infection occurring after 72 hours of life. Outcome in the form of mortality and multiorgan failure was analyzed. Mortality was defined as death before discharge. Infants discharged to home were considered survivors.

For statistical analysis data was expressed as mean ±SD. Analysis was done by using student t test for parametric data. Proportions were compared using X2 test of significance. Values were considered significant if $p< 0.05$ and highly significant if $p<0.01$. The data was analysed using SPSS package.

## III. Results

During the study period, out of total 2240 admissions sepsis was diagnosed in 560 (25%) neonates. Among these 560 neonates 80 near term and term neonates with weight appropriate for gestational age had at least one episode of positive blood culture. Other 480 neonates had clinical features as well as biochemical evidences of sepsis but there blood cultures were persistently sterile Out of 80 blood culture positive neonates 73 were term neonates and 7 were near term. Among these males were 43 (53.75%) and females were 37 (46.25%). Out of 80 neonates, Gram positive sepsis occurred in 21/80 (26.25%), gram negative sepsis occurred in 54/80 (67.5%), and fungal sepsis was diagnosed in 5/80 (6.25%).

**TABLE 1: Frequency of Organisms Causing Neonatal Sepsis**

| **ORGANISM** | | Number of patients | Percent |
|---|---|---|---|
| **Gram Negative (67.5%)** | Klebsella | 32 | 40% |
| | Acenatobacter | 12 | 15% |
| | E.coli | 6 | 7.5% |
| | Pseudomonas | 4 | 5% |
| **Gram Positive (26.25%)** | Staph Aureus | 13 | 16.25% |
| | Enterococcus | 6 | 7.5% |
| | CONS | 2 | 2.5% |
| **Yeast (6.25%)** | 5 | 12 | 6.25% |
| **TOTAL** | 80 | N = 280 | 100% |

The above table depicts gram negative organisms the most common pathogen was Klebsella pneumonia seen in 32/80 (40%). The second common organism isolated was Acenatobacter in 12/80 (15%) followed by Escherichia Coli in 6/80 (7.5%) and Pseudomonas in 4/80 (5%).Among gram positive organisms the most common pathogen was Staphylococcus aureus in 13/80 (16.25%). Enterococcus was seen in 6/80 (7.5%) and Coagulase negative Staphylococcus in 2/80 (2.5%) patients. The most common fungal isolate was Candida albicans.

**Demographic Details of Neonates with Sepsis**

The demographic details of the male and female neonates infected with the three groups of organisms are shown in table 2A and 2B. The average gestational age of all babies was 37.84 ± 1.68 weeks. Average Gestational age of babies with gram negative sepsis was 38.09 ± 1.59 weeks, with gram positive sepsis was 37.33 ± 1.93 and with fungal sepsis was 37.20±1.09 weeks (p=.148).

The average birth weight of all infected babies was 2499±234 grams. Average weight of babies with gram negative sepsis was 2496±261 gram, with gram positive sepsis was 2528±169 gram and fungal sepsis was 2410±156 gram. Although the average birth weight of babies having fungal sepsis was lower than babies with Gram positive or Gram negative sepsis, the difference was statistically insignificant. Out of 80 babies, 43/80 (53.75%) were males and 37/80 (46.25%) females.

Incidence of caesarean deliveries was 25.9%. There was no difference in incidence of caesarean deliveries between groups (p=0.343).

Average age at admission in all neonates was 92.89±24.57 hours. In gram negative sepsis it was 88.70±23.13 hours, in gram positive sepsis it was 93.10±19.62 hours. Average age at onset of fungal sepsis was 137.20±14.80. The difference was statistically significant (p< 0.01).

Average duration of stay in hospital in all patients was 15.96±5.24 days. In gram negative sepsis it was 16.39±5.15 days, in gram positive sepsis it was 15.14±5.56days. In fungal sepsis average duration of hospital stay was 14.80±5.40 days. The difference was statistically insignificant (p=.579).

The average mortality in all septic neonates was 14/80 (17.5%). In gram positive sepsis mortality was 4/80(5%). In gram negative sepsis mortality was 9/80 (11.3%). In fungal sepsis it was 1/80(1.3%). The difference between the groups was statistically insignificant (p=.961).

**Difference between sexes**

**TABLE 2A: Demographic Details of Males and Females.**

| FEATURE | Gestation (Weeks) | Birth Weight (gms) | Caesarean Section | Stay in hospital (days) | Age at admission (hours) | Apgar score at 5 mins. | Mortality |
|---|---|---|---|---|---|---|---|
| MALE (43) | 37.69±1.76 | 2495±266 | 10/80 (12.5%) | 15.76±5.03 | 89.09±24.16 | 8.62±1.06 | 9/80 (11.3%) |
| FEMALE (37) | 38±1.59 | 2503±193 | 11/80 (13.80%) | 16.18±5.54 | 97.29±24.63 | 8.67±o.78 | 5/80 (6.3%) |
| ALL (80) | 37.83±1.68 | 2499±234 | 21 (26.25%) | 15.96±5.24 | 92.88±24.57 | 8.65±o.94 | 14/80 (17.5%) |

Average age at admission in males was 89.09±24.16 hours and in females 97.29±24.62 hours. Average gestation of males and females was 37.69±1.76 weeks and 38±1.59 weeks respectively. Average birth weight of males and females was 2495±266 grams and 2503±193 grams respectively. Number of males with caesarean section was 10/80(12.5%) and females were 11/80(13.80%). Average hospital stay in males and females was 15.76±5.03 days and 16.18±5.54 days.

**TABLE 2B: Demographic Data of Septic Neonates**

| FEATURE | | All Patient (80) | Gram Negative (54) | Gram Positive (21) | Fungal (5) | P.Value |
|---|---|---|---|---|---|---|
| 1 | Gestation (Weeks) | 37.83±1.68 | 38.09±1.59 | 37.33±1.93 | 37.20±1.09 | .148 |
| 2 | Birth Weight (kgs) | 2.49 ± 0.23 | 2.49±0.26 | 2.52±0.16 | 2.41 ±0.15 | .595 |
| 3 | Caesarean Section | 21(26.25%) | 14(17.5%) | 5(6.3%) | 2(2.5%) | .532 |
| 4 | Age (in hours) at Admission | 92.88±24.57 | 88.70±23.13 | 93.10±19.62 | 137.20±14.80 | <.01 |
| 5 | Stay in hospital (days) | 15.96±5.24 | 16.39±5.15 | 15.14±5.56 | 14.80±5.40 | .579 |
| 6 | Mortality | 14(17.5%) | 9(11.3%) | 4(5.0%) | 1(1.3%) | .961 |

**Incidence of Meningitis**

Total of 17/80 (21.3%) neonates were having meningitis. Out of them males were 10 (12.5%) and females were 7(8.8%).

**Organism Distribution In Neonatal Meningitis**

Gram negative organisms were most common pathogens associated with neonatal meningitis 15/17 (88.2%).Gram positive organisms were 2/17 (11.8%).In gram negative organisms the most common being Klebsella in 10/17 (58.8%). Pseudomonas was seen in 1/17 (5.9%), Acenatobacter in 3/17 (17.6%) and E. coli in 1/17(5.9%). Among gram positive organisms Enterococcus was seen in both the patients 2/17 (11.8%), {Table 6}. In addition to meningitis, 3 patients had septic arthritis and all these were having staphylococcal septicemia. Features of pneumonia on chest X-Ray occurred in 17 neonates. Six neonates had acute renal failure and all were having Klebsella septicemia.

**TABLE 3: Organism Distribution in Neonatal Meningitis**

| Organism | Number | Percentage |
|---|---|---|
| Klebsella | 10/17 | 58.8% |
| Acenatobacter | 3/17 | 17.6% |
| Pseudomonas | 1/17 | 5.9% |
| E coli | 1/17 | 5.9% |
| Enterococcus | 2/17 | 11.8% |

## IV. Discussion

because of predominance of gram negative organisms as compared to CONS in United States and Europe, which are less virulent, where meningitis is rare and bacteraemia can be About 1.6 million neonatal deaths occur worldwide every year, 40% of which occur in developing countries, particularly Asia and Africa [15]. Infections such as pneumonia, septicemia, meningitis, and diarrhoea account for 30-50% of neonatal deaths in developing countries [16]. Neonatal sepsis is a life threatening emergency and a delay in treatment may result in death.

This study from a tertiary care hospital in northern India reports on the incidence of neonatal sepsis in NICU, organism distribution, sepsis induced thrombocytopenia, morbidity and mortality associated with neonatal sepsis and efficacy of platelet transfusions used in treatment of neonatal sepsis.

In our study the incidence of neonatal sepsis was 25% (560/2240). Among 560, 80 patients were blood culture positive. Similar incidence has been reported by Manzoni et al from Italy [17]. However, Sanghvi et al in 1996 [39] in his retrospective study had found sepsis in 3.8% of NICU admissions. Kuirin et al, [40] had found incidence in 4.4% of all NICU admissions. The high incidence of neonatal sepsis reported in our study has many reasons. Our unit admits not only patients from the inborn obstetric unit but also from other hospitals and maternity centres around the hospital. 50/80 (62.5%) babies in our study were out born. As these referred neonates are already sick, thereby incidence figures in our study are higher than reported in literature. Most of the out born patients had not received prior good follow up and many of them were not booked deliveries.

In our study we found gram negative organisms to be commonest cause of neonatal sepsis. Similar trend has been reported from developing as well as some developed countries [18]. A sample of 11471 blood samples from all developing nations of the world revealed that gram negative rods were isolated in 60% of positive cultures with Klebsiellapneumoniae being the most common organism [19]. Rehman et al, [20] reported gram negative organisms as the commonest cause of neonatal sepsis with E. coli accounting for most of cases (36%). Khassawneh et al. [21] from Jordan also reported gram negative organisms as the commonest cause of neonatal sepsis. Butta et al [15) reported Klebsiellapneumoniae as the most common pathogen. Our study is consistent with similar observations.

Gram positive organisms caused sepsis in 26.25% of patients in our study. Among gram positive organisms Staphylococcus aureus was the commonest organism (16.25%) followed by Enterococcus (7.5%). Incidence of gram positive sepsis is low in Indian subcontinent [14]. However gram positive organisms are the commonest cause of neonatal sepsis in developed countries with CONS being the commonest organism [22].

In our study early onset sepsis occurred in only one patient with Klebsiellapneumoniae. Gram negative organisms being the commonest cause of EOS has been reported by Stoll JB [16]. However in their study E. Coli was the commonest organism. In developing countries Klebsiella is the commonest cause of early onset sepsis [19]. Khawssawneh et al, [21] in 2009 had similarly reported gram negative organisms responsible for early onset sepsis. Vankatashan et al, [23] reported early onset sepsis in 62% of cases, klebsiellapneumoniae as most common organism responsible during 1995-1998 but during the year 2001-2006 non fermenting gram negative bacilli (Acenitobacler and others) were the predominant organisms. Vankatashan et al, also reported E.Coli in 9% of patients with early onset sepsis in their study. Staph.aureus was the commonest organism in

early onset sepsis seen in (15.9%). Vankateshan (2008) also reported incidence of Staph. aureus as 20% in early onset sepsis.

Vankateshan while comparing the incidence of Enterococcus sepsis in 2 epochs found that Enterococcal sepsis had emerged only in recent years. CONS also were the causative organisms in 4.4% (5/113) of patients. Similar results are reported by Vankateshan et al.

In our study 98.75% (79/80) neonates had late onset/nosocomialsepsis. This is because of admission of out born babies, larger hospital stays and increased invasive procedures device usage. All these factors predispose them to nosocomial/late onset sepsis. Gram negative organisms 67.08% (53/79) were the major agents responsible for late onset sepsis. Data from both developed as well as developing countries have shown gram negative bacilli to be major pathogens of neonatal sepsis [18]. Joshi et al from India reported gram negative sepsis in 87% of their cases [24].

Data from developing countries are more or less similar with K. pneumoniae responsible for 16-28% of blood culture conformed sepsis [25]. In our study Klebsiellapneumoniae was responsible for (31/79) 39.24% of cases. Data from NNPD 2002-2003 from India has shown K. pneumoniae as the major pathogen in (27-32%) both intramural as well as extramural neonates [26].

Khassawneh had reported Klebsiella in 54% among all organisms. K. Pneumoniae was present in 14% of cases of LOS in epoch II in Venkateshan study. Kurien in 1998 also had reported Klebsiella as the most common pathogen in late onset sepsis. The reasons for Klebsiella being commonest cause of both early and late onset sepsis in neonates are many. Klebsiella pneumonia possesses a smooth lypopolysaccharide (LPS with O antigen) and a capsular antigen (K antigen) and both are important for virulence. There is a variation in genetic make-up of "0" antigen between Klebsiellapneumoniae and other gram negative organisms, which allows KlebsiellaPneumoniae strains to constitutely express a polysaccharide capsule for organisms ability to resist complement mediated opsonophagocytic killing. These genetic variations in KlebsiellaPneumoniae may be responsible for the persistent bacteremia and maximum effects on various platelet parameters as seen in our study.

In our study Staph.aureus was the second most common organism (13/79) 16.45% responsible for late onset sepsis. Rehman et al, also reported staph. aureus responsible for neonatal sepsis in 29% of patients. Kurein et al, reported staph. aureus in 13% of cases with LOS. Staph.aureus colonizes skin, Nasopharynx and GIT and spreads via hands of health care workers [23]. This implies a need for better adherence to hygiene practices, cohorting, isolation and decolonization of health care workers. E.Coli was found in 7.59% (6/79) late onset sepsis. Vankateshen had reported incidence of E.Coli in 11% cases of LOS.

CONS was seen in 2.53% (2/79) cases of late onset sepsis in our study. Venkatashan had reported 5-6% incidence of CONS in late onset sepsis. In developed countries CONS is the major causative organism of late onset sepsis [39]. Sanghvi in 1996 had reported CONS in 61% cases of late onset sepsis. CONS was isolated less commonly in our study. Latin America and Middle East have reported high rates of CONS infection, which might indicate a high rate of invasive devise use as compared to our setup and setup in other developing countries [19]. In our study yeast was grown in 6.32% (5/79) cases of LOS. Vankatashan had reported that 11% of septic neonates were having fungal sepsis. Guida et al [27] had reported that 8% of septic neonates in their study were having fungal sepsis . In recent study (2009) Bhat et al [14] reported that 8.5% of septic VLBW neonates were having fungal sepsis. T Calveros in 2007, have reported incidence of fungal sepsis in 1.9% of VLBW neonates [25]. The low incidence of fungal sepsis in this study is because the mean birth weight in our babies was 2500 grams and only small proportion/or neonates were low birth weight. Since fungal sepsis is more common in preterm and low birth weight babies, therefore, incidence of fungal sepsis in our babies was low.

The incidence of meningitis in our study was 21.25% (17/80). Similar pattern of high incidence of meningitis is reported by Greenberg from Israeli [28]. Khassawneh et al had reported that 6.60% of their septic neonates had meningitis. Kurein had reported meningitis in only 3/125 septic neonates. The high incidence in our patients could be easily eradicated.

## V. Conclusion

In conclusion the incidence of neonatal sepsis is very high and gram negative agents are the main pathogens. Neonatal sepsis is a major cause of morbidity and mortality in neonates in Delhi despite recent improvements in the health care system. Clinical manifestations are nonspecific and varied.

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