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# NEONATAL SEPSIS - A PROSPECTIVE STUDY FROM A TERTIARY CARE HOSPITAL OF NORTH DELHI

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**Abstract-** *Background*: Neonatal sepsis is a common cause of morbidity and mortality among newborns in developing world. Most cases are identified based on the clinical manifestations presenting in early or late neonatal period. An early treatment and the appropriate use of antibiotics would minimize the risk of morbidity and mortality in neonatal sepsis. *Objective*: To study demographical, bacteriological, and laboratory profile of neonates presenting with clinically suspected sepsis based on predefined clinical criteria. *Study Design*: A prospective study involving a total of 200 neonates with clinical suspicion of NS, between November 2013 to may 2014 admitted at NICU at NDMC and Hindu Rao Hospital, North Delhi. *Materials and Methods*: Blood cultures were done from 200 neonates admitted in NICU suspected to have sepsis. Samples were incubated in the Bactec 9120. Isolates identified and AST performed by VITEK 2C. The results were evaluated for demographical, bacteriological, and laboratory profile. *Results*: Out of 200 neonates, 119(59.5%) were early onset sepsis and 81 (40.5%) neonates with late onset sepsis. Male constituted 61% (122) and females 39 % (78), ratio being 1.6:1. Septic screen was positive in 72% (144) neonates and culture positive in 23% (46) neonates. Of the organisms cultured, *S.aureus* 39.1% (18) was predominant pathogen in both EONS and LONS. Other isolates include *Klebsiella sp., E. coli, P. aeruginosa* and Gr. B Streptococcus. Isolates showed variable resistance towards various antimicrobial agents. Overall, Imipenem, vancomycin and linezolid were the most effective antimicrobial agents comparatively with statistically significant difference in sensitivity but, these should not be used indiscriminately and kept as reserved options to prevent emergence of MDR strains and treatment failure. *Conclusion*: Knowledge of locally prevalent microorganism and antibiogram pattern is important in the management of neonatal sepsis. GPC were the main cause of neonatal sepsis. The data must be periodically reviewed and antibiotic policy revised accordingly.

**Keywords-** Neonatal Sepsis, Multi Drug Resistance, Antibiogram

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## Introduction

Neonatal sepsis (NS) is a life threatening medical emergency requiring prompt diagnosis and treatment based on high clinical suspicion. NS presents a management challenge to care groups of neonates and infants, worldwide. The situation is further worsened by global emergence of antimicrobial resistance leading to treatment failure.

The incidence of NS is estimated as 7 cases per 1000 live births, which may increase up to 162 per 1000 live births in very low birth weight neonates [1]. Furthermore, it is higher in developing countries than in resource-rich countries. Risk of infection in neonates is associated with various maternal, neonatal, and environmental factors. The incidence of the NS also varies with geographical area, the socioeconomic status and various customs and practices in the perinatal period.

NS is broadly classified into two types according to the time of onset: Early onset neonatal sepsis [EONS] (<72hrs) and late onset neonatal sepsis [LONS] which manifest in the 2nd to 3rd week of postnatal life [1,2]. Diagnosis of NS is based on combination of clinical, microbiological and hematological parameters. An early and aggressive treatment with use of appropriate antibiotics would minimize the risk of morbidity and mortality in neonatal sepsis. Effective management of neonatal sepsis requires a combination of preventive strategies, judicious neonatal evaluation, and early initiation of appropriate therapy to prevent adverse outcomes.

All suspected newborns should have a septic screen to correlate the clinical diagnosis, despite the fact that when there is a strong clinical suspicion, the decision to start antibiotics does not depend on sepsis screen [3].

The causative organisms of NS kept changing from place to place and time to time in different hospital settings [4]. Moreover, their antimicrobial resistance pattern is becoming more and more unpredictable hence should be monitored periodically. Knowledge of locally prevalent pathogens causing infections in neonates along with their antibiogram pattern is crucial for formulating management

strategies and successful management of NS [5]. The present study was undertaken to highlight the importance of various diagnostic methods and to demonstrate the changing pattern of NS along with the drug resistance of common pathogens.

## Material and Methods

A total of 200 neonates with clinical suspicion of NS, between November 2013 to may 2014 admitted at NICU of Hindu Rao Hospital, Delhi were analysed prospectively. Approval was taken to carry out the study from the Ethical committee of our institution.

The neonatal septicemia was categorized according to its time of onset as early-onset sepsis (0-7 days) and late-onset sepsis (8-28 days). Neonates presenting with signs and symptoms of sepsis, based on the risk factors and/or clinical features, were subjected to various hematological screening parameters and blood cultures. The blood cultures were processed in an automated blood culture system (Bactec 9120) and isolates identified and antibiotic susceptibility performed by VITEK 2C as per CLSI guidelines. Cultures were reported as negative when they did not yield any growth at the end of 7 days.

A battery of various sepsis screen tests were carried out on all the blood samples including C-Reactive protein (CRP) test (cut off- >10 unit), total leukocytes (WBC) count, platelet count and Absolute neutrophil count (ANC). Two or more abnormal septic screen parameters were taken as positive for NS.

## Data Collection

All the findings were recorded and comparisons drawn between blood culture results and the sepsis screen tests. Data analysis was done using statistical package for social science (SPSS) software version 17.0, and categorical tables, probability coefficients, sensitivity, specificity, positive predictive values and negative predictive values of these diagnostic methods derived and the results correlated. Conclusions were drawn from the tabulated results. The level of significance for tests was set at $p < 0.05$.

## Results

A total of 200 neonates admitted in NICU with clinical signs and symptoms of sepsis were evaluated, of which 59.5% (119) were presenting as early-onset sepsis and 40.5% (81) as late-onset sepsis. Male constituted 61% (122) and females 39 % (78), ratio being 1.6:1. Septic screen were positive in 72% (144) neonates and culture positive in 23% (46) neonates. Among culture positive cases 56.5% (26) were males and 43.5% (20) were females.

Among 119 neonates with early-onset sepsis, 21% (25) were culture positive and 56.3% (67) were positive only on septic screen. Of these 25 culture positive cases 21 were both culture and septic screen positive [Table-1]. Out of 81babies presenting with late-onset sepsis, 25.9% (21) were culture positive and 69.1% (56) were positive by septic screen. Of these 21 culture positive cases 20 were both culture and septic screen positive. Taking blood culture as standard, the sepsis screen showed overall sensitivity and specificity of 89.1% and 32.1% respectively with the positive predictive value of 28.5% and negative predictive value of 98.1% [Table-2].

Of total 46 culture positive isolates, 67.4% (31) were gram positive cocci, 32.6% (15) were gram negative bacilli [Table-3]. Antimicrobial resistance pattern was studied and evaluated [Table-4]. *S. aureus*, 39.1% (18) was the predominant pathogen among gram positive isolate followed by CoNS 26% (12). Of these of *S. aureus* isolates 33.3% (6) were Methicillin resistant staphylococcus aureus (MRSA). Among gram negative isolates, *K. pneuminiae*. 40% (6) was the most common organism isolated followed by *E. coli* 8.7% (4), *P. aeruginosa* 6.5% (3), and *Acinetobacter sp*. 4.3% (2) in that order.

**Table 1-** Co-relation of sepsis screen parameter with the blood culture status

| Septic screen parameter | Culture positive (n=46) | Culture negative (n=154) | Total (n=200) | p-value |
|---|---|---|---|---|
| C-reactive protein | 41 | 103 | 144 | <0.05 |
| Leucopenia/ Neutropenia | 15 | 38 | 53 | >0.05 |
| Lymphocytosis | 7 | 10 | 17 | >0.05 |
| Thrombocytopenia | 15 | 14 | 29 | <0.05 |
| 2 or > 2 test positive | 32 | 63 | 95 | <0.05 |

**Table 2-** Statistical analysis for septic screen in neonatal sepsis in EONS & LONS

| Parameters | Overall (%) | EONS(%) | LONS(%) |
|---|---|---|---|
| Sensitivity | 89.13 | 84 | 95.24 |
| CI | 95 | 95 | 95 |
| Specificity | 32.12 | 28.72 | 40 |
| CI | 95 | 95 | 955 |
| Positive predictive value | 28.47 | 23.86 | 35.71 |
| Negative predictive value | 91.07 | 87.1 | 96 |
| Positive Likelihood ratio | 1.33 | 1.18 | 1.59 |
| Negative Likelihood ratio | 0.33 | 0.56 | 0.12 |
| Disease prevalence | 23% | 21.01 | 25.93 |

**Table 3-** Distribution (n, %) of microorganisms in neonates with sepsis

| Organisms (n= 46) | Frequency of Isolation (n) | EONS | LONS |
|---|---|---|---|
| *S. aureus* | 18 | 10 | 8 |
| CoNS | 12 | 5 | 7 |
| *K. pneumoniae* | 6 | 4 | 2 |
| *E. coli* | 4 | 3 | 1 |
| *P. aeruginosa* | 3 | 1 | 2 |
| Acinetobacter | 2 | 1 | 1 |
| Gr *B. streptococci* | 1 | 1 | 0 |

Gram positive isolates had an overall sensitivity of less than 50% for most of the antimicrobials tested with resistance as high as 53.3% to penicillin followed by 70% and 50% for ciprofloxacin and gentamicin respectively. Gram positive bacteria showed nil resistance towards vancomycin and linezolid. Considering resistance among gram negative isolates, imipenem and pipracillin plus tazobactam combination (13.3%) fared better than amikacin (26.7%) and gentamicin (66.7%). Although, the number of *P. aeruginosa* and *Acinetobacter sp.* isolates were very low, but most of these isolates were resistant towards various antimicrobials tested [Table-4]. Three neonates succumbed to death during the study resulting in a mortality rate of 1.3%.

## Discussion

Sepsis is a major cause of neonatal morbidity and mortality and the incidence varies worldwide in developed and underdeveloped nations [1-3,5]. The highest incidence is reported from Africa (23-38/1,000 live births) and lowest from US (1.5-3.5 /1,000 live births).

In SEAR countries, the incidence of NS ranges between 1->30/1000 live birth whereas it is approximately 30/1000 live birth in India [4-7].

In our study, majority of neonates (59.5%) presented with early-onset sepsis as also reported by Vinodkumar et al [7] (55.3%), Aletayeb et al [8] (64.7%) while it was 49.6% and 73% respectively as reported by Shaw, et al [9] and Movahedian et al [10]. A male predominance was found with male to female ratio of 1.6:1, which is in agreement with previous reports [9-12]. The male preponderance in neonatal septicemia may be linked to the X-linked immunoregulatory gene factor contributing to the host's susceptibility to infections in males [12].

**Table 4-** Showing resistance pattern of gram-positive and gram-negative organisms

| Antibiotics | *S. aureus* (n=18) | CoNS (n=12) | *K. pneuminiae* (n=6) | *E. coli* (n=4) | *P. aeuginoisa* (n=3) | *Acinetobacter sp.* (n=2) |
|---|---|---|---|---|---|---|
| Penicillin | 10(55.5) | 6(50) | - | - | - | - |
| Gentamicin | 10(55.5) | 5(41.7) | 4(66.6) | 3(75) | 2(66.7) | 1(50) |
| Amikacin | 5(27.7) | 3(25) | 2(33.3) | 1(25) | 1(33.3) | 0 |
| Vancomycin | 0 | 0 | - | - | - | - |
| Linozolid | 0 | 0 | - | - | - | - |
| Cefoxitin | 6(33.3) | - | - | - | - | - |
| Ciprofloxacin | 13(72.2) | 8(66.66) | 5(83.3) | 3(75) | 2(66.6) | 2(100) |
| Cotrimoxazole | - | - | 4(66.6) | 3(75) | - | - |
| Amoxy-clav | 9(50) | 5(41.7) | 4(66.7) | 3(75) | - | - |
| Cefotaxime/Ceftazidime | 9(50) | 4(33.3) | 2(33.3) | 1(25) | 2(66.7) | 1(50) |
| Imipenem | - | - | 1(16.6) | 0 | 1(33.3) | 0 |
| Piperacillin-Tazobactam | - | - | 1(16.6) | 0 | 0 | 1(50) |

Culture positivity in NS varies from 15 to 60% in different setups. In our study, 23% (46) were cultures positive. However, a high and low blood culture positivity rate in NS (56%, 48% and 19%) had been reported by Sharma *et al*, Bhattacharjee *et al* and Jyothi *et al* respectively [13-15].

A total of 144 neonates were septic screen positive, of which 41 cases were confirmed by means of blood culture. This finding can be attributed to non specific septic screen parameters along with low sensitivity of the blood culture due to culturing very small quantities of blood or antibiotic administration before blood sampling or possibility of anaerobic infection. Despite a low sensitivity, the blood culture is considered as gold standard in the diagnosis of sepsis due to non specific nature of most of the septic screen parameters [13-15]. Sepsis screen was positive in 84% of culture positive EONS and 95.2% of LONS cases. This low sepsis screen positivity in EONS cases can be explained due to inability of mounting sufficient immune response owing to the immaturity of immune system as compared to LONS cases.

Literature review suggests that sepsis screen should be considered positive, if two or more parameters are abnormal to reasonably start antimicrobial therapy, a finding also supported by our study (P value < 0.05). Sepsis screen should be repeated within 12 hours when it is negative in cases with strong clinical suspicion. Sepsis can certainly be excluded if the screen result is still negative.

The predominant organisms associated with NS have changed over the years. Studies have shown that *S. aureus* and CoNS are the predominant gram positive organisms whereas *E. coli* and *K. pneumoniae are* among the predominant gram negative organisms implicated in NS [11-15].

The most frequently isolated microorganism for early as well as late -onset sepsis in our study is *S. aureus* and CoNS as also documented by many authors [9-12]. One of the reasons may be the horizontal transmission of *S. aureus* from colonized mothers or health care workers to the infants in the NICU. A study by Sundaram V *et al*, reported an increase in the incidence of neonatal sepsis caused by *S. aureus* while a decreased incidence due to gram negative bacilli [16]. The incidence of CoNS causing NS is increasing now a day's, a finding which is also supported by our study with *CoNS* as the second most predominant organism isolated [12-16]. It may be attributed to CoNS known for biofilm formation, which aids not only in the colonization of intravascular devices but also tissues, and may also allow the organism to persist in hospital environments.

On contrary, many authors reported gram negative bacilli as predominant pathogen implicated in NS [7-9]. In due course, ESBL producing MDR strains evolve under selective drug pressure making the management difficult with the existing empirical treatment regimen [14-18]. In our study predominant gram negative pathogen isolated was *K. pneumoniae* followed by *E. coli.*

Overall, an emergence has been noted for multi drug resistant bacteria causing NS. The widespread and injudicious use of antibiotics is implicated in the evolution of the drug resistance. Analysis of antimicrobial resistance pattern revealed high resistance for various antimicrobials tested among both gram positive and negative organisms as reported by other studies also. More than 50% of the isolates were resistant to most of the commonly prescribed drugs i.e. penicillin, gentamicin and ciprofloxacin.

Among gram positive isolates, resistance as high as (53.3%) for ampicillin, for amoxyclav (46.7%), ciprofloxacin (70%), and gentamicin (50%), was observed. Nil resistance was observed for vancomycin and linezolid. Gram negative isolates also showed high resistance towards amoxyclav (70%), ciprofloxacin (80%), and cotrimoxazole (70%). This alarming level of resistance towards ciprofloxacin, which is commonly used in many empirical treatment regimens, is a matter of serious concern. As far as resistance in other antimicrobial agents is considered, amikacin (26.7%) fared better than gentamicin (66.7%), and piperacillin-tazobactam combination (13.3%) than amoxyclav (70%). Carbapenems emerged as the most effective drug against MDR gram negative organisms.

It is evident from the study that the existing empirical treatment options needs to be revised as high resistance levels has been noted for ciprofloxacin, gentamicin and penicillin. Ciprofloxacin and

gentamicin should no longer be included in empirical treatment regimen due to development of high resistance. Instead, other options like 3rd generation cephalosporins, amikacin and piperacillin-tazobactam combination can be used judiciously to combat with the problem of drug resistance and treatment failure. Overall, Imipenem, vancomycin and linezolid were the most effective antimicrobial agents comparatively with statistically significant difference in sensitivity but, these should not be used indiscriminately and kept as reserved options to prevent emergence of MDR strains and treatment failure.

**Conclusion**

Gram positive organisms are emerging as the leading cause of neonatal sepsis. The pathogens implicated in the causation of NS show high level of resistance towards the commonly used antimicrobials apart from development of multidrug resistance. Blood culture, though considered as gold standard but has limitation due to various practical problems. Conversely, the septic screen parameters are non specific in many cases. Hence we need a multidisciplinary approach for better and rapid diagnosis of NS. An accurate diagnosis coupled with prompt institution of effective and appropriate antibiotics along with supportive care are vital in the management of NS. Furthermore, heightened awareness regarding simple prophylactic measures i.e. proper intra & post partum care, clean environment along with maintenance of strict asepsis in nursery and frequent hand washing practices, are required among health care providers to save the lives of our newborns and neonates. There is a need for ongoing surveillance studies to provide data regarding locally endemic antibiotic resistant organisms and to update the existing empirical treatment options for neonatal infections.

**Conflicts of Interest:** None declared.

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