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ORIGINAL ARTICLE

Bacteriological spectrum and antimicrobial susceptibility pattern of neonatal septicaemia in a tertiary care hospital of North India

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Abstract

Background: Neonatal septicaemia is a clinical entity that is characterised by systemic signs and symptoms of infection and accompanied by bacteraemia in first 4 weeks of life and is one of the four leading causes of neonatal mortality and morbidity in India.
Aim: To determine the bacterial spectrum and antimicrobial susceptibility pattern of neonatal septicaemia in a tertiary care hospital of North India.
Materials and methods: In this prospective observational study, 850 blood samples were collected and processed from clinically suspected neonates according to standard laboratory protocol. Antimicrobial susceptibility of the isolates was done by Kirby Bauer disc diffusion method according to Clinical and Laboratory Standard Institution (CLSI) recommendations.
Results: Blood culture reports were positive in 322 (37.8%) cases. Early onset sepsis (EOS) was present in 61.41% and late onset sepsis (LOS) in 38.59% of cases. Gram-negative septicaemia (60.67%) was encountered more than Gram-positive (32.01%). Coagulase negative *Staphylococci* (17.43%) was the predominant isolate followed by, *Klebsiella spp* in 16.11% cases. Best overall sensitivity among Gram-negative isolates was to Colistin (89.94%), Imipenem (86.43%) and Meropenam (77.88%). Gram-positive isolates had good (97.15%) sensitivity to linezolid, (95.23%) vancomycin and (88.57%) Teicoplanin.
Conclusion: Gram-negative organisms are the leading cause of neonatal septicaemia with *Klebsiella spp* being commonest. Coagulase negative *Staphylococci* is the predominant isolate among Gram-positive organisms. Most of the isolates are resistant to common antibiotics.

Keywords

Antimicrobial susceptibility, blood culture, changing bacterial spectrum, neonatal septicaemia

History

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Introduction

Neonatal septicaemia is a clinical entity characterised by systemic signs and symptoms of infection and is accompanied by bacteraemia in first 4 weeks of life. In developing countries, like India, bacterial sepsis is one of the leading causes of neonatal morbidity and mortality, next to perinatal asphyxia and birth injuries [1]. Incidence of neonatal septicaemia in developed countries varies from 1–10/1000 live birth, whereas it is three times more common in India [2]. The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002–03) is 30/1000 live births in India [3].

Incidence differs among hospitals depending on various factors such as obstetric and nursery practises, sex, gestational age, birth weight, out born or inborn status of babies, perinatal care, and health and nutrition of mother [4].

Neonatal sepsis occurs in two distinct patterns based on the age at onset of symptoms, early and late onset sepsis (LOS). Early onset sepsis (EOS) presents within the first 72 h of life and the source of infection is usually the maternal genital tract. Factors like low birth weight and premature neonates, perinatal asphyxia, febrile illness in the mother within 2 weeks prior to delivery, foul smelling and/or meconium stained liquor, rupture of membranes >24 h, and prolonged labour (sum of 1st and 2nd stage of labour >24 h) are the common risk factor for EOS.

LOS usually presents after 72 h of age and the source of infection is either nosocomial (health care personal or community-acquired). Various factors that predispose to an increased risk of nosocomial sepsis include very low birth weight or extremely low birth weight, prematurity, admission in intensive care unit, mechanical ventilation, invasive procedures, central lines, use of broad spectrum antibiotics, drugs like steroids and proton pump inhibitors, necrotising enterocolitis, prolonged fasting and administration of parenteral fluids. Factors that increase the risk of community-acquired LOS in the neonatal period include poor hygiene, poor cord care, bottle-feeding and pre-lacteal feeds. Prevention of these potential risk factors would help in reduction in incidence of neonatal sepsis [5].

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The spectrum of presentation of neonatal sepsis is varied and includes hypothermia, fever, lethargy, poor cry, refusal to suck or poor feeding, off colour, poor perfusion, shock, absent neonatal reflexes, bradycardia/tachycardia, respiratory distress, hypo/hyperglycaemia and metabolic acidosis. The aetiology of septicaemia is multi factorial. Neonatal sepsis is caused by a variety of Gram-positive as well as Gram-negative bacteria and sometimes yeasts [6].

Group B *Streptococci* is a common cause of neonatal sepsis in developed countries [7] but infrequent in India and other tropical countries where *Staphylococcal aureus, Klebsiella spp, Escherichia coli* along with Coagulase negative *Staphylococci,* Coagulase positive *Staphylococci Pseudomonas spp, Enterobacter spp* and *Acinetobacter spp* are the main organisms responsible for neonatal septicaemia [8].

Uncontrolled use of various potent and broad spectrum antibiotics has led to emergence of resistant strains which has become a major problem in various intensive care units. Due to constantly evolving antimicrobial resistant patterns there is the need for constant antimicrobial sensitivity surveillance. This will help clinicians provide safe and effective empirical therapies, develop rational prescription programmes and make policy decisions and finally assess the effectiveness of all [9].

The present study was conducted to determine the risk factors and organisms associated with bacteraemia and to find out susceptibility pattern of pathogens causing neonatal sepsis so as to provide antibiogram to paediatricians for better patient management in our set up.

Method and material

The present prospective observational study was carried out on 850 blood samples from neonates with clinical suspicion of septicaemia, admitted in NICU and wards of JK Lon and attached paediatric hospitals. Samples were processed in Bacteriology lab of Microbiology department of S.M.S. Medical College and attached hospitals, Jaipur (Rajasthan) from May 2014–April 2015.

Inclusion criteria: Clinically suspected neonate with history of one or more of following signs & symptoms:

(a) Refusal to feed, poor cry, lethargy.
(b) Fever (>37.5 °C), hypothermia (<36.5 °C).
(c) Diarrhoea, vomiting.
(d) Respiratory distress, apnoea, gasping respiration.

Exclusion criteria:

(1) Neonate with age more than 28 days.
(2) Neonate on Antibiotics.
(3) Neonates developing signs and symptoms of septicaemia after admission to hospital.

The neonatal history including sex, gestational age, birth weight, term or preterm, outborn or inborn was taken. The data regarding maternal risk factor for neonatal sepsis including duration of labour, mode of delivery, maternal fever, chorioamnionitis (foul smelling liquor), maternal urinary tract infection (UTI), and duration of rupture of membrane were collected.

Data were collected in a structured proforma and were classified, analysed & evaluated by using SPSS version 21 for Windows as per aims & objectives.

About 1–2 ml of venous blood was drawn by a percutaneous venous puncture following strict aseptic precautions (3 swab technique) and aseptically inoculated into blood culture bottles containing 5–10 ml of brain heart infusion broth. Blood culture bottles were incubated at 37 °C overnight aerobically. Primary subcultures were done after 24 h of incubation on to Blood agar & Mac-Conkey agar. If no growth occurred on plates after overnight incubation, bottles were incubated further & followed up by examining the broth daily and doing a final subculture at the end of day [7] or at appearance of signs of growth, whichever was earlier. The positive growth was identified by conventional methods according to the standard laboratory protocol, including colony morphology, Gram's staining & biochemical reactions.

After the identification of bacteria, antimicrobial susceptibility testing was done by Kirby-Bauer disc diffusion method on Muller Hinton agar as per Clinical and Laboratory Standards Institute (CLSI) guidelines [10]. The antibiotics which were used in our study were based on the standard protocol of the hospital and departmental policies (as per CLSI).

Results

During the study period, a total of 850 neonates with clinical sepsis were studied. The various baseline characteristics of the study cohort including risk factor for neonatal sepsis are included in Table 1. Blood culture positivity was found in 322 cases (37.8%) while 528 (62.20%) were blood culture negative. Bacterial species were found in 298 (92.54%) and Candida species in 24 (7.45%) cases. Six cases of neonatal septicaemia out of 298 bacterial culture positive cases were of poly-microbial aetiology. Out of 322 culture positive cases, there were 205 (68.79%) male and 93 (31.21%) female neonates with the male-to-female ratio of 2.2:1. Early-onset sepsis (EOS) cases were found to be higher than LOS. A total of 183 neonates (61.41%) had EOS and 115 (38.59%) had LOS. Incidence of septicaemia was higher in preterm neonates (70.47%) as compared to term (29.53%).

Among culture positive cases, 89 (29.86%) were of low birth weight, 124 (41.61%) were of very low birth weight, and 22 (7.38%) were of extreme low birth weight. Normal birth weight was found in 63(21.14%) cases. So incidence of neonatal septicaemia was higher in very low birth weight neonates compared to normal birth weight.

Culture positivity was high in outborn 203 (68.13%) neonates than inborn 95 (31.87%) neonates. Refusal to feed was commonest clinical presentation in 26.51% cases followed by respiratory distress (24.16%), congenital pneumonia (16.77%), fever (7.71%) and poor cry (7.71%).

Of the various maternal risk factors affecting neonatal septicaemia, rupture of membranes for more than 18 h was the commonest factor with 21.85% cases followed by maternal UTI in 16.39%, foul smelling liquor in 13.66%, febrile illness in 14.75% and prolonged and difficult labour in 6.56% cases.

Detailed aetiology of the 304 (292 single + 6 polymicrobial) bacterial culture positive isolates is provided in Table 2. These included Gram-negative bacilli (199/304, 65.46%) and Gram-positive cocci (105/304, 34.54%). Coagulase Negative

Table 1. Baseline characteristics of the study cohort (n=850).

Sl. no.	Characteristics	Number	Percentage (%)
1	Mean birth weight (gram)	2025 ± 50	
2	Mean gestational age(weeks)	34.5 ± 1.6	
3	Male sex	603	71
4	Mode of delivery (Caesarean section)	354	41.6
5	Prolonged premature rupture of membrane (PPROM) > 18 h duration	200	23.5
7	Maternal fever	158	18.6
8	Maternal foul smelling liquor (chorioamnionitis)	138	16.2
9	Maternal urinary tract infection	164	19.25
10	Prolonged and difficult labour	82	9.65
11	Outborn	610	71.8
12	Preterm	614	72.3

Table 2. Distribution of bacterial isolates (n=304).

Sl. No.	Organism	Positive bacterial culture	
		Number	Percentage (%)
1	Coagulase Negative *Staphylococci*	53	17.43
2	*Klebsiella spp*	49	16.11
3	*Enterobacter cloacae*	34	11.18
4	Coagulase Positive *Staphylococci*	31	10.19
5	*Pseudomonas spp*	29	9.53
6	*Acinetobacter spp*	28	9.21
7	*Enterococcus spp*	21	6.90
8	*Enterobacter aerogenes*	22	7.23
9	*Escherichia coli*	19	6.25
10	*Burkholderia spp*	12	3.94
11	*Hafnia spp*	04	1.31
12	*Citrobacter spp*	02	0.65

Table 3. Antibiotic sensitivity pattern of Gram-positive bacteria (n=105).

Sl. No.	Antibiotic	Number of isolates	Percentage sensitive (%)
1	Ampicillin	27	25.71
2	Amoxicillin-clavulanic acid	31	29.52
3	Cefotaxime (n=84)	30	35.71
4	Cefoxitin	46	43.80
5	Ceftazidime (n=84)	12	14.28
6	Ciprofloxacin	63	60.00
7	Gentamycin (n=84)	65	77.38
8	Linezolid	102	97.15
9	Piperacillin/Tazobactum	63	60.00
10	Teicoplanin	93	88.57
11	Vancomycin	100	95.23

Staphylococci (17.43%) was the commonest bacterial isolate followed by *Klebsiella spp* (16.11%), *Enterobacter cloacae (11.18%),* Coagulase positive *Staphylococci* (10.19%), *Pseudomonas spp* (9.53%), *Acinetobacter spp* (9.21%), *Enterococcus spp* (6.90%) *Enterobacter aerogenes* (7.23%), *Escherichia coli* (6.25%), *Burkholderia spp* (3.94%), *Hafnia spp* (1.31%) and *Citrobacter spp* (0.65%).

Gram-positive organisms showed highest sensitivity to linezolid (97.15%) followed by vancomycin (95.23%), and teicoplanin (88.57%) and least sensitivity to ceftazidime (14.28%) (Table 3).

Gram-negative organisms showed good sensitivity to Colistin, Imipenem and Meropenam that is 89.89, 86.43 and 77.88%, respectively. Cephalosporins showed poor sensitivity (Table 4).

Discussion

Neonatal septicaemia is one of the most important causes of neonatal morbidity and mortality. The causative organisms in neonatal sepsis vary from place to place and the frequency of the causative organisms is different in different hospitals and even in the same hospital at different time [11]. For the effective management of neonatal septicaemia cases, study of the bacteriological profile with their antibiotic pattern plays a significant role.

Table 4. Antibiotic sensitivity pattern of Gram-negative bacteria (n=199).

Sl. No.	Antibiotic name	Number of isolates	Percentage sensitive (%)
1	Amikacin	115	57.78
2	Cefepime	45	22.61
3	Cefotaxime	44	22.11
4	Ceftazidime	39	19.59
5	Ciprofloxacin	109	54.77
6	Colistin	179	89.94
7	Gentamycin	91	45.72
8	Imipenem	172	86.43
9	Meropenam	155	77.88
10	Ofloxacin	126	63.31
11	Piperacillin/Tazobactum	117	58.79
12	Polymyxin-B	140	70.35

Out of the 850 clinically suspected cases of sepsis in our study, 322 were culture positive with a blood culture positivity rate of 37.80%. According to previous studies blood culture positivity in neonatal septicaemia varies from 18.8 to 64.87% [12]. Our results are comparable with studies conducted by Shah et al. (31.57%) [13], Dias and Vigneshwaran (32%) [14] and Mahapatra et al. (40%) [15], whereas study conducted by Jyothi et al. (19.20%) [16], Rathod et al. (17.09%) [17], and Bhat et al. (17.80%) [18] showed very low positivity. Low positivity might be due to administration of antibiotic before blood collection, possibility of infection with anaerobes or presence of fastidious organisms or because amount of blood sample taken for culture.

We evaluated predisposing factors contributing to neonatal septicaemia, like sex, gestational age, birth weight, outborn or inborn status of babies and maternal risk factors. In the present study males (68.79%) were affected more than females (31.21%) with male to female ratio of 2.2:1 which was similar to finding of Kavita Nimboor et al. [4], Sharma et al. [19], and Garg et al. [20]. Male preponderance may be linked to the X linked immune-regulatory gene resulting in susceptibility to infections.

Preterm neonates are more prone to septicaemia because of the immaturity of immune system as compared to full term babies and also because they are more prone to be admitted in nursery after birth and have various interventions done because of their sickness. In our study, blood culture positivity was found more in preterm neonates (70.47%) than full term (29.53%). Our results are similar to other studies by Rajendraprasad et al. [21] and Shah et al. [13] , who reported 67.37 and 70% rates, respectively in preterm babies.

Khatua et al. [22] stated that low birth weight neonates have low IgG level and are more susceptible to infections. In our study septicaemia was more common in very low birth weight neonates (41.61%) followed by low birth weight (29.86%), which was similar to Rajendraprasad et al. [21] with 43.16% very low birth weight and 32.63% low birth weight.

In our study, 68.13% of outborn neonates developed septicaemia as compared to only 31.87% inborn neonates, which is similar to study by Rajendraprasad et al. [21], indicating septicaemia as a community acquired infection.

Incidence of EOS is more than LOS due to immature immunologic response of neonates in the first week of life, making them more susceptible to infection in this period. We found in our study that EOS 61.41%) was more common than LOS (38.59%). Our findings are compatible with the reports from the others. Higher incidence of EOS was reported by Sheth et al. (56.52%) [23] and Nayak et al. (70.66%) [24].

Of the various clinical presentations of neonates with suspected septicaemia, our study revealed that refusal to feed was the commonest presentation followed by respiratory distress, congenital pneumonia, fever and poor cry. Study by Kavita Nimboor et al. [4] and Garg et al. [20] showed similar results. This indicates that refusal to feed is the most important and earliest symptom to suspect neonatal septicaemia and it should not be ignored.

Of the various maternal risk factors of labour and delivery, our study showed duration of rupture of membrane of more than 24 h as a commonest factor associated with neonatal septicaemia with 21.85% cases followed by maternal UTI in 16.39%, febrile illness in 14.75% cases and foul smelling liquor in 13.66% cases. Similar results were reported by Roy et al. in their study [25].

Gram-negative septicaemia (60.67%) was encountered more than Gram-positive (32.01%) in the present study which is comparable to studies conducted by Tsering et al. [26], Shah et al. [27] and Nayak et al. [24] with 61, 67.17 and 61.33% cases of Gram-negative septicaemia, respectively.

In this study Coagulase negative *Staphylococci* (*CoNS*) (17.43%) was the predominant isolate followed by, *Klebsiella spp* in 16.11% cases. *CoNS* is normally considered as a skin contaminant when isolated from blood. The presence of this bacterium in blood in critically ill babies, should be considered as significant and should be treated, as the clinical manifestation of *CoNS* sepsis can be varied. In our study, we considered *CoNS* as a true pathogen because the antibiotic sensitivity pattern of our *CoPS* and *CoNS* isolates was almost similar and they correlated clinically. Moreover the samples were collected with proper sterile precautions, so the chances of contamination with skin flora were minimal.

Among Gram-negative bacteria, we found *Klebsiella spp* (24.62%) as commonest followed by *Enterobacter cloacae* (17.08%), similar to study by Chug et al. [28] and Sharma et al. [19], who reported *Klebseilla spp* as a predominant Gram-negative bacteria.

In our study *CoNS* was the commonest (50.47%) isolate among Gram-positive cocci. This is in accordance to study by Dias E and Vigneshwaran et al. [14] and Ballot et al. [29] in which *CoNS* was the commonest isolate among Gram-positive organisms.

In the present study, it was observed that Gram-negative bacteria causing EOS (71.58%) outnumbered Gram-positive bacteria (28.41%). *Klebsiella spp* (16.93%) was predominant isolate from EOS cases. Similar results were reported by Rahman et al. [30] and Shaw et al. [31]. Among LOS cases *CoNS* (24.34%) was the commonest isolate followed by *Klebsiella spp* (15.65%), which is supported by Raghunath [32] and Abd Hafez et al. [33].

In our study antibiotic susceptibility revealed that majority of Gram-negative bacteria were sensitive to Colistin (89.94%), Imipenem (86.43%) and Meropenam (77.88%) which is comparable to study be Jyothi et al. [16]. Among aminoglycosides maximum sensitivity was seen to Amikacin

(57.78%) which is in line with Madavi et al. [34]. Least sensitivity was seen to extended spectrum cephalosporins in our study.

In our study Gram-positive bacteria showed good (97.15%) sensitivity to linezolid, (95.23%) vancomycin and (88.57%) teicoplanin, which is comparable to study by Jagoo et al. [35], Shah et al. [13], and Sheth et al. [23]. All the isolates of *Staphylococcus* were 100% sensitive to linezolid and vancomycin, whereas *Enterococcus spp* showed 95.23% sensitivity to linezolid and 85.71% to vancomycin. Vancomycin resistant *Enterococcus spp* were reported in our NICUs. This could be a problem since these bacteria are resistant to all available antibiotics and have the potential of being reservoirs for glycopeptide-resistant genes that can be transferred to other more virulent pathogens. Sensitivity to ceftazidime (14.28%), Ampicillin (25.71%) and Amoxicillin-clavulanic acid (29.52%) was lowest among Gram-positive bacteria in present study.

Multi drug resistance to antimicrobial agents was found in the present study. Cefoxitin resistance was seen in 56.20% of Gram-positive isolates with 41.51% strains of *CoNS*, 61.30% of *CoPS* and 85.72% of *Enterococcus spp.* Our results were compatible to study by Shah et al. [13], Sheth et al. [23], and Shah et al. [27] reported MRSA in 26.67, 50, $\geq$50% isolates, respectively. In our study 32.65% strains of *Klebsiella spp* were also multi drug resistant. There is increase in incidence of ESBL organism as the cause of neonatal sepsis both in EOS and LOS, which is very alarming for the practitioner's worldwide [36].

Carbepenams (Imipenem and Meropenam) and Polymyxins were found to be the most potent antimicrobial agents against Gram-negative isolates. Majority of Gram-positive isolates were sensitive to linezolid and vancomycin. Extended spectrum Cephalosporins were found to be least sensitive in present study.

Conclusion

It is evident from present study that Gram-negative organisms are the leading cause of neonatal septicaemia with *Klebsiella spp* being commonest. Coagulase negative *Staphylococc*i is the predominant isolate among Gram-positive organisms. Most of the isolates are resistant to commonly used antibiotics. Resistance to antibiotics is a worldwide problem that causes ineffectiveness of empirical treatment. However, regular surveillance of neonatal septicaemia in order to follow changes in trends of causative organisms and antibiotic sensitivity pattern would be of great help. The higher antibiotics such as carbepenams should be reserved for multi-drug resistant Gram-negative bacteria, whereas vancomycin and linezolid be reserved for drug resistant Gram-positive isolates. Microbiological studies of this type should be done regularly in all hospitals in order to formulate policies on use of antibiotics and to know the changing spectrum of microorganisms responsible for neonatal septicaemia.

Declaration of interest

The authors have no conflicts of interest and no financial relationships relevant to this article to disclose. No external funding was secured for this study.

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