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Original Research Article

Bacteriological profile and antibiotic susceptibility of neonatal sepsis in neonatal intensive care unit of a tertiary care medical institute of Eastern India: A retrospective cross-sectional study

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ABSTRACT

Background: According to WHO neonatal sepsis is the most important reason for morbidity and mortality in the neonatal period. By the knowledge of bacteriological flora and their antibiotic susceptibility pattern, we can decrease the mortality and morbidity. Multidrug antibiotic resistance is also increasing day by day in neonatal intensive care units. So our aim of the study was to find out the bacteriological profile and antibiotic susceptibility pattern in the NICU of Indira Gandhi Institute of Medical Sciences, a tertiary teaching hospital in Bihar.

Materials and Methods: A retrospective analysis of all blood culture positive sepsis cases among neonates admitted to the neonatal intensive care unit of Indira Gandhi Institute of Medical Sciences Patna Bihar from Feb16, 2019, and Feb 15, 2020, was attempted. Neonate with a risk factor of sepsis having positive blood culture was analyzed bacteriologically and antibiotic sensitivity pattern was identified.

Results: Out of 168 neonates admitted in the NICU, Blood culture reports were positive in 60 cases (35.71%). Among the culture-positive cases, there were 34 (56%) males and 26 (44%) females. Late-onset sepsis (LOS, 56%) higher than Early-onset sepsis (EOS, 44%). Organism isolated were Gram-negative bacilli (19/60, 31.6%), Gram-positive cocci (34/60, 56.6%), and yeast-like fungi (7/60, 11.6%). Klebsiella spp. was the most common cause of early-onset sepsis (8/26, 30.7%) and coagulase-negative staphylococci (CoNS) was the most common cause of late-onset sepsis (n= 12/34; 35%). Gram-negative bacteria (GNB) showed the highest resistance to ampicillin (89.47%), All the Gram-negative bacteria isolates were 100% sensitive to colistin. Methicillin resistance was detected in 44% (n=8/18) of coagulase-negative staphylococci and 62% (n=8/13) of Staphylococcus aureus. Vancomycin is sensitive to almost all the isolates of coagulase-negative staphylococci, Staphylococcus aureus, and enterococci.

Conclusions: In our study CoNS and Klebsiella were the most common causes of neonatal sepsis. Most isolated pathogens showed a high degree of antimicrobial resistance, not only to commonly used antibiotics but also to reserve antibiotics such as extended-spectrum cephalosporins and carbapenems. It is also concluded that indiscriminate use of third-generation cephalosporins, may be responsible for the selection of ESBL-producing multi-drug resistant strains in the neonatal intensive-care unit (NICU). Preventive strategies are necessary to decrease the emergence of antibiotic resistance.

1. Introduction

Neonatal sepsis is one of the most common causes of morbidity and mortality in newborns.[1] It is defined as any sepsis diagnosed during the first 28 days of life and further sub-classified as early-onset neonatal sepsis if clinical features of sepsis appeared within the first 72 of life and late-onset sepsis if clinical features of sepsis are presented after 72 hrs of age.[2] In a global scenario

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sepsis incidence of newborns varies between 1- 10 cases per 1000 live births, and the mortality varies between 15-50%.[3] Despite recent advances in the molecular diagnosis of bacterial and fungal sepsis, blood cultures still the mainstay of investigation of sepsis in infants and children.[4] Over the recent few years, multi-drug resistant organisms (MDROs) have been budding as important pathogens that cause sepsis in the NICU, including extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae.[5] The clinical features of neonatal sepsis are very much nonspecific and subtle, which makes early diagnosis difficult and which allows a high rate of empiric antibiotic utilization that could contribute to the spread of antimicrobial-resistant strains of bacteria. After the knowledge of causative agents of neonatal sepsis and their antimicrobial sensitivity patterns, we can choose appropriate therapy for neonatal sepsis. Appropriate antibiotic therapy according to sensitivity pattern plays a major role in the reduction of antimicrobial resistance.[6,7]

The objective of this study was to know the prevalence and etiology of neonatal sepsis and to provide antimicrobial susceptibility patterns in the neonatal intensive care unit of the Indira Gandhi Institute of Medical Sciences, Patna.

2. Materials and Methods

Neonates admitted to the NICU of Indira Gandhi Institute of Medical Sciences Patna between Feb16, 2019, and Feb 15, 2020, with clinical features of sepsis and who had a positive blood culture were retrospectively analyzed. Indira Gandhi Institute of Medical Sciences is an apex centre for medical care in Bihar. Here the super-specialty department is running and doing well for 20 years. Pediatric is a budding department here and we recently started our well-equipped NICU one year before.

One hundred and sixty-eight cases of suspected neonatal sepsis were enrolled at the neonatal intensive care unit of IGIMS, Patna. Sepsis was assumed in the presence of lethargy, feeding intolerance, temperature instability, respiratory distress, hemodynamic instability, seizure, hypotonia, bleeding diathesis, low birth weight (< 2500 g), history of bag-mask ventilation, rupture of amniotic membrane for more than 18 h (PROM), increased capillary refill time >3 sec, antepartum fever, foul-smelling liquor and repeated (≥3) unclean per vaginal examinations were considered as risk factors for neonatal sepsis. Neonates already on antibiotics, Major congenital anomalies, surgical cases, Refusal of informed consent by parents for blood draws are excluded from the study.

A blood sample was collected for culture from each neonate immediately after enrolment and before initiation of antibiotics. Blood culture sample included a single sample collected from a peripheral vein or artery under aseptic conditions. The local site was cleansed with 70% alcohol and povidone-iodine (1%), followed by 70%alcohol again. About 2ml of blood was inoculated into BacT/ALERT® PF Culture Bottles and processed using the BacT/ALERT® 3D 240 Microbial Detection System. The machine works on calorimetric technology. Antimicrobial neutralization resins were added in the bottles which help to minimize the false-negative results. Positively identified bottles were subjected to gram's stained and subculture on 5%sheep blood agar, chocolate agar and, Mac Conkey agar plates and put for overnight incubation at 37^0C.

Antibiotic sensitivity testing was performed on Mueller-Hinton agar (MHA) plates by the modified Kirby-Bauer disk diffusion method as per the Clinical Laboratory Standard Institute (CLSI) guidelines 2016.[8] The drugs for disc diffusion testing were in the following concentrations: Ampicillin (30μg), Amoxycillin Clavulanic acid (20/10μg), Piperacillin/Tazobactum (100/10μg), Imipenem (10μg), Meropenem (10μg) Tobramycin (30μg) Teigecyclin (10μg), Gentamycin (10μg), Ciprofloxacin (5μg), Levofloxacin (5μg), Co-trimoxazole (25μg-1·25 μg trimethoprim/23·75 μg sulfamethoxazole), Cefotaxime (30μg), Ceftazidime (30μg), Colistin (10μg), Penicillin (10 Unit), Cefoxitin (30μg), Erythromycin (15μg), Linezolid (30μg), Vancomycin (30μg), Clindamycin (02μg), Novobiocin (30μg), Piperacillin (100μg), Amikacin (30μg).

After getting blood culture, empiric antibiotics Ampicillin, and Amikacin (first-line therapy) are intravenously started according to our NICU protocol. If there is no clinical response after 72h, antibiotics are upgraded to intravenous Cefotaxime and vancomycin (second line) or Meropenem and Colistin (third line).when the blood culture reports came we select antibiotics according to culture report.EOS is defined as the onset of clinical features of infection within 72 h of life and the LOS, clinical features present after 72 h of life.[2,9] As per international standard definitions, multidrug-resistant (MDR) strains were defined for acquired resistance and relative to the panel of antibiotics tested for each isolate, as in vitro non-susceptibility to ≥1 agent in ≥3 antimicrobial categories: Penicillins, Cephalosporins, Beta-lactamase inhibitor combinations, Fluoroquinolones, Aminoglycosides, Chloramphenicol, Folate pathway inhibitors, Tetracyclines, Macrolides and Glycopeptides.[10]

Data analysis was done using Statistical Package for Social Sciences (SPSS) software version 25.0. Microbiology laboratory blood culture registers were reviewed and all blood culture positive neonates were identified. The level of significance for tests was set at $P < 0.05$. Microsoft Excel was used for totaling, percentage, and frequency.

3. Results

A total of 168 newborns with clinical sepsis were admitted during the study duration. Blood culture reports were

positive in 60 cases (35.71%). Among the culture-positive cases, there were 34(56%) male and 26(44%) female neonates, with the male to female ratio of 1.3:1. Late-onset sepsis (LOS) cases were found to be higher than Early-onset sepsis (EOS). Out of 60 culture-positive cases, 34(56%) had Late-onset sepsis and 26(44%) had Early-onset sepsis (EOS). Among the neonate birth weight, less than 2500 g is found in (40) %. In the EOS group, majority are preterm neonates which are 73%. Thirty percent had a maternal history of PROM which was common among the EOS group.

General characteristics of newborn shown in Table 1.

Out of 60 blood culture-positive cases Gram-negative bacilli (19/60, 31.6%), Gram-positive cocci (34/60, 56.6%) and yeast-like fungi (7/60, 11.6%). Klebsiella spp. and Coagulase-negative staphylococci (CoNS) were the most common Gram-negative and Gram-positive organisms. The most common organisms isolated from blood cultures were Coagulase-negative staphylococci [Co NS] (18/60, 30%), Staphylococcus aureus (13/60, 21.6%), Klebsiella spp. (12/60, 18%), and yeast-like fungi (7/60, 11.6%) (Table-2).

Klebsiella spp. was the most common cause of early-onset sepsis (8/26, 30.7%) and CoNS was the most common cause of late-onset sepsis (n= 12/34; 35%).

Among GNB isolates Klebsiella spp. were predominant (12/19, 63%) followed by Escherichia coli (2/19, 10.5%) and Acinetobacter baumannii (2/19, 10.5%). Escherichia coli was distributed equally among EOS and LOS. All the Acinetobacter baumannii was recovered from LOS. Other GNB isolates were Proteus mirabilis (1/19, 5%), Pseudomonas aeruginosa (1/19, 5%), and Citrobacter spp. (1/19, 5%). Proteus mirabilis and Citrobacter spp. were isolated from EOS cases while Pseudomonas aeruginosa was isolated from LOS cases. (Table 2)

Antimicrobial sensitivity and resistance patterns were assessed for all 60 isolated bacteria from blood culture. (Table 3) present the antibiotic susceptibility patterns of all gram-negative bacilli isolates excluding Pseudomonas aeruginosa. Multidrug resistance organisms (MDROs) constituted the majority of sepsis episodes after the exclusion of sepsis episodes caused by yeast-like fungi and CoNS, and those included ESBL-PE (extended-spectrum beta-lactamase producing Enterobacteriaceae Klebsiella spp., E. coli, Citrobacter spp. and Proteus mirabilis) MDR Acinetobacter baumannii, and MRSA.

Gram-negative bacilli showed highest resistance to ampicillin (89.47%), cephalosporins [cefotaxime (84%), ceftazidime (79%)], fluoroquinolones [levofloxacin (74%), ciprofloxacin (69%)], amoxicillin-clavulanate (63%) and piperacillin-tazobactam (63%). Less resistance was evident to carbapenems (imipenem 42% and meropenem (42%) and tigecycline (37%). All the GNB isolates were 100% sensitive to colistin (Table 3).

Pseudomonas aeruginosa showed a good antibiotic sensitivity pattern with resistance to aminoglycosides only. Amongst the Gram-positive cocci (n=34) Staphylococcus aureus (13/34, 38%) was the predominant pathogens following CoNS. and was distributed more or less equally among EOS (n=6) and LOS (n=7). Among Gram-positive pathogens, methicillin resistance was detected in 44% (n=8/18) of coagulase-negative staphylococci and 62% (n=8/13) of Staphylococcus aureus. The majority of the coagulase-negative staphylococci and Staphylococcus aureus showed good sensitivity to amikacin and all the isolates of coagulase-negative staphylococci, Staphylococcus aureus, and enterococci isolates were susceptible to vancomycin. A high proportion of GNB isolates were multidrug-resistant. Table 4 shows the comparative antibiotic sensitivity pattern of ESBL and non-ESBL producers.

4. Discussion

Neonatal septicemia is considered the leading cause of infant mortality and morbidity in the NICU. There has been a wide variation in the growth positivity in India; it has ranged from 16% to 54%.[11] Our study, conducted in the NICU of the Indira Gandhi Institute of medical sciences, showed culture positivity of neonatal sepsis to be 35.71%. A reasonably comparable rate of 31.5% was observed by Ashish Khanna et al.[12] Similar studies conducted by Lakhey and Shreshtha et al showed culture positivity to be 48 and 44.9% respectively.[13,14] Differences in culture-techniques and study designs are the cause of variations in the culture positivity rate of neonatal sepsis in different studies.

The male predominance is more than female because of the higher proportion of males included in the study. In our study, it was found that late-onset neonatal sepsis 56 % was more common as compared to early-onset neonatal sepsis which was found to be 44 %. Similar data were reported in a study, which reported late-onset neonatal sepsis (LONS) to be 51% as compared to early-onset neonatal sepsis (EONS) of 49%.[15] Even studies from other Asian countries such as China[16] and Korea[17] have shown a predominance of late-onset sepsis. Common clinical presentation recorded in our study was fever, respiratory distress/asphyxia/pneumonia, tachycardia, neonatal jaundice, and Lethargy and or poor cry. Our study has shown a preponderance of Gram-positive cocci (56.6%) among all culture-positive neonatal sepsis cases as compared to Gram-negative bacilli (31.6%) and yeast-like fungi (10.71%). This is in line with the study conducted by Thakur et al in 2016 that reported 60% and 40% of the isolates to be Gram-positive and Gram-negative respectively.[15] With regards to the etiological agents of neonatal sepsis, Staphylococcus aureus 38% (n=13/34) and Coagulase-negative Staphylococci (CoNS) 52.9% (n=18/34) were found to be the most frequently isolated Gram-positive organism which is quite similar

Table 1: Showing General Characteristics of newborns

Variable	EOS group (n-26)	LOS group (n-34)	Total	Percent
Gender		**Neonatal parameters**		
Male	16	18	34	56
Female	10	16	26	44
Gestational age				
Preterm (<37 weeks)	19	08	27	45
Term (>37 weeks)	07	26	33	55
Birth weight				
< 2500 g	16	08	24	40
≥ 2500 g	10	26	36	60
Mode of delivery				
Per Vaginal	17	21	38	63
Caesarean section	09	13	22	36
Maternal parameters				
History of Maternal fever	04	02	06	10
Rupture of membrane >18 h	12	06	18	30
Foul smelling liquor	02	00	02	03
Neonatal-care-related parameters				
Ionotropic support	17	13	30	50
positive pressure ventilation	21	12	33	55
Central line	14	08	22	36

Table 2: Etiological agents are isolated from different types of neonatal sepsis.

Etiological agents	Isolated fromEOS cases	Isolated from LOS cases	Total No.
Gram-Positive Organism			
Staphylococcus aureus	06	07	13
Coagulase-Negative Staphylococci	06	12	18
Enterococcus spp.	01	02	03
Yeast like fungi	02	05	07
Gram-Negative Organism(GNB)			
Escherichia coli	01	01	02
Klebsiella spp.	08	04	12
Pseudomonas aeruginosa	0	01	01
Proteus mirabilis	01	0	01
Citrobacter spp.	01	0	01
Acinetobacter baumannii	0	02	02
Total isolates	26	34	60

Table 3: Antibiotic sensitivity pattern of GNB isolates excluding Pseudomonas spp.

Antibiotics	Sensitive (%) n-19	Resistant (%) n-19
Ampicillin	02 (10.5%)	17 (89.47%)
Gentamycin	07 (36.8%)	12 (63%)
Ciprofloxacin	06 (21%)	13 (69%)
Levofloxacin	05 (26%)	14 (74%)
Cotrimoxazole	06 (31.5%)	13 (68.5%)
Cefotaxime	03 (16%)	16 (84%)
Ceftazidime	04 (21%)	15 (79%)
Amoxycillin-Clavulanate	07 (37%)	12 (63%)
Piperacillin-Tazobactum	07 (37%)	12 (63%)
Imipenem	11 (58%)	08 (42%)
Meropenem	11 (58%)	08 (42%)
Tobramycin	08 (42%)	11 (58%)
Tigecyclin	12 (63%)	07 (37%)
Colistin	19 (100%)	00

Table 4: Antibiotic sensitivity pattern of ESBL-PE & non-ESBL-PE.

	ESBL Producers (n=09)		Non-ESBL (n=05) Producers	
Antibiotics	**Sensitive (%)**	**Resistant (%)**	**Sensitive (%)**	**Resistant (%)**
Ampicillin	0	09 (100%)	01 (20%)	04 (80%)
Gentamycin	02 (22%)	07 (78%)	03 (60%)	02 (40%)
Levofloxacin	02 (22%)	07 (78%)	01 (20%)	04 (80%)
Ciprofloxacin	02 (22%)	07 (78%)	01 (20%)	04 (80%)
Cefotaxime	0	09 (100%)	02 (40%)	03 (60%)
Ceftazidime	0	09 (100%)	02 (40%)	03 (60%)
Cotrimoxazole	01 (11%)	08 (89%)	03 (60%)	02 (40%)
Amoxyclav	03 (33%)	06 (67%)	02 (40%)	03 (60%)
Piperacillin tazobactun	02 (22%)	08 (78%)	03 (60%)	02 (40%)
Imipenem	06 (67%)	03 (33%)	03 (60%)	02 (40%)
Meropenem	06 (67%)	03 (33%)	03 (60%)	02 (40%)
Tobramycin	02 (22%)	07 (78%)	04 (80%)	01 (20%)
Tigecyclin	05 (56%)	04 (44%)	04 (80%)	01 (20%)
Colistin	09 (100%)	0	05 (100%)	0

as compared to a study conducted by Kumar R et al in Bihar.[18] CoNS has been reported in various studies as the most common cause of neonatal sepsis in NICUs.[19,20] The colonization of the skin and nasopharynx by CoNS and S. aureus in health care workers, the invasive procedures, lack of disinfection practice may lead to the transmission of Gram-positive organisms to neonates. In the present study, Klebsiella spp. 63.1% (n=12/19), Escherichia coli 10.5% (n=2/19) and Acinetobacter spp. 10.5% (n=2/19) were the most common Gram-negative isolates. This is similar to the findings reported by Khanna et al. They found in their study the Klebsiella spp. as a predominant pathogen (20.2%) followed by Escherichia coli (14.6%).[12] Resistance to cephalosporins among Acinetobacter baumanni was neither attributed to ESBL production nor AmpC beta-lactamase production but was attributed to some other mechanism of drug resistance.[21,22]

In our study, up to 100% resistance against 3rd generation cephalosporins was observed among the ESBL producing Enterobacteriaceae. This outcome is in agreement with the study done by Islam et al which reported all ESBL positive strains of E. coli were resistant to cefotaxime, ceftazidime, and ceftriaxone.[23] We observed colistin (100% sensitive) as the most sensitive drug (in agreement with the study done by Islam et al)[23] followed by tigecycline (63% sensitive) and carbapenem [60% sensitive (imipenem and meropenem)]. Resistance of ESBL-positive strains to piperacillin-tazobactam (78%), aminoglycosides [gentamycin (78%), tobramycin (78%)], quinolones [levofloxacin (78%), ciprofloxacin (78%)], cotrimoxazole (89%) and cephalosporins [cefotaxime (100%), ceftazidime (78%)] was significantly higher than that of ESBL-negative ones ($p < 0.05$). This outcome is concordant with the study done by Paterson et al in 2005 and Bush et al in 2011.[24,25] ESBL-producing strains appeared susceptible to carbapenem [meropenem (67%), imipenem (67%)]. The current study reported high resistance against ampicillin (100%) and cotrimoxazole (89%) among the ESBL producing isolates. A similar finding has been reported from Benin in 2015, they reported the most effective antibiotics as imipenem (96.4% sensitive) and gentamicin (54.8% sensitive). High resistance was seen among ampicillin (94%) and cotrimoxazole (85.7%).[26] The resistance among imipenem might be due to Metallo-beta-lactamase producers. Tigecycline resistance was detected in 35% (n=6/17) Gram-negative isolates. In our study cesarean delivery is a risk factor of ESBL-PE acquisition which is concordant with other studies on ESBL-PE infection or carriage.[24,25] Cesarean delivery in the hospital is more at risk suggesting handling by health personnel and have generally longer stay in hospital might increase the risk of acquiring ESBL-PE. During cesarean section lack of contact with the maternal vaginal and intestinal flora deprives newborns of maternal vaginal and gut flora exposure and may influence the newborn microbiome development.[27,28]

The retrospective design, small study population, single centered, and limited yield of some pathogens were the limitations of our study. This study showed more incidence of coagulase-negative staphylococci; because its diagnosis was not based on two simultaneous blood cultures also they are commensals of the mucosa and skin in humans and animals. However, we followed strict protocol-driven practices for skin preparation before obtaining blood culture specimens, and the diagnosis of sepsis caused by coagulase-negative staphylococci (CoNS) was made only after a detailed review of the clinical course. Therefore large-scale, multi-centre prospective studies are needed to validate our findings.

5. Conclusions

In this study, Gram-positive cocci predominated being responsible for (34 out of 60) 56.6 % of cases of septicemia in which culture was positive. The percentage of CoNS 52.9% was higher among GPC followed by Staphylococcus aureus. All the MRSA, Enterococcus spp. and Coagulase-negative Staphylococci 100% sensitive to vancomycin. The majority of septic neonates are colonized by ESBL producing GNB and among those colonized with strains secreting ESBL enzymes; the majority was shown to be colonized by ESBL producing strains of Klebsiella spp. Majority of neonatal sepsis case was caused by MDR gram-negative bacilli. It is also concluded that indiscriminate use of third-generation cephalosporins, preterm low birth weight, prolonged mechanical ventilation (≥ 7 days) may be responsible for the selection of ESBL-producing multi-drug resistant strains in the neonatal intensive-care unit (NICU). Simple hygienic measures, such as hand washing practices, the use of sterile equipment, patient cohorts (i.e. grouping patients with similar infections in the same location), and screening of attending staff and mothers for MRSA and ESBL can help prevent the further spread of these resistant strains.

There is a need to improve and emphasize infection control interventions and antimicrobial stewardship because these are cheap inexpensive strategies to control the increase of multi-resistant gram-negative bacteria.

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7. Conflict of Interest

The authors declare they have no conflict of interest.

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