IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 12 Ser.13 (December. 2020), PP 46-52
www.iosrjournals.org

Neonatal Sepsis and their Microbial Spectrum and Susceptibility in a Tartiary Care Hospital of Eastern India

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Abstract:
Background:
Sepsis is one of the most common causes of neonatal morbidity, mortality and disability especially among LBW babies as the organisms responsible for neonatal sepsis are increasingly becoming resistant to commonly used antimicrobials. In view of the above, present study was undertaken to determine the organisms responsible for neonatal sepsis and the drug sensitivity pattern in a Tartiary Care Hospital of Eastern India.
Methods:
This hospital based study was conducted in a tertiary care hospital of eastern India. A total of 112 clinically suspected sepsis cases admitted during January 2017 to June 2018, 60 were found blood culture positive. The blood samples were collected aseptically from the neonates admitted with clinically suspected sepsis. The organisms were identified based on their colony characteristics and biochemical properties. Drug sensitivity patterns of culture positive isolates was done by Kirby Bauer disc diffusion method, using CLSI guidelines for interpretation.
Results:
Of the culture positive babies 53.3% were male, and 35% had early onset sepsis; Gram-negative septicaemia was 53.3%. Average birth weight was 1850±387g. Mean birth weight was significantly lower in early onset of sepsis (1623±300g) than late onset of sepsis (1971±376g). Predominantly gram negative organisms were Klebsiella pneumonia, E.coli, Pseudomonas, Proteus; Gram positive micro organisms were Staphylococcus aureus, Micrococcus and Enterococcus. Present study found antimicrobial resistance was notable; both gram positive and gram negative bacteria are resistant to commonly used antimicrobials.
Conclusion:
Present study recommends Piperacillin-Tazobactam can be used as first line empirical regimen for neonatal sepsis in this region. Further study in larger augmentation may be required to confirm the findings.
Keywords: *Low birth weight babies, neonatal sepsis, newborn, antibiotic resistant, India*

Date of Submission: 14-12-2020 Date of Acceptance: 28-12-2020

I. Introduction:

Neonatal sepsis alludes to summed up bacterial infection recorded by a positive blood culture in the first 28 days of life encompassing different fundamental contaminations of the new born such as septicaemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections. As a rule, superficial infections like oral thrush and conjunctivitis are not generally included under neonatal sepsis [1]. Worldwide estimate noted one out of four (26%) neonatal mortality might be expected to sepsis [2], the prevalence changes from nation to nation and a lot higher in developing countries [3], rate varies from 30 to 50% [4] contingent upon various socio-demographic factors prevailing in those countries [5,6]. It is likewise regular explanations behind admission to neonatal units in developing countries [7]. Prematurity and or low birth weight (LBW) is the most significant neonatal factor predisposing to infection. Preterm babies have 3 to 10 fold higher incidence of infection than full-term normal birth weight infants [8]. A study of more than 32,000 infants reported attack rate for early-onset sepsis by infection with Group B Streptococci (GBS) in newborn with birth weight

less than 1000gm as 26 times that in term newborn infants and accounted for the greatest number of deaths [9]. Indian research group likewise revealed equivalent outcomes which have been traced back to maternal vaginal colonization with Group B Streptococci [10,11]. Sepsis is defined at the onset of age as early onset sepsis (EOS), symptoms presents within the first 72 hours of age. The source of infection for EOS is generally considered as maternal genital tract. On the other hand, late onset sepsis (LOS) defined as onset of symptoms after 72 hours of age and is typically from hospital acquired infections related with neonatal intensive care or may be community acquired infection. This classification is important to determine the most probable organism, method of transmission and aides empiric treatment [12,13]. According to some other experts EOS is defined as the onset of symptoms before seven days of age and LOS is generally defined as the onset of symptoms at ≥7 days of age [14].

The spectrum of organisms that causes neonatal sepsis changes over time and fluctuates from area to area even within the same hospital. This is because of the changing pattern of anti-microbial use and changes in way of life. The local epidemiology of neonatal sepsis should be constantly updated to distinguish changes in the pattern of causative organisms and their susceptibility to different anti-infection agents. Early diagnosis and legitimate management of neonatal sepsis by sound antimicrobial treatment and supportive care can reduce neonatal mortality. Blood culture technique is the best quality level for finding of sepsis however blood culture reports are normally accessible following 48 to 72 hours. There is have to Identify the basic microscopic organisms causing such infections in every hospital and their susceptibility patterns so as to give vital data to timely intervention [15]. Accordingly, the neonatal septicaemia is the leading cause of mortality, morbidity and disability in the low and middle income countries including India. The empirical antimicrobial therapy remains the mainstay viz. Cefotaxime, Gentamycin, Amikacin, Ampicilin etc. and so forth without exacting clinical practice rules and supportive logistics and infrastructures which may result in increasing resistance by indiscriminate use and overuse by treating physicians.

In view of the above situation, present investigation was led to locate the microbial spectrum of culture positive sepsis in low birth weight babies and their drug sensitivity pattern in a tertiary care hospital.

II. Materials and Methods:

This observational hospital study was carried out among consecutive neonates admitted at the Sick Newborn Care Unit (SNCU) of Midnapore Medical College and Hospital during January 2017 to June 2018. During our study period 112 neonates were included in our study after satisfying inclusion and exclusion criteria. Among them 60 neonates found blood culture positive. This hospital caters the need of lower-middle class socio-economic strata. Out 60, 31.7% practices Muslim religion. Moreover 21.7% belongs to indigenous people of India. In general indigenous people of India are considered as socio-economically underprivileged.

Inclusion criteria: a. Age up to 28 days, b. Weight between 1000g to 2500g, c. Clinical sepsis, d. Did not received any antimicrobials for sepsis.

Exclusion criteria: a. Suspected TORCH [(T)oxoplasmosis, (O)ther Agents, (R)ubella (or German Measles), (C)ytomegalovirus, (H)erpes Simplex)] infection, b. Congenital anomaly, c. Significant co-morbidities viz. History suggestive of birth/perinatal asphyxia, Respiratory distress syndrome (RDS), Meconium aspiration syndrome (MAS), symptoms & signs suggestive of other intrauterine vertical infections, d. Neonates outside the above mentioned inclusion criteria.

Ethical approval:

Ethical approval was obtained from Institute Ethics Committee (IEC) of Midnapore Medical College and Hospital, West Midnapore, West Bengal, India well ahead of data collection. Following Helsinki Declaration on research bioethics in letter and spirit, the participants and their caregivers were given the options not to participate in the study if they wished. Inform consent process was followed sincerely with participatory contribution from the caregivers of the neonates. The caregivers of the neonates were individually explained about the purpose of the study including the research question, was ensured about sanctity of the information collated from the data be kept secret and used only for the research purpose. Thus, after proper counselling of the caregivers, written informed consent was obtained from the individual caregivers of the neonates prior to the study.

Clinical examination & Data collection:

A detailed clinical history was elicited viz. antenatal, intranatal and perinatal including details of history of parturition along with the symptoms suggestive of sepsis (duration sickness, feeding difficulties/refusal to suck, weak/feeble cry, lethargy, vomiting, difficulty in breathing, abnormal movement, temperature instability, respiratory distress, jaundice, convulsions, autonomic disturbances etc). This was followed by a thorough general and systemic clinical evaluation was done for signs suggestive of overt

sepsis or impending sepsis viz. abnormal cry, neurological reflex, activity, temperature, heart rate, pallor, cyanosis, jaundice, capillary refill time, respiratory rate, bleeding diathesis, full/bulged fontanelle, abdominal distension, convulsion, hepatosplenomegaly etc. trough a master sheet. Birth weight was made and recorded by digital weighing scale following standard protocol.

Laboratory analysis:

The standard microbiological methods of blood cultures were practiced using the standard technique described by Mackie and McCartney in this study during the process of the blood culture [16]. About one ml of venous blood was drawn by venous puncture following strict aseptic universal precautions as per standard office procedures and inoculated into blood culture bottle infusion broth, a bile broth and Soyabean Casein Digest Medium (Tryptone Soya Broth) - making dilution of 1 in 10. After inoculation, the blood culture bottles were incubated at 37°C under aerobic conditions in the incubator for 7 days. The first subculture was done after 24 hours of incubation, the second subculture on the 3rd day and a final subculture on the 7th day onto Chocolate agar, 5% sheep blood agar and MacConkey agar plates. These inoculated plates were also incubated aerobically in the incubator at 37°C for 24 hours. These plates were observed for growth of microorganisms, were identified macroscopically by their typical colonial characteristics followed microscopically by Gram stain and all applicable standard biochemical tests. The blood cultures which did not yield any microbial growth following three subcultures were reported negative at the end of 7 days.

Drug sensitivity analysis:

Antibiotic susceptibility testing was done for the isolates on Muller-Hinton agar using commercially available discs (Hi-Media) performed by Kirby-Bauer disc-diffusion method, as recommended in the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. This Clinical Laboratory Standards Institute (CLSI) guidelines help us for for interpretation as resistant, intermediate sensitive and sensitive; control strains of *Escherichia coli* ATCC 25922, *Pseudomonas auroginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 25923 were used. The sensitivity pattern of organisms was observed on commonly used antibiotics e.g. Cefotaxime, Amikacin, Ampicillin, Gentamycin, Meropenam, Vancomycin, Piperacilin-Tazobactam, Linezolid, and Azithromycin [17].

Data analysis: The data was cleaned and entered into Microsoft excel spreadsheet. The statistical analysis involved preliminary data inspection, and interpretation. Percentages and student t-test were used in this study to analyze quantitative analysis.

III. Results:

This study attempted to determine the organisms responsible for neonatal sepsis and identify their drug sensitivity pattern by blood culture and antibiotic sensitivity. This study enrolled 60 neonates, whose blood samples were culture positive, as the participants of our study. The isolation of causative organisms and their drug sensitivity pattern was conducted on these isolates earmarked from neonates with sepsis. In the present study, blood culture positivity rate of 53.6% (60/112); out of 60 babies 32 (53.3%) were male and 21 (35%) suffered from early onset sepsis. Gram-negative septicaemia was encountered in 32 (53.3%) of the total culture positive cases. Mean birth weight of the babies was 1850±387g. Mean birth weight for boys and girls were 1860±382g and 1839±397g. Mean birth weight was significantly lower among neonates with early onset of sepsis (EOS) than neonates with late of sepsis (LOS) (1623±300g vs 1971±376g, t=3.656, $p<0.01$).

The organisms causing sepsis (n=60) were predominantly Gram Negative 53.3% of which *Escherichia coli* was16.7%, *Klebsiella pneumonia* was 28.3%, *Pseudomonas* was 5.0%, *Proteus* was 3.3%. Among Gram positive microorganisms, *Staphylococcus aureus coagulase negative* was 16.7%, *Staphylococcus aureus coagulase positive* was 20%, *Micrococcus* and *Enterococcus* was 3.3%. *Candida albicans* contributed 6.7% of all culture positive isolates (figure 1).

Table 1 presents drug sensitivity and registant matrics of microorganisms. It was observed that *E.coli* had shown resistance to cefotaxime (30%), amikacin (40%), Gentamycin (50%) and Ampicillin (50%). Whereas, Piperacilin-Tazobactam, Meropenam, Azithromycin showed 100% sensitivity.

Klebsiella pneumonia showed resistance to Cefotaxime (41%), Amikacin (41%), Gentamycin (59%), Ampicillin (65%), Piperacilin-Tazobactam (6%), respectively. It was noted that 100% sensitivity to Meropenam. While 94% sensitivity to Piperacilin-Tazobactam.

Staphylococcus aureus coagulase positive (COPS) had resistance to antibiotics as cefotaxime (41.7%), amikacin (41.7%), gentamycin (16.6%), ampicillin (66.7%), vancomycin (16.7%%). About 58.3% and 66.7% sensitive to Piperacilin-Tazobactam and Meropenam.

Staphylococcus aureus coagulase negative (CONS) showed resistance to antibiotics: Cefotaxime (40%), Amikacin (30%), Gentamycin (40%), Ampicillin (50%), Piperacilin-Tazobactam (10%), Vancomycin (10%) and Azithromycin (10%), respectively.

Pseudomonas shows high resistance to antibiotics like Cefotaxime, Amikacin, Gentamycin, Ampicillin and 100% sensitive to Piperacilin-Tazobactam and Meropenam. *Enterococcus* was resistant to Amikacin and sensitive to other antibiotics. In our study, *Micrococcus* found no resistance to all antibiotics tested. The study also found the *Proteus* was high resistance to Cefotaxime, Ampicillin and Meropenam. Moreover, the study found *Candida albicans* was 100% sensitive to Fluconazole, Ketoconazole and Itraconazole.

IV. Discussions:

Research groups are unanimous that for the best outcome of interventions in the neonatal septicaemia systems approach is needed. This will entail high index of suspicion of the attending primary care clinician through referred paediatrician and supportive optimum quality of laboratory support of to find the microbiological profile followed by the antimicrobial sensitivity/ resistance pattern. Research groups are unanimous that the neonatal sepsis is an imperative determinant among all-cause deaths of the newborns worldwide. In regards to the causative pathogens, gram-positive bacteria are found to be the most common pathogens isolated in Very low birth weight (VLBW) infants diagnosed with LOS. While in VLBW infants with EOS, gram-negative pathogens are reported more frequently as the causative organisms. Fewer studies showed that gram-positive bacteria are still common pathogens in VLBW infants with EOS relating that to nosocomial infection [13]. A study from north-east India reported 363 clinical cases of sepsis, blood culture positivity rate was 22 % and Gram-negative septicaemia was 61% of these culture positive cases [18].

Internationally, LOS affects around 25 % of VLBW infants; the incidence increases with decreasing birth weight and gestational age. Infants of lower gestational age and birth weight are more likely to have multiple episodes of sepsis as well. The spectrum of organisms causing LOS included Gram-positive, Gram-negative organisms and fungal infection with a predominance of bacterial causes. The most common organisms reported in the literature which cause LONS are *coagulate negative Staphylococci* (CONS). Two decade ago, a reported that the rate of neonatal sepsis in their unit affected around 41% of VLBW infants [19].

In our study, male neonates (53.3%) admitted for neonatal sepsis has outnumbered the females (46.7%), with a male, female ratio of 1.1:1. Male gender has been noted as the known risk factor in the occurrence of sepsis; 2 to 6 fold higher rate of infection has been found in male babies compared to female babies. Other international research groups also had reported comparable that male babies were more susceptible to sepsis than female babies [20, 21,22]. Thus this observation of our study can correlated with their previous study. The high predilection of male babies for neonatal sepsis may be due to the fact that X-chromosome is potentially more immune in comparison to Y-chromosome or probably due to extra vigilance of parents toward their male babies in our country [23].

In our study incidence of LOS was higher than EOS (68.3% & 31.7%). This observation correlates with earlier studies where they also reported late onset sepsis were 75% and 66.9%, respectively [15,24]. Whereas, Motara et al reported late onset sepsis accounted for 94.3% in their study [25]. Our study differs with highly percentage of EOS seen in studied by Tellur et al and Roy et al, corresponding value of their study was 83.47% and 71.3%, respectively [26, 27]. This could be due to ascending infection following prolonged rupture of membrane or during the passage of baby through infected birth canal [28]. PROM was the most common maternal risk factor associated with neonatal sepsis in the present study, constituting 40.62% followed by MSAF (27.1%) and multiple pervaginal examination (12.5%). Among the neonatal risk factors prematurity (57.3%) was the most common in our study. Earlier study also documented a similar result [7].

Most common organism was isolated in blood culture was gram negative organisms viz. Klebsiella sp (28.3%), E.coli (16.7%) and Gram positive organisms e.g *Staph.aureus Coagulase positive* (20%), *Staph.aureus Coagulase negative* (16.7%). Overall gram-negative organisms were the leading cause of neonatal sepsis. Earlier studies from India have reported gram-negative organisms as the most frequent cause of neonatal septicaemia and Klebsiella is the most common species [28], [29]. *Staphylococcus aureus* was the predominant gram-positive (COPS) organism followed by gram-negative (CONS) in our series; reported literature supported our observations [29,30].

Candida was the only fungal species isolated in 4 cases (6.7%) in our series. This observation of our study is comparable to Indian researchers who had documented fungal infection in their study on preterm babies with Candida as the only isolated fungal organism [31].

The organism isolated in our study also correlates well with NNPD report 2002, Klebsiella was the most common cause followed by staph aureus [1]. Klebsiella pneumoniae showed higher sensitivity to antibiotics like Meropenam, Piperacilin-Tazobactam; showed high degree of resistance to Cefotaxime (41%), Amikacin (41.1%), Gentamycin (58.8%), Ampicillin (64.7%). Similar observation was found by Nazer et

al that resistance to Cefotaxime (42.3%), Amikacin (57.7%), Ampicillin (76.8%) [32]. Mahmood and colleagues in their study showed Klebsiella pneumonia was 90.4% resistance to Gentamycin [33]. Whereas, Movahedian et al reported Klebsiella pneumoniae shows high degree of resistance to commonly used antibiotics like Cefotaxime, Gentamycin, and Ampicillin [34].

CoPS showed resistant to antibiotics Cefotaxime (41.7%), Amikacin (41.7%), Gentamycin (16.6%), Ampicillin (16.7%), Vancomycin (16.7%), Piperacilin-Tazobactam (41.7%) and Meropenam (33.3%). Antibiotics like Meropenam, Vancomycin, Piperacilin-Tazobactam, Linezolid show sensitivity to Gram positive CONS in a range between 90% to100%. This results of study correlates with other studies. Nazer et al and Kairavi et al reported in their study that Gram positive CoNS organisms were having 100% sensitivity to Vancomycin [32, 35]. A study found CONS are highly sensitive to Vancomycin and Piperacilin-Tazobactam (88.9%) [36]. Resistance to Amikacin (30%), Cefotaxime (40%), Ampicillin (50%), Gentamycin (40%) shown by CoNS organisms. Previous study reported that Gram positive organisms displayed a high degree of resistance to Penicillin and Cephalosporin group of antibiotics. Drug sensitivity pattern of E.coli to Cefotaxime (60%), Amikacin (60%), Gentamycin (50%), and Ampicillin (50%) [37]. A recent study documented sensitivity to antibiotics for Gram Negative organisms such as E.coli to Cefotaxime (8.07%), Amikacin (15.07%), Gentamycin (13.9%), and Ampicillin (8.9%) [14]

Present study found that Pseudomonas have drug resistance to Cefotaxime (66.7%), Amikacin (66.7%), Gentamycin (66.7%), Ampicillin (100%). Highly sensitive antibiotics for Pseudomonas are Piperacillin-Tazobactam and Meropenam. A recent study reported Pseudomonas has resistance to Cefotaxime (56.4%), Amikacin (78.2%), Gentamycin (89.1%), Ampicillin (67.3%) and most sensitive drug is Piperacillin-Tazobactam (55.6%) [14].

Antibiotics resistance is a global rising problem. The antibiogram pattern differs from region to region and country to country day by day upon the vulnerability of epidemiology of neonatal sepsis. The present study shows high degree of resistance to commonly used antibiotics to gram negative and gram positive organisms. Resistance is shown to antibiotics like Cefotaxime, Amikacin, Ampicillin, Gentamycin. The increase resistance in Aminoglycosides and third generation cephalosporins are alarming as they are being used in many set-up as empirical therapy. In this study, Piperacillin-Tazobactam, Meropenam, Linezolid, Azithromycin,Vancomycin are highly sensitive to organisms. Higher susceptibility to Vancomycin, Piperacillin-Tazobactam, Meropenam can justify its use. Timely use of these antibiotics will definitely reduce mortality and morbidity in SNCU but these drugs should not be used indiscriminately and kept as a reserve drug otherwise resistance may develop. Hence, the changing antibiotic susceptibility needs continuous monitoring and re-evaluation for putting forth the guidelines for empirical treatment in SNCU. Further, full coverage in a high quality antenatal and perinatal care with 100 % institutional delivery can definitely reduce neonatal sepsis arising out of all the maternal and neonatal risk factors prophylactically [38, 39, 40].

It is important to keep information of prevailing strains and the antimicrobial sensitivity pattern in the area or institute is mandatory for each health care centre because temporal changes in the causative organisms and their susceptibility to common antibiotics. Periodic evaluation not only reveals the recent trend of increasing resistance to commonly used antibiotics yet additionally helps in implementation of a rational empirical therapy. There is an increasing trend of antibiotic resistance to the commonly used first line drugs due to aimless and improper utilization of antibiotics. The pattern of sensitivity is changing henceforth continuous surveillance for antibiotic susceptibility is expected to ensure correct empirical therapy before blood culture reports are available.

Strength of the study:

Census population of the low birth weight neonates admitted in SNCU and satisfying inclusion and exclusion criteria were included in this study to find out the microbial spectrum of culture positive sepsis and their drug sensitivity pattern in a tertiary care hospital by blood culture and antibiotic sensitivity

Limitation of the study:

Among the neonates admitted in this time period with symptoms suggestive sepsis, we excluded all extremely low birth weight neonates (ELBW) and all babies weighing above 2.5kg. Neonates with congenital anomaly or with signs and symptoms suggestive of intrauterine vertical infection and those with history of perinatal asphyxia were also excluded. Both maternal and neonatal risk factors for sepsis were not evaluated.

Future directions of the study:

In future we hope to organize studies on neonatal sepsis as multicentric study to find out epidemiologic pattern of infection in this part of our subcontinent.

V. Conclusion:

After analysing resent study, Piperacillin-Tazobactam can be recommended as first line empirical regimen for neonatal sepsis. Moreover, blood culture is gold standard investigation for neonatal sepsis. There is scarcity of this facility in many district & sub-divisional hospital. So, provision to provide sophisticated blood culture equipment and other logistics for early blood culture report to all district & sub-divisional hospital will be helpful for better management of neonatal sepsis.

Funding: None
Conflicts of interest: None
Acknowledgement: Authors are gratefully acknowledged to the authority of Midnapore Medical College & Hospital and all staff member of Pediatric Department. Authors are also indebted to the caregiver of the neonates to help us collect data and complete the study.

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Table 1: Drug sensitivity of micro-organisms

Micro Organisms	Cefotaxime		Amikacin		Gentamycin		Ampicilin		Pipe+Tazo		Meropenam		Vancomycin		Azithromycin		Linezolid	
	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S
E.coli N=10	3 (30)	7 (70)	4 (40)	6 (60)	5 (50)	5 (50)	5 (50)	5 (50)	0	10 (100)	0	10 (100)	-	-	0	10 (100)	-	-
Klebsiella N=17	7 (41)	10 (59)	7 (41)	10 (59)	10 (59)	7 (41)	11 (64.7)	6 (35.3)	1 (5.8)	16 (94.2)	0	17 (100)	-	-	-	-	-	-
Pseudomonas N=3	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7 %)	1 (33.3)	3 (100)	0	0	3 (100)	0	3 (100)	-	-	-	-	-	-
Proteus N=2	1 (50)	1 (50)	0	2 (100)	0	2 (100)	2 (100)	0	0	2 (100)	1 (50)	1 (50)	-	-	-	-	-	-
Staph Coa+ve N=12	5 (41.67)	7 (58.3)	5 (41.6)	7 (58.4)	2 (16.6)	10 (83.4)	8 (66.7)	4 (33.3)	5 (41.7)	7 (58.3)	4 (33.3)	8 (66.7)	2 (16.7)	10 (83.3)	2 (16.7)	10 (83.3)	1 (8.3	11 (91.7)
Staph Coa-ve N=10	4 (40)	6 (60)	3 (30)	7 (70)	4 (40)	6 (60)	5 (50)	5 (50)	1(10)	9 (90)	0	10 (100)	1 (10)	9 (90)	1 (10)	9 (90)	0	10 (100)
Enterococcus N=1	0	1 (100)	1 (100)	0	0	1 (100)	0	1 (100)	0	1 (100)	0	1 (100)	-	-	-	-	-	-
Micrococcus N=1	0	1 (100)	0	1 (100)	0	1 (100)	0	1 (100)	0	1 (100)	0	1 (100)	-	-	-	-	-	-

Figure 1. Pattern of micro organisms responsible for neonatal sepsis