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Original Research Article

Aetiological Profile of Early and Late Onset Neonatal Sepsis

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Abstract:

Introduction: Neonatal sepsis is defined as a systemic condition of bacterial, viral, or fungal (yeast) origin in newborn infants less than 28 days old that is associated with hemodynamic changes and other clinical manifestations and results in substantial mortality and morbidity. Sepsis continues to be an important cause of neonatal morbidity and mortality. It is a common problem in the newborn intensive care unit (NICU) population particularly in premature neonates. Sepsis is classified as early onset sepsis (EOS) presents within 72 hrs of life, and late onset sepsis (LOS) presents beyond 72hrs of life. EOS presents where the maternal genital tract is the source of infection.

Materials and Methodology: This study was undertaken in new born unit, in department of Pediatrics, in SCB Medical College and SVP Postgraduate institute of Pediatrics, Cuttack, Odisha during the period of 1 year from September 2021 to September 2022. This is a tertiary care unit which caters to a large area of population from odisha and peoples from east west Bengal. The unit functions as an intramural unit round the clock. On an average of about 300 neonates are admitted every month in the new born unit for various reasons. The study was commenced after getting the formal approval of the ethical committee of our hospital. The study population includes all the babies admitted in the neonatal ward with the history and clinical features suggestive of sepsis.

Results: Out of 200 suspected sepsis, 62.5% (n=125) were term neonates and 37.5% (n=75) were preterm neonates. About two fold increases in culture positivity was seen in preterm neonates (44%) when compared to term neonates (22.4%). Gram negative bacilli (70.5%) constituted the majority of culture isolates in this study when compared to Gram positive cocci isolates (29.5%). Klebsiella pneumoniae (54.1%) was found to be the most com- mon GNB isolate followed by Acinetobacter baumannii (9.8%) and Escherichia coli (6.5%) . Among the Gram positive isolate Staphylococcus aureus (16.4%) was the most frequent organism followed by Coagulase negative Staphylococcus (6.5%) whereas both Group B Streptococci and Enterococcus faecalis constituted only 3.27%. Amikacin was sensitive in 60% of S. aureus, 75% of CONS. Gentamicin showed moderate sensitivity (50-60%) among the Gram positive isolates. Third generation cephalosporins had sensitivity of 60% among S. aureus, 75% among CONS and 100% among GBS. Cefepime showed sensitivity of 87.5% in S. aureus and 75% in CONS.

Conclusion: In this study the risk factors commonly associated with neonatal sepsis were found to be prematurity, LBW, instrumental delivery (AVD). EOS was more common than LOS. Gram negative sepsis was predominantly seen and was highly susceptible to Imipenem and Tigecycline. CRP was found to be a sensitive tool for early diagnosis and predicting the outcome of sepsis. But it is neither 100% sensitive nor 100% specific to be relied as a sole marker. The greatest predictability can be achieved by the combination of assays rather than a single biomarker and as of now blood culture remains the gold standard in diagnosing sepsis. Strict antibiotic policy to address the issue of antimicrobial resistance in addition to good infection control and earnest search for an early diagnostic marker widen the horizon of successful encounter with sepsis and lead the neonates to the road of health.

Keywords: Neonatal sepsis, Antibiotic therapy, early onset sepsis, late onset sepsis.

Introduction

Neonatal sepsis is defined as a systemic condition of bacterial, viral, or fungal (yeast) origin in newborn infants less than 28 days old that is associated with hemodynamic changes and other clinical manifestations and results in substantial mortality and morbidity. [1]

Sepsis continues to be an important cause of neonatal morbidity and mortality. It is a common problem in the newborn intensive care unit (NICU) population particularly in premature neonates. National Neonatal Perinatal Database (NNPD) [2] 2003 has reported the incidence of neonatal mortality as 30 per 1000 intramural live births in tertiary care institutions and the incidence of sepsis was 3%. Invasive bacterial infections primarily involve the blood stream during the first month of life. This leads to meningitis, pneumonia, and multiorgan dysfunction, septicemia. [3]

Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. Up to 10% of infants have infections in the 1st month of life [4]. Newborn infection is more common in areas with limited access to healthcare than in areas with well-established healthcare infrastructure. The overall incidence of neonatal sepsis ranges from 1 to 5 cases per 1,000 live births [5]. Estimated incidence rates vary based on the case definition and the population studied. Globally, neonatal sepsis and other severe infections were responsible for an estimated 430,000 neonatal death in 2013, accounting for approximately 15% of all neonatal death [6].

Sepsis is classified as early onset sepsis (EOS) presents within 72 hrs of life, and late onset sepsis (LOS) presents beyond 72hrs of life. EOS presents where the maternal genital tract is the source of infection. The incidence of early onset bacterial infection is variable and ranges from 1 to 5 per 1,000 live births [7]; however it is clear that the incidence has declined as a result of intrapartum antibiotic prophylaxis. Centers for Disease Control and Prevention (CDC, 2007, 2009) first published recommendations for intrapartum antibiotic prophylaxis (IAP) against group B Streptococcus (GBS) in 1996. Recent data from the CDC revealed a downward trend from 2000 to 2003 (from 0.52 to 0.31 cases per 1000 live births). [8]

When stratified by age, the average incidence of early onset sepsis among preterm infants was 2.8 fold higher [9]. Infants described with early onset sepsis frequently have one or more identifiable risk factors. Prematurity is considered the single greatest risk factor for early onset bacterial infections [10]. Because it is accepted that ELBW infants have impairment of host defenses, and since preterm birth may be associated with low grade chorioamnionitis, it is not surprising that the attack rates for infection by pathogens such as GBS are 26 to 30-fold higher in preterm infants [11], compared to term newborn infants, with an associated high mortality.

LOS occurs as a result of postnatal nosocomial infections or community acquired infections, with the peak incidence reported to be between 10th and 22nd day of life [12]. Incidence of LOS is inversely associated with birth weight.

Materials and Methodology

This study was undertaken in new born unit, in department of Pediatrics, in SCB Medical college and SVP Postgraduate institute of Pediatrics, Cuttack, Odisha during the period of 1 year from September 2021 to September 2022. This is a tertiary care unit which caters to a large area of population from odisha and peoples from east west Bengal.

The unit functions as an intramural unit round the clock. On an average of about 300 neonates are admitted every month in the new born unit for various reasons. The study was commenced after getting the formal approval of the ethical committee of our hospital. The study population includes all the babies admitted in the neonatal ward with the history and clinical features suggestive of sepsis.

Inclusion Criteria:

All the new born admitted in the new born unit with clinical feature of sepsis and admitted in NICU for other diagnosis who develop signs of sepsis, >/ 28 weeks gestation and weight more than 1kg are enrolled for study – over a period of 1 year.

Exclusion Criteria:

- Severe hypoxic ischemic encephalopathy (Stage 2 and stage 3).
- Major intracranial injury
- Major congenital anomalies
- Mothers with bad obstetric history

After admission, brief history regarding patient presenting complains, antenatal, natal, postnatal history is taken and a thorough clinical examination of the patient is done and noted in clinical proforma sheet.

Blood Collection Procedure: Under strict aseptic precaution the skin is cleansed over the site in a circle approximately 5cm in diameter, with 70% isopropyl alcohol. Then 2% iodine or povidone iodine is applied and left on the skin for at least one minute. 2ml of venous blood is drawn by venipuncture. About 1ml of blood is inoculated immediately into brain heart infusion broth aseptically and sent to microbiology dept. for culture through BACTEC method. Another 1ml of blood is sent to

lab for neonatal sepsis screen consisting of Total leukocyte count, absolute neutrophil count, immature to total neutrophil ratio, microESR, CRP.

The inoculated blood culture bottles are then inoculated at 37 degree Celsius.

Blood culture is considered negative if no growth occurred on final subculture. Any growth which occurred during the inoculation period is then followed and organism is identified followed by antibiotic sensitivity.

In my study, Bacterial causes of neonatal sepsis is studied eg, Group B streptococcus, E. coli, Klebsiella, Staphylococcus aureus, Coagulase negative staph aureus, Acinetobacter, enterococcus, Pseudomonas, listeria.

Study Tools and Techniques:

All the new born admitted with the clinical features of sepsis and the new born admitted in the NICU for various causes apart from exclusion criteria developed signs of sepsis were enrolled. After getting informed consent from the parents, detailed clinical history, feeding history, any bad child rearing practice, general condition of the mother and the attendees were documented. A detailed history about the complaints was sought and documented in a clinical proforma. Thorough Clinical examination of the baby was made and documented. Baseline hematological investigations were then done after the admission. All other relevant investigations were done after the admission.

Results

Table 1: Gender Distribution of the Cases

Sex	Suspected Sepsis (N=200)	Culture Proven Sepsis (N=61)	Percentage
Male	106	33	31%
Female	94	28	28%

The Male: Female ratio of the neonates included in this study was 1.12:1. Culture positivity showed only a slight rise in male neonates (31%) than females (28%).

Table 2: Distribution Based on Maturity and Birth Weight of the Neonate

Maturity	Suspected sepsis (n=200)	Culture proven sepsis (n=61)	Percentage
Preterm (32-36wk)	75	33	44%
>/ 2500 gm	101	27	26.70%
< 2500 gm	99	34	34.30%

Out of 200 suspected sepsis, 62.5% (n=125) were term neonates and 37.5% (n=75) were preterm neonates. About two fold increase in culture positivity was seen in preterm neonates (44%) when compared to term neonates (22.4%). In this study 99 neonates were LBW (< 2500gm) and 101 neonates were of normal birth weight. Among the LBW neonates culture isolation (n=34) was high 34.3%.

Table 3: Distribution of the Isolates Based On Gram Reaction

Gram reaction No. of isolates (n=61)	EOS	LOS
Gram positive cocci 18(29.5%)	8(44.5%)	10(55.5%)
Gram negative 43(70.5%) bacilli	37(86.1%)	6(13.9%)

Gram negative bacilli (70.5%) constituted the majority of culture isolates in this study when compared to Gram positive cocci isolates (29.5%).

Table 4: Distribution of the Culture Isolates in Eos

Name of the isolate	Number (n=61) of culture proven cases	EOS(n=45)
Klebsiella pneumoniae	33(54.1%)	28 (62.2%)
Staphylococcus aureus	10 (16.4%)	4(8.8%)
Acinetobacter baumannii	6 (9.8%)	5 (11.1%)
CONS	4(6.5%)	2 (4.4%)
Escherichia coli	4 (6.5%)	4 (8.8%)
Group B Streptococci	2 (3.27%)	1 (2.2%)
Enterococcus faecalis	2 (3.27%)	1 (2.2%)

Klebsiella pneumoniae (54.1%) was found to be the most com- mon GNB isolate followed by Acinetobacter baumannii (9.8%) and Es- cherichia coli (6.5%). Among the Gram positive isolate Staphylococcus aureus (16.4%) was the most frequent organism followed by Coagulase negative Staphylococcus (6.5%) whereas both Group B Streptococci and Enterococcus faecalis constituted only 3.27%.

Table 5: Distribution of Culture Isolates in LOS

Name of the isolate	Number (n=61) of culture proven cases	LOS (n=16)
Staphylococcus aureus	10 (16.4%)	6 (37.5%)
Klebsiella pneumoniae	33 (54.1%)	5 (31.2%)
Acinetobacter baumannii	6(9.8%)	1 (6.2%)

CONS	4 (6.5%)	2 (12.5%)
Escherichia coli	4 (6.5%)	-
Group B Streptococcus	2 (3.27%)	1 (6.2%)
Enterococcus faecalis	2 (3.27%)	1 (6.2%)

Table 6: Antibiotic susceptibility Pattern of S. Aureus and Cons

Drug	S. aureus (n=10)	CONS (n=4)
Amikacin	6 (60%)	3 (75%)
Ampicillin	1 (10 %)	Nil
AMC	7 (70%)	4(100%)
Cefotaxime	6 (60%)	3 (75%)
Cefepime	8 (87.5%)	3 (75%)
Gentamicin	6 (62.5%)	2 (50%)
Vancomycin	10 (100%)	4 (100%)
Linezolid	10 (100%)	4 (100%)
Teicoplanin	10 (100%)	4 (100%)

Table 7: Antibiotic Susceptibility Pattern of GBS and E. Faecalis

Name of the antibiotic	Sensitivity for GBS (n=2)	Sensitivity for E.faecalis (n=2)
Ampicillin	2 (100%)	1 (50%)
AMC	2 (100%)	1 (50%)
Cefotaxime	2 (100%)	-
Ceftriaxone	2 (100%)	-
Gentamicin	1 (50%)	-
Linezolid	2 (100%)	2 (100%)
Vancomycin	2 (100%)	2 (100%)
Teicoplanin	2 (100%)	2 (100%)

AMC– Amoxicillin plus clavulanic acid. Amikacin was sensitive in 60% of S. aureus, 75% of CONS. Gentamicin showed moderate sensitivity (50-60%) among the Gram positive isolates. Third generation cephalosporins had sensitivity of 60% among S. aureus, 75% among CONS and 100% among GBS. Cefepime showed sensitivity of 87.5% in S. aureus and 75% in CONS.

Table 8: Antibiotic Susceptibility Pattern of Gram Negative Isolates

Name of the antibiotic	K. pneumonia (n=33)	A. baumannii (n=6)	E. coli (n=4)
Amikacin	24 (72.7%)	4 (66.6%)	3 (75%)
Gentamicin	21 (63.6%)	3 (50%)	3 (75%)
Cefotaxime	18 (54.5%)	4 (66.6%)	2 (50%)
Ceftriaxone	19 (57.6%)	4 (66.6%)	2 (50%)
Ceftazidime	17 (51.5%)	5 (83.3%)	2 (50%)
Cefepime	28 (84.8%)	4 (66.6%)	3 (75%)
CFS	30 (91%)	4 (66.6%)	4 (100%)
PIT	31 (94%)	5 (83.3%)	4 (100 %)
Imipenem	33 (100%)	6 (100%)	4 (100%)
Tigecycline	33 (100%)	6 (100%)	4 (100%)

CFS – Cefoperazone plus sulbactam, PIT – Piperacillin plus tazobactam. Among the Gram negative isolates, all were highly susceptible to Imipenem and Tigecycline followed by Cefoperazone-sulbactam and Piperacillin tazobactam. The sensitivity to Piperacillin-tazobactam was 94%, cefoperazone- sulbactam was 91%. Out of 43 Gram negative isolates, resistance to third generation cephalosporins (Cefotaxime, ceftriaxone, and ceftazidime was predominantly seen in Klebsiella pneumoniae followed by E. coli and A . baumannii.

Discussion

In our study the male: female ratio of the study population was 1.12: 1. There is a slight male preponderance for culture positivity in the present study which is comparable to the other studies by Shrestha NJ et al [13] (2011). The same has been documented by Upadhyay et al and Nelson Textbook of Pediatrics. [12] Though it has been documented in several standard books, the reason for male predominance is unknown. The possible locus of gene for synthesis of immunoglobulins at X chromosome probably accounts for relative resistance of the female infants to infection.

Gram negative bacilli (70.5%) constituted the majority of isolates in this study. Similar pattern of culture isolates has been observed in studies conducted by K.J Desai et al [14] (2011). However, this is in contrast to the findings reported in the studies conducted in developed countries by Karlowicz et al [15] (2000) where predominant cause of sepsis was GBS and CONS. Sanghvi TP et al [16] (2006) also reported the variation in the etiology of neonatal sepsis between developing and developed countries.

The most frequent isolate in this study was Klebsiella pneumoniae (62.2%) in early onset sepsis which is concordant with the other Indian studies by Kayange. In developing countries Klebsiella pneumoniae is the most common agent associated with neonatal sepsis. The capsular polysaccharide and lipopolysaccharide determine the virulence of klebsiella pneumoniae. The genetic constitution of the lipopolysaccharide shows wide variation when compared to the other Gram negative bacteria which makes Klebsiella pneumoniae highly virulent resisting the complement mediated opsonisation and phagocytosis.

Staphylococcus aureus (37.5%) was the most common organism isolated in late onset sepsis followed by Klebsiella pneumoniae (31.2%) where all of them reported a similar pattern of culture isolates. Both K. pneumoniae and S. aureus are nosocomial pathogens as they tend to colonize the hospital environment as well as health care personnel, making these organisms the predominant cause of sepsis.

Higher rates of E. coli isolation has been demonstrated in the studies done by Agarwal A et al (2015) [17] reported that E.coli was the predominant cause of neonatal sepsis. But in studies done by Rahul Kamble [18] lower E. coli isolation rates of < 10% were reported which is similar to this study in which E.coli was isolated from only 4 neonates (6.5%).

Both Acinetobacter and CONS are commonly found in the environment of NICU. Though they are implicated as organisms of low virulence, significant rates of isolation in this study can be attributed to the intrinsic susceptibility of the neonate due to lack of effective immune response. Under these circumstances these organisms acquire high pathogenicity especially in premature neonates. Long term epidemiological studies performed have revealed an increasing trend in incidence of CONS in the recent years. (Upadhyay A et al 2006) [12]

All the Gram-positive organisms were 100% sensitive to Vancomycin, Linezolid and Teicoplanin which correlates with most of the studies including those done by Anil Kuruvilla. [19] S. aureus and CONS were highly resistant to Ampicillin and Gentamicin which correlates well with the studies by Mustafa M et al [20] (2014). GBS showed 100% sensitivity to Ampicillin which correlates with most studies which conclude that penicillin resistance is yet to be documented. Though in vitro susceptibility testing is not routinely recommended for E. faecalis due to intrinsic resistance, in case of multi drug resistant strains causing severe infections testing with high level Gentamicin can be done. This is in the context of using it as an adjunct antibiotic acting synergistically with another drug in combination (vancomycin) unless resistance to HLG is documented.

Among the Gram negative isolates, all were highly susceptible to Imipenem and Tigecycline followed by Cefaperazone – Sulbactam and Piperacillin Tazobactam which is similar to the findings of Mustafa M et al (2014). [20] Acinetobacter baumannii showed higher degree of antibiotic resistance when compared to E. coli and Klebsiella pneumonie. But all of Acinetobacter isolates were susceptible to Tigecycline. Similar pattern of antibiogram was reported by Kamble and Rajesh Ovhal [18].

Third generation cephalosporins resistance (40 to 50%) were more than the resistance to aminoglycosides in both K. pneumoniae and E. coli which is concordant with the study conducted by Mutlu M et al (2011). [21] Sanjay D Rathod et al (2012) [22] reported similar degree of resistance among third generation cephalosporins. Gram negative isolates were found to have high sensitivity to Cefepime, CFS and PIT comparable to most other studies.

Conclusion

In this study the risk factors commonly associated with neonatal sepsis were found to be prematurity, LBW, instrumental delivery (AVD). EOS was more common than LOS. Gram negative sepsis was predominantly seen and was highly susceptible to Imipenem and Tigecycline. CRP was found to be a sensitive tool for early diagnosis and predicting the outcome of sepsis. But it is neither 100% sensitive nor 100% specific to be relied as a sole marker. The greatest predictability can be achieved by the combination of assays rather than a single biomarker and as of now blood culture remains the gold standard in diagnosing sepsis.

Strict antibiotic policy to address the issue of antimicrobial resistance in addition to good infection control and earnest search for an early diagnostic marker widen the horizon of successful encounter with sepsis and lead the neonates to the road of health.

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