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EPIDEMIOLOGY, ETIOLOGY AND RISK FACTORS FOR NEONATAL SEPSIS IN SOUTH-EAST ODISHA REGION--A HOSPITAL BASED STUDY

Paediatrics

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ABSTRACT

Neonatal septicemia is defined as infection in the first 28 days of life. Early-onset neonatal septicemia and late-onset neonatal septicemia are defined as illnesses appearing from birth to three days and from four to twenty-eight days postnatally, respectively. Neonatal sepsis is the third leading cause of neonatal mortality and a major public health problem, especially in developing countries. Although recent medical advances have improved neonatal care, many challenges remain in the diagnosis and management of neonatal infections. The diagnosis of neonatal sepsis is complicated by the frequent presence of non-infectious conditions that resemble sepsis, especially in preterm infants, and by the absence of optimal diagnostic tests. Since neonatal sepsis is a high-risk disease, especially in preterm infants, clinicians are compelled to empirically administer antibiotics to infants with risk factors and/or signs of suspected sepsis. Unfortunately, both broad-spectrum antibiotics and prolonged treatment with empirical antibiotics are associated with adverse outcomes and increase antimicrobial resistance rates. Given the high incidence and mortality of sepsis in preterm infants and its long-term consequences on growth and development, efforts to reduce the rates of infection in this vulnerable population are one of the most important interventions in neonatal care. The aim of the present study was to evaluate the incidence of neonatal sepsis and characterize the microbiological pattern of neonatal sepsis and the antibiotic susceptibility of the isolates to evaluate the empirical antibiotic used in neonatal units of IMS & SUM Hospital hospitals in eastern odisha region.

Methods-This was a hospital based retrospective study conducted at a tertiary care hospital IMS & SUM HOSPITAL the capital city of odisha, from Mar 2017 to April 2018. In this Retrospective hospital based study required tests and Other required informations were noted from the diagnosed infants of neonatal septicemia.

Results- A total of 86 neonatal septicaemia infants were enrolled. Among them, 74 cases were grouped into the sepsis and 12 cases diagnosed as probable sepsis were taken. The most common cultured bacterium from their blood was klebsiella pneumonia 30(34.88%) followed by Escherichia coli 16(18.60%) in both early onset and late onset septicaemia. There was no significant difference in the babies' birth weight, gestational age, modes of delivery, gender between the two groups regarding as a risk factor for sepsis. Other organism less commonly involves are CONS in 11%, Pseudomonas aeruginosa in 5.40% in both groups. Acinetobacter species (3%) was the Gram-negative organism which is more common in early onset septicaemia.

Conclusions. The result of our study reveals that the Klebsiella pneumonia, E.coli, CoNS and Acinetobacter sp. are the most common etiological agents of neonatal septicemia. In particular, since rate of Klebsiella pneumonia,E.coli causing sepsis is alarming in both early and late onset septicaemia. Appropriate measure should be taken care to curb the excess burden of these infections in this region.

KEYWORDS

Neonatal sepsis, blood culture, sepsis screen and early and late onset septicemia

1. Introduction

Septicemia in neonates refers to generalized bacterial infection documented by a positive blood culture in the first 4 weeks of life [1]. Septicemia in neonates can lead to sepsis that is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia [4]Sepsis occurring in the first 72 hours of life is defined as early-onset sepsis (EOS) and that occurring beyond 72 hours as late-onset sepsis (LOS) [6]..Longitudinal trends in the demographics, pathogens, and outcome were observed in a single-center database on neonatal sepsis at Yale–New Haven Hospital from 1928.[1]2. *Streptococcus pneumoniae* and group A streptococci were the major causes of neonatal sepsis from 1933 to 1943. From the late 1940s to the mid-1960s, Gram-negative organisms, especially *Escherichia coli* (*E. coli*), were the most common causes of neonatal sepsis.[20] .Thereafter, group B streptococci infections emerged as the foremost cause of EOS in the1970s.[25]. Organisms associated with early-onset sepsis (EOS).[20]. .Group B streptococcus (GBS, *Streptococcus agalactiae*) is a gram-positive encapsulated bacterium and remains the leading cause of neonatal sepsis and meningitis in the United States. Stoll et al. has recently described *Escherichia coli* (*E. coli*) to have emerged as the major pathogen of neonatal sepsis in preterm infants and the second most common cause in term infants.[20]

E. coli is frequently associated with severe infections and meningitis and is the leading cause of sepsis related mortality among VLBW infants (24.5%)[15] GBS and *E. coli* together account for about 70% of cases of EOS in the neonatal period.[3] Although less common, *Listeria monocytogenes* is associated with invasive disease in the newborn, spontaneous abortions or stillbirth if acquired during pregnancy.With improved survival of preterm infants, LOS has become an important cause of morbidity and mortality among low birth weight infants.[27] LOS is mainly associated with the organisms acquired from the environment after birth. In a study on 6215 infants admitted to National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) centers, 70% of first episode late-onset infections were caused by gram-positive organisms, with coagulase-negative staphylococci accounting for 48% of the infections.[22] Death rates were highest for infants infected with *Pseudomonas aeruginosa*, *Candida albicans*, *Serratiamarcescens*, and *E. coli*.[28] The incidence of late-onset GBS disease has remained unchanged despite intrapartum antibiotic prophylaxis. Meningitis remains a common presentation of late-onset GBS disease, with serious neurologic sequelae and permanent impairment among many survivors.[16,17,11].Despite advances in health care, neonatal sepsis, and especially that caused by Gram-negative rod bacteria, is a significant cause of morbidity and mortality among neonates [6].An increase in sepsis caused by Gram-negative organisms has been reported in recent years from Nepal [7] Neonatal sepsis caused by Gram-negative microorganisms is responsible for 18%–78% of all neonatal sepsis [9].Microorganisms implicated in neonatal septicemia have developed increased drug resistance to commonly used antibiotics and thus making treatment extremely difficult [12].Thus, the knowledge of both the common

pathogens causing septicemia in neonates and their antimicrobial susceptibility is essential in order to select appropriate antimicrobial treatment. Moreover, antimicrobial susceptibility patterns of pathogens vary geographically and are temporally dependent on local pathogens and patterns of antibiotic used. Hence, the present study was conducted to document the bacteriological profile of neonatal septicemia and their antibiotic susceptibility profile for planning strategy for the management of neonatal septicemia.

2. Methods

Patients and Methods

A retrospective study was carried out from Mar 2017 to April 2018 at a tertiary care hospital IMS & SUM HOSPITAL the capital city of odisha, District of khordha. Study Population-A total of 86 subjects aged up to 28 days diagnosed as neonatal sepsis were taken for our study. Criteria taken for the diagnosis of neonatal sepsis was from the NNF Clinical Practice Guidelines and Haque KN. Definitions of bloodstream infection in the new-born. [33],[36]

A panel of sepsis screen tests were performed from the blood samples of all the neonates as per NNF guidelines of neonatal Septicemia [33],[36].i.e. Sepsis screen (according to NNF criteria)

a. Total leukocyte count
b. I/T ratio (band cell ratio)
c. Absolute neutrophil count
d. m-ESR
e. C reactive protein Radiological tests and CSF study were done wherever indicated.

Interpretation -Neonatal sepsis: Defined as the presence of generalized systemic features of sepsis associated with pure growth of organisms from one or more sites. This includes septicemia, pneumonia, meningitis, urinary tract infection, dysentery, osteomyelitis, septic arthritis and deep-seated infections.

Probable sepsis: clinical and laboratory findings consistent with bacterial infection without a positive culture.

Sample collection and Bacteriological Processing- For blood culture, about 1-2 ml of blood was collected aseptically prior to administration of empirical antibiotics from each baby and inoculated into a broth containing 20 ml of brain heart infusion and incubated aerobically at 37◦ c for 24 hr by Bactalert method. Subcultures were done on Blood agar and MacConkey's agar and incubated overnight at 37◦c.The growth was identified by colony characteristics, Gram's stain and standard biochemical tests.

Antibiotic Susceptibility Testing-Antibiotic susceptibility testing including detection of methicillin resistance Staphylococcus aureus (MRSA), D test (inducible clindamycin resistance) and screening tests for extended spectrum beta lactamase (ESBL), metallo-beta lactamase (MBL) among Gram negative bacilli were carried out as per CLSI guidelines[13][34].

3. Results

Of total 86 enrolled neonates, 60.46% were males and 39.53% were females with male to female ratio of 1.52: 1(**Table-3**).out of total 86 cases 54 babies are delivered by normal vaginal delivery and rest (n-32) by LSCS.48 number of cases having normal birth weight ,22 have LBW, 14 cases have VLBW and 2 cases have Extremely LBW .More of positive cases by culture were preterm with a statistically significant correlation regarding gestational age(**table-4**).The ratio of outpatients and inpatient in total sepsis group is 66% vs. 34% respectively. Higher formula feeding rate was present in both early and late onset septicaemia group i.e. 72% and 69.44% respectively(**table-1**)($p< 0.05$).Male gender baby are outnumber the female 60.46% vs. 39.53% respectively. Maternal risk factor present in 60% cases of early onset septicemia i.e. 23 out of 39 cases. Among total suspected cases the septicemia was confirmed in 74 (86.04%). 12 cases diagnosed as probable/possible sepsis as per NNF guidelines[36] culture negative probable/Possible sepsis depending on clinical manifestation. Early-onset septicemia (EOS) was observed in 44 infants and late-onset septicemia (LOS) in 42 infants (**table-2**)..Most common clinical manifestation are respiratory distress (66.27%),temperature instability (56.97%),poor activity/hypotonia(45.34%),neonatal jaundice (48. 83%),cardiovascular collapse (30.23%),pneumonia (27.90%).Other clinical signs found are convulsion, hypoglycaemia, meningitiss epticarthritis, apnea and intraventricul arhaemoharrage are depicted in **table no-5.** We observed that the respiratory distress (74.70%) was commonest symptom. In this study, 92.94% babies were with leucocytosis. 58 cases were found to have leukopenia. Absolute neutrophil count (ANC) was highly specific but very low sensitive test in our study. CRP and I/TN ratio showed high sensitivity but low specificity. When two or more sepsis screen tests were combined together, both sensitivity and specificity increased.

Isolates Distribution Among a total of 74 bacterial isolates recovered, 15 (17.44%) were Gram-positive isolates and 57 (66.27%) were Gram-negative isolates. Fungal sepsis was identified in 2 cases one in each category of early and late septicaemia (**table-2)**. Of total positive cases Klebsiella pneumonia found in 30(34.88%) followed by ,E.coli in 16(18.60%) CoNS were recovered from 11 cases (12.79%), S. aureus one case in EONS category, Acinetobacter spp. 3 (3.48%), whereas viridans streptococci was recovered from a single case **table-2**.Klebsiella pneumonia and E. coli were recovered from LOS and EOS cases more frequently than other gram positive organism .Vancomycin,teicoplanin and linezolid showed almost 100% efficacy against Gram-positive isolates. Most of the Gram-positive isolates were resistant to Ampicillin,amoxyicillin-cavulanicacid,oxacillinand gentamicin whereas amikacin,cefotaxim and ,piperacilin-tazobact umshowed a promising efficacy among tested antibiotics. Among Gram-negative isolates, around 50% isolates were resistant to ampicillin and most of the isolates were also resistant to ampicillin and cefotaxime while amikacin was found to be most effective among tested antibiotics and importantly vancomycin and linezold showed 100% efficacy **table-6& figure 1**. Neutropenia, positive CRP, thrombocytopenia and I/T >0.2 found in more number cases in sepsis cases than probable sepsis cases.**Table-7**.

Table 1 -Neonatal septicaemia& type of milk consumed

Group	Number	Percentage (%)
Breast milk	12	13.95
Non Breast milk	40	46.51
Mixed feeding	22	25.58

Table 2: Distribution of isolated organisms.

Organism isolated	Frequency		Total (%)
	Early-onset (EOS)	Late-onset (LOS)	
Gram-negative organisms	29	28	57(77.02)
Klebsiellapneumonia	16	14	30(40.54)
E. coli	06	10	16(21.62)
Citrobacter spp.	01		01(1.35)
Pseudomonas aeruginosa	03	01	04(5.40)
Acinetobacter spp.	02	01	03(4.05)
Proteus mirabilis	01	02	03(4.05)
Gram-positive organisms	10	05	15(20.27)
CoNS	07	04	11((14.86)
Enterococcus spp.	00	01	01(1.35)
Viridans streptococci	01	00	01(1.35)
Streptococcus	02	00	02(4.05)
Candidaspp.	01	01	02(2.70)

Table 3Sepsis type and age distribution among 86 neonates with suspected sepsis

Variables	Neonates with EOS (≤72 hr) number (%)	Neonates with LOS (>72 hr) number (%)	Total number (%)
Proven sepsis	40	34	74(86.04)
Possible sepsis	04	08	12(13.95)
Sex			
Male	30	22	52(60.46)
Female	14	20	34(39.53)

Table 4 Maternal and neonatal data of the 86 neonates investigated for sepsis

Characteristics	Total (*n* = 86)	Percentage (%)
(A) Maternal data		
Gestational age		
<28 weeks	02	2.32
28-34 weeks (preterm)	04	4.65
34–37 weeks (late preterm)	28	32.55
≥37 weeks (term)	52	60.46
Maternal risk factor present	46	53.48
Place of delivery		
Hospital(inborn)	41	47.67
Out born	45	52.32
Mode of delivery		
Vaginal	54	62.79
Caesarean section	32	37.20
Neonatal data		
Weight at birth		
≤1000 g (VLBW)	02	2.32
1001–1500 g (VLBW)	14	16.27
1501–2500 g (LBW)	22	25.58
>2500 g	48	55.81
PROM	21	24.41

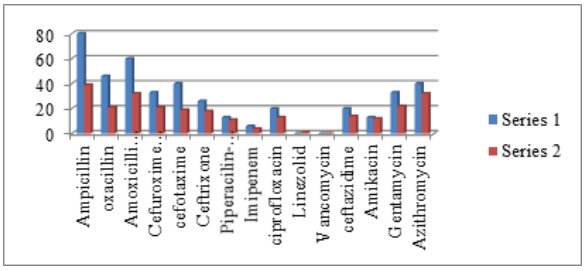
Table 5 Clinical signs/accompanied diagnoses among neonates with suspected sepsis

Clinical signs/accompanied diagnoses	Total (*n* = 86)	Percentage(%)
Respiratory distress	57	66.27
Pneumonia	24	27.90
Temperature instability	49	56.97
Convulsions	18	20.93
Hypoglycemia	33	38.37
Hypocalcemia	17	19.76
Fetal distress	19	22.09
Meningitis	22	25.58
Surgical problems	2	2.32
Congenital heart disease	3	3.48
Diseases of genitourinary	14	16.27
Cardiovascular collapse (shock)	28	32.55
Hematological symptoms (purpura/DIC)	06	6.96
Hypotonia/poor activities	39	45.34
Neonatal jaundice	62	72.09
Septic arthritis	2	2.32
Retinopathy of prematurity	6	6.97
IVH	7	8.13
Apnea	11	12.79

Table 6 Comparative percentage of resistance to the tested antimicrobial agents among Gram-negative and Gram-positive isolates

Antibiotics	Gram-positive cocci resistances (%) (*n* = 15)	Gram-negative resistances (%) (*n* = 57)
Ampicillin	80(12)	39(68.42)
Oxacillin	46.66(07)	21(36.84)
Amoxicillin-clavulanic acid	60(09)	32(56.14)
Cefuroxime axetil	33.33(5)	21(36.84)
Cefotaxime	40(06)	19(33.33)
Ceftriaxone	26.66(04)	18(31.57)
Ceftazidime	20(03)	14(24.56)
Piperacilin-tazobactum	13.33(02)	11(19.29)
Imipenem	6.66(01)	04(07.01)
Ciprofloxacin	20(03)	13(22.80)
Linezolid	00	01(1.75)
Vancomycin	00	00
Amikacin	13.33(02)	7(12.28)
Gentamicin	33.33(05)	22(38.59)
Azithromycin	40(06)	18(31.57)

Figure 1 Comparative percentage of resistance to the tested antimicrobial agents among Gram-negative and Gram-positive isolates



Series 1 Gram positive Bacteria
Series 2 Gram negative Bacteria

7: The sepsis screen parameters of neonatal septicaemia group cases

Screening test	Culture positive(74)		Culture negative(12)	
	Number	Percentage (%)	Number	Percentage (%)
Increased TLC	18	24.32	4	33.33
Neutropenia	58	78.37	8	66.66
CRP+	62	83.78	7	58.33
I/TN >0.2	63	85.13	8	66.66
Decreased Platelet	54	72.97	3	25
Two or more tests positive	53	71.62	8	66.66

Discussions

Current neonatal mortality rate (NMR) in India is 32.30/1000 live births[44].Sepsis remains one of the most important causes of morbidity and mortality in the newborn despite considerable progress in hygiene, introduction of new antimicrobial agents, and advanced measures for early diagnosis and treatment [14]. In sepsis isolation of bacteria from blood is the gold standard for the diagnosis of sepsis. Normally it takes 24–48 h for culture results. Inoculation of only 0.5–1.0 ml of blood may give false negative results, as approximately 60 % of infants have a low level of bacteremia. Theoretically, for optimal results, 6 ml of blood would be required which is practically not feasible [31]. Sepsis cannot always be excluded even when blood cultures are found to be negative. Conversely, isolation of bacteria in a blood culture may reflect asymptomatic bacteraemia or contamination [31]. Components of the white cell count, including absolute neutrophil count (ANC) and immature to total neutrophil ratio (I:T) have also been shown to be more useful for excluding infants without infection rather than identifying newborns who are infected.[23,32]. Of the infants born at a tertiary care center located at Bharatpur of central Nepal between January 2012 and December 2013, the septicemia was suspected in 918 infants. Among them 61.4% infants were males and 38.6% were female infants. Similar rate of suspected septicemia in male and female infants was also reported by Karambin and Zarkesh from Iran [41] and Al-Shamahy et al. from Yemen [43].In our study more number of male affected than female.The male preponderance in neonatal septicaemia may be due to the X- linked immuneregulatory gene factor which making the host more susceptible to infection.There is male preponderance, which is due to the prevalent custom of taking male babies preferentially to healthcare institutions and also because female babies are immunologically more competent.[28] In our setting, the burden of septicemia among total suspected cases was confirmed in 86 infants giving a prevalence rate of 9% which is a lower rate than previously reported by Khanal et al. [7]. The lower rate observed in our study may be due many regions i.e. increasing awareness , prevention of preterm labour, earlier and more aggressive enteral feeding and better hand hygiene practices[42]. However our prevalence rate closely matches with Dagnew et al. from Ethiopia [37]. Due toPrematurity, LBW,Mechanical ventilation, more use of catheters, use of TPN, and antibiotic resistance are common causes of change in the etiology of neonatal sepsis [38].Bacterial septicemia was observed mostly in male neonates (60 %) in the present study whereas it was confirmed to be 39% in female neonates. Similar finding of septicemia in male and female neonates was also detected by Karambin and Zarkesh[41]. K. H. Haque,[33]and Naher and Khamael from Iraq [18]. EOS was found in

49(56.97%) neonates and LOS was found in 37 (43.02%) neonates which is less in number than EOS. The result indicated that the incidence of EOS septicemia was more common than LOS which is consistent with other reports from Iran[19,21] ,Iraq [18] and Bangladesh [22]. Early-onset neonatal sepsis is caused by microorganisms acquired from the mother before or during birth (vertically transmitted and perinatally acquired); thus, microorganisms from the maternal genital tract may play an important role in early infection [24]. Among Gram-positive group of organisms CoNS was the most common cause of both EOS and LOS accounting for nearly half of the cases (25%) followed by Streptococcus. Similar rates of CoNS isolates were also reported by Dagnew et al. from Ethiopia [37]. Ozkan et al. from Turkey [38] and Ghotaslou et al. [26]" from Iran.Gram-negative organisms Klebsiella pneumonia found in 30(34.88%) followed by ,E.coli in 16(18.60%), Acinetobacter spp. (4.05%) were the most common organism isolated from both EOS and LOS cases .

In our study the sensitivity pattern of the common pathogens isolated from EOS as well as LOS to commonly used antibiotics. Aminoglycosides (gentamicin and amikacin) and Vancomycinwere the most sensitive antimicrobial agents against both Gram-positive and Gram-negative organisms while β-lactam antibiotics (ampicillin and cephalosporins) were resistance to many common organism causing both EOS and LOS in our hospital the result being similar to that reported by Mhada et al. from Tanzania [39]. Similar sensitivity pattern of amikacin was also showed by the literatures from Turkey[40] Similar proportion of resistance rate in Gram-positive organisms to common antibiotics was also reported by Gheibi et al. from Iran [21]. Similar pattern of susceptibility was also reported from Nepal [27], India [28]; andTureky[38]. Vancomycin and teicoplanin remained the most effective antibiotics against all the Gram-positive isolates from EOS as well as LOS cases.Similarly, vancomycin was also found as the most effective antibiotic in a study by Komolafe and Adegoke from Nigeria [30] and Desai and Malek from India [28].All of the Gram-positive organisms isolated from both EOS and LOS cases were also found to be susceptible to vancomycin by Ozkan et al. from Turky[38] Amikacinwas found one of the cost effective and effective among the tested antibiotics.The antimicrobial sensitivity pattern differs in different studies as well as at different times in the same hospital. This is because of emergence of resistant strains as a result of indiscriminate use of antibiotics.

5. Conclusions

Neonatal sepsis is a life threatening emergency and thus any delay creates a significant burden due to its impact on neonatal mortality and long-term morbidity. In spite of on-going efforts in early diagnosis, treatment, and prevention, neonatal sepsis still remains an enigmatic area for neonatologists due to changes in epidemiology and the lack of ideal diagnostic markers .The knowledge of the etiological organisms as well as their antimicrobial sensitivity profile is necessary for commencement of antibiotic therapy empirically while awaiting blood culture results. The initial empiric antibiotic therapy must therefore be a combination of drugs to cover the prevalent bacterial organisms in that region. This research study identified Klebsiella pneumonia, E. Coli and CoNS as the predominant etiological agents of bloodstream infection among neonates. Effective prophylactic measures, prompt and accurate diagnoses and subsequent administration of targeted therapy are vital to curb the excessive burden of the disease. An alarmingly high degree of antibiotic resistance observed calls for an urgent evaluation and development of antibiotic policies and protocols for neonatal sepsis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

2.5. Ethical Aspects

This study was approved by the Ethical committee IMS& SUM Hospital Medical College, Bhubaneswar, India.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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