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Assessment of factors responsible for neonatal sepsis in ANMMCH Gaya, Bihar

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Abstract
Neonatal sepsis is invasive infection, usually bacterial, occurring during the neonatal period. Signs are multiple, nonspecific, and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures, and jaundice. Hence based on above findings the present study was planned to evaluate the various factors and occurrence of neonatal septicemia in the children admitted to the Department of Paediatrics of Anugrah Narayan Magadh Medical College, Gaya, Bihar.
The study was planned by enrolling 200 neonates admitted in Neonatal Intensive Care Unit of Department of Paediatrics of Anugrah Narayan Magadh Medical College, Gaya, Bihar. The 50 neonates diagnosed with the septicemia were enrolled in the present study. Neonatal septicemia was diagnosed as per the clinical criteria given by Vergnano *et al*. Blood sample(0.5 to 2 ml) was collected with all aseptic precaution and was inoculated into blood culture bottle BactT/Alert® PF (BIOMERIEUX, INC. Durhams, NC 27704) containing 20 ml of broth.
The data from the present study revealed that there is need to undertake research to understand the pathogenesis of early-onset sepsis and to devise measures to prevent related morbidity and mortality. Also to improve the survival rate, better approach suggested is a risk approach with early initiation of appropriate antibiotics and aggressive supportive care based on local sensitivity pattern and fatal risk factors.

Keywords: neonatal sepsis, epidemiology, microbiology

Introduction
Neonatal sepsis is invasive infection, usually bacterial, occurring during the neonatal period. Signs are multiple, nonspecific, and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures, and jaundice. Diagnosis is clinical and based on culture results. Treatment is initially with ampicillin plus either gentamicin or cefotaxime, narrowed to organism-specific drugs as soon as possible.
Early-onset neonatal sepsis usually results from organisms acquired intrapartum. Most infants have symptoms within 6 h of birth. Most cases are caused by Group B streptococcus (GBS) and gram-negative enteric organisms (predominantly Escherichia coli). Vaginal or rectal cultures of women at term may show GBS colonization rates of up to 35%. The density of colonization determines the risk of early-onset invasive disease in neonates, which is 40 times higher with heavy colonization. Although only 1/100 of neonates colonized develop invasive disease due to GBS, > 50% of those present within the first 6 h of life. Nontypeable Haemophilus influenzae sepsis has also been identified in neonates, especially premature neonates. Other cases tend to be caused by gram-negative enteric bacilli (eg, Klebsiella spp) and certain gram-positive organisms (Listeria monocytogenes, enterococci [eg, Enterococcus faecalis, E. faecium], group D streptococci [eg, Streptococcus bovis], alpha-hemolytic streptococci, and staphylococci). Also, S. pneumoniae, H. influenzae type b, and, less commonly, Neisseria meningitidis have been isolated. Asymptomatic gonorrhea occurs occasionally in pregnancy, so N. gonorrhoeae may rarely be a pathogen.
Late-onset neonatal sepsis is usually acquired from the environment (see Neonatal Hospital-Acquired Infection). Staphylococci account for 30 to 60% of late-onset cases and are most frequently due to intravascular devices (particularly central vascular catheters). E. coli is also becoming increasingly recognized as a significant cause of late-onset sepsis, especially in extremely LBW infants. Isolation of Enterobacter cloacae or Cronobacter (formerly Enterobacter) sakazakii from blood or CSF may be due to contaminated feedings. Contaminated respiratory equipment is suspected in outbreaks of hospital-acquired Pseudomonas aeruginosa pneumonia or sepsis.
Although universal screening and intrapartum antibiotic prophylaxis for group B streptococcus have significantly decreased the rate of early-onset disease due to this organism, the rate of late-onset GBS sepsis has remained unchanged, which is consistent with the hypothesis that late-onset disease is usually acquired from the environment. The role of anaerobes (particularly Bacteroides fragilis) in late-onset sepsis remains unclear, although deaths have been attributed to Bacteroides bacteremia. Candida spp are increasingly important causes of late-onset sepsis, occurring in 12 to 18%

of extremely LBW infants. Hematogenous and transplacental dissemination of maternal infection occurs in the transmission of certain viral (eg, rubella, cytomegalovirus), protozoal (eg, Toxoplasma gondii), and treponemal (eg, Treponema pallidum) pathogens. A few bacterial pathogens (eg, L. monocytogenes, Mycobacterium tuberculosis) may reach the fetus transplacentally, but most are acquired by the ascending route in utero or as the fetus passes through the colonized birth canal.

Though the intensity of maternal colonization is directly related to risk of invasive disease in the neonate, many mothers with low-density colonization give birth to infants with high-density colonization who are therefore at risk. Amniotic fluid contaminated with meconium or vernix caseosa promotes growth of group B streptococcus and *E. coli*. Hence, the few organisms in the vaginal vault are able to proliferate rapidly after PROM, possibly contributing to this paradox. Organisms usually reach the bloodstream by fetal aspiration or swallowing of contaminated amniotic fluid, leading to bacteremia. The ascending route of infection helps to explain such phenomena as the high incidence of PROM in neonatal infections, the significance of adnexal inflammation (amnionitis is more commonly associated with neonatal sepsis than is central placentitis), the increased risk of infection in the twin closer to the birth canal, and the bacteriologic characteristics of early-onset neonatal sepsis, which reflect the flora of the maternal vaginal vault [1].

At the XXIV Annual Meeting of the National Neonatology Forum this year, a number of papers were presented, on the incidence and outcome of sepsis, the organisms causing neonatal sepsis, and their sensitivity to antibiotics. The common themes that emerged from these papers: (*a*) the organisms causing early onset sepsis are very similar to those causing late onset sepsis, (*b*) the commonest organisms causing early and late onset sepsis are Gram negative bacilli, particularly Klebsiella, Enterobactor and *Escherichia coli*. *Staphylococcus aureus* is the commonest Gram positive organism. Group B streptococcus is virtually never isolated, (*c*) there was a high incidence of fungal infection causing late onset sepsis, and anecdotally many of the infected babies weighed >1500g at birth, and some were even full term. Most worrying was that there are exceedingly high rates of resistance of Gram negative bacilli to almost all antibiotics. Resistance to aminoglycosides is about 50% for amikacin, higher for netilmicin and over 75% for gentamicin. Resistance to third generation cephalosporins is 80% plus. Bacteria are less resistant (30-46%) to piperacillin-tazobactam. Imipenem resistance is already appearing (about 20%). It appeared that the major reason for these frightening data were that Doctors often do not take blood cultures before starting antibiotics, if blood cultures are performed and are negative, antibiotics are almost always continued, if the baby remains "sick", more and more potent broad spectrum antibiotics are used, and the belief that a raised serum C-reactive protein (CRP) is proof of sepsis, even if blood cultures are negative [2].

The currently available multisite studies on sepsis are from well-established surveillance networks in high income countries such as the USA, the UK, and Germany. Such infection surveillance networks are a rarity in low-income and middle-income countries; the few available ones have used passive surveillance (eg, the National Neonatal Perinatal Database [NNPD] and the Asia-Pacific Neonatal Infections Study [APNIS]). Most of the other studies from low-income and middle-income countries are typically from a single site, retrospective, or have relied on routine laboratory reports. They often lack rigorous data collection and reporting methods, and run the risk of mis classification and underestimation or overestimation of the incidence of sepsis [3-5].

Hence based on above findings the present study was planned to evaluate the various factors and occurrence of neonatal septicemia in the childrens admitted to the Department of Paediatrics of Anugrah Narayan Magadh Medical College, Gaya, Bihar.

Methodology

The study was planned by enrolling the 200 neonates admitted in Neonatal unit of Department of Paediatrics of Anugrah Narayan Magadh Medical College, Gaya, Bihar. The study duration was from August 2017 to July 2018. The 50 neonates diagnosed with the septicemia were enrolled in the present study. Neonatal septicemia was diagnosed as per the clinical criteria given by Vergnano *et al* [6]. Blood sample(0.5 to 2 ml) was collected with all aseptic precaution and was inoculated into blood culture bottle BactT/Alert® PF (BIOMERIEUX, INC. Durhams, NC 27704) containing 20 ml of broth.

The blood and broth were mixed gently and bottles were transported to laboratory for incubation in BacT/Alert 3D system and further processing was done as per manufacturer's guideline.

Those blood culture bottles which were indicated positive, query positive and query negative by Bact/ Alert 3D system were sub cultured on Sheep blood agar and MacConkey agar. The blood agar and MacConkey's medium were incubated at 35 ± 20 Celsius for 18 - 24 hours in aerobic atmosphere. Various organisms were identified on the basis of colony morphology and standard biochemical tests. Those blood culture bottles which were indicated as negative by 5 days (as per setting of Bact / Alert 3D system) were reported as "no growth". The isolates were subjected to antimicrobial susceptibility testing by Kirby Bauer disk diffusion method as per CLSI guidelines 2011 [7].

Results & Discussion

India is a developing nation with a distant dream to achieve to achieve MDG 4 but remains unfulfilled due to the lack of appropriate neonatal care. The maintenance of neonatal health should be the priority of every society.

Following was the observations from the data generated from the present study.

Table 1: Clinical Details of Mother

Parameters	No. of Cases
Mother Age:	
• Less than 20 years	15
• 20 to 30 years	28
• Above 30 years	7
Literacy:	
• Literate	18
• Illiterate	32
Economic Status:	
• Lower	32
• Middle	15
• Higher	3
Parity of Mother:	
• 1	37
• 2	9
• More than 2	3
Antenatal Care:	
• Less than 3	32
• More than 3	18
Predisposing Factors:	
• Positive	6
• Negative	44
Mode of Delivery:	
1. Normal	21
2. Caesarean	29

Table 2: Type & Causative Microbes

Parameters	No. of Cases
Type of Sepsis:	
Early Onset Sepsis	18
Late Onset Sepsis	32
Causative Bacteria	
Gram Positive	15
Gram Negative	35

Table 2: Positive Cases and Drug Sensitivity

Organisms	Blood culture positive Cases
Gram-positive	
Staphylococcus aureus	7
Methicillin-resistant Staphylococcus aureus	4
Staphylococcus epidermidis	4
Total Cases	15 cases
Gram-negative:	
Klebsiella pneumoniae	19
Acinetobacter	8
Citrobacter	4
Pseudomonas	4
Total Cases	35 cases

In this study the most common bacteria found associated with neonatal sepsis in the inborn unit was Klebsiella (37.2%) followed by E. coli and Pseudomonas, 16.28% each, and Staphylococcus aureus was 13.95%. According to a report published by ICMR on newborn health two thirds of isolates were Gram-negative including Acinetobacter spp. (21.9%), Klebsiella spp. (16.6%), and Escherichia coli (13.7%) in inborn cohort. [8] A study done in SP medical college, Bikaner also showed Klebsiella as the most common (48.21%) micro-organism associated with sepsis in inborn unit [9].

In an another study done in Indore, Madhya Pradesh Klebsiella was found to be the most commonly associated organism [10]. Whereas in a study done in GMCH Chandigarh from 2008- 12 the most common organism was found to be Staph. aureus and Klebsiella took the second position, also a study in Manipal found most common organism to be Pseudomonas (33.2%) followed by Klebsiella (31.4%) [11]. This may be due colonisation of different bacteria in different set ups. Similarly, in a study done in 2007 in Burdwan MCH Klebsiella (34.48%) was the most common organism isolated [12]. Similar results were reported according to NNPD 2002-03 in which among intramural births Klebsiella was the most frequently associated pathogen (32.5%) followed by Staph. aureus (13.6%). Similar, results with Klebsiella as the most common isolate was found in other studies [13].

Prior studies have identified maternal risk factors such as age, literacy, socioeconomic status, parity, antenatal care, PPROM, predisposing factors like maternal fever/foul smelling liquor and mode of delivery [14-15]. In our study, maternal risk factors significantly associated with fatal outcome were: Illiteracy, poor socioeconomic statu, inadequate antenatal care, premature rupture of membranes, assisted vaginal delivery. Babies of poor, illiterate mother have a higher incidence of sepsis because they are usually of low birth weight, delivered premature thus diminishing their immunity and predisposing them to infection. There is also delay in appreciating and seeking treatment. Besides, most deliveries in these families are conducted at home under improper aseptic conditions [16]. Adequate antenatal cares is crucial for a favourable outcome of pregnancy. Lack of adequate antenatal care associated with home deliveries without aseptic precautions, conducted by untrained dais are the preconditions for sepsis. Studies have reported 3 times higher mortality in babies with inadequate antenatal care compared to those with adequate antenatal care [17]. Instrument assisted deliveries had higher mortality as shown in a number of other studies due to increasing chance of infection [18-19].

Neonatal risk factors significantly associated with higher mortality were gestational age, gender, birth weight, IPPV, time of onset of symptoms, delay in starting treatment and presence of complications. Gestational age and neonatal mortality were inversely related. Preterm babies need NICU admission and are subjected to invasive procedures and mechanical ventilation which increases the risk of infection. Increased incidences of sepsis and its mortality were noticed among male infants in our study as reported by authors of other studies [21]. Once again as observed in other studies neonates who had IPPV demonstrated high risk of infection and significant fatality [22]. The time gap of >12 h from the onset of symptoms and starting of treatment and consequent complications like DIC/multi organ dysfunction syndrome leads to higher mortality [23].

It can be concluded that though we are on the track of minimising morbidities and mortalities but still there is a long way to go, still we have a higher prevalence of neonatal sepsis even in inborn units and most common associated bacteria is Klebsiella pneumonae, and most common indication for admission was respiratory distress which further led to neonatal sepsis. Among the patients with sepsis maximum

patients were males and maximum patients belonged to urban areas and were successful in availing the government facilities for transportation upto the health facility. Neonates with sepsis were mainly preterm term and with low birth weight. Most of the neonates who had sepsis were admitted on the first day of their birth and maximum duration of stay of most of the neonates was 8 days and most of them were treated and discharged successfully.

Conclusion

The data from the present study revealed that there is need to undertake research to understand the pathogenesis of early-onset sepsis and to devise measures to prevent related morbidity and mortality. Also to improve the survival rate, better approach suggested is a risk approach with early initiation of appropriate antibiotics and aggressive supportive care based on local sensitivity pattern and fatal risk factors.

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