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Assessment of the cases of neonatal septicemia with respect to antibiotic susceptibility pattern of isolates from Bihar region

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Abstract
Neonatal sepsis refers to systemic and generalized bacterial infection of the new born documented by a positive blood culture in the first four weeks of life and is one of the four leading causes of neonatal mortality in India. The gold standard for diagnosis of septicemia is the isolation of bacterial agent from blood culture. The prevalence of bacterial profile of blood culture and their susceptibility patterns in an area, provide guidance to start empirical treatment which is the cornerstone in the management of sepsis. Hence present study was planned to evaluate the neonatal septicemia and antibiotic susceptibility pattern of isolates in Bihar region.
The present study was planned in Jawaharlal Nehru Medical College Bhagalpur, Bihar, India. The study was conducted from July 2015 to Jun 2016. Out of the total 477 cases admitted to our hospital 20 cases were found positive for the Neonatal Septicemia. A detailed history of age, sex, birth weight, gestational age, and clinical symptoms of septicemia was recorded. Neonatal sepsis were suspected when any of the signs and symptoms or predisposing factors such as reduced activity, fever, refusal of feed, seizures, prolonged jaundice, birth asphyxia, umbilical sepsis, prematurity were noted in the new born.
Gram negative bacteria were more commonly the cause of septicemia in neonates, and Klebsiella pneumoniae was the predominant pathogen. We also noticed that these Gram negative bacteria were resistant to routinely used antibiotics, hence their resistant pattern should be considered essential before deciding the empirical treatment. There is a need to implement Antimicrobial stewardship programmes to rationalise antibiotic usage to reduce neonatal mortality due to sepsis. Early detection of sepsis and judicial use of antibiotics are useful to decrease neonatal mortality and the emergence of multidrug resistant bacteria.

Keywords: septicemia, neonates, gram positive, gram negative, Bihar region, Antibiotics, etc

Introduction
Neonatal sepsis is a type of neonatal infection and specifically refers to the presence in a newborn baby of a bacterial blood stream infection (BSI) (such as meningitis, pneumonia, pyelonephritis, or gastroenteritis) in the setting of fever. Older textbooks may refer to neonatal sepsis as "sepsis neonatorum". Criteria with regards to hemodynamic compromise or respiratory failure are not useful clinically because these symptoms often do not arise in neonates until death is imminent and unpreventable. Neonatal sepsis is divided into two categories: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS refers to sepsis presenting in the first 7 days of life (although some refer to EOS as within the first 72 hours of life), with LOS referring to presentation of sepsis after 7 days (or 72 hours, depending on the system used). Neonatal sepsis is the single most common cause of neonatal death in hospital as well as community in developing country.
It is difficult to clinically exclude sepsis in newborns less than 90 days old that have fever (defined as a temperature > 38 °C (100.4 °F). Except in the case of obvious acute viral bronchiolitis, the current practice in newborns less than 30 days old is to perform a complete workup including complete blood count with differential, blood culture, urinalysis, urine culture, and cerebrospinal fluid (CSF) studies and CSF culture, admit the newborn to the hospital, and treat empirically for serious bacterial infection for at least 48 hours until cultures are demonstrated to show no growth. Attempts have been made to see whether it is possible to risk stratify newborns in order to decide if a newborn can be safely monitored at home without treatment despite having a fever. One such attempt is the Rochester criteria [1].
Note that, in neonates, sepsis is difficult to diagnose clinically. They may be relatively asymptomatic until hemodynamic and respiratory collapse is imminent, so, if there is even a remote suspicion of sepsis, they are frequently treated with antibiotics empirically until cultures are sufficiently proven to be negative. In addition to fluid resuscitation and supportive care, a common antibiotic regimen in infants with suspected sepsis is a beta-lactam antibiotic (usually ampicillin) in combination with an aminoglycoside (usually gentamicin) or a third-generation cephalosporin (usually cefotaxime—ceftriaxone is generally avoided in neonates due to the theoretical risk of kernicterus.) The organisms which are targeted are species that predominate in the female genitourinary tract and to which neonates are especially vulnerable to, specifically Group B Streptococcus, Escherichia coli, and Listeria monocytogenes (This is the main rationale for using ampicillin versus other beta-lactams.) Of course, neonates are also vulnerable to other common pathogens that can

cause meningitis and bacteremia such as Streptococcus pneumoniae and Neisseria meningitidis. Although uncommon, if anaerobic species are suspected (such as in cases where necrotizing enterocolitis or intestinal perforation is a concern, clindamycin is often added.

Granulocyte-macrophage colony stimulating factor (GM-CSF) is sometimes used in neonatal sepsis. However, a 2009 study found that GM-CSF corrects neutropenia if present but it has no effect on reducing sepsis or improving survival [2].

Trials of probiotics for prevention of neonatal sepsis have generally been too small and statistically underpowered to detect any benefit [3], but a randomized controlled trial that enrolled 4,556 neonates in India reported that probiotics significantly reduced the risk of developing sepsis [4]. The probiotic used in the trial was Lactobacillus plantarum.

A very large meta-analysis investigated the effect of probiotics on preventing late-onset sepsis (LOS) in neonates. Probiotics were found to reduce the risk of LOS, but only in babies who were fed human milk exclusively. It is difficult to distinguish if the prevention was a result of the probiotic supplementation or if it was a result of the properties of human milk. It is also still unclear if probiotic administration reduces LOS risk in extremely low birth weight infants due to the limited number of studies that investigated it. Out of the 37 studies included in this systematic review, none indicated any safety problems related to the probiotics. It would be beneficial to clarify the relationship between probiotic supplementation and human milk for future studies in order to prevent late onset sepsis in neonates [5].

The infectious agents associated with neonatal sepsis have changed since the mid-20th century. During the 1950s, S aureus and E coli were the most common bacterial pathogens among neonates in the United States. Over the ensuing decades, Group B Streptococcus (GBS) replaced S aureus as the most common gram-positive organism causing early-onset sepsis. Currently, GBS and E coli continue to be the most commonly identified microorganisms associated with neonatal infection. Additional organisms, such as coagulase-negative Staphylococcus epidermidis, L monocytogenes, Chlamydia pneumoniae, H influenzae, Enterobacter aerogenes, and species of Bacteroides and Clostridium have also been identified in neonatal sepsis.

Meningoencephalitis and neonatal sepsis can also be caused by infection with adenovirus, enterovirus, or coxsackievirus. Additionally, sexually transmitted diseases (eg, gonorrhea, syphilis, herpes simplex virus [HSV] infection, cytomegalovirus [CMV] infection, hepatitis, human immunodeficiency virus [HIV] infection, rubella, toxoplasmosis, trichomoniasis, and candidiasis) have all been implicated in neonatal infection. Bacterial organisms with increased antibiotic resistance have emerged and have further complicated the management of neonatal sepsis [6]. The colonization patterns in nurseries and personnel are reflected in the organisms currently associated with nosocomial infection. In neonatal intensive care units (NICUs), infants with lower birth weight and younger gestational ages have an increased susceptibility to these organisms.

S epidermidis, a coagulase-negative Staphylococcus, is increasingly seen as a cause of nosocomial or late-onset sepsis, especially in the premature infant, in whom it is considered the leading cause of late-onset infections. Its prevalence is likely related to several intrinsic properties of the organism that allow it to readily adhere to the plastic mediums found in intravascular catheters commonly required for the care of these infants. The bacterial capsule polysaccharide adheres well to the plastic polymers of the catheters. Also, proteins found in the organism (AtlE and SSP-1) enhance attachment to the surface of the catheter. The adherence creates a capsule between microbe and catheter, preventing C3 deposition and phagocytosis [7-8].

Biofilms are formed on indwelling catheters by the aggregation of organisms that have multiplied under the protection provided by the adherence to the catheter. Slimes are produced at the site from the extracellular material formed by the organism, which provides a barrier to host defense as well as to antibiotic action, making coagulase-negative staphylococcal bloodstream infection (BSI) more difficult to treat. The toxins formed by S epidermidis have also been associated with necrotizing enterocolitis.

In addition to being a cause of neonatal sepsis, coagulase-negative Staphylococcus is ubiquitous as part of the normal skin flora. Consequently, it is a frequent contaminant of blood and cerebrospinal fluid (CSF) cultures. When a culture grows this organism, the clinical presentation, colony counts, and the presence of polymorphonuclear neutrophils (PMNs) on Gram staining of the submitted specimen often help differentiate true infection from contaminated culture specimens.

In addition to the specific microbial factors mentioned above, numerous host factors predispose the newborn to sepsis. These factors are especially prominent in the premature infant and involve all levels of host defense, including cellular immunity, humoral immunity, and barrier function. Immature immune defenses and environmental and maternal factors contribute to the risk for neonatal sepsis, morbidity, and mortality, particularly in preterm and/or very low birthweight (VLBW) infants [9-10]. There may also be a genetic association.

Neonatal sepsis refers to systemic and generalized bacterial infection of the newborn documented by a positive blood culture in the first four weeks of life and is one of the four leading causes of neonatal mortality in India. The gold standard for diagnosis of septicemia is the isolation of bacterial agent from blood culture. The prevalence of bacterial profile of blood culture and their susceptibility patterns in an area, provide guidance to start empirical treatment which is the cornerstone in the management of sepsis [11]. Hence present study was planned to evaluate the neonatal septicemia and antibiotic susceptibility pattern of isolates in Bihar region.

Methodology

The present study was planned in Jawaharlal Nehru Medical College Bhagalpur, Bihar, India. The study was conducted from July 2015 to Jun 2016. Out of the total 477 cases admitted to our hospital 20 cases were found positive for the Neonatal Septicemia. A detailed history of age, sex, birth weight, gestational age, and clinical symptoms of septicemia was recorded. Neonatal sepsis were suspected when any of the signs and symptoms or predisposing factors such as reduced activity, fever, refusal of feed, seizures, prolonged jaundice, birth asphyxia, umbilical sepsis, prematurity were noted in the newborn.

Neonatal septicemia was diagnosed as per the clinical criteria given by Vergnano *et al* [12]. Blood sample(0.5 to 2

ml) was collected with all aseptic precaution and was inoculated into blood culture bottle Bact T/Alert® PF (BIOMERIEUX, INC. Dur hams, 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 [13].

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Neonatal sepsis were suspected when any of the signs and symptoms or predisposing factors such as reduced activity, fever, refusal of feed, seizures, prolonged jaundice, birth asphyxia, umbilical sepsis, prematurity were noted in the newborn.

Exclusion criteria: Neonates already on antibiotics and with diagnosis of intrauterine infection and congenital anomalies were excluded from the study

Results and Discussion

Neonatal sepsis is a life threatening emerging infection in the developing countries and it is estimated about 5 million neonatal death occur every year worldwide. The invasive procedures in the postnatal period and inadequate hand washing before and after handling babies also contributes to the neonatal sepsis in intensive care units.

The overall incidence of culture proven sepsis varies between 1-8 cases per 1000 live births with equal distribution of early and late onset cases [14-17]. Neonatal sepsis can be divided into two sub-types depending upon whether the onset of symptoms is before 72 hours of life [early onset sepsis (EOS)] or later [late onset sepsis (LOS)]. Early-onset infections are caused by organisms prevalent in the maternal genital tract or in the delivery area. Late- onset septicemia is caused by the organisms thriving in the external environments of the home or the hospital [18]. The organisms commonly associated with EOS are group B streptococcus and E coli in the west, while in India most cases are due to Gram- negative organisms especially E. coli, klebsiella, and enterobacter sp [19-20]. Organisms that have been implicated in LOS are coagulase-negative Staphylococci (CONS), Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Enterobacter spp., Pseudomonas aeruginosa and anaerobes [20-21]. Prompt diagnosis and effective treatment is necessary to prevent deaths and complications due to septicemia. The blood culture remains the "Gold Standard" for the diagnosis for neonatal sepsis though its sensitivity is 50-80 percent [21]. But the results of blood culture takes hours to days, thus necessitating initial empirical treatment of suspected cases.

Table 1: Clinical details of Mother

Parameters	No. of Cases
Mother Age	
▪ Less than 20 years	3
▪ 20 to 30 years	5
▪ Above 30 years	12
Literacy:	
▪ Literate	15
▪ Illiterate	5
Economic Status:	
▪ Lower	6
▪ Middle	8
▪ Higher	6
Parity of Mother:	
▪ 1	14
▪ 2	4
▪ More than 2	2
Antenatal Care:	
▪ Less than 3	17
▪ More than 3	3
Mode of Delivery:	
▪ Normal	9
▪ Caesarean	11

Table 2: Type & Causative Microbes

Parameters	No. of Cases
Type of Sepsis:	
Early Onset Sepsis	12
Late Onset Sepsis	8
Causative Bacteria:	
Gram Positive	7
Gram Negative	1

Table 3: Positive Cases and Drug Sensitivity

Organisms	Blood culture positive Cases
Gram-positive :	
Staphylococcus aureus	6
Methicillin-resistant Staphylococcus aureus	1
Staphylococcus epidermidis	1
Total Cases	8 cases
Gram-negative:	
Klebsiella pneumonae	7
Acinetobacter	2
Citrobacter	2
Pseudomonas	1
Total Cases	12 cases

Table 4: Resistance of Isolates to Antibiotic

Antibiotics	Staphylococcus aureus	Kleibsella spp.	E. Coli	Pseudomonas spp.
Amoxicillin	20	18	18	20
Cotrimoxazole	16	14	11	19
Gentamycin	14	16	15	14
Piperacillin	0	0	1	1
Cefoperazone	1	1	1	1
Cefotaxime	8	7	7	10
Ciprofloxacin	14	15	13	14
Ceftriaxone	6	6	5	4

Antibiotic resistance has become a global threat. Reports of multidrug-resistant bacteria causing neonatal sepsis in developing countries are increasing, particularly in neonatal

intensive care units. There is a constant change of bacterial flora and sensitivity patterns in different regions from time to time. For effective management of neonatal septicemia, study of bacteriological profile along with the antimicrobial sensitivity pattern plays a crucial role. The correct and timely identification of microorganisms and their antibiotic sensitivity patterns are essential to guide the paediatricians regarding both the empirical and definitive treatment.

In the present study, the Gram negative bacteria and Gram positive bacteria accounted for (60%) and (40%) respectively. This is in comparable with the studies done by Tak SK *et al*, [22] Shrestha *et al*, [23] Rajana R *et al*, [24] which also showed that gram-negative organisms were more common causes of neonatal sepsis. The probable reasons being, newborns most probably acquire these Gram-negative organisms from the maternal genital tract. Importance of both vertical transmission from the mother and postnatal acquisition of infection from the environment has been suggested in the literatures for pathogenesis of neonatal sepsis. Two of the isolates were candida albicans which was similar to the study done by Gandhi S *et al*. [25]

Higher incidence of many complications of labour and resuscitation are more common in preterm babies than full term neonates. Premature babies are relatively immunocompromised and immuno-inexperienced. These factors predispose them to infection. Khatua *et al*. [26] observed that out of 92 babies with neonatal septicemia 58 were preterm in 56.52%. Vinod kumar *et al*. [27] in their study stated that Preterm babies were highly significantly more susceptible to infection than term babies (61.9% vs 16 40.4%).

The organisms causing neonatal septicaemia differ from area to area and also change with respect to time even in the same area, which may be due to different life conditions. Gram negative bacterial isolates were more than Gram positive isolates in our study. This is in contrast to developed countries, where Gram positive bacteria were more commonly reported. This was in concordance with National Neonatal Perinatal Database (NNPD) [28], Aletayeb *et al* [29], and Sundaram *et al* [30].

The culture positivity rate (39%) depends on a multitude of factors. Studies showed culture positivity rates in the same range (28.6–47.5%) [31-33]. Klebsiella was the most frequently isolated organism in this study, whereas E. coli was the most common organism in the past. GBS which is one of the most common isolates in West was not grown in significant numbers in any Indian study. Enterococcus has emerged as a major pathogen which is associated with LOS in preterms and nosocomial infections. The frequencies of bacterial isolates are comparable to studies in India and abroad. [34-35]

A survey of the studies reveals varying predominance of microbes at different times and places and even within the same setup. Hence, in any NICU, it is very essential to have periodic survey to define the organisms and their sensitivity pattern. Antibiotic sensitivity pattern varied among studies probably due to the antibiotic usage differences. Drugs used for sensitivity testing were also not the same in all the studies. A comparison of antibiotic sensitivity of organisms among North and South Indian studies.

Conclusion

Gram negative bacteria were more commonly the cause of septicemia in neonates, and Klebsiella pneumoniae was the predominant pathogen. We also noticed that these Gram negative bacteria were resistant to routinely used antibiotics, hence their resistant pattern should be considered essential before deciding the empirical treatment. There is a need to implement Antimicrobial stewardship programmes to rationalise antibiotic usage to reduce neonatal mortality due to sepsis. Early detection of sepsis and judicial use of antibiotics are useful to decrease neonatal mortality and the emergence of multidrug resistant bacteria.

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