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Evaluation of prevalence of neonatal sepsis relating to microbial profile and sensitivity pattern in cases from Darbhanga medical college and hospital, Darbhanga, Bihar

Dr. Ved Prakash Gupta[1], Dr. Binit Singh[2*]

[1] Senior Resident, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India
[2] Senior Resident, Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai Darbhanga, Bihar, India
[*] Corresponding Author: Dr. Binit Singh

Abstract
Neonatal septicemia is an important cause of Neonatal morbidity and mortality. it is one of the indicator for measuring the health status of a nation. According to World Health Organization (WHO) estimates there are 5 million neonatal deaths a year with 98% occurring in developing countries. The incidence of neonatal sepsis varies from 11-24.5 /1000 live births in India. Neonatal deaths account for over a one-third of 1 the global burden of child mortality. Neonatal sepsis can be divided into two main classes depending on the onset of symptoms namely Early-onset sepsis, which usually presents within the first 72 hours of birth and Late2,3 onset sepsis, which usually presents 72 hours after birth. Hence based on above findings the present study was planned for Evaluation of Prevalence of Neonatal Sepsis Relating to Microbial Profile and Sensitivity Pattern in Cases from Darbhanga medical College and Hospital, Darbhanga, Bihar.

The present study was planned in Department of Paediatrics, Darbhanga medical College and Hospital, Darbhanga, Bihar, India. The study was conducted from May 2019 to Nov 2019. In the present study 20 cases of neonates suffered from the septicemia were enrolled and evaluated in the present study.

The data generated from the present study concludes that Gram negative bacteria were more commonly the cause of septicemia in neonates, and Klebsiella pneumoniae was the predominant pathogen. The positive blood culture with antibiotic sensitivity of the isolated organism is the best guide to antimicrobial therapy, as resistance to antibiotics is a worldwide problem that causes ineffectiveness of empirical treatment. More so, strict infection control practices combined with judicious use of antibiotic therapy are the main solutions to this problem.

Keywords: neonatal sepsis, microbial profile, sensitivity pattern, etc

Introduction

Sepsis is the commonest cause of neonatal mortality and is probably responsible for 30- 50% of the total neonatal deaths each year in developing countries [1, 2]. It is estimated that 20% of all neonates develop sepsis and approximately 1% die of sepsis related causes. Sepsis related mortality is largely preventable with rational antimicrobial therapy with aggressive supportive care [2]. Indian data According to recent data from National Neonatal Perinatal Database (NNPD) 2000, the incidence of neonatal sepsis has been reported to be 38 per 1000 intramural live births in tertiary care institutions [3]. Septicemia was the commonest clinical category with an incidence of 24 per 1000 live births. Meningitis was diagnosed in 0.5 per 1000 live births. Neonatal sepsis was one of the common causes of neonatal mortality contributing to 23% of all neonatal deaths [3]. Klebsiella pneumoniae was the most frequently isolated pathogen (31.2%), followed by Staphylococcus aureus (17.5%) among the intramural live births. Among extramural babies admitted for neonatal problems, Klebsiella pneumoniae was the commonest organism (36.4%), followed by Staphylococcus aureus (14.3%) and Pseudomonas (13.2%).

Neonatal sepsis may be categorized as early onset (day of life 0-3) or late onset (day of life 4 or later). Of newborns with early-onset sepsis, 85% present within 24 hours (median age of onset 6 hours), 5% present at 24-48 hours, and a smaller percentage present within 48-72 hours. Onset is most rapid in premature neonates.

Early-onset sepsis is associated with acquisition of microorganisms from the mother. Infection can occur via hematogenous, transplacental spread from an infected mother or, more commonly, via ascending infection from the cervix. Organisms that colonize the mother's genitourinary (GU) tract may be acquired by the neonate as it passes through the colonized birth canal at delivery.

Trends in the epidemiology of early-onset sepsis show a decreasing incidence of GBS disease following the widespread adoption of prenatal screening and treatment protocols [4].

In a study involving 4696 women, prenatal cultures showed a GBS colonization rate of 24.5%, with a positive culture rate of 18.8% at the time of labor [5]. As many as 10% of prenatally culture-negative women were found to have positive cultures at the time of labor. In the study, intrapartum antibiotic prophylaxis occurred appropriately in 93.3% of cases, with 0.36 of 1000 infants developing early-onset GBS disease [5].

Trends in late-onset sepsis show an increase in coagulase-negative streptococcal sepsis, with most isolates showing susceptibility to first-generation cephalosporins. The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract, and umbilicus may become colonized via contact with the environment or caregivers. Pneumonia is more common

in early-onset sepsis, whereas meningitis and bacteremia are more common in late-onset sepsis. Early-onset sepsis is 10 to 20 times more likely to occur in premature, very low birthweight infants [6]. Premature infants often have nonspecific, subtle symptoms; considerable vigilance is therefore required in these patients so that sepsis can be identified and treated in a timely manner.

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 [7]. 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 [8, 9].

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 [10]. 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 [10, 11]. There may also be a genetic association [10].

PMNs are vital for effective killing of bacteria. However, neonatal PMNs are deficient in chemotaxis and killing capacity. Decreased adherence to the endothelial lining of blood vessels reduces their ability to marginate and leave the intravascular space to migrate into the tissues. Once in the tissues, they may fail to degranulate in response to chemotactic factors.

Furthermore, neonatal PMNs are less deformable and thus are less able to move through the extracellular matrix of tissues to reach the site of inflammation and infection. The limited capacity of neonatal PMNs for phagocytosis and killing of bacteria is further impaired when the infant is clinically ill. Finally, neutrophil reserves are easily depleted because of the diminished response of the bone marrow, especially in the premature infant [12].

Neonatal monocyte concentrations are at adult levels; however, macrophage chemotaxis is impaired and continues to exhibit decreased function into early childhood. The absolute numbers of macrophages are decreased in the lungs and are likely decreased in the liver and spleen as well. The chemotactic and bactericidal activity and the antigen presentation by these cells are also not fully competent at birth. Cytokine production by macrophages is decreased, which may be associated with a corresponding decrease in T-cell production [13].

Although T cells are found in early gestation in fetal circulation and increase in number from birth to about age 6 months, these cells represent an immature population. These naive cells do not proliferate as readily as adult T cells do when activated, and they do not effectively produce the cytokines that assist with B-cell stimulation and differentiation and granulocyte/monocyte proliferation.

Formation of antigen-specific memory function after primary infection is delayed, and the cytotoxic function of neonatal T cells is 50%-100% as effective as that of adult T cells. At birth, neonates are deficient in memory T cells. As the neonate is exposed to antigenic stimuli, the number of these memory T cells increases.

Natural killer (NK) cells are found in small numbers in the peripheral blood of neonates. These cells are also functionally immature in that they produce far lower levels of interferon gamma (IFN-γ) upon primary stimulation than adult NK cells do. This combination of findings may contribute to the severity of HSV infections in the neonatal period.

The fetus has some preformed immunoglobulin (Ig), which is primarily acquired through nonspecific placental transfer from the mother. Most of this transfer occurs in late gestation, such that lower levels are found with increasing

prematurity. The neonate's ability to generate immunoglobulin in response to antigenic stimulation is intact; however, the magnitude of the response is initially decreased, rapidly rising with increasing postnatal age [14].

The neonate is also capable of synthesizing IgM in utero at 10 weeks' gestation; however, IgM levels are generally low at birth, unless the infant was exposed to an infectious agent during the pregnancy, which would have stimulated increased IgM production [15].

IgG and IgE also may be synthesized in utero. Most IgG is acquired from the mother during late gestation. The neonate may receive IgA from breastfeeding but does not secrete IgA until 2-5 weeks after birth. Response to bacterial polysaccharide antigen is diminished and remains so during the first 2 years of life.

Complement protein production can be detected as early as 6 weeks' gestation; however, the concentration of the various components of the complement system varies widely from one neonate to another. Although some infants have had complement levels comparable to those in adults, deficiencies appear to be greater in the alternative pathway than in the classic pathway [16].

The terminal cytotoxic components of the complement cascade that lead to the killing of organisms, especially gram-negative bacteria, are deficient. This deficiency is more marked in preterm infants. Mature complement activity is not attained until infants reach 6-10 months of life. Neonatal sera have reduced opsonic efficiency against GBS, E coli, and Streptococcus pneumoniae because of decreased levels of fibronectin, a serum protein that assists with neutrophil adherence and has opsonic properties.

The physical and chemical barriers to infection in the human body are present in the newborn but are functionally deficient. Skin and mucous membranes are broken down easily in the premature infant. Neonates who are ill, premature, or both are at additional risk because of the invasive procedures that breach their physical barriers to infection.

Because of the interdependence of the immune response, the individual deficiencies of the various components of immune activity in the neonate conspire to create a hazardous situation when the neonate is exposed to infectious threats.

The intestines are colonized by organisms in utero or at delivery through swallowing of, and exposure to, amniotic fluid and genitourinary tract secretions. The immunologic defenses of the gastrointestinal tract are not mature, especially in the preterm infant. Lymphocytes proliferate in the intestines in response to mitogen stimulation; however, this proliferation is not fully effective in responding to a microorganism, as antibody response and cytokine formation are immature until approximately 46 weeks' gestation.

Necrotizing enterocolitis has been associated with the presence of a number of species of bacteria in the immature intestine. Overgrowth of these organisms in the neonatal lumen can be a component of the multifactorial pathophysiology of necrotizing enterocolitis.

Ventriculitis is the initiating event in meningitis, with inflammation of the ventricular surface. Exudative material usually appears at the choroid plexus and is external to the plexus. Ependymitis then occurs, with disruption of the ventricular lining and projections of glial tufts into the ventricular lumen. Glial bridges may develop near these tufts and cause obstruction, particularly at the aqueduct of Sylvius.

The lateral ventricles may become loculated, a process that is similar to the formation of abscesses. Multiloculated ventricles can lead to the development of localized pockets of infection, making treatment more difficult.

Meningitis is likely to arise at the choroid plexus and extend via the ventricles through aqueducts and into the subarachnoid space to affect the cerebral and cerebellar surfaces. The high glycogen content in the neonatal choroid plexus provides an excellent medium for the bacteria. When meningitis develops from ventriculitis, effective treatment is complicated because adequate antibiotic levels in the cerebral ventricles are difficult to achieve, particularly if ventricular obstruction is present.

Arachnoiditis is the next phase of the process and is the hallmark of meningitis. The arachnoid is infiltrated by inflammatory cells producing an exudate that is typically thick over the base of the brain and more uniform over the rest of the brain. Early in the infection, the exudate primarily contains PMNs, bacteria, and macrophages. It is prominent around the blood vessels and can extend into the brain parenchyma.

In the second and third weeks of infection, the proportion of PMNs decreases; the dominant cells are histiocytes, macrophages, and some lymphocytes and plasma cells. Exudate infiltration can occur in cranial roots 3-8. After this period, the exudate decreases. Thick strands of collagen form along with arachnoid fibrosis, ultimately leading to obstruction of CSF flow. Hydrocephalus results. Early-onset GBS meningitis is characterized by much less arachnoiditis than late-onset GBS meningitis.

Vasculitis extends the inflammation of the arachnoid and ventricles to the blood vessels surrounding the brain. Occlusion of the arteries rarely occurs; however, venous involvement can be severe. Phlebitis may be accompanied by thrombosis and complete vessel occlusion. Multiple fibrin thrombi are especially associated with hemorrhagic infarction. This vascular involvement is apparent within the first days of meningitis and becomes more prominent during the second and third weeks of infection.

Cerebral edema may occur during the acute state of meningitis and may be severe enough to diminish the ventricular lumen substantially. The cause is unknown but is likely to be related to vasculitis and the increased permeability of blood vessels. It may also be related to cytotoxins of microbial origin. Herniation of edematous supratentorial structures does not generally occur in neonates, because of the cranium's distensibility.

Infarction is a prominent and serious feature of advanced neonatal meningitis, occurring in 30% of infants who die. Lesions occur because of multiple venous occlusions, which are frequently hemorrhagic. The loci of infarcts are most often in the cerebral cortex and underlying white matter but may also be subependymal within the deep white matter. Neuronal loss occurs, especially in the cerebral cortex, and periventricular leukomalacia may subsequently appear in areas of neuronal cell death [17].

Neonatal septicemia is an important cause of Neonatal morbidity and mortality. it is one of the indicator for measuring the health status of a nation. According to World Health Organization (WHO) estimates there are 5 million neonatal deaths a year with 98% occurring in developing countries. The incidence of neonatal sepsis varies from 11-

24.5 /1000 live births in India. Neonatal deaths account for over a one-third of 1 the global burden of child mortality. Neonatal sepsis can be divided into two main classes depending on the onset of symptoms namely Early-onset sepsis, which usually presents within the first 72 hours of birth and Late2,3 onset sepsis, which usually presents 72 hours after birth. Hence based on above findings the present study was planned for Evaluation of Prevalence of Neonatal Sepsis Relating to Microbial Profile and Sensitivity Pattern in Cases from Darbhanga medical College and Hospital, Darbhanga, Bihar.

Methodology

The present study was planned in Department of Paediatrics, Darbhanga medical College and Hospital, Darbhanga, Bihar, India. The study was conducted from May 2019 to November 2019. In the present study 20 cases of neonates suffered from the septicemia were enrolled and evaluated in the present study.

Two samples of blood were collected from each case using aseptic precautions. About 2 ml of blood was added immediately into 20 ml of brain-heart infusion broth with 0.025% sodium polyethanol sulphonate as anticoagulant. The bottles were incubated for seven days and subcultures were done appropriately. The organisms were isolated and identified 5 by standard microbiological techniques as per CLSI guidelines. Antibiotic sensitivity pattern was evaluated by Kirby Bauer's disc diffusion method.

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.

Results & Discussion

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.

Early empirical antibiotic treatment of neonates suspected of having septicemia is the standard practice. The spectrum of organisms that cause neonatal septicemia varies in different countries, and sometimes changes from one centre to another within the same country. The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries.

Depending on the onset of symptoms, it can be classified into early onset sepsis within 72 h of life and late onset sepsis usually after 72 h of age [18]. Knowledge about potential risk factors would help in the early diagnosis of sepsis. Early signs of sepsis are frequently non-specific and subtle. It has been one of the major diagnostic problems for physicians due to the non-specificity of its symptoms and the absence of a reliable paraclinical marker. Furthermore, the gold standard for detection of blood culture is unreliable when intrapartum antibiotics have been administrated [19, 20].

The spectrum of organisms that cause neonatal septicemia varies in different countries, and sometimes changes from one center to another within the same country [21]. Group B streptococci (GBS) and E. coli predominate in the USA and Europe, whereas Staphylococci and Gram-negative bacilli are much more common in developing countries [22]. The management of these infections is complicated by the emergence of antibiotic resistance. Multidrug-resistant bacteria are increasingly being reported from intensive care units as well as the community [23].

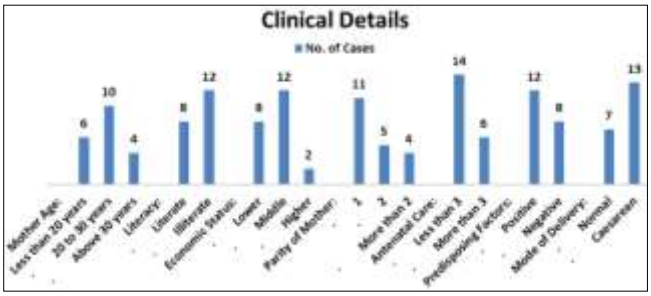

Fig 1: Clinical Details of Mother

Table 1: Type & Causative Microbes

Parameters	No. of Cases
Type of Sepsis	
Early Onset Sepsis	11
Late Onset Sepsis	9
Causative Bacteria	
Gram Positive	7
Gram Negative	13

Table 2: Positive Cases and Drug Sensitivity

Organisms	Blood culture positive Cases
Gram-positive	
Staphylococcus aureus	4
Methicillin-resistant Staphylococcus aureus	2
Staphylococcus epidermidis	1
Total Cases	7 cases
Gram-negative	
Klebsiella pneumonae	7
Acinetobacter	2
Citrobacter	1
Pseudomonas	1
Total Cases	13 cases

The organisms most often implicated in neonatal sepsis in developing countries are Gram-negative organisms; notably, Klebsiella, E. Coli, Pseudomonas, and Salmonella. Among the Gram-positive isolates, S. Aureus, CONS, Streptococcus pneumoniae, and Streptococcus pyogenes have been most commonly noted [24]. Group B streptococcus (GBS) has rarely been described by Kuruvilla *et al*. [25]. It may not be seen at all [26], although it must be remembered that maternal rectovaginal carriage rates of GBS may be actually similar to those that have been noted in developed countries [27]. Studies on the African perspective reveal a low incidence [28], except in South Africa [29]. In Asia too, GBS infection has been noted to be rare [8].

Jyothi *et al* stated in their study that Gram negative bacteria accounted for (55.7%) of cases and Gram positive (44.3%) of cases. Klebsiella Spp, Acinetobacter Spp and Coagulase negative Staphylococcus (CoNS) were most common organisms isolated [30].

Desai *et al* (2011) showed that Gram negative were

(67.85%) and Gram positive were (28.57%). Klebsiella species and Staphylococcus aureus were the most common Gram negative and Gram positive organisms accounting for (47%) and (25%) of the isolates respectively [31].

In a survey in Saudi Arabia, Al-Harthi *et al*. identified K. pneumoniae and Serratia sp. as being the prominent pathogens responsible for causing neonatal meningitis. They also reported the high frequency of Serratia infection as being unique, as this organism has been rarely implicated in other regions across the globe. However, no GBS was isolated, which was in stark contrast to reports obtained from Europe and America [32]. In a study conducted in Malaysia by Boo and Chor, it was reported that the most common pathogens isolated in 1986 and 1987 were Streptococcus epidermidis and S. Aureus. However, after 1988, Klebsiella species emerged as the most commonly implicated organism [33].

The pathogens most often encountered in neonatal sepsis in developing countries differ from those seen in developed countries. The report of the National Neonatal Perinatal database showed Klebsiella as the predominant (29%) pathogen [36]. In the studies undertaken in other developing countries Gram negative organisms were common and Klebsiella and Enterobacter were the most frequently occurring organisms [34, 35]. In the developed countries Gram positive cocci are the most common bacterial isolates. Group B Streptococci was reported as the most common pathogen in term infants in United States by National Institute of Child Health Development.

Neonatal sepsis is usually caused by a variety of Gram-positive as well as Gram-negative bacteria, and sometimes yeasts. Overall, Gram-negative organisms are more common and are mainly represented by Klebsiella, Escherichia coli, Pseudomonas, and Salmonella. Of the Gram-positive organisms, Staphylococcus aureus, Coagulase negative staphylococci (CONS), Streptococcus pneumoniae, and S. pyogenes are most commonly isolated [37]. Early diagnosis and appropriate therapy of septicemia is of utmost importance to prevent morbidity and mortality

Multidrug antibiotic resistance is an emerging problem in neonatal intensive care units particularly in developing countries. Neonatologists who supervise neonatal intensive care unit (NICU) always face a continuous challenge in managing the neonatal infections due to the changing patterns of the microbial flora. The knowledge of bacteriological profile and its antibiotic sensitivity pattern is of great use to paediatricians in choosing antibiotics optimally to treat neonates with septicaemia. In suspected clinical septicaemia, rational empirical therapy has to be started. Antibiotics should be re-evaluated when the results of the cultures and sensitivity are available.

In the present situation antibiotic resistance has become a serious problem. Higher prevalence of resistant pathogens indicates injudicious overuse of different antibiotics. So it is very important to use all the antibiotics according to epidemiological studies with their rational indications of usage. Although positive blood culture is the gold standard in the diagnosis of neonatal sepsis, but in the absence of proof of sepsis many neonatologists felt obliged to continue antibiotics treatment for a full of 10 day course. There is also emergence of resistant pathogens. If this continues there will be lack of effective antibiotics. A meticulous hand-washing, judicious use of antibiotics is the main solution to this serious problem. It is important to continue proper surveillance of neonatal sepsis in order to follow closely changes in trends and risk factors, and take necessary steps as earliest to prevent outbreaks.

Conclusion

The data generated from the present study concludes that Gram negative bacteria were more commonly the cause of septicemia in neonates, and Klebsiella pneumoniae was the predominant pathogen. The positive blood culture with antibiotic sensitivity of the isolated organism is the best guide to antimicrobial therapy, as resistance to antibiotics is a worldwide problem that causes ineffectiveness of empirical treatment. More so, strict infection control practices combined with judicious use of antibiotic therapy are the main solutions to this problem.

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