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Original Article

Bacteriological Profile and Antibiogram of CSF Culture Isolates from a Neonatal Intensive Care Unit in a Tertiary Care Hospital in North India

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Abstract

Neonatal infection is a foremost cause of admission in Neonatal intensive care unit (NICU), accounting annually about 1.6 miilion newborn deaths in developing countries and a big hurdle for achievement of the Millenium Development Goal for child survival. Neonatal meningitis is still a disease with high morbidity, although advances in perinatal care over the last few decades have been able to reduce its mortality rates to approximately 10%. Changing bacterial flora and emergence of resistant strains adds to the problem. Thus, neonatal meningitis requires accurate diagnosis and proper management for better outcome.

Methods: *This prospective study was conducted among suspected neonatal meningitis cases admitted to the NICU at SMGS hospital from May 2016 to May 2017. After taking applied assent from the parents of the neonates, a total of 340 CSF samples were collected and processed by automated identification and susceptibility testing system as per validated laboratory protocols of Microbiology laboratory. Data of positive culture isolates was analysed by appropriate tools.*

Results: *Out of 340 clinically suspected meningitis cases in neonates, a total of 67 (19.7%) were positive. 42 neonates (62.7%) had Gram-negative isolates, 21 (31.3%) were Gram-positive pathogens and 4 (6%) had fungal infection. Among the Gram-negative isolates, common species isolated were Escherichia coli (38%), Acinetobacter sp. (23.8%) and Enetrobacter sp. (16.7%) followed by Klebsiella sp. (9.6%), Pseudomonas sp. (4.8%) along with the isolation of rare organisms like Stenotrophomonas sp., and Serratia sp. Antibiotic pattern suggested high degree of resistance to first line penicillins and gentamicin, moderate to amikacin and cefoperazone – sulbactum. Among the Gram-positive isolates, Enterococcus sp. and CONS were found in highest numbers, each contributing 38% of the total gram positive isolates, followed by Staphylococcus aureus (24%). Antibiotic pattern suggested 100% resistance to penicillins with all the isolates as Methicillin Resistant Staphylococcus aureus (MRSA). Moderate to high level resistance was seen in aminoglycosides (42.8%) and quinolones (52.3%) with 14.2 % of Vancomycin resistant enterococcus sp.*

Conclusion: *The present study highlights the presence of rare organisms causing meningitis and increasing trend of high to moderate level of antibiotic resistance calling for continuous monitoring by rapid detection and consecutive adjustment of empirical treatment regime. Further studies are required to study the trends and pattern of antibiotic resistance to develop hospital antibiotic policy.*

Keywords: *Meningitis, CSF culture, antibiotic resistance.*

Introduction

Neonates are more prone to infections due to poor immune response and may acquire infections via different way: In utero, intrapartum, or postnatally. Neonatal infection is a foremost cause of admission in Neonatal intensive care unit (NICU), accounting annually about 1.6 miilion newborn deaths in developing countries and a big hurdle for achievement of the Millenium Development Goal for child survival. Bacterial sepsis and meningitis are among the predominant causes.[1] Incidence of neonatal sepsis in India according to data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. Neonatal Sepsis or Sepsis Neonatorum is a clinical syndrome characterised by signs and symptoms of infection with or without accompanying systemic bacterial infection (bacteremia) occuring in the first month of life. Neonatal meningitis is caused by the same pathogen causing neonatal sepsis and incidence of meningitis is around one tenth to one fourth of that of neonatal sepsis.[2] It is a devastating and deadly disease that kills the patient within hours.[3] Microbial agents may enter and contaminate the fetus through the placental route, ascending route (after membrane ruptures) or at last when passing through the birth canal, or later, by contact with the extra-uterine environment.[1] When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection without much localization (septicemia) or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis)[4] Neonatal meningitis is infection of the meninges and CNS in the first month of life and is diagnosed if Cerebrospinal fluid (CSF) culture is positive or CSF microscopy and biochemistry are suggestive of meningitis in the setting of septicaemia.[5]

Neonatal meningitis is still a disease with high morbidity, although advances in perinatal care over the last few decades have been able to reduce its mortality rates to approximately 10%. Nevertheless, 20 to 58% of survivors show neurological sequelae. Another worrisome issue is the association of sepsis with meningitis, which has remained constant and rather frequent, showing rates of approximately 25%. A recent review study on neonatal infections has reported meningitis incidence ranging from 0.8 to 6.1 cases in every 1,000 live newborns.[6] Bacterial meningitis being a life-threatening condition requires prompt diagnosis and treatment, but diagnosis in newborn is a challenge for clinicians because symptoms and signs are often subtle and non-specific at its early stage. Several studies from India have reported the spectrum of bacterial pathogens and the existence of antibiotic resistance among the isolates from neonatal sepsis/meningitis cases.[7] A similar study has been done to find out the spectrum of bacterial pathogens causing Neonatal Septicaemia reporting Gram negative bacilli as the predominant pathogens and isolation of few rare organisms causing the disease.[8] Against the same background, the present study was planned emphasizing on Neonatal Meningitis as it is a life-threatening illness which warrants early diagnosis and aggressive therapy. There have been several published studies regarding Neonatal Meningitis conducted in hospitals in the developed countries but there is paucity of data regarding similar surveys in the developing countries like ours. Regional information regarding trends in terms of aetiology and antimicrobial susceptibility are essential for correct and timely management of meningitis in neonates. This study was therefore conducted to analyse the trends in bacterial aetiology and antimicrobial resistance in neonatal meningitis at a tertiary care hospital of North India with emphasis on the prevalence of Methicillin Resistant Staphylococcus Aureus (MRSA) and Vancomycin Resistant Enterococcus (VRE).

Aim and Objectives

To study the changing patterns in the bacteriological profile and antibiogram of CSF culture isolates from neonatal meningitis cases in a Neonatal Intensive Care Unit of SMGS hospital, Jammu, J&K.

Methods

This collaborative study was done prospectively in the Department of Microbiology in association with Department of Paediatrics at Neonatal Intensive Care Unit (NICU) of SMGS Hospital, Jammu. A total of 340 suspected neonatal meningitis cases admitted in the NICU, during the period from May 2016 to May 2017 were recruited in the study.

A structured performa was used to collect demographic details after taking applied assent from the parents of the neonates. The information included age, gender, birth weight, gestational age, mode of delivery of the neonate and age of onset of illness. Cerebrospinal fluid (CSF) samples were collected from all neonates suspected for meningitis. 1-2 ml of CSF was collected by lumbar puncture taking all the aseptic precautions.[9] The specimens were processed immediately and in case of delay, they were kept in the incubator at 37^0C. The collected sample was transferred immediately to the specific automated aerobic paediatric culture bottle [Bact/Alert PF Plus Fastidious Antibiotic Neutralization bottle (bioMerieux # 410853)] used for testing of sterile fluids. The samples thus transferred were cultured by automated BacT/Alert and VITEK2 system as per validated laboratory protocol of Microbiology laboratory for rapid isolation and sensitivity test. Data of positive CSF cultures was analysed by appropriate tools.

Results

Out of 340 clinically suspected meningitis cases in neonates, a total of 67 (19.7%) were positive. 42 neonates (62.7%) had Gram-negative isolates, 21 (31.3%) were Gram-positive pathogens and 4 (6%) had fungal infection.

Among the Gram-negative isolates, common species isolated were *Escherichia coli* (38%), *Acinetobacter sp.* (23.8%) and *Enetrobacter sp.* (16.7%) followed by *Klebsiella sp.* (9.6%), Pseudomonas sp. (4.8%) along with the isolation of rare organisms like *Stenotrophomonas sp.*, and *Serratia sp.* (Table 1)

Table 1 Distribution of Gram-negative isolates causing Neonatal Meningitis

Bacterial pathogen (n=42)	No. (%)
Escherichia coli	16 (38%)
Acinetobacter sp.	10 (23.8%)
Enterobacter sp.	07 (16.7%)
Klebsiella sp.	04 (9.6%)
Pseudomonas sp.	02 (4.8%)
Others	03 (7.1%)

Table 2 Percentage of antibiotic resistance in Gram-negative isolates causing Neonatal Meningitis

Antibiotic	E.coli (n=16)	Acinetoacter sp. (n=10)	Enterobacter (n=07)	Klebsiella sp. (n=04)	Pseudomonassp. (n=02)	Others (n=03)	No (%) (n=42)
Ampicillin	16	10	07	04	02	03	42 (100%)
Gentamicin	11	07	06	03	02	03	32 (76.1%)
Amikacin	02	02	02	01	01	03	11 (26.1%)
Cefoperazone- sulbactum	05	03	02	01	01	03	15 (35.8%)
Imipenem	02	02	0	01	01	01	07 (16.7%)
Meropenem	01	03	01	0	0	02	07 (16.7%)
Tigecycline	0	01	0	0	0	0	01 (2.38%)
Colistin	0	0	0	0	02	02	04 (9.6%)

Antibiotic pattern suggested high degree of resistance to first line penicillins and gentamicin, moderate to amikacin and cefoperazone – sulbactum. (Table 2)

Table 3 Distribution of Gram-positive isolates causing Neonatal Meningitis

Isolates (n=21)	No. (%)
Enterococcus sp.	08 (38 %)
CONS	08 (38 %)
Staphylococcus aureus	05 (24 %)

Table 4 Percentage of antibiotic resistance in Gram-positive isolates causing Neonatal Septicaemia

Antibiotic	Enterococcus sp. (n=08)	CONS (n=08)	*S. aureus* (n=05)	No (%)
Penicillin	08	08	05	21 (100%)
Cefoxitin	08	08	04	20 (95.2%)
Aminoglycosides	08	0	01	09 (42.8%)
Quinolones	07	02	02	11 (52.3%)
Linezolid	0	0	0	0
Vancomycin	03	0	0	03 (14.2%)

Among the Gram-positive isolates, *Enterococcus sp*. and CONS were found in highest numbers, each contributing 38% of the total gram positive isolates, followed by *Staphylococcus aureus* (24%). Antibiotic pattern suggested 100% resistance to penicillins with all the isolates as Methicillin Resistant *Staphylococcus aureus* (MRSA). Moderate to high level resistance was seen in aminoglycosides (42.8%) and quinolones (52.3%) with 14.2 % of Vancomycin resistant enterococcus sp. (Table 4)

Discussion

Neonatal infection is one of the major causes of neonatal deaths in India. Bacterial meningitis being a life-threatening condition requires prompt diagnosis and treatment, but diagnosis in newborn is a challenge for clinicians because symptoms and signs are often subtle and non-specific at its early stage.[7] The age at presentation with meningitis will suggest both the probable organisms and their likely mode of acquisition. Presentation in the first week of life (early onset) and particularly in the first two days of life, reflects vertical transmission, while late onset infection suggests nosocomial or community acquisition. The corresponding organisms are different; early onset meningitis is more likely to be caused by group B streptococcus (GBS), Escherichia coli, and Listeria monocytogenes, while late onset meningitis may be caused by other gram negative organisms as well as staphylococcal species.[10] Gram-negative enteric bacilli and GBS currently are responsible for most cases. Organisms that cause acute bacterial meningitis in older children and adults—Streptococcus pneumoniae, Neisseria meningitidis, and type b and non typable Haemophilus influenza are relatively infrequent causes of meningitis in the neonate. [11] Moreover, these organisms are important, however in parts of Asia, especially parts of East and Southeast Asia, a variety of gram negative bacilli are proportionately more important.[12] Before development of the sulfonamides, gram-positive cocci including S. aureus and b-hemolytic streptococci caused most cases of neonatal sepsis. With the introduction of antimicrobial agents, gram-negative enteric bacilli, particularly E. coli, became the predominant cause of serious infection in the newborn.[11] There have been several published studies regarding meningitis conducted in hospitals in the developed countries but there is paucity of data collected from developing countries, particularly the Indian subcontinent. Regional information regarding trends in terms of etiology and antimicrobial susceptibility are essential for correct and timely management of meningitis. Keeping the current dismal scenario in mind, the following study was undertaken to evaluate the changing trends in aetiology and antimicrobial resistance pattern of pathogens causing Neonatal meningitis over a period of one year in a tertiary care hospital of North India.

During one year study, out of 340 clinically suspected cases of meningitis in neonates, a total of 67 (19.7%) were positive. The frequency (19.7%) of bacterial isolation from the CSF culture of neonates in this study was in accordance with many previous studies done in other countries. [13, 14] A limited number of bacteria associated with meningitis vary according to geographic location and age of onset. In most industrialized countries, the bacteria most

frequently isolated in the CSF are group *streptococcus agalactiae*, *E. coli* and *Listeria monocytogenes*. In developing countries like ours, Gram-negative are most frequently involved with a predominance of *E. Coli* followed by Gram-positive organisms.[15] The same is the case in present study where gram negative bacteria were predominant as compare to gram-positive ones, *Escherichia coli* being the commonest pathogen. This correlates with many other studies from India. [13, 16, 17] E. coli is the second leading cause of early onset sepsis (EOS) in neonates, accounting for about 24% of all EOS episodes, with 81% of cases occurring in preterm infants. When very low birth weight infants are considered alone, *E. coli* is the most frequent cause of EOS, accounting for 33.4% of episodes in a large, multicenter study. Coliforms, including *E. coli*, are frequently colonizers of the maternal vaginal canal, and infants acquire them at or just before delivery. EOS secondary to E. coli often presents with bacteraemia with or without meningitis at the time of delivery. Septic shock with clinical features associated with endotoxaemia may be present. While the antigenic structure of E. coli is diverse and complex, some virulence factors have been specifically identified as being important in neonatal sepsis. The K1 capsular antigen present in some strains is closely linked to neonatal meningitis and is the best-described virulence factor. [18] J.Nageswararao et al in Guntur, India did a study of bacterial meningitis in tertiary care hospital in all age groups and found that *E. coli* was the predominant pathogen in neonatal age group. [19] Other gram negative pathogens isolated in the present study were Acinetobacter sp. (23.8%), Enterobacter sp. (16.7%), klebsiella sp. (9.6%), Pseudomonas sp. (4.8%) with the isolation of rare organisms like Stenotrophomonas sp. and Serratia sp. (7.1%). Another study done by Utpala Devi et al in North-East India depicted Acinetobacter, Klebsiella and Pseudomonas as other important pathogenic causative agents of Neonatal Meningitis which is similar to the present study. These organisms can be isolated from various environmental sources including the hospital environment. Thus, it is likely that these can colonize the neonate and cause infection. [16] Furthermore, few rare organisms like Serratia sp. and Stenotrophomonas sp. were isolated in the present study. This observation is corroborated with the parallel study which identified Serratia sp. as the causative agent of Neonatal Meningitis.[20] This observation appears unique as this organism is rare in other reports across the globe and some reports have described the capacity of Serratia sp. to cause serious nosocomial infections in particularly ill patients, including neonates. [21] Another rare organism which has the propensity to cause Early Onset Neonatal Sepsis as documented by R. Viswanathan et al in 2010 [22] was also isolated. It was isolated in a premature baby born at 28 weeks of gestation after spontaneous rupture of membranes. It is a non fermentative gram negative bacillus, found in several environments such as water, soil and hospital settings and increasingly recognised as a significant cause of Hospital acquired infections particularly among severly debilitated and immunocompromised patients. [23]

Bacterial meningitis is a medical emergency. The therapeutic goal is to initiate antibiotic therapy within 60 minutes of a patient's arrival in the emergency room. In neonates suspected of having bacterial meningitis, cerebrospinal fluid (CSF) should be obtained for cultures and empirical antimicrobial therapy initiated without delay. Diagnosis of bacterial meningitis is confirmed by CSF culture the "gold standard" for diagnosis of meningitis and it is equally important to obtain the antimicrobial susceptibility of the causative microorganism to rationalize treatment. However, many infectious diseases are becoming increasingly difficult to treat because of antimicrobial-resistant organisms. Both the epidemiology of bacterial meningitis and the sensitivity to antibiotics are changing as a result of the widespread use of antimicrobials and other factors. Antimicrobial susceptibility data among CNS pathogens is therefore important to

effectively manage meningitis neonates in the first critical hours of their treatment. Empirical antibiotic therapy should be adjusted to local drug resistance patterns and clinical subgroups. It is therefore essential to monitor the emergence of resistance to antibiotics that are used for the empirical treatment as delay in providing effective treatment may adversely affect the outcome. [24] In our study, antibiotic pattern suggested high degree of resistance to first line penicillin and gentamicin, moderate to Amikacin and Cefoperazone-Sulbactum and least to carbapenems in case of Gram-negative isolates. Laving AM et al evaluated the antibiotic senstivity pattern in neonates suspected to have bacterial meningitis in NICU and found that almost all the isolates were resistant to Ampicillin and Gentamicin but showed moderate sensitivity pattern to Amikacin and Cephalosporins which correlates with our findings. [13] Another study done by Fatima Khan et al in Aligarh Muslim University [12] depicted good sensitivity percentage against Amikacin and Cefoperazone-Sulbactum which is again similar to our study. Thus, Amikacin and Cefoperazone-Sulbactum are emerging as effective groups in Gram negative meningitis.

Among the Gram-positive isolates, Enterococcus sp. and CONS were found in highest numbers, each contributing 38% of the total gram positive isolates, followed by *Staphylococcus aureus* (24%) which correlates with a study done in India by Utpala Devi et al. [16] 10% cases of neonatal bacteraemia and septicaemia are caused by *Enterococci* as reported by Shantala GB et al. [25] Enterococci rarely cause bacterial meningitis, though newborns seem more susceptible to this infection as they can acquire the infection from vaginal flora of the mother. [26] Antibiotic pattern of gram positive isolates suggested high degree resistance to penicillin and cefoxitin with almost all isolates as Methicillin resistant *Staphylococcus sp.* and moderate to high level resistance to aminiglycosides and quinolones. Studies have described a variety of risk factors that predispose infants to colonization and infection with MRSA. Low birth weight has been shown to be associated with increased risk of MRSA colonization and/or infection in multiple studies. Prematurity and younger gestational age have also been shown to be risk factors for MRSA colonization and infection, as has multiple gestations. A variety of procedures and devices that neonates in NICUs often require during their hospital stay are also associated with increased risk of MRSA, including endotracheal tube intubation and mechanical ventilation, percutaneous central venous catheterization, and surgery. Feeding methods, including gavage feedings and parenteral feedings, have also been associated with higher risk of MRSA infection. Longer length of hospital stay, kangaroo mother care, and presence of eye mucous in neonates' eyes have been shown to be independent risk factors for MRSA infection. [27] In conformity to our findings, other studies have also reported high level resistance against penicillins, probably better results against Amikacin and excellent coverage to Vancomycin and Linezolid. [28, 29]

The most striking observation in the present study was isolation of three isolates of *Vancomycin Resistant Enterococcus sp. VRE* sepsis is emerging as a significant problem in the intensive care setting. The infection can be acquired from the carrier mother or as cross infection from the hospital. The treatment at any age is challenging, but there is a dearth of information on the cause of infection and its treatment in neonates. [25] VRE infection has become an increasingly threatening infection especially for neonatologists. The reported incidence is nearly 10% of all cases of neonatal sepsis. [30] Serious enterococcal infections are often difficult to treat since the organism exhibit intrinsic resistance to many commonly used antibiotics. *Enterococcus faecium* strains as compared to *E. faecalis* display a higher degree of drug resistance to multiple other antibiotics as well, including ampicillin, gentamicin, ciproflox-acin and vancomycin as in the present study where all the three isolates were *Enterococcus Faecium*

resistant to the commonly used antibiotics including Vancomycin. [25] Seven types of glycopeptides resistance have been described among *enterococci*: Van A and Van B are considered the most clinically relevant phenotypes and are usually associated with *E.faecalis* and *E.faecium* isolates. In India, Van A VRE has been reported mainly in *E.faecalis*. There are very few case reports of Neonatal sepsis caused by Vancomycin resistant *Enterococcus faecium* which made us report these cases stressing the need for strict enforcement of infection control practices. Mohanty et al., first documented isolation of vancomycin- resistant *E. faecium* of VanA phenotype from a 3-year-old child with PDA in India.[31] Another case report given by Shantala et al also reported E. faecium as the causative agents in neonatal sepsis. [25] The primary therapeutic options for patients with VRE infection include quinupristin/dalfopristin and Linezolid, but the use of quinupristin/dalfopristin is limited because of its adverse effects profile, need for a central line and because of its lack of coverage against *Enterococcus faecalis*. Linezolid is active against *E. faecium* and *Enterococcus faecalis*. Hapnes et al., reported a case of Vancomycin resistant *Enterococcus faecium* in a 10 d old infant who was successfully treated with Linezolid. [32] Fortunately, all the three isolates were well senstive to Linezolid in the present study. Surveillance cultures triggered by detection of VRE in even a single clinical culture appear justified, because it may detect a large hidden reservoir of VRE colonization among infants.

Conclusion

In conclusion, it may be emphasized that there is utmost need to conduct area specific monitoring studies to profile different pathogens responsible for Neonatal meningitis and their resistance patterns so as to generate data that would help clinicians to choose the correct empirical treatment. The Microbiology Laboratory plays a pivotal role in early detection and reporting of VRE. In addition, close liaison between the clinicians and the microbiologists will facilitate a significant reduction in mortality and morbidity caused by VRE. The emergence & spread of these pathogens can be significantly curtailed if appropriate infection control procedures, strict enforcement of antibiotic policies and screening programs are implemented immediately.

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