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Etiology of Neonatal Meningits at a Tertiary Care Centre in North India

Amber Azim[1]*, Gopa Banerjee[1], Amita Jain[1], Vimala Venkatesh[1], Prashant Gupta[1], Nishtha Singh[1], Mala Kumar[2] and Shalini Tripathi[2]

[1]*Department of Microbiology, King George's Medical University*

[2]*Department of Pediatrics, King George's Medical University*

***Corresponding Author:** Amber Azim, Department of Microbiology, King George's Medical University.

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Abstract

Introduction: Neonatal meningitis is a medical emergency having consistently high rate of mortality and morbidity in spite of leveled up vaccination, increased institutional deliveries with intrapartum prophylactic antibiotics and asepsis, and good hospital practices.

Material and Methods: Total 718 neonates were enrolled. CSF samples were cultured and read at 24, 48 and 72 hours. WBC Count of CSF of 30 / mm^3 was considered cutoff to rule out possible contamination. Culture positive isolates were identified by MALDI-TOF VITEK MS. Antimicrobial susceptibility pattern was noted. PCR was done *for* atr gene of *Streptococcus agalactiae* of all culture negative samples.

Result: Out of 718 neonates enrolled 73 CSF were culture positive and 645 cultures were sterile. 5 isolates were probable contamination. Total 68 samples were positive with 63 bacterial isolates and 5 *Candida species*. Most commonly isolated bacteria were *Acinetobacter spp* (42%). and *Klebsiella pneumoniae* (15.9%). Among fungal isolates *Candida albicans* (4.4%) and *Candida parapsilosis* (2.9%) were isolated. PCR detected 2 cases of *Streptococcus agalactiae* causing meningitis.

Conclusion: Percentage positivity of bacterial and fungal meningitis was found to be 9.1 % and 0.7% respectively. Out of 68 samples, 51 had Gram negative and 12 had Gram positive bacteria on culture. Fungal isolates grew in 5 samples. Rare organism like *Elizabethkingia anophelis* (2.9 %), *Chryseobacterium indologenes* (2.9 %) *Aerococcus viridians* (1.4%) were isolated. PCR detected 2 cases of *Streptococcus agalactiae* (atr gene) of bacterial meningitis. *Streptococcus agalactiae* being a common etiology, had not been isolated in our cultures.

Keywords: Neonatal meningitis; Etiology; Antimicrobial Susceptibility Pattern; Risk Factors

Introduction

Meningitis during the neonatal period remains a highly devastating condition with a morbidity rate of 20 to 60 percent [1]. It is the inflammation of the pia and arachnoid mater along with subarachnoid space, Most of the data regarding on etiology of neonatal meningitis is from developed countries where hospital facilities, vaccination status, institutional deliveries, intrapartum antibiotics with adequate hospital asepsis is maintained. In developing countries, the reported incidence of neonatal meningitis is much higher at 0.8-6.1 per 1000 live births, with mortality of 40-58% [2, 3]. In countries such as India there are not many studies done regarding the etiology and thereby the burden of neonatal meningitis is always under reported. In a thorough examination of mortality estimates in

2010, 7.6 million fatalities in children younger than 5 years old were estimated to have occurred with 64.0% (4.879 million) owing to infectious causes and 40.3% (3.072 million) occurring in neonates. 5.2% (0.393 million) of these infant deaths were caused by sepsis or meningitis [4].

Worldwide, the common bacterial causes of meningitis are *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, and *S. agalactiae* with > 40%, >35%, and >5.5% of Bacterial Meningitis (BM) in Africa respectively [5]. Jayaraman et al [6] in their study from north India found *Group B Streptococcus* was the most common pathogen detected in 49.3% (40) patients followed by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae type b*, *Escherichia coli*, *Klebsiella pneumoniae*, and Neisseria meningitidis ACYW135 in 23.4% (19), 7.4% (6), 6.1% (5), 6.1% (5), 6.1% (5), and in 1.2% (1) patients, respectively.

The incidence of early-onset neonatal meningitis [EONM] has been greatly reduced by the initiation of intrapartum antibiotics to combat Group B Streptococcus (GBS) infection still it remains the most common cause of both meningitis and neonatal sepsis [7]. The next common pathogen is Escherichia coli and has emerged as the most common cause of early-onset sepsis and meningitis [8].

In the late-onset neonatal meningitis [LOMN], most common offenders are Coagulase-Negative *Staphylococci* and *Staphylococcus aureus*, followed by *E. coli* and *Klebsiella*. Both rarA and marA may provide alternative pathways for the emergence of multidrug resistance in K. pneumoniae in the absence of the ramA gene [A].

[A] Elgendy SG, Abdel Hameed MR, El-Mokhtar MA. Tigecycline resistance among *Klebsiella pneumoniae* isolated from febrile neutropenic patients. J Med Microbiol. 2018 Jul;67(7):972-975.

Late-onset illnesss include additional organisms in the nosocomial environment, especially those in neonatal intensive care units, including *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* [9]. Also the common offenders like Klebsiella are found to be multidrug resistant as both rarA and marA may provide alternative pathways for the emergence of multidrug resistance in K. pneumoniae in the absence of the ramA gene [24].

The major problem for the clinicians is the non specific and subtle signs and symptoms in the neonates plus lack of any rapid laboratory investigations. Neonates usually present with fever, lethargy, irritability, poor suck, vomiting, diarrhea, respiratory distress, seizures and bulging fontanel [8]. Kernig sign and Brudzinski sign are often absent [10] making the diagnosis more difficult. It is widely known that the formation of the blood-brain barrier (BBB) begins in late gestation, continues into the postnatal period and the immune system of the neonates is immature [11]. Due to these neonatal characteristics, bacterial meningitis can result in acute problems affecting the brain parenchymal vessels (vasculitis), ventriculitis, systemic complications (including pneumonia), and septic shock, all contribute to an unfavorable prognosis [12]. Approximately 25-50% of survivors suffer from neurologic sequelae, such as deafness, blindness, cerebral palsy, seizures, hydrocephalus, or cognitive impairment [13].

The age of the patient (e.g., early-onset meningitis), specific risk factors, data regarding pathogens and their susceptibility within the nursery, and the ability of antibiotics to penetrate the CSF are used to determine which antibiotics to use empirically to cover the likely pathogens [14].

Inspite of the difficulty in diagnosis, high mortality rates and long term sequelae limited data is available. Also due to the use of antibiotics before culture lead to more cultures being negative and thereby under reporting of the cases. Hence this study was conducted to enumerate the common etiological agents and its antibiotic susceptibility pattern at a tertiary care centre that caters to a huge population of North India so that correct empirical antimicrobial can be initiated at the earliest. Therefore the study could serve its purpose to help decrease mortality and morbidity in fragile age group of neonates.

Material and Methods

The study was conducted in the Department of Microbiology in collaboration with Department of Pediatrics, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, to study the etiology and antimicrobial susceptibility pattern of meningitis in neonates.

Inclusion Criteria: Neonates (28 days or less than) who presented with a fever (100.4 F) should undergo a septic workup [1]. This includes a complete blood count (CBC) with differential, blood culture, catheterized urine routine and culture, chest radiograph, and lumbar puncture. Exclusion Criteria: Neonates with any anatomical malformation, structural defects, having any shunt (example: VP shunt) or those whose parents/guardian refused to give consent. We evaluated 1005 neonates; from among these we excluded 287 neonates as per the set criteria. We finally enrolled 718 neonates with signs and symptoms suggestive of infection (as part of septic screen) CSF and Blood samples were collected and send to Department of Microbiology, KGMU.

CSF was collected by lumbar puncture with complete asepsis and transported to laboratories within 2 hours of collection. Patient's name on all the labels and requisition form were verified. Gross appearance of CSF was noted. First culture was done on Chocolate agar, 5% Sheep Blood and MacConkey agar. Plates were then incubated in at 37°C for 72 hours. Plates were read at 24, 48 and 72 hours. Secondly, wet mount and direct Gram stain were seen for pus cells and microorganisms. WBC Count was noted and more than 30 per mm^3 was considered positive; to rule out possible contamination. CSF samples were then stored at -20°C for further processing. Identification of culture positive isolates was done by MALDI-TOF VITEK MS, Biomeriux, France. Antimicrobial susceptibility testing was done by standard Kirby Bauer disk diffusion method on Muller Hinton agar (MHA) plates as per Clinical and Laboratory Standards Institute (CLSI) guidelines 2022, M100. Colistin MIC by Broth dilution where the isolates were resistant to most of the antibiotics. If white opaque moist colonies of *Candida* grew on Sheep Blood Agar along with supportive findings of wet mount and direct gram stain (presence of Budding Yeast samples were further processed for identification of microorganism by MALDI-TOF VITEK MS, or by various Biochemical tests, Germ tube test and India Ink. Antifungal susceptibility testing was done by Broth Micro dilution method according to CLSI M27 A4 guidelines.

In case where there was no growth on culture plates for 72 hours, PCR was done for atr gene of *Streptococcus agalactiae* (from the samples that were stored at -20°C). *atr* primers 5'- CAA CGA TTC TCT CAG CTT TGT TAA-3' and 5'-TAA GAA ATC TCT TGT GCG GAT TTC-3' were used [16].

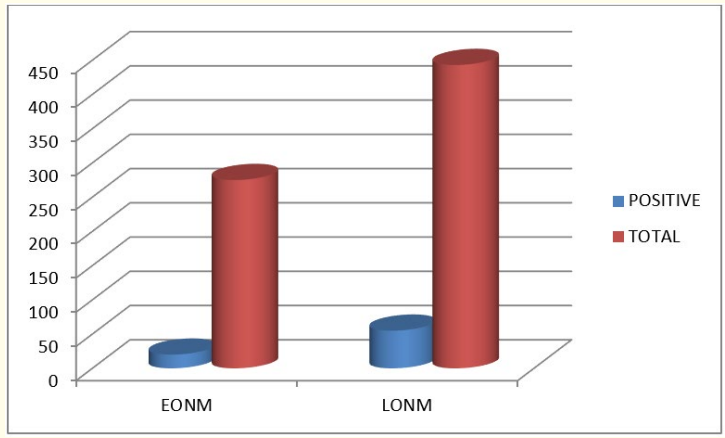
The amplification was performed with an initial denaturation at 94°C for 1 min followed by 30 cycles of 1 min at 94°C, 45 s at 55°C for primer annealing, 1 min at 72°C for elongation and a final period of extension at 72°C for 10 min. The amplification products were detected by electrophoresis using 10 µL of the amplified reaction mixture in agarose gel 2%, containing ethidium bromide [15]. Visualization was performed with ultraviolet light transilluminator. A 100-bp molecular weight marker (Invitrogen®, Calbad, USA " Ladder") and a positive control of S. agalactiae were used to evaluate the PCR products. The samples presenting a 780-bp amplicon were considered positive for *Streptococcus agalactiae*.

Results

Out of 718 neonates enrolled, 73 CSF samples were culture positive and 645 cultures were sterile on culture.5 isolates from 73 positive samples were Coagulase negative Staphylococcus with wet mount and direct gram stain negative for pus cells and microorganism and WBC count less than cutoff of 30/µl, hence were considered contamination. Total 68 samples were positive with 63 bacterial isolate and 5 were *Candida species*.

Out of total 718 neonates enrolled 394 were males and 317 were females. Among 394, 44 males (11.2%) whereas 26 females (24 culture positive and 2 PCR positive for *Streptococcus agalactiae* atr gene: 8.2%) were diagnosed as proven cases of meningitis. The difference between the two genders was found to be statistically insignificant. 275 neonates presented early and 443 had late presentation of sign and symptoms. Out of these, 20 and 55 samples were positive (either by culture or PCR) in Early and Late onset cases of

neonatal meningitis respectively. Cases of Late onset neonatal meningitis was significantly higher (12% vs. 6.9% cases of early onset meningitis) {the p-value is 0.028511. Significant at p< 0.05}. [Graph 1]. Fatality was higher in EONM than late onset ones (35% vs. 16%).



Graph 1: Positive and Total Cases of Early Onset and Late Onset Neonatal Meningitis.

Gram negative bacteria were reported more in LONM than in EOMN. There were 4 *Candida spp*. isolated from late onset cases.

Common presenting symptoms of neonates suspected of meningitis were refusal to suck (98.8%), fever (88.8%) and irritability (82.6%), vomiting (66.0%), respiratory distress (47.9%) and seizures (21.6%). Other presenting symptoms were drowsiness, bulging fontanelle, neck rigidity, unconsciousness, cyanosis, anuria. Seizure was found to be significantly associated with culture positive meningitis (51.7% vs. 12.9%).

Low/Very low birth weight (22% vs. 6%), premature delivery (24% vs. 3%) premature rupture of membrane (14% vs. 1.5%) was significantly higher among culture positive meningitis cases than culture negative cases.

Most commonly isolated bacteria were *Acinetobacter spp* (42%). and *Klebsiella pneumoniae* (15.9%). Among fungal isolates *Candida albicans* (4.4%) and *Candida parapsilosis* (2.9%) were isolated. In one sample, 2 mixed microorganisms were isolated on culture (*Acinetobacter baumanii* and *Pseudomonas aeruginosa*). Table 1

PCR done in all culture negative samples, detected additional 2 cases of *Streptococcus agalactiae* (atr gene) of bacterial meningitis.

Discussion

In the demographic characteristics of the study, overall males were reported more and culture positive percentage was higher (11.2 % vs. 8.2% females) but the actual percentage of males and females with proven meningitis was not significantly different.

Nada Abdelghani Abdelrahim, et al [16], Devi U et al [17] had higher percent of males among all the neonates with microbiologically proven meningitis in their studies. Though Al-Harthi AAet al [18] found no dominance of any gender in their study.

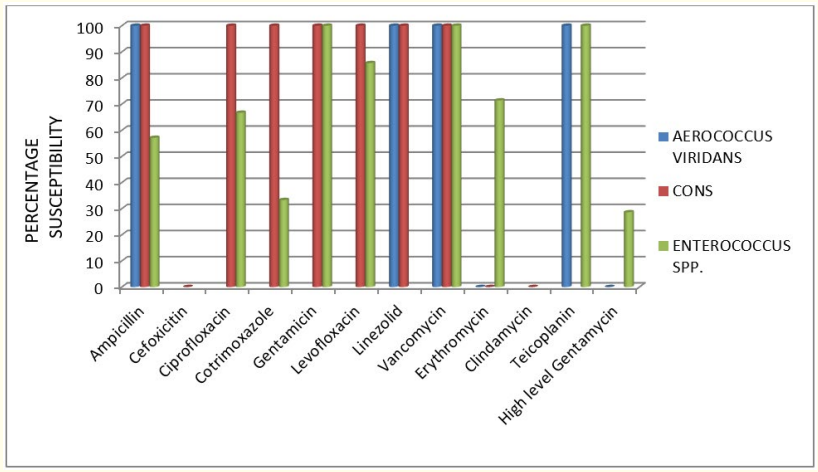
S. No.	Microorganism isolated	No. of cases
1.	*Acinetobacter baumanii*	25
2.	*Acinetobacter lwoffii*	2
3.	*Acinetobacter schindleri*	1
4.	*Acinetobacter junii*	1
5.	*Aerococcus viridians*	1
6.	*Chryseobacterium indologenes*	2
7.	*Citrobacter freundii*	1
8.	*Elizabethkingia anophelis*	2
9.	*Enterobacter cloacae*	1
10.	*Enterobacter hormachii*	1
11.	*Enterococcus faecalis*	7
12.	*Enterococcus faecium*	1
13.	*Escherichia coli*	2
14.	*Klebsiella pneumonia*	11
15.	*Pseudomonas aeruginosa*	3
16.	*Staphylococcus haemolyticus*	2
17.	*Staphylococcus hominis*	1
18.	*Candida albicans*	3
19.	*Candida parapsilosis*	2
	Total	69

Table 1: Bacterial and Fungal species isolated from CSF samples.

Early onset meningitis (EONM) was considered when features of meningitis/ infection were noted within or on 3rd day of birth and late onset is in neonates who presented after 3 days of birth. Neonates with late onset meningitis were more in number than early onset (12% vs. 6.9%) but it was found that fatalities were more in early onset meningitis (35% vs. 16%). The number of culture / PCR proven cases of LONM was significantly higher than EONM. {p value< .05}. [Graph 2]. There were 5 *Candida spp*., all isolated from late onset cases.

In a similar study conducted by Jean Gaschignard, et al [19] on Neonatal Meningitis over a period of 7 years got same results. They took 444 cases among which LONM was more common than EONM (68% (301) vs. 32% (143)). In a brief report by E Nel [20] that included eighty-eight neonates reported that 34 percent fatalities were within 72 hours of admission.

In the present study we found total 73 culture positive isolates. 5 Coagulase Negative *Staphylococcus* were considered and excluded as contamination as no pus cells or microorganisms were found in wet mount or direct gram stain and WBC count was less than 30 per mm3. There were Gram negative bacteria in 51 cases (75 %) and 12 were gram positive bacteria (20.5 %) out of 68 isolates grown, excluding contamination. *Candida spp*. were isolated in 5 (7.3%) of cases. Various microorganisms isolated on CSF culture are enlisted in table 1. Two mixed isolates, *Acinetobacter baumanii* and *Pseudomonas aeruginosa* were detected from a single sample. PCR (atr gene) detected additional 2 cases of *Streptococcus agalactiae* of bacterial meningitis. Being one of the commonest etiological agents in neonatal meningitis, an enhanced search by PCR for *Streptococcus agalactiae atr* gene was done. Anouk M Oordt-Speets et al [5] had done similar analysis specifically for *Streptococcus agalactiae*.



Graph 2: Percentage Susceptibiity of Antimicrobial Agents for Gram Positive Bacteria.

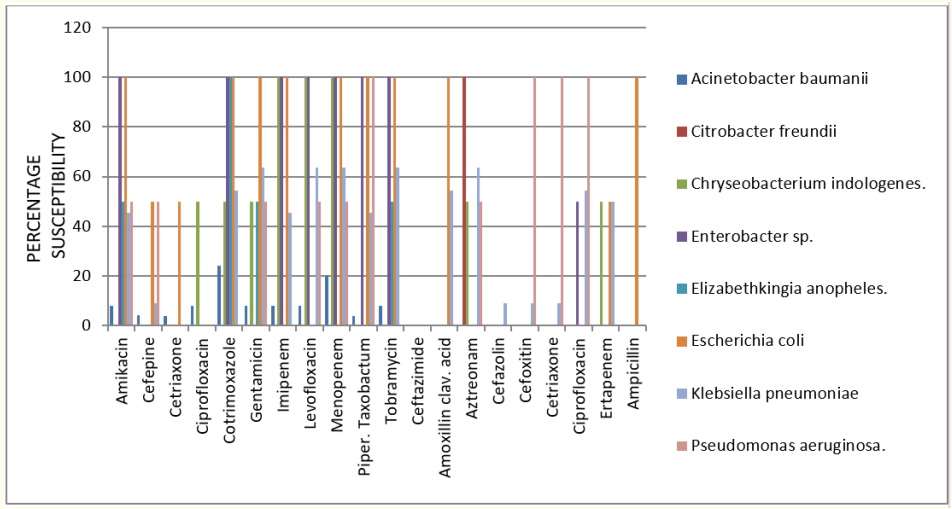
In a study by Devi U et al [17] in North East India, out of 303 CSF samples tested, 67 were positive for microorganism. Of these, 52 were positive by culture and another 15 by 16S rRNA gene PCR. Five of these were excluded as probable contaminant. Similarly in a study by Gupta K et al [21] Out of approximately 65.6% of culture positive cases, *Escherichia coli* was the most commonly implicated pathogen. Other important pathogens isolated were *Klebsiella spp*. and *Staphylococcus aureus*.

In our study, antimicrobial sensitivity pattern of gram positive bacteria showed that *Enterococcus* and *Staphylococcus* were sensitive to most of the drugs. In case of gram negative bacteria, *Acinetobacter spp*. was frequently found to be resistant to most of the drugs. It showed highest sensitivity to Cotrimoxazole (24%) and Meropenems (20%). Colistin MIC was intermediate in sensitivity. The pan resistant isolates prompts towards the possibility that these could be a hospital acquired infection. *Citrobacter freundii* was sensitive to Aztreonam only among all the antibiotics that were tested. *Klebsiella pneumoniae* showed alarming resistance with percentage sensitivity to gentamicin, tobramycin, meropenem, levofloxacin, aztreonam as 63%, next cotrimoxazole, ciprofloxacin and amoxicillin-clavalunic acid and least sensitive were cephalosporins (9%). GRAPH 3.

Another extensive study done by Pelkonen T, et al [22] performed susceptibility testing for most relevant antibiotic for 96 isolates found. They showed that 20 (34%) of the 59 these gram-negative bacteria tested were resistant to 3rd -generation cephalosporins, all being extended-spectrum β-lactamase (ESBL)-producing isolates. *Klebsiella spp*. and *Escherichia coli* were resistant against 3 rd -generation cephalosporins in 11/24 (46%) and 4/13 (31%) cases, respectively, but less so to gentamicin (1/18; 6% and 4/12; 33%, respectively.

In the present study, most commonly *Candida albicans* (4.4%) followed by *Candida parapsilosis* (2.9%) were isolated. MIC of *Candida albicans* and *Candida parapsilosis* were sensitive in all the 5 isolates.

In a prospective multicenter study by Leroy O, of 300 ICU patients in France with proven invasive candidiasis, *C. albicans* was the most common species isolated (57 percent), followed by *C. glabrata* (17 percent), *C. parapsilosis* (8 percent), *C. krusei* (5 percent), and *C. tropicalis* (5 percent) [23].



Graph 3: Antimicrobial Susceptibility Pattern of Gram Negative Bacteria.

Resistance among C. albicans represents a serious therapeutic problem that is mainly attributed to the over expression of efflux pump genes encoded by CDR1, CDR2 (related to azole cross-resistance), and MDR1 genes (confined to selective resistance to fluconazole) [25, 26]. The high costs of prophylaxis and treatment of fungal infections and the developed resistance in limited local resources are considerable clinical problems [27]. Hence correct empirical treatment at the earliest could only warrant in reducing both mortality and morbidity along with improving the prognosis of the disease.

Conclusion

Percentage positivity of bacterial and fungal meningitis was found to be 9.1 % and 0.7% respectively. Low/Very low birth weight, premature delivery, premature rupture of membrane was significantly higher among culture positive meningitis cases than culture negative cases.

There is a marked increase in number of cases having pan resistant *Acinetobacter spp*. as the causative agent of neonatal meningitis in tertiary care setting followed by *Klebsiella pneumoniae*. One of the commonest etiological agents of neonatal meningitis was *Streptococcus agalactiae* that had been extensively searched for, is not a common agent in the institute that caters to a huge Northern India population. *Candida spp*. forms only a small proportion of total culture positive cases of neonatal meningitis and was found to be susceptible to commonly used antifungal, (azoles and echinocandins).

There were few limitations in our study. Firstly, the samples collected were not necessarily before the commencement of antimicrobials that may lead to lesser culture positive isolates and thus under reporting of cases. Secondly, being a tertiary care centre possibility of hospital acquired infections cannot be ruled.

A continuous change in trend of etiological agents is observed attributed to vaccination or change in hospital / child birth practices. The conclusions would make it easier for the clinician to start the right choice of antimicrobials empirically and thereby reducing adverse outcomes.

Ethics approval

Institutional Ethical community Ref. Code: 107th ECM II B-Thesis/P14.

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