ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 6, Issue – 1, January – 2021 , Page No. : 102 - 112

Bacteriological Profile of Acute Bacterial Meningitis in Children in a Tertiary Care Hospital in Madurai

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Citation this Article: Sugumari Chandrasegaran, Ram Murugan Navaneetha Krishnan, "Bacteriological Profile of Acute Bacterial Meningitis in Children in a Tertiary Care Hospital in Madurai", IJMSIR- January - 2021, Vol – 6, Issue - 1, P. No. 102 – 112.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Context: Acute Bacterial Meningitis (ABM) is a medical emergency requiring immediate diagnosis and treatment. The bacterial pathogens responsible for ABM may vary with time, geographic distribution, age and preceding medical and/or surgical conditions of the patient. Information regarding the changing trends in terms of aetiology and antibiotic susceptibility in a particular region is essential for the correct and timely management of ABM.

Aim: This study was done to determine the bacterial pathogens responsible for ABM in children of 0-5 years of age and study their antibiotic susceptibility pattern.

Settings and Design: A cross-sectional study was carried out on clinically suspected cases of ABM at Government Rajaji Hospital, Madurai Medical College, for a period of one year.

Methods And Materials: Samples of Cerebrospinal Fluid (CSF) collected aseptically from clinically suspected cases of ABM were centrifuged and subjected to culture, Gram staining and antigen detection by Latex Agglutination Test (LAT). Antibiotic susceptibility testing was performed on all the isolates.

Results: CSF samples were collected from 138 clinically suspected cases of ABM and processed. The bacterial pathogen could be identified by centrifuged Gram stain in 27 cases (19.6%), by culture in 21 cases (15.21%) and by LAT in 19 cases (13.7%). Streptococcus pneumoniae was the predominant pathogen isolated in 5 cases (24%) followed by Group B Streptococcus, Coagulase Negative Staphylococcus, Klebsiella pnuemoniae & Citrobacter koseri, in 34 cases each(14.28%), Acinetobacter baumannii and Coagulase Negative Staphylococci (CoNS) in 2 cases each (12.5%) and Staphylococcus aureus in one case (6.25%) Drug resistance was common among Gram negative isolates in three cases (50%).

Conclusion: Streptococcus pneumoniae remains the most common aetiological agent of ABM in children. Multidrug resistant Gram negative bacilli are also important emerging causes of ABM. This study shows the importance of centrifuged CSF Gram smear along with culture for the accurate diagnosis of ABM in developing countries. LAT can be used as a simple,

rapid and convenient test to establish the bacterial aetiology in ABM.

Keywords: Acute Bacterial Meningitis, Streptococcus Pneumoniae, Latex Agglutination Test.

Introduction

Meningitis is an acute inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges[1].The World Health Organisation (WHO) estimated that annually BM causes at least 1.2 million cases worldwide and of those 135,000 result in deaths. [2] Acute Bacterial Meningitis(ABM) is among the top 10 causes of infection-related deaths worldwide. [3] The case fatality rate in India and other developing countries has been reported as 16-30%.[4] It is an acute medical emergency that requires urgent rational antibiotic therapy, especially in neonates and young infants. Neisseria meningitides, Streptococcus pneumoniae, and Haemophilusinfluenzae type b are pathogens most commonly associated with bacterial meningitis globally, accounting for almost 90% of reported cases in patients between 2 months and 5 years of age.[5]The most common symptoms are fever, headache and neck stiffness. Other symptoms include confusion or altered consciousness, vomiting, and an inability to tolerate light or loud noises. Young children often exhibit only nonspecific symptoms, such as irritability, drowsiness, or poor feeding[6].

The types of bacteria that cause bacterial meningitis vary according to the infected individual's age group. In premature babies and newborns up to three months old, common causes are group B streptococciand Escherichia coli (carrying the K1 antigen).

Older children are more commonly affected by Neisseria meningitidis (meningococcus) and Streptococcus pneumoniae (serotypes 6, 9, 14, 18 and 23) and those under five by Haemophilus influenzae type B[7].

In adults, Neisseria meningitidis and Streptococcus pneumoniae together cause 80% of bacterial meningitis cases. Meningitis occurs in 25% of newborns with bloodstream infections due to group B streptococci; this phenomenon is less common in adults.

The CSF sample is examined for presence and types of white blood cells, red blood cells, protein content and glucose level.[8] Gram staining of the sample may demonstrate bacteria in bacterial meningitis.CSF glucose to serum glucose ratio ≤ 0.4 is indicative of bacterial meningitis. In the newborn, a ratio below 0.6 (60%) is therefore considered abnormal. High levels of lactate in CSF indicate a higher likelihood of bacterial meningitis [9].

Microbiological culture of the sample is more sensitive (it identifies the organism in 70–85% of cases) but results can take up to 48 hours to become available. A latex agglutination test may be positive in meningitis caused by Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Escherichia coli and group B streptococci.Polymerase chain reaction (PCR) is a technique used to amplify small traces of bacterial DNA in order to detect the presence of bacterial or viral DNA in cerebrospinal fluid; it is a highly sensitive and specific test since only trace amounts of the infecting agent's DNA is required.

Meningitis caused by H. influenzae and meningococci has a better prognosis than cases caused by group B streptococci, coliforms and S. pneumonia. In adults, too, meningococcal meningitis has a lower mortality (3–7%) than pneumococcal disease[10] .

Therefore, the objective of this current study was, to analyze the pattern and antimicrobial sensitivity of pathogens isolated from the cerebrospinal fluid (CSF)

of children with suspected ABM in Government Rajaji Hospital, Madurai.

Materials and Methods

The study was carried out on 138 clinically suspected cases of ABM in children of 0 – 5 years of age, admitted at Government Rajaji hospital, Madurai for a period of one year from January 2014 to December 2014. The study was approved by our Institutional Ethics Committee. Criteria used for a definitive diagnosis of ABM in our study included a positive CSF culture with/without a positive Gram stain and/or a positive LAT along with at least one of the classical clinical manifestations of ABM and any one of the features of meningeal inflammation: a) CSF cell count >10 cells/mm3 with predominant polymorphonuclear neutrophils, b) CSF protein >45 mg%, and c) CSF glucose <40 mg%.

All CSF samples were collected aseptically in a dry sterile container and processed in the Microbiology Laboratory immediately. 2 mL of CSF was aliquoted into a sterile test tube and was subjected to centrifugation at 1000 rpm for 10-15 minutes. The deposit was used for culture and Gram staining. All CSF samples were inoculated on 5% sheep blood agar with staphylococcal touch colony, chocolate agar, MacConkey's agar and brain-heart infusion broth for enrichment from which subcultures were done. Blood agar with staphylococcal touch colony and chocolate agar were kept in a candle jar with 10% CO2 and all media were incubated at 37ºC. The culture plates were inspected for the presence of growth after overnight incubation. When growth appeared, a secondary smear was performed from the colony. When no growth occurred, all the plates were further incubated for a minimum period of 48 hours.

The isolates were identified by Standard Microbiological techniques and Antibiotic susceptibility pattern was determined by Kirby-Bauer disc diffusion method on appropriate media in accordance with Clinical Laboratories Standards Institute (CLSI) guidelines. When organisms were present in the Gram smear, a direct antibiotic sensitivity testing was done. For Gram positive organisms, the following antibiotics were tested: Ampicillin, Penicillin (10 units), Oxacillin (1 μg), Cefotaxime (30 μg), Cefazolin (30 μg) and Vancomycin (30 μg), Levofloxacin, Linezolid & Erythromycin. The antibiotics tested for Gram negative bacilli were Ampicillin, Cotrimoxazole, Gentamicin (10 μg), Amikacin (30 μg), Cefotaxime (30 μg), Ceftazidime (30 μg), Chloramphenicol, Piperacillin (100 μg), and Meropenem (10 μg).

The CSF supernatant was drawn off aseptically and used for detection of soluble antigens of Streptococcus pneumoniae; Haemophilus influenzae type b; Neisseria meningitidis A, B, C, Y and W135; E. coli K1 and Group B streptococcus by LAT using commercially available kits (Wellcogen Bacterial Antigen Kit, Remel Europe Ltd, U. K.). The procedure was performed as per the manufacture's guidelines.

Results

During the one-year study period, a total of 138 CSF samples were collected and processed from clinically suspected cases of Acute Bacterial Meningitis. The bacterial pathogens were isolated by culture in 21 cases (15.21%). CSF cell count varied from 150-11,600 cells/mm3 with a predominant Neutrophilic pleocytosis. All culture proven cases had an elevated CSF protein above 45 mg% and 8 (38.09%) cases had CSF protein above 200mg%. All 21 (100%) cases had CSF glucose less than 40 mg%.

Table 1: Age & Sex Wise Distribution of Study Population (N=21)

Age	Male	Female
0 – 12 months	8(38.09%)	6(28.57%)
13 – 24 months	2(9.52%)	0
25 – 36 months	2(9.52%)	1(4.76%)
37– 48 months	0	2(9.52%)
49– 60 months	0	0
Total	12(57.14 %)	09(42.86 %)

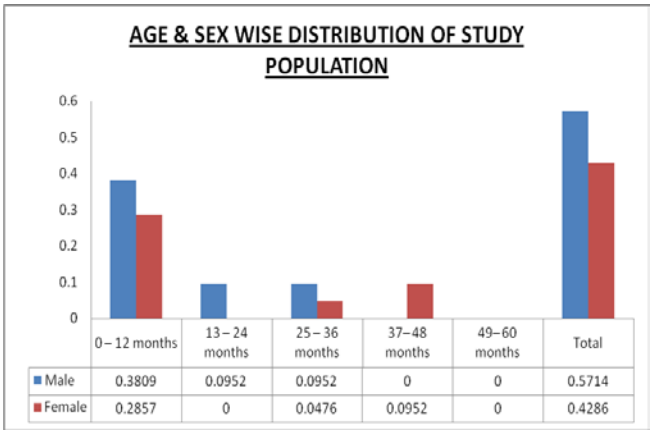

Table 1(Chart 1) Shows that out of the 21 culture confirmed cases, 14 (66.7%)cases were identified (0-12months) below 1 year of age. Of the total 21 cases, 12 (57.14%) were males and 9(42.86%) were females.

Table 2: CSF Gram Reaction of Study Population (N=21)

Sn.	Gram Reaction	Number (%)
1.	Gram Positive Cocci	13(61.91%)
2.	Gram Negative Bacilli	8 (38.09%)
	Total	21(100%)

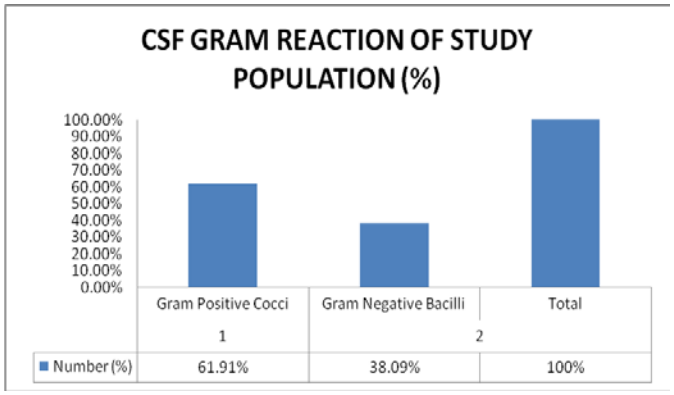

Table 2: (Chart -2) Shows that out of 21 culture positive cases, 13(61.91%) were Gram positive cocci and 8(38.09%) were Gram negative bacilli.

Table 3: Bacterial Agents Isolated In CSF Culture (N=21)

Sn.	Organisms	Number (%)
1.	Streptococcus pnuemoniae	5 (24%)
2.	Group B Streptococcus	3 (14.28%)
3.	Coagulase Negative Staphylococcus	3 (14.28%)
4.	Klebsiellapnuemoniae	3 (14.28%)
5.	Citrobacterkoseri	3 (14.28%)
6.	Staphylococcus aureus	2 (9.52%)
7.	Escherichia coli	2 (9.52%)
	Total	21 (100%)

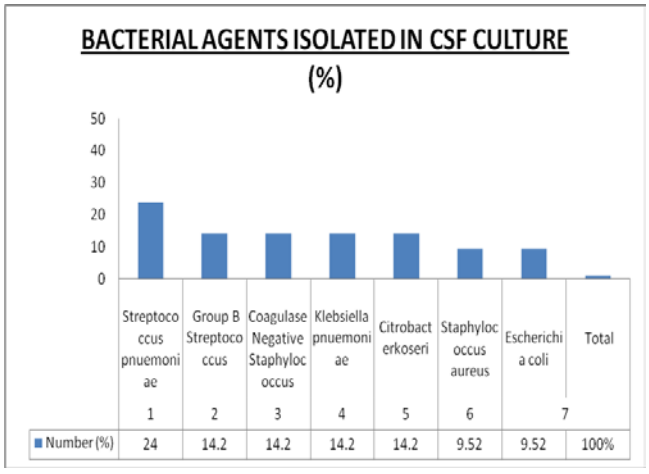

Table -3(Chart -3) shows that, Streptococcus pneumoniae was the predominant pathogen isolated in 5 cases (24% of total culture positives) followed by Group B Streptococcus, Coagulase Negative Staphylococcus (CoNS), Klebsiella pnuemoniae & Citrobacter koseri, in 3 cases each(14.28%), Escherichia coli and Staphylococcus aureus in 2 cases each (9.52%) The rest of the CSF samples were sterile on routine bacterial culture.

Table 4: CSF Gram Smear and Culture Isolates (N=138)

Sn.	Gram Smear	Number	Isolates	Number	%
1.	Pus cells with Gram Positive Diplococci	8	Streptococcus pneumoniae	5	62.5%
2.	Pus cells with Gram Positive cocci in clusters	6	1.Staphylococcus aureus 2.CONS	2 3	33.3% 50%
3.	Pus cells with Gram Positive cocci in chains	3	Streptococcus species	3	100%
4.	Pus cells with Gram Negative bacilli	10	1.Klebsiella pneumonia 2.Citrobacter koseri 3.Escherichia coli	3 3 2	30% 30% 20%
5.	Pus cells	16	-		
6.	No pus cells&No Bacteria	95	-		
	Total	138	-	21	

Table 5: Correlation of CSF Gram Smear with Culture Isolates **(n=138)**

Sl. No.	ORGANISMS	Culture Positive	Culture Negative	Total
1	Smear Positive	21	6	27(19.6%)
2	Smear Negative	0	111	111(80.4%)
	Total	21(15.2%)	117(84.8%)	138 (100%)

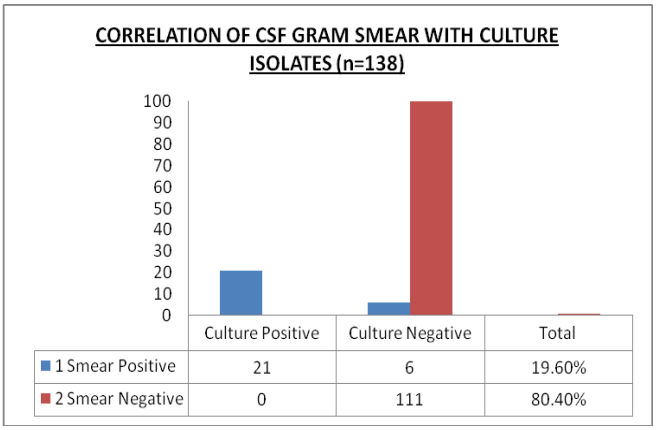

Table -4 & Table -5 (Chart - 4) Shows that, out of 138, 21 culture positive cases (15.21%) were also Gram smear positive. Additional 6 cases, which included 4 cases of meningitis due to Gram positive cocci, which are culture negative and 2 cases of culture negative Gram negative bacillary meningitis could be detected by their typical morphology in the centrifuged Gram smear .Thus Gram smear were positive in 27 samples (19.6%), though pus cells could be detected in CSF by Gram stain in 43 samples (31.15%) (See Table 4 and 5).

Out of 138 samples, 95samples (68.84%) had no finding on Gram stain, culture or latex agglutination test. LAT could detect the capsular antigen of Streptococcus pneumoniae in 5 CSF samples (3.6%), which included ,3 culture positive and two culture negative cases. Out of the five culture positive cases of Streptococcus pneumoniae, one was negative by LAT. Among 3 smear positive cases of Streptococcus pneumoniaewhich were culture negative, 2 were positive by LAT. Other than Streptococcus pneumoniae, 8 cases of Group B Streptococci, 3 cases of Haemophilus influenzae& Neisseria meningitidis each were detected by LAT. Thus the aetiological agent could be detected in 37 cases (26.8%) by Gram stain and culture and/or LAT.

Table 6: Antibiotic Susceptibility Patterns of Gram Positive Isolates

Antibiotics	Streptococcus pneumonia (n =5)	Group B Streptococcus (n= 3)	Staphylococcus aureus (n= 2)	CONS (n= 3)
Ampicillin	NT	3 (100%)	1(33.3%)	3 (100%)
Penicillin	4 (80%)	3 (100%)	0	3 (100%)
Oxacillin	3 (60%)	3 (100%)	0	0
Cefotaxime	4 (80%)	3 (100%)	2 (100%)	3 (100%)
Cefazolin	NT	1 (33.3%)	2 (100%)	3 (100%)
Vancomycin	5 (100%)	NT	NT	NT
Levofloxacin	5 (100%)	NT	NT	NT
Linezolid	5 (100%)	NT	NT	NT
Erythromycin	4 (80%)	NT	NT	NT

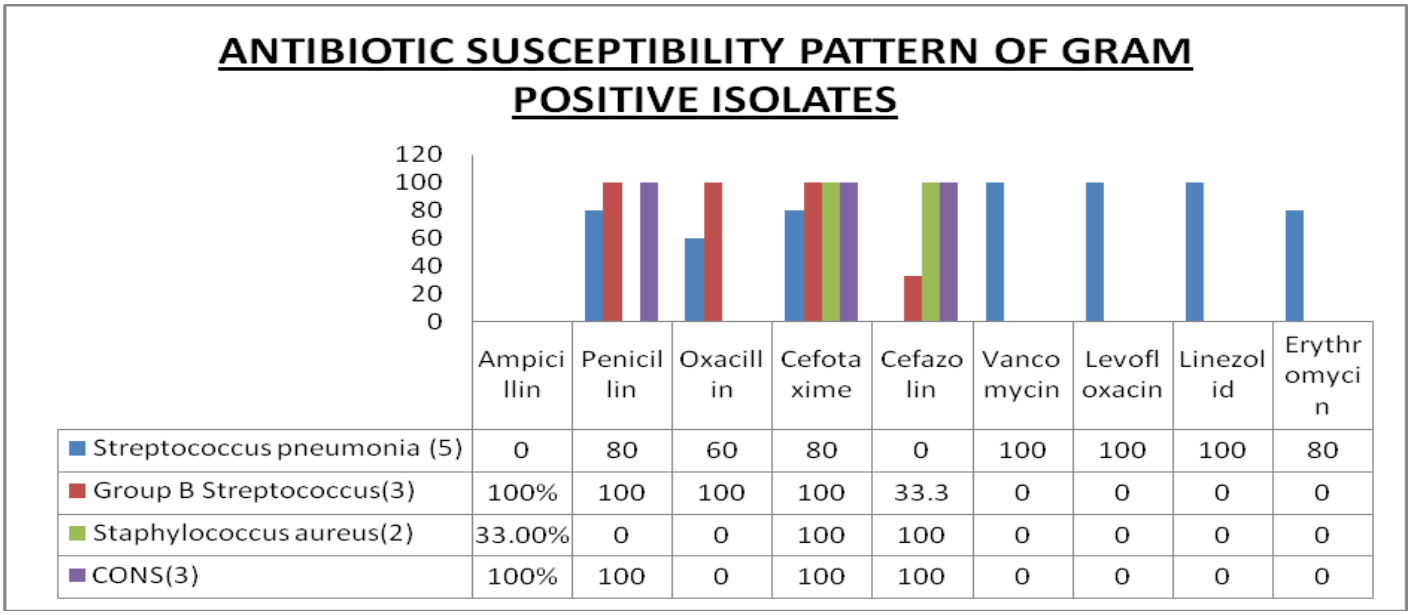

Table 7: Antibiotic Susceptibility Patterns of Gramnegative Isolates

Antibiotics	Klebsiella pneumonia (n=3)	Citrobacter koseri (n=3)	Escherichia coli (n=3)
Ampicillin	1(33.3%)	1(33.3%)	0
Cefotaxime	2 (67%)	3 (100%)	0
Ceftazidime	1(33.3%)	0	0
Gentamycin	2(67%)	3(100%)	0
Cotrimoxazole	2(67%)	2(67%)	0
Amikacin	3(100%)	3(100%)	1(50%)
Chloramphenicol	2(67%)	2(67%)	1(50%)
Piperacillin	3(100%)	3(100%)	2(100%)
Meropenam	3(100%)	3(100%)	2(100%)

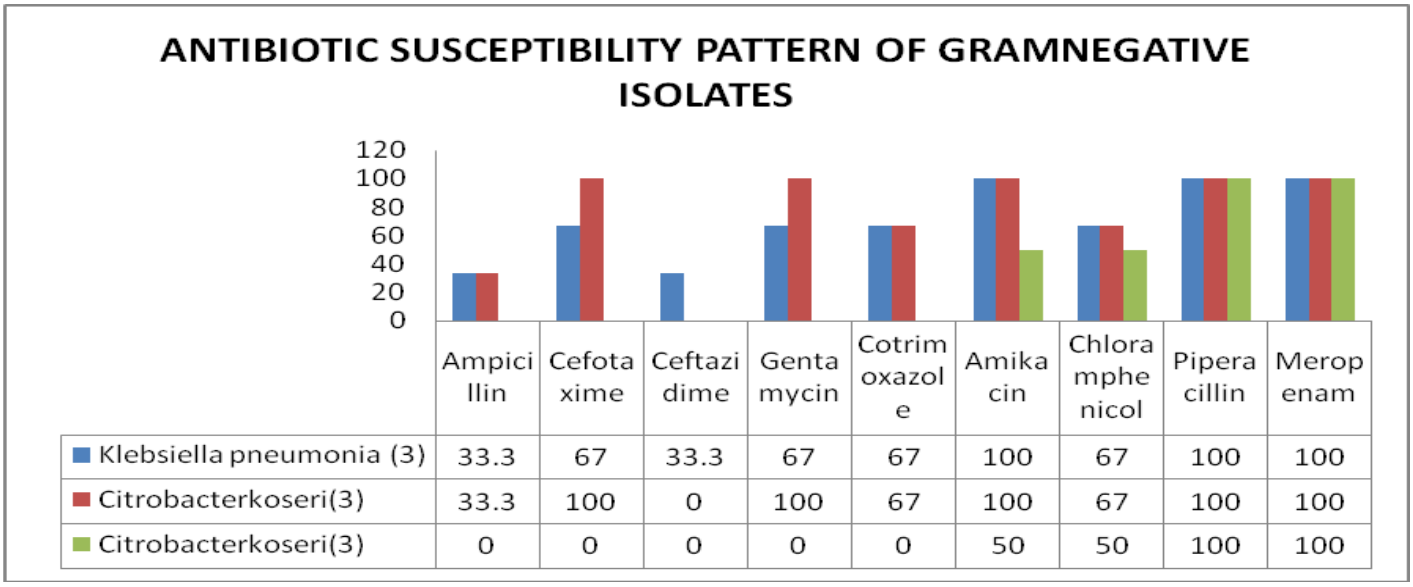

Table 6 &7 shows that, Streptococcus pneumoniae is highly susceptible to Vancomycin, Linezolid & Levofloxacin (100%)each. Methicillin resistance was detected in both Staphylococcus aureus and CoNS.& Group B Streptococcus was resistant to Cefazolin only. In present study, among Gram negative bacteria .Klebsiella pneumoniae ,Meropenam , Amikacin & Piperacillin(100%),. were highly sensitive while the less sensitive drugs were. Cefotaxime ,Gentamycin, Cotrimoxazole & Chloramphenicol (67%) with lowest sensitivity to ceftazidime & Ampicillin(33.3%). The Citrobacter showed lowest sensitivity towards Ampicillin. (33.3%). whereas their sensitivity to Cotrimoxazole & Chloramphenicol (67%), showing high sensitivity to Amikacin ,Meropenam , Piperacillin, Gentamycin &Cefotaxime(100%). Escherichia coli isolates showed multi-drug resistance. All of the Gram negative isolates were sensitive to Meropenem and Piperacillin.

Discussion

Acute bacterial meningitis is a medical emergency and immediate steps should be taken to establish the specific cause and initiate effective therapy. The choice of antimicrobial therapy depends largely on the most common pathogens encountered in that particular area, antibiotic susceptibility pattern and the age of the patient. In our study, Streptococcus pneumonia remains the major aetiological agent of ABM in children of 0-5 years of age. This is in concordance with the study conducted by **Amreshkumar et al , (12)**

A total 138 cases of acute bacterial meningitis (ABM) in children of 0-5 years of age admitted in the hospital during this 1 year period were included in the study. The bacterial pathogens were isolated by culture in 21 cases (**15.21%),** among which 14 number of isolates (66.7%) were identified below 1 year of age. Males (57.14%) were more common than females (42.86)(19)

The most common organisms were Gram positive bacteria (61.91%) which is supported by Amreshkumar **et al ,**who showed 66.18 % of Gram positive bacteria in his study.

The raised levels of CSF proteins and decreased CSF sugar levels were observed by us, which is similar to the findings in other studies(14)The aetiological agent could be detected in 37 cases(26.8%) by Gram stain and culture and/or LAT in our study, which is in concordance with the study of **Mani et al,(11)**who also

had some proof of infecting agent in 73.7 by culture/ smear and or LAT.

The bacterial pathogen could be identified by centrifuged Gram stain in 27 cases (19.6%), by culture in 21 cases (15.21%) and by LAT in 19 cases (13.7%) in our study , which is similar to the findings of **Das BK et al (15)**

Streptococcus pneumoniae was the predominant pathogen isolated in 5 cases (24% of total culture positives in our study which is in concordance with **Majed et al** who studied 160 CSF samples from patients with bacterial meningitis and found that 31 (19.4%) were culture positive, revealing the growth of H. influenzae (45%), S. pneumoniae (29%), and N. meningitides (19%); among children under 5 years old, S. pneumoniae was found in 80% of culture-positive cases.

No Penicillin resistance was detected among the pneumococcal isolates in this study. Resistance to Penicillin among Streptococcus pneumoniae isolated in India appears to be low, though it has been reported to vary between 1 to 12% according to **Deva A et al.(16)**However, resistant strains may create problems in treating the patients in the future, Whereas, **Chawla et al.(17)** detected 14% strains of S. pneumoniae had reduced penicillin susceptibility .Ceftriaxone or cefotaxime alone or in combination with vancomycin have been found to useful in treating these infections (13)This is in accordance with our finding. Treatment with an intravenous Ceftriaxone resulted in rapid clinical improvement without any neurological sequelae.

No Meropenem resistance was detected among Gram negative isolates. Antibiotic options for these multi-drug resistant strains were restricted to Meropenem(20)

Though the primary pathogens associated with ABM are Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis, these aetiological agents and their relative frequencies may vary in different geographical areas.(11) As compared to that which is seen in western studies, the relative incidence of meningitis caused by Haemophilus influenzae and Neisseria meningitidis is less in South East Asia.(11,18)No cases of Haemophilus influenzae or meningococcal meningitis were detected by Gram stain, culture in our study. As ours being a tertiary care hospital, majority of our patients were referred from nearby hospitals and were already on antibiotic therapy before presentation. This could be the main reason for a low percentage of bacterial isolates on culture in our study. CSF sterilization might have occurred more rapidly with parenteral antimicrobial therapy. Moreover, our study being conducted only for a period of one year, a study for a longer period of time may help to detect these meningeal pathogens.

Several newer molecular techniques for detecting bacterial DNA in CSF by Polymerase Chain Reaction (PCR) with a high sensitivity and specificity have emerged as powerful tools in the diagnosis of patients with culture negative meningitis. Unfortunately, PCR was not available in our hospital during the study period.

Gram staining is the single most useful test for identifying ABM, as it revealed more positive cases than cultures.(18)In our study, Gram stain provided evidence of causative bacteria in 27 CSF samples (19.6%). Of these, 21samples yielded growth on culture and 6 were culture negative. It needs to be reiterated that simple tests like centrifuged Gram smear can help to establish the crucial diagnosis of ABM in our setup, especially in culture negative cases. **Mani et al,**has

attributed their high yield of pathogens on Gram stain to their routine use of cytospin to concentrate the smear.(11)

A properly interpreted LAT can be used as a simple, rapid procedure suitable to be used as an adjunct laboratory test in patients pre-treated with antimicrobial therapy and whose Gram stain and CSF culture are negative. The false-negative LAT in case of culture positive pneumococcal meningitis could possibly be due to very low antigen titres in CSF. It is also possible that the antiserum used in the diagnostic LAT kits does not detect all the capsular serotypes prevalent in a particular geographical area or probably as yet unrecognized serotypes are the causative agents.(11) As LAT is mainly used to detect the specific pathogens of community-acquired meningitis, CSF samples which yielded organisms other than Streptococcus pneumoniae on culture gave a negative LAT test. A negative bacterial antigen test does not rule out infection caused by a specific meningeal pathogen. As the high costs of LAT kits is a drawback for its routine use in our laboratories, affordable indigenous LAT kits can help to detect the serotypes prevalent in our geographical area.1 To increase the cost effectiveness in a resource poor setting, LAT for pneumococcal antigen should be performed first, as it is the most common pathogen causing ABM in paediatric age (11)

Limitations of The Study

Being a tertiary care centre, most of the patients referred to our hospital were already on antimicrobial therapy. Minimum Inhibitory Concentration (MIC) of the antibiotic could not be done for the isolates.

Conclusion

Streptococcus pneumoniae still remains the major aetiological agent of ABM in children. Multi-drug resistant Gram negative bacilli are also important emerging causes of ABM. This study highlights the importance of centrifuged CSF Gram smear for accurate and early diagnosis of ABM. LAT can be used as a simple, rapid and convenient test to establish the bacterial aetiology in ABM.

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