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Original Work

Antimicrobial sensitivity pattern of gram positive CSF isolates in children with septic meningitis in a Tertiary Care Hospital

Yashpal Chugh*, Arun Kumar Kapoor†Ψ and Anodita Bhargava‡

***Regional Medical Advisor, Astra Zeneca Pharma India Limited, New Delhi, India**
†Head, Department of Pharmacology, Rohilkhand Medical College, Bareilly (UP), India
‡Associate Professor and Head, Department of Microbiology, M L N Medical College, Allahabad (UP), India

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ABSTRACT: The present study was conducted with the objective to determine antimicrobial susceptibility of Gram positive CSF isolates in septic meningitis in a tertiary care hospital. CSF (3-5 ml) was collected from 638 admitted children clinically suspected of septic meningitis. Bacterial isolates were identified and microbial sensitivity was assessed by the Kirby-Bauerâ€™s disk diffusion method. Of the samples tested 102 (15.99%) were culture positive of which 45 (44.12%) culture positives were found in children aged 1-12 years. M: F ratio was 1.62:1. Maximum incidence (51 cases) was in summer-rainy season and in institutional delivery (58 cases). Primary immunization did not protect against septic meningitis. The isolates in 66 (64.71%) cases were Gram positive of which 36 (54.55%) were *Streptococcus spp*., 24 (36.36%) *Staphylococcus aureus* and 6 (9.09%) cases coagulase negative Staphylococcus (CONS). Both *Streptococci* and coagulase negative *Staphylococci* were highly sensitive (100%) to Linezolid, Vancomycin and Piperacillin-Tazobactam. However, *Staphylococcus aureus* were 100% sensitive to Linezolid and Vancomycin but were only 87.5% sensitive to Piperacillin-Tazobactam combination. The *Streptococcus species* showed a high degree of resistance to Tetracyclin 91.67%, Co-trimoxazole 88.89% and Penicillin 63.89%. *Staphylococcus aureus* showed resistance to the tune of 83.33% each to Tetracycline and Co-trimoxazxole and 79.17% with Penicillin. In case of coagulase negative *Staphylococcus*, Co-trimoxazole showed resistance in 83.33%, Penicillin in 66.67% and Tetracycline in 50% cases. In septic meningitis Gram positive isolates predominate. Therapy should be based on trends of bacterial sensitivity.

KEY WORDS: ***Antimicrobial Sensitivity; Gram Positive Organisms; Cerebrospinal Fluid***

INTRODUCTION

Bacterial meningitis is one of the most potentially serious infections occurring in infants and older children and is associated with a high incidence of acute complications and risk of long-term morbidity[1]. Systemic bacterial infections are known by the generic term neonatal sepsis which incorporates septicaemia, pneumonia and meningitis of the new born. Neonatal sepsis is the single most important cause (about 50%) of neonatal deaths in the community. About one-third of the neonates with septicaemia may have coexistent meningitis[2].

Despite great advances in antimicrobial therapy, neonatal and paediatric life support measures and early detection of risk factors, bacterial sepsis and meningitis continue to be a major cause of morbidity and mortality in newborns, particularly in low-birth-weight infants[3]. A wide variety of organisms has been described for cases of septic meningitis with wide fluctuations in their

Ψ**Correspondence at:** Department. of Pharmacology, Rohilkhand Medical College, Pilibhit Bypass Road, Bareilly, Uttar Pradesh, India; Cell: +919415373166; Email: drakkapoor@rediffmail.com

prevalence rate and antimicrobial sensitivity patterns subject to geographical alterations. The organisms isolated are more often multi-drug resistant, making treatment more difficult leading to grave sequelae. Thus there is a need for bacteriological monitoring in paediatric wards and determination of the antibiotic sensitivity patterns of isolated organisms. Neonates are particularly vulnerable to infections, so any delay in the initiation of empirical therapy or wrong choice of antibiotic may be fatal. Antibiotics are usually administered before the laboratory results of CSF culture and sensitivity are available. To ensure appropriate therapy, current knowledge of the organisms that cause septic meningitis and their antibiotic susceptibility pattern in a particular setting or region is of the utmost importance.

The initial antibiotic regimen should be such that it covers all the likely pathogens according to the age of the child, it should achieve sufficient bactericidal concentration in the CSF and the combination of antimicrobials should not be antagonistic. Later the treatment can be modified depending upon the result of Gram stain and CSF culture. CSF culture provides a confirmatory evidence of acute bacterial meningitis (ABM) and is essential for selecting the appropriate antibiotic for the etiological organisms[4]. The present study has been undertaken to evaluate the spectrum of pathogens causing septic meningitis and their antimicrobial susceptibility pattern in clinically suspected cases of ABM, also known as septic meningitis (SM) who were admitted to our tertiary care hospital.

METHODOLOGY

Our study group comprised of all children aged up to 12 years, of either sex who were clinically suspected of suffering with septic meningitis and admitted to S. N. Children Hospital attached to M. L. N. Medical College, Allahabad, Uttar Pradesh, India during the study period (2007-08). Patients diagnosed repeatedly with events of bacterial meningitis due to structural defects of the central nervous system and cases of meningitis caused by *Mycobacterium tuberculosis* were excluded[5].

CSF (3-5 ml) was collected by lumbar puncture with complete aseptic precautions: the rate of collection was 3-5 drops/minute[6]. The specimen of CSF was transported to the microbiology laboratory as soon as possible usually within 30 minutes with all proposed precautions, since delay may result in the death of delicate pathogens such as *meningococci*, and the disintegration of leucocytes. Samples were not kept in a refrigerator as this may kill *H. influenzae*. If delay for a few hours was unavoidable, the specimen was kept in an incubator at 37^0C[6]. CSF should be collected preferably prior to administration of antimicrobials, from all cases of suspected meningitis and sent for culture and sensitivity examination in a timely fashion to ensure accurate results.

A portion of the sample was inoculated on blood agar, chocolate agar, and McConkey agar by a standard loop method. The culture plate was incubated under 5-10% CO_2 at 37^oC for 18-24 hrs. The remaining CSF sample was inoculated in 5ml brain heart infusion broth and then incubated overnight. Next day the culture was observed for turbidity. If turbidity appeared and there was no growth on any of the solid media then subculture was performed from brain heart infusion broth on the three solid media mentioned as above.

The bacterial growth was interpreted by semi-quantitative method in terms of heavy, moderate and scanty growth on primary plating. No quantification was done if growth was observed after enrichment. Specimens that showed no bacterial growth after 48 hours of incubation in any of the four culture media was labelled as 'sterile'. Cultures showing growth of *Candida spp*. were not further evaluated.

Identification of bacterial isolates was carried out by Gram staining, motility, colony characteristics and biochemical tests. Antibiotic susceptibility tests and interpretations were carried out for bacterial isolates by the Kirby–Bauer's disc diffusion method following NCCLS guidelines[7-9]. The test was done by applying commercially available (HiMedia Laboratories Pvt. Limited, Mumbai, India) filter paper discs impregnated with a specific amount of an antibiotic on to Mueller–Hinton Agar/Blood agar surface, over which a saline suspension of micro-organism had been poured.

The strains under test were reported as *sensitive, moderately sensitive* or *resistant* comparing the diameter of zone of inhibition to the standard antimicrobial sensitivity chart.

RESULTS

Clinical presentation(s) of the patient with septic meningitis at the time of admission showed marked variability and more than one clinical signs and symptoms could be seen. Among neonates abnormal body temperature either fever or hypothermia was the most frequent presentation in 25 cases, followed by convulsions in 22 and refusal to feed in 19. Among infants, convulsions were the most frequent symptom in 19, followed by fever 18, shrill cry 17, irritability 15, vomiting 10 and anterior fontanel bulging in 8 cases. While in older children the most frequent symptom was convulsions 42 followed by fever 40, altered sensorium 39, headache 27, vomiting 24, neck rigidity 18 and photophobia in 11 cases.

CSF samples from 638 clinically suspected cases of septic meningitis were collected. Of these, 102 (15.99%) samples displaying single bacterial growth; termed as 'Culture Positive', were included

in the study. In none of 102 culture positive cases there was growth of two different micro-organisms. Of the samples, 505 (79.15%) showed no bacterial growth (sterile), and 31 (4.86%) exhibited three or more bacterial growths an were considered to be grossly contaminated thus altogether these 536 (84.01%) samples were discarded for the purpose of the study. It was noted that the rate of bacterial isolation was affected by antibiotic use prior to lumbar puncture, and that rate was increased if direct plating of CSF was done at the bedside.

Out of 102 culture positive samples, 63 (61.76%) were from males and 39 (38.24%) females with M:F ratio 1.62:1. Maximum numbers of culture positive CSF samples 45 (44.12%) were from children of age group 1- 12 years with M:F ratio of 0.67:1, this was followed by neonatal age group (0-28 days) with 36 (35.29%) culture positive samples and M:F ratio of 11:1. The lowest numbers of samples found culture positive (20.59%) were from the infants age group (1 month-1 year) with M:F ratio of 1.33:1.

Maximum incidence of 51 cases was noted during 4 months of May to August (Summer-Rainy season) as compared to 15 cases during 4 months of Winter season (September to December) suggesting more prevalence of septic meningitis during Summer-Rainy season.

Place and mode of delivery as well as vaccination status is shown in **Table 1**. Of the institutionally delivered cases 58 were found culture positive compared to 44 home delivered cases. Incidence was higher (77.45%) in vaginally delivered cases compared to caesarean (22.55%) cases. Seventy four (72.55%) cases were vaccinated whereas 27.45% were not immunised. This suggested that vaccinated cases were more involved in septic meningitis and that usual national vaccination schedule did not afford protection against the septic meningitis. Of 102 culture positive cases, 66 (64.71%) were Gram positive and 36 (35.29%) cases Gram negative suggesting a predominance of Gram positive cases in our study. Of 66 Gram positive isolates, 36 (54.55%) were of *Streptococcus spp*. followed by *Staphylococcus aureus* in 24 (36.36%) and Coagulase negative *Staphylococcus* (CONS) in 6 (9.09%) cases.

The sensitivity patterns for *Streptococcus spp., Staphylococcus aureus and* Coagulase negative *Staphylococcus* (CONS) are given in **Table 2, 3** and **4** respectively. Both *Streptococci* and coagulase negative *Staphylococci* were highly sensitive (100%) to linezolid, vancomycin and piperacillin-tazobactam. However, *Staphylococcus aureus* were 100% sensitive to linezolid and vancomycin but were only 87.5% sensitive to piperacillin-tazobactam combination. The *Streptococcus* species showed a high degree of resistance to tetracycline 91.67%, co-trimoxazole 88.89% and penicillin 63.89%. *Staphylococcus aureus* showed resistance to the tune of 83.33% each to tetracycline and co-trimoxazole and 79.17% with penicillin. In case of coagulase negative *Staphylococcus* co-trimoxazole showed resistance in 83.33%, penicillin in 66.67% and tetracycline in 50% cases.

Table 1: Place, Mode of Delivery and Vaccination Status of Septic Meningitis cases (N=102)

Gram stain	Place of delivery		Mode of delivery		Vaccination status	
	Institutional No. (%)	Home No. (%)	Vaginal* No. (%)	Caesareans No. (%)	Immunized No. (%)	Non-immunized No. (%)
Gm+ve N_1=66 (64.71)	39 (38.24)	27 (26.47)	50 (49.02)	16 (15.69)	49 (48.04)	17 (16.67)
Gm-ve N_2=36 (35.29)	19 (18.63)	17 (16.67)	29 (28.43)	7 (6.86)	25 (24.51)	11 (10.78)
Total N=102 (100)	58 (56.86)	44 (43.14)	79 (77.45)	23 (22.55)	74 (72.55)	28 (27.45)

*Place of delivery in vaginal mode may be home or institutional.

Table 2: Sensitivity pattern of *Streptococcus spp.* to various antimicrobial agents (N=36)

S. No.	Antibiotic	No. of cases (% Sensitivity)		
		Sensitive	Moderately Sensitive	Resistant
1	Amikacin	33 (91.67)	0 (0)	3 (8.33)
2	Gentamicin	21 (58.33)	3 (8.33)	12 (33.33)
3	Cefepime	33 (91.67)	0 (0)	3 (8.33)
4	Cefotaxime	19 (52.78)	4 (11.11)	13 (36.11)
5	Cefuroxime	18 (50)	1 (2.78)	17 (47.22)
6	Ceftazidime	20 (55.56)	4 (11.11)	12 (33.33)
7	Ceftriaxone	25 (69.44)	4 (11.11)	7 (19.44)
8	Meropenem	30 (83.33)	0 (0)	6 (16.67)
9	Oxacillin	23 (63.89)	0 (0)	13 (36.11)
10	Penicillin G	13 (36.11)	0 (0)	23 (63.89)
11	Amoxicillin-Clavulanic Acid	28 (77.78)	0 (0)	8 (22.22)
12	Cefoperazone-Sulbactam	30 (83.33)	0 (0)	6 (16.67)
13	Piperacillin-Tazobactam	36 (100)	0 (0)	0 (0)
14	Gatifloxacin	27 (75)	3 (8.33)	6 (16.67)
15	Levofloxacin	23 (63.89)	3 (8.33)	10 (27.78)
16	Chloramphenicol	10 (27.78)	0 (0)	26 (72.22)
17	Co-trimoxazole	4 (11.11)	0 (0)	32 (88.89)
18	Linezolid	36 (100)	0 (0)	0 (0)
19	Pristinamycin	25 (69.44)	0 ()	11 (30.56)
20	Tetracycline	3 (8.33)	0 (0)	33 (91.67)
21	Vancomycin	36 (100)	0 (0)	0 (0)

Table-3: Sensitivity pattern of *Staphylococcus aureus* to various antimicrobial agents (N=24)

S. No.	Antibiotic	No. of cases (% Sensitivity)		
		Sensitive	Moderately Sensitive	Resistant
1	Amikacin	21 (87.5)	0 (0)	3 (12.5)
2	Gentamicin	17 (70.83)	0 (0)	7 (29.17)
3	Cefepime	15 (62.5)	0 (0)	9 (37.5)
4	Cefotaxime	12 (50)	0 (0)	12 (50)
5	Cefuroxime	16 (66.67)	0 (0)	8 (33.33)
6	Ceftazidime	18 (75)	0 (0)	6 (25)
7	Ceftriaxone	15 (62.5)	0 (0)	9 (37.5)
8	Meropenem	21 (87.5)	0 (0)	3 (12.5)
9	Oxacillin	8 (33.33)	0 (0)	16 (66.67)
10	Penicillin G	5 (20.83)	0 (0)	19 (79.17)
11	Amoxicillin-Clavulanic Acid	18 (75)	0 (0)	6 (25)
12	Cefoperazone-Sulbactam	21 (87.5)	0 (0)	3 (12.5)
13	Piperacillin-Tazobactam	21 (87.5)	0 (0)	3 (12.5)
14	Gatifloxacin	18 (75)	0 (0)	6 (25)
15	Levofloxacin	12 (50)	6 (25)	6 (25)
16	Chloramphenicol	7 (29.17)	3 (12.5)	14 (58.33)
17	Co-trimoxazole	4 (16.67)	0 (0)	20 (83.33)
18	Linezolid	24 (100)	0 (0)	0 (0)
19	Pristinamycin	24 (100)	0 (0)	0 (0)
20	Tetracycline	4 (16.67)	0 (0)	20 (83.33)
21	Vancomycin	24 (100)	0 (0)	0 (0)

Table 4: Sensitivity pattern of Coagulase Negative *Staphylococcus* (CONS) to various antimicrobial agents (N=6)

S. No.	Antibiotic	No. of cases (% Sensitivity)		
		S	MS	R
1	Amikacin	6 (100)	0 (0)	0 (0)
2	Gentamicin	5 (83.33)	0 (0)	1 (16.67)
3	Cefepime	3 (50)	0 (0)	3 (50)
4	Cefotaxime	5 (83.33)	1 (16.67)	0 (0)
5	Cefuroxime	4 (66.67)	2 (33.33)	0 (0)
6	Ceftazidime	6 (100)	0 (0)	0 (0)
7	Ceftriaxone	6 (100)	0 (0)	0 (0)
8	Meropenem	6 (100)	0 (0)	0 (0)
9	Oxacillin	6 (100)	0 (0)	0 (0)
10	Penicillin G	2 (33.33)	0 (0)	4 (66.67)
11	Amoxicillin-Clavulanic Acid	6 (100)	0 (0)	0 (0)
12	Cefoperazone-Sulbactam	6 (100)	0 (0)	0 (0)
13	Piperacillin-Tazobactam	6 (100)	0 (0)	0 (0)
14	Gatifloxacin	6 (100)	0 (0)	0 (0)
15	Levofloxacin	6 (100)	0 (0)	0 (0)
16	Chloramphenicol	5 (83.33)	0 (0)	1 (16.67)
17	Co-trimoxazole	0 (0)	1 (16.67)	5 (83.33)
18	Linezolid	6 (100)	0 (0)	0 (0)
19	Pristinamycin	6 (100)	0 (0)	0 (0)
20	Tetracycline	3 (50)	0 (0)	3 (50)
21	Vancomycin	6 (100)	0 (0)	0 (0)

DISCUSSION

Septic meningitis is one of the most important causes of morbidity and mortality among children including neonates. A wide spectrum of microorganisms has been described for the cases of septic meningitis and this spectrum is affected by geographical location. Two basic problems in reference to septic meningitis are: 1) non-specific clinical features and difficult laboratory confirmation making the diagnosis difficult, and 2) neonates are particularly vulnerable to infections as they have immature immune system. Moreover, the organisms isolated are more often multi-drug resistant, which makes the treatment more difficult leading to consequences such as increased hospital stay and even mortality. Multiple antimicrobial resistance is a growing clinical problem and a major threat to life in septic meningitis cases. Therefore, area specific bacteriological monitoring studies designed to gain knowledge about the type of pathogen responsible for septic meningitis and their susceptibility patterns may help clinicians to choose correct empirical treatment. This study not only throws light on the spectrum of micro-organisms isolated from CSF in cases with septic meningitis but has also in evaluated antimicrobial sensitivity patterns to formulate empirical antimicrobial therapy.

The study observed an age-wise variability in symptoms at the time of admission amongst neonates, infants and children. Thus among neonates abnormal body temperature either fever or hypothermia was the most frequent presentation, followed by convulsions and refusal to feed. Among infants, convulsion was the most frequent symptom, followed by fever, shrill cry, irritability, vomiting and anterior fontanel bulging. While in children the most frequent symptom was convulsion followed by fever, altered sensorium, headache, vomiting, neck rigidity and photophobia. Other workers in the field also noted a similar spectrum of presentation. It may be emphasized that one patient might have more than one clinical signs and symptoms at the time of admission. Thus, 102 cases depicted a total of 390 signs and symptoms at the time of admission. Our findings corroborate those of Salam[10] who observed that children of all ages (newborn to 12 years) attended paediatric emergency as suspected cases of meningitis with fever, convulsions and altered sensorium.

Importantly, institutionally delivered cases are more prone to septic meningitis compared to domestic deliveries despite primitive facilities and unhygienic conditions prevailing in the latter. This is probably due to increased prevalence of nosocomial infections in hospital settings. Further,

incidence was greater in vaginally delivered cases compared to caesarean cases.

The findings of sterile cultures in the present study may be due to the fact that some organisms cannot survive more than an hour delay in transportation, hence there should be better training for proper sample handling and its timely transportation. Additionally, 31 samples were found to be grossly contaminated indicating the relevance of proper aseptic precautions by the clinician.

The culture positivity in our study was 15.99%. Our findings are in agreement with those of Kalghatgi et al[11] (15%), Sonavane et al[12] (ranges between 6-50%), and at variance with those of Surinder et al[13] (23.1%), Salam[10] (27.27%), Singhi et al[14] (30%). In contrast a very high culture positivity was reported by Al Khosarani and Banajeh[15] (95.6%), Mani et al[16] (73.8%) and Theodoridou et al[5] (53.7%). This is primarily because of regional – geographical variations. Also, there are many other clinical conditions such as aseptic meningitis, tuberculous meningitis which clinically simulate septic meningitis and need to be differentiated.

Our finding in respect to predominance of male involvement (M: F ratio 1.62:1) was in agreement with those of Keshari et al[17] (M: F ratio 1.7:1) and Sonavane et al[11] (1.35:1) and was at variance to those of Singhi et al[14] (M: F ratio of 3.21: 1). It is of relevance that in present study M: F ratio in different age groups was found to be quite variable. Thus, culture positive cases in neonatal age groups were predominantly males with M: F ratio of 11:1.

Singhi et al[14] reported that the greatest number of cases were from infant's age group (62.5%) which was in contrast to our findings of least involvement of infants (20.59%). Sigauque et al[18]while dealing with acute bacterial meningitis among children in Manhica, a rural area in Southern Mozambique reported that incidences were more than three times higher in <1 year age group which was at much variance to our findings.

Maximum incidence (51 cases) was seen during the summer and rainy season i.e., from May to August. Our findings were in contrast to those by Faraget al[19] who reported maximum incidence in winter season (48.5%) in Egypt. They observed that this was in families with high crowding index. This probably may be due to geographical variation. While in tropical countries like India the incidence of infection is usually more during summer and rainy seasons.

The present study noted predominance (64.71%) of Gram positive organisms. Sigauque et al[18] (57.75%) and Mani et al[16] (65.9%) also reported predominance of Gram positive organisms. While other workers[11,13,15,17,20] reported a predominance of Gram negative organisms incidence ranging from 58.69% to 80.93% contrary to our observations.

A 100% correlation between Gram staining and culture was recorded. Our findings were in conformity with those of Sonavane et al[12] who also reported a 100% correlation between Gram's staining and culture. Dunbar et al[21] reported that CSF Gram stain was 92% sensitive and concluded that microscopic examination of Gram-stained, concentrated CSF was highly sensitive and specific in early diagnosis of bacterial or fungal meningitis. In contrast, Surinder et al[13] reported that Gram stain and culture showed 16.9% and 23.1% positivity respectively i.e., correlation of 73.16%. Thus, Gram stain was a gold standard method to assess about the causative agent of septic meningitis.

Of 66 Gram positive isolates, most 36 (54.55%) were *Streptococcus spp*. followed by *Staphylococcus aureus* (36.36%) and Coagulase negative *Staphylococcus* (CONS) (9.09%) cases. Supporting our observations, a number of workers in the field reported variable incidences of *Streptococcus spp*.-Tang et al[20] (71.1%), Sigauque et al[18] (92.67%), and Mani et al[16] (97.27%). Thus, *Streptococcus spp.* was found to be the most common cause of meningitis among children in developing countries[22,23].

In our study overall Gram positive isolates were highly sensitive (100%) to linezolid and vancomycin followed by piperacillin-tazobactam (95.45%), amikacin (90.91%), cefoperazone-sulbactam (86.36%), meropenem (86.36%) and pristinamycin (83.33%). Maximum resistance was observed to cotrimoxazole (86.36%), followed by tetracycline (84.85%) and penicillin G (69.7%). In agreement with our findings Gupta and Jain[24] reported that Gram positive isolates were sensitive to vancomycin and ceftriaxone. The authors noted that Gram positive isolates were also sensitive to penicillin G contrary to our findings. Al Khosarani and Banajeh[15] supported our observations that Gram positive isolates were resistant to penicillin G. Kapil[25] reported that the isolates showed total resistance to penicillin and were also multi drug resistant namely to cefotaxime, erythromycin, chloramphenicol and Trimethoprim-sulphamethoxazole. Further, Shah and Narang[26] reported that Gram-positive organisms were highly susceptible to meropenem including *Staphylococci* (penicillinase negative and positive), Coagulase-Negative *staphylococci* (CONS), Streptococci, *Enterococcus.* The order of susceptibility was meropenem (99%) > piperacillin/tazobactam (77%) > ciprofloxacin (43%) > aminoglycosides and other β-lactams (30-40%).

In a retrospective study in cases of neonatal sepsis by Shaw et al[27] spread over for a period of 6 years in a tertiary care hospital in Western Nepal, the most common organism to be isolated was *Staphylococcus aureus* (42.75%) followed by *Klebsiella pneumoniae* (18.32%) and *Escherichia coli* (12.21%). Pathogenic *Streptococci*

(*Streptococcus pyogenes*) were much less common. The authors observed that Gram positive organisms displayed a high degree of resistance to most penicilllins and cephalosporins but glycopeptides and monobactams were effective. *Staphylococci* were 100% resistant to penicillin and 100% sensitive to vancomycin. Their observations are in concurrence with those of ours. Namani et al[28] in another retrospective study of 124 culture positive cases of bacterial meningitis in children at the University Clinical Centre of Cosovo, a developing country observed that the most common pathogens were *N. meningitidis* (57.25%), *H. influenzae* type B (17.74%), *S. pneumoniae* (13.70%) and Gram negative *bacilli* (8.87%). Out of 124 isolated pathogens, 95.16% of strains were susceptible to antibiotics, while 4.83% were resistant to antibiotic. The authors observed that meningococci were susceptible to penicillin in all cases. Strains of *H. influenzae* were susceptible to antibiotics in all but one isolate that was susceptible to cephalosporins but resistant to ampicillin and chloramphenicol. Strains of *pneumococci* were susceptible to antibiotics in the cases of all but one isolate which was resistant to penicillin but susceptible to cephalosporins. *S. aureus* was methicillin susceptible in one case but methicillin resistant and vancomycin susceptible in another case. The authors noted that antibiotic resistant was low among Gram positive pathogens. They observed that penicillin was the drug of choice for *meningococci*, ceftriaxone for *H. influenzae* and *pneumococci*. Roca et al[29] while studying acute bacterial meningitis (ABM) among children admitted to a district hospital in rural Mozambique observed that ABM was confirmed in 43 patients (7% of 642 CSF samples collected from children with suspected meningitis). The causative organisms included *H. influenza* type B 33%, *Pneumococcus* 21%, *Meningococcus* 16%, *Staphylococcus aureus* 9% and others 21%. There were only 2 cases each of *Streptococcus* group B and group D. All 9 pneumococcal isolates were susceptible to chloramphenicol and 8 isolates were susceptible to penicillin and the remainder was of intermediate susceptibility. For 10 *Haemophilus influenzae* type B isolates tested, 1 was susceptible to chloramphenicol and 5 were susceptible to ampicillin. All meningococcal isolates tested (4 isolates) were susceptible to both chloramphenicol and ampicillin. It may be mentioned that authors had used chloramphenicol as first line antibiotic for ABM caused by *Haemophilus influenzae* type B, *Pneumococci* and *Meningococci* and 14/23 cases were susceptible to chloramphenicol.

Considerable variability in respect to culture and sensitivity of *Streptococcus* was reported. We observed 100% sensitivity with linezolid, vancomycin and piperacillin-tazobactam. Enting et al[30] reported that all streptococcal isolates were susceptible to ceftriaxone, a third generation cephalosporin. Gupta and Jain[24] also reported that *Streptococcus spp.* were sensitive to vancomycin, ceftriaxone and ciprofloxacin. Sonavane et al[12] observed that *Streptococcus spp*. was sensitive to amikacin and vancomycin. Our findings contradicted to those of Sigauque et al[18] who reported 93% streptococcal susceptibility to chloramphenicol probably due to geographical variations in the susceptibility of organisms. However, contrasting views were expressed by Kulkarni et al[31] that all the streptococcal isolates were sensitive to ampicillin, erythromycin, penicillin followed by chloramphenicol and were resistant to gentamicin, followed by tetracycline 94.4% and kanamycin 88.8%. Shaw et al[27] observed that the *Streptococcus species* (Group A and B) (n=7) were all sensitive to most penicillins, cephalosporins and erythromycin with a comparatively high degree of resistance to aminoglycosides (28.6% to 83.7%).

Staphylococcal isolates were 100% sensitive to linezolid, pristinamycin, and vancomycin. These isolates were also highly sensitive to amikacin, meropenem, piperacillin-tazobactam and cefoperazone-sulbactam (87.5% each). High resistance to tetracycline (83.33%), cotrimoxazole (83.33%) and penicillin G (79.17%) was observed **(Table 3).** Our findings were in agreement with other workers[24],[26] who reported that Staphylococci (both penicillinase negative and positive) were highly susceptible to meropenem.

In our study all strains of Coagulase Negative *Staphylococcus* (CONS) were 100% sensitive to amikacin, ceftazidime, ceftriaxone, meropenem, oxacillin, amoxicillin-clavulanic acid, cefoperazone-sulbactam, piperacillin-tazobactam, gatifloxacin, levofloxacin, linezolid, pristinamycin and vancomycin. This was followed by gentamicin, cefotaxime and chloramphenicol (83.33% each). These isolates were resistant to co-trimoxazole (83.33%), penicillin G (66.67%), cefepime (50%) and tetracycline (50%) **(Table 4)**. Shaw et al[27] reported that all 4 cases of CONS were resistant to all antibiotics except vancomycin.In support to our study Shah and Narang[26] stated that CONS were susceptible to meropenem, but they noted that methicillin resistant strains of CONS and Staphylococci were not susceptible to meropenem and β-lactam antibiotics. Al Khosarani and Banajeh[15] also supported our findings about susceptibility of these pathogens to various cephalosporins. It was found that *Staphylococcus* isolates as well as all strains of Coagulase negative *Staphylococcus (CONS)* were 100% sensitive to pristinamycin. In variance, Keshari et al[32] reported two cases of pristinamycin resistant *Staphylococcus aureus*. Thus, it may be emphasized that sensitivity studied must be carried out locally since there is variation in different regions and countries.

It may be stated that moderately sensitive microbes become sensitive with judiciously increased high doses of antimicrobials. So, if we have no option left of using highly sensitive antimicrobials, due to resistance or hypersensitivity to a particular antimicrobial agent, we can judiciously increase the dose of the moderately sensitive drug which may be effective.

Shaw et al[27]observed that neonatologists remain consistently baffled by the changing patterns of microbial flora and their sensitivity patterns, making neonatal septicaemia a difficult problem to tackle. Basseti et al[33] also observed that accurate information on local epidemiology and antimicrobial resistance patterns of pathogens among children is essential to select a clinically effective antimicrobial therapy for infection. As septic meningitis is an emergency medical condition, an empirical therapy must be instituted immediately after CSF collection which should be broad spectrum and sensitive against most of the prevailing causative microbes, without waiting for culture and sensitivity results. According to observations of our study an 'Empirical Therapy' should be a combination of i.v. 'piperacillin-tazobactam' or 'cefoperazone-sulbactam' as these agents were found to be effective against most of the causative pathogens (>85%) whether Gram positive or Gram Negative. Further, some drugs should be kept as 'Reserve drugs' such as; 'linezolid' and 'vancomycin' for Gram positive pathogens and 'meropenem' for both Gram positive as well as Gram negative microbes. Once results of culture and susceptibility become available, a 'definitive therapy' can be started depending upon specific causative pathogen cultured and its sensitivity. This will also be cost effective. Oral antimicrobials can be started when patient becomes alert and able to take oral medicines.

It was observed that primary immunization as per current national programme of immunization has no protective role towards septic meningitis, since many of the isolates were *Streptococcus pneumoniae.* It may be advised that, for prevention of meningitis among children, 'pneumococcal vaccine' should be included with primary immunization in National Immunization Programme and if not possible it must be given at least to children at high risk. It may be mentioned that vaccines against meningeal pathogens have successfully been implemented into the national immunization programme around the world. Effective conjugate vaccines for young children are available for Pneumococcal and *Haemophilus influenzae* type B infections.

The speed of diagnosis, the identity of the causative pathogens and the initial antimicrobial therapy instituted represent vital factors for the prognosis of septic meningitis cases. Initiation of appropriate antimicrobial therapy in this emergency condition cannot be over-emphasized. High resistance to antimicrobial agents was due to irrational and irrelevant use of antimicrobial agents including inappropriate and incorrect administration of antimicrobial agents in empirical therapy and lack of appropriate infection control strategies. The emergence of multi-drug resistant strains of Gram-negative bacteria and Gram-positive organisms is more worrisome in the present therapeutic scenario. Resistance to some agents can be overcome by modifying the dosage regimens or inhibiting the resistance mechanism (e.g., beta-lactamase inhibitors), whereas other mechanisms of resistance can only be overcome by using an agent from a different drug class. It is highly recommended that practicing physicians should become aware of the magnitude of existing problem of antibacterial resistance and help in fighting this threat by rational prescribing.

The study has helped in determining a panel of antimicrobial agents to be used in testing the susceptibility of individual Gram positive organism.

CONCLUSION

In conclusion, it may be emphasized that there is utmost need to conduct area specific monitoring studies to profile different pathogens responsible for septic meningitis and their resistance patterns so as to generate data that would help clinicians to choose the correct empirical treatment.

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