Original Article

Bacterial meningitis in north India: trends in antimicrobial resistance

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Abstract

Background: The mortality rate in ABM remains significant and has been reported in the range of 8-40%. It is important to know the regional bacterial etiology in semitropical countries like India along with their sensitivity profile to allow optimum management of such patients. This study was undertaken to evaluate the trends in etiology of bacterial meningitis and the antimicrobial resistance pattern of the pathogens prevalent in North India over a period of 8 years.

Material and Methods: The study was performed from June 2001 to June 2009. CSF samples were collected from all patients suspected of meningitis and cultured on chocolate agar, blood agar and MacConkey agar. Antimicrobial susceptibility testing was done using Kirby Bauer disc diffusion method. Detection of MRSA, HLAR, ESBL, AmpC and MBL was also done.

Results: 401 samples were positive on culture. *S. aureus* was the most common pathogen isolated. Among the gram positive cocci as well as the gram negative bacilli a gradual decline in the antimicrobial susceptibility was seen. The aminoglycosides were found to be most effective group of antimicrobial. Towards the end of the study an alarming rise of methicillin resistance in *S. aureus* to 69.4%, HLAR among the *Enterococci* to 60% was noticed and among the *Enterobacteriaceae* ESBL and AmpC production was found to be 16.67% and 42% respectively.

Conclusion: The high prevalence of drug resistant pathogens should be dealt with by rational use of antimicrobials. Frequent revision in drug policy may be necessitated for optimum management of patients.

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Introduction

Acute bacterial meningitis (ABM) is a significant worldwide cause of death in adults. Even in the antibiotic era, the mortality rate in ABM remains significant and has been reported in the range of 8-40%. [1]Despite advances in vaccine development and chemoprophylaxis, bacterial meningitis remains a major cause of death and long term neurological disabilities.[2] Microbiology laboratories play a critical role not only in the early identification of the causative bacterium and its antibiotic susceptibility pattern but also in providing valuable information regarding the common incriminating pathogens in that area and also which drugs to start empiric treatment with. [3]

There have been several published studies regarding 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 etiology and antimicrobial susceptibility are essential for correct and timely management of meningitis. This study was conducted to analyse the trends in bacterial etiology and antimicrobial resistance in meningitis in North India with emphasis on the prevalence of methicillin resistant *Staphylococcus aureus* (MRSA), high level aminoglycoside resistance in *Enterococcus species* (HLAR), extended spectrum β lactamases (ESBL), Amp C and metallo -betalactamases (MBL).

Materials and Methods

This retrospective study was performed at a tertiary care centre between June 2001 and June 2009. Cerebrospinal fluid (CSF) samples were collected from all consecutive patients suspected for meningitis. 3-5 ml of CSF was collected at a rate of 4-5 drops/second by lumbar puncture taking all the aseptic precautions. [4] The specimens were processed immediately and in cases of delay, they were kept in the incubator at 37^0C.

After the naked eye examination for the presence of turbidity, microscopic examination was done by Gram's staining of the centrifuged deposit of CSF. Immediately after centrifugation of CSF, culture was done on a plate of chocolate agar, 5% sheep blood agar, MacConkey and a tube of brain heart infusion broth. These plates were incubated for 24-48 hours in humid air plus 5-10% CO_2 at 37^0C. Any sample showing growth was tested using standard biochemicals to identify the pathogens. [4]

Antibiotic susceptibility testing: Sensitivity to relevant antibiotics was determined by the Kirby Bauer Disc diffusion method as per the CLSI guidelines,[5] using the commercially available antibiotic discs from Hi Media (Mumbai, India). At the beginning of the study period in 2001 the antimicrobials used for gram negative bacilli were gentamicin (10µg), amikacin (30µg), tobramycin (10µg), amoxicillin (20µg), cotrimoxazole (trimethoprim/sulphamethoxazole 1.25/23.75µg), ceftriaxone (30µg), cefotaxime (30µg), cefoperazone+sulbactum (75/75µg), ciprofloxacin (5µg) and imipenem (10µg). Due to the development of resistance to these antibiotics during 2003-4 , which we called the watershed years from 2005 we started assessing the sensitivity to a large number of antibiotics namely gentamicin (10µg), amikacin (30µg), netilmicin (30µg), ceftazidime (30µg), cefixime(15µg), ceftriaxone(30µg), cefotaxime (30µg), cefoperazone (75µg), cefoperazone-sulbactum (75/75µg), cefepime (30µg), gatifloxacin (5µg), ofloxacin (5µg) and imipenem (10µg). In 2008 the drug policy was reassessed and since then the following most effective drugs were used: gentamicin (10µg), amikacin (30µg), cefixime (15µg), cefoperazone (75µg), cefoperazone + sulbactum (75/75µg), cefepime (30µg), gatifloxacin (5µg) and ofloxacin (5µg) as the first line drugs and pipercillin (100µg), pipercillin-tazobactum (100/10µg), ceftazidime-clavulanic acid (30/10µg) and imipenem (10µg) as the second line drugs. We also actively looked for the ESBL, AmpC and MBL production. Screening of possible ESBL production was done by using ceftriaxone (30µg) and cefoperazone (75µg). Those isolates with zone diameters less than 25mm for ceftriaxone and less than 22mm for cefoperazone were subsequently confirmed for ESBL production. Confirmation was done by noting the potentiation of the activity of cefoperazone in the presence of cefoperazone sulbactum. An increase in zone diameter of

more than 5mm was considered positive for ESBL production. [6] Detection of Amp C betalactamase was done on isolates resistant to ceftriaxone (30µg), cefixime (15µg), cefoperazone (75µg) and cefoperazonesulbactum (75/75µg). Induction of Amp C synthesis was based on the disc approximation assay using imipenem as inducer. The assay was performed according to the CLSI guidelines. [7] Detection of MBL was done if the zone of imipenem was reduced to ≤16mm or heaping occurred, or if the zone was ≥16mm but ≤20mm. Hodge test and Double Disc synergy test using EDTA was used for detection of MBL. The method was as described by Lee et al. [8]In the new drug policy the drugs used for *Pseudomonas species* were: gentamicin (10µg), amikacin (30µg), cefoperazone (75µg), cefoperazone-sulbactum (75/75µg), cefepime (30µg), ofloxacin (5µg), piperacillin(100µg), pipercillin-tazobactum (100/10µg), ceftazidime-clavulanic acid (30/10µg) and imipenem(10µg).

The antibiotics used for the gram positive cocci at the start of the study period were gentamicin (10µg), amikacin (30µg), tobramycin (10µg), ampicillin (10µg), cotrimoxazole (trimetoprim/ sulphamethoxazole 1.25/23.75µg), cefotaxime (30µg), ciprofloxacin (5µg), erythromycin (15µg) and vancomycin (30µg) for the *Staphylococcus species* and gentamicin (10µg), amikacin (30µg), tetracycline (30µg), ampicillin (10µg), ciprofloxacin (5µg) and erythromycin (15 µg) and vancomycin (30µg) for the *Streptococcus species.* After 2005 for the gram positive cocci and gentamicin (10µg), amikacin (30µg), ofloxacin (5µg), gatiofloxacin (5µg), clindamycin (2µg) erythromycin (15 µg), cefaclor (30µg), oxacillin (1µg) and vancomycin (30µg) were selected for the *Staphylococcus species*. In this new drug policy most significant was the introduction of oxacillin (1µg) for the detection of MRSA and 120µg gentamycin and 300µg streptomycin disc for detection of high level resistance to aminoglycosides (HLAR) in Enterococci. [9] Statistical analysis was done students t-test.

Result

During the 8 year study period 5859 CSF samples were collected from patients admitted in various wards of JNMCH, Aligarh, India. Out of these a total of 401 patients were confirmed as cases of bacterial meningitis on Gram's staining and culture. It was noted that majority of cases were reported during the early part of the study period (2001-3), followed by a decrease in the number of cases and then again a rise in the number of culture positive cases during 2008-9 (Fig 1). Majority of the patients 336 (83.79%) were upto 12 years of age, out of which the maximum 147(36.66%) were infants (Fig 2 describes etiology with age). Among infants, most cases 78 (53.6%) belonged to the three months to one year age bracket.

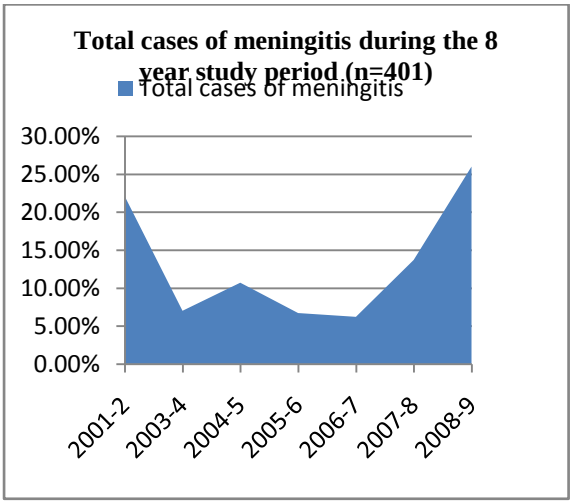

Figure 1: Graphical representation of Total cases of meningitis during the 8 year study period

Etiology:

Gram positive bacteria were responsible for a majority of cases of meningitis (59.60%). The most common pathogen isolated in this study was *Staphylococcus aureus* (37.91%) which predominated across all age groups. *Streptococcus species* (8.73%) and *Enterococcus faecalis* (4.49%) were the other gram positive organisms isolated. *Streptococcus pneumoniae* was isolated in only a single patient. An unusual finding was the increased isolation of coagulase negative staphylococci (CONS) in patients with meningitis. It was observed that it clustered in patients of 3 months of age to 20 years. Among the gram negative bacteria, the *Enterobacteriaceae*

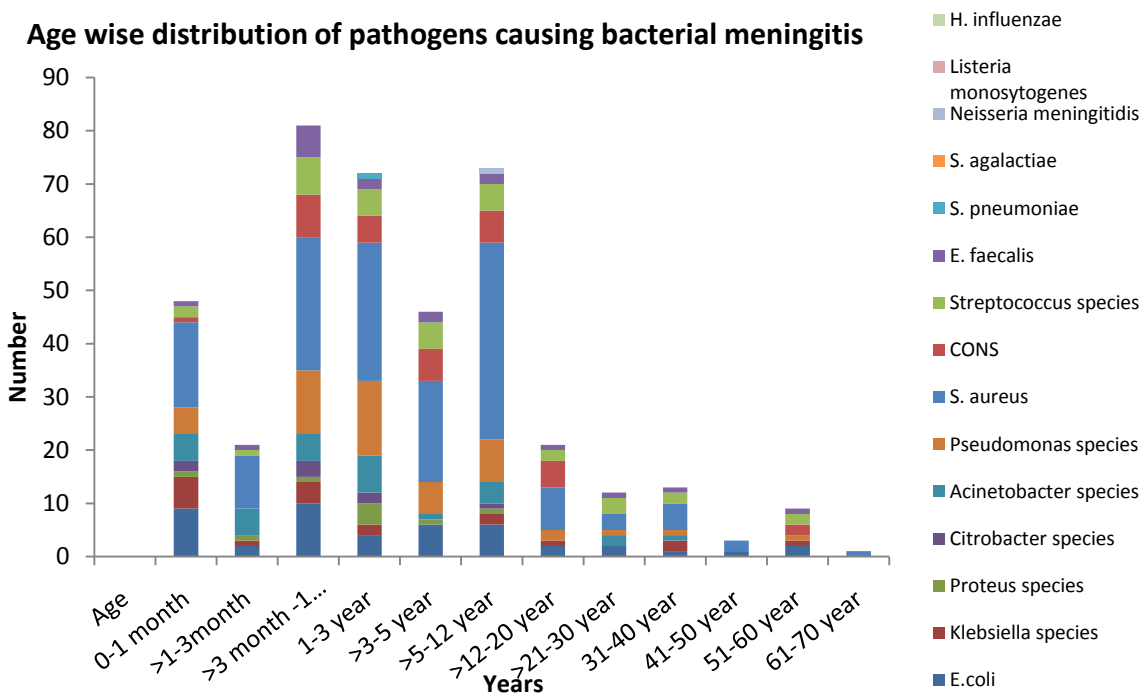

Figure 2: Age wise distribution of pathogens causing bacterial meningitis

family predominated (20.45%) with *Esherichia coli* accounting for 11.22% cases followed by *Klebsiellapneumoniae* (4.74%) with *Proteus mirabilis* and *Citrobacterkoseri* accounting for (2.24%) each. Among the nil-fermenters, *Pseudomonas aeruginosa* and *Acinetobacter species* were isolated in 49 (12.22%) and 30 (7.48%) cases respectively (Graph 2). In the neonates *S. aureus, E. coli* and *K. pneumoniae* predominated. Overall among gram negative bacilli (GNR) *Pseudomonas* spp accounted for a majority of cases of meningitis. *Neisseria meningitides* was isolated in only one patient. One isolate each of *Rhodococcus equi, Stomatococcus mucilaginosus* and *Corynebacterium aquaticum* were also isolated in the study all of which were isolated in children less than five years of age. None of the cultures were positive for *Haemophilus influenzae, Listeria monocytogenes* and *Streptococcus group B*.

Overall *S. aureus* predominated in all the eight years accounting for a total of almost 38% of all isolates followed by *Pseudomonas species* which were way behind at 12% and *E. coli* at 11%. *Streptococcus species* and *CONS* were associated with 8.7% and 8.2% cases of meningitis respectively which was unusual. *Acinetobacter species* again accounted for a relatively large number of meningitis cases (7.4%) among GNRs. *C. koseri* and *P. mirabilis* were increasingly isolated in the later years (2007-09). Majority of cases (26%) occurred in June 2008-May 2009 followed by 22% in 2001-02. In the remaining years the number of isolates ranged from 6.2% to 13.7%.

Across all age groups *S. aureus, E. coli, K. pneumoniae, Ps. aeruginosa, Streptococcus species* and *E. faecalis* were most commonly isolated. *Acinetobacter species* and *CONS* were seen mostly in the younger age groups: patients less than forty years in case of the former and less than twenty years in case of the latter. *Proteus* and *Citrobacter* infection occurred only in children less than 12 years of age. *S. pneumoniae* was isolated in a two year old child while *N. meningitis* occurred in a ten year old girl.

Antibiotic resistance profile:

Gram positive cocci: (Table 1)

2001-2:

At the initiation of the study period (2001) the antibiotics tested against the staphylococci were gentamycin, amikacin, ciprofloxacin, cotrimoxazole, ampicillin, cefotaxime, erythromycin and vancomycin. During this period 33 isolates of S.aureus were identified. As is seen in table 1 the highest sensitivity was noticed against aminoglycosides 28(84.8%), followed by the fluoroquinolones 25(75.7%), sulphonamides 18(55.5%). The β-lactams were found to have low sensitivity; with sensitivity to penicillin group being 17(51.5%) and to cephalosporins 18(54.54%). However the macrolides were observed to have least sensitivity 16(48.5%).

2003-04:

First 4 years of the 21st century showed a general decline in sensitivity to all groups of antibiotics. The steepest decline was observed against the penicillin group (ampicillin) from 17(51.5%) in 2001-2 to 2(14.3%) in 2003-4. A similar but less sharp decline was noticed against cephalosporins from 18(54.54%) to 5(35.71%). A similar trend was seen for cotrimoxazole (from 54.54% to 21.4%) and the fluoroquinolones (75.7% to 55.6%). Least decline was noticed against the aminoglycosides (84.8% to 78.6%). During this period, the macrolides which were least sensitive at the beginning of the study, showed improvement in the sensitivity (from 48.5% to 76.8%).

2005:

After the introduction of the new drug policy in 2005, improvement in sensitivity was seen to almost all groups of drugs. There was a marked increase in sensitivity against penicillin group with the introduction of oxacillin from 14.3% to 55.6% and also against cephalosporins to which an increase of approximately 22.21% was noticed. Sensitivity to aminoglycosides improved by a margin of 10% and to fluoroquinolones by approximately 5%. However, there was a dip of about 20% in the sensitivity against the macrolides.

2006-9:

It was observed that with the period of time (2006-2009) there was again a decline in the sensitivity even to the drugs introduced in the new drug policy. A dip in sensitivity of about 17%, 13%, 23% and 45% was noted for the aminoglycosides, fluoroquinolones, penicillins and cephalosporins respectively. The sensitivity remained almost the same against sulphonamides and macrolides. Most marked was the increase in the prevalence of MRSA causing meningitis from 44.4% in 2005 to 69.4%in 2008-9. Among the *E. faecalis* isolates an increase in HLAR was noticed from 52.9%in 2005 to 60% in 2008-9. However, this increase in MRSA and HLAR was not statistically significant (<0.001). All the isolates were sensitive to the glycopeptides and no VRE or VRSA was detected in our study.

Gram negative bacilli: (Table 2)

2001-2002

The antibiotics tested against the gram negative bacilli at the start of the study period were gentamicin, amikacin, tobramycin, amoxycillin, cotrimoxazole, ceftriaxone, cefotaxime, cefoperazone-sulbactum, ciprofloxacin and imipenem. As is seen in Figure 2 among the members of Enterobacteriaceae, cephalosporins were found to have the best sensitivity of 66.7% for cefotaxime and 78.26% for cefoperazone-sulbactum. This was followed by the aminoglycosides (65.21%), fluoroquinolones (60.87%) and the sulphonamides i.e., cotrimoxazole (56.525). All the isolates were sensitive to imipenem.

Among the nil-fermenters, *Ps. aeruginosa* were found to have a sensitivity profile of 76.9%, 69.2%, 38.4%, 30.7% and 23% against amikacin, ciprofloxacin, cefotaxime, amoxicillin and cotrimoxazole respectively. However all the isolates were sensitive to imipenem. Only 2 *Acinetobacter species* were isolated during 2001-2, both of which were sensitive only to gentamicin, ciprofloxacin and imipenem.

Table 1: Trend of antimicrobial susceptibility among Gram Positive cocci

Organism	Penicillin					Aminoglycosides					Flouroquinolones					Macrolides					Glycopeptide				
	2001-2	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**
S. aureus	17(51.5)	2(14.3)	5(55.6)	15(50)	12(30.6)	28(84.8)	11(78.6)	8(88.9)	24(80)	23(61.22)	25(75.7)	10(71.4)	5(55.6)	18(60)	18(46.94)	16(48.5)	11(76.8)	5(55.6)	16(52.9)	20(53.04)	33(100)	14(100)	9(100)	30(100)	38(100)
CONS	3(42.86)	1(25)	1(50)	2(50)	9(27.27)	5(71.43)	3(75)	1(50)	3(75)	4(57.14)	5(71.43)	3(75)	1(50)	2(50)	3(42.86)	3(42.86)	3(75)	1(50)	2(50)	4(57.14)	7(100)	4(100)	2(100)	4(100)	7(100)
Strep.Sp	1(50)	2(33.33)	1 (50)	2(50)	2(33)	4(66.67)	2(66.67)	1(50)	3(75)	3(50)	4(66.67)	2(66.67)	1(50)	2(50)	3(33.33)	3(50)	2(66.67)	1(50)	2(50)	2(66.67)	6(100)	3(100)	2(100)	4(100)	6(100)
E. faecalis	1(33.33)	-	1(33.33)	-	1(20)	-	-	-	-	-	2(66.67)	1(100)	1(33.33))	1(100)	1(20)	1(33.33)	1(100)	1(33.33)	-	2(40)	3(100)	1(100)	3(100)	1(100)	5(100)

Table 2: Trend of antimicrobial susceptibility among Enterobacteraciae

Organism	Sensitivity to																								
	Aminogycosides					**Flouroquinolones**					**Cephalosporins**					**Cefoperazone + sublactum**					**Carbepenems**				
	2001-2	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**	**2001-2**	**2003-4**	**2005**	**2006-7**	**2008-9**
E. coli	12 (75)	4(57.14)	2 (100)	5 (71.43)	3 (50)	12 (75)	4(57.14)	2 (100)	5 (71.43)	3 (50)	12 (75)	4(57.14)	2 (100)	5 (71.43)	3 (50)	12 (75)	4(57.14)	2 (100)	5 (71.43)	3 (50)	12 (75)	4(57.14)	2 (100)	5 (71.43)	3 (50)
Klebseilla	2(40)	2(66.67)	1(50)	1 (33.33)	2(50)	2(40)	2(66.67)	1(50)	1 (33.33)	2(50)	2(40)	2(66.67)	1(50)	1 (33.33)	2(50)	2(40)	2(66.67)	1(50)	1 (33.33)	2(50)	2(40)	2(66.67)	1(50)	1 (33.33)	2(50)
Proteus	-	-	1 (50)	-	1 (25)	-	-	1 (50)	-	1 (25)	-	-	1 (50)	-	1 (25)	-	-	1 (50)	-	1 (25)	-	-	1 (50)	-	1 (25)
Citro-bacter	-	-	-	-	2 (40)	-	-	-	-	2 (40)	-	-	-	-	2 (40)	-	-	-	-	2 (40)	-	-	-	-	2 (40)

2003-04:

Similar to gram positive cocci, a decrease in sensitivity was noticed among the gram negative bacilli in 2003-4. Sensitivity to aminoglycosides decreased from 65.2% to 60.0%, to cotrimoxazole from 56.52% to 50%, to cephalosporins (i.e. cefotaxime from 66.7% to 52.3% but not to cefoperazone-sulbactum, which remained almost the same i.e. 80%). Surprisingly, there was a significant increase in sensitivity of approximately 10% (from 60.87% in 2001-2 to 70% in 2003-4) for fluoroquinolones. The *Ps. aeruginosa* isolates also showed a marked increase in sensitivity in 2003-4. The sensitivity to all the groups was reduced to just 25% except aminoglycosides which remained sensitive to 75% isolates and imipenem which was found to have 100% sensitivity.

2005:

With the change in drug policy in 2005, an increase in sensitivity was noted for the aminoglycosides by about 6%. However sensitivity to fluoroquinolones decreased by 4% and there was a marked decrease in the sensitivity of cotrimoxazole to just 33%. On comparing the efficacy of 3rd generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefixime, cefoperazone) introduced in the new drug policy it was found that cefotaxime was least sensitive with 33% sensitivity. Sensitivity to ceftazidime, cefixime and ceftriaxone was comparable with 34%, 37% and 38% respectively. Sensitivity to cefoperazone was markedly higher at 60%. During this period ESBL production was detected in 10% isolates of Enterobacteriaceae family. No AmpC or MBL was observed in these isolates. In *Pseudomonas* species ESBL was detected in one isolate (25%) and AmpC β lactamase was observed in another isolate (25%). No MBL was observed during this period. The two isolates of *Acinetobacter* were not only multidrug resistant but also ESBL producers.

2006-9:

As observed with GPCs a decrease in sensitivity was noticed against all groups of antimicrobials during 2006-2009, although the decline in susceptibility amongst the GNRs was greater in comparison to GPCs. Sharpest decline was observed in the sensitivity of 3rd generation cephalosporins from 60% to 16.67%.Sensitivity to cefepimeand cefoperazone-sulbactum was better at 22.25 and 33.3% respectively. ESBL production increased to 16.67% (3 out of 18 isolates). A sudden and unexpected surge in AmpC production was noticed during this time frame: from none in 2006 to 11(42%) in 2009. In 36.36% (4 out of 11) of these AmpC producing isolates ESBL was also present. However no MBL was detected during the entire study with 100% sensitivity to imipenem. A marked increment in resistance (33.33%) was observed against fluoroquinolones with sensitivity being only 16.67% in 2009.However, on comparing drug resistance organism wise, statistically significant increase in drug resistance against fluoroquinolones (>0.05), cephalosporins (>0.001) and cephalosporin combination (cfs) (>0.001) was observed in *E. coli* while in *Klebsiellasp* significant increase was seen only in fluoroquilones(>0.05). Aminoglycosides had the best sensitivity profile at 44.44% although a decline of 22% occurred in this group as well.

Discussion

Acute bacterial meningitis is a medical emergency which warrants early diagnosis and aggressive therapy. Most often therapy for bacterial meningitis has to be started before the etiology is known. The choice of antimicrobial therapy is based on the most common pathogen prevalent in a particular geographical area and age group and their antibiotic susceptibility pattern. Though the common pathogens associated with bacterial meningitis in the west are *H. influenzae, N. meningitidis, S. pneumonia* and *Listeria monocytogenes* the relative incidence of meningitis caused by these agents is less in South East Asia.[10,11,12]

In our study we observed that *S. aureus* has emerged as the most common pathogen causing bacterial meningitis in all age groups. In the neonates *S. aureus, E. coli* and *Klebsiella species* predominated. *H. influenzae, N. meningitidis, S. pneumoniae, S. agalactiae* and *Listeria monocytogenes* were not isolated. Most Indian studies have quoted a low isola-

tion rate of these pathogens.[13,14,15]Across all age groups *S. aureus, E. coli, K. pneumoniae, Ps. aeruginosa, Streptococcus species* and *E. faecalis* were most commonly isolated. *Acinetobacter species* and *CONS* were seen mostly in the younger age groups while *Proteus* and *Citrobacter species* occurred only in children. Moreover *Citrobacter* and *Proteus species* were increasingly isolated in the later years suggesting an insidious emergence of these pathogens in causing meningitis.

The difference in etiology from the temperate west may be due to the fact that India is a semi-tropical country where hardy bacteria like *S. aureus, CONS* and gram negative bacilli flourish and the relatively more fragile bacteria like *H. influenzae, N. meningitidis, S. pneumoniae, S. agalactiae* and *Listeria monocytogenes* in comparison do not have a survival advantage. Secondly the predominance of patients from low socio-economic status with poor hygiene, poor nutrition and low birth weight leading to protein energy malnutrition gives an opportunity for *Streptococcus species* and *CONS* to cause meningitis. Finally, unfortunately most of the patients turn to the tertiary care centre after taking treatment from local practitioners which may lead not only to culture negative results but also to lower isolation of *H. influenzae, N. meningitides, S. pneumoniae, S. agalactiae* and *Listeria monocytogenes* which have not developed significant resistance to the usual antimicrobials. These results highlight the very different etiological profile in India in comparison to that of the west. Three uncommon bacteria were also isolated during the course of the study suggesting their possible emergence in future namely *S. mucilaginosus, R. equii*and*C. aquaticum*.

It is particularly useful for the clinicians to possess the susceptibility data on Gram positive and Gram negative bacteria rather than for particular organisms only. During the initial part of the study period (2001-02) among the Enterobacteriaceae lowest resistance was observed to the cephalosporins followed by the aminoglycosides, fluoroquinolonesand sulphonamides. Subsequently a general decline in the sensitivities to all groups of drugs was noticed upto 2004. The simultaneous decline in sensitivities to different group of drugs can be correlated to the rampant indiscriminate use of antibiotics leading to a large scale drug resistance. This can be attributed to the general tendency of the Indian populace to prefer private practitioners or quacks that do not follow proper antibiotic prescription norms. During this period i.e., between 2001-2004 most noticeable was marked increase in the resistance shown to cefotaxime. This increased resistance to cefotaxime was subsequently also corroborated by genotypic studies where it was reported that CTX-M gene causing cefotaxime resistance was significantly higher in India.[16,17]The rise of cefotaxime resistant GNRs can be correlated with increased consumption of extended spectrum cephalosporins, beta lactam-beta lactamase inhibitor combinations in our hospital. These beta lactamase genes are often associated with resistance determinants to non beta lactam agents e.g. aminoglycosides and fluoroquinolones. During 2005 ESBL production among the *Enterobacteriaceae* was found to be around 10%. However no AmpC or MBL was detected. However, in a study from Brazil during this time period reported around 49% gram negative isolates from various clinical samples to be ESBL producers.[18] Along with a perceptible deterioration in the susceptibility to the various antibiotics during 2006-2009, an increase in ESBL production to 17% and AmpC production to a high of 42% was noticed. Aminoglycosides maintained the best sensitivity profile at 44.44%.

As observed with the gram negative bacilli, a similar pattern of increasing drug resistance was seen among the *Staphylococcal species* and the *Enterococcus* while *Streptococcus species* maintained a uniform sensitivity throughout the study period.. A significant increase in the incidence of MRSA was noted from 44.4% in 2005 to 69.4% in 2009 and in HLAR among the *Enterococci* from 52.9% in 2005 to 60% in 2009. However, fortunately no vancomycin resistance was detected in *S. aureus* or *Enterococcus species.* Certain studies have reported low level resistance to vancomycin in *Staphylococcal* isolates which indicate an upcoming resistance to even this reserve drug.[19]

Similar to the GNRs aminoglycosides were the most effective antimicrobials in GPCs as well. Thus aminoglycosides emerged as the most effective group barring glycopeptides (vancomycin) and carbepenems (imipenem) against both GPCs and the GNRs.

Conclusion

The eight year long study has revealed the altered trend in etiology in cases of meningitis in a tropical country like India while clearly highlighting that antimicrobial susceptibility pattern is changing every three to four years thus necessitating a frequent review in drug policy.

These results signify the varying levels of drug resistance amongst the gram positive and the gram negative microbes and the need to control the spread of these resistant strains before they reach the alarming levels in this region. Stress should be given on the restrained and rationale use of antimicrobials both in and outside the hospital. This study also indicates the urgent need for more of such studies in the patients of meningitis via etiology and drug resistance along with the need for the in-house review of drug policy within hospitals at least once in every five years. In deciding how to approach antimicrobial therapy for meningitis, guidelines for initial antimicrobial therapy need to be modified to take into account local patterns of antimicrobial resistance. Likewise, health care systems will need to consider their own policies according to patient populations and local patterns of pathogen distribution in interpreting the way that national guidelines are implemented in their own institutions. Our study suggests that regulations designed to deal with treatment based on other institutions are not likely to be either successful or cost-effective. There is also an urgent need to develop institutional programs to enhance antimicrobial stewardship thus minimizing the emergence and spread of antimicrobial resistance.

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Competing Interests

None declared

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