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Evolving etiology and resistance patterns in bacterial meningitis: A comparative study over two decades

[1]Fatima Khan *MD Microbiology*, [1]Arsalan Kamaluddin, [2]Meher Rizvi *MD, PhD Microbiology*, [1]Asfia Sultan *MD Microbiology*, [1]Anees Akhtar *MD Microbiology*, [1]Areeb Shahid Rao, [1]Bhanu Chaudhary

[1]Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, India; [2]Sultan Qaboos University, Oman

Abstract

This study examines the evolution of bacterial meningitis etiology and antimicrobial resistance patterns over 20 years at a tertiary care centre in Aligarh, India. Comparing two periods (2001-2009 and 2015-2021), we identified a shift from gram-positive to gram-negative bacteria as the primary pathogens, with *Staphylococcus aureus* decreasing from 37.7% to 26.6% and *Klebsiella pneumoniae* increasing from 4.7% to 14.4%. Resistance trends show a significant decline in the effectiveness of antibiotics, particularly macrolides, fluoroquinolones, and cephalosporins. Aminoglycosides retained moderate efficacy, while carbapenem resistance increased from 0% to 56.3%, and Extended-Spectrum Beta-Lactamase (ESBL) production rose from 10% to 22.2%. The study highlights an urgent need for updated treatment protocols and enhanced surveillance to address the rising resistance and evolving pathogen landscape in bacterial meningitis.

Keywords: Meningitis, antimicrobial resistance, methicillin-resistant Staphylococcus aureus, MRSA, Extended-Spectrum Beta-Lactamase, ESBL, high-level aminoglycosides resistance, HLAR.

INTRODUCTION

Microbiology laboratories serve an essential role that goes beyond timely detection of the bacterial strain responsible for an infection and its susceptibility to antimicrobial agents. The laboratories also function as significant sources of epidemiological knowledge, allowing for the identification of common pathogenic agents in a certain area and providing evidence-based treatment approaches.[1]

While a number of studies provide extensive information about meningitis in developed hospital settings, there is a lack of data regarding its prevalence and distinctive features in developing regions such as our own. The need for a comprehensive and current regional representation that illustrates patterns in the causes and effectiveness of antimicrobial treatments is crucial for competent clinical decision-making.

The aim of our study was to determine the changes observed in the spectrum of bacterial meningitis and trends in antimicrobial resistance pattern in meningitis cases, recruited from a large tertiary university hospital in Aligarh (India) over the last 20 years. It specifically focuses on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), Enterococcus strains that exhibit high-level resistance to aminoglycosides (HLAR), Extended spectrum β-lactamases (ESBL), Amp C, Metallo-β-lactamases (MBL).

METHODS

This retrospective study of acute bacterial meningitis was performed at the Department of Microbiology, Jawaharlal Nehru Medical College and Hospital (JNMCH), a tertiary care centre in Aligarh, India between 2001-2009 (period I) and 2015-2021 (period II). The following were used as diagnostic criteria for bacterial meningitis in this study: (i) features of meningitis, such as fever, consciousness disturbance, seizure, or symptoms of meningeal irritation; (ii) a positive culture for bacterial pathogen(s); and (iii) a purulent CSF characteristic, i.e., leukocytosis with a leukocyte count >2.5x109/L and predominance of polymorphonuclear cells; a lactate concentration >3.5mmol/L; a protein concentration >0.45g/L; a glucose ratio (CSF glucose/ serum glucose) 0.4; or a glucose level 2.5mmol/L if no instantaneous blood glucose level was determined. All the

Address correspondence to: Arsalan, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, India. Email: saifarsalan5@gmail.com.
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samples that were sent to the laboratory were included in this study. But not all cerebrospinal fluid (CSF) samples were sent to our laboratory, only the CSF samples processed within our institution's laboratory were included.

Cerebrospinal fluid (CSF) and blood samples were collected taking all aseptic precautions for all patients suspected of meningitis admitted at JNMC Hospital. Gross examination was done to note the colour, turbidity and/or any surface pellicle or deposits. Microscopic examination was done using Gram's staining of the centrifuged CSF deposit. Subsequently, culture was done on chocolate agar, 5% sheep blood agar, Mac-Conkey agar, and brain heart infusion broth. These plates were then incubated at 37°C in an environment of humid air containing 5-10% CO2 for a duration of 24-48 hours. In instances where growth was observed, the pathogen was identified through standard biochemical testing during the first study period and by VITEK-2 (bioMérieux) automated system during the second study period.[2] In this study, patients with negative CSF cultures were not included in the analysis. We focused solely on culture-positive cases to evaluate the evolving etiology and resistance patterns. No additional methods, such as multi-array PCR panels, were employed to identify microorganisms in culture-negative cases. This approach was chosen to maintain consistency in data collection and analysis across the study period.

For the antibiotic susceptibility testing, the sensitivity to relevant antibiotics was assessed using the Kirby Bauer Disc diffusion method in accordance with the guidelines set forth by the Clinical and Laboratory Standards Institute (CLSI).[3] Commercially available antibiotic discs from HiMedia (Mumbai, India) were employed for this purpose. The panel of antimicrobial agents for gram-negative bacilli encompassed gentamicin (10μg), amikacin (30μg), tobramycin (10μg), amoxicillin (20μg), cotrimoxazole (trimethoprim/sulphamethoxazole 1.25/23.75μg), ceftriaxone (30μg), cefotaxime (30μg), cefoperazone sulbactam (75/75μg), ciprofloxacin (5μg), and imipenem (10μg). In the year 2005, an expanded panel was introduced, including netilmicin (30μg), ceftazidime (30μg), cefixime (15μg), cefoperazone (75μg), cefepime (30μg), gatifloxacin (5μg), ofloxacin (5μg), pipercillin (100μg), pipercillin-tazobactam (100/10μg), ceftazidime-clavulanic acid (30/10μg), and imipenem (10μg) as second-line agents. The assessment for possible extended- spectrum β-lactamase (ESBL) production was initiated using ceftriaxone (30μg) and cefoperazone (75μg) as screening agents. Isolates with zone diameters less than 25mm for ceftriaxone and less than 22mm for cefoperazone underwent subsequent confirmation for ESBL production. This was achieved by observing the enhancement of cefoperazone activity in the presence of cefoperazone sulbactam.[4] The detection of AmpC β-lactamase was executed on isolates resistant to ceftriaxone (30μg), cefixime (15μg), cefoperazone (75μg), and cefoperazone sulbactam (75/75μg). AmpC synthesis induction was based on the disc approximation assay utilising imipenem as an inducer.[5] Detection of metallo-β-lactamase (MBL) was performed through the Hodge test and Double Disc synergy test using EDTA, following the method delineated by Lee *et al*.[6]

For the gram-positive cocci, the antibiotics panel included gentamicin (10μg), amikacin (30μg), tobramycin (10μg), ampicillin (10μg), cotrimoxazole (trimethoprim/sulphamethoxazole 1.25/23.75μg), cefotaxime (30μg), ciprofloxacin (5μg), erythromycin (15μg), ofloxacin (5μg), gatifloxacin (5μg), clindamycin (2μg), cefaclor (30μg), oxacillin (1μg), and vancomycin (30μg) for Staphylococcus species. The antibiotic spectrum for Streptococcus species comprised gentamicin (10μg), amikacin (30μg), tetracycline (30μg), ampicillin (10μg), ciprofloxacin (5μg), erythromycin (15μg), gentamycin (120μg), streptomycin (300μg), and vancomycin (30μg). The assessment for methicillin-resistant *Staphylococcus aureus* (MRSA) involved the use of oxacillin (1μg), while detection of high-level aminoglycoside resistance (HLAR) in Enterococci utilised 120μg gentamicin and 300μg streptomycin discs.[6] Only the first CSF sample received was included for patients with more than one sample. During the first and also in second period of study, ceftriaxone and amikacin were used as empiric therapy for suspected meningitis cases in children. However, in adults, ceftriaxone amikacin and ceftriaxone vancomycin was used interchangeably depending upon the history of patient.

RESULTS

During the study period I, a total of 5,859 cerebrospinal fluid (CSF) samples were collected. This collection occurred between 2001 and 2009, referred to as period I. Among these samples, 401 (6.8%) cases were confirmed (through Gram's staining and culture). In comparison to period I, during the II period (2015-2021) CSF

samples received reduced to less than half i.e., 2,598. Among these samples, 213 (8.2%) cases were confirmed as meningitis. All samples were obtained from patients admitted to various wards of JNMCH in Aligarh, India.

Etiology

Comparing the two study periods reveals notable shifts in the etiology of meningitis (Figure 1, Table 1). In the first period, gram-positive bacteria were responsible for the majority of cases (240, 59.8%), while in the second period, gram-negative bacteria took the lead (126, 59.1%). *Staphylococcus aureus* remained the most common pathogen in both periods, though its prevalence decreased from 151 (37.6%) to 65 (30.5%). Streptococcus species and *Enterococcus faecalis* exhibited reduced presence in the second period with 35 (8.7%) decreasing to 9 (4.2%), and 18 (4.5%) decreasing to 14 (7%) respectively. *Streptococcus pneumoniae* incidence dropped significantly from 33 (8.2%) to 3 (1.4%). Among gram-negative bacteria, the Enterobacteriaceae family's prevalence increased, particularly with Klebsiella pneumoniae rising from 19 (4.7%) to 29 (13.6%) and Escherichia coli from 45 (11.2%) to 27 (12.6%). Pseudomonas aeruginosa and Acinetobacter species occurrence among nil-fermenters remained relatively steady, with slightly decreased proportions in the second period, 49 (12.2%) to 41 (19.2%) and 8 (2.0%) to 5 (2.3%) respectively. The dominance of Pseudomonas species persisted among gram-negative bacilli, as did the unusual prevalence of Streptococcus species and *S. pneumoniae* with 8.7% and 8.2% in the first period, and *K. pneumoniae*'s increased prominence among neonates in the second period (24.1%). These shifts highlight changes in meningitis causative agents and suggest potential shifts in epidemiology.

Antibiotic resistance profile

Gram-positive cocci: (Figure 2)

In the first study period (2001-2005), aminoglycosides maintained high effectiveness with susceptibility rates generally above 79%, though there was a slight decline to 62% in 2005. In the second period (2015-2021), effectiveness remained high, except for a dip to 66.6% in 2017. Macrolides showed moderate effectiveness in the first period, with susceptibility rates ranging from 48% to 77%, but experienced a sharp decline in the second period, with rates dropping significantly after 2017. Fluoroquinolones exhibited moderate to high effectiveness in the first period (50-77%), but their effectiveness declined in the second period, with significant fluctuations and notable drops. Cephalosporins were consistently moderately effective in the first period (34-56%), but their effectiveness fluctuated in the second period, ending at 22.2% in 2021. Sulfonamides and penicillins showed moderate effectiveness in the first period (20-56% for sulfonamides and 14-55% for penicillins) but lacked data for the second period, limiting

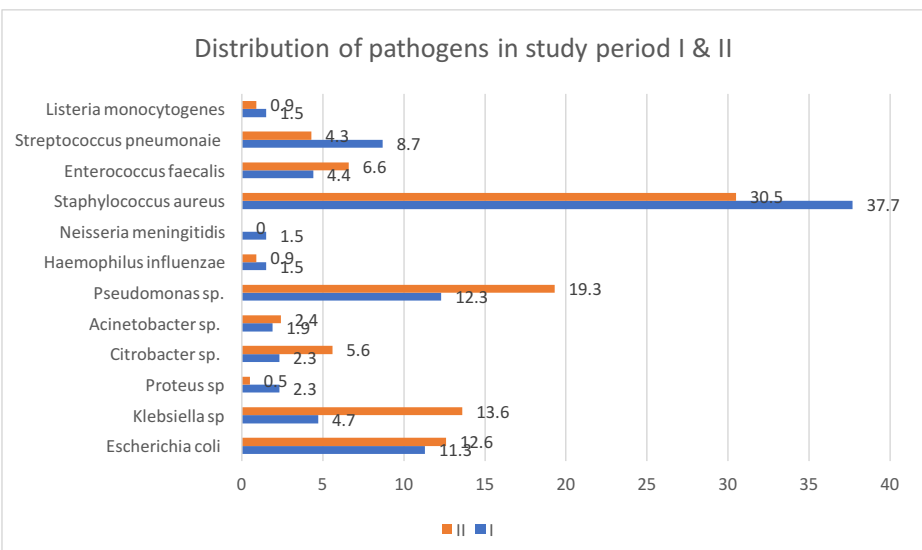

Figure 1. Distribution of pathogens in study period I & II

Table 1: Distribution of pathogens across different age groups during study period I & II

Age	E.coli	Klebsiella species	Proteus species	Citrobacter species	Acinetobacter species	Pseudomonas species	*S. aureus*	*S. pneumoniae*	Strepto-coccus species	*E. faecalis*	Others	Total
0-1 M (1st)	9	6	1	3	1	4	15	1	3	1	4	48 (12.0)
0-1 M (2nd)	5	6	1	5	-	4	-	-	1		1	23 (10.8)
1-3 M (1st)	2	1	1	-	1	0	10	-	1	1	5	22 (5.5)
1-3 M (2nd)	2	12	-	1		4	12	-	2		1	34 (15.9)
3 M-1 Y (1st)	10	4	1	3	1	12	25	8	7	6	3	81 (20.2)
3 M-1 Y(2nd)	6	3	-	-		9	8	-	2	1	0	29 (13.6)
1y-5Y (1st)	10	2	5	2	2	20	45	11	10	4	8	119 (29.7)
1Y-5Y (2nd)	4	3	0	2	1	8	19	0	2	3	1	43 (20.2)
5Y-10Y (1st)	6	2	1	1	0	8	37	6	5	2	4	72(17.9)
5Y-10Y (2nd)	2	3	-	1	-	10	14	3	1	1	2	37 (17.4)
10Y-19 Y (1st)	2	1	0	0	0	2	8	5	2	1	0	21 (5.2)
10Y-19 Y (1st)	3	-	-	-	1	5	5	-	1	1	2	18 (8.5)
19Y- 60 Y (1st)	6	3	0	0	3	3	11	2	7	3	0	38 (9.5)
19Y- 60 Y (1st)	5	2	0	3	3	1	7	0	0	8	0	29 (13.6)
Total (1st)	45 (11.2)	19 (4.7)	9 (2.2)	9 (2.2)	8 (2.0)	49 (12.2)	151 (37.7)	33 (8.2)	35 (8.7)	18 (4.5)	25 (6.2)	401 (100)
Total (2nd)	27 (12.7)	29 (13.6)	1(0.4)	12 (5.6)	5 (2.4)	41 (19.2)	65 (30.5)	3 (1.4)	9 (4.2)	14 (6.6)	7 (3.2)	213 (100)

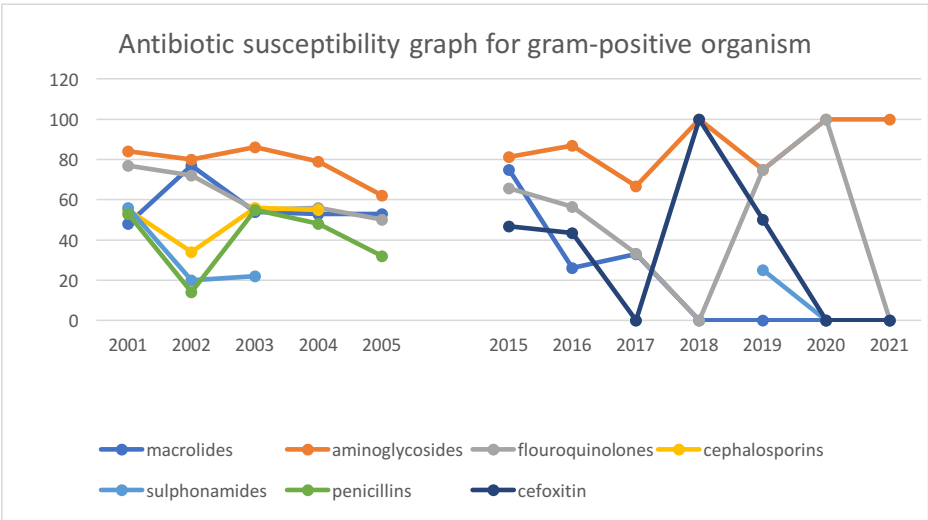

Figure 2. Antibiotic susceptibility graph for gram-positive organism

further analysis. Cefoxitin, tested only in the second period, showed variable effectiveness with rates of 46.8% in 2015 and 43.4% in 2016, followed by significant fluctuations. Enterococcus faecalis isolates showed an increase in High-Level Aminoglycoside Resistance (HLAR) from 52.9% in 2005 to 60% in 2008-2009, and an average HLAR of 50% with multi-drug resistance at 75% during the second period. In the first period, all isolates were sensitive to glycopeptides, with no vancomycin-resistant Enterococcus (VRE) or vancomycin-resistant *Staphylococcus aureus* (VRSA) detected, while the second period saw one VRE case but no vancomycin-resistant Staphylococcus.

Overall, the data indicates a troubling decline in the effectiveness of macrolides, fluoroquinolones, and cephalosporins against Gram-positive organisms over time, while aminoglycosides largely maintained their effectiveness.

Gram-negative bacilli: (Figure 3)

In the first study period (2001-2005), cephalosporins exhibited high effectiveness with susceptibility rates of 78-79% initially, but these rates fell to 34% by 2005. In the second period (2015-2021), their effectiveness further declined, starting at 29.4% in 2015 and ending at 22.2% in 2021. Aminoglycosides showed moderate effectiveness during the first period, with susceptibility ranging from 48% to 66%. In the second period, effectiveness varied, beginning at 35.3% in 2015, peaking at 50% in 2017, and ending at 44.4% in 2021. Fluoroquinolones demonstrated moderate to high effectiveness initially (60-68%), but their susceptibility dramatically decreased to 18% by 2005. In the second period, their effectiveness decreased further, starting at 41.2% in 2015 and ending at 22.2% in 2021. For the second dataset on cephalosporins, effectiveness was moderate in the first period (34-67%) but declined significantly in the second period, starting at 5.8% in 2015 and reaching 22.2% in 2021. Sulfonamides showed variable effectiveness in the first period (32-57%), with generally low effectiveness in the second period, peaking at 42.9% in 2016 but dropping significantly in other years. Carbapenems, studied only in the second period, had high effectiveness at 85.7% in 2015 but fluctuated between 33.3% and 55.5% in subsequent years. ESBL production increased from 10% in 2005 to 16.67% in 2009, and AmpC production rose from 0% in 2005 to 42% in 2009. There was no detection of Metallo-Beta-Lactamase (MBL) in the first period, and imipenem remained 100% effective. However, during the second period, a significant rise in resistance was noted: ESBL production reached 22.2%, AmpC increased to 53.1%, and carbapenem resistance climbed to 56.3% By the end of the study, resistance to colistin and tigecycline was observed. Overall, the data shows a decline in the effectiveness of most antibiotics against Gram-negative organisms over time, with notable decreases in cephalosporins and fluoroquinolones, while aminoglycosides maintained moderate effectiveness, and sulfonamides and carbapenems exhibited declining trends in the second period.

Overall, the data indicates a decline in the effectiveness of most antibiotics against gram-negative organisms over time. Cephalosporins

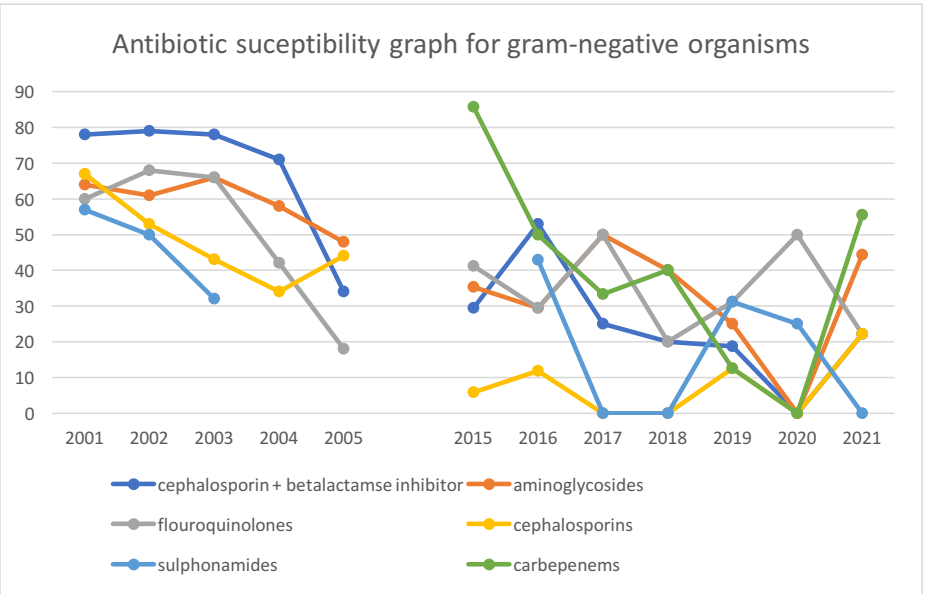

Figure 3. Antibiotic susceptibility graph for gram-negative organisms.

and fluoroquinolones, initially effective, experienced notable decreases in susceptibility. Aminoglycosides maintained moderate levels, while sulfonamides and carbapenems showed declining trends in the second period.

DISCUSSION

The etiology of meningitis has evolved significantly between the two study periods, reflecting broader trends observed in similar research. In the first period (2001-2005), gram-positive bacteria predominated, with Staphylococcus aureus as the most common pathogen. However, this shifted in the second period (2015-2021), where gram-negative bacteria, particularly *Klebsiella pneumoniae*, became more prevalent. These findings align with several studies highlighting the increasing role of gram-negative organisms in meningitis. For example, a study by De Silva *et al*.[7] reported a rise in gram-negative pathogens, notably Klebsiella pneumoniae, in cases of community-acquired meningitis. Similarly, Goktas *et al*.[8] observed a shift from gram-positive to gram-negative bacteria in their cohort of meningitis patients.

The decline in *Staphylococcus aureus*, from 37.7% in the first period to 26.6% in the second, mirrors findings by Johnson *et al*.[9], who noted a decrease in *Staphylococcus aureus* infections over time. *Streptococcus pneumoniae*'s significant drop from 8.2% to 1.4% is consistent with the trends observed by Richards *et al*.[10], who documented a reduction in *Streptococcus pneumoniae* cases, likely due to the impact of vaccination programs. The decline in Streptococcus species and *Enterococcus faecalis* in the second period is also supported by Patel *et al*.[11] who found similar trends in their study on bacterial meningitis. Conversely, the increased prevalence of *Klebsiella pneumoniae* and *Escherichia coli* in our study corroborates findings from Lee *et al*.[12], who identified an upward trend in these gram-negative pathogens. The steady occurrence of *Pseudomonas aeruginosa* and Acinetobacter species, despite slight decreases, is consistent with findings by Wang *et al*.[13] who observed stable proportions of these non-fermenters in their analysis of meningitis cases.

The rise of *Klebsiella pneumoniae* among neonates, as noted in our study, is in line with the observations of Kim *et al*.[14], who reported a similar increase in neonatal infections caused by *Klebsiella pneumoniae*. This shift underscores the need for ongoing surveillance and adaptation of treatment protocols to address emerging pathogens effectively.

Our study also reveals a significant decline in antibiotic effectiveness over time against both Gram-positive and Gram-negative pathogens, with notable trends aligning with previous research. Macrolides exhibited a sharp decrease in susceptibility from the first to the second period, consistent with the findings of Sader *et al*.[15] who documented similar declines. Fluoroquinolones

also showed a marked reduction in effectiveness, echoing the trends reported by and Karlowsky *et al*.[16], where susceptibility rates fell notably over time. Cephalosporins, which initially demonstrated high effectiveness, saw a decline that supports the observations of Giske *et al*.[17], who noted similar patterns of reduced susceptibility.

In contrast, aminoglycosides maintained their effectiveness relatively well throughout the study period, aligning with the stability observed by Livermore *et al*.[18] This contrasts with the fluctuating effectiveness of sulfonamides and penicillins, which showed moderate effectiveness in the first period and lack of data in the second period. This variability is consistent with Peirano *et al*.[19], who also reported fluctuating effectiveness and data gaps. The rise in carbapenem resistance observed in our study reflects trends documented by Borer *et al*.[20], who reported increasing resistance rates and fluctuating effectiveness. Additionally, our findings of increased Extended-Spectrum Beta-Lactamase (ESBL) and AmpC production align with the observations of Bush *et al*.[21], who highlighted growing concerns over these resistance mechanisms. The emergence of resistance to reserve antimicrobials like colistin and tigecycline, noted in our study, corroborates the findings of Falagas *et al*.[22], who reported rising resistance trends in these critical treatments.

The limitations of this study are: 1. Sample Size Reduction: One significant limitation is the decrease in the number of samples received by our institutional microbiology lab from 2017 onwards. This reduction in sample size can impact the generalisability of our results and introduce potential bias, as a substantial proportion of samples began going to private laboratories. Consequently, the observed trends may not fully represent the entire population, especially during the latter part of the study. 2. External Factors: The study did not account for external factors such as changes in clinical practises, immunisation rates, or patient demography that could influence bacterial aetiology and antibiotic resistance. These variables could contribute to differences in our findings. 3. Single-Center Study: Our research was carried out at a single medical centre in North India. As a result, the findings may not be completely representative of the region or country. Regional differences in healthcare practises and patient populations may have an impact on the generalisability of our findings.

DISCLOSURE

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Conflicts of interest: None

REFERENCES

1. You MD. Ampicillin in the treatment of meningitis due to Haemophilus influenza: an appraisal after 6 years of experience. *J Pediatr* 1969; 74:848-51.
2. Collee JG, Fraser AG, Marmion BP, Simmons A. Mackey and McCartney practical medical microbiology. In: Collee JG, Miles RS, Watt B, eds: Tests for the identification of Bacteria. 14th ed. New Delhi, India: Elsevier, 2006:131-49.
3. Clinical and Laboratory Standards Institute 2020. Performance standards for antimicrobial susceptibility testing: 30th informational supplement: Approved standards M100-S18. Clinical and Laboratory Standards Institute, Baltimore, USA. 2008. https://clsi.org/media/3481/m100ed30_sample.pdf
4. Rizvi M, Fatima N, Rashid M, *et al*. Extended spectrum AmpC and metallo-beta-lactamases in Serratia and Citrobacter spp. in a disc approximation assay. *J Infect Dev Ctries* 2009; 3(4):285-94. https://pubmed.ncbi.nlm.nih.gov/19759492/
5. Murray PR, Baron EJ, Jorgenson JH, *et al*. Manual of clinical microbiology. In: Swenson JM, Hindler JF, Jorgenson JH, eds: Special phenotypic methods for detecting antibacterial resistance.8th ed. Washington DC: ASM Press, 2003:1179.
6. Lee KY, Chong HB, Shin YA, Yong KD, Yum JH. Modified Hodge test and EDTA disc synergy tests to screen metallo beta lactamase producing strains of Pseudomonas and Acinetobacter species. *Clin Microbiol Infect* 2001; 7:88-91. doi: 10.1046/j.1469-0691.2001.00204.x.
7. De Silva HJ, Jayasinghe S, Fernando S, *et al.* Changing patterns in the etiology of bacterial meningitis in Sri Lanka. *J Infect Dev Ctries* 2021;15(4):527-33.
8. GBD 2019 Meningitis Antimicrobial Resistance Collaborators. Global, regional, and national burden of meningitis and its aetiologies, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2023;22(8):685-711. doi: 10.1016/S1474-4422(23)00195-3.
9. Rodrigues MM, Patrocínio SJ, Rodrigues MG. Staphylococcus aureus meningitis in children: a review of 30 community-acquired cases. *Arq Neuropsiquiatr* 2000;58(3-B):843-51. https://doi.org/10.1590/S0004-282X2000000500009
10. Farfán-Albarracín JD, Camacho-Moreno G, Leal AL, *et al*. Changes in the incidence of acute bacterial meningitis caused by *Streptococcus pneumoniae* and the implications of serotype replacement in children in Colombia after mass vaccination with PCV10. *Front Pediatr.* 2022;10:1006887. doi:10.3389/fped.2022.1006887.
11. Dery MA, Hasbun R. Changing epidemiology of bacterial meningitis. *Curr Infect Dis Rep* 2007;9(4):301-7. doi:10.1007/s11908-007-0047-7.
12. Oh H, Heo ST, Kim M, Kang CH, Yoo JR. Devastating community-acquired bacterial meningitis

caused by hypervirulent *Klebsiella pneumoniae* in an immunocompetent patient. *J Clin Neurol* 2021;17(3):484-6. doi:10.3988/jcn.2021.17.3.484.
13. Sarkar M, Jena J, Pattnaik D, Mallick B. Prevalence of nonfermentative gram-negative bacilli and their antimicrobial susceptibility profiles in a tertiary care hospital of Eastern India. *Int J Adv Med* 2018;5(2):366-70. doi:10.18203/2349-3933.ijam20181070.
14. Ravi V, Vijay DD, Sujhithra A, Jayanthi S, Subramanian TK, Harish N. Neonatal sepsis: The impact of Hypervirulent *Klebsiella pneumonia* in a tertiary care hospital. *J Pure Appl Microbiol* 2022;16(3):2035-44. doi: 10.22207/JPAM.16.3.56
15. Sader HS, Farrell DJ, Jones RN. Antimicrobial susceptibility of gram-positive cocci isolated from skin and skin-structure infections in European medical centres. *Int J Antimicrob Agents* 2010;36(1):28-32. doi: 10.1016/j.ijantimicag.2010.03.016.
16. Hoban DJ, Biedenbach DJ, Mutnick AH, Jones RN. Pathogen of occurrence and susceptibility patterns associated with pneumonia in hospitalized patients in North America: results of the SENTRY Antimicrobial Surveillance Study (2000). *Diagn Microbiol Infect Dis* 2003;45(4):279-85. doi: 10.1016/s0732-8893(02)00540-0.
17. Giske CG, Monnet DL, Cars O, Carmeli Y; ReAct-Action on antibiotic resistance. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother* 2008;52(3):813-21. doi: 10.1128/AAC.01169-07.
18. Bush K. Past and present perspectives on β-lactamases. *Antimicrob Agents Chemother* 2018;62:10. https://doi.org/10.1128/aac.01076-18
19. Rubin JE, Pitout JD. Extended-spectrum β-lactamase, carbapenemase and AmpC producing Enterobacteriaceae in companion animals. *Vet Microbiol* 2014;170(1-2):10-8. doi: 10.1016/j.vetmic.2014.01.017..
20. Rahal JJ. The role of carbapenems in initial therapy for serious gram-negative infections. *Crit Care* 2008;12 (Suppl 4):S5. doi: 10.1186/cc6821.
21. Bush K, Bradford PA. Interplay between β-lactamases and new β-lactamase inhibitors. *Nat Rev Microbiol* 2019;17(5):295-306. doi: 10.1038/s41579-019-0159-8. Erratum in: *Nat Rev Microbiol* 2019;17(7):459. doi: 10.1038/s41579-019-0206-5. Erratum in: *Nat Rev Microbiol* 2019;17(7):459-60. doi: 10.1038/s41579-019-0221-6.
22. Sharma J, Sharma D, Singh A, Sunita K. Colistin resistance and management of drug resistant infections. *Can J Infect Dis Med Microbiol* 2022;2022:4315030. doi: 10.1155/2022/4315030