Microbes and Infectious Diseases

Original article

Bacterial profile and resistance trends of pathogens implicated in bacterial meningitis: A four years retrospective study

Lamiaa M. El-Moussely [1], Nashwa Naguib Omar[2], Nahla Gamaleldin AbdelHakim Hanafy [3], Manal M. Darwish [1, 4]*

1- Department of Medical Microbiology and Immunology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
2- Department of Clinical Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
3- Department of Pediatrics, Faculty of Medicine, Modern University for Technology, and Information, Cairo, Egypt.
4- Department of Microbiology and Immunology, Faculty of Pharmacy, October university for modern science and Arts, Egypt

A B S T R A C T

Background: Study aims to determine the bacterial profile associated with bacterial meningitis, their antimicrobial resistance pattern providing antimicrobial stewardship guidance and improving the efficacy of empirical treatment. **Methods:** Four years case-series retrospective study (December 2019- December 2023), of positive CSF cultures in 432 patients of various age groups and departments in Ain Shams University Hospital, Cairo, Egypt were analyzed. **Results:** Predominance of Gram-negative bacteria constituting 79.1%, while 19.6% were attributed to gram-positive in bacterial meningitis. Notably, *Klebsiella pneumoniae (K. pneumoniae)* had the highest prevalence at 34%, followed by *Acinetobacter* species (spp) at 19.6%. Whereas, *Streptococcus pneumoniae (S. pneumonia)* exhibited a lower prevalence of 1.8%. The age group >16-50 years demonstrated the highest prevalence at 26.6%, followed by infants aged 2 months to <1 year, with a prevalence of 23.3%. Antimicrobial resistance was predominantly against ceftriaxone 89%, and ampicillin 87.9%. Conversely, pathogens exhibited greater sensitivity to tobramycin (46.2%) and gentamicin (43.1%) than other antimicrobials. Multidrug resistance was identified in 53.5% of Gram-negative bacteria. These results highlight Gram-negative bacteria role in meningitis. **Conclusion:** This study revealed significant changes in meningitis bacterial profiles, highlighting the importance of reinforcing antimicrobial stewardship efforts to effectively combat the evolving landscape of bacterial meningitis.
.

Introduction

Bacterial meningitis (BM) is a life-threatening global medical challenge [1]. It is responsible for more than 300,000 deaths worldwide [2] with incidence 0.7–0.9 per 100,000 in developed countries and 40 per 100,000 in developing countries [3]. Bacterial meningitis is endemic in various regions globally with incidence and mortality rates depending on areas, causative micro-organism, and patient's age [4]. According to a global systematic review in 2019, most meningitis-related deaths, spanning all age groups and children under 5 years old, were primarily caused by

* *Corresponding author:* Nashwa Naguib Omar
  E-mail address: nousha_22@hotmail.com

Streptococcus pneumoniae, followed by *Neisseria meningitidis* (*N. meningitidis*) and *K. pneumoniae*. *Group B Streptococcus* accounted for the highest mortality in neonates. Effective vaccines like Hib, pneumococcal, and meningococcal conjugate vaccines reduced children mortality rate over the past 30 years. WHO's global targets, aim to reduce cases of vaccine-preventable BM by 50% and associated deaths by 70% by 2030 [5]. Recently, Gram-negative bacteria including *Acinetobacter baumannii, Klebsiella pneumoniae* and *Escherichia coli* causing meningitis has increased significantly [6].

Antimicrobial susceptibility test-results appear 2-3 days after CSF (cerebrospinal fluid) specimen collection; accordingly, BM is often treated empirically [7]. Prompt empirical antimicrobials are paramount, as any treatment-delay significantly increases patient morbidity and mortality. However, if not correctly given the risk of antimicrobial resistance (AMR) increases. WHO estimated that annually multidrug-resistant (MDR) bacterial infection results in 700,000 deaths across all ages globally, with nearly 200,000 newborns [8].

Up-to-date Surveillance on BM and antimicrobial resistance patterns are notably scarce. Such researches are crucial to pinpoint vaccination targets, formulate and update preventive strategies, and antimicrobial stewardship program. This comprehensive study aims to determine the bacterial profile of the implicated BM pathogens, their AMR pattern and seasonal variation to update antimicrobial stewardship related to this infection.

Materials and methods

This study was conducted at Microbiology Laboratories, Ain Shams University Hospital, Cairo, Egypt. Ethical committee Approval (with Federal Wide Assurance number: R361a/2023/2024) were taken from Ethics Committee Center at Ain Shams University. Measures were taken to ensure confidentiality and privacy of data.

This four-year retrospective investigation (December 2019- December 2023) involved patients from neonates to elderly. Data records of 4,018 CSF samples were collected and analysed. Information gathered were results of bacterial cultures, antimicrobial susceptibility and demographic details as age, sex, and denoted departments. Eventually, 432 positive CSF cultures were included after removing duplicated samples.

Samples were collected from different wards including neurosurgery units, neonatal intensive care units (NICU), ICU, outpatient, and emergency departments under complete aseptic conditions and delivered immediately to the laboratory. Samples were processed according to the laboratory's standard microbiological operative procedures. Samples that were culture positive were subjected to further analysis, and the isolates obtained were identified using standard microbiological methods [9] including colony morphology on agar, Gram's stain reaction, and other standardized biochemical tests including; lactose fermentation, urea hydrolysis, citrate utilization, lysine decarboxylation, oxidase test, motility test, mannitol fermentation, catalase, slide and tube coagulase tests and DNase production testing .In addition Vitek automated system for identification and Susceptibility was used for confirmation of isolated organisms.

Antibiotic susceptibility testing: Susceptibility testing of isolates was performed on pure culture isolates using the disc diffusion method [10] with strict adherence to the Clinical Laboratory Standards Institute (CLSI) guidelines [11] antimicrobials commonly used in cases of bacterial meningitis and can cross the blood brain barrier were tested: Penicillin (P 10 ug), ampicillin (AMP 2 ug), cefoxitin (FOX 30 ug), ceftazidime (CAZ 30 ug), cefipime (FEP 30 ug), meropenem (MEM 10 ug), tobramycin (TOB 10 ug), cefotaxime (CTX 30 ug), linezolid (LZD 30 ug), vancomycin (VAN 30 ug), cefuroxime (CXM 30 ug), ceftriaxone (CRO 30 ug), trimethoprime/sulphamethoxazole (STX 25ug), ampicillin/sulbactam (SAM 20 ug), amoxicillin/clavulanic (AMC 30 ug), amikacin (AK30 ug), gentamicin (GN 10 ug), tazocin (TZP 110 ug).

Reference strains: *Escherichia coli (E. coli)* ATCC 25922, *N. meningitides* ATCC CDC327, *S. pneumonia* ATCC 49619, *Haemophilus influenza (H. influenza)* ATCC 49766 and *Staphylococcus aureus* (*S. aureus*) ATCC 25923 were tested as quality controls.

Definitions

MDR: non-susceptibility to at least one agent in three or more antimicrobial categories.

Statistical analysis

Analysis of data was done using SPSS program version 24.
Qualitative data were presented using count and

percentage, bar and pie charts. Chi square test was used to compare qualitative data between different groups. Fisher exact test was used instead of chi square test when expected value in > 25% of cells is less than 5 or one of the cells has expected value of zero. *P* value less than or equal to 0.05 was considered statistically significant.

Results

Between year 2019-2023, 432/4018 positive CSF cultures were collected from various hospital departments, with isolation rate 10.7%.

Table 1 presented patients' demographic data, 56% were males (242/432), while 43.9% were females (190/432), with male-to-female ratio 1.2:1. Patient age ranged from neonates to > 50 years, segmented into seven age-groups, median age was >5-16 years. Over half of the cases (n=218) occurred in children <5 years old.

Neurosurgery (40.2%) and ICU (30%) departments showed the highest BM rates. Significant association was identified between isolated bacteria and sex (*p* value = 0.01). However, no statistically significant relationship was found between isolated bacteria and various age groups. Lastly, a statistically significant difference was observed between isolated bacteria and departments (*p* value = 0.05).

Concerning isolated bacteria, 342 / 432 (79.1%) were Gram-negative, while 85 / 432 (19.6%) were Gram-positive. *Klebsiella pneumoniae* was the predominant species (spp) (34%), as shown in **table (2),** followed by *Acinetobacter* (19.6%) then *Pseudomonas* spp (16.2%). Conversely, *Streptococcus pneumoniae* showed lower prevalence (1.8%). The least isolated bacterial pathogens were *Citrobacter, Burkholderia,* and *Serratia marcescens* with prevalence (0.2%) each. Noteworthy mixed infections occurred in 7.1% of the total samples.

TOB: tobramycin, MEM: meropenem, FEP: cefepime, TZP: piperacillin/tazobactam, AK: amikacin, CAZ: ceftazidime, SAM: ampicillin/sulbactam, AMC: amoxicillin/clavulanic, CTX: cefotaxime, SXT: trimethoprim/sulfamethoxazole, P: penicillin, AMP: ampicillin, CXM: cefuroxime, CRO: ceftriaxone, LZD: linezolid, N/A: Not Assessed.

Table 3 Illustrates the bacterial AMR patterns. All isolates of *Klebsiella* (100%) exhibited resistance to ampicillin/sulbactam, with (97%) and (95%) resistance to ceftriaxone and ceftazidime. In

contrast, sensitivity was observed in 29% and 26.6% of cases for gentamicin and amikacin. *Acinetobacter* spp demonstrated high resistance to cefotaxime (96.8%) and piperacillin/tazobactam (96%), while exhibiting relative sensitivity to tobramycin (45.8%) and trimethoprim/sulfamethoxazole (27.5%). *Pseudomonas* spp displayed resistance to cefotaxime and ceftriaxone (82.4%), and to cefepime (80%), however, all isolates (100%) were sensitive to piperacillin/tazobactam, and (45.5%) showed sensitivity to gentamicin. Among Gram-positive bacteria 85/432 patients, high resistance rates were noted for penicillin (88.2%) and ampicillin (86.5%). Hopefully, linezolid (98.8%) and vancomycin (97.9%) showed high sensitivity. Collectively, Pathogens displayed good sensitivity to tobramycin (46.2%), gentamicin (43.1%), and amikacin (41.6%) whereas; resistance across all pathogens was prominent against ceftriaxone (89%), ampicillin (87.9%), penicillin (87.5%), and cefotaxime (86.6%).

183/342 Gram-negative bacteria (53.5%) were MDR as shown in **figure (1A).** *Klebsiella pneumoniae* represented 92/183 cases (50.2%), *Acinetobacter* comprised 48/183 (26.2%), and 9/183 (4.9%) *were Pseudomonas* (**Figure 1B**). Furthermore, 9/15 *Staphylococcus aureus* cases (60%) were *MRSA* as detected by resistance to cefoxitin disc.

A statistically significant difference was observed in Methicillin-resistant *Staphylococcus aureus (MRSA)* and various departments. NICU had the highest MRSA cases (25%) of all NICU cases, followed by neurosurgery (1.72%) then ICU (1.54%). No MRSA cases were detected in either outpatient or emergency departments. Concerning MDR pathogens, no statistical significance was identified, with the highest percentage detected in ICU department (48.4%), and the lowest in outpatient unit (29.4%) **(Table 4).**

Regarding bacterial pathogens prevalence in different age groups, *Acinetobacter* was predominant in <2 months age-group (37.5%), followed by *K. Pneumonia* (18.8%), whereas *Streptococci, Staphylococci and Pseudomonas* incidence were all the same (12.5%).

Acinetobacter was the dominant pathogen (41.9%) in patients aged >3-5 years. *Klebsiella pneumoniae* meningitis had its highest incidence (39%) in >5-16 of age, with relatively similar rates across other age groups, except for the lowest incidence observed in >2 months-1year age group

(29.7%). *Pseudomonas* meningitis peaked age group >3-5 years (19.4%) and its lowest incidence in >5-16 years (9.4%). *Staphylococcus* BM was most prevalent in >2 months-1year age group (26.7%) and least prevalent in patients aged >3-5 years (9.7%) (**Figure 2).**

Table 5 shows *Klebsiella pneumoniae* as the commonest pathogen in ICU, 36 isolates (27.7%) of all organisms detected in ICU, followed by *Acinetobacter,* 31 isolates (23.8%). Predominant organisms in neurosurgery department were *K. pneumoniae* (29.3%), followed by *Staphylococci* (24.1%). Within NICU, *Acinetobacter* took the lead with 6 isolates (37.5%), followed by *Klebsiella pneumoniae* (18.8%). In outpatient setting*, K. pneumoniae* was the most isolated organism 27

isolates (34.6%). The table showed statistically significant difference between the isolated organism and various departments

BM cases varied each year from December 2019-December 2023; with 110, 99, 140, 86 cases respectively. Out of the 432 cases, highest cases were isolated in the year 2022 (32.4%) and the least (19.9%) isolated in 2023. Seasonal variation was detected in *K. pneumonia* meningitis, *Acinetobacter* meningitis and *Staphylococcus spp* meningitis with most cases of *K. pneumonia and Acinetobacter* isolated in winter more than other seasons of the year showing (42 %) and (48%) respectively. On the other hand, *Staphylococcus spp* showed prevalence more in summer more than all other seasons (**Figure 3).**

Table 1. Demographic data of studied CSF samples regarding gender, age group and departments of patients.

		N= 432	**%**
Sex	Male	242	56.0%
	Female	190	43.9%
Age (years)	0-<2 months	16	3.7%
	2 months-< 1yr	101	23.3%
	>1yr -3yrs	70	16.2%
	>3yrs-5yrs	31	7.17%
	>5yrs-16yrs	53	12.2%
	>16yrs-50yrs	115	26.6%
	>50yrs	46	10.6%
Department	Adult ICU	130	30%
	Neurosurgery	174	40.2%
	NICU	16	3.7%
	Outpatient	80	18.5%
	Emergency department	32	7.4%

Table 2. Pathogen Prevalence in CSF from December 2019 to December 2023.

		N	**%**
Organism name	*E coli*	22	5%
	Klebsiella pneumoniae	147	34%
	Acinetobacter spp	85	19.6%
	Streptococcus pneumoniae	8	1.8%
	Staphylococcus Coagulase Negative	46	10.6%
	S. aureus	15	3.4%
	Pseudomonas	70	16.2%
	Enterococcus spp	16	3.7%
	Enterobacter	8	1.8%
	Proteus	7	1.6%
	Cryptococcus neofomans	2	0.4%
	Candida	3	0.6%
	Citrobacter	1	0.2%
	Burkhulderia	1	0.2%
	Secratia marcescens	1	0.2%
	Total	432	100.0%

Table 3. AMR and susceptibility patterns in all isolated pathogens.

		Klebsiella Spp	Acineto-bacter	Pseudo-monas	E. coli	Entero-bacter	Proteus	Strept. Peumoniae	Staph. spp	Enterococci
TOB	Sensitive	13.0%	45.8%	25.0%	40.0%	0.0%	81.8%	0.0%	0.0%	0.0%
	Resistant	87.0%	54.2%	75.0%	60.0%	0.0%	18.2%	0.0%	0.0%	100%
MEM	Sensitive	9.7%	14.3%	64.3%	50.0%	100%	52.9%	50.0%	21.3%	0.0%
	Resistant	90.3%	85.7%	35.7%	50.0%	0.0%	47.1%	50.0%	78.7%	0.0%
FEP	Sensitive	5.1%	15.8%	20.0%	60.0%	100%	78.9%	0.0%	23.7%	0.0%
	Resistant	94.9%	84.2%	80.0%	40.0%	0.0%	21.1%	0.0%	76.3%	100%
TZP	Sensitive	6.5%	4.0%	100%	50.0%	100%	84.2%	100%	22.4%	33.3%
	Resistant	93.5%	96.0%	0.0%	50.0%	0.0%	15.8%	0.0%	77.6%	66.7%
AK	Sensitive	26.6%	25.6%	37.5%	100%	100%	72.0%	0.0%	80.0%	0.0%
	Resistant	73.4%	74.4%	62.5%	0.0%	0.0%	28.0%	0.0%	20.0%	0.0%
CAZ	Sensitive	5.0%	16.0%	36.4%	50.0%	100%	66.0%	0.0%	24.6%	N/A
	Resistant	95.0%	84.0%	63.6%	50.0%	0.0%	34.0%	0.0%	75.4%	N/A
CRO	Sensitive	3.0%	5.5%	17.6%	33.3%	0.0%	0.0%	66.7%	23.7%	N/A
	Resistant	97.0%	94.5%	82.4%	66.7%	0.0%	0.0%	33.3%	76.3%	N/A
SAM	Sensitive	0.0%	11.1%	N/A	100%	100%	0.0%	100%	22.4%	30.0%
	Resistant	100%	88.9%	N/A	0.0%	0.0%	0.0%	0.0%	77.6%	70.0%
GEM	Sensitive	29.2%	17.4%	45.5%	66.7%	100%	68.4%	100%	61.4%	N/A
	Resistant	70.8%	82.6%	54.5%	33.3%	0.0%	31.6%	0.0%	38.6%	N/A
AMC	Sensitive	4.3%	25.0%	N/A	50.0%	100%	0.0%	100%	22.4%	30.0%
	Resistant	95.7%	75.0%	N/A	50.0%	0.0%	0.0%	0.0%	77.6%	70.0%
CTX	Sensitive	7.6%	3.2%	17.6%	100%	100%	0.0%	100%	22.0%	N/A
	Resistant	92.4%	96.8%	82.4%	0.0%	0.0%	0.0%	0.0%	78.0%	N/A
SXT	Sensitive	12.2%	27.5%	33.3%	50.0%	0.0%	0.0%	100%	74.1%	0%
	Resistant	87.8%	72.5%	66.7%	50.0%	100%	100%	0.0%	25.9%	100%
P	Sensitive	N/A	N/A	N/A	N/A	N/A	N/A	28.6%	7.9%	30.0%
	Resistant	N/A	N/A	N/A	N/A	N/A	N/A	71.4%	92.1%	70.0%
AMP	Sensitive	N/A	N/A	N/A	N/A	N/A	N/A	25.0%	11.3%	20.0%
	Resistant	N/A	N/A	N/A	N/A	N/A	N/A	75.0%	88.7%	80.0%
CXM	Sensitive	N/A	N/A	N/A	N/A	N/A	N/A	0.0%	21.4%	0.0%
	Resistant	N/A	N/A	N/A	N/A	N/A	N/A	0.0%	78.6%	100%
LZD	Sensitive	N/A	N/A	N/A	N/A	N/A	N/A	100%	98.5%	100%
	Resistant	N/A	N/A	N/A	N/A	N/A	N/A	0.0%	1.5%	0.0%
VAN	Sensitive	N/A	N/A	N/A	N/A	N/A	N/A	90.9%	98.6%	100%
	Resistant	N/A	N/A	N/A	N/A	N/A	N/A	9.1%	1.4%	0.0%

Table 4. Relation between frequency of MDR and MRSA isolates in each department.

		MDR		MRSA	
		N	%	N	%
Department	**Adult ICU**	63	48.4%	2	1.54%
	Neurosurgery	66	37.9%	3	1.72%
	NICU	6	37.5%	4	25%
	Outpatient	23	29.4%	0	0.0%
	Emergency department	14	43.7%	0	0.0%
X^{2*}		8.07		8.24 FE	
P value		0.09		0.05	

*Chi square test (FE: Fisher Exact)

Table 5. Relation between various departments and isolated bacterial pathogens.

	Department										X*	P value
	ICU		Neurosurgery		NICU		Outpatient		Other			
	N	%	N	%	N	%	N	%	N	%		
E coli	7	5.4%	11	6.3%	1	6.3%	3	3.8%	1	3.1%	62.34 FE	0.05
Klebsiella pneumonia	36	27.7%	51	29.3%	3	18.8%	27	34.6%	16	50.0%		
Acinetobacter	31	23.8%	31	17.8%	6	37.5%	16	20.5%	5	15.6%		
Streptococci	4	3.1%	4	2.3%	2	12.5%	1	1.3%	1	3.1%		
Staphylococci	24	18.5%	42	24.1%	2	12.5%	11	14.1%	2	6.3%		
Pseudomonas	21	16.2%	22	12.6%	2	12.5%	17	21.8%	2	6.3%		
Enterococci	3	2.3%	8	4.6%	0	0.0%	0	0.0%	1	3.1%		
Enterobacter	3	2.3%	3	1.7%	0	0.0%	0	0.0%	1	3.1%		
Proteus	0	0.0%	1	0.6%	0	0.0%	2	2.6%	2	6.3%		
Cryptococcus neoformans	0	0.0%	1	0.6%	0	0.0%	0	0.0%	0	0.0%		

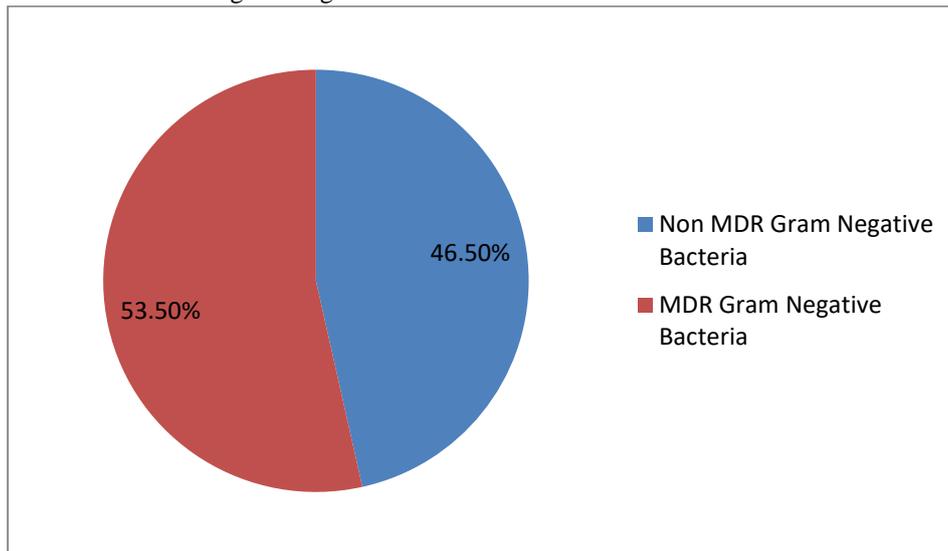**Figure 1A.** Prevalence of MDR gram-negative bacteria isolated from CSF.

Figure 1 B. Percentage of MDR among different Gram-negative bacteria.
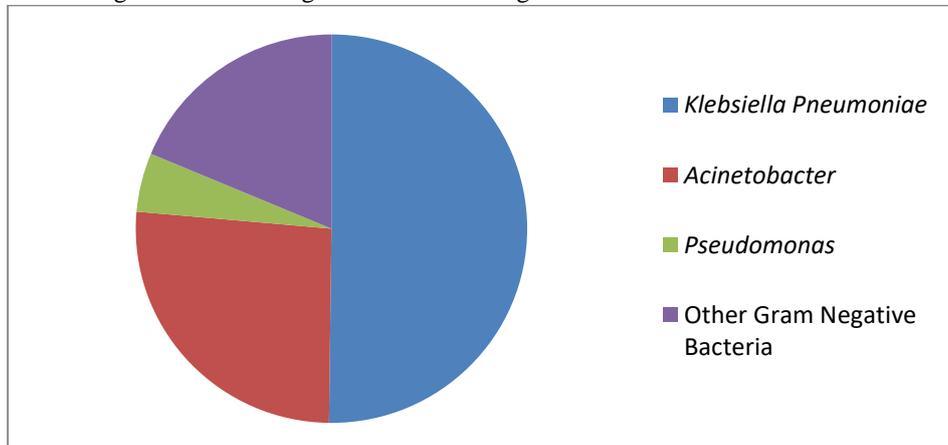
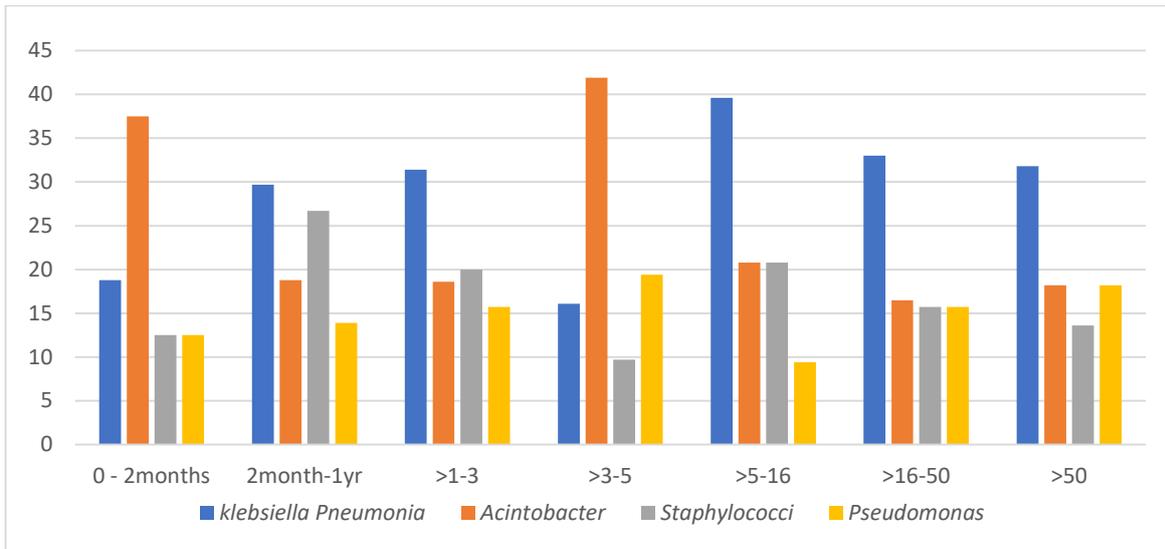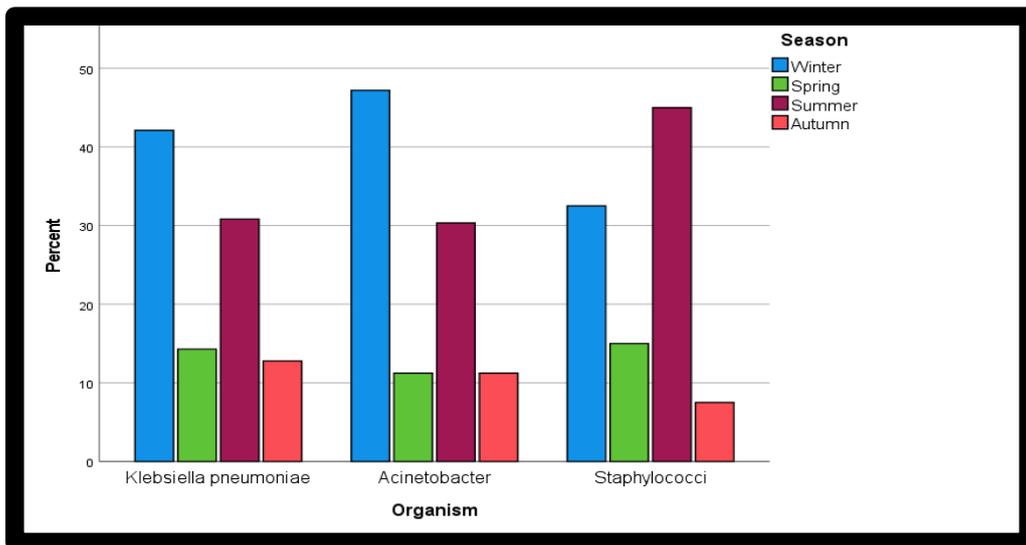**Figure 2.** Distribution of commonest isolated pathogens in different age groups.

Figure 3. Seasonal variations of the two most common isolated. Gram-negative bacteria and the most prevalent Gram-positive bacteria.

Discussion

      Meningitis infections are prevalent in Egypt, leading to elevated complication and fatality rates, thereby posing a significant medical emergency. According to the World Health Organization (WHO), approximately 1 million cases occur globally each year, resulting in 135–200,000 fatalities [12]. Despite strides in diagnosing and treating infectious diseases, meningitis persists as a significant contributor to mortality and morbidity. Critical factors in mitigating the impact include early diagnosis and prompt empirical therapy. Given the gravity of these conditions, continuous assessment of potential predictors of adverse outcomes is imperative. This study was

undertaken to discern the bacterial profile, AMR patterns and seasonal dynamics of bacterial meningitis across diverse age cohorts. Results revealed a statistically significant disparity in the prevalence of isolated bacteria concerning gender, while no statistically significant association was observed in various age groups. Noteworthy, > 50% of the samples exhibited positive BM samples, among children <5 years old. This aligns with a similar study done in Egypt who identified children as the most susceptible demographic group [12]. Furthermore, this research detected BM in (26.6%) of patients aged >16-50 years old. Similarly, in a prior Egyptian research study, 18.6% were found in the 25-40 age range, and 28.6% were observed in

those surpassing 40 years. It is noteworthy to emphasize that both findings closely align within the specified age group [13].

The goals of the present study involved identifying predominant bacteria within various age-groups to enhance the understanding of the evolving microbial landscape during different developmental stages; age group 0-2 months, most common causative organism was *Acinetobacter* (37.5%), followed by *Klebsiella Pneumonia* (18.8%) whereas *Streptococci, Staphylococci* and *Pseudomonas* incidence were all the same at (12.5%). *Klebsiella pneumonia* took precedence in age group >2 month - 1 year showing (29.7%) and (31.4%) in >1-3 years of age, followed *by Staphylococcus* spp representing (26.7%) and (20%) in age groups >2 month – 1 year and >3-5 years respectively, while *Acinetobacter* accounted for (18.8%) and (18.6%) in same age groups. Within the >3-5 age group, *Actinobacteria* dominated with an incidence of (41.9%), followed by *Staphylococcus* spp at (19.4%). *Klebsiella pneumonia* declined to (16.1%) in this age. Regarding the age group >5-50 years *Klebsiella* meningitis was the predominant pathogen. Previous study done in 2021 revealed that among patients diagnosed with BM, 52% were < 1 year. The primary causative agent was *S. pneumoniae* 36.5%, followed by *Neisseria meningitidis* 28.8% and *Streptococcus agalactiae* 15.4%. The incidence rates for *H. influenzae, Listeria monocytogenes,* and *E. coli* were 7.7%, 1.9%, and 9.6%, respectively. *Escherichia coli* emerged as the primary pathogen in 1- 10 years patients as well as above 30 years old [14]. A prospective Asian study of 8 NICU units*,* brought attention the variability in bacterial etiology in developing countries, emphasizing that gram-negative bacilli including *Klebsiella, and E. coli* may be more prevalent than *GBS*, particularly in late-onset meningitis [15]. Differences could be attributed to enhanced antenatal GBS screening, licensed conjugate pneumococcal vaccines, geographical shifts, and potential misuse of antimicrobials. These factors ensure the importance of continuous surveillance and adapting clinical approaches based on contextual factors and regional variations.

Our investigation revealed a significant correlation between isolated BM and different department. Neurosurgery emerged as the predominant department, accounting for 40.2% of cases, followed by ICU (30%), and outpatient clinics (18.5%). This aligns with a narrative review emphasizing the prevalence of post-neurosurgical bacterial meningitis (PNBM) as a common complication in patients undergoing neurosurgical procedures [16]. Moreover, a Chinese retrospective study on PNBM highlighted its inevitability despite global adherence to aseptic practices in neurosurgical settings, reporting an incidence rate ranging from 0.3% to 10% across various neurosurgical diseases [17]. Discrepancies in percentages underscore the importance of patient numbers and aseptic techniques employed in neurosurgical operations.

The notable incidence of BM in the ICU at 30% aligned with a prospective cohort study in Netherland*,* who reported a similar trend with 51% of patients with community-acquired BM being admitted to ICU [18]. Variance in percentages might be related to COVID-19 pandemic. During the pandemic, the demands on ICU capacity have influenced the proportion of ICU admissions for BM.

The 18.5% prevalence of BM diagnosed in outpatient clinics may reflect the potential proportion of community-associated BM. This observation coincided with a seminar*,* who emphasised the persistent burden of community-acquired BM despite advances in prevention and treatment. Despite the global decline in disease incidence due to conjugate vaccines targeting pathogens like *S. pneumoniae, N. meningitidis,* and *H. influenzae*, challenges endure [19].

A predominance of Gram-negative bacteria (79.1%) of the isolated spp, whereas Gram-positive bacteria accounted for (19.6%) in this study. *Klebsiella* was the most isolated spp with prevalence rate (34%), followed by *Acinetobacter* (19.6%) and *Pseudomonas* (16.2%). Among Gram-positive bacteria, *S. pneumoniae* was surprisingly observed at (1.8%), with Coagulase-negative *Staphylococci (CoNS)* (10.6%), *S. aureus* (3.2%), and *Enterococcus* (3.7%). In contrast*,* **Robinson and Bausl** identified *S. epidermidis* and *S. aureus* as the primary Gram-positive cocci causing nosocomial meningitis. This can be attributed to the fact that our study was not confined to nosocomial meningitis [20].

A retrospective study in Portugal reported an increased proportion of Gram-negative bacteria, such as *Acinetobacter baumannii, K. pneumoniae, and E. coli* coinciding with current study [21]. On

the other hand, a cross sectional study identified *N. meningitidi*s as the primary cause of meningitis [13]. This variance concerning *N. meningitidi*s could be attributed to a more robust vaccination preventing its isolation in our study. In a study conducted in Egypt, the predominant Gram-positive BM was *Streptococcus pneumoniae*, contributing significantly to the overall cases [22]. Current study verifies these trends, revealing *CoNS* at 10.6%, *Staphylococcus* at 3.4%, and *S. pneumoniae* at 1.8% among the identified Gram-positive organisms. This decline *S. pneumoniae* incidence may be attributed to the high vaccination coverage against this pathogen.

In this study, *Klebsiella* spp showed the highest sensitivity to gentamicin, amikacin, and tobramycin with percentages 29.2%, 26.6 and 13.0% to. *Acinetobacter* showed sensitivity to tobramycin, SXT, amikacin, cefepime, meropenem with percentages 45.8%, 27.5%, 25.6%, 15.8% and14.3% respectively. While *Pseudomonas* showed sensitivity to piperacillin/tazobactam, meropenem, gentamicin and amikacin 100%, 64.3%, 45.5% and 37.5% respectively. This aligns with a multicenter retrospective study conducted in China*,* where *K. pneumoniae and A. baumannii* isolates exhibited susceptibility rates greater than 50% to aminoglycosides with susceptibility rates of *P. aeruginosa* isolates to TZP, aminoglycosides, and carbapenems greater than 60.0% [23].

In this study gram-positive bacteria exhibited high resistance rates 88.2% and 86.5% to penicillin and ampicillin. however, they displayed notable sensitivity to linezolid (98.8%) and vancomycin (97.9%). *Streptococcus pneumoniae and Staphylococcus* spp showed 9.1% and 1.4% resistance to vancomycin. Overall, resistance across all pathogens was most pronounced for ceftriaxone (89%), ampicillin (87.9%), penicillin (87.5%), and cefotaxime (86.6%). In contrast, all pathogens exhibited higher sensitivity to tobramycin (46.2%), gentamicin (43.1%), and amikacin (41.6%). These findings partially align with the results of study conducted in Egypt from 3 different hospitals in a 2-year period who identified MDR Gram-positive isolates from bacterial meningitis. In both studies, there is a noteworthy resistance to penicillin and ampicillin among Gram-positive organisms. However, this study additionally highlights higher sensitivity to linezolid and vancomycin [24].

In this study, the assessment of *S. aureus* using cefoxitin discs revealed that 60% of the strains were identified as *MRSA*. Notably, a statistically significant difference was observed between MRSA and various hospital departments. Highest MRSA prevalence was identified in NICU, constituting 25% of total NICU cases. Additionally, 1.72% and 1.54% of MRSA cases were isolated from the Neurosurgery and ICU. On the other hand, no *MRSA* were detected in either outpatient or Emergency departments. Comparatively, a retrospective study done in Japan*.* reported that the incidence rate of BM caused by MRSA is lower than that caused by other Gram-positive bacteria [25]. Furthermore, A cohort study conducted in Spain found a 34% prevalence of MRSA meningitis, primarily associated with postoperative infections and nosocomial acquisition [26]. An Egyptian study revealed that within Gram-positive bacterial isolates, *S. aureus* and CONS were commonly detected, each comprising 6% of the isolates. Approximately half of these isolates were identified as MRSA strains. [24].

Within the cohort of Gram-negative bacteria, a substantial portion, accounting for 53.5%, exhibited MDR. Among them, *Klebsiella* spp constituted 50.2%, *Acinetobacter* spp were 26.2%, and *Pseudomonas* spp accounted for 4.9%. Focusing on *Klebsiella* spp, all isolates demonstrated complete resistance (100%) to ampicillin/sulbactam, ceftriaxone (97%) and ceftazidime (95%). *Acinetobacter* spp showed heightened resistance, particularly to cefotaxime (96.8%) and piperacillin/tazobactam (96%), along with notable resistance rates of (88.9%) and (85.7%) to ampicillin/sulbactam and meropenem. In *Pseudomonas* cases, resistance levels were equally pronounced for cefotaxime and ceftriaxone (82.4%) and cefepime (80%). This observed pattern aligned with a systematic review with > 50% of isolated Gram-negative bacteria displayed resistance to amoxicillin/clavulanate. *Pseudomonas aeruginosa, Klebsiella* spp*,* and *Citrobacte*r spp universally demonstrated complete resistance (100%) to cefepime. Furthermore, over 60% of isolated *K. peumoniae, P. aeruginosa,* other *Acinetobacter* spp*,* and *Citrobacter* spp exhibited resistance to ceftriaxone. *Klebsiella* spp also displayed notable resistance rates to ceftazidime (86.67%) and gentamicin (86.78%) [27]. This comparative analysis underscores the consistent emergence of resistance patterns among gram-negative bacteria in various studies. Emphasizing the urgent need for

effective antimicrobial stewardship programs and robust surveillance mechanisms to address the escalating challenge of MDR.

Finaly, a distinct Seasonal variation was detected in *K. pneumonia*, *Acinetobacter,* and *Staphylococcus* spp meningitis with most cases of *K. pneumonia* and *Acinetobacter* isolated in winter more than other seasons of the year showing (42 %) and (48%) respectively. On the other hand, *Staphylococcus spp* showed prevalence more in summer more than all other seasons. These observations emphasize the need for further investigations into the intricate relationship between seasonal patterns and the incidence of meningitis-causing pathogens. This seasonality is confirmed by a study conducted in India who reported maximum number of cases (534/950) was seen during September and December, where commonest organism was *Acinetobacter* (35%) followed by *S. aureus* (30%) [28]. According to a cross sectional study (42.9%) of meningitis cases were detected in February and the defending organism was *N. mennigitidis* [13]. In both studies, although the peak-time of meningitis, occurring in winter, aligned with this study, there were differences in the isolated organisms. Thus, highlights the variability of the causative agents with the region during the same season.

This study has limitations that need acknowledgment. Firstly, the research focused on confirmed BM cases, potentially missing culture-negative instances with different causative pathogens. Secondly, the study couldn't confirm the pathogenicity of potential contaminants in immunocompetent hosts. Lack of clinical data, including immune status and shunt presence, hindered confirming BM diagnoses, especially for CoNS. Finally, deficiency of clinical data also restricted analysis of risk factors, age groups, infection origins, and outcomes of BM.

Conclusion

This study provides a vital analysis of BM, revealing significant changes in the types of bacteria causing infections and their antimicrobial susceptibility, including the decline in *pneumococcal, Meningococcal* and *Haemophilus meningitis* due to implemented immunization programs. However, challenges persist with emerging gram-negative organisms like *Klebsiella pneumoniae, Acinetobacter,* and *Pseudomonas,* emphasizing the need for ongoing surveillance of bacterial profiles and AMR patterns with reinforced antimicrobial stewardship efforts to address evolving threats

This study provides a guide to clinicians at this hospital in adjusting the empirical antibiotics given to suspected BM patients according to the causative organisms in the previous 4-years thus decreasing rate of BM which is one of the main sub-goals of sustainable developmental goal

Recommendations

Strict following Infection control standard precautions with special emphasis on effective hand hygiene according to Center for Disease Control and prevention especially in high-risk units at health care settings: NICU, ICU, and neurosurgery departments, is highly recommended.

Multidrug resistant (MDR) meningitis treatment needs continuous hospital antimicrobial stewardship review at fixed intervals and updating them when necessary, according to bacterial culture results, to provide guided empirical antimicrobial therapy. Empirical antibiotics recommended according to this current study results are as follows; in pediatric patients age groups 0-2 months and >3-5 yrs *Acintobacter* was the predominant implicated organism and was sensitive to both tobramycin and pipercillin/tazobactam. However, as pipercillin/tazobactam is not approved for infants less than 2 month only tobramycin is recommended for this age group. As for age group >2m-1yr, >1-3yrs and >5-16yrs gentamicin and amikacin to be used in BM empirical treatment as *K. pneumoniae* was the predominant BM causing organism. In adults BM age groups *K. pneumoniae* was the predominant organism and use of gentamicin and amikacin as empirical treatment is recommended.

Declarations

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nashwa Naguib Omar, Lamia M. El Moussely. The first draft of the manuscript was written by Nahla Gamal eldin abdel hakim hanafy, Nashwa Naguib Omar, Lamia M. El Moussely and Manal M. Darwish. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

All data supporting the findings of this study are available within the paper; any additional data are available from the corresponding author upon reasonable request.

Conflict of interests

The authors declare that they have no competing interests.

References

1-Liu L, Oza S, Oza S, Hogan D, Chu Y, Perin J et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the sustainable development goals. The Lancet 2016; 388(10063):3027–35.

2-Roos KL. Acute bacterial meningitis. Semin Neurol 2000; 20(3):293-306.

3-Brouwer MC, van de Beek D. Epidemiology of community-acquired bacterial meningitis. Curr Opin Infect Dis 2018; 31(1):78–84.

4-Al Bekairy AM, Al Harbi S, Alkatheri AM, Al Dekhail S, Al Swaidan L, Khalidi N. Bacterial meningitis: an update review. Afri J Pharm Pharmacol 2014; 8(18), 469–478.

5-Brenda Kwambana-Adams. 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: 685–711 Crossref DOI link:

6-Valdoleiros SR, Torrão C, Freitas LS, Mano D, Gonçalves C, Teixeira C. Nosocomial meningitis in intensive care: a 10-year retrospective study and literature review. Acute Crit Care 2022; 37:61–70.

7-Akoachere JFTK, Yvonne S, Akum NH, Seraphine EN. Etiologic profile and antimicrobial susceptibility of community-acquired urinary tract infection in two Cameroonian towns. BMC Research Notes 2012; 7(5):219.

8-4th Global Conference of Women Deliver. WHO Regional Office for Europe; Copenhagen, Denmark (2016) Fight Antimicrobial Resistance: Protect Mothers and Newborns. Available online: http://who.int/drugresistance/activities/Women-Deliver-AMR-side-event-Handout-May2016.pdf?ua=1

9-M. Cheesbrough. Details of Part 1. In District Laboratory Practice in Tropical Countries. Cambrid Uni Press (CUP) 2006;3-380.

10-Bauer AW, Kirby WM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol 1966; 45(4):493-6.11.

11-Clinical Laboratory Standard Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 31st ed. CLSI Supplement M100. CLSI USA.

12-Hanaa S, Walid S, Rasha SH, Sahar AD. Pattern and Epidemiological Characters of Meningitis Infections, Cairo Egypt. 2016–2019, QJM: An Intern J Med 2023; 116(1) 069.693.

13-Dawod H, Naguib A, Amer S, Mohamed L. The Frequency of Meningitis Cases in Zagazig Fever Hospital: A Cross-sectional Study Afro-Egypt. J Infect Endem Dis 2019; 5(2):158-166.

14-Zeighami H, Roudashti S, Bahari S, Haghi F, Hesami N. Frequency of etiological agents of acute bacterial meningitis using culture and polymerase chain reaction assay. New Microbes New Infect. 2021 Aug 10; 43:100930.

15-Tiskumara R, Fakharee SH, Liu CQ, Nuntnarumit P, Lui KM, Hammoud M et

al. Neonatal infections in Asia. Arch Dis Child Fetal Neonatal Ed 2001; 94:144–8.

16- **Hussein K, Bitterman R, Shofty B, Paul M, Neuberger A.** Management of post-neurosurgical meningitis: narrative review. Clin Microbiol Infect 2017; 23:621–28.

17- **Zhang Y, Xiao X, Zhang J, Gao Z, Ji N, Zhang L.** Diagnostic accuracy of routine blood examinations and CSF lactate level for post-neurosurgical bacterial meningitis. Int J Infect Dis 2017; 59:50.

18- **Chekrouni N, Kroon MHGM, Drost E, van Soest TMW, Bijlsma MC.** Brouwer M. Characteristics, and prognostic factors of bacterial meningitis in the intensive care unit: a prospective nationwide cohort study. Ann. Intensive Care 2023; 13, 124.

19- **Van de Beek D, Brouwer MC, Koedel U, Wall EC.** Community-acquired bacterial meningitis. Lancet 2021; 398(10306):1171-1183.

20- **Robinson CP, Busl KM.** Meningitis, and encephalitis management in the ICU. Curr Opin Crit Care. 2019; 25:423–9.

21- **Valdoleiros SR, Torrão C, Freitas LS, Mano D, Gonçalves C, Teixeira C.** Nosocomial meningitis in intensive care: a 10-year retrospective study and literature review. Acute Crit Care 2022; 37:61–70.

22- **Abdelkader MM, Aboshanab KM, El-Ashry MA, Aboulwafa MM.** Prevalence of MDR pathogens of bacterial meningitis in Egypt and new synergistic antibiotic combinations. PLOS ONE 2017; 12(2):e0171349.

23- **Peng X, Zhu Q, Liu J , Zeng M, Qiu Y, Zhu C et al.** Prevalence and antimicrobial resistance patterns of bacteria isolated from cerebrospinal fluid among children with bacterial meningitis in China from 2016 to 2018: a multicenter retrospective study. Antimicrob Resist Inf Cont 2021; 30;10(1):24.

24- **Helmy AK, Sidkey NM, El-Badawy RE, Hegazi AG.** Emergence of microbial infections in some hospitals of Cairo, Egypt: studying their corresponding antimicrobial resistance profiles. BMC Infect Dis. 2023 Jun 22; 23(1):424.

25- **Takafumi N, Yasuko M, Tomomi K, Yutaka U, Tadahiro I, Susumu K, Kentaro O et al.** Influence of Empirical Therapy Utilizing Vancomycin in Patients with Suspected Bacterial Meningitis: A Single-Center Retrospective Study. BPB report 2020; 3 (5): 150-156.

26- **Pintado V, Pazos R, Jiménez-Mejías ME, Rodríguez-Guardado A, Díaz-Pollán B, Cabellos C et al.** Staphylococcus aureus meningitis in adults: A comparative cohort study of infections caused by meticillin-resistant and meticillin-susceptible strains. J Hosp Infect. 2019; 102(1):108-115.

27- **Kebede B, Yihunie W, Abebe D, Addis Tegegne B, Belayneh A.** Gram-negative bacteria isolates and their antibiotic-resistance patterns among pediatrics patients in Ethiopia: A systematic review. SAGE Open Med 2022; 10:20503121221094191.

28- **Kasana D.** Changing pattern of pathogens and their antibiogram in pyogenic meningitis - a two years study from India. J Bacteriol Mycol Open Access. 2020; 8(3):69-70.