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ORIGINAL ARTICLE

Neurological and Bacteriological assessment of suspected meningitis cases at Suez Canal University Hospital

[1]Mohamed Elsamahy, [2]Asmaa Hashem*, [3]Amani El-Kelany, [4]Wafaa H. Omar, [5]Mona Salama, [5]Rasha Emad

[1] Department of Neurology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
[2]Department of Medical Microbiology and Immunology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
[3]Department of Pediatrics, Faculty of Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
[4]Department of Infectous and Endemic Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
[5]Department of Clinical Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

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Corresponding Author:
Asmaa abd elkreem hashem
Department of Medical Microbiology and Immunology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
Tel.: 01064027524
asmamicro82@gmail.com

ABSTRACT

Introduction: *Acute Bacterial Meningitis (ABM) are a potent cause of morbidity and mortality in all age groups, with long-term neurological disability.* ***Objective:*** *to determine the neurological events and bacterial pathogens, isolated from cerebrospinal fluids of suspected bacterial meningitis cases.* ***Methods****: Descriptive study included 181 cerebrospinal fluid from suspected ABM cases, aged from 13 to 26 years old, Biochemical, hematological tests, and bacteriological culture were done.* ***Results****: The most cerebrovascular symptoms were ventriculoperitoneal (VP) shunt (13.3%), convulsions (10.5%) then brain edema (8.3%), commonest CSF bacterial pathogens were Streptococcus species, E.coli and N. Meningitidis. The susceptibility pattern for isolated bacteria to Meropenam, Levofloxacin, Ciprofloxacin, Rifampicin and Ampicillin were 95%, 85%, 82.5%, 75% and 70%, respectively.****Conclusion****:* Gram negative bacteria show highest susceptibility to Aztroenam and highest susceptibility to Erythromycin for Streptococcus spp. *Ampicillins and cephalosporins are still active in the treatment of ABM.*

INTRODUCTION

Meningitis is an inflammatory process of the leptomeninges and the spinal cord **1**. Viral, bacterial or fungal pathogens may cause the infection to the meninges. The most serious occurring in infants and older children is bacterial meningitis with complications and a high risk of long-term morbidity[2].

The Most common complications of bacterial meningitis are Ischemic and hemorrhagic strokes reported in 14-37% of patients with neurological deficits and increased mortality. Predictors of infarction or cerebral narrowing in adults are reduced level of consciousness, seizures, low CSF white cell counts, and high ESR [3].

Studies demonstrated Haemophilus influenzae, Neisseria meningitidis and Streptococcus pneumoniae were the most common contributing organisms of bacterial meningitis in childhood [4]. Information obtained from laboratory based surveillance is important in determining the most common etiology of meningitis pathogens. Penicillin/ampicillin and chloramphenicol combination was the first choice antibiotic in Africa, However, due to bacterial resistance this combination of drugs became not appropriate to use [5].

Doctors often prescribe antibiotics before getting the results of CSF culture and sensitivity. Knowledge of organisms causing meningitis and their antibiotic susceptibility is of utmost importance to provide appropriate therapy [4].

Our aim of work is to determine the neurological manifestation and bacterial pathogens isolated from CSF of suspected meningitis cases.

SUBJECT AND METHODS

Study population:

Descriptive study included 181 cerebrospinal fluid from suspected bacterial meningitis cases, aged from 13 to 26 years old, admitted to Suez Canal University Hospital-Ismailia, from January 2017 to January 2019. The diagnostic laboratory criteria for bacterial meningitis included: glucose concentration below 40mg/ L, protein concentration above 50mg / dL, white cell count above 100 cells per mm3, and neutrophil concentration above 50 percent [6].

Collection of CSF:

Cerebrospinal fluid (CSF) sample were obtained aseptically from the arachnoid space via Lumbar puncture (LP), a sterile wide-borne needle was inserted between the fourth and fifth lumbar vertebrae and the CSF was allowed to drip into a dry sterile container.

***Processing of CSF sample*:**

When the volume of CSF sample was < 1 ml of CSF (we didn't centrifuged) and the CSF was plated directly onto primary culture media and also used for the Gram stain, While when volume was > 1 ml of CSF it was centrifuged at 10.000 RPM for 10-15 minutes to sediment the bacteria, The sediment mixed (e.g., in a closed tube using a vortex machine), one or two drops of sediment were used to prepare the Gram stain and one drop should be used to streak the primary culture media [7].

***Biochemical assessment of CSF*:**

The supernatant was drawn off with a Pasteur pipette and reserved for antigen detection by latex agglutination and was examined for chemical fluid analysis (LDH, glucose, protein) using a colorimetric assay kits[7], and for hematology (differential cell count) DIAGON@Ltd D-Cell 60.

Bacteriological assessment of CSF:

Centrifuged CSF sediment was cultured within 1 hour of specimen collection on blood agar plate (BAP) incubated aerobically and on chocolate agar plate incubated in (5% CO2) candle jar at 37℃ for 24-48 hours[8]. The isolated colonies from bacterial culture were identified by colony morphology, Gram staining and biochemical tests[9].

Antibiotic Susceptibility testing:

Zone diameters interpretation was done according to Clinical and Laboratory Standard Institute (CLSI)[10]. Amikacin, Ampicillin, Aztronam, Chloramphenicole, Cefetriaxone, Ciprofloxacin, Erythromyycin, Levofloxacin, Merponem, Peniciilin, Rifampicin, Trimethoprim/Sulphamethoxazole and Tetracycline were chosen to cover CSF causative pathogens.The antimicrobial discs and powder were purchased from (Oxoid, Basingstoke, UK).

Compliance with Ethical Standards:

All procedures performed in the current study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. The authors declare no conflict of interest.The ethical committee has approved the manuscript on January 2018.

Data analysis:

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 16 (SPSS Inc., Chicago, IL, USA). Descriptive statistics including, frequency, mean and standard deviation (SD) were done. Analytical statistics included Chi-square to detect significant differences between two groups of qualitative variables, and Student's t-test was used to indicate the presence of any significant difference between two groups of quantitative variables. Spearman correlation analysis was used to show strength and direction of the association between quantitative and qualitative variables. P-value, was considered a significant difference if $p < 0.05$.

RESULTS

In this study, the mean age of the studied population was 13.3±16 years old. The most CNS disorders were ventriculoperitoneal (VP) shunt (13.3%), convulsions (10.5%) then brain edema (8.3%). Half of the studied population had a Glasgow coma score between 8 to 15.

The CSF analysis showed that the mean Total leuckocytic count (TLC) was 68.1±27.8 cells, the mean level of glucose was 41.4±16.9 mg/dl, the LDH was 57.2±14.4and protein levels were 76.3±37.7g/L. In blood, there was leucocytosis as the white blood cell was 11210±4555.7cells.

Table1: Demographic, clinical and laboratory data of the studied population.

Number =181		
Age (mean±SD) (year)	13.3±16	
Cerebrovascular events	NO	%
- Brain edema	15	(8.3%)
- Neck rigidity	8	(4.4%)
- Papilledema	15	(8.3%)
- Convulsions	19	(10.5%)
- Vomiting	12	(6.6%)
- Hemiplegia	10	(5.5%)
- VP shunt	24	(13.3%)
- **Others Glasgow Coma Score**	78	(43.1%)
- 15	45	
- <15 to 7	89	(24.9%)
- <8	47	(49.2%)
CSF Analysis		(26%)
- TLC /cell	68.1±27.8	
- Glucose mg/dl	41.4±16.9	
- LDH u/L	57.2±14.4	
- Protein mg/dl	76.3±37.7	
In blood		
- TLC /cell	11210±4555.7	
- Neutrophils /cell	7313.8±2439	
- Lymphocytes /cell	5178.4±1753.7	

The relationship between the bacterial growth, the clinical and laboratory data of the studied population, showed VP shunt and hemiplegia were the most CNS disorders associated with bacterial growth with a statistically significant difference.

In CFS analysis, an elevation of TLC, LDH and protein, although a decrease in glucose levels were observed in patients with bacterial growth compared with patients with no bacterial growth with statistically significant difference. In blood there was no significant difference in TLC between both groups. Table (2)

Table 2: Relationship of bacterial growth with clinical and laboratory data

CNS disorders	Growth (n=40) NO	%	No growth (n=141) NO	%	p- value
- **Brain odema**	2	(5%)	13	(9.2%)	0.393
- **Neck rigidity**	1	(2.5%)	7	(4.9%)	0.503
- **Papilodema**	2	(5%)	13	(9.2%)	0.393
- **Convulsion**	3	(7.5%)	16	(11.3%)	0.483
- **Vomiting**	2	(5%)	10	(7.1%)	0.639
- **Hemiplegia**	9	(22.5%)	1	(0.7%)	<0.001*
- **VP shunt**	13	(32.5%)	11	(7.1%)	<0.001*
-					
Others	8	(20%)	70	(49.5%)	<0.001*
Glasgow coma score					
- **15**	13	(32.5%)	32	(22.7%)	0.057
- **<15 to 7**	13	(32.5%)	76	(53.9%)	
- **<8**	14	(35%)	33	(23.4%)	
Outcome					0.213
- **Recovery**	37	(92.5%)	129	(91.5%)	
- **Severe disability**	3	(7.5%)	5	(3.5%)	
- **Mortality**	0		7	(4.5%)	
-					
CSF Analysis					
- TLC /cell	117.5±24.5		10.8±5.5		<0.001
- Glucose mg/dl	16.0±7.9		53.36±8.7		0.001
- LDH u/L	82.1±38.6		27.5±16		<0.001
- Protein mg/dl	103.2±63.1		39.8±19.5		<0.001
In blood					
- TLC /cell	12900±4041		300±2927		0.230
- Neutrophils /cell	8257.5±2542.3		6356.7±2625.1		0.074
- Lymphocytes /cel	5092.5±1921.4		5202.8±1709.7		0.726

The microbiological culture of CSF samples showed that *Streptococcus* species were the commonest isolated organism (45%) (*S. pneumoniae* was (37.5%), *group B streptococcus* was 7.5%), then *E.coli* (20%) and *N. Meningitidis* (17.5%) Table (3).

Table 3: microbiological profile of CSF culture of the studied population (n=40)

Microorganism	Number	Percent
Streptococcus pneumoniae	15	37.5%
E.coli	8	20%
Neisseria Meningitidis	7	17.5%
H.Influenzae	4	10%
Group B strep	3	7.5%
Pseudomonas	3	7.5%
Total	40	100%

The susceptibility pattern for isolated bacteria to Meropenam, Levofloxacin, Ciprofloxacin, Rifampicin and Ampicillin were 95%, 85%, 82.5%, 75% and 70%, respectively. Table (4)

The antibiotic sensitivity of *S.pneumonie* for each of Meropenam and Rifampin were (100%), to Fluroquinolone (Ciprofloxacine, Levofloxacine) was 86.6%, for each of B. lactam antibiotics (ampicillin, ceftriaxone) and Tetracycline susceptibility were 73.3%, while to Erythromycin was 66.6%; with statistical significance to Rifampin and Erythromycin.

The most effective antibiotic against *N.meningititis* were Meropenam, Rifampine, Ciprofloxacine, Levofloxacine, their sensitivity rate were 100% , then Rifampcin 85.7% and Amikacin 71.4% respectively.

E.coli was highly sensitive to Azetroenam (100%), for each of Meropenam, Ampicilin,Trimethoprime-sulfamethoxazole (87.5%), also for Ciprofloxacine, Levofloxacine and Chloramphenicole (75%).

Isolated Gram negative bacteria; *E.coli* ,*H.influenza*, and *Pseudomonas* were highly sensitive to Aztroenam; also 13 out of 18 (72.2%) isolated *Streptococcus* spp. were susceptible to Erythromycin with a statistically significance difference (Table 4 and 5).

Table 4: Antimicrobial sensitivity pattern of isolated organisms

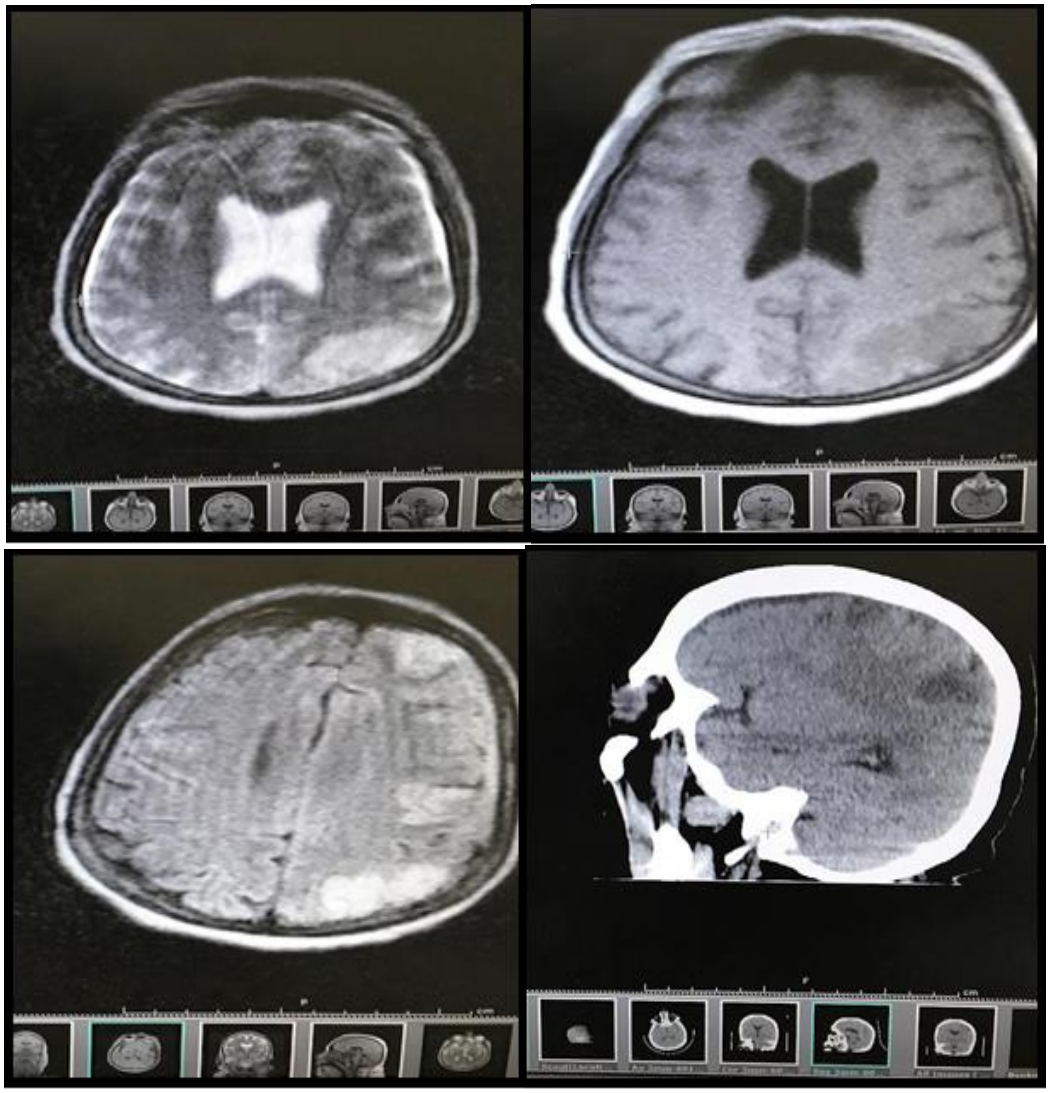
Antibiotics	Sensitive		Resistant	
	Frequancy	%	Frequancy	%
Amikacin	33	82.5%	7	17.5%
Ampicillin	29	72.5%	11	27.5%
Aztorenam (Gram negative only)	19	86%	3	14%
Chloramphenicol	26	65%	14	35%
Ciprofloxacin	33	82.5%	7	17.5%
Cefetriaxone	28	70%	12	30%
Erythromycin (Gram positive only)	14	78%	4	22%
Levofloxacin	34	85%	6	15%
Meronam	38	95%	2	5%
Penicillin	21	52.5%	19	47.5%
Rifampcin	32	80%	8	20%
Trimethoprime-Sulphamethoxazole	22	55%	18	45%
Tetracyclin	26	65%	14	35%

Table 5: Antibiotic sensitivity patterns of isolated micro-organisms

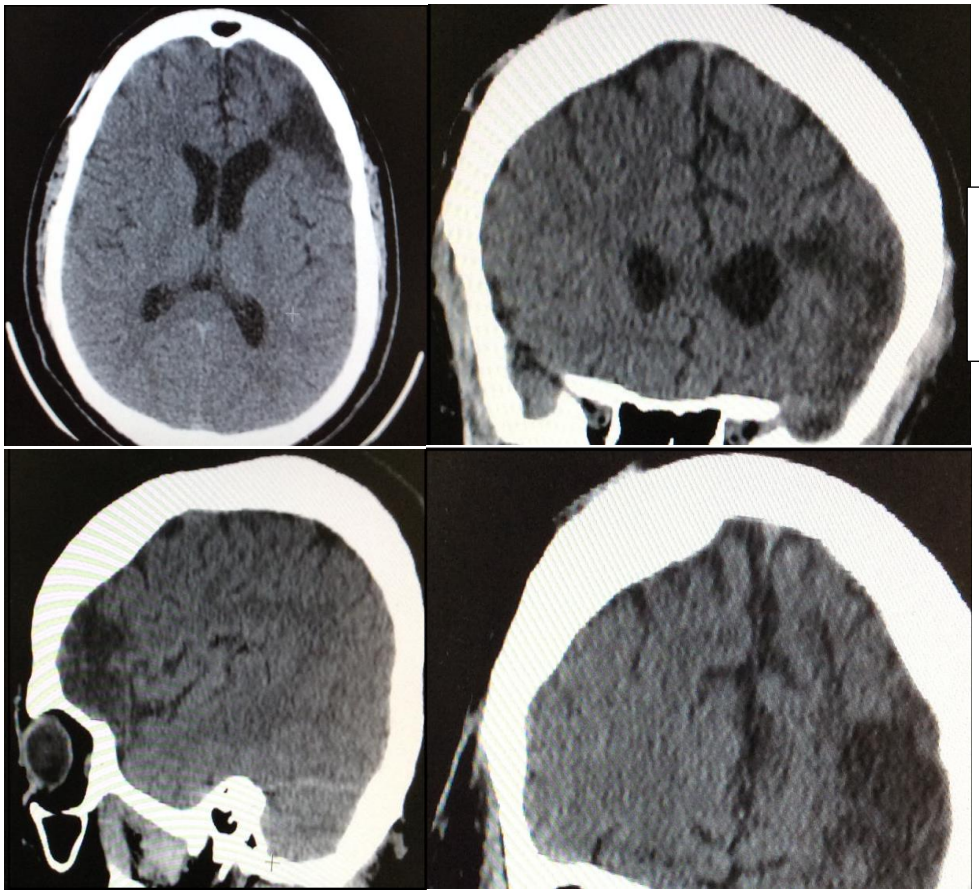
	S.Pneumonie	E.coli	Nisseria	Hemophylus	Group - B Strep.	Pseudomonas	P -value
Amikacin	93%	62.5%	71%	100%	100%	67%	0.304
Ampicillin	73%	87.5%	43%	50%	100%	100%	0.295
Aztroenam	--	87.5%	86%	75%	--	100%	0.001*
Chloramphenico	66%	75%	57%	50%	67%	67%	0.945
Ciprofloxacin	87%	75%	100%	75%	100%	23%	0.177
Cefetriaxone	73%	50%	57%	75%	100%	100%	0.573
Erythromycin	67%	--	--	25%	100%	--	0.001*
Levofloxacin	87%	75%	100%	100%	100%	23%	0.097
Meronam	100%	87.5%	100%	100%	100%	67%	0.087
Penicillin	33%	62.5%	57%	75%	23%	100%	0.364
Rifampcin	100%	62.5%	86%	75%	67%	23%	0.090
TMP –	47%	87.5%	28.5%	50%	67%	67%	0.181
Tetracyclin	73%	62.5%	57%	50%	67%	67%	0.937

TMP - Trimethoprim- Sulphamethoxazole

Case 1: 26 years old female patient presented with fever, disturbed level of consciousness and convulsions, she has signs of meningeal irritation, as neck stiffness, +ve Brudzinki sign and +ve kernig sign. The patient isolated in ICU, empirical antibiotics (ampicillin, cefrtriaxon and vancomycin) given. LP done which showed CSF turbid and pressurized. Chemistry showed high protein, low glucose, cytology showed neutrophils.



Case 2: 23 years old male presented to ER due to sudden loss of consciousness with generalized tonic clonic convulsions. The temp. 39, BP 130/80 HR 90/min. He has neck stiffness and +ve Brudzinski sign. History of head trauma 3 years ago with residual SDH, frontal contusion, fissure fracture of the skull. Empirical antibiotics were given, CSF was turbid, chemistry showed high protein and low glucose.



The condition improved, he became fully conscious, good concentration and no fever, but still has CSF rhinorrhea.

DISCUSSION

Bacterial meningitis often present with cerebrovascular complications at the beginning of infection, during hospitalization, or even appears several weeks after effective treatment .These complications happen in 14-37% of patients and are related to increased mortality [9] . In our study, 8.3% of patients were presented with brain edema. There are three phases of meningitis-induced cerebral angiopathy. Vasospasm is generated as a first step by the nearby purulent material in the subarachnoid space and Virchow Robin spaces. Myonecrosis of the vessel wall then follows ending in vasodilatation. Finally, edema of the subendothelium and proliferation of smooth muscleoccur cause vascular stenosis [11].

The pathogenesis of increased intracranial pressure in bacterial meningitis is initiated by the rise of intracerebral fluid volume, resulting in cerebral edema. The cytotoxins produced by bacteria and neutrophils, edema caused by increased blood-brain barrier permeability and poor CSF reabsorption due to arachnoiditis all contribute to vasogenic edema [12].

In the current study Glasgow coma scale of patients was 49% of score between (15 and 7) while patients less than 8 were 26%. *Streptococcus pneumoniae* meningitis leads to a high mortality and morbidity rate in spite of optimal intensive care management. This results from severe ischemia and inflammation leading to thrombosis of microvessels[13].

The etiology of central nervous system infections differs according to places and with different age groups[14]. Studies have shown that bacterial meningitis is responsible for about 30%– 40% of central nervous system infections. The remaining 60-70% are due to other etiologies such as viral meningitis, Cryptococcal meningitis, brain abscess, tuberculosis meningitis, tuberculoma and others [12-15].

This current study showed that the most common pathogen causing meningitis isolated from CSF samples

were *Streptococcus* species (45%) especially *S.pneumoniae* (37.5%); followed by *E.coli* (20%), *N.meningitidis* (17.5%) and *H.influenzae* (10%). This agree with Assegid Mengistu and his colleagues 16 who reported that the most common pathogens causing meningitis that were isolated from the CSF samples were *Streptococcus* species , also Scarborough and colleagues[17] found that 58% (272/465 bacterial meningitis cases) were caused by *S.pneumococci* .

Van de Beek et al.[18] found that *S. pneumoniae* and *N. meningitidis*, causing 75 to 90% of community-acquired bacterial meningitis in adults [18], A study that was conducted in Egypt reported that *S. pneumoniae* is the leading cause of bacterial meningitis, this might reflect a change in disease epidemiology since *N. meningitides* was considered previously as the main causal pathogen of bacterial meningitis [19]. The Introduction of conjugate vaccines against the three most common causes bacterial pathogens modifies bacterial meningitis epidemiology [20], the increased use of polysaccharide meningococcal vaccines decreased the incidence of meningococcal meningitis in Egypt[19].

Our results were closer to previous studies, which identified *E. coli* (28.5%) as most prevalent pathogen causing bacterial neonatal meningitis [21]**.** In contrary to our results; Yang and colleagues 22 found that *E.coli* cause only 5% of adult bacterial meningitis. Also Fahmi Yousef and colleagues[23] reported four cases of nosocomial *E. coli* meningitis, in patients with accidental and neurosurgical trauma.

In a study conducted by Jiang et al [24] isolate *E. coli* (28.5%), *S.pneumoniae* (17.8%), *S.epidermidis* (10.0%), *H. influenzae type b* (9.5%), and *group B streptococcus* (7.2%) were most prevalent CSF pathogens in children diagnosed as bacterial meningitis.

Bieden bach et al [25] declared that Aztreonam, a β-lactam antibiotic, has a clinical potency against aerobic Gram-negative bacteria, with good penetration to CSF .

In our study ,the highest susceptibility pattern for isolated bacteria were found to Meropenam, Levofloxacin, Ciprofloxacin, Rifampicin and Ampicillin respectively, Allan and colleagues studied the effect of two carbapenem agents among bacterial meningitis patients, Imipenem has a potential for seizure activity, while a broad range of in vitro activity and less seizure activity for meropenem than imipenem [26], Breilh and colleagues [27] suggested that Carbapenems exhibit broad spectrum activity against gram-negative bacteria. Good activity was also observed for most *Streptococcus spp*, including penicillin-resistant strains.

Kaplan [28] reported that Rifampin is an excellent agent for meningitis treatment that has a good CSF penetration and in vitro activity against many meningeal pathogens.Cédric Bretonnière and colleagues [29] treated acute community-acquired meningitis in the ICU with a third-generation cephalosporin and vancomycin. At the same time, other antibiotics, such as fosfomycin and rifampin, could be considered good candidates for the treatment of meningeal infections. Nau et al 30 in their experimental study suggested that rifampin reduces the inflammatory response caused by β-lactam–induced bacterial lysis.

The fluoroquinolones (especially Ciprofloxacin) have been used successfully in meningitis cases due to gram-negative organisms, specifically to multidrug-resistant gram-negative bacilli [31].

Kameshwar Prasadand colleagues[32] compared the third generation cephalosporins and conventional antibiotics (benzylpenicillin, or ampicillin, with or without chloramphenicol), they found no statistically significant difference in the combined endpoint of death or deafness .

CONCLUSIONS

Bacterial meningitis causes high death rates in adults and children. The nervous system structures are affected, such as cerebral and spinal vessels, cranial nerves, ventricles, brain parenchyma, spinal nerve roots, spinal cord, hypothalamus, and the pituitary. In our study *the highest susceptibility was detected with statistical significance to both Aztroenam used for Gram negative bacteria E.coli, H.influenzae and Pseudomonas and Erythromycin (72.2%) for Streptococcus spp.* the highest susceptibility pattern for isolated bacteria were found to Meropenam, Levofloxacin, Ciprofloxacin, Rifampicin and Ampicillin respectively. We recommend Ampicillins to be used to Third generation drugs if not available as an alternative empiric treatment, bearing in mind the resistance pattern and availability while treating community acquired acute bacterial meningitis acute bacterial meningitis (ABM).

Conflicts of interest:

- The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.
- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

REFERENCES

1. Theodoridou, M., Vasilopoulou, V., Atsali, E., Pangalis, A., Mostrou, G., Syriopoulou, V. et al. Meningitis registry of hospitalized cases in children: epidemiological patterns of acute bacterial meningitis throughout a 32-year period. BMC

Infectious Diseases 2007; 7(1):101 .DOI: 10.1186/1471-2334-7-101 ·

2. Edmond K,Edmond K, Clark A, Korczak VS, Sanderson C et al. Global and regional risk of disabling sequelae from bacterial meningitis: asystematic review and meta-analysis. Lancet Infect Dis 2010 ;10(5):317-328.
3. Schut ES, Lucas MJ, Brouwer MC, Vergouwen MDI, van der Ende A et al ; Cerebral infarction in adults with bacterial meningitis. Neurocrit Care 2012; 16(3):421–7.
4. Fluegge K, Siedler A, Heinrich B, Schulte-Moenting J, Moennig MJ et al ; German Pediatric Surveillance Unit Study Group. Incidence and clinical presentation of invasive neonatal group B streptococcal infections in Germany. Pediatrics 2006; 117: e11 39-45.
5. Kiwanuka, J.P., and Mwanga, J; Childhood bacterial meningitis in Mbarara Hospital, Uganda: antimicrobial susceptibility and outcome of treatment. African health sciences 2001; 1: 9-11.
6. Heydaria B, Khalilib H, Karimzadehc I, Emadi-Kochak H. "Clinical, paraclinical, and antimicrobial resistance features of community-acquired acute bacterial meningitis at a large infectious diseases ward in Tehran, Iran," Iranian Journal of Pharmaceutical Research, 2014, vol. 15, pp. 347–354,.
7. Cheesebrough M, "Biochemical tests to identify bacteria," in District Laboratory Practice in Tropical Countries, M. Cheesbrough, Ed., pp. 116–124, Cambridge University Press, Cambridge,UK, 2nd edition, 2007
8. Michael Owusu, Samuel Blay Nguah,Yaw Agyekum Boaitey,Ernest Badu-Boateng,[3]Abdul-Raman Abubakret al; Aetiological agents of cerebrospinal meningitis: a retrospective study from a teaching hospital in Ghana. Ann ClinMicrobiolAntimicrob 2012; 11-28.
9. Bodilsen J, Dalager-Pedersen M, Schønheyder HC, Nielsen H. Stroke in community-acquired bacterial meningitis: a Danish population-based study. Int J Infect Dis 2014; 20:18–22.
10. 10-CLSI. Performance Standards for Antimicrobial Susceptibility Testing;28 th ed , CLSI supplement M100.Wayne ,PA: Clinical and Laboratory Standards Institute . 2018.
11. Coureuil M, Mikaty G, Miller F, Lecuyer H, Bernard C, et al; Meningococcal type IV pili recruit the polarity complex to cross the brain endothelium. Science 2009; 325:83–87. doi:10.1126/science.1173196
12. Yamashima T, Kashihara K, Ikeda K, Kubota T, Yama¬moto S; Three phases of cerebral arteriopathy in meningitis: vasospasm and vasodilatation followed by organic stenosis. Neuro¬surgery 1985; 16(4):546–53.
13. Katchanov J., Heuschmann P. U., Endres M., Weber J. R; Cerebral infarction in bacterial meningitis: Predictive factors and outcome. Journal of Neurology. 2010;257(5):716–720. doi: 10.1007/s00415-009-5395-9.
14. Sutinen J, Sombrero L, Paladin FJ, Julkunen I, Leinikki P et al; Etiology of central nervous system infections in the Philippines and the role of serum C-reactive protein in excluding acute bacterial meningitis. Int J Infect Dis 1998–1999, 3(2):88–93.
15. Huttunen P, Lappalainen M, Salo E, Lönnqvist T, Jokela P, Hyypiä T; Differential diagnosis of acute Central Nervous System Infections in children using Modern Microbiological methods. Acta Paediatr 2009, 98 (8):1300–1306.
16. Assegid Mengistu, Johannes Gaeseb, Gottfried Uaaka, Christophine Ndjavera, Kennedy Kambyambya, et al; Antimicrobial sensitivity patterns of cerebrospinal fluid (CSF) isolates in Namibia: implications for empirical antibiotic treatment of meningitis. Journal of Pharmaceutical Policy and Practice 2013: 6-4.
17. Scarborough, M., S. B. Gordon, C. J. Whitty, N. French, Y. Njalale, A. et al; Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N. Engl. J. Med 2007. 357: 2441-2450.
18. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, et al; Clinical features and prognostic factors in adults with bacterial meningitis. N. Engl. J. Med 2004. 351:1849-1859
19. Youssef FG, El-Sakka H, Azab A, Eloun S, Chapman GD, Ismail T, et al. Etiology, antimicrobial susceptibility profiles, and mortality associated with bacterial meningitis among children in Egypt. Ann Epidemiol.2004;14(1):44–8.
20. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, et al; Bacterial meningitis in the United States, 1998–2007. N Engl J Med. 2011;364(21): 2016–25.
21. van de Beek D, J. de Gans, A. R. Tunkel, and E. F. M.Wijdicks; "Community-acquired bacterial meningitis in adults," New England Journal of Medicine 2006, vol. 354,(1), 44–53.
22. Yang TM, Lu CH, Huang CR, Tsai HH, Tsai NW et al; Clinical characteristics of adult Escherichia coli meningitis. Jpn J Infect Dis. 2005;58(3):168-70.
23. Fahmi Yousef Khan, Mohammed Abukhattab, and Deshmukh Anand; Nosocomial Escherichia coli meningitis in adults: Report of four cases and literature review. J Neurosci Rural Pract. 2013; 4(3): 349–351.
24. Jiang H, Su M, Kui L, Huang H, Qiu L et al ; Prevalence and antibiotic resistance profiles of cerebrospinal fluid pathogens in children with acute bacterial meningitis in Yunnan province, China,

2012-2015. PLoS ONE 2017; 12(6): https://doi.org/10.1371/journal.pone.e0180161.
25. Bieden bach DJ, Kazmierczak K, Bouchillon SK; In vitro activity of aztreonam-avibactam against a global collection of Gram-negative pathogens from 2012 and 2013 . Antimicrob Agents Chemother 2015;59 : 4239–48.
26. Allan R. Tunkel Barry J. Hartman Sheldon L. Kaplan Bruce A. Kaufman et al; Practice Guidelines for the Management of Bacterial Meningitis . Clinical Infectious Diseases 2004;39(9): 1267–1284.
27. Breilh D, Texier-Maugein J, Allaouchiche B, Saux MC, Boselli E; "Carbapenems". J Chemother 2013. 25 (1): 1–17.
28. Kaplan SL; Management of pneumococcal infections, Pediatr Infect Dis J , 2002, 21:589-91.
29. Cédric Bretonnière, Mathieu Jozwiak, and Christophe Guitton; Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study. Crit Care. 2015; 19(1): 303.
30. Nau R, Wellmer A, Soto A, Koch K, Schneider O et al; Rifampin reduces early mortality in experimental Streptococcus pneumoniae meningitis. J Infect Dis. 1999; 179:1557–60. doi: 10.1086/314760.
31. Lo WT, Wang CC, Lee CM, Chu ML. Successful treatment of multi-resistant Stenotrophomonas maltophilia meningitis with ciprofloxacin in the pre-term infant, Eur J Pediatr. , 2002, 161 :680-2.
32. Kameshwar Prasad, Neha Karlupia, Amit Kumar; Treatment of bacterial meningitis: An overview of Cochrane systematic reviews. Respiratory Medicine 2009 (103)7: 945-950.