

# INFREQUENT ISOLATES ON CULTURE OF CEREBROSPINAL FLUID IN PATIENTS WITH MENINGITIS IN ADULTS

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## ABSTRACT:

**Objective:** To identify common pathogens causing meningitis, emerging resistance to antibiotics as delay in treatment may adversely affect outcome.

**Material and Methods:** It was descriptive observational study which was conducted in the Department of Medicine, KRL Hospital, Islamabad, Pakistan from January 2014 to December 2016. It enrolled 200 patients with age ranging from 12 to 90 years in whom meningitis was suspected. Two cerebrospinal fluid (CSF) samples were collected, one for routine examination while other for culture and sensitivity. Data was analyzed using Statistical package for social sciences (SPSS) version 20. Frequencies and percentages were taken where required.

**Results:** Eighteen (9%) patients showed growth of microorganisms. Among culture isolates 17 (8.5%) were bacteria, 1(0.5%) was Cryptococcus. Relatively more cultures were positive in trauma and surgery related patients mainly gram negative organisms, being sensitive to Tigecycline, Colistin followed by Imipenem/Meropenem. Staphylococcus aureus was sensitive to Linezolid and Vancomycin. There is increasing resistance to cephalosporin.

**Conclusion:** Cerebrospinal fluid (CSF) shows low rates of bacterial growth on culture. Empirical therapy may be tailored according to underlying clinical condition.

**Key Words:** Meningitis, Antibiotics, Resistance, Staphylococcus aureus, Cryptococcus, Linezolid, Vancomycin.

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## INTRODUCTION

Bacterial meningitis is an acute purulent infection within subarachnoid space and is characterized by severe headache, fever and vomiting. It is associated with Central Nervous System (CNS) inflammatory reaction that may result in decrease consciousness and seizures<sup>1</sup>. Only a minority presents with the classical triad of fever, altered mental status, and neck stiffness<sup>2</sup>. Elderly patients presents frequently with altered mental status and focal neurological deficits<sup>3</sup>. According to Centers for Disease Control and Prevention it was observed that incidence of meningitis is 1.3 cases per 100,000 population in adults (age > 18). Bacterial meningitis incidence declined from 2.0 to 1.38 cases per 100,000 populations between 1998 to 1999 and 2006-2007<sup>4</sup>. About

5% mortality rates have been reported in children from developed countries, whereas in developing countries, the rates have been estimated at 30%<sup>5</sup>. About 10% - 20% of those who survive from bacterial meningitis may have complications like epilepsy, mental retardation and sensorineural deafness<sup>6</sup>. The therapeutic goal is to initiate antibiotic therapy within 60 minutes of a patient's arrival in the emergency room. In two large case series, for example, the case-fatality rate for adults with bacterial meningitis was approximately 25 percent, and transient or permanent neurologic morbidity occurred in 21 to 28 percent of survivors<sup>7,8</sup>. In patients suspected of having bacterial meningitis, CSF shall be obtained for cultures and empirical antimicrobial therapy initiated without delay<sup>9,10</sup>. Diagnosis of bacterial meningitis is confirmed by CSF culture the "gold standard" for diagnosis of meningitis and the antimicrobial susceptibility of the causative microorganism<sup>11</sup>. Prior antibiotic treatment makes diagnosis difficult. This result in negative CSF culture growth. Antimicrobial therapy, along with adjuvant dexamethasone when indicated, shall be initiated as quickly as possible after necessary cultures are sent<sup>12</sup>. In adults Haemophilus influenzae (H. influenzae) type b (Hib), Streptococcus pneumoniae (S. pneumoniae) and Neisseria meningitidis (N.meningitidis) causes

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meningitis in 75 to 90% of cases<sup>2</sup>. Worldwide Hib meningitis has the greatest incidence in children aged <5 years, one fourth of whom die from the infection<sup>13</sup>. With availability of H. influenzae type b conjugate vaccines in the United States, H. influenzae accounts for only 7% of cases<sup>14</sup>. S. pneumoniae is now the most common etiological agent of bacterial meningitis in developing countries, accounting for 61% of total cases<sup>15</sup>. More than 98% of cases of invasive meningococcal disease in the United States are sporadic<sup>16</sup>. S. pneumoniae and Listeria monocytogenes are most common organism among elderly. In a prospective case series involving 257 patients aged 60 years or older, S. pneumoniae was cultured in 176 episodes (68%), N. meningitidis was cultured in 36 episodes (14%), Listeria monocytogenes was cultured in 18 episodes (7%), and other bacteria were cultured in 27 episodes (11%)<sup>17</sup>. Both the epidemiology and the sensitivity to antibiotics are changing as a result of the widespread use of antimicrobials. Such a data is important to manage meningitis patients in the first critical hours of their treatment<sup>18</sup>. The rationale of this study was to effectively introduce antibiotic policy in meningitis, especially empirical treatment in first 24-48 hours before culture results if any were available.

### MATERIAL AND METHODS

This was a descriptive observational study carried out to identify causative organisms in patients with suspected meningitis and their sensitivity and resistance to antibiotics. It was carried out from January 2014 to December 2016 in Department of Medicine, KRL Hospital Islamabad. Patients aged 12 to 90 years were included. They had either no preceding illness (86%) or were with head trauma and surgery (14%). Two CSF samples were collected, one for routine examination while other for culture and sensitivity. CSF was inoculated as soon as it was received. In case of any delay it was kept in incubator at 37°C. Bacterial culture is accomplished using blood agar (5-10% CO<sub>2</sub>) or chocolate agar for N. meningitidis, S. pneumoniae and H. influenzae and MacConkey agar for gram negative bacilli aerobically at 37°C, Lowenstein-Jensen medium for tuberculosis meningitis and Sabouraud's and blood agar aerobically

for Cryptococcus neoformans. Results were read after 24 hours of incubation. In case it was negative it was re-examined after 48 hours. Data was analyzed using Statistical package for social sciences (SPSS) version 20. Frequencies and percentages were taken where required.

### RESULTS

A total of 200 CSF samples were considered for examination. Patient's age ranged from 12-90 years. 57% were males and 43% were females. Out of these, 18 (9%) showed growth of microorganisms. Among them, 17 (8.5%) were bacteria and 1 (0.5%) was Cryptococcus. This is shown in Table 1. More than sixty percent of bacterial isolates were gram negative organisms including Klebsiella 5 (29.4%), Acinetobacter 3 (17.6%), and Pseudomonas 2 (11.7%), and Escherichia coli 1 (5.8%). Gram positive organisms included Staphylococcus aureus 3 (17.6%), S. Pneumoniae 2 (11.7%) and Enterococcus 1 (5.8%). More than eighty percent of culture positive patients in this study were between twelve and fifty years as shown in Table 2. Tigecycline, Colistin, Ceftriaxone, Imipenem/Meropenem and Linezolid were the most common antibiotics used. Table 3 shows a comparison recommended guidelines and results of this study. Proteins were raised more than 50mg/dl in 57% of cases, with a mean value of 129±86.88. CSF glucose was less than 50mg/dl in 22% of cases with 8% having less than 30mg/dl. It has a mean of 37.5±11.24.

**Table 1: Type of micro-organisms isolated from CSF**

Type of organism	No. of patients & percentages
Gram Negative	11 (5.5%)
Gram Positive	6 (3%)
Fungus	1 (0.5%)
No Growth	182 (91%)
Total	200 (100%)

**Table 2: Frequency of organisms isolate by age group**

Organism	12-50 years (%)	>50 years (%)	Total
Klebsiella spp	4 (22.2%)	1 (5.55%)	27.8%
Acinetobacter	2 (11.1%)	1 (5.55%)	16.65%
Staphylococcus aureus	3 (16.65%)	0 (0%)	16.65%
Pseudomonas spp.	2 (11.1%)	0 (0%)	11.1%
Escherichia coli (ESBL)	1 (5.55%)	0 (0%)	5.55%
Streptococcus Pneumoniae	2 (11.1%)	0 (0%)	11.1%
Enterococcus spp.	1 (5.55%)	0 (0%)	5.55%
Cryptococcus spp.	1 (5.55%)	0 (0%)	5.55%
Total	16 (88.9%)	2 (11.1%)	100%

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**Table 3: Comparison of recommended guidelines for pyogenic meningitis and results of this study**

<b>Organism</b>	<b>Recommended Antibiotics</b>	<b>Our study results</b>
➤ Streptococcus Pneumoniae	• Vancomycin	• Vancomycin And • Ceftriaxone
	And Third-generation cephalosporin	
	• Ceftriaxone Or	
	• Cefotaxime	
➤ Neisseria meningitidis	• Vancomycin	No growth
	And Third-generation cephalosporin	
	• Ceftriaxone Or	
	• Cefotaxime	
➤ Haemophilus influenzae	• Vancomycin	No growth
	And Third-generation cephalosporin	
	• Ceftriaxone Or	
	• Cefotaxime	
➤ Klebsiella pneumoniae	• Vancomycin and	• Colistin Or • Tigecyclin And • Meropenem
	• Ceftazidime Or	
	• Cefepime Or	
	• Meropenem	
➤ Pseudomonas spp	• Vancomycin And	• Colistin Or • Polymixin B And • Meropenem
	• Ceftazidime Or	
	• Cefepime Or	
	• Meropenem	
➤ Escherichia coli (ESBL)	• Vancomycin And	• Amikacin And • Meropenem Or • Tigecycline
	• Ceftazidime Or	
	• Cefepime Or	
	• Meropenem	
➤ Acinetobacter spp.	• Vancomycin And	• Tigecycline Or • Colistin And • Sulbactam-cefoperazone
	• Meropenem Or	
	• Colistin Or	
	• Polymixin B	
➤ Staphylococcus aureus (MRSA)	• Vancomycin	• Vancomycin And • Tigecycline
	And Third-generation cephalosporin	
	• Ceftriaxone Or	
	• Cefotaxime	
	• Cefotaxime	
➤ Enterococcus spp	• Ceftriaxone And	• Linezolid And • Chloramphenicol
	• Vancomycin	

**DISCUSSION**

Previously, bacterial meningitis was a greatly feared infectious disease due to its high morbidity and mortality, many of its victims were children, and as many as 25% of survivors had sequelae such as mental retardation, permanent brain damage, or hearing loss. There were once 10,000 to 20,000 cases each year in the United States, but there have been major efforts to improve treatment and prevent bacterial meningitis<sup>19</sup>. Meningitis is mainly diagnosed on the basis of history, clinical examination and cerebrospinal fluid examination. Conventional culture methods, though gold standard diagnostic technique, cannot

be relied upon in certain situations, due to delay in results availability and relatively limited bacterial growth on culture that is reported worldwide specially in situations where prior antimicrobial therapy was administered. Three factors such as hypotension, altered mental status, and seizures were indicative of an adverse outcome<sup>7</sup>. A median delay of four hours in starting treatment was associated with a worsening of these markers. A retrospective study of 119 adults with bacterial meningitis examined effects of delay in antibiotic administration before presentation to emergency. The adjusted odds ratio for mortality was 8.4 for a door-to-antibiotic time greater than six hours<sup>20</sup>.

Demographic data analysis of patients revealed that males were 57% and females 43%. Fouad et al who confirmed that males were frequently affected with bacterial meningitis than females (61% versus 39%, respectively)<sup>21</sup>. In our study, 9% of the CSF samples were culture positive. CSF cultures are expected to be positive in 70%–85% of patients with bacterial meningitis who had no prior antimicrobial therapy<sup>22</sup>. Prior antibiotic treatment and aseptic meningitis may have contributed to low bacteria growth<sup>23</sup>. A similar situation appears to be occurring in our case. According to Brouwer et al CSF culture is documented to be positive only in 1/10th of the previously antibiotic treated patients in developing countries<sup>22</sup>. Same result was found by Affifi et al who reported low rates of culture positive CSF samples (8%) of suspected cases with bacterial meningitis<sup>24</sup>. In a study on different body fluids culture, CSF showed bacterial growth in 1.96% of cases only<sup>25</sup>. *S. pneumoniae* is found to be the commonest etiology of meningitis in the United States and Europe accounting for 61% of total cases in the United States<sup>26</sup>. But in this study most common pathogens isolated from the CSF were gram negative bacteria being related to surgical and trauma cases. There has been rise in klebsiella species in recent years<sup>27</sup>. These strains are highly virulent and significantly increase mortality. Organisms isolated from CSF showed high resistance to ceftriaxone. Only exception was *S. pneumoniae* being 100% sensitive to ceftriaxone. There is increasing resistance to cephalosporins by gram negative bacteria. An elevated CSF protein indicates bacterial meningitis. This study revealed that 57% of samples with suspected meningitis have elevated protein i.e. greater than 50mg/dl. It was found that 22% of CSF samples have low glucose level. Delayed presentation and often antibiotic use by general practitioner was possibly responsible for low bacterial growth on culture of CSF. In cases of low CSF culture yield, newer laboratory aids can be of practical value. In a study CSF lactate was found to provide pertinent, rapid and reliable diagnostic information in distinguishing bacterial from viral meningitis<sup>28</sup>. Additionally Latex Particle Agglutination (LPA) and Polymerase Chain Reaction (PCR) can be useful diagnostic tool in rapid etiological diagnosis of bacterial meningitis in cases of infections by *H. influenzae*, *S. pneumoniae* and *N. meningitidis*. It was found that LPA was relevant in 26 out of 166 (15.66%) of cases and the organisms were *H. influenzae* type b in 10 cases, *S. pneumoniae* 15 cases and *N. meningitidis* only one case. PCR was positive in 65 out of 166 (39.15%) cases and the isolates were *H. influenzae* type b 16 cases, *S. pneumoniae* 48 cases and *N. meningitidis* one case<sup>29</sup>.

## LIMITATIONS

Low culture yields fell short of formulating effective antibiotic policy because common pathogens grew far less frequently.

## CONCLUSION

CSF shows low rates of bacterial growth on culture. Therapy may be tailored according to underlying clinical condition.

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### **AUTHOR'S CONTRIBUTION**

Following authors have made substantial contributions to the manuscript as under:

- Ali A:** Concept design, analysis, interpretation of data.  
**Shaikh JI:** Literature review, data collection.  
**Nisar A:** Bibliography.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.