DOI: 10.7860/NJLM/2022/51902.2631

Original Article

Microbiology Section

Identification of Bacterial Agents causing Meningitis in Adult Population using BACTEC FX40 System

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ABSTRACT

Introduction: Bacterial meningitis among adults is a medical emergency and requires immediate diagnosis as well as immediate treatment. As clinical diagnosis is not always reliable, laboratory isolation along with antimicrobial susceptibility results are crucial. Conventional agar culture methods gives poor sensitivity and delayed results. Automated culture methods like BACTEC are suitable option for culture of sterile fluids beside blood culture.

Aim: To determine the bacterial agents causing meningitis in this region, along with their antibiogram by using automated culture system BACTEC FX40.

Materials and Methods: This cross-sectional, observational study was conducted between October 2019-September 2020 in Department of Microbiology, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India. Cerebrospinal Fluid (CSF) samples received from medicine Intensive Care Unit (ICU) and wards were processed by inoculating them on BD BACTEC Peds Plus/F bottle and then incubating them on BACTEC BD FX40 system. The bottles flagged and positive were subcultured and further processed according to standard laboratory procedures. The antibiotic sensitivity test was performed from isolated organisms by Kirby-Bauer Disc Diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines.

Results: A total of 108 CSF were received for culture by automated methods from patients suspected of meningitis during the study period. Out of them 84 (77.8%) beeped as positive while 24 (22.2%) were sterile. From the positives, 77 showed growth of gram positive cocci, three were gram negative bacilli and four showed growth of environmental and skin contaminants that were excluded from the study. All gram positive cocci were identified as *Staphylococcus aureus (S. aureus)*. The antibiotic sensitivity testing showed 100% sensitivity to vancomycin and linezolid. Only 25 isolates of *S. aureus* were sensitive to cefoxitin. Both the isolates of *Escherichia coli (E. coli)* were sensitive to cefazolin, ceftazidime, aztreonam. *Pseudomonas aeruginosa (P. aeruginosa)* was sensitive to amikacin and piperacillin/tazobactum.

Conclusion: A shift in the trend was observed in the aetiology of bacterial meningitis with Methicillin Resistant *Staphylococcus aureus* (MRSA) as the most predominant isolate among adult population. BACTEC FX40 system was found more sensitive in detecting pathogens over the conventional methods with reduced time to positivity. Early detection of causative organism will facilitate early initiation of suitable antibiotic therapy, thereby reducing mortality and meningitis associated complications.

Keywords: Antibiotic sensitivity, Automated culture method, Bacterial meningitis, Cerebrospinal fluid

INTRODUCTION

Meningitis is a serious public health problem and the most common cause of morbidity and mortality in human population all over the world. Early diagnosis and rapid initiation of antibiotic therapy can be lifesaving in such a scenario. The key goals of early management lies in distinguishing between the symptoms, identification of responsible pathogen, and initiation of appropriate antimicrobial therapy [1].

The role of antibiotics is very crucial in treatment of meningitis, if there is delay in diagnosis and treatment, then it can result in poor outcomes. Antimicrobial susceptibility of causative agents of meningitis has been changing over the years due to extensive and indiscriminate use of antimicrobial agents, and this has resulted in appearance of antimicrobial resistance like penicillin and cephalosporin resistant *Streptococcus pneumoniae (S. pneumoniae)* and isolates of *Neisseria meningitidis (N. meningitidis)* with moderate resistant to penicillin [2]. Effective empirical treatment requires knowledge of microorganisms and antimicrobial susceptibility pattern of the isolated organisms.

Isolation of microorganisms traditionally involves Gram staining and Ziehl-Neelson staining of centrifuged deposit of CSF, bacteriological culture in enriched media like Brain Heart Infusion (BHI) broth and subculture on blood agar, MacConkey agar and chocolate agar. These traditional methods have their own drawbacks of longer detection time, poor sensitivity and more chances of contamination. The BACTEC method is more suitable for rapid isolation of bacteria from all sterile fluids including CSF in terms of turnaround time [3]. Therefore, this study was undertaken for detection of causative agents of acute bacterial meningitis using BACTEC FX40 system.

MATERIALS AND METHODS

This cross-sectional, observational study was conducted between October 2019-September 2020 in Department of Microbiology, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India. The study was approved by Institutional Ethical Committee (IEC) (IEC/07/2019/SEP).

Inclusion criteria: Patients having signs and symptoms of meningitis i.e., neck rigidity, positive kernig's sign (severe stiffness of the hamstrings causing an inability to straighten the leg when the hip is flexed to 90°) and Brudzinski's sign (severe neck stiffness causing the patient's hip and knee to flex when the neck is flexed) were included in the study [4].

Exclusion criteria: Patients who had received antibiotic for the past one-week from their visit to the hospital and those patients who developed meningitis following head trauma, neurosurgical procedure, having spine deformity, raised intracranial pressure and brain haemorrhage were excluded from the study [5].

Sample size calculation: The positivity rate as found by Mahmoudi S et al., in 31 patients is 20 (64.5%) positive CSF cultures by BACTEC

method [6]. On this basis using formula for sample size ($n=4pq/l^2$) the sample size calculated was 100, where 'p' is prevalence, q=100-p and l=relative error. A total of 108 CSF samples were received during the study duration from medicine ICU and ward. These CSF samples were taken from 108 different patients suspected to be suffering from bacterial/fungal meningitis after obtaining informed written consent from their attendants.

Sample Collection

For the study, CSF was collected aseptically by lumbar puncture with prior informed consent, and distributed in three vials, one for biochemical analysis, second for pathological analysis and third for microbiological analysis [7]. Approximately, 1.5 mL of aseptically collected fresh CSF was directly inoculated in a BD BACTEC Peds Plus/F blood culture bottle, the septum of which had been prior cleaned with 70% isopropyl alcohol. The BACTEC bottle was properly labelled and all the patient particulars were indicated on the bottle. The BACTEC bottles were immediately inserted in BACTEC FX40 automated system and processed according to the standard protocol.

Sample Processing

BACTEC bottles containing CSF were incubated in BACTEC FX40 automated system. Any growth of microorganisms was detected by the positive signal indicated by the system. CSF/broth mixture from such bottles was subcultured on Blood agar, MacConkey agar and Chocolate agar. The chocolate agar plates were kept in candle jar (5-10% Co_2) to stimulate the growth of fastidious organisms. Isolated microbial pathogens were identified on the basis of colony characteristics, Gram's staining and biochemical reactions [8].

Antimicrobial Susceptibility Test

The antimicrobial sensitivity test was performed for isolated organisms by Kirby-Bauer Disc Diffusion method according to CLSI guidelines [9].

STATISTICAL ANALYSIS

Descriptive analysis was done and data was processed and arranged into numbers and percentages.

RESULTS

Out of 108 CSF sample received, 84 (77.8%) CSF culture flagged as positive, 24 (22.2%) were sterile while four showed growth of environmental and skin contaminations like *Bacillus subtilis* and diptheroids which were excluded from the study [Table/Fig-1]. The overall isolation rate of pathogenic microorganism from CSF was 74.1%.

Result	Number	%
Positive	80	74.1
Contaminated from positive	4	3.7
Negative	24	22.2
Total	108	100

[Table/Fig-1]: Showing distribution of CSF cultures received during study period n=108.

Out of 80 positive CSF culture included in the study, Gram positive cocci were found in 77 (96.3%) CSF cultures and all of them were identified and confirmed as *S. aureus*. Gram negative bacilli isolated were only 3 (3.7%) in number, that included 2 (2.5%) *E. coli* and 1 (1.2%) *P. aeruginosa* as shown in [Table/Fig-2].

Out of the 80 positive CSF samples showing bacterial growth, most were from patients in the age group 18-40 years, 48 (60%) were male and remaining 32 (40%) were from female patients [Table/Fig-3].

All the isolates of *S. aureus* were sensitive to vancomycin and linezolid, 96.10% to levofloxacin, 90.90% to gentamicin, 88.31% to tetracyclin. Only 32.46% of *S. aureus* were sensitive (zone size >22 mm) to cefoxitin. Total 52 (68%) of *S. aureus* isolates were reported as MRSA [Table/Fig-4].

Both the isolates of *E. coli* were 100% sensitive to cefazolin, ceftazidime, aztreonam, imipenem, meropenem and tobramycin. *P. aeruginosa* was sentitive to ceftazidime, aztreonam, imipenem, meropenem, amikacin and piperacillin/tazobactum [Table/Fig-5].

The time analysis for positivity of BACTEC CSF is shown in [Table/Fig-6].

Fever (96.29%), headache (95.37%), neck stiffness (92.59%), nausea (94.44%) and vomiting (97.22%) were common clinical

Type of isolated organism	Number of organisms (n=80)	Type of organism	%
Gram positive organism	77	*Staphylococcus aureus*	96.3%
Gram negative organism	3	*Escherichia coli=2*	2.5%
		Pseudomonas=1	1.2%

[Table/Fig-2]: Showing gram positive cocci and gram negative bacilli from positive CSF culture.

Age group (in years)	Total positive samples n=80 (%)	Male n=48 (%)	Female n=32 (%)
18-30	26 (32.5)	15 (31.25)	11 (34.37)
31-40	31 (38.75)	17 (35.41)	14 (43.75)
41-50	12 (15)	8 (16.66)	4 (12.5)
51-60	8 (10)	5 (10.41)	3 (9.37)
>60	3 (3.75)	3 (7.31)	0
Total	80	48	32

[Table/Fig-3]: Age and sex-wise distribution of patients.

Antibiotic name	*S. aureus* (n=77)	%
Penicillin	0	0
Cefoxitin	25	32.46
Vancomycin	77	100
Linezolid	77	100
Gentamicin	70	90.90
Erythromycin	40	51.94
Tetracyclin	68	88.31
Levofloxacin	74	96.10
Clindamycin	33	42.85
Trimethoprim/Sulfamethoxazole	18	23.37

[Table/Fig-4]: Showing antibiotic susceptibility pattern of gram positive isolates from positive CSF cultures (n=77).

Antibiotic name	*E. coli* (n=2)	*P. aeruginosa* (n=1)
Ampicillin	0	Not indicated
Cefazolin	2 (100%)	Not indicated
Cefipime	1 (50%)	0
Cefuroxime	0	Not indicated
Ceftazidime	2 (100%)	1 (100%)
Cefexime	1 (50%)	Not indicated
Cefotaxime	0	Not indicated
Aztreonam	2 (100%)	1 (100%)
Imipenem	2 (100%)	1 (100%)
Meropenem	2 (100%)	1 (100%)
Gentamycin	1 (50%)	0
Tobramycin	2 (100%)	Not indicated
Amikacin	1 (50%)	1 (100%)
Tetracycline	0	Not indicated
Ciprofloxacin	0	0
Piperacillin/Tazobactum	0	1 (100%)
Levofloxacin	0	0

[Table/Fig-5]: Showing antibiotic susceptibility pattern of gram negative isolates from positive CSF cultures (n=3).

findings. Six patients (5.55%) had seizures, while eight (7.4%) had loss of consciousness. Four patients (3.7%) presented with bleeding manifestation, mostly skin bleeding or subconjunctival haemorrhage. Hypotension was noted in 12 patients (11.11%) and skin rash was seen in 6 patients (5.55%) [Table/Fig-7].

Time (Hours)	Samples	%
24	51	47.2
48	28	25.9
72	3	2.8
96	2	1.9
Not detected after 5 days	24	22.2
Total	108	100

[Table/Fig-6]: Showing time of positivity of CSF samples by BACTEC FX40 system.

S. no.	Clinical Features	Total n=108 (%)	*Staphylococcus aureus* n=77 (%)	*E. coli* n=2 (%)	*Pseudomonas* n=1(%)	Pathogen not detected or contaminated sample n=28
1.	Fever	104 (96.29)	77 (100)	2 (100)	1 (100)	24 (85.71)
2.	Headache	103 (95.37)	77 (100)	2 (100)	1 (100)	23 (82.14)
3.	Neck stiffness	100 (92.59)	77 (100)	2 (100)	1 (100)	20 (71.42)
4.	Nausea	102 (94.44)	76 (98.70)	2 (100)	1 (100)	23 (82.14)
5.	Vomiting	105 (97.22)	76 (98.70)	2 (100)	1 (100)	26 (92.85)
6.	Seizures	6 (5.55)	6 (7.79)	0	0	0
7.	Loss Of Consciousness (LOC)	8 (7.4)	8 (10.38)	0	0	0
8.	Bleeding manifestation	4 (3.7)	4 (5.19)	0	0	0
9.	Hypotension	12 (11.11)	10 (12.98)	1 (50)	1 (100)	0
10.	Rash	6 (5.55)	1 (1.29)	0	0	5 (17.85)
11.	Kernigs sign positive	60 (55.5)	60 (77.9)	0	0	0
12.	Brudzinski sign positive	60 (77.9)	62 (80.5)	0	0	0

[Table/Fig-7]: Clinical features in acute bacterial meningitis based on aetiology.

DISCUSSION

Meningitis is a serious public health problem and a major cause of morbidity and mortality in human population all over the world. Early recognition, efficient decision making and early institution of antibiotic are the corner stones in the effective management of meningitis. Making an early diagnosis requires clinical assessment as well as laboratory isolation. Since clinical signs and symptoms can't be always relied upon, laboratory support is crucial to achieve early diagnosis. Also, the antibiotics have to be initiated even before the aetiological microorganism is known. The choice of antibiotics in such a scenario is often based on prevalence of microorganism in that particular area and age-group along with their local antibiogram [1]. A clear difference in the frequency of bacterial meningitis cases caused by different aetiological agents has been observed between age groups and between geographic regions by Oordt-Speets AM et al., [10].

The most common causes of bacterial meningitis world-wide are *Haemophilus influenzae (H. influenze)*, *S. pneumoniae* and *N. meningitidis* in all age groups [11]. A review article by Oordt-Speets AM et al., reported *S. pneumoniae* and *N. meningitidis* as predominant pathogens accounting for 25.1-41.2% and 9.1-36.2% of bacterial meningitis cases respectively in all regions and in all age groups [10]. In developed countries, due to effective vaccination programs, the incidence of *H. influenzae* and *N. meningitidis* has shown decreasing trends [12]. For example in United states after the introduction of *H. influenzae* type b vaccination, the commonest causes of bacterial meningitis in all age groups are *S. pneumoniae, N. meningitidis*, Group B streptococci, *Listeria monocytogenes (L. monocytogenes)* and *H. influenzae* type b, in decreasing order of incidence [10]. In England and Wales, the commonest causes are meningococcal, *H. influenze* type b, pneumococcal, Group B streptococci, *E. coli, Listeria* and Staphylococci [11]. In Asia, however the causes of bacterial meningitis are different. There is relatively less incidence of these organisms from South East Asia including India and other neighbouring countries [11,13]. Like in Hong Kong though bacterial meningitis is uncommon, the commonest cause of non viral meningitis is tuberculous meningitis in children [11]. In Indonesia and Taiwan, gram negative bacilli are important causes of bacterial meningitis, with *K. pneumoniae* (26%) as the commonest isolate, followed by *Acinetobacter* and *Staphylococcus* (14%) [11,13]. Similarly, *S. agalactiae* (38%) was reported as commonest cause of adult bacterial meningitis from a study of Singapore and Hong Kong [11]. This could be the result *H. influenzae* vaccine (Hib) implementation in paediatric immunisation program [12] and availability of conjugate vaccine that target specific serogroup or serotype of *S. pneumonia* and *N. meningitidis* resulting in a change in epidemiological pattern of the pathogens [12]. Other associated factors, could be the semi tropical temperature and climatic conditions, easy accessibility to antibiotics in this region leading to more culture negative and decreased isolation of relatively fragile bacteria like *H. influnzae, N. meningitidis* which are sensitive to commonly used antibiotics [12].

In current study, *S. aureus* was found as the predominant microorganism causing acute bacterial meningitis in adult population. Other organisms found to be associated were *E. coli* and *P. auruginosa*. Not a single specimen grew the time noted conventional pathogens of acute bacterial meningitis like *N. meningitidis*, *S. pneumoniae* and *L. monocytogenes* during the study but emergence of *S. aureus* as a major pathogen causing meningitis in adults was noteworthy. This major shift in trend of aetiological agents and epidemiology of bacterial meningitis from India has recently been reported by several authors [13-15]. Khan F et al., from Aligarh, India in year 2011 have also reported *S. aureus* as a major isolate both from nosocomial and community acquired cases of meningitis (nosocomial=46% and community acquired=54%), other being *Pseudomonas, Klebseilla, E. coli, E. faecalis* and *Acinetobacter* [13]. They were not able to isolate any case of *N. meningitidis, S. pneumoniae* and *H. influenzae* both in nosocomial and community acquired cases over the past eight years [13]. Current results were in concordance to above data but the major drawback of present study was short duration of study and inability to classify the aetiological cases into nosocomial and community acquired meningitis.

Bhagawati G et al., also isolated *S. aureus* (29%), in all age groups followed by *Klebsiella* (15%), *E. coli* (11%), *Acinetobacter* (7%), *Cryptococcus neoformans* (7%), *Pseudomonas* (5%) and *Candida albicans* (5%). They also isolated 4% *N. meningitidis* and *S. pneumoniae* each in age group >5 years [14]. Both the above authors have discussed about change in epidemiological trends of isolated organisms in meningitis, reason being vaccine implementation against these organisms or antibiotic treatment prior to lumbar puncture [13,14].

Singh AK et al., from Gorkhpur have reported Coagulase Negative *Staphylococcus aureus* (CoNS) species 44.5% predominant in all age groups [15]. Similar results with CoNS (22%) as the major isolate has also been cited by Barnawal RK et al., from Jharkhand [16].

In contrast to above study Sonavane A et al., from Mumbai reported *P. aeruginosa* as the commonest isolate followed by *Klebsiella, Acinetobacter* and *S. pneumoniae* [17]. A continued surveillance of aetiological trends of meningitis is thus recommended both for nosocomial and community acquired meningitis in coming years to establish the above documented change in trends by various authors and the present study. They also observed higher recovery rate of microorganisms by automated BACTEC system as compared to conventional methods [18]. The highly enriched media namely

Trypticase soy broth with polymeric binding resin neutralises any antimicrobial present in the CSF, leading to enhanced isolation by this method. This is of particular importance in a country like ours where a majority of CSF are reported as sterile due to prior intake of antibiotics. In a comparative study by Venkataswamy MM et al., on cases of tuberculous meningitis the isolation rates were 93% and 39% for the BACTEC system and Lowenstein-Jensen (LJ) medium, respectively [19]. In present study, as CSF was directly inoculated in BACTEC culture bottles immediately after lumbar puncture, a comparative study of conventional and automated methods could not be done. CSF is a precious fluid and collection of large volume could lead to post lumbar puncture headache. However, CSF received during the study period for culture by agar methods only, showed all CSF to be sterile. The BACTEC system has for long been used for the detection of agents causing bacteraemia and septicaemia but its use has been limited to blood culture only, in majority of laboratories, while it is suitable for all sterile fluids including CSF. CSF culture by BACTEC system helps in early identification of microbes causing meningitis. In present study 47% isolates were detected in less than 24 hours and 25% in less than 48 hours. Thus use of BACTEC should be extended to use of CSF and other sterile fluids like pleural fluid, pericardial fluid, ascitic fluid and synovial fluid and not remain restricted to blood culture only. Calderaro A et al., have also reported a higher recovery rate from CSF samples by BACTEC culture (95.8%) over agar culture (53.3%) [20]. Sharifi-Mood B et al., and Udayan U et al., have also recommended use of BACTEC automated system for CSF culture and other sterile fluids [21,22].

Thus, increase in isolation rate with reduced time to positivity gives BACTEC culture, an edge over conventional methods for culture of CSF as well as other sterile fluids. Furthermore, 68% of *S. aureus* in present study were found to be MRSA, sensitive to vancomycin and linezolid. As such these drugs should be kept in mind at the time of empirical treatment of acute bacterial meningitis.

Limitation(s)

Though *Mycobacterium tuberculosis* is cause of bacterial meningitis, as only small quantity of CSF was available, inoculation in both PEDS F and MYCO F lytic bottles could not be done. BACTEC Peds F bottles (enriched Soybean-Casein Digest broth with CO_2) are for aerobic cultures (mainly bacteria and yeast) while Myco F Lytic culture medium is used as an adjunct to aerobic culture media for the recovery of mycobacteria, yeast and fungi from sterile body fluids. As such no tubercular meningitis patients could be identified.

CONCLUSION(S)

A significant increase in isolation rate along with reduced time to positivity was observed using BACTEC CSF culture methods, conventional methods of culture should be replaced by automated culture methods. More studies from this region are required to strengthen the emergence of *S. aureus* as the predominant organism causing acute bacterial meningitis. Meanwhile vancomycin and linezolid should be included amongst the drugs prescribed for empirical antimicrobial therapy against acute bacterial meningitis.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 17, 2021
- Manual Googling: Mar 03, 2022
- iThenticate Software: Mar 30, 2022 (11%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 13, 2021**
Date of Peer Review: **Nov 24, 2021**
Date of Acceptance: **Mar 04, 2022**
Date of Publishing: **Jul 01, 2022**