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# Antimicrobial Susceptibility of Bacteria Isolated from Cerebrospinal Fluids in an Iranian Referral Pediatric Center, 1998-2008

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**ABSTRACT**

*Antimicrobial susceptibility patterns of bacterial meningitis provide essential information regarding selection of antibiotic therapy for patients with bacterial meningitis. This study presents data on causes of bacterial meningitis and their susceptibility pattern among children at Children's Medical Center (CMC), a referral tertiary care center in Iran. In this comprehensive retrospective study we reviewed microbiology records of all inpatients suspected to bacterial meningitis, during 1998-2008 of period. Of 11269 CSF cultures examined in the study, 329 (2.9%) were positive for bacterial growth. Overall, coagulase negative staphylococci (CONS) were the most frequent group of organism recovered from our CSF cultures (40%), followed by gram negative enteric bacilli (19.7%). Also, high rates of oxacillin and vancomycin resistance were found among staphylococci. In our study more than 80% of gram-negative enteric bacteria were resistant to ampicillin; we also found high rates of cephalosporin resistance among these organisms. Over 55% of S. pneumoniae were resistant to penicillin. Staphylococci species and gram-negative enteric organisms were the most common pathogens isolated from CSF cultures in this study. It seems that nosocomial meningitis is the main cause of bacterial meningitis in CMC Hospital. Our report draws attention to the importance devising a national strategy to control the spread of resistance in Iran.*

**Keywords:** bacterial meningitis, antimicrobial susceptibility, CSF

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## INTRODUCTION

Bacterial meningitis is a significant cause of morbidity and mortality in adults and children. At least 125000 infants and young children die each year from this disease. Ninety six percent of them are in less developed countries, where fatality rate reaches to 47% and up to 50% of survivors have neurological sequelae (1). This disease can be either community acquired or nosocomial infection with different epidemiological characteristics such as differences in causative agents and their antimicrobial susceptibility patterns. Beyond the neonatal period, the three most common pathogens that cause bacterial meningitis are *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b (Hib). In developed countries the routine use of vaccines against these organisms, has decreased the incidence of meningitis (2). Unlike the community acquired bacterial meningitis, gram-negative bacilli (40-60%) and staphylococci, mainly coagulase negative (30-50%), are the most common causative agents of nosocomial meningitis (3). Antimicrobial resistance, however, in nosocomial infections is higher than community acquired infections.

Consequently, it is important to isolate meningitis pathogens and identify resistance patterns accurately, for prescribing appropriate antibiotics for resistant bacteria and directing standard policies in other similar settings (1). In this study we reviewed the report of prevalence and antimicrobial susceptibility profiles of CSF isolates from patients in Children's Medical Center (CMC) Hospital in Tehran, Iran. ❑

| No. | Bacteria | Frequency | Percent |
|---|---|---|---|
| 1 | Coagulase negative staphylococci | 132 | 40.1 |
| 2 | *S. pneumoniae* | 30 | 9.1 |
| 3 | *S. aureus* | 25 | 7.6 |
| 4 | *Klebsiella* spp. | 20 | 6.1 |
| 5 | *P. aeruginosa* | 20 | 6.1 |
| 6 | *Haemophilus* spp. | 19 | 5.8 |
| 7 | *E. coli* | 17 | 5.3 |
| 8 | *Acinetobacter* spp. | 15 | 4.6 |
| 9 | β-hemolytic streptococci (expect *S. pneumoniae*) | 15 | 4.6 |
| 10 | *N. meningitidis* | 9 | 2.7 |
| 11 | *Enterobacter* spp. | 8 | 2.4 |
| 12 | Non-hemolytic streptococci | 8 | 2.4 |
| 13 | Enterococci | 7 | 2.1 |
| 14 | β-hemolytic streptococci | 2 | 0.6 |
| 15 | Micrococci | 2 | 0.6 |
| | Total | 329 | 100 |

**TABLE 1.** Frequency of occurrence of bacterial species or groups isolated from CSF cultures in Children's Medical Center

## METHOD

### Study design

A ten-year comprehensive retrospective study was conducted during 1998-2008 period. We reviewed microbiology laboratory records of all inpatients of CMC Hospital which were suspected to bacterial meningitis. This center is a referral tertiary care center and also one of the teaching hospitals affiliate to Tehran University of Medical sciences. CMC hospital admits patients from all regions of Iran.

### Microbiology data

We reviewed 11269 CSF cultures, which belonged to all inpatients suspected to bacterial meningitis. We recorded positive cultures with the information on each pathogen isolated from these cultures, including the name and susceptibility profile.

### Susceptibility testing

Kirby-Bauer disk diffusion method was used for antimicrobial susceptibility testing in accordance with National Committee for Clinical Laboratory Standards (NCCLS) guidelines (4). Due to high morbidity and mortality of bacterial meningitis in children, we categorized intermediate susceptible isolates as resistant isolates. ❑

## RESULTS

Of 11269 CSF cultures examined in this study, 329 (2.9%) were positive for bacterial growth. Table 1 lists the bacterial species or groups isolated from cultures. Overall, coagulase negative *Staphylococci* (CONS) were the most frequent group of organisms recovered from CSF cultures (40.1%), followed by *S. pneumoniae* (9.1%), *S. aureus* (7.6%), *Klebsiella* spp. (6.1%), *P. aeruginosa* (6.1%), *Haemophilus* spp. (5.8%), *E. coli* (5.3%), *Acinetobacter* spp. (4.6%), α-hemolytic streptococci (except of *S. pneumoniae*) (4.6%), *N. meningitides* (2.7%). (Table 1)

Table 2 shows *in vitro* antimicrobial susceptibility of bacterial species or groups isolated from CSF cultures. Rates of oxacillin resistance among CONS and *S. aureus* isolates were 82% and 64%, respectively. Less than 13% of staphylococcal isolates were resistant to vancomycin.

Gram-negative enteric bacteria, comprising 19.8% of all bacteria, were recovered from CSF cultures. *Klebsiella* spp. and *P. aeruginosa* were the most prevalent bacteria; each of them included 6.1% of all bacteria isolated from CSF cultures, followed by *E. coli* (5.3%) and *Enterobacter* spp. (2.4%).

In our study more than 80% of gram-negative enteric bacteria were resistant to ampicillin. *Klebsiella* spp. resistance rates to aminoglycosides and cephalosporins were more than 50% and 57%, respectively. Resistance rate to aminoglycosides ranged from 60% to 100%, and also to cephalosporins from 42.2% to 94.7% in *P. aeruginosa* isolates (Table 2).

Among aminoglycosides only amikacin was quite effective against *E. coli,* with susceptibility rate of 82.4%; and the most effective cephalosporin was ceftizoxime with susceptibility rate of 61.5%. For *Enterobacter* spp. gentamycin and ceftriaxone were the most effective antibiotics with susceptibility rates of 75% and 60%, respectively. Susceptibility rate of this organism to chloramphenicol was 80%.

Frequency of *Haemophilus* spp. isolates was 5.8% (n=19). Resistance rates of this microorganism to ampicillin, chloramphenicol, ceftriaxone and ceftizoxime were 81.8%, 27.3%, 28.6% and 33.3%, respectively.

*N. meningitides* was the 10$^{th}$ pathogen isolated from CSF cultures in our study. Notably among 4 of 9 isolates tested for third-generation cephalosporin susceptibility, we found one resistant isolate to ceftriaxone and one resistant to ceftazidime; but all of them were susceptible to ceftizoxime. *Acinetobacter* spp. made up 4.6% of all isolates. Rates of resistance to aminoglycosides were more than 53% and all isolates were resistant to ceftriaxone, ceftazidime, and ceftizoxime.Enterococci made up 2.4% of all isolates. Resistance rates to ampicillin, gentamycin, and amikacin were 71.4%, 85.7%, and 57.1% respectively. Ampicillin resistant should be confirm by another laboratory method like micro broth dilution test. Although all of these isolates were sensitive to vancomycin, all of them were resistant to ceftriaxone and ceftazidime.

In our study vancomycin and ceftizoxime were the most effective antibiotics against Enterococci and *N. meningitides,* respectively.

| Bacteria | Antimicrobial agent | Total No. | Susceptibility (%) |
|---|---|---|---|
| Coagulase negative staphylococci | amikacin | 132 | 77.2 |
| | ampicillin | 132 | 27.2 |
| | cefalexin | 118 | 64.4 |
| | cefazolin | 113 | 61.9 |
| | ceftriaxone | 21 | 52.3 |
| | cephalotin | 132 | 66.6 |
| | chloramphenicol | 132 | 81 |
| | clindamycin | 113 | 63.7 |
| | cotrimoxazole | 132 | 43.9 |
| | erythromycin | 132 | 37.8 |
| | gentamycin | 132 | 62.8 |
| | oxacillin | 115 | 18.2 |
| | penicillin | 132 | 15.1 |
| | vancomycin | 123 | 87.8 |
| *S. aureus* | amikacin | 25 | 64.0 |
| | ampicillin | 25 | 24.0 |
| | cefalexin | 22 | 68.2 |
| | cefazolin | 21 | 66.7 |
| | ceftriaxone | 13 | 61.5 |
| | cephalotin | 25 | 68.0 |
| | chloramphenicol | 25 | 88.0 |
| | clindamycin | 22 | 77.3 |
| | cotrimoxazole | 25 | 72.0 |
| | erythromycin | 25 | 52.0 |
| | gentamycin | 25 | 48.0 |
| | oxacillin | 25 | 36.0 |
| | penicillin | 25 | 0.0 |
| | vancomycin | 23 | 87.0 |
| *Enterococci* spp. | amikacin | 7 | 42.9 |
| | ampicillin | 7 | 28.6 |
| | cefalexin | 5 | 40.0 |
| | cefazolin | 5 | 20.0 |
| | cefixime | 2 | 0.0 |
| | ceftazidime | 2 | 0.0 |
| | ceftizoxime | 2 | 50.0 |
| | ceftriaxone | 5 | 0.0 |
| | cephalotin | 7 | 28.6 |
| | chloramphenicol | 7 | 57.1 |
| | clindamycin | 5 | 40.0 |
| | cotrimoxazole | 7 | 28.6 |
| | erythromycin | 5 | 0.0 |
| | gentamycin | 7 | 14.3 |
| | kanamycin | 2 | 50.0 |
| | oxacillin | 6 | 0.0 |
| | penicillin | 4 | 50.0 |
| | tobramycin | 2 | 0.0 |
| | vancomycin | 5 | 100.0 |

**TABLE 2.** Frequency of occurrence of bacterial species or groups isolated from CSF cultures in Children's Medical Center

| Bacteria | Antimicrobial agent | Total No. | Susceptibility (%) |
|---|---|---|---|
| | amikacin | 15 | 46.7 |
| | ampicillin | 15 | 6.7 |
| | cefixime | 14 | 0.0 |
| | ceftazidime | 14 | 0.0 |
| | ceftizoxime | 14 | 0.0 |
| | ceftriaxone | 14 | 0.0 |
| *Acinetobacter* ssp. | cephalotin | 15 | 6.7 |
| | chloramphenicol | 15 | 20.0 |
| | cotrimoxazole | 15 | 13.3 |
| | erythromycin | 1 | 0.0 |
| | gentamycin | 15 | 26.7 |
| | kanamycin | 15 | 13.3 |
| | oxacillin | 1 | 0.0 |
| | tobramycin | 14 | 14.3 |
| | amikacin | 20 | 50.0 |
| | ampicillin | 20 | 0.0 |
| | cefixime | 14 | 28.6 |
| | ceftazidime | 14 | 28.6 |
| | ceftizoxime | 14 | 35.7 |
| | ceftriaxone | 14 | 42.9 |
| | cephalotin | 20 | 15.0 |
| | chloramphenicol | 20 | 60.0 |
| | cotrimoxazole | 20 | 60.0 |
| | gentamycin | 20 | 30.0 |
| *Klebsiella* spp. | kanamycin | 20 | 35.0 |
| | tobramycin | 16 | 37.5 |
| | amikacin | 11 | 72.7 |
| | ampicillin | 11 | 18.2 |
| | cefalexin | - | - |
| | cefazolin | - | - |
| | cefixime | 7 | 71.4 |
| | ceftazidime | 11 | 72.7 |
| | ceftizoxime | 9 | 66.7 |
| | ceftriaxone | 7 | 71.4 |
| | cephalotin | 11 | 27.3 |
| | amikacin | 11 | 72.7 |
| | ampicillin | 11 | 18.2 |
| | cefalexin | - | - |
| | cefazolin | - | - |
| | cefixime | 7 | 71.4 |
| | ceftazidime | 11 | 72.7 |
| | ceftizoxime | 9 | 66.7 |
| | ceftriaxone | 7 | 71.4 |
| *Haemophilus* spp. | cephalotin | 11 | 27.3 |
| | chloramphenicol | 11 | 72.7 |
| | clindamycin | - | - |
| | cotrimoxazole | 11 | 27.3 |
| | erythromycin | 6 | 100.0 |
| | gentamycin | 11 | 81.8 |
| | kanamycin | 11 | 9.1 |
| | penicillin | 8 | 37.5 |
| | tobramycin | 9 | 77.8 |
| | vancomycin | - | - |

**TABLE 2.** Frequency of occurrence of bacterial species or groups isolated from CSF cultures in Children's Medical Center

Of note, the seasonal distribution of positive CSF cultures showed a decreasing number in winter months. ❑

## DISCUSSION

Bacterial meningitis in Iran as other developing countries is still a major medical problem that takes many lives each year and in survivors have devastating consequences. In this 10 year investigation we clarified the microbiology properties of bacterial meningitis in one of the most important referral centers of our country.

In this study rate of CSF positive cultures was low; this may be because of pre-hospital use of antibiotics. In CMC Hospital we did not access to automate culture system like BACTEC. This system can significantly increase the sensitivity of culture for diagnosis of infection of sterile body fluids, especially in patients with previous antibiotic therapy.

In our study the most frequently causing infections of indwelling CNS prostheses is CONS. The second most frequent pathogen is *S. aureus*. CONS were reported to be 52.8% of pathogens of ventriculoperitoneal shunt infections in pediatric patients less than 8 years of age (5). In our hospital we have a surgical ward with 34 beds, including more than 10 beds for neurosurgical patients that most of them are hydrocephalous cases whom were inserted indwelling shunt. We think the high frequency of Staphylococci isolates may be related to these patients and also patients with myelomeningocel and head trauma.

The extremely high rate of oxacillin resistance (82%) found among CONS isolates is consistent with those reported from the SCOPE (80.4%) and ICARE (75%) and SENTRY (77.3%-76.9%) programs (6). Incidence of CONS with reduced vancomycin susceptibility is low, and in *S. aureus* is less common than in CONS or Enterococci (7). Compared with other studies, we also found higher rates of vancomycin resistant CONS (12.2%) and *S. aureus* (13%) (8-10). We did not confirm the vancomycin resistant staphylococci by MIC test. As disk diffusion method may misclassify intermediately resistant isolates as resistant, we may have overestimated these rates (11).

We found that 56.7% of *S. pneumoniae* isolates were resistant to penicillin. This rate is higher than reports from India (1.3%), Ethiopia

(17%), South Africa (43%), USA (50%) and Mediterranean area (Italy 10%, Greece 15%, Lebanon 50%, Turkey 36% and Egypt 50%) (12). The resistant rate to penicillin in our *S. pneumoniae* isolates is lower than reports from Spain (60%), Korea (79.7%) and Nigeria (67%) (13, 14). Although rate of chloramphenicol resistance in this study was lower than penicillin-resistant pneumococci (20% vs. 56.7%), it was higher than those reported by other countries (1).

In Asia, the reported incidence of invasive Hib disease is relatively lower than that in Europe and North America. Several factors, such as widespread use of antibiotics in infants and children, may have led to an underestimation of the true burden of Hib disease in this region (15). In our study rate of this organism is much lower than those reported by other Asian countries, such as India (17%), Bangladesh (30%), Saudi Arabia (28%) and United Arab Emirates (46%) before institution of routine Hib vaccination (15). It could be related to limited laboratory facilities and expertise. Hib is suspected to contribute to a large number of negative bacterial cultures, therefore this rate probably represents a minimal estimate of the true rate of Hib meningitis in this hospital and will require further studies (16).

Ampicillin resistance in Hib isolates was higher than the rates reported by other countries, such as Bangladesh (32.5%), United Arab Emirates (19%) and Japan (60.1%) (15).

Notably in one study in Egypt (17) that applied Kirby Bauer method as we did, resistant rate plus intermediate resistant rate (63%+16%) was 79% in Hib isolates. In our study the rate 81.8% was sum of resistant rate (72.72%) and intermediate resistant rate (9.09%). By comparing these results, again resistant rate to ampicillin in our study was higher. Unfortunately, we found high rates of third generation cephalosporin resistant among Hib isolate (28.6% to ceftriaxone, and 33.3% to ceftizoxime). Having searched through literature, we found only one study which reported the rate of 3% cefotaxime resistant among Hib isolates (18).

Rate of *N. meningitidis* isolates in this study was low, similar to Libya (0%) and Saudi Arabia (4%) (17). We found a high rate of penicillin resistance among our isolates (44.4%) but we did not confirm it by another laboratory methods like micro broth dilution test penicillin resistance in this microorganism has been documented worldwide, but the clinical significance of this is uncertain, and no case of treatment failure was reported (19).

In our study, similar to the previous report, antibiotic resistance among gram negative enteric bacteria was frequent (4). High resistance rates to ceftriaxone and ceftizoxime among these organisms are suggestive of presence of extended spectrum β-lactamases (ESBLs). Organisms that express ESBLs are frequently resis-

| Bacteria | Antimicrobial agent | Total No. | Susceptibility (%) |
|---|---|---|---|
| *E. coli* | amikacin | 17 | 82.4 |
| | ampicillin | 17 | 17.6 |
| | cefixime | 11 | 45.5 |
| | ceftazidime | 13 | 46.2 |
| | ceftizoxime | 13 | 61.5 |
| | ceftriaxone | 15 | 53.3 |
| | cephalotin | 17 | 41.2 |
| | chloramphenicol | 17 | 58.8 |
| | cotrimoxazole | 17 | 35.3 |
| | gentamycin | 17 | 41.2 |
| | kanamycin | 17 | 29.4 |
| | tobramycin | 15 | 60.0 |
| *P. aeruginosa* | amikacin | 20 | 40.0 |
| | ampicillin | 20 | 0.0 |
| | cefixime | 18 | 0.0 |
| | ceftazidime | 18 | 16.7 |
| | ceftizoxime | 19 | 5.3 |
| | ceftriaxone | 19 | 5.3 |
| | cephalotin | 20 | 0.0 |
| | chloramphenicol | 20 | 10.0 |
| | cotrimoxazole | 20 | 15.0 |
| | gentamycin | 20 | 30.0 |
| | kanamycin | 20 | 0.0 |
| | tobramycin | 20 | 25.0 |
| *S. pneumoniae* | amikacin | 28 | 28.6 |
| | ampicillin | 30 | 80.0 |
| | cefazolin | 23 | 91.3 |
| | ceftriaxone | - | - |
| | cephalotin | 30 | 83.3 |
| | cephalotin | 26 | 88.5 |
| | chloramphenicol | 30 | 80.0 |
| | chloramphenicol | 24 | 83.3 |
| | cotrimoxazole | 30 | 36.7 |
| | erythromycin | 30 | 80.0 |
| | gentamycin | 30 | 23.3 |
| | oxacillin | 30 | 13.3 |
| | penicillin | 30 | 43.3 |
| | vancomycin | 28 | 100.0 |

**TABLE 2.** Frequency of occurrence of bacterial species or groups isolated from CSF cultures in Children's Medical Center

| Bacteria | Antimicrobial agent | Total No. | Susceptibility (%) |
|---|---|---|---|
| *N. meningitidis* | amikacin | 9 | 88.9 |
| | ampicillin | 9 | 66.7 |
| | cefalexin | 5 | 80.0 |
| | cefazolin | 3 | 100.0 |
| | cefixime | 4 | 75.0 |
| | ceftazidime | 4 | 75.0 |
| | ceftizoxime | 4 | 100.0 |
| | ceftriaxone | 4 | 75.0 |
| | cephalotin | 9 | 66.7 |
| | chloramphenicol | 9 | 88.9 |
| | clindamycin | 4 | 75.0 |
| | cotrimoxazole | 9 | 33.3 |
| | erythromycin | 6 | 66.7 |
| | gentamycin | 9 | 88.9 |
| | kanamycin | 4 | 75.0 |
| | oxacillin | 5 | 40.0 |
| | penicillin | 9 | 55.6 |
| | tobramycin | 4 | 100.0 |
| | vancomycin | 7 | 71.4 |
| *Enterobacter* spp. | amikacin | 8 | 62.5 |
| | ampicillin | 8 | 12.5 |
| | cefixime | 4 | 50.0 |
| | ceftazidime | 4 | 50.0 |
| | ceftizoxime | 7 | 42.9 |
| | ceftriaxone | 5 | 60.0 |
| | cephalotin | 8 | 12.5 |
| | chloramphenicol | 8 | 37.5 |
| | cotrimoxazole | 8 | 37.5 |
| | gentamycin | 8 | 75.0 |
| | kanamycin | 8 | 62.5 |
| | tobramycin | 7 | 57.1 |

**TABLE 2.** Frequency of occurrence of bacterial species or groups isolated from CSF cultures in Children's Medical Center

tant to other antimicrobial agents and treatment of infections caused by these organisms is difficult (4). In this study we did not test the presence of ESBL enzymes genetically.

Amikacin seems to have greater *in vitro* activity against our *Acinetobacter* spp. isolates than gentamycin, as SENTRY program reported (20). This organism is a rare cause of community acquired bacterial meningitis in children (21).

Similar to the previous report from CMC Hospital, among blood culture isolates, all of Enterococci were susceptible to vancomycin; but they made up high rates of aminoglycoside resistance (4). Therefore, it seems that using vancomycin for the treatment of Enterococcal meningitis will be helpful in our hospital. ❑

## CONCLUSION

Staphylococci species and gram-negative enteric organisms were the most common pathogens isolated from CSF cultures in this study. Our report draws attention to the importance of identifying resistant bacteria during treatment of patients with bacterial meningitis and underscores the need for devising a national strategy to control the spread of resistance in Iran.

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