Etiology of Acute Bacterial Meningitis in Iran: a Systematic Review

Reza Ghotaslou[1], Fatemeh Yeganeh Sefidan[1], Behnaz Salahi-Eshlaqi[2], and Hamed Ebrahimzadeh Leylabadlo[2]

[1] *Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

[2] *Department of Microbiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*

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Abstract- Acute bacterial meningitis (ABM) is one of the most severe infectious diseases, causing neurologic sequel, and a case fatality rate of 20-30%. The aim of this paper was to summarize the main causes of ABM in Iran. We searched the data for relevant articles using meningitis, etiology, and Iran as search terms. We found 23 papers for inclusion in the review that focused specifically on the ABM, addressing etiology and acute meningitis. Finally, during the 23 years, a total of 18163 cases were recorded, and 1074 cases of which met the criteria for bacterial meningitis. The most common agent associated with bacterial meningitis was *S. pneumoniae*, followed by *H. influenzae*, Enterobacter spp., *N. meningitidis*, and group B streptococcus. The total incidence of ABM during 1991 to 2002 was higher than during 2003-2013. *S. pneumoniae* still remains a main cause of bacterial meningitis. For improved outcomes, studies are needed to further clarify the etiology of meningitis in Iran, explore simple, accurate, and practical diagnostic tools as PCR, and investigate the most appropriate specific and supportive interventions to manage and prevent meningitis as vaccination.

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Keywords: Acute bacterial meningitis; Etiology; Iran

Introduction

Acute bacterial meningitis (ABM) is defined as an acute inflammation of leptomeninges caused by bacteria (1). Acute bacterial meningitis is one of the most severe infectious diseases, causing neurologic sequel and accounting for an estimated 171,000 deaths worldwide for each year (2). Today, despite increased availability of strong antibiotics and sophisticated intensive care units, bacterial meningitis continues to be a significant cause of morbidity and mortality, and ABM has a case fatality rate of 20-30% (3). Unfortunately, mortality and morbidity of meningitis and total cost of meningitis management annually did not clarify in Iran. In the United States, meningitis accounts for about 72,000 hospitalizations and up to $1.2 billion in hospital costs annually (4).

The four most common etiologic agents of ABM are *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae, Neisseria meningitidis, and Streptococcus agalactiae* which account for 90% of reported cases of ABM in the world (2-3,5-6).

In Iran, studies on the epidemiology of ABM often have mainly focused on single causative organism and specific geographic areas, while a well nationwide surveillance system was not established. According to the significant morbidity and mortality associated with ABM in Iran and throughout the world, exact information is necessary regarding the important etiological agents to initiate appropriate empirical management. Additionally, accurate determination of the etiology of bacterial meningitis and estimating cost of the disease may be essential in guiding vaccination policies.

This study is important as it provides information on meningitis causing pathogens and also justifies the importance of vaccines as a strategy for improving population health. The aim of this study was to find out the pathogens responsible for bacterial meningitis in Iran.

Materials and Methods

We searched the database for related articles using meningitis, etiology, and Iran as search terms. The full text of each of the selected papers was studied. MEDLINE, EMBASE, and local database were searched

Corresponding Author: R. Ghotaslou
Department of Microbiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
Tel: +98 41 3364661, Fax: +98 41 3364661, E-mail address: rzgottaslo@yahoo.com

from 1991 to 2013. For articles published in Persian and English, if identical data were presented, the English language article was used. Results were limited to human studies. All titles and abstracts were read; relevant articles were identified and full texts obtained, and also references were also manually searched for related titles.

The case meaning of meningitis was evidence of either (i) bacterial isolation in cerebrospinal fluid, or in blood and elevated cerebrospinal fluid WBC count, together with characteristic signs and symptoms of meningitis as recognized by a clinician (ii) detection of bacterial DNA in CSF with characteristic signs and symptoms of meningitis as recognized by a clinician.

Endnote (version X, Thomson, Inc., Philadelphia, U.S.A.) bibliographic software was used to make an electronic library of citations identified in the database searches and duplicate records were deleted. Three reviewers trained to achieve the title/abstract screening and thereafter full-text selection were assigned.

Results

Studies on meningitis caused by bacteria, published between 1991 and 2013 were identified. Scientific articles published in English and Persian languages were sought through searching PubMed (United States), Magiran (Iranian Literature Service System), SID (Iranian Literature Service System), Google scholar (United States), and Ovid online (United States) databases. Standardized medical subject heading (MeSH) terms: Meningitis, Etiology, and free word: Iran, were established for searching. In this investigate, during the 23 years, a total of 18163 cases were recorded, 1074 (5.9%) of which met the criteria for bacterial meningitis (Table 1).

Table 1. Etiology of acute bacterial meningitis in Iran

Location (reference)	Year	Method	Patients (Meningitis)	Microorganisms (N, %)
Ahvaz (7)	1998-1999	Culture	204 (30, %14.7)	*S. pneumoniae (11, %36.7),* Enterobacter spp. *(8, %26.7), N. meningitidis (3, %10), S. aureus (3, %10), S. marcescens (1, %3.33), K. pneumoniae (1, %3.33), P. aeruginosa (1, %3.33), E. coli (1, %3.33),* Haemophilus spp.*(1, %3.33)*
Mashhad (8)	2004-2005	Culture	230 (9, 3.91%)	*H. influenzae (4, %44.45), S.pneumoneae (3, %33.33), N. meningitidis (1, %11.11),* Citrobacter spp.*(1, %11.11)*
Tehran (9)	2004-2005	Culture and PCR	203 (39, %19.21)	*S. epidermidis (10, %25.64), S.pneumoneae (6, %15.38), N. meningitidis (5, %12.82), H. influenzae (5, %12.82),* Klebsiella spp. *(2, %5.12),* Acintobacter spp. *(2, %5.12), C. diphtheriae (2, %5.12), S. aureus (1, %2.56), S. saprophyticus (1, %2.56),* Pseudomonas spp. *(2, %5.12), E. coli (1, %2.56),* Streptococci spp. *(2, %5.12),*
Shiraz (10)	2000-2002	Culture	1062 (67, %6.3)	*H. influenzae (24, %35.82), S.pneumoneae (23, %34.32), N.* meningitidis *(17, %25.37),* Salmonella spp. *(1, %1.49),* Pseudomonas spp. *(1, %1.49),* Citrobacter spp. *(1, %1.49)*
Tabriz (6)	2009-2011	Culture and PCR	277 (11, %3.97)	*H. influenzae(2, %18.18), S.pneumoneae (5,%45.45), N. meningitidis (3,%27.27), P. aeruginosa (1, %9.09)*
Hamadan (11)	2000-2003	Culture	582 (46, %7.9)	*S.pneumoneae (11, %23.91), S. aureus (6, %13.04), E. coli (5, %10.86), N. meningitidis (3, %6.52), P. aeruginosa (3, %6.52),* Streptococci *spp. (4, %8.69), S. epidermidis (4, %8.69),* Citrobacter spp. *(2, %4.34),* Klebsiella spp. *(2, %2.17),* Enterococcus *spp. (1, %2.17),* Proteus spp. *(1, %2.17), H. influenzae (2, %4.35),* Unknown *(2, %4.34)*
Tehran (12)	1999-2000	Culture	526 (14, %2.66)	*H. influenzae(4,%28.57) , N. meningitidis (3, %21.43), S. pneumoniae (3, %21.43),* Enterococcus spp. *(3, %21.43),* Unknown *(1, %7.14)*
Kerman (13)	2004-2006	Culture	126 (12, %9.52)	*H. influenzae (6, %50) , S.pneumoneae (3, %25), N. meningitidis (3, %25)*
Tehran (14)	1997-1998	Culture	130 (80, %61.54)	*H. influenzae (35, %43.75), S.pneumoneae (30,%37.5) , N. meningitidis (11, %13.75), S. agalactiae (3, %3.75), L. monocytogenes(1, %1.25)*
Tehran (15)	2003-2009	Culture and PCR	1800 (121, %6.72)	*S.pneumoneae (21, %17.35), H. Influenzae (19, %15.7), P. aeruginosa (13, %10.74)***,** coagulase-negative staphylococci *(11, %9.09), S. agalactiae (11, %9.09), E. coli (9, %7.4), S. aureus (9, %7.4),* other pathogens *(28, %23)*
Tabriz (16)	2012-2013	PCR	106 (3, %2.83)	*N. meningitidis (1, %0.9), H. influenzae (2, %1.9)*
Qazvin (17)	2008	Culture	100 (36, %36)	*S.pneumoniae (8, %22.22), H. influenzae (6, %16.66), N. meningitidis (2, %5.55 S.pneumoniae (2, %5.55),* Enterobacter spp. *(2, %5.55), S. aureus (10, %27.77), S. epidermidis (2, %5.55),* Pseudomonas spp. *(2, %5.55), Acinetobacter spp.(2, %5.55)*

Continuance Table 1.

Location (reference)	Year	Method	Patients (Meningitis)	Microorganisms (N, %)
Tehran (18)	2003-2004	Culture and PCR	300 (32, %10.66)	coagulase-negative staphylococci *(8,%25), H. influenzae (5, %%15.62), S. aureus (3, %9.37), S.pneumoniae (3, %9.37), N. meningitidis (2, %6.25), E. coli (2, %6.25),* Acinetobacter spp. *(2, %6.25),* Pseudomonas spp. *(2, %6.25),* Enterococcus spp.*(1, %3.12), S. saprophyticus (1, %3.12), S. viridans (1, %3.12), Streptococci spp. (1, %3.12),* klebsiella spp. *(1, %3.12)*
Tehran (19)	1999-2010	Culture	11269 (329, %2.91)	coagulase-negative staphylococci *(132, %40.12), S. pneumoniae (30, %9.11), S. aureus (25, %7.59),* Klebsiella spp. *(20, %6.07), P. aeruginosa (20, %6.07),* Haemophilus spp. *(19, %5.8), E. coli (17, %5.16),* Acinetobacter spp. *(15, %4.55), S. pneumoniae (15, %4.55), N. meningitidis (9, %273),* Enterobacter spp. *(8, %2.43), Streptococci (10, %2.83),* Enterococcus *(7, %2.12),* Micrococcus *(2, %0.6)*
Ahvaz (20)	2004-2008	Culture	312 (42, %13.46)	*N. meningitidis (20, %47.61), S. pneumoniae (16, %38.09), H. influenzae (4, %9.52),* Klebsiella spp.*(2, %4.76)*
Tehran (21)	1994-2004	Culture	123 (85, %69.1)	*S. pneumoniae (40, %47.05), H. influenzae (22, %25.9), N. meningitidis (13, %15.29), E. coli (4, %4.7),* Klebsiella *(3, %3.52),* Enterobacter spp.*(1, %1.17),* β hemolytic Streptococci *(1, %1.17), S. viridans (1, %1.17)*
Tehran (22)	1995-2000	Culture	294 (15, %5.1)	β hemolytic Streptococci *(5,% 33.33), E. coli (3, %20),* Klebsiella spp.*(2, %13.33), S.pneumoniae (1, %1.65), S. viridans (1, %1.65),* Moraxella spp.*(1, %1.65), H. influenzae (1, %1.65),* Unknown *(1, %1.65)*
Brojen (23)	1991-1992	Culture	262 (19, %7.25)	*H. influenzae (7, %36.84), S.pneumoniae (5, %26.32), N. meningitidis (2, %10.53), Salmonella paratyphi A (2, %10.53), E. coli (1, %5.26),* unknown *(2, %10.53)*
Tehran (24)	2004-2005	Culture	100 (28, %28)	*S. pneumoniae (10, %35.71), N. meningitidis (5, %17.85), H. influenzae (2, %7.1),* coagulase-negative staphylococci *(4, %14.28), E. coli (4, %14.28), P. aeruginosa (1, %3.57), N. sica (1, %3.57), M.* catarrhalis *(1, %3.57)*
Tehran(25)	1998-1999	Culture	57 (49, %85.96)	*S.pneumoneae (40, %81.63) , N. meningitidis (3, %6.12), S. aureus (1, %2.04), H. influenzae (1, %2.04),* Listeria spp.*(3, %6.12), E. coli (1, %2.04)*
Gorgan (26)	2000-2001	Culture	100 (7, %7)	*S.pneumoniae (3, %42.85), H. influenzae (1, %14.28),* Listeria spp. *(1, %14.28),* unknown *(2, %28.57)*
Total			18163 (1074, %5.9)	

After exploratory the titles, we selected 41 ones as relevant to the topic and 23 studies were included. All titles and abstracts were read; relevant papers were identified and full texts obtained, and references were also manually searched for relevant titles. Articles were excluded if they addressed other types of meningitis (e.g. tubercular or virus), or if they did not address interventions for ABM but were found by the search strategy for the reason that the word 'meningitis' was mentioned for other reasons as chemical or radiation. All the included papers were selected after searching the literature in various databases. The most common agent associated with bacterial meningitis was *S. pneumoniae* (22.38%), followed by *H. influenza* (12.42%), Enterobacter spp. (12.24%), *N. meningitidis* (10.5%), and group *B Streptococcus* (10.04%) (Figure 1). Gram-positive bacteria were isolated from 44 percent of culture positive cases, and Gram-negative in 56 percent, so ABM due to Gram-negative bacteria was higher than Gram-positive bacteria in Iran. The trend of meningitis in Iran presented at Table 2. The total incidence of acute bacterial meningitis during 1991 to 2002 was higher than during 2003-2013 .

Five of these studies were identified by PCR. The rate of bacterial detection by PCR was more than culture method (Figure 2). The rates of meningitis were significantly higher between Northern populations. In the years 1991-2013, the northern regions of Iran, for instance, recorded 895 cases of meningitis and, 179 cases of meningitis (one-fifth) have been reported in the south parts of Iran. The rate of meningitis varied significantly according to Iranian states. Although, the rates of meningitis due to *H. influenzae* did not differ according to area.

Table 2. Incidence of the most common acute bacterial meningitis in Iran from 1991 to 2013 by culture

Pathogen	1991-2002 year (%)	2003-2013 year (%)
N.meningitidis	%8.95	%11.15
S. agalactiae	%17.24	%4.84
H. influenzae	%16.45	%8.4
S. pneumoniae	%26.55	%18.21

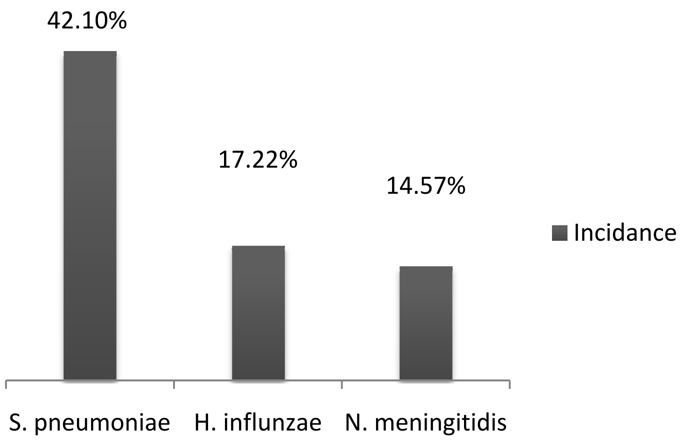

Figure 1. Distribution of three common causes of acute bacterial meningitis in Iran during 2003-2013 by PCR

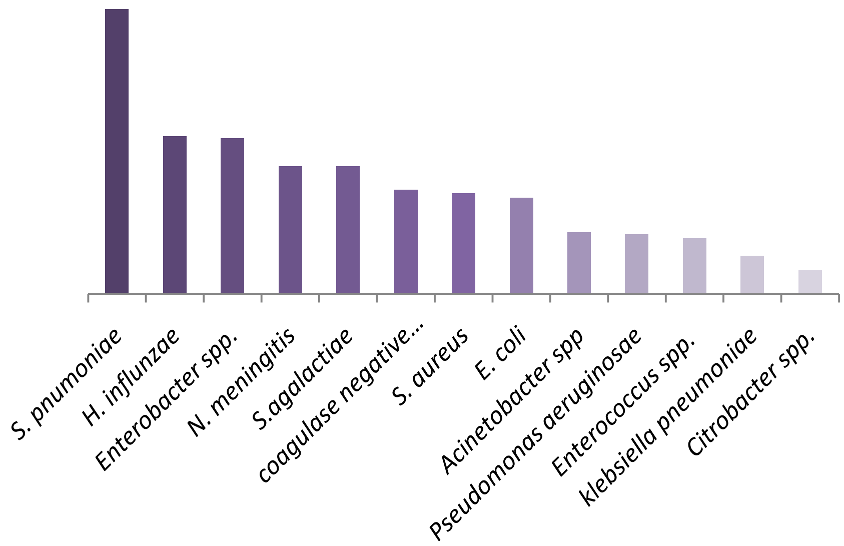

Figure 2. Total etiology of acute bacterial meningitis in Iran

Discussion

Until recently, bacterial meningitis was a seriously feared infectious disease, many of its victims were children and as many as 25% of survivors had a sequel. There were once 10,000 to 20,000 cases each year in the United States, but there have been major efforts to recover treatment and prevent bacterial meningitis (27).

Although advances in neuro-imaging and critical care, the case mortality rate of ABM remains around 20–30%. Effective preventive and treatment strategies are required to reduce mortality and morbidity (1).

This broad systematic review of available English and Persian literature was conducted between 1991 and 2013 and aimed to identify the meningitis load in Iran. In this study, the total prevalence of confirmed meningitis was 5.9%. The current result is similar to other surveillance (based on cultures) of meningitis in other parts of Asia (1,2). The prevalence appears low compared to some reports from Greece and Ghana (3,28). However, we suppose the incidence could have been higher if methods using PCR were applied in testing the samples. Another cause that could contribute to the low meningitis incidence is the possible use of antibiotics before hospital admission, a common practice in several developing countries as Iran.

Distribution of meningitis is varied in Iran; cases of meningitis are mostly reported in the northern part of the country and probably have been attributed to the high humidity in this area.

Almost all microbes that are pathogenic to human beings have a potential to cause meningitis, but a relatively small number of pathogens account for most cases of ABM, although the reasons for this association remain partly understood (29). Studies have demonstrated that four pathogens (*S. pneumoniae, H. influenzae type* b, *N. meningitidis*, and group *B* streptococcus) caused at least 80 percent of all cases of bacterial meningitis (1,6,30). The present study showed these pathogens caused more than 69% ABM in this area.

In Iran, pathogens of ABM due to Enterobacter spp., coagulase-negative staphylococcus, *S. aureus* and *E. coli* is relatively high, and undoubtedly show the relative importance of these pathogens. This finding highlights that treatment and management programs have been designed to address these bacteria too. The microorganism spectrum responsible for meningitis in developing countries is different. Reasons for this difference may comprise population differences in colonization, genetic differences in immune response and possibly geographic differences in laboratory techniques for pathogen isolation and reporting (31). In this research, the most prevalent bacteria were *S. pneumoniae.* In an article based on surveillance data, in the United States, from 1998 to 2007, the most common cause of bacterial meningitis among adults was *S. pneumoniae*. Among young adults, *N. meningitidis* is nearly as common as *S. pneumoniae* (32). Meningitis caused by pneumococcal has the highest case mortality and neurological disability rates compared to those caused by *N. meningitidis* or *H. influenzae* type b (33). Additionally, pneumococcal disease is the leading cause of vaccine-preventable deaths universal accounting for, 800,000 deaths annually among children, 5 years of age (30). Serogroups A–C of *N. meningitidis* account for most cases of meningococcal meningitis throughout the world. Although serogroup A dominates across Africa, serogroups B, and C are responsible for most cases in industrialized countries, so large epidemics of serogroup A occur in the sub-Saharan 'meningitis belt' that extends from Ethiopia in the east to Senegal in the west (1,9,10).

Hib (*H. influenzae* type b) is one of the 'huge three' causes of ABM in kids under five years of age. It is estimated to cause at least three million cases of serious disease and hundreds of deaths annually in the world (1). We found 190 cases of Hib over the 23 years period. However, infections due to Hib are one of the most important causes of child meningitis in Iran. Other developing countries such as Turkey have also reported same Hib meningitis prevalence (34). According to the prevalence of Hib in Iran (12.42%) and the cost of the vaccine, it seems vaccination of children is necessary.

Gram-negative enteric bacilli usually cause meningitis after head trauma or neurosurgery and are very strange causes of community-acquired meningitis (35). However, in Iran, Enterobacteriaceae was a common etiology agent of ABM. The contribution of other bacteria pathogens to meningitis has not been widely reported in various developing countries (28).

The present study identified, Gram negative species as *H. influenzae*, *N. meningitidis*, Enterobacteriaceae, non-fermentative Gram-negative bacilli contributing to 56% of all bacterial isolates among children and adults. Some studies in developing countries have similarly reported these observations (36-38). However, reports from developed countries indicate a predominance of Gram positive bacteria (39). The reasons for the low or no identification of *Listeria monocytogenes* as Gram-positive bacteria in Iran could be due to less attention given to the laboratory diagnosis of this pathogen.

Over a period of 23 years, the rate of meningitis due to the 4 pathogens surveyed in this study has decreased really: from 17.32 % during 1991-2002 to 12.56% during 2003-2013 (Table 2). Although slight declines in meningitis incidence were noted during the 2003-2013, we believe that major advances in survival and decrease of long-term morbidity did not happen over the past several decades in Iran. For meningitis, culture positive blood or CSF specimens were not considered sufficiently sensitive to provide relatively exact estimates of disease load. However, for meningitis, the amount we obtained from microbiologic studies may not be sensitive enough to establish the true amount of meningitis and is more likely an underestimate of the exact rate. We did not determine whether there has been a decline in the use of lumbar punctures for suspected meningitis, which could reduce the sensitivity of our observation method.

However, certain limitations and problems should be noted. There are usual difficulties encountered in conducting studies assessing disease in developing countries such as Iran. Iranian surveillance system did not record cases of clinical meningitis without positive cultures of cerebrospinal fluid or blood and may have underestimated the real burden caused by these infections. Finally, the hospital-based studies determining etiologies of meningitis which were included in this analysis were mostly conducted in academia tertiary hospitals, where patients were likely more severe and thus may not be representative of the spectrum of diseases in the population. We did not assess disease caused by pathogenic agents identified in small towns, although non- academic cities may be an important source of meningitis. When rural patients do not arrive at the health care centers, disease rates could be underestimated. As a component of community-acquired bacterial meningitis, however, such meningitis is not likely to represent a major burden of disease. The overuse of antibiotics in the early stage of disease could lower the culture positivity rate. In developing countries, where antibiotics are readily available without prescriptions, high previous antibiotic usage among patients presenting in the health care center is reported (6,30). Ideal and perfect diagnosis of the meningitis etiology is complicated by the overlap in clinical management, inadequate diagnostic sources, and antibiotic use. The selection of empiric antibiotics should take into consideration local epidemiology if known, early detection of agents, antibiotic resistance patterns and accessibility within resource constraints. Empirical antibiotic therapy should be effective against common causative pathogens (31). Early and focused treatment of established disease is vital and further investigates into optimum empirical antibiotic therapy is needed.

Current data probably can be used to estimate the burden of meningitis and thus set main concern for vaccine development, because it indicated 23 years trend of meningitis in this region. In this context, an important point is childhood Hib meningitis. In some developed countries, widespread use of Hib conjugate vaccines has severely reduced the threat of bacterial meningitis in children from one month to five years of age. Some countries may consider introducing the vaccines to prevent meningococcal disease in their national immunization programs, depending on public health load and cost-effectiveness (1). The development and usage of effective vaccines for the meningococcus, the pneumococcus, and the Hib raises the wish of making bacterial meningitis largely a problem of the past (40). In this review, the most recent search on meningitis was carried out between 1991 to 2013, showed that the most common bacterial agent is S. *pneumoniae*, *H. influenzae* and, Enterobacter spp., *N. meningitidis*, there is evidence to show that polysaccharide polyvalant vaccines may be protective. Prevention programs for group B streptococcal infections and for listeriosis could further reduce the disease load, even without the introduction of new vaccines. We require continued evaluation of the epidemiology of the disease to identify suitable targets for immunization or other preventive strategies. However, surveillance linked to laboratory report of isolates, as this study, is critical to the diagnosis of the most common agents of ABM and the development of appropriate vaccines.

Significant differences in etiology have been identified and, S. *pneumoniae* still remains a main cause of bacterial meningitis. These findings highlight that the ultimate advantage of laboratory methods improvements in empirical therapy. In Iran, according to a high mortality rate of ABM, using newer microbiologic techniques such as PCR may be useful. This study emphasizes the need for wide hospital based surveillance of meningitis causing pathogens in Iran. This review supports the use of vaccines to prevent pneumococcal, meningococcal meningitis, and Hib to prevent fatal meningitis.

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