ARTICLE INFO

Article history:
Received 1 May 2019
Revision 15 May 2019
Accepted 19 May 2019
Available online 27 May 2019

Keywords:
Streptococcus pneumoniae
Meningitis
Systematic review
Meta-analysis
Iran

OBJECTIVE: To estimate the frequency of pneumococcal meningitis among patients with bacterial meningitis in Iran.

METHODS: PubMed, Embase, Web of Science and Scientific Information Database (www.sid.ir) were searched from 2000 to 2016 to identify studies on the frequency or prevalence of pneumococcal meningitis in Iran. Stata 14.0 (StataCorp, College Station, Texas, USA) was used to analyze the data.

RESULTS: Of the 131 records identified from the databases, 21 studies fulfilled the eligibility criteria. The analyses showed that 25.0% (95% CI: 19.0-32.0; I²=71%) of the confirmed bacterial meningitis (including children and adults) cases were caused by pneumococcus.

CONCLUSIONS: The large fraction of meningitis cases caused by pneumococcus demonstrates that pneumococcal meningitis is a major public health problem in Iran, and the introduction of pneumococcal vaccines merits further attention from health authorities.

1. Introduction

Streptococcus pneumoniae (S. pneumoniae) is an important pathogen causing serious illnesses such as sepsis, meningitis, and pneumonia[1-3]. This Gram-positive bacterium is one of the most common pathogens of bacterial meningitis in children younger than 2 years worldwide[4]. Pneumococcus causes 10% to 60% of meningitis cases among patients in different age groups, but the incidence is higher in adults patients than in children[5,6]. Other pathogens [i.e. group B streptococcus, Escherichia coli, Listeria monocytogenes, Haemophilus influenzae type b (Hib), and Neisseria meningitides] account for most cases of bacterial meningitis in children younger than 2 years; however, the causes of this age pattern are not fully understood[7-9]. In recent years, despite advances in infection treatment strategies, the overall frequency of death associated with bacterial meningitis was between 19% to 37%[10,11]. Antibiotic-resistance and treatment failure is a major concern, as 15%-30% of S. pneumoniae strains have become multidrug resistance[12-14]. Despite antibiotic treatment, some of the patients showed significant side effects including seizures, cognitive impairment, hearing loss and other deficiencies[15].

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How to cite this article: Tabatabaei SR, Shamshiri AR, Nasiri MJ, Weinberger DM, Dadashi M, Karimi A. Pneumococcal meningitis in Iran: a systematic review and meta-analysis. J Acute Dis 2019; 8(3): 99-105.
The epidemiology of bacterial meningitis has been changed by several preventive measures introduced since the early 1990s, such as the introduction of the Hib conjugate vaccines and the pneumococcal conjugate vaccines for infants[16]. Although Hib and pneumococcal vaccines have been available for more than a decade in developed countries, they have only recently been available to children in low-income countries[17]. Iran does not yet use pneumococcal vaccinations routinely. Recommendations have been provided for the targeted use of the 23-valent pneumococcal polysaccharide vaccine and PCV13 among people with underlying medical conditions that increase their risk for contracting pneumococcal disease or experiencing complications of pneumococcal disease if infected. In USA, the incidence of pneumococcal meningitis in children aged <2 years has declined from 7.7% to 2.6% following the introduction of PCV18. Since the epidemiology of pneumococcus varies with time and geographic area, the local incidence of pneumococcal meningitis is useful for health care decision-makers. Therefore, this study was designed to analyze the national data of pneumococcal meningitis in Iran using a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[19].

2. Materials and methods

2.1. Information sources and search strategy

A literature search of the bibliographic database, including PubMed, Embase, Web of Science and Scientific Information Database (www.sid.ir), was performed from 2000 to 2016. The search strategies were based on the following search terms: (Streptococcus pneumoniae OR S. pneumonia OR pneumococcus) AND (meningitis) AND (Iran). This combination of terms was used for searching in article title, abstract or keywords. Reference lists of selected articles (backward citation) and the relevant articles found during the initial search were searched and forward citation tracking was carried out, to identify further relevant studies. The records found through database searching were merged and the duplicates and overlap of patient population and date of the study were removed using EndNote X7 (Thomson Reuters, New York, NY, USA). The records were initially screened by title and abstract to exclude those not related to the current study. Then the full-text of potentially eligible records were retrieved and examined.

2.2. Inclusion and exclusion criteria

Studies were included if they met all of the following criteria: (1) Studies evaluating bacterial meningitis; (2) Reporting standard laboratory-confirmed bacterial meningitis (cerebrospinal fluid culture) and (3) Presenting the frequency of S. pneumoniae.

Our exclusion criteria were: (1) Data on bacterial meningitis and S. pneumoniae were not available; (2) Nonstandard methods were used for diagnosis of bacterial meningitis (e.g. clinical presentation of patients), and (3) Data were restricted to viral meningitis.

2.3. Data extraction

The following items were extracted from each article: first author, publication date, study year, place of study, study sample size, patients’ age, diagnostic methods, the number and the prevalence or frequency of patients with S. pneumoniae. Any disagreements or discrepancies were resolved in consensus with a third investigator.

2.4. Quality assessment of studies

We assessed the study quality by using a checklist provided by the Joanna Briggs Institute[20].

2.5. Statistical analysis

For each study, the overall frequency of S. pneumoniae, and the corresponding standard errors and 95% confidence intervals (95%CI) were calculated. Analyses were performed using random-effects weights. In order to estimate a pooled effect, we utilized the “metaprop” command. We used “fit cimethod” (score) or Freeman-Tukey transformation procedures for collecting binomial data. The between-study heterogeneity was assessed by using Cochran’s Q, and the I-squared statistic and Galbraith graph. To check for publication bias, we used Egger’s and Begg’s tests (P<0.05 was considered indicative of statistically significant publication bias). All the analyses were conducted using Stata 14.0 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Study selection

A total of 131 articles were found in the initial search, of which 87 records were screened by title and abstract, 31 full-text articles were reviewed, and 21 studies were included in the final analysis (Figure 1).

3.2. Study characteristics

Table 1 summarizes the main characteristics of the included studies[21-41]. In all included studies, bacterial meningitis was confirmed by cerebrospinal fluid culture as the gold standard method. Standard microbiological procedures were used to assign the isolated bacteria to species. All of the included observational studies reported the frequency of S. pneumoniae among patients with bacterial meningitis. A total of 1 022 patients with bacterial meningitis were included in the meta-analysis. In all included studies, hospital-acquired pneumonia was not diagnosed in patients.
Search in electronic data bases \((n=131)\)
PubMed: 32
Embase: 47
WEB OF SCIENCE: 37
Iranian databases: 15

Excluded duplicates \((n=44)\)

Title and abstract screening \((n=87)\)

Excluded irrelevant \((n=60)\)

Full text assessed for eligibility \((n=27)\)

Excluded irrelevant \((n=10)\)
Reason for exclusion:
Overlap of patient population and date of study \((n=3)\)
No data on sample size \((n=7)\)

Included studies through backward/forward citation check \((n=4)\)

Studies included in quality assessment and meta-analysis \((n=21)\)

Figure 1. Flow diagram of review process and study selection.

Table 1. Characteristics of the included studies investigating frequency of \(S.\ pneumoniae\) among Iranian patients with confirmed bacterial meningitis.

| First author | Publication date | Study duration | City           | Suspected cases | Abnormal lumbar puncture | Confirmed bacterial meningitis | Total No. of S. pneumoniae included |
|--------------|------------------|----------------|----------------|------------------|--------------------------|--------------------------------|-----------------------------------|
| Abdi [21]    | 2005             | 1991-2000      | Tehran         | NA               | NA                       | 131                            | 40                                | No                                |
| Zamani [22]  | 2005             | 1994-1999      | Tehran         | 294              | NA                       | 15                             | 1                                 | Yes                               |
| Ehsanipour [23]| 2004            | 1997-2002      | Tehran         | 245              | 9                        | 4                              | 2                                 | No                                |
| Aletayeb [24]| 2010             | 1997-2007      | Ahvaz          | NA               | NA                       | 31                             | 0                                 | Yes                               |
| Ghaemi [25]  | 2001             | 1999-2000      | Gorgan         | 100              | NA                       | 7                              | 3                                 | No                                |
| Tavasoli [26]| 2014             | 2000-2010      | Tehran         | 422              | 19                       | 7                              | 3                                 | No                                |
| Haghiashiteian [27]| 2008        | 2001-2007      | Tehran         | 1 800            | NA                       | 121                            | 21                                | Yes                               |
| Qurbanalizadegan [28]| 2010      | 2002-2006      | Tehran         | NA               | 130                      | 36                             | 13                                | Yes                               |
| Kanani [29]  | 2005             | 2002-2005      | Sanandaj       | 161              | NA                       | 14                             | 3                                 | No                                |
| Bahador [30] | 2009             | 2003-2005      | Kerman         | 126              | 12                       | 3                              | No                                |
| Alavi [31]   | 2010             | 2003-2007      | Ahvaz          | 569              | 312                      | 42                             | 16                                | No                                |
| Abdinia [32] | 2014             | 2003-2013      | Tabriz         | 7 112            | NA                       | 107                            | 37                                | Yes                               |
| Ataee [33]   | 2010             | 2005-2009      | Tehran         | NA               | 270                      | 171                            | 61                                | No                                |
| Heydarian [34]| 2014            | 2005-2012      | Mashhad        | 453              | 80                       | 5                              | 1                                 | No                                |
| Bagheri [35] | 2015             | 2006-2012      | Sari           | NA               | 137                      | 14                             | 7                                 | No                                |
| Ghadiri [36] | 2014             | 2007-2009      | Kermandshah    | NA               | NA                       | 11                             | 4                                 | No                                |
| Rezae [37]   | 2013             | 2008-2009      | Tehran         | NA               | 55                       | 11                             | 0                                 | Yes                               |
| Mahmoudi [38]| 2013             | 2009-2011      | Tehran         | NA               | 31                       | 20                             | 7                                 | No                                |
| Yousefi [39] | 2014             | 2009-2013      | Hamadan        | 582              | 582                      | 146                            | 35                                | Yes                               |
| Attarpour [40]| 2014            | 2011-2012      | Tehran         | 182              | 114                      | 40                             | 40                                | Yes                               |
| Amin [41]    | 2016             | 2014-2015      | Ahvaz          | 196              | NA                       | 3                              | 0                                 | No                                |
3.3. Risk of bias assessment

Based on the quality assessment of the included studies, all studies were identified as having a low risk of bias (quality assessment score >7).

3.4. Frequency of S. pneumoniae

The pooled frequency of *S. pneumoniae* among patients with confirmed bacterial meningitis was 25.0% (95% CI: 19.0-32.0; I²=71%) (Figure 2). While it was not possible to do a formal analysis of age-stratified data due to the sample size, there did appear to be variation in the frequency of pneumococcus as a cause of bacterial meningitis by age group. Among <1-month-old children, just 1 case of bacterial meningitis out of 46 (2.2%) was due to pneumococcus. In contrast, among those age >14 years, 68/197 (34.5%) cases were pneumococcal. Pneumococcus was of intermediate importance as a cause of bacterial meningitis in children age 1-24 months (4/38; 10.5%) and 5-14 years (3/33, 9.1%).

3.5. Frequency of other bacterial meningitis

The pooled frequency of *Haemophilus influenzae, Neisseria meningitidis, Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* among patients with bacterial meningitis was: 17.2% (95% CI: 11.4-26.0), 17.1% (95% CI: 10.0-29.4), 9.4% (95% CI: 7.2-12.2), 8.0% (95% CI: 4.0-19.0) and 6.4% (95% CI: 4.2-9.8), respectively.

3.6. Patient’s outcome and clinical presentation

The mortality rate among patients with bacterial meningitis was 20.4% (95% CI: 12.1-34.3, n/N: 66/318). The most clinical presentation of patients with bacterial meningitis was nausea (89.2%, 95% CI: 12.1-34.3, n/N: 66/318), lethargy (45.4%, 95% CI: 27.5-74.8, n/N: 51/122) and seizures (23.2%, 95% CI: 10.2-53.0, n/N: 74/334), respectively.

3.7. Heterogeneity and bias

As it is presented in the Galbraith plot in Figure 3, one study was seen outside the range between -2 and 2 and considered as the major source of heterogeneity. As per Begg's (*P*=0.1) and Egger's (*P*=0.7), there was no evidence of publication bias.

![Figure 2. Forest plots of studies, investigating the frequency of *S. pneumoniae* in patients with bacterial meningitis.](image1)

![Figure 3. Galbraith plot of the frequency of *S. pneumoniae* in patients with bacterial meningitis. (The study outside the range between -2 and 2 was seen as the outlier and the major source of heterogeneity).](image2)
4. Discussion

Bacterial meningitis continues to be a serious cause of death in all age groups worldwide[42,43]. In Iran, despite the improvement of infection control and therapeutic strategies, bacterial meningitis still remains a major public health problem. Based on previous studies in Iran[44,45], pneumococcus is the most common bacterium isolated from patients with meningitis. In the current systematic review and meta-analysis, we show the results of 16 years of pneumococcal meningitis surveillance in Iran. Our analyses showed that the prevalence of bacterial meningitis caused by S. pneumoniae was 25.0%.

Several studies have reported on the prevalence of S. pneumoniae around the world. For example, according to studies from Pakistan, France, Kuwait and USA, the prevalence of S. pneumoniae among meningitis cases was 38.5%, 29%, 40%, and 33%, respectively[46-49]. The different prevalence of S. pneumoniae in bacterial meningitis in Iran may be due to lack of an efficient vaccination program to control and prevent pneumococcal meningitis. Due to the epidemiology of pneumococcus, children and adults are the main target populations for pneumococcal vaccines[50].

Currently, there are two types of PCV available on the global market, synflorix (PCV10) and prevnar 13 (PCV13), which is linked to carrier proteins[51,52]. PCV10 and 13 protect against ten (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and thirteen (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) serotypes of pneumococcus, respectively[53-55]. The PCV serotypes are among the main and common causes of pneumococcal meningitis infection in children[51,56]. The remarkable reduction of the incidence rate of pneumococcal meningitis among children after PCV vaccination in developed countries has been demonstrated previously, which testified the effectiveness of these vaccines[37,38]. Different pneumococcal vaccines have been used in different countries, with the choice depending on which serotypes dominate in a particular location and the cost of the vaccines[57,58]. The most common serotypes isolated from pneumococcal meningitis in our country were 18, 14, 19A, 6A, 7F, 4, 3, 9V, 23F and 5[45,56,59], which are covered by the 13-valent PCV[60,61]; hence, the use of the PCV13 for general coverage of pneumococcal meningitis infections are recommended.

The frequency of antibiotic-resistant pneumococcal strains is increasing worldwide, with some variations between different countries[62,63]. Also, based on the results of previous studies, resistance to macrolides has been observed among pneumococcal strains isolated from children with pneumococcal meningitis[64]. Moreover, antibiotic-resistance is more common among vaccine serotypes[51]. Hence, the use of PCVs can be the best option for both preventions of pneumococcal meningitis and for reducing the frequency of antibiotic resistance in the short term.

Neurologic abnormalities occur with increased frequency in those who have had bacterial meningitis. Thus, the causes of the death resulted from pneumococcal meningitis may be due to the neurological complications[65]. Based on the study conducted by Kastenbauer et al, more than half of the patients had meningitis-associated intracranial complications (e.g., seizures, arterial cerebrovascular complications, brain swelling, and hydrocephalus) [66]. Furthermore, they reported that seizures, cerebrovascular complications, brain swelling, and hydrocephalus were associated with adverse outcome[66]. Østergaard et al. has also indicated that most of the patients with bacterial meningitis had neurological sequelae (i.e., neurological deficits)[65]. Likewise, in the current study, several patients developed neurological abnormalities during the clinical course of the disease (i.e., seizures developed in 74 of 334 episodes). Seizures as one of the most important neurological complications, the incidence (23%) of it was very similar to that of previous studies on pneumococcal meningitis[66,67].

There were some limitations to this study which should be discussed. First, as a systematic review, the existence of potential publication bias should be considered. Second, it cannot fully represent the prevalence of S. pneumoniae in bacterial meningitis in Iran because the extent of S. pneumoniae has not yet been examined in many regions of the country. Third, being a prevalence survey, this study is unable to determine risk factors for S. pneumoniae colonization or infection. Forth, the proportion of pneumococcus with reduced penicillin susceptibility could not be analyzed because of the limited information obtained from the studied articles.

In conclusion, the high percentage of bacterial meningitis in Iran caused by pneumococcus merits further attention from health authorities, physicians, and microbiologists. The regular surveillance of meningitis infection and the deployment of an effective vaccine may help to reduce the burden of meningitis in Iran.

Conflict of interest statement

The authors report no conflict of interest.

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