Prevalence of etiological agents of acute bacterial meningitis in adult population at the Quillota's San Martin Hospital between years 2012-2018.

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Introduction: Acute bacterial meningitis (ABM) is defined as the inflammation of leptomeninges due to the presence of pyogenic bacteria. Epidemiology is variable and multifactorial. In spite of advances in medicine, ABM's mortality has remained stable, hence the need to study the causative microorganisms in order to guide prevention and treatment strategies. Objectives: To determine the prevalence of the etiological agents of ABM confirmed in adults in a medium complexity hospital located in Quillota, Chile, between 2012 and 2018, to establish the rate of resistance of these to antibiotics. Determine the profile of the patients and establish the relationship between profile, etiological agent identified and outcome. Methods: A sample of 38 cases with ABM was evaluated, the prevalence of the pathogens involved was established and a statistical analysis was carried out considering the risk factors of patients, their days of in-hospital stay and their condition at hospital discharge. Results: We analyzed 38 cases, 15 without isolated pathogens, 13 of Streptococcus pneumoniae, 4 of Haemophilus spp., 3 of Neisseria meningitidis, 2 of Staphylococcus spp. and we obtained one case of Mycobacterium tuberculosis. In the group without isolated pathogens, a better prognosis was observed, lower blood CRP values and higher glucose on spinal fluid values. 6 deaths per ABM were recorded. Conclusion: The prevalence of etiological agents was similar to that described in the literature, with pneumococcus as the most frequent microorganism, no cases of Listeria monocytogenes were reported. Probably in the group in which no agent was isolated, cases of viral meningitis were included.

Key words: Meningitis, etiology, bacterial agents, prognosis, survival, epidemiology

Introduction

Acute Bacterial Meningitis (ABM) corresponds to the inflammation of the leptomeninges due to the presence of pyogenic bacteria. It constitutes a medical emergency where early diagnosis and treatment can considerably reduce morbimortality (1)(2).

The epidemiology is variable and depends on multiple factors such as age, the agent involved, and the presence of certain risk factors (3). Over the last 30 years, the epidemiology of ABM has changed substantially in terms of the pathogens that causes it, as well as the affected age groups. These changes are in large part due to the implementation of conjugate vaccines against Haemophilus influenzae type b, Streptococcus pneumoniae (pneumococcus), and Neisseria meningitidis (meningococcus). In the United States of America (USA) and Europe, the rate of incidence varies between 0.1 - 0.7 for every 100,000 people. Currently in adults, the

The author does not have any conflict of interests to disclose - There was no financing of any kind.

Accepted:
Received:

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leading cause is pneumococcus, followed in frequency by meningococcus and then Listeria monocytogenes (4), commonly found in patients with certain risk factors such as being over the age of 50, immunodeficient, suffering from alcoholism, cancer, and undergoing immunosuppressive therapy (5). Most ABM cases are contracted through contact with other people, whereas other bacteria such as Staphylococcus spp. and gram-negative bacilli occur in a nosocomial context or secondary to trauma (6)

Antibiotic resistance tends to be low. In the study from Diederik Van Beek et. al (2004), an immediate resistance to penicillin was recorded in 0.36% of pneumococcal strains and 1.56% of meningococcal strains. These results are consistent with another study from the same author from 2002 (7)(8). However, in the USA, France, Spain, and other countries, the rate of resistance reported in pneumococcus is greater (24% on average) (9).

Clinical symptoms of ABM are going to depend on multiple factors such as the patient's age and the microorganism involved (2). The classic triad involves fever, generalized headaches associated with stiffness in the neck, and unconsciousness. A study conducted in the Netherlands demonstrated this triad in only 41% of the cases. Other associated symptoms can be focal neurological deficits, seizures, or paralysis of cranial nerves. There can also be skin events like a petechial rash, a characteristic sign of bacteremia due to meningococcus, but it can also be present in pneumococcal meningitis (1).

Regularly included in the diagnostic study of ABM are blood cultures, neuroimaging, and a lumbar puncture with CSF analysis, which is the primary part, and it includes a cytochemical study, Gram staining, culture, and sometimes other more specific tests, such as the molecular biology methods. It is important to note that, if there is a well-founded suspicion, the diagnostic study must not delay the start of empirical antibiotic treatment (regularly with third-generation cephalosporins), because it has been demonstrated that this delay produces an increase in morbimortality (1)(10)(11).

According to a Cochrane review from 2015, the use of corticosteroids would be recommended as a coadjuvant therapy, given that a significant reduction was seen in potential neurological after-effects (1)(12)(13) (14).

Despite progress in intensive medicine and a wide array of antibiotics available, a study conducted in the USA, where data were analyzed on bacterial meningitis in adults between 1998 and 2007, demonstrated that the mortality of ABM has remained relatively stable over most recent decades (15), and thus the need emerges to study the microorganisms causing this to be able to tailor prevention strategies and treatment(4). This is even more important in our country as local studies on this subject matter were not found. Thus, in this study, the main objective is to determine the prevalence of the etiological agents of ABM confirmed in adults in the HSMQ between 2012 and 2018, and, in turn, establish the rate of resistance of these to regularly used antibiotics. Another aim is to determine the profile of patients included in the sample according to sex, age, and risk factors, and establish the relationship between this profile, the etiological agent identified, and the outcome of each patient.

Methodology

Prior to conducting the research study, approval was requested from the Bioethics Committee of the School of Medicine of the Universidad Andrés Bello of Viña del Mar, and authorization was requested from HSMQ management.

A retrospective, observational cohort study was conducted based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (16). The following was requested from the Diagnosis-Related Groups (DRG) of the HSMQ Management Control Department: the record number, number of in-hospital days, the condition of discharge (alive, deceased), and destination of the discharge (home or transfer) of the patients aged 16 or older who were hospitalized between 2012 and 2018. Next, the records of said patients were requested through the Medical Sub-Management of HSMQ and reviewed.

Inclusion criteria were: patients aged 16 or older who have been hospitalized at HSMQ between 2012 and 2018, and who have been

diagnosed with ABM through Gram staining or CSF analysis. In the event that the pathogen had not been isolated in the studies mentioned, ABM was considered for the cases that met two or more of the following criteria: white blood cells in the CSF over 100 per mm3, the glucose in spinal fluid level in CSF is under 40 mg/dl or less than 40% of glycemia, an increase in the rate of proteins over 45 mg/dL, and the clinical diagnosis of ABM in discharge summary (18).
Excluded from the study were cases with a diagnosis of ABM associated with healthcare, viral meningitis, a history of recent neurosurgery (fewer than 6 months ago), and patients without a confirmatory CSF study.
Once the patients were selected, hospitalization data such were gathered: age, sex, comorbidities, pregnancy at the time of diagnosis, CSF study, pathogen detected through Gram staining or culture, associated antibiogram, treatment received, C-reactive protein, and a leukocyte count in the peripheral blood upon admission. Using this information along with the information from the DRG, a database was created, and a retrospective analysis conducted considering the follow-up time as the time passed since the admission of the patient into the HSMQ Adult Emergency Unit up until hospital discharge.
The following were used for the descriptive analysis of quantitative variables: mean, median, standard deviation, and inter-quartile range; for qualitative variables: absolute and relative frequencies. On the other hand, Fisher's Exact Test was used in the inferential analysis in search of associations among qualitative variables, the Mann-Whitney Test for comparing means, and the Kaplan-Meier Survival Curve for assessing outcome variables. The SPSS software v15 for Windows 7 was used.

Results

General Characterization: 55 clinical records were requested, out of which 51 were received, because 4 of these were not available in the HSMQ file. The records were reviewed, exclusion and inclusion criteria were applied, and a total of 17 were excluded: 9 did not have an ABM diagnosis (record error or initial diagnostic hypothesis that was ruled out), 2 were empirical treatment with spinal tap that was not performed or abandoned and 2 due to recent neurosurgery. Due to this, 38 cases were studied, and these were used to create a database on which the statistical analysis was conducted.
Characterization of patient profiles: half of the cases (19) were female patients. The average age was 47 years old (SD 18.17). In terms of the risk factors studied, 1 case was observed due to infection from the Human Immunodeficiency Virus (HIV), 3 from alcoholism, 10 from Diabetes Mellitus, and 10 older adults over the age of 60. No pregnant patient was found

Table 1. Characterization of patients with ABM confirmed in adults in HSMQ between 2012 and 2018

	N	Mean	Standard deviation	95% Confidence Interval
Age	38	46.74	18.17	40.76 - 52.71
RBG in CSF	14	4420.43	7431.67	129.50 - 8711.35
Increase in protein in the blood	24	314.27	287.05	193.06 - 435.49
Glucose in spinal fluid	35	30.55	31.97	19.57 - 41.53
PCR in blood	38	145.71	122.30	105.51 - 185.915
RGB in blood	38	18410.3	9800.43	15189.2 - 21631.85
In-hospital days	38	15.53	8.58	12.70 - 18.35

Prevalence of etiological agents: in 15 cases, a pathogen was not isolated in CSF; in the rest of the cases, 13 ABM due to pneumococcus were found, 4 due to Haemophilus spp, 3 due to meningococcus, 2 due to Staphylococcus spp and 1 due to Mycobacterium tuberculosis. No cases of *Listeria monocytogenes* were found. (Table 2).

Prevalence of antibiotics used: regarding the antibiotics used, it was observed that third-generation cephalosporins were used in 34 cases, while 12 cases were associated with Ampicillin, and 2 with Vancomycin. Other antibiotics for managing ABM were used in 4 patients. On the other hand, 3 cases of resistance to third-generation cephalosporins were found, 2 were Staphylococcus spp., and 1 case of pneumococcus (Table 2).

Characterization of the Prognosis: the Kaplan-Meier survival curves were applied according to age older than or younger than 60 in terms of in-hospital days, where a statistically significant relationship was obtained ($p<0.00$), which showed that patients over the age of 60 had one stay. By contrast, patients under 60 showed longer hospitalization times, with deaths over 28 days of hospitalization (Figure 1). Moreover, Kaplan-Meier survival curves were performed according to isolated agents and in-hospital days. The log rank test was applied, and it showed that the days of stay according to isolated and non-isolated agents were not statistically significant ($p=0.278$) (Figure 2).

The data were also analyzed regarding the glucose values in CSF and the presence of isolated and non-isolated Agents. The Mann-Whitney test was applied, where a statistically significant relationship was obtained ($p=0.001$) showing a glucose value that was lower, with a dispersion range that was lower in the group of isolated agents versus the non-isolated group (Figure 3).

In terms of the blood CSF values between the groups of cases with isolated bacterial agents and non-isolated in CSF, the Mann-Whitney test was applied, and a statistically significant relationship was obtained ($p=0.008$), where the lower values appeared in patients with non-isolated agents (Figure 4).

Table 2. Prevalence of the etiological agents of ABM confirmed in adults in HSMQ between 2012 and 2018, and the antibiotics used for their treatment.

ABM etiological agents	Frequency	Percentage	95% Confidence Interval
Non-isolated pathogen	**15**	**39.5**	**25.60 - 55.30**
Streptococcus pneumoniae	**13**	**34.2**	**21.21 - 50.10**
Haemophilus spp	**4**	**10.5**	**4.17 - 24.13**
Neisseria meningitidis	**3**	**7.9**	**2.72 - 20.80**
Staphylococcus spp	**2**	**5.3**	**1.46 - 17.29**
Mycobacterium tuberculosis	**1**	**2.6**	**0.47 - 13.49**
Antibiotic used			
Third-generation cephalosporins	**20**	**52.6**	
Third-generation cephalosporins associated with Ampicillin	**12**	**31.5**	
Third-generation cephalosporins associated with Vancomycin	**2**	**5.2**	
Other	**4**	**10.5**	
Total	**38**	**100**	

Characterization of the condition for hospital discharge: of the 38 cases, 32 were discharged alive to their homes and 6 died in the context of their ABM; of these, 2 were due to pneumococcus, 2 due to Staphylococcus aureus, 1 due to Mycobacterium tuberculosis, and, lastly, 1 case without an isolated microorganism.

Figure 1. Kaplan Meier survival curves according to an age of 60 or older

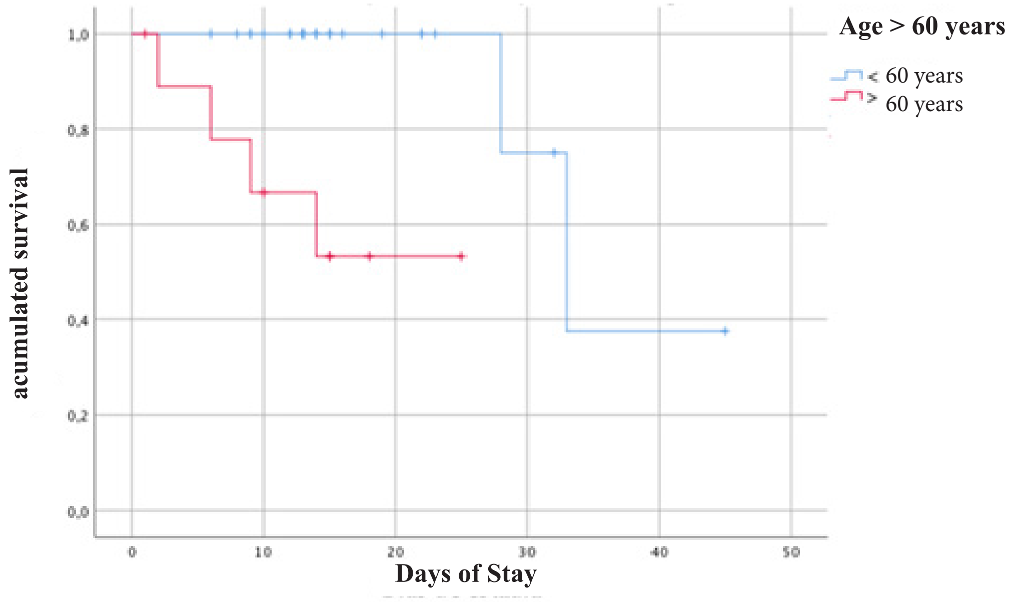


Figure 2. Kaplan Meier survival curves according to isolated agents

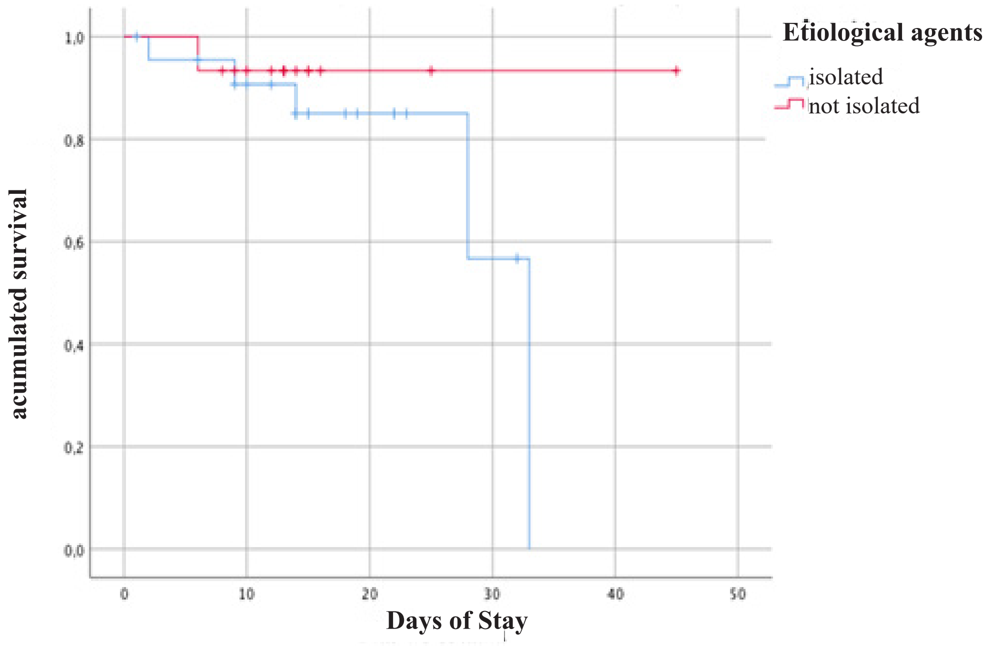


Figure 3. Box-and-whisker diagram of glucose in spinal fluid by isolated and non-isolated agent

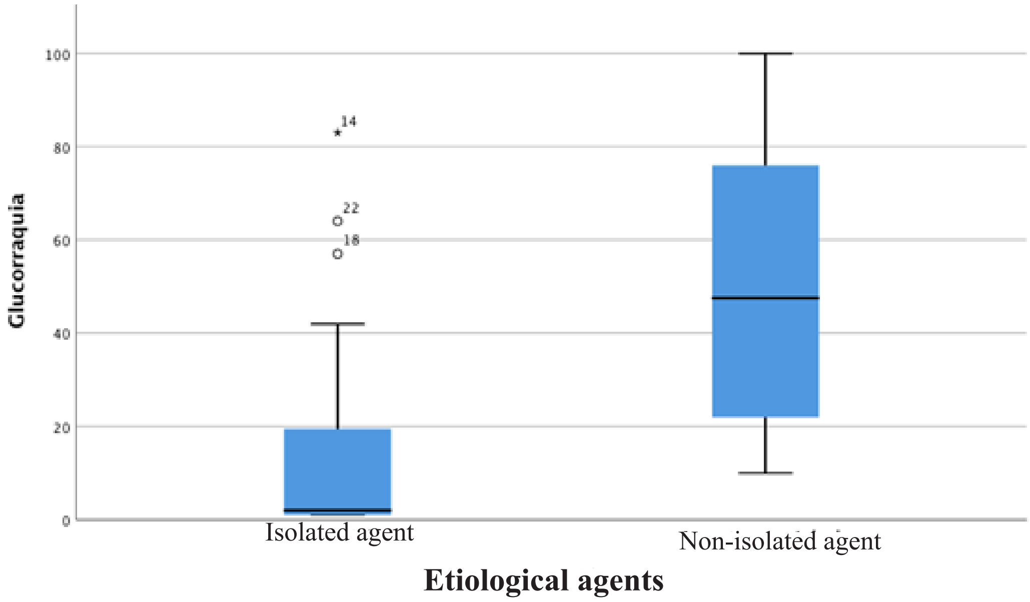
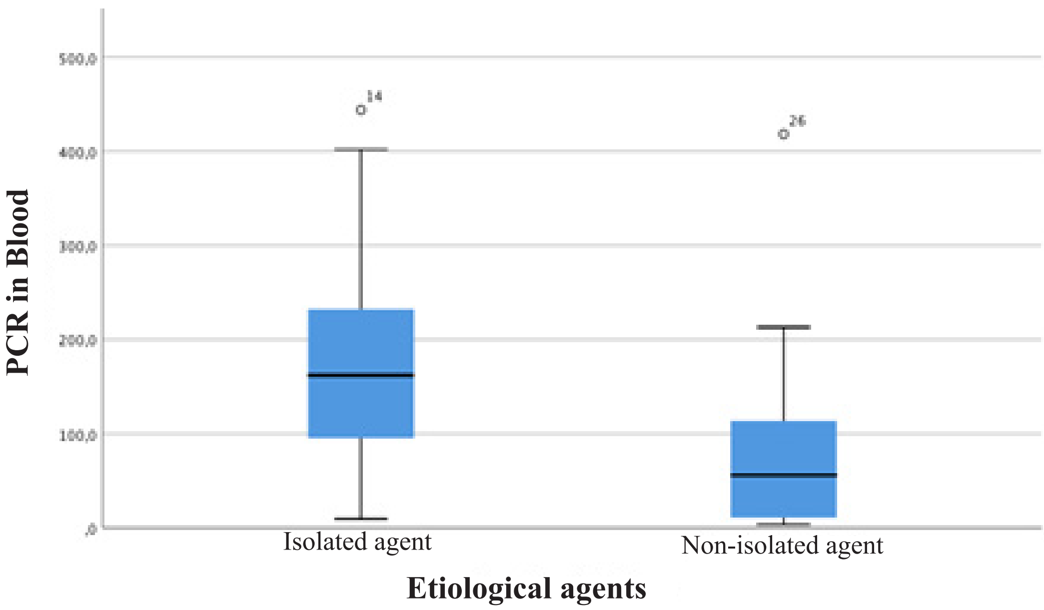


Figure 4: Diagram of boxes and whiskers of PCR in blood by isolated agents and not CSF isolates



Discussion

It was possible to include a total of 38 cases of ABM confirmed in adults at the HSMQ between 2012 and 2018. Given the reduced sample size, non-parametric tests were used, but the information obtained is relevant to best understand the local reality.

In terms of the prevalence of bacterial agents, the pneumococcus was the most frequent microorganism (13 cases), which coincides with the international series reviewed. On the other hand, 4 cases of Haemophilus spp., 3 of meningococcus, and 2 of Staphylococcus spp. were found, which also coincides with current knowledge. Cases of Listeria monocytogenes were not recorded, despite the fact that patients with risk factors for developing this type of ABM were included, and which holds around the 3rd place in frequency in the reviewed series. This absence can be attributed to the reduced sample size, to the lack of specific cultures (not included in the order of exams of the HSMQ prior to 2015), and to the fact that the Gram staining and culture of the CSF have a sensitivity of around 70-85% (17).

The greatest group was formed by cases without isolated bacterial agents. Although there could be different causes explaining this phenomenon, such as the use of prior treatments and the lack of sensitivity of the lab exams and cultures, when conducting different analyses and comparing the other variables, it was demonstrated that the values of the rate of glucose in the group where the pathogen was not isolated were significantly higher (p=0.001), the PCR values in the blood were significantly lower (p=0.008), and they also showed lower mortality (p=0.00). Thus, it could be proposed that a significant percentage of these cases would correspond to viral meningitis. Considering that treatment for viral meningitis is symptomatic, over-treatment with antibiotics and corticosteroids should not entail a large problem; furthermore, when there is well-founded suspicion of ABM, it should be treated as such. However, it is worth taking a hard look at the inclusion criteria, the lack of precision in the diagnostic process, and the need to incorporate new laboratory strategies that single out the diagnosis of ABM with greater certainty, or that identify the viral agents in the most sensitive and specific way.

The antibiotics used were primarily third-generation cephalosporins (34 cases). In 12 cases, Ampicillin was associated, and only 2 with Vancomycin, which is in line with the national and international recommendations for the treatment of ABM.

The sample was separated into two groups to study the age ranges: over and under the age of 60. It was observed that the patients from the older group presented greater mortality (p=0.00) and earlier (before 20 days of hospitalization). On the one hand, this may be somewhat expected, and on the other, it would make it possible to explain why the hospital stays for younger patients are longer.

The general prognosis was favorable. Only 6 of the 38 cases (15.8%) died due to ABM. This can partially be explained by the possibility that there might have been viral meningitis in the group in which the pathogen was not isolated. Only one death was recorded in this group. On the other hand, given the reduced sample size, representative statistics on mortality due to ABM could not be formulated.

One of the constraints of this study is that the potential after-effects of ABM were not considered, which is something that could be analyzed in a new research study with a greater sample size.

Conclusion

The prevalence of the etiological agents of ABM was similar to what was described in the literature, featuring S. pneumoniae as the most frequent microorganism and the absence of L. monocytogenes. On the other hand, the microorganism was not isolated in a large number of cases, and after performing the analysis, it was deduced that some of these could correspond to viral meningitis.

This research study could be used as a point of comparison and foundation for future local studies where a larger number of cases could be included to better represent the reality of ABM at the regional and national levels, so as to be able to establish new protocols and management strategies with the aim of reducing morbimortality

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