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Etiological profile of bacterial meningitis in children

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Abstract

Objective:to determine the etiologic profile and analyze some epidemiological aspects of children with bacterial meningitis admitted to a public teaching hospital.

Methods: a prospective study was conducted on children with clinical and laboratory diagnosis of bacterial meningitis, admitted to Hospital das Clínicas da Universidade Federal de Uberlândia, from January 1987 to January 2001. Patients with meningitis associated with trauma, intracranial devices or malformations of the neural tube, and tuberculosis, were not included in the study.

Results: from a total of 415 children with bacterial meningitis, the etiologic agent was detected in 315 (75.9%): *Haemophilus influenzae* b in 54.2%, meningococci in 20.6%, pneumococci in 18.1% and other agents, in 6.9%. Previous antibiotic treatment, observed in 47.2% of the cases, led to a significant decrease in positive blood cultures (from 50.8% to 38.7%) and in cerebrospinal fluid cultures (from 71.7% to 57.6%). Among children younger than 48 months *Haemophilus influenzae* b was predominant, particularly when compared to meningococci. The overall mortality was 10.1%, with a significant difference between the rates of pneumococcal (17.5%) and meningococcal meningitis (4.6%).

Conclusions: children affected by *Haemophilus influenzae* b and by pneumococci were younger than those with meningitis caused by meningococci. The blood and/or cerebrospinal fluid culture remains an important laboratory tool for etiologic diagnosis, despite the negative impact caused by antibiotic previous treatment. The agents most commonly detected were *Haemophilus influenzae* b, meningococci and pneumococci. Bacterial meningitis continues to present an important mortality among children, particularly when caused by pneumococci.

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Introduction

Bacterial meningitis (BM) is responsible for high levels of both morbidity and mortality in children, despite recent advances in diagnostic methods, antimicrobial and support treatments, monitoring and prophylactic techniques.[1,2] In the pre-antibiotic era, lethality was approximately 100%

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and the rare survivors developed serious neurological sequelae; nowadays between 5% and 40% of affected children still die as a result of BM, depending on the age of the patient and on the pathogen involved, among other factors.[3,4] Neurological sequelae occur in between 5% and 30% of survivors and are primarily the result of delays in establishing the diagnosis and initiating effective antimicrobial treatment.[3]

Definitive diagnosis is based upon cerebrospinal fluid examination, the typical results of which include pleocytosis, mainly of neutrophils (normally corresponding to 80% of the number of cells), high concentration of proteins and low concentration of glucose in the cerebrospinal fluid, a positive Gram test (from 25% to more than 90% of cases) and a positive culture (from 70% to 90% of cases not previously treated). Samples should preferably be obtained before initiating antimicrobial treatment, although the use of antibiotics should not become a negative stimulus to the search for etiology. The latex agglutination test, offers variable sensitivity (from 50% to 100%, with lower values for serogroup B meningococcus), and high specificity, for these reasons a negative result does not rule out BM diagnosis, but a positive result does confirm it.[3-6]

The most complete populational data on BM come from developed countries, obtained through nation-wide epidemiological surveillance studies. In underdeveloped and developing countries epidemiological knowledge is scarce, generally with intense underreporting and the extrapolation of figures obtained in small, restricted surveys to other parts of the country. In addition to regional variations in the etiological profile and rates of occurrence of BM, there is also variation over time in any given geographical area which makes the periodic updating of local epidemiological data necessary. Multiple factors contribute to the discrepancies between data obtained in different communities, at different times. These factors include the different degrees of suspicion of infection, the different levels of community medical service availability, the indiscriminate use of antibiotics previous to definitive diagnosis and hospitalization, the difficulty of obtaining cerebrospinal fluid for cultures, the high cost of etiological diagnostic methods (immunological or microbiological) and underreporting.[7]

Studies performed in different parts of the world indicate that three types of bacteria are responsible for more than 90% of BM cases outside the neonatal period: *Haemophilus influenzae* b (Hib), *Neisseria meningitidis* (meningococcus) and *Streptococcus pneumoniae* (pneumococcus). The relative importance of each of them varies according to geographical location and the endemic profile at the time studied,[4,5] and also, more recently, according to the percentage of children less than five years old vaccinated against Hib infection.[7-13]

Prognosis in cases of bacterial meningitis appears to improve with earlier diagnosis and the implementation of antimicrobial treatment and appropriate supportive measures.[3] Taking into consideration that initial antibiotic therapy is generally empirical with respect to etiology and antimicrobial sensitivity, knowledge about the epidemiological data of each community is fudamental.[3-5]

This study was undertaken with the primary objective of acquiring some more knowledge about the etiologic profile of bacterial meningitis in children in the region of Uberlândia, state of Minas Gerais (MG), Brazil.

Patients and Methods

Data were analyzed from the medical charts of all children with BM between 29 days and 13 years old, who were admitted to the Hospital de Clínicas da Universidade Federal de Uberlândia (HCUFU), between January 1st 1987 to January 31st 2001.

Uberlândia is located in the southwestern portion of the state of Minas Gerais, in the region known as the Região do Triângulo Mineiro, at an average altitude of 860 meters. The characteristic features of its climate are a rainy summer and a dry winter. According to the IBGE (Brazilian Institute of Geography and Statistics) census performed in 1996, the city has a total of 460,000 inhabitants, of whom 3.2% were up to four years old and 19.9%, between five and 14 years old.[14] For the provision of medical care to this population the city has a large municipal primary care network supported by hospital admission units.[15] The HCUFU is a public university hospital, part of the Unified Health System (SUS), and has a maximum capacity of 461 beds, 105 of which are reserved for the admission of children. As this is a regional reference center, the majority of these beds are occupied by patients with complaints which require complex handling, classified as level II or III.

The laboratory tests were performed by the Laboratory of Clinical Analysis of the HCUFU, using their habitual methodology and techniques. The media used for bacterial cultures were those traditionally employed to isolate the most common agents of BM. Positive CSF culture or blood test results were counted only once per patient, irrespective of the number of positive results.

The inclusion criteria were:

1. CSF positive for bacteria, and/or a latex agglutination test that was positive for bacteria in the cerebrospinal fluid, in a patient with compatible CSF test results and clinical status, or a blood culture which tested positive for bacteria in a patient with compatible CSF test results and clinical status; or
2. Pleocytosis, predominantly of neutrophils, associated with positive bacterioscopy for the CSF and/or a nonspecific clinical and laboratory status compatible with bacterial etiology, in partially treated patients.

Children were excluded from the analysis if they presented one of the following: meningitis confirmed by CSF examination or congenital defect of the neural tube, meningitis following head trauma, tuberculous meningitis

and lymphocytic meningitis, associated with the absence of positive results for bacteria in the CSF and/or a positive latex agglutination test for bacteria in the CSF.

The project was approved by the local Ethics and Research Committee. For the statistical analysis of the results, both parametric and nonparametric tests were employed, using SPSS (Statistical Package for Social Analysis) 8.0 for Windows. The null hypothesis rejection level was set at 5% ($p < 0.05$). For the contingency table analysis, the chi-square test was used (χ^2).

Results

During the period of 14 years and one month between January 1st 1987 and January 31st 2001, 415 patients with BM were identified, according to the inclusion criteria. The majority (59%) were male and the ages in months oscillated between one and 161 with a mean average of 26.8 months and a median of 13. The etiologic agent was identified in 315 patients (75.9%), with a definitive diagnosis in 289 (69.3%) and presumptive diagnosis, by means of bacterioscopy, in 26 (6.6%) patients. Blood cultures and/or CSF cultures were positive in 258 cases (62.2% out of 415), as shown in Table 1. The most commonly identified etiologic agents were Hib (171 occasions), meningococcus (65) and pneumococcus (in 57 cases).

There were statistically significant differences between etiology and age range as illustrated in Table 2. There was a predominance of children younger than 58 months affected with Hib, comparatively to pneumococcus and meningococcus, especially concerning Hib versus meningococcus ($p = 0.0001$). The etiology between Hib and pneumococcus ($p = 0.0001$) and between pneumococcus and meningococcus ($p = 0.0014$) were also statistically significant. The values for the mean and median ages of patients affected by Hib were 16.0 months and 12 months; for those affected by pneumococcus they were 23.9 months and 6 months and for patients affected by meningococcus they were 47.2 months and 36 months, respectively.

Previous use of antimicrobials was considered positive when present within 24 hours, and at least for 24 hours prior to diagnosis and before implementation of BM treatment. It was possible to detect previous antimicrobial use in 196 patients (47.2% of 415), whose effect on identification of the agent in blood and CSF cultures can be observed in Tables 3 and 4, respectively. The blood culture, carried out in 351 patients, was positive in 136 (38.7%), and the CSF culture, performed in 397 cases, was positive in 229 (57.6%). Excluding children who had already undergone treatment, these figures rise to 50.8% (92 positive cultures on 181 occasions) and 71.7% (147 out of 205), respectively.

Of 415 patients, 42 (10.1%) died, and it was only possible to establish a statistically significant relationship between the occurrence of death and etiology when comparing pneumococcus BM cases with those caused by meningococcus ($p = 0.043$) (Table 5).

Discussion

In this study, it was possible to detect a predominance of male patients (59%) amongst children with BM, which is consistent with data found in extant literature.[5,16-19] The predominance of male patients is more evident in surveys of sepsis and BM during the neonatal period, particularly when caused by Gram negative bacilli in comparison with Gram positive cocci. This fact suggests the participation of a genetic basis, linked to chromosome X , in the susceptibility to the disease; nevertheless other factors are also important as this predominance is greatly diminished or disappears after the neonatal period[16] and, of the three most common agents of BM, only Hib appears to predominate in males.[13,20,21]

Table 1 - Distribution of patients hospitalized with BM according to the positivity of the method used for etiologic diagnosis

Positive diagnostic method	n. of patients	%
Only culture	49	11.81
Only bacterioscopy	26	06.26
Only latex agglutination	16	03.85
Culture and latex agglutination	23	05.54
Culture and bacterioscopy	69	16.63
Bacterioscopy and latex agglutination	15	03.61
Culture and bacterioscopy and latex agglutination	117	28.20
No detection	100	24.10
Total	415	100.00

Table 2 - Distribution of patients hospitalized with BM according to age (months) and etiology

Class in months	Etiology *			Total †
	Hib	Sp	Nm	
1 –| 3	9	17	6	32
3 –| 48	159	31	33	223
48 –| 161	3	9	26	38
Total	171	57	65	293

Pearson's $\chi^{2,}$ four degrees of freedom = 92.799 (p = 0.0001).
* Hib = *Haemophilus influenzae b*; Sp = *Streptococcus pneumoniae*; Nm = *Neisseria meningitidis*.
† 100 patients without etiology and 22 patients with other etiologies were excluded.

The ages of the children in this series varied from 1 to 161 months, with a mean of 26.8 and a median of 13 while the majority (70.4%) were up to 48 months old. Although these data coincide with those published, there are variations in peak age, dependence on the agent involved and in local epidemiological conditions. In developed countries, the age range with the greatest incidence is 6 to 9 months for Hib[7,12] and pneumococcus.[22,23] Meningococci can cause invasive disease, sporadically, endemically or epidemically. In developed countries two incidence peaks are described; the first, of greater intensity, occurs in children less than 5 years old (6 to 24 months) and the second, between 15 and 24 years of age. Around 46% of cases occur in children less than two years old.[21,24]

Table 3 - Distribution of patients hospitalized with BM according to blood culture results and previous use of antimicrobials

Blood culture	Previous treatment		Total *
	Present	Absent	
Positive	44	62	136
Negative	126	89	215
Total	170	181	351

Pearson's χ^2, with Yates' correction, one deggre of freedom = 21.947 (p = 0.0001).
* From 415 patients, 315 presented an etiology. Among these, 258 presented etiologic diagnosis based on blood culture and/or CSF. The blood culture, performed in 351 patients, was not performed in 26 children who had received previous treatment, and in 38 children without previous treatment.

In Brazil, as with other developing countries, BM occurs with great frequency and affects younger children. Data from the Brazilian Health Foundation (*Fundação Nacional de Saúde*), regarding the period from 1994 to 1996, show that 48% of BM cases caused by Hib occurred in infants less than one year old, and that 88% occurred in children less than 5 years old.[25]

Among BM cases admitted to Hospital Emílio Ribas, in the district of São Paulo, during 1993 and 1994, 68% of the patients were children less than 5 years old and 30.5% were less than two years old. The peak incidence of meningococcal disease occurred between 2 months and 4 years of age (63.4% of meningococcal BM cases), and among the children with pneumococcal BM, 46.1% were less than one year old and 74.3% were less than 5.[20,25] According to the State Department of Health of São Paulo, in 1997 the peak incidence of pneumococcal BM, in the municipality of São Paulo, occurred in the first two years of life.[26] In fact, in a recent analysis of 55 children with pneumococcal meningitis, in the municipality of São Paulo, 72.4% were less than 12 months old and 52.5%, less than six months.[27]

In this series, the mean age of patients affected by Hib, pneumococcus and meningococcus, were 16.0, 23.9 and 47.2 months, respectively. Of the 171 cases of Hib meningitis, 98.2% (168) were less than 48 months old; of the 57 cases with a pneumococcal etiology, 29.8% were less than three months old and 84.2%, less than 48 months, and of the 65 children affected by meningococcus, 40% were older than 48 months.

The etiologic agent was identified in 315 patients (75.9%), with a definitive diagnosis in 289 (69.3%) and with a presumptive diagnosis, by means of bacterioscopy, in 26 (6.6%). The most frequently identified agents were Hib, in 41.2% (171), meningococcus in 15.6% (65) and

Table 4 - Distribution of patients hospitalized with BM according to CSF culture results and previous use of antimicrobials

CSF culture	Previous treatment		Total *
	Present	Absent	
Positive	82	147	229
Negative	110	58	168
Total	192	205	397

Pearson's χ^2, with Yates' correction, one degree of freedom = 32.978 (p = 0.0001).
* From 415 patients, 315 presented an etiology. Among these, 258 presented etiologic diagnosis based on blood culture and/or CSF. The CSF culture, performed in 397 patients, was not performed in four children who had received previous treatment, and in 14 children without previous treatment.

pneumococcus, in 13.7% (57) of the 415 cases. Incidence rates vary around the world. Currently, in the USA, pneumococcus is the pathogen that most causes BM in children, overrunning meningococcus (except during epidemic peaks) and Hib (in widely vaccinated communities).[28] In Brazil, according to data regarding the years from 1987 to 1995 from the Brazilian Health Foundation, the Ministry of Health and data for the years 1993 and 1994 from the Hospital Emílio Ribas, in São Paulo, the most frequently identified etiologic agent in children with BM was meningococcus, which accounts for around 2/3 of the cases, followed by Hib and pneumococcus.[20,25] Notwithstanding, in children less than one year old, the most common agents are Hib (44% of the cases), pneumococcus (34%) and meningococcus (22% of the cases), according to a national survey carried out from 1994 to 1996.[25] These figures are undoubtedly influenced by the epidemic of meningococcal meningitis, occurring in the city of São Paulo since the early 1990s.[20,25]

In a recently published study of the etiologic profile of BM in children, conducted at a small hospital in the town of Ribeirão Preto, state of São Paulo, it was possible to detect the etiologic agent in 72.8% of the 103 children studied between January 1992 and July 1996. The agents detected were: Hib in 32%, meningococcus in 25.6% and pneumococcus in 8.7% of cases.[29] In another study, carried out in Belo Horizonte, state of Minas Gerais, among 59 children with a definitive diagnosis of BM, Hib was identified in 42.3%, meningococcus in 28.8% and pneumococcus, in 25.4% of cases.[19] Different results were obtained in Taubaté, state of São Paulo, when 82 children with a BM diagnosis were analyzed. The etiology was identified in 22 of them, as follows: meningococcus 17.0%, Hib 6.1% and pneumococcus 1.2%.[18]

By considering only the three most common bacterial agents, the department of Epidemiological Surveillance of the Municipal Department of Health of Uberlândia, state of Minas Gerais,[15] registered the relative participation of Hib

Table 5 - Distribution of patients hospitalized with BM according to outcome and etiology

Outcome	Etiology*			Total†
	Hib	Sp	Nm	
Survival	149	47	62	258
Death	22	10	3	35
Total	171	57	65	293

Pearson's χ^2, two degress of freedom = 5.156 (p = 0.076).
* Hib = *Haemophilus influenzae b*; Sp = *Streptococcus pneumoniae*; Nm = *Neisseria meningitidis*.
† 100 patients without etiology and 22 patients with other etiologies were excluded.

in 30% (in 1995) and 40% (in 1997), of pneumococcus in 14% (in 1996) and 38.3% (in 1995) and that of meningococcus in 28.5% (in 1998) and 31.6% of the cases (in 1996). Therefore, except in communities with a widespread coverage of Hib vaccine and in situations of either endemic or epidemic meningococcal infection peaks, Hib remains the most frequently identified bacterial agent in children with BM under five years old.

There was a statistically significant difference between etiology and age range as shown in Table 2. For patients with etiologic diagnoses of Hib, pneumococcus and meningococcus, rates of occurrence in children up to 48 months were, respectively, 98.2% (168 of 171 cases), 84.2% (48 out of 57) and 60% (39 of 65 cases). There was a predominance of children up to 48 months affected by Hib comparatively to pneumococcus and meningococcus, particularly when comparing Hib and meningococcus ($p = 0.0001$).

In previously healthy children, the risk of contracting BM is higher in those younger than 5 years, especially those less than one year old. Excluding the neonatal period, the highest rates of BM occurrence refer to children between 3 months and two years old. The predominance of BM in younger children is not only the result of epidemiological aspects. The natural acquisition of antibodies against the polysaccharide antigens of the bacterial capsules may take place throughout infancy, despite the low immunogenicity of this type of antigen in children under the age of two years.[30]

Previous use of antimicrobials was detected in 196 patients (47.2% of 415), whose effects on the identification of the agent in blood culture and CSF culture are shown in Tables 3 and 4, respectively. The blood culture, performed in 351 patients, was positive in 136 (38.7%), and the CSF culture, performed in 397 cases, was positive in 229 (57.6%). Excluding children who had previously undergone treatment, these figures rise to 50.8% for blood culture (92 positive cultures among 181 cases) and 71.7% for the CSF cultures (147 out of 205). The same impact was observed in another study, whose blood culture positivity for Hib, pneumococcus and meningococcus rose from 80% to 90%, 52% to 80% and 33% to 91%, respectively, when children previously treated with some type of antimicrobial were excluded (40%).[31] In another series, blood culture positivity (86%) was greater in patients affected by Hib (94%), particularly when subjects previously treated with antimicrobials were excluded (100%).[17]

Of the 415 patients, 42 (10.1%) died, and it was only possible to establish a statistically significant relationship between occurrence of death and etiology when comparing pneumococcal BM cases with those caused by meningococcus ($p = 0.043$) (Table 5). BM mortality rates in children have varied from 5% to over 40%, depending on the patient age, on the pathogen involved and on the socioeconomic level of the studied population, among other factors.[3,4] In developed countries rates of around 6% for Hib,[3] 7% to 10% for meningococcus[21,24] and 30% to 40%, for pneumococcus have been described.[3,22,28] The highest values are described for younger infants, particularly when affected by pneumococcal meningitis.[3,22,28] In poor countries, death rates between 20 and 50% are attributed to Hib.[25] In a recent study of children with pneumococcal meningitis, in the district of São Paulo, mortality was 20%.[27] According to Professor Alexandre Vranjac Surveillance Center, affiliated with the State Department of Health of São Paulo, mortality rates in children under five years old due to pneumococcus, meningococcus and Hib were respectively 29.3%, 21.7% and 16.6%, in 1996.[26] In the present series mortality rates were 17.5% for pneumococcus, 12.8% for Hib and 4.6% for meningococcus.

Of the 415 patients with BM admitted to the hospital, the etiologic agent was identified in 315 (75.9%), with a definitive diagnosis in 289 (69.3%) and with a presumptive diagnosis (exclusively by means of bacterioscopy) in 26 (6.6%). The culture yield of 89.2% out of 289 patients with a definitive diagnosis was comparable to figures described in literature.[17,19,32] Gram staining is one of the most useful resources in a microbiology laboratory. It is based on the different staining characteristics of bacteria under direct microscopy. It is relatively quick and simple to perform, and often allows a presumptive identification of the etiologic agent, and may help with the indication for initial empirical antibiotic therapy. Gram staining, when correctly performed with a CSF smear from a previously untreated patient, is capable of detecting the agent in 25 to over 90% of BM cases, depending on bacterial density.[5] Low density samples (less than 105 colony-forming units/ml) are better analyzed after centrifugation.[5] Technical difficulties; the lack of qualified personnel to perform and interpret the exam, and previous use of antimicrobials compromise the efficiency of the method. In this study, bacterioscopy was positive in 227 cases (54.7% of 415) and, in only 26 of them (6.2%), the color and morphological aspect of the bacteria on the smear test was the only laboratory clue to etiology. Values of 76% and 2.2% were respectively obtained in another series.[17]

The tests for the detection of bacterial antigens consist of quick trials that employ antibodies to identify antigens in organic fluids. As these tests do not require the presence of viable bacteria they can still produce positive results some days after the implementation of antibiotic therapy. The tests detect the capsular antigens of bacteria such as Hib, meningococcus and pneumococcus, to which they have a sensitivity in CSF between 50% and 100%, with an average value of approximately 70%.[4-6,32] Despite their high specificity, their use in the screening of diseases such as meningitis and sepsis has been questioned, since a negative result does not rule out a positive diagnosis.[6] In our patient population, the latex agglutination test was positive in 171 cases (41.2% out of 415) and, in 16 of these cases (3.8%) it was the only etiological evidence. These values are lower than those found by Romanelli et al. (70.1% and 12.2%,

respectively),[19] and greater than those described by Coant et al. (positivity of 4.1%).[17]

Three-hundred ninety-seven CSF samples and 351 blood samples were cultured, yielding positivity rates of 57.6% (229 out of 397 samples) and 38.7% (136 out of 351), respectively. Excluding patients who had undergone previous treatment, the rates rise to 71.7% (147 out of 205) and 50.8% (92 out of 181), respectively. Yields with similar[18,29] or higher[17,31] values are described by other authors. In previously treated children these figures drop to 42.7% (82 in 192) for CSF culture positivity and to 25.8% (44 in 170), for blood cultures. Therefore, in this patient population, as in others,[17,31] previous use of antimicrobials resulted in a significantly lower positivity for the cultures (Tables 2 and 3). In fact, CSF sterilization may occur due to parenteral administration of effective antimicrobials, in a variable period of time, depending on the agent involved: up to 2 hours for meningococcus and over 4 hours for pneumococcus.[33]

Conclusions

With regard to the children admitted with bacterial meningitis, we conclude that most of them were male (59%); the overall mean age (26.8 months) was greater than the mean age for the cases of Hib meningitis (16 months) and pneumococcus (23.9 months), and lower than that of the cases of meningococcal meningitis (47.2 months); etiological diagnosis was established in most of the cases (75.9%), especially by means of blood and/or CSF culture (62.2%); the most frequently isolated agents were Hib (54.2%), meningococcus (20.6%) and pneumococcus (18.1%); there was a predominance of Hib in children between 3 and 48 months old, especially when compared to meningococcal meningitis; there was a small, but significant increase in mortality due to pneumococcal infection (17.5%), in relation to meningococcus (4.6%) and, finally, that the previous use of antimicrobials, detected in 47.2% of the patients, significantly affected the yield of blood and CSF cultures.

References

1. Farhat CK. Meningites Bacterianas Purulentas. In: Farhat CK, Carvalho ES, Carvalho LHFR, Succi RCM. Infectologia Pediátrica. 2nd ed. São Paulo: Atheneu; 1999.p.89-103.
2. Faria SM, Farhat CK. Meningites bacterianas. J Pediatr (Rio J) 1999;75(Supl 1):46-56.
3. Tunkel AR, Scheld WM. Pathogenesis and Pathophysiology of Bacterial Meningitis. Clin Microbiol Rev 1993;6:118-36.
4. Quagliarello VJ, Scheld WM. Treatment of Bacterial Meningitis. N Engl J Med 1997;336:708-16.
5. Klein JO, Feigin RD, McCracken GH Jr. Report of the Task Force on Diagnosis and Management of Meningitis. Pediatrics 1986;78(Suppl 2):959-982.
6. Hayden RT, Frenkel LD. More laboratory testing: greater cost but not necessarily better. Pediatr Infect Dis J 2000;19:290-292.
7. Ward JI, Zangwill KM. *Haemophilus influenzae* vaccines. In: Plotkin SA, Orenstein WA. Vaccines. 3rd ed. Philadelphia: WB Saunders; 1999.p.183-221.
8. Centers for Disease Control and Prevention. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children - United States, 1987-1997. MMWR 1998;47:993-8.
9. Bricks LF. Análise crítica sobre o uso das vacinas conjugadas contra o *Haemophilus influenzae* do tipo b em diferentes países. Pediatria (São Paulo) 1998;20:216-29.
10. Landaverde M, Fabio JLD, Ruocco G, Leal I, Quadros C. Introducion de la vacuna conjugada contra Hib en Chile y Uruguay. Rev Panam Salud Publica 1999;5:200-6.
11. Ruocco G, Curto S, Savio M, Laurani H, Frocht R. Vacunacion contra *Haemophilus influenzae* tipo b en el Uruguay: experiencia e impacto. Rev Panam Salud Publica 1999;197-9.
12. American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Pickering LK, editor. 2000 Red Book - Report of the Committee on Infectious Diseases. 25th ed. Elk Grove Village, (IL): American Academy of Pediatrics; 2000.p.262-272.
13. Takemura NS, Andrade SM. Meningite por *Haemaphilus influenzae* tipo b em cidades do estado do Paraná, Brasil. JPediatr (Rio J) 2001;77:387-92.
14. Instituto Brasileiro de Geografia e Estatística. Acessível em http://www.ibge.gov.br/
15. Prefeitura Municipal de Uberlândia. Secretaria Municipal de Saúde, 1999. Acessível em http//www.uberlandia.mg.gov.br. Acessado em maio de 2002.
16. Klein JO, Marcy SM. Bacterial Sepsis and Meningitis. In: Remington JS, Klein JO. Infectious Diseases of the Fetus and Newborn Infant. 2nd ed. Philadelphia: W B Saunders; 1983. p.679-735.
17. Coant PN, Kornberg AE, Duffy LC, Dryja DM, Hassan SM. Blood culture results as determinants in the organism identification of bacterial meningitis. Pediatr Emerg Care 1992;8:200-5.
18. Nascimento LFC. Meningites bacterianas no Hospital Universitário de Taubaté, 1995 a 1998: epidemiologia, etiologia, e evolução de 82 casos. Pediatria Moderna 2000;36:828-34.
19. Romanelli RMC, Araújo CA, Dias MW, Boucinhas F, Carvalho IR, Martins NRL, et al. Etiologia e evolução das meningites bacterianas em centro de pediatria. J Pediatr (Rio J) 2002; 78:24-30.
20. Farhat CK, Marques SR. Doença Meningocócica. In: Farhat CK, Carvalho ES, Carvalho LHFR, Succi RCM. Infectologia Pediátrica. 2nd ed. São Paulo: Atheneu; 1999.p.288-299.
21. Leake JAD, Perkins BA. Meningococcal Disease: Challenges in Prevention and Management. Infect Med 2000;17:364-77.
22. Kornelisse RF, Westerbeek CML, Spoor AB, Spanjaard HJ. Pneumococcal meningitis in children: prognostic indicators and outcome. Clin Infect Dis J 1995;21:1390-7.
23. Arditi M, Mason EO Jr, Bradley JS, Tan TQ, Barson WJ, Schutze GE. Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics and outcome related to penicillin susceptibility and dexamethasone use. Pediatrics 1997;102:1087-97.
24. Lepow ML, Perkins BA, Hughes PA, Poolman JT. Meningococcal vaccine. In: Plotkin SA, Orenstein WA. Vaccines. 3rd ed. Philadelphia: W B Saunders; 1999.p.711-727.
25. Martins RM. Infecções por *Haemophilus influenzae*. In: Farhat CK, Carvalho ES, Carvalho LHFR, Succi RCM. Infectologia Pediátrica. 2nd ed. São Paulo: Atheneu; 1999.p.268-80.
26. Brandileone MCC. Distribuição de sorotipos, resistência antimicrobiana e perfil molecular de *Streptococcus pneumoniae* isolado de doença invasiva no Brasil: 1993 a 1998 [tese]. Universidade Federal de São Paulo - Escola Paulista de Medicina.

São Paulo;1999.p.207.
27. Berezin EN, Carvalho LH, Lopes CR, Sanajotta AT, Brandileone MCC, Menegatti S, et al. Meningite pneumocócica na infância: características clínicas, sorotipos mais prevalentes e prognóstico. J Pediatr (Rio J) 2002;78:19-23.
28. Fedson DS, Musher DM, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA. Vaccines. 3rd ed. Philadelphia: WB Saunders;1999.p.553-608.
29. Elias MLC, Almeida S, Camara A. Perfil etiológico das meningites bacterianas em um hospital de pequeno porte. J Pediatr (Rio J) 1998;74:45-8.
30. Janeway CA, Travers P, Walport M, Capra JD. The humoral immune response. In: Janeway CA, Travers P, Walport M, Capra JD. Immunobiology: The immune system in health and disease. 4th ed. London: Current Biology Publications; 1999.p.307-61.
31. Feigin RD. Bacterial meningitis beyond the neonatal period. In: Feigin RD, Cherry JD. Textbook of Pediatric Infectious Diseases. 2nd ed. Philadelphia: W B Saunders; 1987.p.439-65.
32. Tunkel AR, Scheld WM. Issues in the Management of Bacterial Meningitis. Am Family Phys 1997;56:1355-62.
33. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar Punctures in Pediatric Bacterial Meningitis: Defining the Time Interval for Recovery of Cerebrospinal Fluid Pathogens after Parenteral Antibiotic Pretreatment. Pediatrics 2001;108:1169-74.

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