International Journal of Infectious Diseases (2008) **12**, 380—386

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Epidemiology and outcomes of bacterial meningitis in Mexican children: 10-year experience (1993—2003)

Carlos Franco-Paredes*, **Lorena Lammoglia, Isabel Hernández, José Ignacio Santos-Preciado**

Hospital Infantil de México Federico Gómez, Doctor Marquéz No. 162, Col. Doctores, Delegación Cuauhtémoc CP 06720, Mexico City, Mexico

Received 25 June 2007; accepted 18 September 2007
Corresponding Editor: William Cameron, Ottawa, Canada

KEYWORDS
Bacterial meningitis;
Children;
Mexico;
Haemophilus influenzae type b;
Streptococcus pneumoniae

Summary
Background: Acute bacterial meningitis remains an important cause of morbidity, neurologic sequelae, and mortality in children in Latin America.
Methods: We retrospectively reviewed the hospital-based medical records of children diagnosed with acute bacterial meningitis, aged 1 month to 18 years, at a large inner city referral Hospital in Mexico City, for a 10-year period (1993—2003). To characterize the epidemiology, clinical features, and outcomes of acute bacterial meningitis, we subdivided our study into two time periods: the period prior to the routine use of *Haemophilus influenzae* type b (Hib) vaccine (1993—1998) and the period after the vaccine became available (1999—2003).
Results: A total of 218 cases of acute bacterial meningitis were identified during the study period. The most frequently affected age group was that of children aged between 1 and 6 months. Hib was the most commonly isolated pathogen, found in 50% of cases. However, its incidence declined significantly after the introduction of the combined diphtheria, tetanus, pertussis, hepatitis B, and conjugated Hib (DTP—HB/Hib) pentavalent vaccine into the universal vaccination schedule for children in 1998. *Streptococcus pneumoniae* followed as the second most commonly isolated bacterial pathogen. *Neisseria meningitidis* was isolated in only a few cases, confirming the historically low incidence of this pathogen in Mexico. Identified risk factors for death were found to include the presence of septic shock and intracranial hypertension, but were not attributable to any particular bacterial pathogen.
Conclusions: In our hospital, acute bacterial meningitis remains a severe disease with important sequelae and mortality. The incidence of Hib meningitis cases has declined since the introduction of the Hib vaccine. However, *S. pneumoniae* persists as an important cause of bacterial meningitis, highlighting the need for the implementation of vaccination policies against this pathogen.

* Corresponding author. Tel.: +52 55 57610181/57611963; fax: +52 55 57618974.
E-mail address: cfranco@sph.emory.edu (C. Franco-Paredes).

1201-9712/$32.00
doi:10.1016/j.ijid.2007.09.012

Introduction

Acute bacterial meningitis (BM) constitutes a significant global public health problem. Worldwide, it has been estimated that 1–2 million cases of BM occur annually.[1–4] The problem is more significant in resource-poor countries including those in some regions of Sub-Saharan Africa, Southeast Asia, and Latin America.[5,6]

The initial treatment approach to a child with suspected BM depends on early recognition of the meningitis syndrome, rapid diagnostic evaluation, and early antimicrobial and adjunctive therapy.[7–9] Once suspected, blood cultures, cranial computed tomography (CT scan) when indicated, and lumbar puncture to obtain cerebrospinal fluid (CSF) for examination is considered the standard of care. Management algorithms for BM in children include the initiation of dexamethasone plus empirical antimicrobial therapy.[10–12] However, BM remains a neurological and infectious disease emergency with a high mortality rate, despite advances in diagnostic techniques, antimicrobial chemotherapy, and adjuvant use of anti-inflammatory agents.[10] Sequelae, such as hearing loss, blindness, seizure disorders, hydrocephalus, developmental delay, and motor deficit occur even with the rapid institution of adequate therapy.[11,12] Indeed, BM can often be rapidly progressive, resulting in permanent sequelae in a relatively short period of time.[11] This is the reason why vaccination strategies to prevent the invasive bacterial disease of organisms capable of causing meningitis, such as *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*, are considered public health priorities.[13–19]While there are six serotypes of *Haemophilus influenzae* known to cause disease, type b is responsible for over 90% of BM in children.[5,16,18] Indeed, prior to the widespread use of conjugate vaccines against Hib, this organism was the most common cause of severe invasive infections in children, resulting in approximately 300 000 to 500 000 deaths annually worldwide. In the USA, with the advent of the Hib conjugate vaccine, Hib cases in children under 5 years of age declined by 99% from 1986 to 1995; this decline has also occurred in other resource-rich countries. This beneficial shift in the epidemiology of BM prompted the World Health Organization (WHO) to recommend that the Hib vaccine should be included in routine infant immunization programs for all children, as appropriate to national capacities and priorities.[5,15]With these dynamic changes in the epidemiology of BM in many areas of the world resulting in decreasing numbers of cases due to Hib, *S. pneumoniae* and *Neisseria meningitidis* have become the predominant causes of meningitis in children aged 1 month and older.[13] In fact, recent WHO estimates have suggested that approximately 1.6 million people die of pneumococcal disease every year, including 0.7–1 million children under 5 years of age, most of whom are from resource-poor countries.[11,13] This is the rationale behind the WHO and other leading public health agencies promoting the introduction of a conjugate pneumococcal vaccine into routine childhood immunization programs. In addition, countries are encouraged to conduct appropriate surveillance for pneumococcal disease to establish the baseline and monitor the impact of vaccination.[13]

In Mexico, BM remains an important cause of morbidity, neurologic sequelae, and mortality. However, there are limited epidemiologic and microbiologic data on this disease in children and adults.[7] In particular, there are limited data evaluating the impact of routine childhood vaccination against Hib, which was initiated in 1998. Therefore, we conducted this comprehensive, hospital-based retrospective study to describe the epidemiology, clinical features, and outcomes for Mexican children with BM aged 1 month and older, seen at the Hospital Infantil de México Federico Gómez, a major national pediatric referral center.

Methods

We retrospectively reviewed the hospital-based medical records of children diagnosed with acute BM, aged 1 month to 18 years (beyond the neonatal period), evaluated at the Hospital Infantil de México Federico Gómez (HIMFG), for a 10-year period (1993–2003). Founded in 1943, HIMFG is the oldest of Mexico's 12 National Institutes of Health, and is the leading national referral pediatric institution. The study period was subdivided into the period prior to the introduction of the conjugate Hib vaccine (1993–1998) and the period after its introduction (1999–2003).

We included 218 cases of BM based on the presence of clinical symptoms consistent with a meningitis syndrome and the following ancillary laboratory criteria: (1) positive bacterial culture in CSF; (2) CSF pleocytosis $\geq 5 \times 10^6$/l with a negative CSF culture plus one of the following: positive blood culture, positive CSF antigen test, positive Gram stain of the CSF, or a positive throat culture for *N. meningitidis* in patients with a purpuric rash; (3) CSF pleocytosis $\geq 5 \times 10^6$/l with a negative CSF culture, negative blood or throat culture, or negative co-agglutination test. We excluded patients with tuberculous meningitis, immunocompromised patients, and cases of nosocomial meningitis. Demographic data (including age and gender) and data on symptoms at presentation, physical examination on admission, previous vaccination schedule, laboratory results, CSF examination, CT scan results, and treatment and outcomes were collected using a standarized data collection form. Death due to BM was classified as meningitis-related if death was secondary to meningitis or any of its complications as recorded by the medical record and/or autopsy data.

Statistical analysis was carried out by proportion comparisons using the Mantel–Haenszel Chi-square test or Fisher's exact test as appropriate. The Wilcoxon rank sum test was used to compare medians of continuous variables when the two-sample *t*-test was not appropriate. All tests were two-sided and a *p*-value of ≤ 0.05 was considered significant. To determine the association between potential risk factors and death due to BM, logistic regression was used to estimate odds ratios (OR) and their 95% confidence intervals (CI). Those variables that in bivariate analysis would have achieved a significance level of 0.05 were included in the model as main effects, along with effect modifiers and confounders of the association between death and shock (our main outcome of interest). A hierarchical backwards elimination strategy was performed, with proper evaluation of interaction and confounding. The goodness of fit of the model was assessed using the Hosmer and Lemeshow Chi-square test. Assessment of collinearity was done by analyzing the condition indices and the respective variance decomposition proportions (VDPs). All statistical analyses were performed using SAS software (version 8.2, SAS Institute, Cary,