Journal of Infection (2013) **66**, 147—154

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BIAMM British Infection Association

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The changing pattern of bacterial meningitis in adult patients at a large tertiary university hospital in Barcelona, Spain (1982—2010)

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Accepted 31 October 2012
Available online 17 November 2012

KEYWORDS
Bacterial meningitis;
Epidemiology pattern;
Meningococcal disease;
Neisseria meningitidis;
Streptococcus pneumoniae;
Outcome;
Sequelae;
Spectrum

Summary *Background:* We conducted a prospective, observational study in Barcelona (Spain) to determine changes in the spectrum of adult patients with bacterial meningitis (BM) over a 29-year period.
Methods: The observation was divided into two periods: 1982—1995 (I) and 1996—2010 (II). All patients underwent clinical examination on admission and at discharge following a predefined protocol.
Results: We evaluated 635 episodes of BM. The most frequent etiologic agents were *Neisseria meningitidis* and *Streptococcus pneumoniae* in periods I and II, respectively. Patients in period II were older (Median: 47.5 [95%CI: 23.0—64.5] vs. 58.0 [39.0—73.0] years, $P < 0.0001$), had a longer interval from admission to therapy (Median: 2.3 [95%CI: 1.0—5.0] vs. 4.0 [2.0—12.0] hours, $P < 0.0001$), and more frequently had co-morbid conditions (39.1% vs. 62%, $P < 0.0001$). Meningococcal meningitis decreased by 66% ($P < 0.0001$), whereas meningitis by *Listeria monocytogenes* increased by 110% ($P = 0.0007$) in period II. There were no differences in the overall case-fatality and post-meningitic sequelae rates between both periods.
Conclusions: BM in adult patients has substantially changed over 29 years in terms of population affected, aetiology, and management, but not in terms of its overall mortality rate and appearance of post-meningitic sequelae.

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0163-4453/$36
http://dx.doi.org/10.1016/j.jinf.2012.10.030

Introduction

Bacterial meningitis (BM) is highly dependent in its epidemiology on geographical factors, the development of society, and the number of preventive interventions.[1] BM has an incidence of 0.6—4 cases per 100,000 adults/year in developed countries.[2—4] It is associated with a considerable burden of mortality, and 30—50% of people who survive infection may have permanent neurological sequelae.[2,4,5]

The most important changes we have witnessed in the epidemiology of BM are the dramatic decline in incidence of meningitis due to *Haemophilus influenzae* serotype b (Hib) in countries that have implemented mass immunization of infants with conjugate Hib vaccine[6] and the decline in early-onset disease caused by group B Streptococcus through universal culture-based screening and use of intra-partum antibiotic prophylaxis.[7] However, no such breakthroughs have been seen in adult BM patients. In developed countries the most frequent etiologic agents of BM in adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*.[2—4]

The aim of our study was to determine the changes observed in the spectrum of BM in adults recruited from a large tertiary university hospital in Barcelona (Spain) over the last 29 years.

Patients and methods

Study population

We used data from a large, prospective, single-hospital cohort of patients with BM enrolled over a 29-year period at the *Hospital de la Santa Creu i Sant Pau* (Barcelona, Spain). Our institution is a 620-bed tertiary university hospital providing care for 441,392 inhabitants. From 1982 to 2010 all consecutive adults in whom BM was diagnosed were prospectively identified and followed. The study and its subsequent amendments were approved by the Ethical Review Committee of the *Hospital de la Santa Creu i Sant Pau*.

All cases of BM have been followed and recorded in a 157-variable computer-assisted protocol. Cases were identified through a triple detection system: (i) review of all admissions to the Hospital; (ii) review of all cerebrospinal fluid (CSF) culture requests, and (iii) systematic review and consultation at the Intensive Care Unit and Emergency Ward.

Patients were followed upon diagnosis by one of the authors until death or hospital discharge.

Diagnosis of bacterial meningitis

The diagnosis of BM of known aetiology was based on the presence of consistent clinical findings and one of the following: a positive CSF culture; or a negative CSF culture with neutrophilic pleocytosis and at least one of the following: a positive CSF antigen test, a positive blood culture, or identification of gram-negative diplococci on Gram stain of CSF in patients with a petechial or purpuric rash and a fulminant course (considered to be caused by *N. meningitidis*).[8] Episodes of BM without etiologic diagnosis had a consistent clinical picture and CSF cyto-biochemical findings of purulent meningitis (pleocytosis of >100 polymorphonuclear leukocytes/mm^3, plus hypoglycorrhachia [CSF/blood glucose ratio < 0.50] and/or hyperproteinorrachia [>0.45 g/l]).[9,10] Patients with viral, fungal, mycobacterial, and post-neurosurgical BM were excluded.

Microbiological methods

Isolates were obtained from routine cultures and were identified using standard methods.[11] The disc diffusion susceptibility test was performed according to Clinical Laboratory Standards Institute (CLSI) guidelines,[12] using commercially available discs (Bio-Rad, Marnes La Coquette, France). MICs were determined using the broth micro dilution method according to the CLSI guidelines[13] using commercial panels (Sensitre, Trek diagnostic systems, West Sussex, England) or Etest (AB Biodisk, Solna, Sweden) according to the recommendations of the manufacturer.

Resistance breakpoints for penicillin were MIC ≥ 0.12 mg/L for pneumococcus and meningococcus.[14] Moderate resistance to penicillin was defined by a MIC between 0.12 and 1 mg/L of the pneumococcal strain, whereas high resistance occurred when the MIC was ≥ 2 mg/L.[14]

Definitions

Meningeal triad has been previously defined.[15] For the present study, an individual aged more than 14 years was considered to be an adult. Individuals aged ≥ 65 years were considered as elderly patients. Preadmission receipt of adequate antibiotic therapy was only considered when the patient had received at least one adequate dose of antibiotics active against the bacterial pathogen at intervals considered to be adequate from a therapeutic point of view.[16]

The interval in hours from onset of symptoms and signs of BM to admission to the hospital (interval of symptoms to admission) was the time elapsed between the first symptom or sign attributable to BM and admission to the hospital. When the precise beginning of symptoms could not be determined, the onset of illness was assumed to be the mean interval between the last time the patient was asymptomatic as observed by a household member and the first time the patient was seen ill. The interval in hours from admission to the hospital to the first dose of antibiotic for the treatment of meningitis was the interval admission-therapy (IAT).

Co-morbid conditions were considered to be present if the patient had a confirmed diagnosis of one or more of the following: cancer, when there was a definitive histopathologic diagnosis of neoplasia except for basocellular carcinoma; systemic vasculitis when there was a histopathologic diagnosis; cirrhosis of the liver, when the diagnosis had been established by histopathologic study of a liver biopsy or the patient had clinical features consistent with cirrhosis; diabetes, if that disease had been diagnosed and the patient was receiving hypoglycaemic drugs; chronic renal failure, if the patient had an estimated glomerular filtration rate <60 ml/min or was undergoing dialysis; human immunodeficiency virus (HIV) infection if the patient had a positive enzyme-linked immunosorbent