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FULL PAPER

Acute Community-Acquired Bacterial Meningitis: Update on Clinical Presentation and Prognostic factors

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SUMMARY

The epidemiology of community-acquired bacterial meningitis (CABM) in adults has changed significantly in the past several years. Despite substantial improvement in patient care, CABM remains a major cause of morbidity and mortality. Thus, new prognostic factors could help improve patient stratification.
We conducted a multicenter retrospective study to determine the clinical pattern of CABM in an urban area of Western Europe and to identify potential predictors of unfavorable prognosis and complicated course.
Over a period of 6-8 years, 79 adult CABM cases were treated at three tertiary hospitals. A Glasgow Outcome Scale (GOS) score of ≤4 was defined as unfavorable outcome. Predictors of unfavorable prognosis or complicated course were identified through logistic-regression analysis.
S. pneumoniae was the most frequent pathogen (34%). 82% of patients exhibited at least two of five signs, including fever, neck stiffness, altered mental status, headache and nausea. Almost 50% presented focal neurological deficits; the overall mortality rate was 15%. In the multivariate analysis, risk factors for an unfavorable outcome included a GCS score of ≤13, female sex, and etiology by *L. monocytogenes* and gram-negative bacilli. However, risk factors for systemic complications were a GCS score of ≤13 and reduced platelet count, whereas C-Reactive Protein (CRP) increase was associated with a higher rate of neurological complications.
Patients with non-pneumococcal CABM were more prone to an unfavorable outcome, probably because of underutilization of empiric ampicillin in patients at risk of listeriosis and because the suspicion of pneumococcal infection was facilitated by the existence of otitis and the higher yield of Gram's stain. Patients presenting a GCS of ≤13, thrombocytopenia and/or increased CRP, may benefit from more aggressive care to avoid in-hospital complications and neurological sequelae.

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INTRODUCTION

The epidemiology of acute community-acquired bacterial meningitis (CABM) in adults has changed significantly in the past several years. Today, CABM is usually caused by *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Listeria monocytogenes*, and appears with an estimated annual incidence of 0.6-4 cases per 100,000 adults (Fitch, van de Beek, 2006 a; van de Beek *et al.*, 2004 b). Despite substantial improvement in patient care, including the recommendation for adjunctive dexamethasone, CABM remains a major cause of morbidity and mortality in adult patients, ranging from 3% to 37%, and 3% to 30% of cases, respectively. The combination of early diagnosis and prompt antibiotic therapy has a dramatic impact on prognosis (Auburtin *et al.*, 2006; Proulx *et al.*, 2005). Most large studies have been epidemiological, and only a few of them have focused on identifying potential predictors of unfavorable outcome in terms of mortality (Durand *et al.*, 1993; Tsai *et al.*, 2006). Moreover, both its aggressive course and relatively low incidence hinder the design of other, retrospective analyses. Recent studies with smaller samples were dedicated to identifying predictors of the need for Intensive Care Unit (ICU) referral or the occurrence of cerebrovascular complications during hospitalization (Dauchy *et al.*, 2007; Katchanov *et al.*, 2010; Kastenbauer S, Pfister H-W, 2003). However, health care providers must now recognize clinical features and markers of severity in a context of changing epidemiology. Therefore, we conducted an 8-year observational study with two objectives: first, to describe the clinical pattern of CABM episodes in a large urban area of Western Europe (Madrid, Spain) and, second, to identify potential associations between characteristics on admission and both the risk of unfavorable prognosis in terms of neurological sequelae (Glasgow Outcome Scale) and risk of a complicated course of hospitalization.

Key words:
Community-acquired bacterial meningitis, epidemiology, prognosis, complications.

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MATERIALS AND METHODS

Patients and Data Analysis

We retrospectively reviewed the medical records, laboratory and microbiological data of 79 adult patients (≥18 years) admitted to three tertiary university hospitals in Madrid, Spain with the diagnosis of CABM. Participating institutions were 665-bed Fundación Jiménez Díaz Hospital (FJD), 554-bed La Princesa Hospital (LPR) and 613-bed Puerta de Hierro Hospital (PH), which provide care to an urban area with an estimated overall population of 1.4M inhabitants. CABM cases occurred over a period of 6-8 years, coinciding with the implementation of electronic medical records systems: FJD, January 2007-December 2014; LPR and PH, January 2009-December 2014. Subsequent years were not included in the study because free hospital selection for patients was set up in 2015. We hypothesized that this change in health policies, which granted access to our hospital resources to a more heterogenous population (including from rural areas or foreign countries), could significantly alter the microbiological ecosystem and hamper data analysis by defining two time frames.

All patients met established diagnostic criteria, including compatible clinical (headache, fever, nausea, vomiting, neck stiffness, altered mental status) and biochemical and microbiological findings (positive cerebrospinal fluid (CSF) culture, or negative CSF culture with CSF pleocytosis (>1,000 leukocytes/ul with >60% neutrophils), positive CSF antigen test or positive blood culture) (Durand *et al.*, 1993). Patients with nosocomial meningitis (i.e., clinical evidence more than 48h after hospital admission or within 7 days after discharge) or meningitis related to head trauma with skull fractures, CSF fistulae, craniospinal congenital malformations or recent neurosurgical procedures were not included. We also excluded cases of mycobacterial and syphilitic meningitis.

All CABM patients were treated according to internal guidelines with empiric antibiotic therapy (generally cefotaxime/ceftriaxone ± vancomycin ± ampicillin) until the pathogen was identified and the results of sensitivity tests were available. Adjuvant therapy with glucocorticoids (dexamethasone) was added to the regimen in 32 of the 67 patients evaluated (48%), starting with the first dose of antibiotics as recommended (Tunkel *et al.*, 2004).

Clinical data were collected from medical files reporting at least once a day from admission to discharge or exitus. The outcome at discharge was graded according to the Glasgow Outcome Scale (GOS) based upon medical records. A score of 5 indicates mild or no patient disability; a score of 4, moderate disability (patient is unable to return to work or school or may require special assistance); a score of 3, severe disability (patient is unable to live independently); a score of 2, a vegetative state, and a score of 1 indicates *exitus*. A favorable outcome was defined as a score of 5, and an unfavorable outcome as a score of ≤4 in conformity to previous reports (van de Beek *et al.*, 2004b; Kastenbauer, Pfister, 2003; Bodilsen *et al.*, 2014; Brouwer *et al.*, 2006).

The GOS is a well-validated instrument with good interobserver agreement (Jennett, Bond, 1975). The study was approved by the Ethical Review Committee of each hospital. Retrospective patient data was retrieved from de-identified hospital databases. No specific consent was deemed necessary by the Ethical Review Committees.

Statistical analysis

Categorical variables were summarized with absolute numbers and percentage, and were analyzed with X^2 test or Fisher's exact test when indicated. Continuous variables were represented with means and standard deviation (SD) or medians and interquartile range (IQR) depending on their homogeneity, and were compared using t-Student test, ANOVA, Mann-Whitney U test or Kruskall-Wallis test when appropriate.

A multivariate logistic regression analysis was performed to identify clinical and biological factors at presentation independently associated with an unfavorable outcome at discharge and with the occurrence of systemic or neurological complications during hospitalization. Variables with a p value of ≤0.1 in bivariate analysis were identified and entered into the logistic regression model. All statistical tests were two-tailed, and a p value of <0.05 was considered statistically significant. Statistical analyses were performed using Statistical Product and Service Solutions (SPSS) software version 20.

RESULTS

A total of 190 episodes of bacterial meningitis were retrieved from the hospital electronic databases in the specified period. 111 patients were excluded - 75 patients with nosocomial meningitis, CSF fistulae or associated malformation, or recent history of neurosurgery, 4 patients with mycobacterial or syphilitic meningitis, and 32 patients under 16 years of age - leaving a total of 79 episodes of CABM in adult patients.

The annual incidence of CABM was 1.5, 0.8 and 0.7 cases per 100,000 adults for the areas covered by FJD, LPR and PH hospitals, respectively.

Characteristics of the study population

Patients had a mean age of 59 years, ranging from 19 to 97, and 58% were men (*Table 1*). Predisposing conditions were present in 58% of episodes, the most common of which were otitis (21%), immunocompromised state (19%), malignancy (15%) and pneumonia (12%). The antecedent of otitis in the previous month was more common in patients with pneumococcal meningitis than in other etiologies (69% vs 31%, p=0.015). When compared by age groups (≤50, 51-75, >75), the burden of chronic debilitating conditions (i.e., immunosuppression, asplenia, liver cirrhosis, chronic renal failure) was more prevalent among patients aged 50-75 years (p=0.044). Classic symptoms and signs of bacterial meningitis were present in a large proportion of patients.

Headache occurred in 71% of episodes, fever (≥38ºC) in 58%, neck stiffness in 58%, nausea in 43%, and change in mental status (defined by Glasgow Coma Scale, GCS, below 14) in 53%. However, only 18% of episodes were characterized by the classic triad of fever, neck stiffness, and change in mental status. At least two of five signs and symptoms (the classic triad plus headache and nausea) were present in 82% of episodes. Duration of symptoms before hospital admission was less than 24 h in 41% of episodes and more than 72 h in 21%. Presence of classic symptoms was not different when compared by age groups or microbiological etiology. However, patients over 50 years of age scored below 14 in GCS more frequently (78% vs 22%, p=0.04). In 13% of episodes the patients were comatose on admission, and in 45% of epi-

sodes focal neurologic deficits were present on admission, the most common of which were aphasia (9 cases), limb weakness (7 cases), and third cranial nerve paralysis (7 cases).

Table 1 - *Characteristics of the Study Population (No. of cases of meningitis, N=79).*

Age (years) – mean±SD	59±20
Male – no. (%)	46 (58)
Glasgow Coma Scale (score)	*No./No. eval. (%)*
>13	32/68 (47)
≤13 (indicating change in mental status)	36/68 (53)
≤8 (indicating coma)	9/68 (13)
Symptoms on presentation	*No./No. eval. (%)*
Fever (≥38C)	44/76 (58)
Headache	48/68 (71)
Nausea	29/67 (43)
Neck stiffness	39/67 (58)
Rash	2/73 (3)
Positive Kernig/Brudzinski signs	15/59 (25)
Seizures	7/73 (10)
SBP (mmHg) - mean±SD	135±25
DBP (mmHg) - mean±SD	76±13
Triad of fever, neck stiffness, and change in mental status	10/56 (18)
Focal neurological deficits on presentation	*No.*
Cranial-nerve palsy	
3rd nerve	7
6th nerve	3
7th nerve	4
9th nerve	1
Aphasia	9
Hemiparesis	3
Limb weakness	7
Instability	4
Duration of symptoms	*No./No. eval. (%)*
<24 hours	23/56 (41)
24-72 hours	21/56 (37)
>72 hours	12/56 (21)
Comorbidity	*No. (%)*
Hypertension	36 (46)
Diabetes mellitus	10 (13)
Dislipemia	13 (17)
Tabaquism	16 (21)
Alcoholism	12 (16)
Atrial fibrillation	6 (8)
Previous cerebrovascular accident	5 (6)
Predisposing conditions	*No. (%)*
Otitis	17 (21)
Sinusitis	6 (8)
Pneumonia	9 (11)
Inmunocompromise	15 (19)
Asplenia	2 (3)
Chronic kidney disease	1 (1)
Cirrhosis	3 (4)
Malignancy	12 (15)
Blood examination	
Leukocytes (10^3 cels./µl) - Mean±SD	16±7
Platelets (10^3/µl) - Mean±SD	203±101
CRP (mg/dl) - Mean±SD	14±11
Creatinine (mg/dl) – median [IQR]	0.9 [0.5]
pH - Mean±SD	7.42±0.1
CSF examination	
Leukocytes (cels./µl) - median [IQR]	800 [3446]
Proteins (mg/dl) - median [IQR]	300 [310]
Glucose (mg/dl) - Mean±SD	41±31
CSF/blood glucose ratio (mg/dl)- Mean±SD	0.29±0.18

Diagnosis, microbiology and treatment

Lumbar puncture and cerebral CT were performed on all patients. At least one CSF finding suggestive of acute bacterial meningitis was present in all patients: pleocytosis, increased protein concentration, decreased glucose concentration, and decreased ratio of CSF glucose to blood glucose. Patients 50-75 showed the highest CSF protein concentration (p=0.047) and the lowest CSF glucose to blood ratio (p=0.048), and also tended to show the highest C-Reactive Protein (CRP) (p=0.051). The Gram's stain of CSF was positive in 37% of patients, whereas CSF culture was positive in 53%. Gram's staining observations were consistent with the final etiology in 54% of episodes, with best results in pneumococcal infection (67%) and worst results in listeria infection (22%). The most frequent etiological agent was *S. pneumoniae* (34%), followed by *L. monocytogenes* (13%), and up to 28% of microbiological studies produced negative results (*Table 2*). The severity of the disease at presentation, as reflected by a higher frequency of focal neurologic deficits and a lower level of consciousness, was not different when compared by microbiological etiology. Imaging abnormalities were detected in 30% of cases, 50% of which corresponded to sinusitis and/or otitis. At least one focal neurologic deficit (excluding cranial-nerve abnormalities), GCS score of ≤12, immunosuppression, new-onset seizure and history of brain infarction or other central nervous system disease was present in 65% of patients. CT was performed before lumbar puncture in 86% of these episodes and in 89% of patients who did not meet any of these criteria. The median time between admission and first administration of antibiotics was 2h (IQR: 4.25; retrieved from 66% of patients) and was not affected by the performance of CT before lumbar puncture.

Most frequent initial antibiotic regimens consisted of third-generation cephalosporin alone (18%), in combination with vancomycin (24%), or vancomycin plus ampicillin (14%). 44% of patients received other combinations and treatments, 50% of which included a third-generation cephalosporin. There was no correlation between time of administration of antibiotics and risk of a complicated course (systemic p=0.7; neurological p=0.6) or an unfavorable prognosis (p=0.5). Interestingly, 55 out of 74 (74%)

Table 2 - *Microbiological analysis*

Causative pathogen	*No. cases (%)*
Streptococcus pneumoniae	27 (34)
Listeria monocytogenes	10 (13)
Other	20 (25)
Streptococcus species *S. viridans* *S. mitis* *S. agalactiae* *S. milleri*	6
Neisseria meningitidis	2
Haemophilus influenzae	1
Escherichia colli	2
Staphylococcus species *S. aureus* *S. hominis*	4
Klebsiella pneumoniae	2
Enterococcus	1
Pseudomonas aeruginosa	1
Pasteurella multocida	1
Negative culture	22 (28)

patients presented at least one risk factor for listeria infection (i.e., ≥50 years of age, immunosuppression, history of alcoholism), but only 38% received empiric ampicillin. Adjuvant corticosteroids were administered to 48% of patients, and to 65% of patients with pneumococcal meningitis, but this did not affect prognosis.

Spectrum of complications and clinical outcome

During hospitalization, systemic complications occurred in 48% of episodes (*Table 3*), the most common of which were the requirement of mechanical ventilation (23%), hyponatremia (16%) and shock (13%). Neurological complications were found in 45% of episodes, the most common of which were hearing loss (15%), brain edema (10%) and seizures (10%). Only 5 cases of cerebrovascular complications were reported: 1 ischemic stroke, 2 hemorrhagic strokes and 2 episodes of vasculitis. Two of these patients died and two others were categorized as GOS 3 at discharge. Factors associated with the occurrence of cerebrovascular events by bivariate analysis were female sex (p=0.011) and reduced CSF/blood glucose ratio (p=0.02). Duration of hospitalization was less than 2 weeks in 45% of episodes and more than 3 weeks in 23%; half of the patients were transferred to the intensive care unit (ICU) during their hospital stay. Patients aged 50-75 years were admitted to the ICU more often (p=0.001). Overall mortality rate was 15% and was almost 5 times higher in immunocompromised patients (*N*=15) (OR, 4.53; 95% CI 1.18-17.24; p=0.034). None of the microbiological pathogens were associated with a higher risk of complications during hospitalization or exitus. 21% of survivors had moderate-to-severe disability (GOS score of ≤4).

A multivariate model was established to identify features on presentation independently associated with an unfavorable outcome or a complicated course. Characteristics associated with an unfavorable outcome (GOS score of ≤4) included female sex (OR, 9.93; 95% CI, 1.39-70.70; p=0.02) and a GCS score of ≤13 (OR, 6.82; 95% CI 1.06-44.01; p=0.04) (*Table 4*). The causative microorganism had an independent effect when it was added to the multivariate model. The odds of an unfavorable outcome were notably higher in patients infected with *L. monocytogenes* (*N*=10; p=0.002) or gram-negative bacilli (*N*=7; p=0.03) and in patients infected with *S. pneumoniae*. Concurrently, patients infected with *S. pneumoniae* were referred to the ICU more often (p=0.004). Characteristics associated with a higher risk of systemic complications by multivariate modeling included a GCS score of ≤13 (OR, 3.07; 95% CI 1.03-9.20; p=0.045) and reduced platelet count (for each 10^4 platelets reduction: OR, 1.1; 95% CI 1.03-1.16; p=0.005), whereas CRP increase was associated with a higher risk of neurological complications (for each 1mg/dl increase: OR, 1.14; 95% CI 1.03-1.26; p=0.01) (*Table 5*). For the latter, a recent history of alcoholism tended toward statistical significance. All multivariate models were calibrated according to the Hosmer-

Table 3 - *Clinical Course and Outcome*

Adjunctive dexamethasone – no./no. eval. (%)	32/67 (48)
Systemic complications – no./no. eval. (%)	38/79 (48)
Mechanical ventilation	18/78 (23)
Hyponatremia	12/77 (16)
Disseminated intravascular coagulation	2/77 (3)
Arthritis	3/77 (4)
Sepsis/Shock	10/77 (13)
Acute renal failure	9/76 (12)
Endocarditis	1/77 (1)
Duration of hospitalization – no./no. eval. (%)	
<2 weeks	34/75 (45)
2-3 weeks	24/75 (32)
>3 weeks	17/75 (23)
ICU admission – no./no. eval. (%)	38/76 (50)
Neurological complications – no./no. eval. (%)	35/78 (45)
Seizures	8/78 (10)
Brain edema	8/78 (10)
Hydrocephalus	7/78 (9)
Brain abscess	1/78 (1)
Myelitis	2/78 (2)
Hearing loss	12/78 (15)
Ischemic stroke	1/78 (1)
Hemorrhagic stroke	2/78 (3)
Vasculitis	2/78 (3)
Glasgow Outcome Scale, GOS (score)	
5 (mild or no disability)	52 (67)
≤4 (moderate disability – exitus)	26 (33)

Table 4 - *Multivariate Analysis of Factors on Presentation Associated with an Unfavorable Outcome*

	Favorable Outcome (GOS 5, N=52)	*Unfavorable Outcome (GOS ≤4, N=26)*	*Odds Ratio (95% CI)*	*P Value*
Age (years) – mean±SD	54±20	70±16		0.38
Sex – groups				
Male	36 (80)	9 (20)		
Female	16 (49)	17 (51)	9.93 (1.39-70.70)	**0.022**
Glasgow Coma Scale (score)				
>13	27 (84)	5 (16)		
≤13	19 (54)	16 (46)	6.82 (1.06-44.01)	**0.044**
Predisposing condition				
Otitis	15 (88)	2 (12)		0.40
Chronic debilitating condition	6 (37)	10 (63)		0.13
Etiology				
S. pneumoniae	20 (74)	7 (26)		
L. monocytogenes	3 (30)	7 (70)	244.69 (8.18-17,319)	**0.002**
Gram-negative bacilli	2 (29)	5 (71)	26.10 (1.43-476)	**0.028**
Other	9 (69)	4 (31)		0.12
Negative study	12 (82)	3 (18)		0.25
CSF examination				
Leukocytes (cels./µl) – median [IQR]	997 [3619]	498 [1398]		0.79

Table 5 - *Multivariate Analysis of Factors on Presentation Associated with a Complicated Course*

	Systemic complications			
	Without complication (N=41)	*With complication (N=38)*	*Odds Ratio (95% CI)*	*P value*
Glasgow Coma Scale (score)				
>13	22 (69)	10 (31)		
≤13	13 (36)	23 (64)	3.07 (1.03-9.20)	**0.045**
Blood examination – mean±SD				
Platelets (10^3/µl)	231±98	170±94	1.1 (1.03-1.16)	**0.005**
	Neurological complications			
	Without complication (N=43)	*With complication (N=35)*	*Odds Ratio (95% CI)*	*P value*
Glasgow Coma Scale (score)				
>13	22 (69)	10 (31)		
≤13	16 (46)	19 (54)		0.17
Comorbidity				
Alcoholism	3 (25)	9 (75)	11.34 (0.77-167.15)	0.077
Blood examination – mean±SD				
CRP (mg/dl)	9.93±8.39	18.44±11.93	1.14 (1.03-1.26)	**0.01**
CSF examination – mean±SD				
CSF/blood glucose ratio (mg/dl)	0.35±0.15	0.23±0.19		0.16

Lemeshow test (outcome p=0.89, systemic complications p=0.86, neurological complications p=0.52).

DISCUSSION

Clinical and Microbiological Spectrum

The significant morbidity and mortality rates associated with CABM demand a high level of clinical suspicion by health care providers. An adequate estimation of pretest probability of CABM, based on a thorough evaluation of signs and symptoms on presentation, may dramatically impact patient prognosis (*Figure 1*). In our population, the prevalence of the classic triad of fever, neck stiffness, and altered mental status on presentation was low (18%), but almost all patients (82%) exhibited at least two of five signs and symptoms (the classic triad plus headache and nausea). Unlike some published data, manifestations on presentation did not significantly vary when compared by age groups (Domingo *et al.*, 2013; Lai *et al.*, 2011). In addition, a high percentage (45%) of patients were admitted with focal neurological deficits. In general, these percentages are consistent with previous studies (van de Beek *et al.*, 2004 b; Dauchy *et al.*, 2007; Bodilsen *et al.*, 2014; Domingo *et al.*, 2013; Lai *et al.*, 2011). As expected, *S. pneumoniae* was the most frequent pathogen (34%), and the incidence of both *L. monocytogenes* (13%) and gram-negative bacilli (9%) was also similar to existing reports. Conversely, only 2 cases of infection by *N. meningitidis* were detected. Our epidemiological environment has been one of high endemicity of meningococcal disease for many years (Martínez *et al.*, 2009; Schwartz *et al.*, 1989), which motivated the inclusion of the meningococcal C conjugate vaccine in the routine vaccination schedule (Salleras *et al.*, 2003). We hypothesize that the vaccination campaign may have contributed to decreased incidence of meningococcal meningitis in our population, likely by development of herd immunity (Trotter, Maiden, 2009). Finally, it should be noted that the group of negative microbiological studies accounted for 28% of episodes, a fraction which does not significantly differ from previous reports and may be explained by prompt antibiotic administration. This group was not included when studying etiological associations.

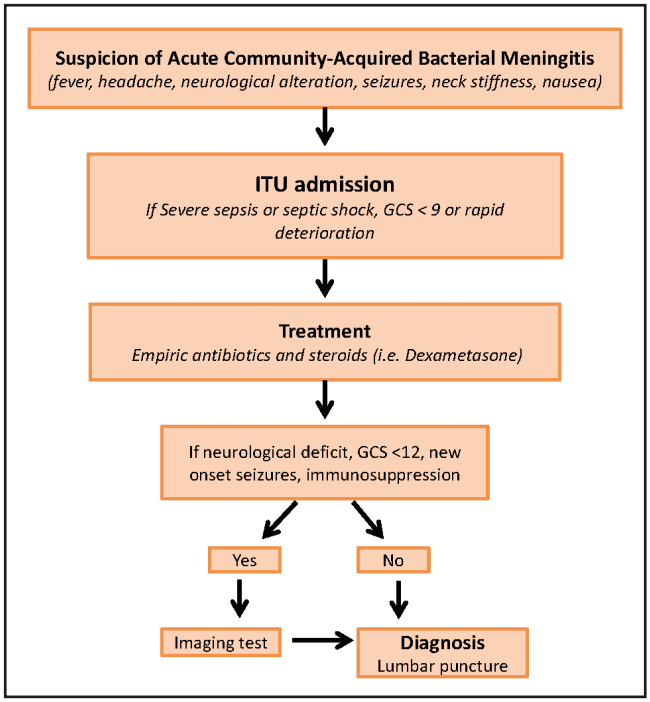

Figure 1 - *Algorithm for Acute Comunity-Acquired Bacterial Meningitis. CABM should be suspected after symptoms of fever, headache, neurological alteration, seizures, neck stiffness, nausea or vomiting. ITU admission for CABM should be considered when GCS <9, severe sepsis or septic shock, or clinical deterioration. Then, treatment must be rapidly initiated with broad spectrum antibiotics and intravenous dexametasone (10 mg). For ABM diagnosis, a lumbar puncture is recommended. Special attention should be paid if presence of GCS <12, neurological deficits, immunosuppression or new onset of seizures, in which, an imaging test is encouraged to discard other neurological disorders.*

Age and underlying conditions in our cohort of CABM cases
Elderly patients and those who have severe underlying conditions are at increased risk of an unfavorable prognosis in CABM (van de Beek *et al.*, 2004 b; Brouwer *et al.*, 2006; Domingo *et al*., 2013; Lai *et al*., 2011). In 68% of episodes, patients were older than 50, and 25% were older than 75. In our study, old age was not significantly associated with a complicated course or an unfavorable outcome. However, the group of patients aged 50-75 was found to be more vulnerable, as reflected by a lower GCS on presentation (p=0.04) and a higher risk of ICU referral (p<0.001), the latter likely influenced by old age being an exclusion criterion for ICU assistance itself. Moreover, GOS score in this group was lower than in younger patients (p=0.003). Although we did not identify significant associations between specific microbiological etiology and age groups, patients aged 50-75 showed CSF analytic signs of a more aggressive course of infection. This may be explained in part by the higher prevalence of chronic debilitating conditions in these patients. In this sense, both *Listeria* and gram-negative bacilli were linked to a worse outcome, and have been described as occurring more frequently in patients who are elderly and/or present important comorbidities (Fernández Guerrero *et al*., 2012; Pomar *et al.*, 2013). Furthermore, predisposing conditions appeared in 58% of patients but were not found to significantly affect the clinical course or prognosis at discharge in multivariate analysis. This may be due to the differential impact of the two most frequent morbidities. First, the antecedent of otitis in the previous month was associated with pneumococcal infection, which in our study was linked to a better outcome. Second, the association between the coexistence of chronic debilitating conditions (mostly immunosuppression) and an unfavorable outcome approached statistical significance.

Diagnostic and therapeutic approach
A lumbar puncture is mandatory when CABM is suspected (van de Beek *et al*., 2006 a) (*Figure 1*). However, clinical guidelines highlight the associated risk of brain herniation and subsequent need of early CT in certain patients. Cranial imaging should precede lumbar puncture in patients with a history of stroke, immunocompromised state, new-onset seizures, signs leading to suspicion of space-occupying lesions, focal neurological deficits (excluding cranial-nerve abnormalities) or moderate-to-severe impairment of consciousness (van de Beek *et al*., 2004c; Tunkel. *et al*., 2004; Hasbun. *et al.*, 2001). In this study, 86% of patients who met at least one of these criteria underwent CT before lumbar puncture, but so did 89% of patients without any criteria. This excess in CT indication prior to lumbar puncture may be explained by two facts. First, a high percentage of patients presented with cranial-nerve involvement and/or mild decrease of consciousness, common symptoms for many other neurological entities such as space-occupying lesions or cerebrovascular accidents. Second, fundus examination by direct ophthalmoscopy is usually underutilized and poorly performed in the emergency department, and thus indirect signs of intracranial hypertension may not be properly assessed. Performance of CT before lumbar puncture has been associated with a serious delay in administration of the first dose of antibiotics, which may lead to a poor outcome, especially in patients with clinical deterioration (Proulx *et al*., 2005; Dauchy. *et al*., 2007; Aronin *et al*., 1998) (*Figure 1*). In our study, time between admission and the first dose of antibiotics was not significantly different when CT was performed. In addition, adjunctive treatment with dexamethasone before or with the first dose of antibiotics has been shown to reduce the risk of unfavorable outcome from 25 to 15% in CABM patients (de Gans, van de Beek, 2002), likely by reducing mortality and systemic complications in pneumococcal meningitis (van de Beek, de Gans, 2004c). The early addition of dexamethasone did not seem to influence patient prognosis or the likelihood of systemic or neurological complications, either when we considered all-etiology or only pneumococcal episodes (*Figure 1*). However, reduced mortality nearly reached statistical significance (p=0.08), which may be due primarily to the modest sample size and to the unexpectedly better outcome of patients with pneumococcal infection.

Identification of patients with poor prognosis remains a challenge for everyday clinical practice
CABM has high case fatality rates, and long-term sequelae are very common among survivors (van de Beek *et al*., 2006a). According to our multivariate model, a low level of consciousness on admission was predictive of an unfavorable outcome, as were female sex and microbiological etiology by *L.monocytogenes* and gram-negative bacilli. There is compelling evidence that invasive listeriosis occurs mainly in patients with underlying chronic conditions, especially immunosuppressive disorders (Fernández Guerrero *et al.*, 2012). Significantly, these cases did not present temporal aggregation. Because the mortality rate remains high (20-40%) (Mylonakis *et al*., 1998; Mitjà *et al*., 2009; Goulet, Marchetti P, 1996), empiric ampicillin should be added to antibiotic regimens in all patients above 50 years of age, with immunocompromised state of any origin, or a history of alcoholism (*Figure 1*). In our population, two facts may have contributed to such worse prognosis: first, patients who received empiric ampicillin accounted for only 38% of patients at risk (74% overall); and second, consistency between Gram's staining observations and final etiology was lowest in listeria infection, thus hindering therapeutic handling. Other groups have previously reported similar findings on listeria-associated meningitis (Brouwer *et al*., 2006). CABM by gram-negative bacilli has also been described as occurring most frequently in elderly patients or those with severe comorbidities, and its associated mortality has reached 53% of episodes in recent reports (Pomar *et al*., 2013). Our limited sample size did not allow us to identify features on presentation or during hospitalization that could contribute to such unfavorable outcome. Finally, it is significant that 24% of patients who suffered from pneumococcal infection had an unfavorable outcome at discharge, significantly less than in previous series (van de Beek *et al*., 2004b; Kastenbauer, Pfister H, 2003). The combination of a clear diagnosis (suggested by the existence of otitis during the previous month and the higher yield of Gram's staining), and early ICU admission may have influenced prognosis in these patients.
Concurrently, our multivariate model detected several features on presentation which may predict a complicated course of hospitalization. Among patients with a GOS score of ≤4, 50% suffered a systemic complication and 51% suffered a neurological complication. Moreover, exitus was mainly related to the occurrence of systemic complications (83% vs 58%), which is consistent with previous literature (van de Beek *et al*., 2004 b; Dauchy *et al*., 2007). Our results suggest that a GCS score of ≤13 and a reduced platelet count on presentation may warn clinicians of a potentially fatal progression and eventual death, and thus lead to more aggressive therapeutic measures, including ICU re-

ferral. Notably, half of the patients discharged as GOS ≤4 presented with less than 150,000 platelets/µl. In addition, early consideration of systemic inflammation through CRP may encourage actions to prevent the development of neurological complications and sequelae. Among neurological complications, the number of cerebrovascular complications was low compared with other retrospective studies (Katchanov *et al*., 2010; Kastenbauer, Pfister, 2003; Klein *et al*., 2011). This may be related to the generalization of early dexamethasone administration and to the benign profile of pneumococcal infection in our series.

Limitations of the study

This study has inherent limitations. First, it is a retrospective study that considered a relatively small number of cases (N=79) over a period of 6 to 8 years, and some uncontrolled factors could have confused our results. However, CABM has low prevalence in our society (0.6-4 cases/year) (Fitch, van de Beek, 2007; van de Beek *et al*., 2004) and our observational results may serve to generate new hypotheses and therapeutic strategies. Moreover, our study is based on three tertiary hospitals closely located in the center of the urban area of Madrid, which may imply that the results may be applicable only to places with a population structure and local ecology similar to ours. However, the fact that all CABM episodes occurred after 2007 and were seen by health care providers with similar training and who used the same diagnostic and therapeutic tools allows us to consider our sample as a homogenous group. Second, we chose the rate of complications during hospitalization and neurological status at discharge as principal variables, which do not reflect meningitis outcome at a specific time after diagnosis.

CONCLUSION

Our understanding of CABM is changing as life expectancy grows, comorbidities become more tolerable, and better preventive measures are made available. Because CABM mortality and morbidity rates remain unacceptably high, a continuous update of presenting and predictive features is essential. In conclusion, our study showed that patients infected with *L. monocytogenes* and gram-negative bacilli may be at increased risk of developing permanent neurological sequelae. Prompt antibiotic therapy against these organisms is seldom employed. Decreased consciousness, thrombocytopenia and elevated CRP levels on admission may be predictive factors for in-hospital complications. Further studies are needed to delineate the epidemiology of CABM and to identify factors on presentation which can discriminate patients who are most likely to benefit from more aggressive maneuvers.

Conflicts of interest

The authors declare no conflict of interest.

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