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# Community-acquired bacterial meningitis in adults: in-hospital prognosis, long term disability and determinants of outcome in a multicentre prospective cohort

Sarah Tubiana[1], Emmanuelle Varon[2], Charlotte Biron[3], Marie-Cecile Ploy[4], Bruno Mourvillier[5], Muhamed-Kheir Taha[6], Mathieu Revest[7], Claire Poyart[8], Guillaume Martin-Blondel[9], Marc Lecuit[10], Eric Cua[11], Blandine Pasquet[12], Marie Preau[13], Bruno Hoen[14]*, Xavier Duval[15]* and the COMBAT study group.

* These authors contributed equally

1 Sarah Tubiana, ST: Paris University, IAME, INSERM, F-75018 Paris, France; Inserm Clinical Investigation Center 1425, Paris, France. sarah.tubiana@aphp.fr

2 Emmanuelle Varon, EV: National Reference Centre for Pneumococci, Centre Hospitalier Intercommunal de Créteil, Créteil, France.

3 Charlotte Biron, CB : Infectious Diseases Department, CHU Hôtel Dieu and INSERM UIC 1413 Nantes University, Nantes, France

4 Marie-Cécile Ploy, MCP : CHU Limoges, Observatoires Régionaux du Pneumocoque, Limoges, France.

5 Bruno Mourvillier, BM: Medical and Infectious Diseases Intensive Care Unit, AP-HP, Bichat Hospital, Paris University, Paris, France.

6 Muhamed-Kheir Taha, MKT: Institut Pasteur, Invasive Bacterial Infections Unit, National Reference Centre for Meningococci and Haemophilus Influenza, Paris, France.

7 Mathieu Revest, MR: Infectious diseases and Intensive care Unit, Inserm U 1230, CHU Rennes, Rennes University, F-35033 Rennes, France

8 Claire Poyart, CP: Department of Bacteriology, University Hospitals Paris Centre-Cochin, French National Center for Streptococci, APHP, France.

9 Guillaume Martin-Blondel, GMB: CHU de Toulouse, Service des Maladies Infectieuses et Tropicales, Toulouse, F-31300 France ; INSERM, UMR1043, Toulouse, F-31300 France.

10 Marc Lecuit, ML: Institut Pasteur, Biology of Infection Unit, Inserm U1117, National Reference Center and WHO Collaborating Center for Listeria, Paris, France. Université de Paris, Hôpital Universitaire Necker-Enfants Malades, Service des Maladies Infectieuses et Tropicales, Institut Imagine, APHP, Paris-France

11 Eric Cua, EC: Infectious Diseases Department, CHU Nice, France

12 Blandine Pasquet, BP: Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Unité de Recherche Clinique Paris Nord, F-75018 Paris, France.

13 Marie Preau, MP: GRePS, Lyon 2 University, Lyon, France.

14 Bruno Hoen, BH : CHU de Nancy, hôpitaux de Brabois, service de maladies infectieuses et tropicales, 54511 Vandœuvre-lès-Nancy cedex, France.

15 Xavier Duval, XD: Paris University, IAME, INSERM, F-75018 Paris, France; Inserm Clinical Investigation Center 1425, Paris, France; Inserm, F-CRIN, Innovative clinical research network in vaccinology (I-REIVAC), Paris, France

**Running title:** Outcome of bacterial meningitis

## Abstract (250 words)

***Objectives.*** To identify factors associated with unfavorable in-hospital outcome (death or disability) in adults with community-acquired bacterial meningitis (CABM).

***Methods.*** In a prospective multicenter cohort study (COMBAT; February 2013-July 2015), all consecutive cases of CABM in the 69 participating centers in France were enrolled and followed up for 12 months. Factors associated with unfavorable outcome were identified by logistic regression and long-term disability analyzed.

***Results.*** Among the 533 enrolled patients, (*S. pneumoniae* 53.8% (280/520 isolates identified), *N. meningitidis* 21.3% (111/520), others 24.9% (129/520)), case fatality rate was 16.9% (90/533) and unfavorable outcome occurred in 45.0% (225/500). Factors independently associated with unfavorable outcome were: age > 70 years (aOR=4.64; 95%CI [1.93-11.15]), male gender (aOR=2.11; [1.25-3.57]), chronic renal failure (aOR=6.65; [1.57-28.12]), *purpura fulminans* (aOR=4.37; [1.38-13.81]), localized neurological signs (aOR=3.72; [2.29-6.05]), disseminated intravascular coagulation (aOR=3.19; [1.16-8.79]), cerebrospinal fluid (CSF) white-cell count < 1500 cells/µL (aOR=2.40; [1.42-4.03]), CSF glucose concentration (0.1-2.5g/L: aOR=1.92; [1.01-3.67]; <0.1g/L: aOR=2.24; [1.01-4.97]), elevated CSF protein concentration (aOR=1.09; [1.03-1.17]), time interval between hospitalization and lumbar puncture > 1 day (aOR=2.94; [1.32-6.54]), and *S. pneumoniae* meningitis (aOR=4.99 ; [1.98-12.56]), or meningitis other than *N. meningitidis* (aOR=4.54; [1.68-12.27]). At twelve months, 26.7% (74/277) had hearing loss, 32.8% (87/265) depressive symptoms, 31.0% (86/277) persistent headache, and 53.4% had a Physical HRQL (142/266) < 25th percentile of the distribution of the score in the general French population (p<0.0001).

***Conclusions.*** The burden of CABM (death, disability, depression, impaired quality of life, and hearing loss) is high. Identification of cases from the first symptoms may improve prognosis.

## Introduction

Community-acquired adult bacterial meningitis (CABM) is a rare disease with an annual incidence around 2/100 000 inhabitants, affecting all age groups and responsible for high morbidity and mortality [1–3]. The epidemiology of community-acquired bacterial meningitis has changed after the introduction of conjugate vaccines [3–5]. Therapeutic challenges, particularly poor penetration of antibiotics into the cerebrospinal fluid and bacterial strains with decreased susceptibility to antibiotics make management complex. Recent therapeutic improvements have mainly relied on the adjunctive use of dexamethasone, whose indications differ according to guidelines [6–9]. Guidelines also differ regarding the antibiotic treatment of meningitis caused by pneumococci with reduced susceptibility to third-generation cephalosporins; only the French recommendations are recommending very high doses of cephalosporins without the systematic addition of vancomycin [9].

Despite meningitis high morbidity and mortality, few large studies have evaluated either the determinants of in-hospital mortality-morbidity or the long-term consequences: disability, quality of life, and depressive symptoms in discharged patients [10–12]. This prospective cohort was designed to describe epidemiological, clinical, and management profiles of adult patients with CABM, with the objective of identifying factors associated with in-hospital unfavorable outcome, and assessing outcome and quality of life one year after diagnosis.

## Methods

### *Study design and setting*

The COMBAT study is a national prospective multicenter cohort study in which adults with CABM were consecutively enrolled in 69 hospitals between February 2013 and July 2015.

### *Participants*

Eligible patients were adults (age ≥18) presenting with a CABM or a *purpura fulminans*. CABM was defined by at least one of the following 1) a CSF culture positive for bacteria; 2) the combination of CSF pleocytosis with a positive blood culture or a positive CSF PCR or antigen test for a meningitis-causing bacterium; or 3) the identification of *Neisseria meningitidis* by culture or specific PCR from a skin biopsy in case of petechiae.

### *Procedures*

In each center, patients were pre-enrolled in the study. Patients or their legal representatives received written information about the study. Only those who gave consent were definitely enrolled. Clinical and microbiological data were prospectively collected and strains were sent to the corresponding national reference centers (see Supplementary Methods). Patients were followed up throughout hospitalization and were contacted by phone twelve months after enrollment. For patients lost to follow-up, vital status was obtained using the French Epidemiology Centre on Medical Causes of Death (CepiDc) database.

### *Variables*

Neurological examinations were performed immediately upon enrollment and before discharge. In-hospital outcome was graded at discharge according to the modified Rankin Scale [13,14]. The

primary endpoint was unfavorable in-hospital outcome, defined by a score of 2–6 (i.e., slight to severe disability, or death) on the modified Rankin scale at discharge [15].

At twelve months, depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale [16], hearing loss using Hearing Handicap Inventory for the Elderly-screening version (HHIE-S) (see Supplementary Methods). Health-related quality of life (HQRL) was evaluated using the SF-12 Health Survey . Two composite scores can be derived from the SF-12 Health Survey: a Physical Component Summary (PCS) and a Mental Component Summary (MCS) HRQL score. An individual was defined as having a "impaired" physical (or mental) HRQL if his PCS (or MCS) was lower than the 25th percentile of the distribution of the score in the general French population of the same age group and gender, using an existing approach to clinically interpret the results [17-18].

***Statistical methods***

First, a descriptive analysis was performed in the cohort population and according to the most frequent causative microorganism (*S. pneumoniae* and *N. meningitidis*). Categorical variables were summarized as counts (percentage) and frequency distributions were compared with the Chi square test or the Fisher exact test as appropriate. Continuous variables were expressed as median (IQR) and differences were tested with the independent t-test for normally distributed variables or the Mann-Whitney U test otherwise.

Second, we searched for factors associated with an unfavorable in-hospital outcome among the following variables: patient's background characteristics, initial clinical presentation (from symptoms onset to 48 hours after inclusion), biological results at inclusion, causative microorganisms and initial treatments [3,12]. We assessed the linearity of the association between continuous variables and outcome with the Lemeshow goodness of fit and by visual inspection. If there was no linear relationship, the continuous variable was categorized for further analyses. We estimated univariable crude ORs using logistic regression on complete cases. In the multivariate analyses, we

used multiple imputations using the SAS statistical software (PROC MI) to impute missing values on all variables of interest. Variables included in the imputation models were those included in the multivariable model and those related to patient clinical course. We used fully conditional specification (FCS) method with linear regression for continuous variables and with discriminant function for categorical variables. We obtained ORs estimates for the multivariate logistic regression model by averaging results across 30 imputed datasets using Rubin's rules [19]. All variables were entered into multivariate model without using any method of selecting variables. Goodness of fit was evaluated by the Hosmer–Lemeshow test and the predicted probabilities validation by c-statistic. The statistical tests were two-tailed; we estimated Wald confidence limits and we deemed p values of less than 0.05 as statistically significant.

We also aimed to identify factors associated with unfavorable in-hospital outcome separately for *S. pneumoniae* and *N. meningitidis* and to identify factors associated with in-hospital death. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC).

***Ethics and regulatory issues***

This study was registered with ClinicalTrials.gov (NCT02916732) and received ethics approval by the Comité de Protection des Personnes Ile de France CPP 4 (IRB 00003835) (2012-16NI), and the French Data Protection Authority (Commission nationale de l'informatique et des libertés) - (EGY/FLR/AR128794).

## Results

### *Patient's characteristics*

A total of 533 patients with bacterial meningitis were enrolled with median age of 58.4 [42.0-68.5] years male sex accounted for 55.2% (294/533; sex ratio: 1.2) (Figure 1; Table 1). Patients with pneumococcal meningitis were older (median 60.2 years, IQR [48.4–68.3]) than those with meningococcal meningitis (median age 30.0 years, IQR [21.4–56.0]) p<0. 001) (Table S1). Risk factors were noted in 353/527 (67.0%) patients and included alcoholism in 83 patients (15.9%), diabetes in 77 (14.8%), CSF leak in 66 (12.6%), history of cancer in 54 (10.3%), immunosuppressant drug use in 21 (4.0 %), or prior splenectomy in 16 patients (3.0%).

### *Initial clinical presentation from symptoms onset to 48 hours after inclusion*

An episode of influenza-like illness prior to meningitis diagnosis was less frequently reported in patients with pneumococcal (91/270; 33.7%) than meningococcal meningitis (56/108; 51.9%) (p=0.001). Antibiotics had been administered during the 48 hours preceding hospital admission to 36.2% (188/520) patients (Table 1). Seizures before hospitalization, fever and altered mental status were all more likely to occur in pneumococcal than in meningococcal meningitis (Table 1).

Distant foci of infection (otitis or sinusitis n=147, pneumonia n=55 or endocarditis n=27) and localized neurological signs were more frequent in patients with pneumococcal than meningococcal meningitis (54.3% vs 6.3%; p<0.0001 and 39.6% vs 22.5%; p=0.0014 respectively)(Table S1).

### *Cerebrospinal fluid findings and brain imaging*

The median time interval [Q1; Q3] between the meningitis symptom onset and the lumbar puncture was 1 day [1-3]. All CSF laboratory parameters are displayed in Table 1. CSF Gram staining was positive in 366/521 (70.2%) episodes, 228/276 (82.6%) of pneumococcal meningitis, 73/107 (68.2%) of meningococcal meningitis, 12/32 (37.5%) of *Listeria* meningitis and 21/36 (58.3%) of other streptococcal meningitis.

114 Brain imaging was performed on admission before lumbar puncture in 224 (58.9%) patients
115 (see Supplementary Results).
116
117 ***Causative microorganisms***
118 The most common pathogen was *S. pneumoniae* (280 (53.8%) of 520 isolates identified).
119 Pneumococcal serotype was available for 195 (87.8%) of 222 episodes with positive blood or CSF
120 culture (Figure 2) (see Supplementary Results). Four *S. pneumoniae* strains had reduced susceptibility
121 to third-generation cephalosporins (MIC>0.5mg/l) and 21 (8.7%) to amoxicillin (MIC > 0.5 mg/L).
122 *N. meningitidis* was responsible for 111 (21.3%) of which 109 cases (98.2%) with known
123 serogroup. Serogroup B (57 (52.3%) of the 109 episodes) was the most frequent, followed by
124 serogroup C (33.0%), serogroup Y (9.2%), serogroup W (2.8%), and others (2.8%). All strains were
125 susceptible to third-generation cephalosporins and one strain was resistant to rifampicin (MIC > 0.25
126 mg/L).
127 Other streptococci accounted for 37 (7.1%) and *Listeria monocytogenes* for 32 (6.2%) of the
128 520 isolates.
129
130 ***Initial treatment***
131 Overall, 493/533 patients (92.5%) received a third-generation cephalosporin containing initial
132 regimen, either alone in 273 (51.2%) patients or combined with amoxicillin in 125 (23.5%), or
133 combined with amoxicillin plus aminoglycoside in 42 additional patients (7.9%); adjunctive
134 dexamethasone was administered to 376 (71.8 %) of 524 patients, before or together with the
135 antibiotics in 244 (65%) and after antibiotics in 129 (35%) patients with data available.
136
137 ***Clinical course***
138 Complications were noted in 459/533 patients (86.1%). Mechanical ventilation was used in 210
139 (40.6%) of the 517 patients with data available and was more frequent among patients with

pneumococcal meningitis (49.4%) than with meningococcal meningitis (30.6%) (p=0.0008), as were seizures during hospitalization (Table S1).

***In-hospital outcome and factors associated with unfavorable outcome***

Overall, case fatality rate was 90 (16.9%) of 533 episodes: 22.5%, 4.5%, 13.5% and 28.1% in pneumococcal, meningococcal, other streptococcal and *Listeria* meningitis, respectively. An unfavorable in-hospital outcome occurred in 225 (45.0%) of 500 episodes with data available: 144 (54.3%) of 265 episodes of pneumococcal meningitis, 19 (18.1%) of 105 episodes of meningococcal meningitis, 14 (37.8%) of 37 episodes of meningitis due to other streptococci and 23 (76.7%) of 30 episodes of *Listeria* meningitis (Table S1).

The following factors were associated with an unfavorable in-hospital outcome: age > 70 years (adjusted OR=4.64; 95%CI [1.93-11.15]), male gender (aOR=2.11; 95%CI [1.25-3.57]), chronic renal failure (aOR=6.65; 95%CI [1.57-28.12]), *purpura fulminans* (aOR=4.37; 95%CI [1.38-13.81]), localized neurological signs (aOR=3.72; 95%CI [2.29-6.05]), disseminated intravascular coagulation (aOR=3.19; 95%CI [1.16-8.79]), cerebrospinal fluid white-cell count lower than 1500 cells per µL (aOR=2.40; 95%CI [1.42-4.03]), cerebrospinal fluid glucose concentration (between 0.1-2.5g/L: aOR=1.92; 95%CI [1.01-3.67]; lower than 0.1g/L: aOR=2.24; 95%CI [1.01-4.97]),, elevated cerebrospinal fluid protein concentration (aOR=1.09; 95%CI [1.03-1.17]), time interval between hospitalization and lumbar puncture higher than 1 day (aOR=2.94; 95%CI [1.32-6.54]), and meningitis due to *S. pneumoniae* (aOR=4.99 ; 95%CI [1.98-12.56]), or meningitis due to other microorganisms as compared to meningitis due to *N. meningitidis* (aOR=4.54; 95%CI [1.68-12.27]). Adjunctive dexamethasone treatment was not associated with an unfavorable in-hospital outcome (aOR=1.02; 95%CI [0.57-1.80]) (Table 2).

***Long-term follow-up***

At twelve months, 5 additional deaths have occurred. Of the 438 living patients, 284 (64.8%) were successfully contacted by phone (Figure 1; see Supplementary Results). Modified-Rankin score could be determined in 282 of these 284 patients. Overall, 47 patients (16.7%) had an unfavorable long-term outcome) with poorer scores in patients with pneumococcal (20.7%) than meningococcal (5.6%) meningitis (p=0.0045).

Among 265 of the 284 patients with CES-D score available, depressive symptoms were recorded in 87 patients (32.8%) with no significant difference in rates between patients with pneumococcal (33.6%) and meningococcal meningitis (34.3%) (p=0.92).

Hearing loss was recorded in 74 of the 277 patients (26.7%) with data available and was more frequent in patients with pneumococcal (31.3%) than meningococcal (15.5%) meningitis (p=0.015). Overall, 86 (31.0%) of the 277 patients had persistent headache with no significant difference in rates between patients with pneumococcal (27.1%) and meningococcal meningitis (32.9 %) (p=0.40).

At twelve months, 53.4% of patients (142/266) had a Physical HRQL score lower than the 25th percentile of the distribution of the score in the general French population (p<0.0001) (54.0% of patients (67/124) with *S. pneumoniae* meningitis and 48.6% of patients (34/70) with *N. meningitidis* meningitis (p<0.0001 for both)).

At twelve months, 29.7% of patients (79/266) had a Mental HRQL score lower than the 25th percentile of the distribution of the score in the general French population (p=0.077) (34.7% of patients (43/124) with *S. pneumoniae* meningitis (p=0.013) and 28.6% of patients (20/70) with *N. meningitidis* meningitis (p=0.49)).

Among 281 patients who had professional activities before admission, 37.8% had not returned to work and 48% of the 282 patients with data available reported trouble concentrating.

## Discussion

With this prospective multicenter cohort, we confirm the high burden of CABM in terms of in-hospital morbidity and mortality and one-year morbidity, especially for depressive symptoms, impaired health-related quality of life, and hearing loss.

COMBAT cohort patients' characteristics closely resemble those reported in other industrialized countries, regarding patients' background characteristics, initial clinical presentation, and distant foci of infections [3]. As expected, patients 'characteristics and initial clinical presentation differed between patients with pneumococcal and meningococcal meningitis with higher rates of comorbidities and more severe neurological conditions in patients with pneumococcal meningitis than in those with meningococcal meningitis. However, the highly frequent extra-cerebral localizations in the former could impede diagnosis especially in elderly people with clinical presentation of an endocarditis or pneumonia associated with altered mental status, or conversely suggest possible bacterial meningitis in cases of acute otitis complicated by altered mental status. Among atypical or confusing clinical presentations, consecutive occurrence of an influenza-like illness followed by a febrile neurological picture revealing a bacterial meningitis was frequent, markedly more so in meningococcal meningitis, as previously reported [20,21].

Distribution of causative microorganisms was close to those of French surveillance data over the same study period [22] and consistent with that reported in the literature [2,3,5,23] with *S. pneumoniae* the most common pathogen followed by *N. meningitidis.* Pneumococcal meningitis due to serotypes in currently available vaccines (7, 13, and 23-valent pneumococcal vaccines) represented more than 60% of all pneumococcal meningitis. Considering the high rate of patients with risk factors who were candidates for vaccination, pneumococcal vaccine coverage was unfortunately low: reported in approximately one third of this population, this rate is nonetheless higher than the 16.4% reported in France in 2011 in a similar population [24].

212 The overall case fatality rate of 16.9% and its variation according to the causative
213 microorganisms are concordant with previous studies [3,25]. Except for meningococcal meningitis,
214 outcome including death and short-term disability was poor in all patients, especially in those with
215 *Listeria monocytogenes* infections. In contrast with some studies, we chose a modified Rankin score
216 over the Glasgow Outcome Scale to measure the degree of disability at discharge, the latter scale
217 being designed to assess independence in the community several months after brain injury, a
218 measure which was not assessable at discharge. Of note, the new "Glasgow Outcome at Discharge
219 Scale (GODS)" has since been published in 2013 [26], after the launch of the current study. Most of
220 the factors independently associated with in-hospital unfavorable outcome, whatever the
221 responsible microorganism, were related to patients' predisposing conditions such as older age, male
222 gender, and chronic renal failure, or to the initial meningitis presentation, such as localized
223 neurological signs, *purpura fulminans* or disseminated intra-vascular coagulation, features
224 practitioners cannot influence. Among factors modifiable by practitioners, the time interval between
225 hospitalization and lumbar puncture was associated with poor in-hospital outcome. The threshold
226 value above which the prognosis was unfavorable was long (1 day). This corresponded to atypical
227 presentations such as pneumonia in patients with altered mental status, for which the diagnosis of
228 meningitis had been mentioned in a second stage. Adjunctive dexamethasone, treatment extensively
229 used in our cohort, was not found to be independently associated with in-hospital unfavorable
230 outcome (death or disability), contrary to reports in the Netherlands cohort [3]; however, it was
231 associated with a decrease in in-hospital death in the univariate analysis.

232 One of our study's strengths is the extended survivor follow-up. Whereas modified Rankin
233 score improved in most patients between discharge evaluation and M12 evaluation still concerning
234 16.5 % of the surviving population with an unfavorable outcome at M12, the rate of those suffering
235 from depressive symptoms and headaches was two-fold higher, affecting one-third of patients. It is
236 noteworthy that although M12 motor disability was much less common in meningococcal meningitis
237 patients than in patients with pneumococcal meningitis, the percentage of meningoccal meningitis

patients with depressive symptoms, headache and altered physical health-related quality of life was much higher and not significantly different from patients with pneumococcal meningitis. As previously reported, over a quarter of patients reported hearing loss, especially in pneumococcal meningitis subgroup [27]. This underlines the importance of addressing all dimensions of disability in long-term follow-up assessment of meningitis patients.

This study suffers from limitations. First, limited 2-year inclusion period did not allow detection of change in *S. pneumoniae* meningitis incidence or serotypes, as shown elsewhere for adults and children, as a consequence of vaccination. Second, the twelve months' evaluation could not be carried out in all survivors. Differences in the patient characteristics of these evaluated and those not does not allow us to impede extrapolation of these characteristics to all survivors.

The burden of bacterial meningitis in adults remains particularly high in the early 21st Century despite progress in intensive care. Rapidity of care, especially during pre-hospitalization, following the symptoms onset, could be improved, particularly through development of an educational tool for the general population. Extended survivor's follow-up is essential to refer them towards appropriated rehabilitation care for both pneumococcal meningitis and meningococcal meningitis. Furthermore, broader adherence to vaccination recommendations deserves special attention.

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**Combat study group**

**Principal investigator:** DUVAL Xavier

**Steering Committee:** HOEN Bruno, MOURVILLIER Bruno, PLOY Marie-Cécile, TUBIANA Sarah, VARON Emmanuelle.

**Scientific committee:** steering committee and the following members CARON François, BOLLAERT Pierre-Edouard, GAILLOT Olivier, TAHA Muhamed-Kheir, POYART Claire, BONACORSI Stephane, VANDENESCH François, CAMBAU Emmanuelle, LECUIT Marc, GRAVET Alain, FRACHET Bruno, De BROUCKER Thomas, LEVY BRUHL Daniel, RAFFI François.

**COMBAT Clinical Centers:** ANGUEL Nadia, ARGAUD Laurent, ARISTA Sophie, ARMAND-LEFEVRE Laurence, BALAVOINE Stéphanie, BARADUC Régine, BARNAUD Guilène, BERAUD Guillaume, BERNARD Louis, BERNARS Georges, BERTEI Dominique, BESSEDE Emilie, BILLARD POMARES Typhaine, BIRON Charlotte, BLAND Stéphane, BOILEAU Julien, BOUBEAU Patrice, BOURDON Sandra, BOUSQUET Aurore, BOYER Sophie, BOZORG-GRAYELI Alexis, BRET Laurent, BRETONNIERE Cédric, BRICAIRE François, BROCAS Elsa, BRUN Michel, BURET Jennifer, BURUCOA Christophe, CABALION Jean, CABON Mathieu, CAMBAU Emmanuelle, CAMUSET Guillaume, CANEVET Christophe, CARON François, CARRICAJO Anne, CASTAN Bernard, CAUMES Eric, CAZANAVE Charles, CHABROL Amélie, CHALLAN-BELVAL Thibaut, CHANTEPERDRIX-MARILLIER Vanessa, CHAPLAIN Chantal, CHARLIER-WOERTHER Caroline, CHAUSSADE Hélène CHIROUZE Catherine, CLAIR Bernard, COLOT Julien, CONIL Jean-Marie, CORDEL Hugues, CORMIER Philippe, COUSSON Joël, CRONIER Pierrick, CUA Eric, DAO-DUBREMETZ Anne, DARGERE Sylvie, DEGAND Nicolas, DEKEYSER Sophie, DELAUNE Deborah, DENES Eric, DEQUIN Pierre-Francois, DESCAMPS Diane, DESCLOUX Elodie, DESMARETZ Jean-Luc, DIEHL Jean-Luc, DIMET Jérôme, DINH Aurélien, DUVAL Xavier, ESCAUT Lelia, FABE Claude, FAIBIS Frédéric, FLATEAU Clara, FONSALE Nathalie, FORESTIER Emmanuel, FORTINEAU Nicolas, GAGNEUX-BRUNON Amandine, GARANDEAU, GARCIA Magali, GAROT Denis, GAUDRY Stéphane, GOEHRINGER François, GRAVET Alain, GREGOIRE-FAUCHER Valérie, GROSSET Marine, GUBAVU Camélia, GUEIT Isabelle, GUELON Dominique, GUIMARD Thomas, GUINARD Jérôme, HADOU Tahar, HELENE Jean-Pierre, HENARD Sandrine, HENRY Benoit, HOCHART Anne-Cécile, HOEN Bruno, ILLES Gabriela, JAFFUEL Sylvain, JARRIN Irène, JAUREGUY Françoise, JOSEPH Cédric, JUVIN Marie-Emmanuelle, KAYAL Samer, LACASSIN Flore, LAMAURY Isabelle, LANOTTE Philippe, LAURENS Etienne, LAURICHESSE Henri, LE BRUN Cécile, LE MOING Vincent, LE TURNIER Paul, LECUYER Hervé, LEDRU Sylvie, LEGRIX Céline, LEMAIGNEN Adrien, LEMBLE Chantal, LEMEE Ludovic, LESENS Olivier, LEVAST Marion, LHOMMET Claire, MALES Silvija, MALPOTE Edith, MARTIN-BLONDEL Guillaume, MARX Matthieu, MASSON Raphael, MATRAY Olivier, MBADI Aurore, MECHAI Frédéric, MELLON Guillaume, MERENS Audrey, MEYOHAS Marie Caroline, MICHON Adrien , MOOTIEN YOGANADEN Joy, MORQUIN David, MOULY Stéphane, MROZEK Natacha, NGUYEN Sophie, NGUYEN Yohan, OGIELSKA Maja, OZIOL Eric, PAGE Bernard, PATRAT-DELON Solène, PATRY Isabelle, PECHINOT André, PICOT Sandrine, PIERREJEAN, PIROTH Lionel, PLASSART Claire, PLESSIS Patrice, PLOY Marie-Cécile, PORTEL Laurent, POUBEAU Patrice, POUPARD Marie, POYART Claire, PRAZUCK Thierry, QUAESAET Luc, RAFFI François, RAMANANTSOA Adriatsiferana, RAPP Christophe, RASKINE Laurent, RAYMOND Josette, REVEST Matthieu, RICHE Agnès, ROBADAY-VOISIN Stéphanie, ROBIN Frédéric, ROMASZKO JP, ROUSSEAU Florence, ROUX Anne-Laure, ROYER Cecile, SAADA Matthieu, SALMON Dominique, SAROUFIM Carlo, SCHMIT Jean Luc, SEBIRE Manuela, SEGONDS Christine, SIVADON-TARDY Valérie, SOISMIER Nathalie, Solen KERNEIS, SON Olivia, SUNDER Simon, SUY Florence, TANDE Didier, TANKOVIC Jacques, VALIN Nadia, VAN GRUNDERBEECK Nicolas, VANDENESCH François, VARON Emmanuelle, VERDON Renaud, VERGNAUD Michel, VERNET-GARNIER Véronique, VIDAL Magali, VITRAT Virginie, VITTECOQ Daniel, VUOTTO Fanny.

**Coordination and statistical analyses (Clinical trial unit, Hôpitaux Universitaires Paris Nord Val de Seine, AP-HP, Paris):** GORENNE Isabelle, LAOUENAN Cédric, MARCAULT Estelle, MENTRE France, PASQUET Blandine, ROY Carine, TUBIANA Sarah.
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**Figure 1:** Study flow chart

**Figure 2:** Distribution of S*. pneumonia* serotypes (%) in the COMBAT study (N=195)

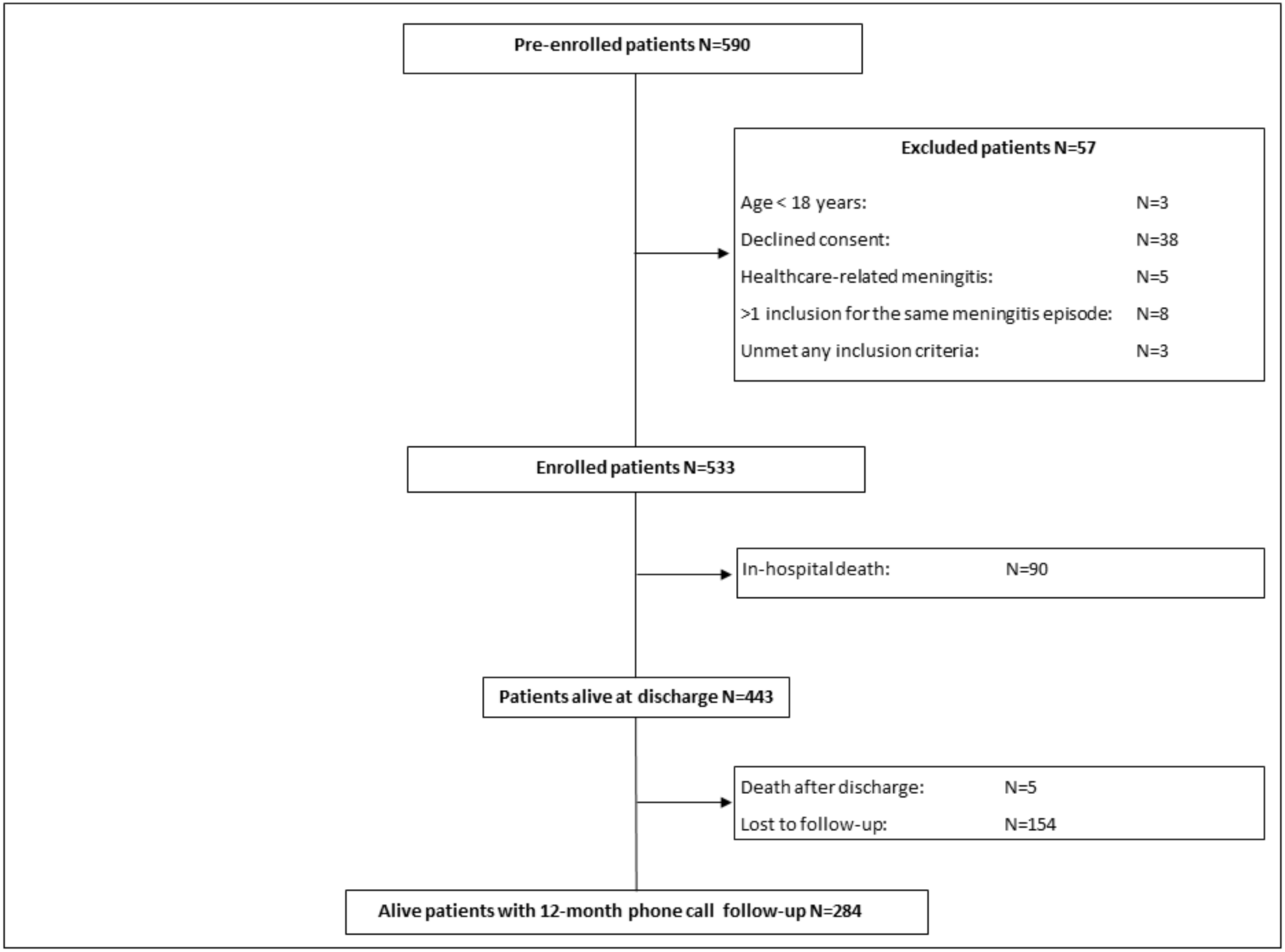
Note:

*Green bars correspond to the additional serotypes included in the 13-valent vaccine as compared to those included in the 7-valent*

*Orange bars correspond to serotypes include in the 7-valent vaccine; 19 (9.8%) of meningitis cases were due to a pneumococcal serotype included in the 7-valent vaccine*

*Purple bars correspond to serotype include only in the polysaccharide 23-valent vaccine; 119 (61.0%) of meningitis were due to a pneumococcal serotype included in the 23-valent polysaccharide vaccine*

*Blue bars correspond to serotypes non-included in any current vaccines*


Pre-enrolled patients N=590
Excluded patients N=57
Age < 18 years: N=3
Declined consent: N=38
Healthcare-related meningitis: N=5
>1 inclusion for the same meningitis episode: N=8
Unmet any inclusion criteria: N=3
Enrolled patients N=533
In-hospital death: N=90
Patients alive at discharge N=443
Death after discharge: N=5
Lost to follow-up: N=154
Alive patients with 12-month phone call follow-up N=284

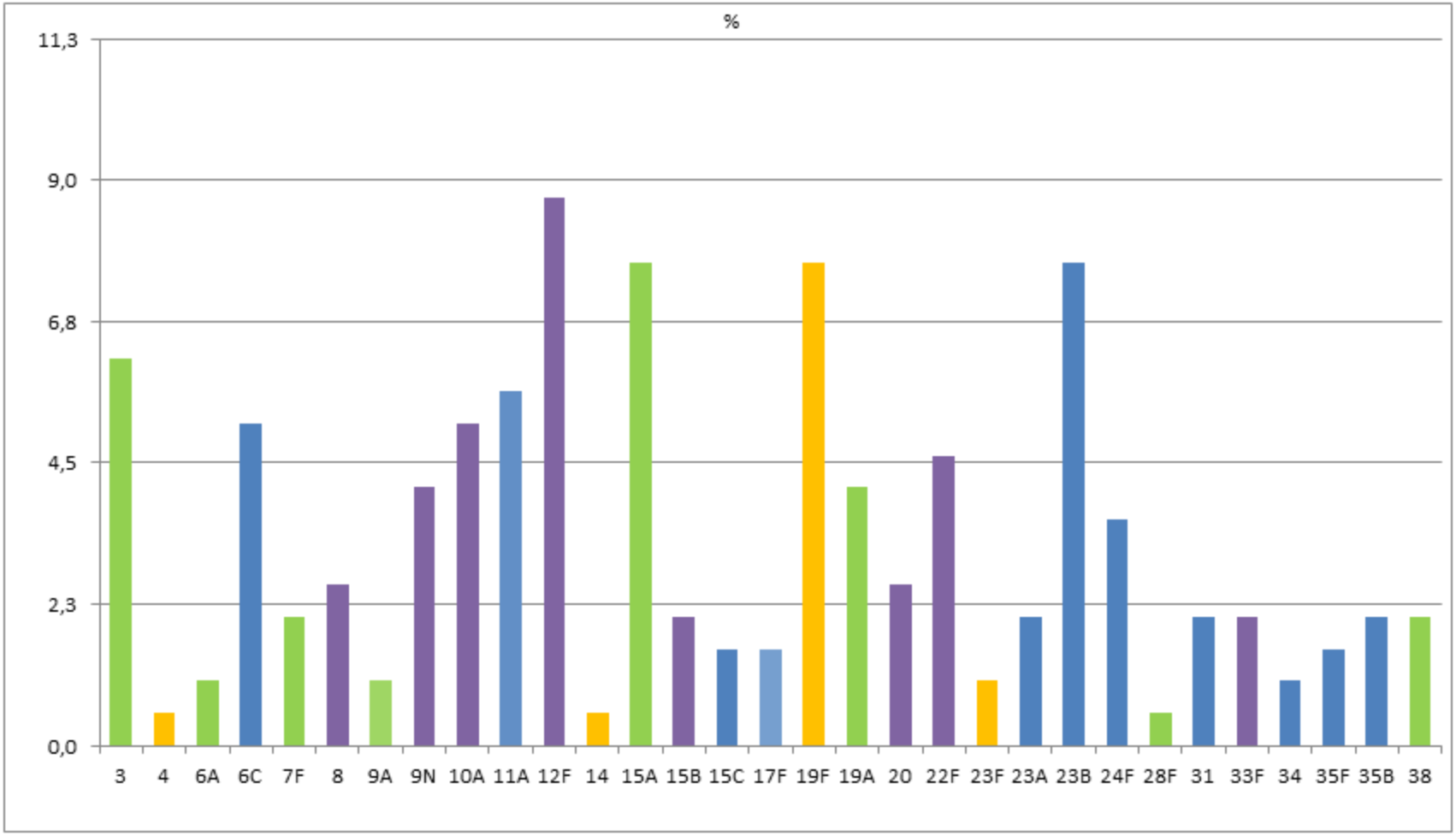

%
11,3
9,0
6,8
4,5
2,3
0,0
3
4
6A
6C
7F
8
9A
9N
10A
11A
12F
14
15A
15B
15C
17F
19F
19A
20
22F
23F
23A
23B
24F
28F
31
33F
34
35F
35B
38

**Table 1: Characteristics of the study population, COMBAT study (N=533)**

| | n /N (%) |
|---|---|
| **Background characteristics** | |
| Age, Median [IQR] | 58.4 [42.0-68.5] |
| Male/female Ratio | 1.2 |
| ≥ 1 risk factor for meningitis | 353/527 (67.0) |
| Alcoholism | 83/522 (15.9) |
| Diabetes | 77/522 (14.8) |
| CSF leak | 66/522 (12.6) |
| History of cancer (< 5 years) | 54 /525 (10.3) |
| History of cardiac failure | 31/524 (5.9) |
| Immunosuppressant drug use | 21/526 (4.0) |
| History of chronic renal failure | 21/523 (4.0) |
| History of splenectomy | 16 /525 (3.0) |
| **Initial clinical presentation from symptoms onset to 48 hours after inclusion** | |
| Episode of influenza-like illness within 15 preceding days | 190/513 (37.0) |
| Admission in intensive care unit | 417/527 (79.1) |
| Pre-treatment with antibiotics | 188/520 (36.2) |
| Body temperature (Median [IQR]) | 38.5 [37.7-39.3] |
| Seizures before hospitalization | 37/518 (7.1) |
| Altered mental status | 373/523 (71.3) |
| Headache | 361/511 (70.6) |
| Neck stiffness | 325/515 (63.1) |
| Nausea | 263/515 (51.1) |
| Distant foci of infection | 205/533 (38.5) |
| Localized neurological signs | 183/533 (34.3) |
| Purpura | 49/524 (9.4) |
| **Cerebrospinal fluid findings** | |
| White cells count (cells per mm3) | 1530.0 [332.0-5000.0] |
| % of neutrophils (Median [IQR]) | 92.0 [80.0-96.0] |
| Protein (g/L) | 4.1 [2.1-6.7] |
| Glucose (mM) | 0.6 [0.1-2.5] |
| Positive Gram Stain | 366/521 (70.2) |

| | n /N (%) |
|---|---|
| **Causative microorganisms** | |
| *Streptococcus pneumoniae* | 280/520 (53.8) |
| *Neisseria meningitidis* | 111/520 (21.3) |
| Other streptococci | 37/520 (7.1) |
| *Listeria monocytogenes* | 32/520 (6.2) |
| *Haemophilus influenzae* | 25/520 (4.8) |
| *Staphylococcus aureus* | 11/520 (2.1) |
| *Escherichia coli* | 7/520 (1.3) |
| *Mycobacterium tuberculosis* | 2/520 (0.4) |
| Others | 15/520 (2.9) |
| **Clinical course** | |
| ≥ 1 complication | 459/533(86.1) |
| Assisted ventilation | 210/517 (40.6) |
| Coma (Glasgow score <8) | 134/523 (25.6) |
| Increased fever | 83 /509 (16.3) |
| Seizures | 64/525 (12.2) |
| Ventriculitis | 46/523 (8.8) |
| **In-hospital outcome (modified Rankin score)** | |
| Death (6) | 90/533 (16.9) |
| Major disability (5) | 14/410 (3.4) |
| Moderately severe disability (4) | 27/410 (6.6) |
| Moderate disability (3) | 40/410 (9.8) |
| Mild disability (2) | 54/410 (13.2) |
| Low disability (1) | 107/410 (26.1) |
| No disability (0) | 168/410 (41.0) |
| **Unfavorable outcome*** | **225/500 (45.0)** |

Data are median (IQR) or n/N (%)

*Data available for 500 patients; unfavorable outcome was defined as a modified Rankin score of 2–6

**Table 2: Factors associated with an in-hospital unfavorable outcome (death or disability), COMBAT study (N=500)**

| | **Unfavorable outcome N=225** N (%) | **Favorable outcome N=275** N (%) | **Univariable odds ratio for unfavorable outcome** [95%CI] | **Multivariable odds ratio for unfavorable outcome** [95%CI] | **p value of multivariable analysis** |
|---|---|---|---|---|---|
| **Background characteristics** | | | | | |
| Age (years) | | | | | |
| 18-39 | 24/225 (10.7) | 94/275 (34.2) | 1 | 1 | |
| 40-70 | 119/225 (52.9) | 147/275 (53.5) | 3.17 [1.91-5.28] | 1.79 [0.87-3.67] | 0.1144 |
| >70 | 82/225 (36.4) | 34/275 (12.4) | 9.45 [5.18-17.22] | 4.64 [1.93-11.15] | **0.0006** |
| Men sex | 135/225 (60.0) | 142/275 (51.6) | 1.41 [0.98-2.01] | 2.11 [1.25-3.57] | **0.0054** |
| Alcoholism | 48/219 (21.9) | 32/275 (11.6) | 2.13 [1.31-3.47] | 1.18 [0.62-2.25] | 0.6163 |
| Immunosuppressant drug use | 12/223 (5.4) | 9/275 (3.3) | 1.68 [0.70-4.06] | 0.47 [0.14-1.64] | 0.2391 |
| History of Cancer (< 5 years) | 34/222 (15.3) | 17/275 (6.2) | 2.75 [1.49-5.06] | 1.46 [0.63-3.37] | 0.3779 |
| Diabetes | 45/220 (20.5) | 24/274 (8.8) | 2.68 [1.57-4.56] | 1.93 [0.93-4.01] | 0.0767 |
| History of cardiac failure | 21/221 (9.5) | 10/275 (3.6) | 2.78 [1.28-6.04] | 0.80 [0.29-2.20] | 0.6619 |
| History of chronic renal failure | 17/220 (7.7) | 3 /275 (1.1) | 7.59 [2.20-26.25] | 6.65 [1.57-28.12] | **0.0100** |
| **Initial clinical presentation from symptoms onset to 48 hours after inclusion** | | | | | |
| Nausea or vomiting | 83/213 (39.0) | 162/274 (59.1) | 0.44 [0.31-0.64] | 0.99 [0.58-1.69] | 0.9831 |
| Headache | 118/210 (56.2) | 224/273 (82.1) | 0.28 [0.19-0.42] | 0.65 [0.37-1.15] | 0.1417 |
| Seizures | 47/218 (21.6) | 31/275 (11.3) | 2.16 [1.32-3.55] | 1.43 [0.75-2.72] | 0.2800 |
| Otitis or sinusitis | 57/221 (25.8) | 73/272 (26.8) | 0.95 [0.63-1.42] | 0.79 [0.45-1.38] | 0.4063 |
| Pneumonia | 36/221 (16.3) | 16/272 (5.9) | 3.11 [1.68-5.78] | 2.00 [0.88-4.51] | 0.0964 |
| *Purpura fulminans* | 16/225 (7.1) | 25/275 (9.1) | 0.77 [0.40-1.47] | 4.37 [1.38-13.81] | **0.0120** |
| Triad of fever, neck stiff ness, altered mental status | 60/223 (26.9) | 75/275 (27.3) | 0.99 [0.66-1.45] | 1.03 [0.61-1.75] | 0.9076 |
| Localized neurological signs | 117/225 (52.0) | 61/275 (22.2) | 3.80 [2.58-5.59] | 3.72 [2.29-6.05] | **<.0001** |
| **Biological results at inclusion** | | | | | |
| C-reactive protein ≥ 200 mg/L | 93/177 (52.5) | 100/237 (42.2) | 1.52 [1.03-2.24] | 1.29 [0.75-2.23] | 0.3565 |
| Blood leucocytes ≥10 000 $mm^3$ | 140/216 (64.8) | 207/267 (77.5) | 0.53 [0.36-0.80] | 0.70 [0.40-1.22] | 0.2097 |
| Disseminated intra-vascular coagulation | 21/219 (9.6) | 12/273 (4.4) | 2.31 [1.11-4.80] | 3.19 [1.16-8.79] | **0.0250** |
| CSF glucose concentration (g/L) | | | | | |

| | **Unfavorable outcome N=225** N (%) | **Favorable outcome N=275** N (%) | **Univariable odds ratio for unfavorable outcome** [95%CI] | **Multivariable odds ratio for unfavorable outcome** [95%CI] | **p value of multivariable analysis** |
|---|---|---|---|---|---|
| <0.1 | 57/202 (28.2) | 50/258 (19.4) | 1.72 [1.01-2.94] | 2.24 [1.01-4.97] | **0.0482** |
| 0.1-2.5 | 100/202 (49.5) | 140/258 (54.3) | 1.08 [0.68-1.70] | 1.92 [1.01-3.67] | **0.0469** |
| >2.5 | 45/202 (22.3) | 68/258 (26.4) | 1 | 1 | |
| CSF Protein (g/L) (Mean (std))* | 6.2 (5.3) | 4.3 (4.5) | 1.11 [1.05-1.16] | 1.09 [1.03-1.17] | **0.0066** |
| CSF white cell count < 1500 cells/ $mm^3$ | 135/219 (61.6) | 96/268 (35.8) | 2.88 [1.99-4.17] | 2.40 [1.42-4.03] | **0.0010** |
| CSF % polymorphonuclear cells (Mean (std))** | 82.1 (21.4) | 86.8 (18.6) | 0.89 [0.81-0.98] | 0.99 [0.87-1.13] | 0.8691 |
| **Causative microorganisms** | | | | | |
| *N. meningitidis* | 19/223 (8.5) | 86/264 (32.6) | 1 | 1 | |
| *S. pneumoniae* | 144/223 (64.6) | 121/264 (45.8) | 5.39 [3.10-9.36] | 4.99 [1.98-12.56] | **0.0007** |
| Other microorgansims | 60/223 (26.9) | 57/264 (21.6) | 4.76 [2.58-8.81] | 4.54 [1.68-12.27] | **0.0028** |
| **Initial treatment** | | | | | |
| Time interval between hospitalization and lumbar puncture (Day) | | | | | |
| 0 | 125/221 (56.6) | 207/274 (75.5) | 1 | 1 | 1 |
| 1 | 54/221 (24.4) | 53/274 (19.3) | 1.69 [1.09-2.62] | 1.24 [0.68-2.26] | 0.4788 |
| >1 | 42/221 (19.0) | 14/274 (5.1) | 4.97 [2.61-9.46] | 2.94 [1.32-6.54] | **0.0083** |
| Pre-treatment with antibiotics | 88/217 (40.6) | 92 /274 (33.6) | 1.35 [0.93-1.95] | 0.89 [0.53-1.47] | 0.6442 |
| Dexamethasone use | 153/221 (69.2) | 208/272 (76.5) | 0.69 [0.46-1.03] | 1.02 [0.57-1.80] | 0.9544 |

CSF=cerebrospinal fluid.

* odds ratio for a 1 g/L increase.

** odds ratio for 10 percent increase.

In univariate analysis, percentage of missing value ranged from 0.0% to 3.6% excepted for C-reactive protein (17.2%), CSF glucose concentration (8.0%) and CSF polymorphonuclear cells (6.8%). The multivariable analysis used an imputed dataset with 30 imputation rounds, all variables in the table were entered in the multivariable logistic regression model simultaneously