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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**

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**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/ $\mu$ L (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.

# 1 **Introduction**

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

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

## 18 **Methods**

### 19 ***Study design and setting***

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

22

### 23 ***Participants***

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

29

### 30 ***Procedures***

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

38

39

### 40 ***Variables***

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

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

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

54

#### 55 ***Statistical methods***

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

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

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

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

82

### 83 ***Ethics and regulatory issues***

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

## 88 **Results**

### 89 ***Patient's characteristics***

90 A total of 533 patients with bacterial meningitis were enrolled with median age of 58.4 [42.0-68.5]  
91 years male sex accounted for 55.2% (294/533; sex ratio: 1.2) (Figure 1; Table 1). Patients with  
92 pneumococcal meningitis were older (median 60.2 years, IQR [48.4–68.3]) than those with  
93 meningococcal meningitis (median age 30.0 years, IQR [21.4–56.0])  $p < 0.001$  (Table S1). Risk factors  
94 were noted in 353/527 (67.0%) patients and included alcoholism in 83 patients (15.9%), diabetes in  
95 77 (14.8%), CSF leak in 66 (12.6%), history of cancer in 54 (10.3%), immunosuppressant drug use in  
96 21 (4.0%), or prior splenectomy in 16 patients (3.0%).

97

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

99 An episode of influenza-like illness prior to meningitis diagnosis was less frequently reported in  
100 patients with pneumococcal (91/270; 33.7%) than meningococcal meningitis (56/108; 51.9%)  
101 ( $p = 0.001$ ). Antibiotics had been administered during the 48 hours preceding hospital admission to  
102 36.2% (188/520) patients (Table 1). Seizures before hospitalization, fever and altered mental status  
103 were all more likely to occur in pneumococcal than in meningococcal meningitis (Table 1).

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

107

### 108 ***Cerebrospinal fluid findings and brain imaging***

109 The median time interval [Q1; Q3] between the meningitis symptom onset and the lumbar puncture  
110 was 1 day [1-3]. All CSF laboratory parameters are displayed in Table 1. CSF Gram staining was  
111 positive in 366/521 (70.2%) episodes, 228/276 (82.6%) of pneumococcal meningitis, 73/107 (68.2%)  
112 of meningococcal meningitis, 12/32 (37.5%) of *Listeria* meningitis and 21/36 (58.3%) of other  
113 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

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

142

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

144 Overall, case fatality rate was 90 (16.9%) of 533 episodes: 22.5%, 4.5%, 13.5% and 28.1% in  
145 pneumococcal, meningococcal, other streptococcal and *Listeria* meningitis, respectively. An  
146 unfavorable in-hospital outcome occurred in 225 (45.0%) of 500 episodes with data available: 144  
147 (54.3%) of 265 episodes of pneumococcal meningitis, 19 (18.1%) of 105 episodes of meningococcal  
148 meningitis, 14 (37.8%) of 37 episodes of meningitis due to other streptococci and 23 (76.7%) of 30  
149 episodes of *Listeria* meningitis (Table S1).

150 The following factors were associated with an unfavorable in-hospital outcome: age > 70  
151 years (adjusted OR=4.64; 95%CI [1.93-11.15]), male gender (aOR=2.11; 95%CI [1.25-3.57]), chronic  
152 renal failure (aOR=6.65; 95%CI [1.57-28.12]), *purpura fulminans* (aOR=4.37; 95%CI [1.38-13.81]),  
153 localized neurological signs (aOR=3.72; 95%CI [2.29-6.05]), disseminated intravascular coagulation  
154 (aOR=3.19; 95%CI [1.16-8.79]), cerebrospinal fluid white-cell count lower than 1500 cells per  $\mu\text{L}$   
155 (aOR=2.40; 95%CI [1.42-4.03]), cerebrospinal fluid glucose concentration (between 0.1-2.5g/L:  
156 aOR=1.92; 95%CI [1.01-3.67]; lower than 0.1g/L: aOR=2.24; 95%CI [1.01-4.97]), elevated  
157 cerebrospinal fluid protein concentration (aOR=1.09; 95%CI [1.03-1.17]), time interval between  
158 hospitalization and lumbar puncture higher than 1 day (aOR=2.94; 95%CI [1.32-6.54]), and meningitis  
159 due to *S. pneumoniae* (aOR=4.99 ; 95%CI [1.98-12.56]), or meningitis due to other microorganisms as  
160 compared to meningitis due to *N. meningitidis* (aOR=4.54; 95%CI [1.68-12.27]). Adjunctive  
161 dexamethasone treatment was not associated with an unfavorable in-hospital outcome (aOR=1.02;  
162 95%CI [0.57-1.80]) (Table 2).

163

### 164 ***Long-term follow-up***

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

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

173 Hearing loss was recorded in 74 of the 277 patients (26.7%) with data available and was  
174 more frequent in patients with pneumococcal (31.3%) than meningococcal (15.5%) meningitis  
175 ( $p=0.015$ ). Overall, 86 (31.0%) of the 277 patients had persistent headache with no significant  
176 difference in rates between patients with pneumococcal (27.1%) and meningococcal meningitis (32.9  
177 %) ( $p=0.40$ ).

178 At twelve months, 53.4% of patients (142/266) had a Physical HRQL score lower than the  
179 25th percentile of the distribution of the score in the general French population ( $p<0.0001$ ) (54.0% of  
180 patients (67/124) with *S. pneumoniae* meningitis and 48.6% of patients (34/70) with *N. meningitidis*  
181 meningitis ( $p<0.0001$  for both)).

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

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

## 188 Discussion

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

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

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

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

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

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

255

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281 CHALLAN-BELVAL Thibaut, CHANTEPERDRIX-MARILLIER Vanessa, CHAPLAIN Chantal, CHARLIER-  
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285 Eric, DEQUIN Pierre-Francois, DESCAMPS Diane, DESCLOUX Elodie, DESMARETZ Jean-Luc, DIEHL Jean-  
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288 Amandine, GARANDEAU, GARCIA Magali, GAROT Denis, GAUDRY Stéphanie, GOEHRINGER François,  
289 GRAVET Alain, GREGOIRE-FAUCHER Valérie, GROSSET Marine, GUBAVU Camélia, GUEIT Isabelle,  
290 GUELON Dominique, GUIMARD Thomas, GUINARD Jérôme, HADOU Tahar, HELENE Jean-Pierre,  
291 HENARD Sandrine, HENRY Benoît, HOCHART Anne-Cécile, HOEN Bruno, ILLES Gabriela, JAFFUEL  
292 Sylvain, JARRIN Irène, JAUREGUY Françoise, JOSEPH Cédric, JUVIN Marie-Emmanuelle, KAYAL Samer,  
293 LACASSIN Flore, LAMAURY Isabelle, LANOTTE Philippe, LAURENS Etienne, LAURICHESSE Henri, LE  
294 BRUN Cécile, LE MOING Vincent, LE TURNIER Paul, LECUYER Hervé, LEDRU Sylvie, LEGRIX Céline,  
295 LEMAIGNEN Adrien, LEMBLE Chantal, LEMEE Ludovic, LESENS Olivier, LEVAST Marion, LHOMMET  
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315 **Scientific partnership**: SPLIF, CMIT, SRLF, SFM, REIVAC, SFORL, APNET, SPF

316 **Partners**: ORP (MC PLOY), GPIP/ACTIV (Corinne Levy)

317

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319

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322

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393

394 **Figure 1:** Study flow chart

395

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

397 **Note:**

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

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

402  
403 *Purple bars correspond to serotype include only in the polysaccharide 23-valent vaccine; 119 (61.0%) of*  
404 *meningitis were due to a pneumococcal serotype included in the 23-valent polysaccharide vaccine*

405  
406 *Blue bars correspond to serotypes non-included in any current vaccines*  
407

408

**Pre-enrolled patients N=590**

<b>Excluded patients N=57</b>	
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**

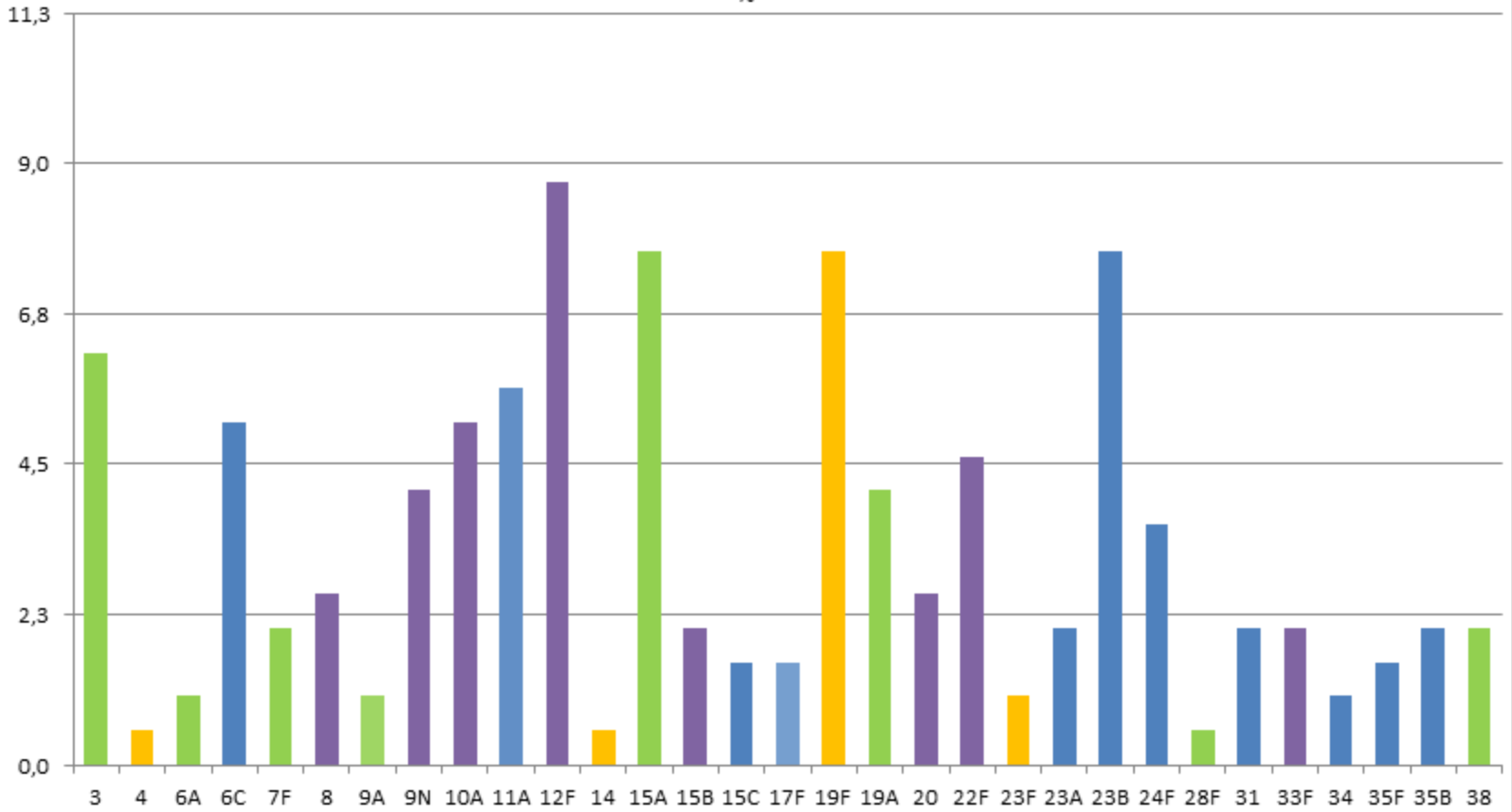
**In-hospital death: N=90**

**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**

%



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

	n /N (%)
<b>Background characteristics</b>	
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)
<b>Initial clinical presentation from symptoms onset to 48 hours after inclusion</b>	
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)
<b>Cerebrospinal fluid findings</b>	
White cells count (cells per mm <sup>3</sup> )	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 (%)
<b>Causative microorganisms</b>	
<i>Streptococcus pneumoniae</i>	280/520 (53.8)
<i>Neisseria meningitidis</i>	111/520 (21.3)
Other streptococci	37/520 (7.1)
<i>Listeria monocytogenes</i>	32/520 (6.2)
<i>Haemophilus influenzae</i>	25/520 (4.8)
<i>Staphylococcus aureus</i>	11/520 (2.1)
<i>Escherichia coli</i>	7/520 (1.3)
<i>Mycobacterium tuberculosis</i>	2/520 (0.4)
Others	15/520 (2.9)
<b>Clinical course</b>	
≥ 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)
<b>In-hospital outcome (modified Rankin score)</b>	
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)
<b>Unfavorable outcome*</b>	<b>225/500 (45.0)</b>

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
<b>Background characteristics</b>					
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]	<b>0.0006</b>
Men sex	135/225 (60.0)	142/275 (51.6)	1.41 [0.98-2.01]	2.11 [1.25-3.57]	<b>0.0054</b>
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]	<b>0.0100</b>
<b>Initial clinical presentation from symptoms onset to 48 hours after inclusion</b>					
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
<i>Purpura fulminans</i>	16/225 (7.1)	25/275 (9.1)	0.77 [0.40-1.47]	4.37 [1.38-13.81]	<b>0.0120</b>
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]	<b>&lt;.0001</b>
<b>Biological results at inclusion</b>					
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 <sup>3</sup>	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]	<b>0.0250</b>
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]	<b>0.0482</b>
0.1-2.5	100/202 (49.5)	140/258 (54.3)	1.08 [0.68-1.70]	1.92 [1.01-3.67]	<b>0.0469</b>
>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]	<b>0.0066</b>
CSF white cell count < 1500 cells/ mm <sup>3</sup>	135/219 (61.6)	96/268 (35.8)	2.88 [1.99-4.17]	2.40 [1.42-4.03]	<b>0.0010</b>
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
<b>Causative microorganisms</b>					
<i>N. meningitidis</i>	19/223 (8.5)	86/264 (32.6)	1	1	
<i>S. pneumoniae</i>	144/223 (64.6)	121/264 (45.8)	5.39 [3.10-9.36]	4.99 [1.98-12.56]	<b>0.0007</b>
Other microorganisms	60/223 (26.9)	57/264 (21.6)	4.76 [2.58-8.81]	4.54 [1.68-12.27]	<b>0.0028</b>
<b>Initial treatment</b>					
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]	<b>0.0083</b>
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