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/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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References

1. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev **2010**; 23:467–492.

2. Brouwer MC, van de Beek D. Epidemiology of community-acquired bacterial meningitis. Curr Opin Infect Dis **2018**; 31:78–84.

3. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study. Lancet Infect Dis **2016**; 16:339–347.

4. McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. Lancet Lond Engl **2012**; 380:1703–1711.

5. Polkowska A, Toropainen M, Ollgren J, Lyytikäinen O, Nuorti JP. Bacterial meningitis in Finland, 1995-2014: a population-based observational study. BMJ Open **2017**; 7:e015080.

6. van Ettekoven CN, van de Beek D, Brouwer MC. Update on community-acquired bacterial meningitis: guidance and challenges. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis **2017**; 23:601–606.

7. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis **2016**; 22 Suppl 3:S37-62.

8. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis Off Publ Infect Dis Soc Am **2004**; 39:1267–1284.

9. Société de Pathologie Infectieuse de Langue Française, Collège des Universitaires des Maladies Infectieuses et Tropicales (CMIT), Association Pédagogique Nationale pour l'Enseignement de la Thérapeutique (APNET), et al. [Management of acute community-acquired bacterial meningitides, except in newborn infants. Short text. November 2008. Société de Pathologie Infectieuse de Langue Française]. Rev Neurol (Paris) **2009**; 165 Spec No 3:F205-216.

10. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. Pediatrics **2009**; 123:e502-509.

11. van de Beek D, Schmand B, de Gans J, et al. Cognitive impairment in adults with good recovery after bacterial meningitis. J Infect Dis **2002**; 186:1047–1052.

12. Weisfelt M, Hoogman M, van de Beek D, de Gans J, Dreschler WA, Schmand BA. Dexamethasone and long-term outcome in adults with bacterial meningitis. Ann Neurol **2006**; 60:456–468.

13. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J **1957**; 2:200–215.

14. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke **2007**; 38:1091–1096.

15. Nguyen THM, Tran THC, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med **2007**; 357:2431–2440.

16. Vilagut G, Forero CG, Barbaglia G, Alonso J. Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. PloS One **2016**; 11:e0155431.

17. Gandek B, Ware JE, Aaronson NK, et al. Tests of data quality, scaling assumptions, and reliability of the SF-36 in eleven countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol **1998**; 51:1149–1158.

18. Carrieri P, Spire B, Duran S, et al. Health-related quality of life after 1 year of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 1999 **2003**; 32:38–47.

19. Donald B. Rubin. Multiple Imputation for Nonresponse in Surveys. New York: Wiley, 1987.

20. Harrison LH, Armstrong CW, Jenkins SR, et al. A cluster of meningococcal disease on a school bus following epidemic influenza. Arch Intern Med **1991**; 151:1005–1009.

21. Bacterial meningitis after influenza. Lancet Lond Engl **1982**; 1:804.

22. Hoen B, Varon E, de Debroucker T, et al. Management of acute community-acquired bacterial meningitis (excluding newborns). Long version with arguments. Med Mal Infect **2019**; 49:405–441.

23. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis **2014**; 14:813–819.

24. Guthmann JP. Publié le 22/12/2011 Maladies infectieuses Enquête nationale de couverture vaccinale, France, janvier 2011 Couverture vaccinale contre la grippe saisonnière dans les groupes cibles et mesure de l'efficacité vaccinale. Couverture vaccinale par les vaccins diphtérie-tétanos-poliomyélite (dTP) et antipneumococcique chez les personnes âgées de 65 ans et plus. France: Institut de veille sanitaire, 2011.

25. Bodilsen J, Dalager-Pedersen M, Schønheyder HC, Nielsen H. Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. BMC Infect Dis **2016**; 16:392.

26. McMillan TM, Weir CJ, Ireland A, Stewart E. The Glasgow Outcome at Discharge Scale: an inpatient assessment of disability after brain injury. J Neurotrauma **2013**; 30:970–974.

27. Heckenberg SGB, Brouwer MC, van der Ende A, Hensen EF, van de Beek D. Hearing loss in adults surviving pneumococcal meningitis is associated with otitis and pneumococcal serotype. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis **2012**; 18:849–855.

Figure 1: Study flow chart

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

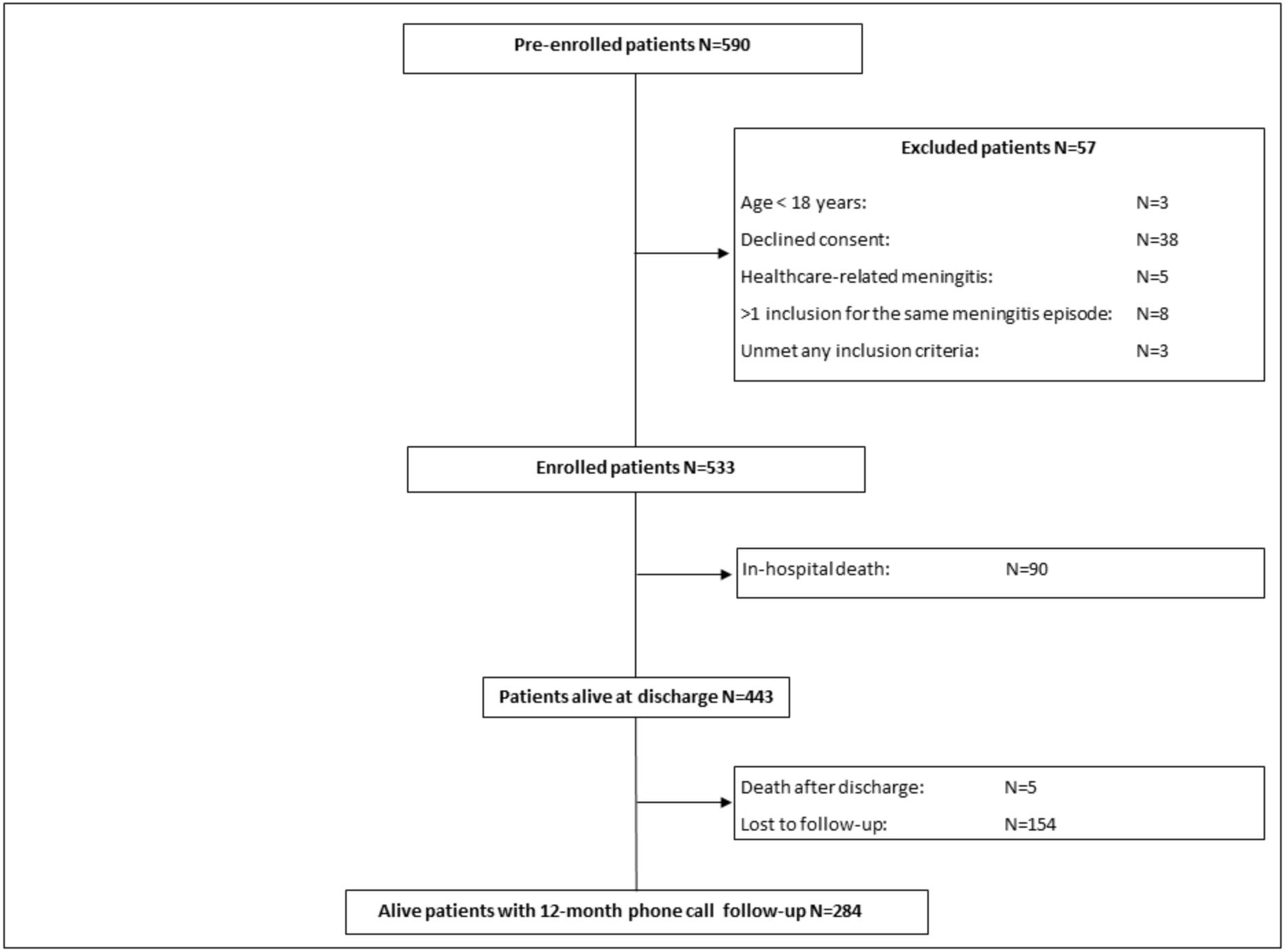
Note:

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

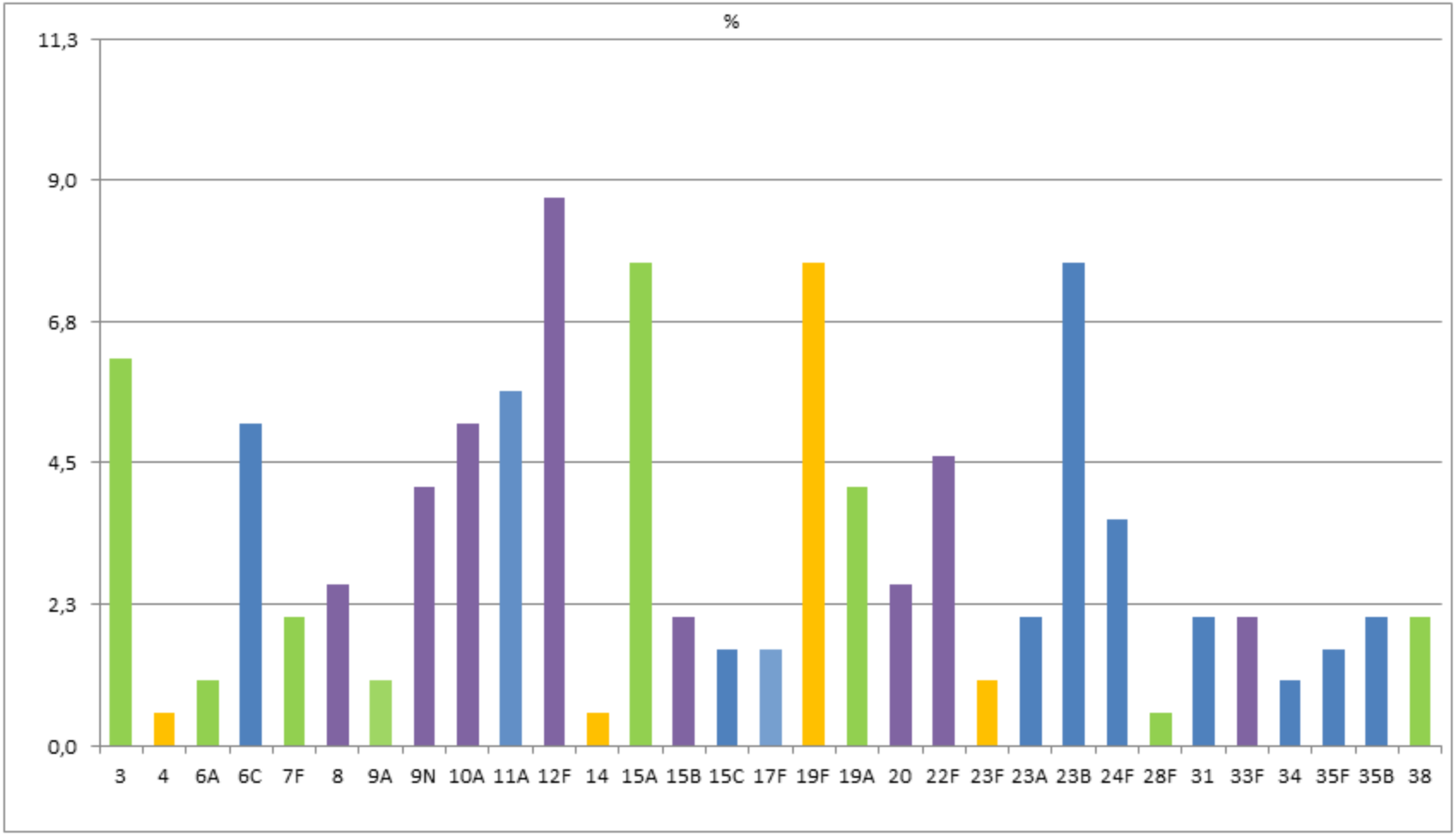

%
11,3
9,0
6,8
4,5
2,3
0,0
3
4
6A
6C
7F
8
9A
9N
10A
11A
12F
14
15A
15B
15C
17F
19F
19A
20
22F
23F
23A
23B
24F
28F
31
33F
34
35F
35B
38

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