One-Year Sequelae and Quality of Life in Adults with Meningococcal Meningitis: Lessons from the COMBAT Multicentre Prospective Study

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BRIEF REPORT

One-Year Sequelae and Quality of Life in Adults with Meningococcal Meningitis: Lessons from the COMBAT Multicentre Prospective Study

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ABSTRACT

Introduction: COMBAT is a prospective, multicentre cohort study that enrolled consecutive adults with community-acquired bacterial meningitis (CABM) in 69 participating centres in France between February 2013 and July 2015 and followed them for 1 year.

Methods: Patients aged at least 18 years old, hospitalised with CABM were followed during their hospitalisation and then contacted by phone 12 months after enrolment. Here we present the prevalence of sequelae at 12 months in a subgroup of patients with meningococcal meningitis.

Results: Five of the 111 patients with meningococcal meningitis died during initial hospitalisation and two died between discharge

The COMBAT study group Collaborators members are listed in the Acknowledgement section.

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and 12 months, leaving 104 patients alive 1 year after enrolment, 71 of whom provided 12-month follow-up data. The median age was 30.0 years and 54.1% of the patients had no identified risk factor for meningitis. More than 30% reported persistent headache, more than 40% were not satisfied with their sleep and 10% had concentration difficulties. Hearing loss was present in about 15% of the patients and more than 30% had depressive symptoms. About 13% of the patients with a previous professional activity had not resumed work. On the SF-12 Health Survey, almost 50% and 30% had physical component or mental component scores lower than the 25th percentile of the score distribution in the French general population. There was a non-significant improvement in the patients' disability scores from hospital discharge to 12 months ($p = 0.16$), but about 10% of the patients had residual disability.

Conclusions: Although most patients in our cohort survive meningococcal meningitis, the long-term burden is substantial and therefore it is important to ensure a prolonged follow-up of survivors and to promote preventive strategies, including vaccination.

Trial Registration: ClinicalTrial.Gov identification number NCT01730690.

Keywords: Community-acquired bacterial meningitis; France; Long-term follow-up; Meningococcal meningitis

Key Summary Points

Why carry out this study?

Little is known about the long-term sequelae in patients hospitalised with meningococcal meningitis

We assessed the sequelae at 12 months in a subgroup of patients from the COMBAT study who were hospitalised with meningococcal meningitis

Hospital and 1-year outcomes were assessed using the modified Rankin and Glasgow outcome scale scores; depressive symptoms were assessed at 12 months using the Centre for Epidemiologic Studies Depression (CES-D) scale; hearing loss was assessed using the Hearing Handicap Inventory for the Elderly–screening version (HHIE-S); and health-related quality of life (HQRL) was assessed using the SF-12 Health Survey

What was learned from the study?

The frequency of disabilities in adult survivors of meningococcal meningitis was high with a substantial impact on patients' quality of life

Although most patients survive meningococcal meningitis, the long-term burden is substantial and therefore survivors should be offered long-term follow-up

Preventive strategies, including vaccination, should be promoted to avoid community-acquired bacterial meningitis

INTRODUCTION

Invasive meningococcal disease is a severe infectious diseases caused by *Neisseria meningitides*, a Gram-negative diplococcus. Its presentation includes mainly community-acquired bacterial meningitis (CABM), and purpura fulminans (i.e. fulminant meningococcemia). Its incidence is between 0.11 and 1.76 cases/100,000 inhabitants in Europe [1]. Meningococcal CABM is a serious bacterial infection that affects the meninges and the cerebrospinal fluid and can cause severe brain damage. It is fatal in up to 50% of cases if untreated but the overall mortality rate can be as high as 10%, despite antibiotic treatment [2–4]. *N. meningitidis* is the second most common cause of CABM. It is carried in the nasopharynx and is transmitted from person to person through droplets of respiratory or throat secretions from carriers. The

estimated carriage rate is the general population is about 10% but varies according to the age group; in infants it is 4.5% and increases to a peak of about 24% in 19-year-olds and then decreases to about 8% in 50-year-olds [5]. Meningococcal meningitis affects mainly children and young adults, but it can occur at any age [6, 7]. Although the in-hospital mortality rate for patients with meningococcal meningitis is low and its prognosis is better than that for CABM caused by other bacteria, after-effects such as brain damage, hearing loss or physical disability have been reported in 10–20% of survivors [8].

Invasive meningococcal diseases are analysed in France through a national reference centre that receives mandatory notification data, including some clinical data, from clinicians and bacterial strains from microbiologists. This epidemiological and microbiological surveillance enables disease outbreaks to be detected and evolution of the disease to be followed over time [9]. However, it is not possible to follow up the patients beyond hospitalisation or to assess long-term disability through this surveillance system. COMBAT was a prospective, multicentre cohort study of CABM in France that identified risk factors associated with death or long-term disability in adults with CABM caused by any bacteria [10]. As little is known specifically about the long-term disability of patients hospitalised with meningococcal meningitis, we performed analyses on the subgroup of patients with meningococcal meningitis in the COMBAT study to assess the prevalence of sequelae and the quality of life after 1-year follow-up.

METHODS

Study Design and Participants

The COMBAT study design and methods have been described elsewhere [10]. In summary, patients aged at least 18 years old and hospitalised with a CABM were enrolled between February 2013 and July 2015 in France. Clinical and microbiological data were collected prospectively during their hospital stay and the patients were subsequently contacted by telephone 12 months after enrolment. In this post hoc analysis, we included data for patients who had been diagnosed with meningococcal meningitis with or without purpura fulminans. The vital status of patients lost-to-follow-up was obtained from the French Epidemiology Centre for Medical Causes of Death (CepiDc: Centre d'épidémiologie sur les causes médicales de Décès) national database [11].

The study received ethics approval from 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). Although the use of the CepiDc national database does not require ethics committee approval, it use for this study was approved by the ethics committee.

Objectives

The primary objective of this post hoc analysis was to describe the prevalence of sequelae in a subgroup of adults in the COMBAT study with meningococcal meningitis after 1-year follow-up. The secondary objectives were to describe the prevalence of sequelae by meningococcal serogroup (B, C, Y), and to describe the evolution of modified Rankin scores, Glasgow outcome scale scores and physical handicap from hospital discharge to the 1-year assessment.

Measurements

Risk factors for CABM were recorded. The hospital discharge and 1-year outcomes were graded using the modified Rankin scale [12, 13]. In survivors, an unfavourable outcome was defined as a score of 2 to 5 (i.e., mild to severe disability). Glasgow outcome scale scores were also assessed at discharge and at 12 months.

Depressive symptoms were assessed at 12 months using the Centre for Epidemiologic Studies Depression (CES-D) scale, and hearing loss using the Hearing Handicap Inventory for the Elderly–screening version (HHIE-S) [10]. Health-related quality of life (HQRL) was evaluated using the SF-12 Health Survey, using the

derived composite physical component summary (PCS) and mental component summary (MCS) HRQL scores. Impaired physical or mental HRQL was defined as a PCS or MCS score lower than the 25th percentile of the score distribution in the French general population with the same age and gender [14, 15].

Statistical Methods

Categorical variables were summarized as counts (percentages) and continuous variables were expressed as medians and interquartile ranges (IQR). The McNemar test for paired samples was used for comparisons between data at hospital discharge and at the 12-month follow-up visit. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC).

RESULTS

Among the 533 patients in the COMBAT study cohort, 111 were diagnosed with meningococcal meningitis (Fig. 1). The median age of these patients was 30 years [interquartile range (IQR) 21.4–56.0] (Table 1). Almost half (45.9%) had at least one risk factor for meningitis. The majority of the patients had headache and neck stiffness and had been admitted to an intensive care unit. Distribution of *N. meningitidis* serogroups is presented in Table 2. An in-hospital unfavourable outcome, defined as a modified Rankin score of 2–6, was reported for 19 patients, including 5 (4.5%) patients who died in hospital. Another two patients died between hospital discharge and the 12-month follow-up visit. At 12 months, 71 of the 104 patients alive at 12 months were contacted and provided information about their health.

At 12 months, 24 of the 70 patients (34.3%) with an available CES-D score had depressive symptoms (Table 2). Persistent headache was reported by 23 (32.9%) patients and hearing loss by 11 (15.5%). The PCS and MCS HRQL scores for 34/70 (48.6%) and 20/70 (28.6%) of the patients, respectively, were lower than the 25th percentile of the score distribution in the French general population but only the decrease in physical HRQL was statistically significant ($p < 0.0001$). These results were similar, irrespective of the serogroup, with the exception of hearing loss that was more frequent in patients with serogroup Y meningitis ($p = 0.002$) (Table 2).

The modified Rankin score was at least 2 for 8/69 (11.6%) of the patients at the time of hospital discharge and in 4/71 (5.6%) at 12 months (p (McNemmar) = 0.16). Similar results were observed for the Glasgow outcome scale.

DISCUSSION

Most patients who had been hospitalised with meningococcal meningitis reported a good outcome at 12 months, but about 10% of the patients reported a poor outcome, irrespective of the serogroups. The patients in this study

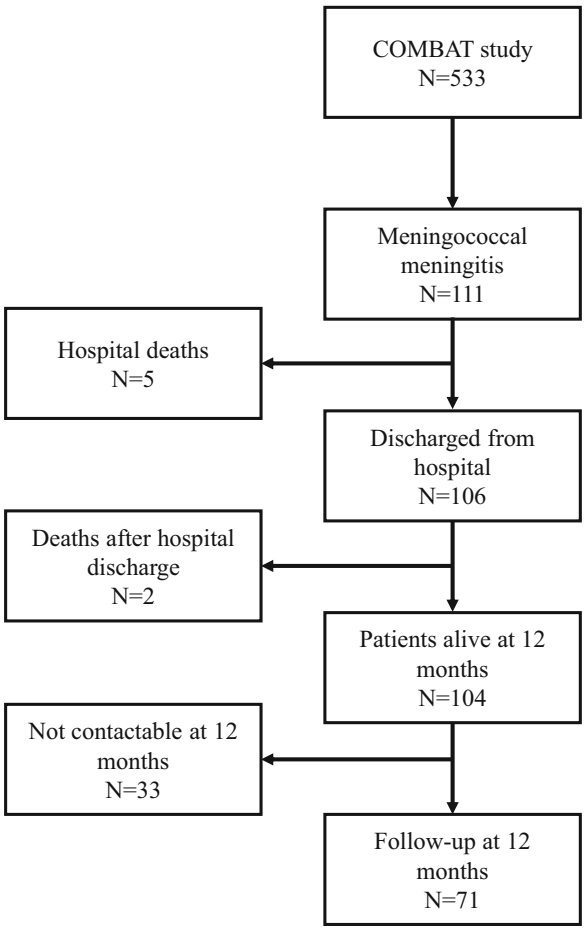

Fig. 1 Study flow chart

Table 1 Baseline characteristics of the 111 patients with meningococcal meningitis included in the COMBAT cohort

Variables	
Background characteristics	
Age, median [IQR]	30.0 [21.4–56.0]
Male/female ratio	1:1.2
≥ 1 risk factor for meningitis	51/111 (45.9)
Alcoholism	8/111 (7.2)
History of cancer (< 5 years)	5/111 (4.5)
Diabetes	4/111 (3.6)
Cerebrospinal fluid leak	1/111 (0.9)
Chronic renal failure	1/110 (0.9)
Immunosuppressant drug use	1/111 (0.9)
HIV	6/111 (5.4)
Cardiac failure	0/111 (0)
Splenectomy	0/111 (0)
Episode of influenza-like-illness in previous 15 days	56/108 (51.9)
Pre-treatment with antibiotics	37/110 (33.6)
Initial clinical presentation (from symptom onset to 48 h after inclusion)	
Body temperature, °C (median [IQR])	38.2 [37.1–39.0]
Headache	93/109 (85.3)
Neck stiffness	75/107 (70.1)
Nausea	65/108 (60.2)
Altered mental status	52/111 (46.8)
Purpura fulminans[a]	41/111 (36.9)
Localized neurological signs	25/111 (22.5)
Seizures before hospitalisation	3/110 (2.7)
Distant foci of infection (pneumoniae, arthritis, pericarditis)	7/111 (6.3)
Admission to intensive care unit	90/111 (81.1)
Cerebrospinal fluid findings at inclusion	
White cell count, cells per mm^3 (median [IQR])	2237.5 [315–6450]
Protein, g/L (median [IQR])	4.1 [1.6–6.3]
Glucose mmol/L (median [IQR])	0.8 [0.1–2.3]
Smear detection	73/107 (68.2)
Clinical course	
≥ 1 complication	90/111 (81.1)

Table 1 continued

Variables	
Assisted ventilation	33/108 (30.6)
Coma (Glasgow outcome scale score < 8)	14/110 (12.7)
Increased fever	13/107 (12.1)
Seizures	5/110 (4.5)
Ventriculitis	4/110 (3.6)
In-hospital outcome (modified Rankin score)	
Death (6)	5/111 (4.5)
Major disability (5)	2/100 (2.0)
Moderately severe disability (4)	0/100 (0.0)
Moderate disability (3)	4/100 (4.0)
Mild disability (2)	8/100 (8.0)
Low disability (1)	29/100 (29.0)
No disability (0)	57/100 (57.0)
Unfavourable outcome (modified Rankin score of 2–6)	19/105 (18.1)

The data shown are *n/N* and percentages, unless otherwise indicated

[a]Meningitis was not biologically confirmed for patient who had a contraindication to lumbar puncture

were young (median 30 years old) with low (4.5%) in-hospital mortality. There was a non-significant improvement in the patients' disability scores from hospital discharge to 12 months, as measured by the modified Rankin score and the Glasgow outcome scale.

Most of the previously published studies have analysed the sequelae of invasive meningococcal infections in children and report hearing impairment, learning or concentration difficulties or mental retardation [16–27]. The few studies devoted to adults report only neurological or auditory complications, essentially from an economic perspective [28–32]. To the best of our knowledge, no previous study has evaluated the sequelae of invasive meningococcal infections in adults and their consequences on depression and quality of life in a prospective cohort in France, although it has been evaluated retrospectively using an administrative health insurance database [8].

Our study highlights the high frequency of disabilities in adult survivors of meningococcal meningitis and the substantial impact of the disabilities on patients' quality of life. More than 30% of the patients reported persistent headache, more than 40% sleep disturbances, 10% concentration difficulties and more than 30% depressive symptoms. Hearing loss was reported in about 15% of the patients, which is consistent with previous reports [31]. In addition, among the patients who worked prior to their meningococcal meningitis, about 13% had not resumed work at 12 months. These results could explain why the PCS HRQL score was lower than the 25th percentile of the score distribution in the French general population for almost half of the patients and the MCS HRQL score lower than the 25th percentile for almost 30% of them.

Risk factors for developing meningococcal meningitis have been identified using a case control study; however, one in two patients did not have any risk factor for meningitis in our population, making the identification of patients at risk and the prevention of this

Table 2 Sequelae, modified Rankin score and Glasgow outcome scale score at 12 months in surviving patients, overall and by *N. meningitidis* serogroup

Variable	All patients with follow-up at 12 months (*N* = 71)	Patients with known serogroup and follow-up at 12 months (*N* = 69)			
		B/C/Y (*N* = 69)	B (*N* = 36)	C (*N* = 27)	Y (*N* = 6)
Persistent headache					
Yes	23/70 (32.9%)	23/68 (33.8%)	13/36 (36.1%)	9/26 (34.6%)	1/6 (16.7%)
MCS (SF 12)					
Median [IQR]	50.8 [39.6–55.5]	50.9 [40.5–55.7]	51.3 [42.0–57.2]	49.7 [39.6–55.0]	53.0 [35.1–55.0]
PCS (SF12)					
Median [IQR]	53.4 [44.3–55.5]	54.1 [42.0–55.5]	52.2 [44.2–55.0]	53.5 [52.6–60.1]	54.1 [42.0–55.5]
Difficulties to concentrate (WHOQOL-BREF)					
Not at all able to concentrate	7/70 (10.0%)	7/68 (10.3%)	5/35 (14.3%)	2/27 (7.4%)	1/6 (16.7%)
A little to extremely well	63/70 (90.0%)	61/68 (89.7%)	30/35 (85.7%)	25/27 (92.6%)	5/6 (83.3%)
Satisfied with sleep (WHOQOL-BREF)					
Dissatisfied or very dissatisfied	30/70 (42.9%)	29/68 (42.6%)	15/35 (42.9%)	13/27 (48.2%)	1/6 (16.7%)
Neither satisfied nor dissatisfied	11/70 (15.7%)	11/68 (16.2%)	5/35 (14.3%)	5/27 (18.5%)	1/6 (16.7%)
Satisfied or very satisfied	29/70 (41.4%)	28/68 (41.2%)	15/35 (42.9%)	9/27 (33.3%)	4/6 (66.7%)
Resumed professional activity (among those working at baseline)					
Yes	48/55 (87.3%)	46/53 (86.8%)	22/26 (84.6%)	21/23 (91.3%)	3/4 (75.0%)
Depressive symptoms (CES-D)					
Yes	24/70 (34.3%)	22/68 (32.4%)	12/35 (34.3%)	9/27 (33.3%)	1/6 (16.7%)
Hearing loss (HHI)					
Yes*	11/71 (15.5%)	11/69 (15.9%)	2/36 (5.6%)	5/27 (18.5%)	4/6 (66.7%)
Modified Rankin score					
Score 0 or 1 (no or low disability)	67/71 (94.4%)	65/69 (94.2%)	35/36 (97.2%)	25/27 (92.6%)	5/6 (83.3%)
Glasgow outcome scale					
Good recovery	63/69 (91.3%)	61/67 (91.0%)	32/34 (94.1%)	24/27 (88.9%)	5/6 (83.3%)

*Hearing loss was the only statistically significant difference between serogroups (Fisher exact test, $p = 0.002$)

disease difficult [33]. To add to the difficulty, many patients presented with an influenza-like illness which was followed by febrile neurological symptoms due to the meningococcal meningitis, as has been previously reported [34–36]. The non-specific clinical presentation of meningococcal meningitis in some patients could have led to a delay in diagnosis and appropriate treatment.

The major strength of this study is the length of the follow-up, since previous studies have rarely reported 12-month follow-up. We were able to show that about 10% of the patients had poor disability scores even 12 months after hospital discharge and sequelae, such as hearing loss, and depression, which could compromise their ability to return to work. This emphasizes the importance of extended multidisciplinary follow-up for patients that are hospitalised for meningococcal meningitis.

We acknowledge three main limitations to this study. The first is the lack of 12-month data

for 33 (32%) of the 104 surviving patients. We were able to determine that these 33 patients were alive 12 months after hospital discharge using the French CepiDc database, but we cannot extrapolate the results from those patients in this analysis to the whole population, given the differences in baseline characteristics [10]. The second is the distribution of meningococcal serogroups with 40% of serogroup C which may not be extrapolated to all countries; vaccination against serogroup C was introduced in France in 2010 and the initial vaccine strategy did not induce enough immunity to protect unvaccinated infants and adults, as has been observed in other countries [9]. Finally, as not all French hospitals participated in the study, we did not include all cases of meningococcal meningitis that occurred in France during this period. Although management and treatment of patients with meningococcal meningitis have improved and in-hospital mortality is relatively low, the important impact on patients' health status at 1 year persists, making it is important to take preventive measures such as vaccination. This is important because, despite the introduction of meningococcal C vaccination in France in 2010 for children aged 12 months in the immunization schedule, the vaccination coverage was below 40% for those aged 10 years or older, 32% for those aged 10–14 years, 23% for those aged 15–19 years and 7% in those aged 20–24 years in 2015 [9], emphasising the need to improve efforts to increase vaccination uptake with available meningococcal vaccines.

CONCLUSION

Although most patients survive meningococcal meningitis, the long-term burden is substantial and therefore survivors should be offered long-term follow-up. Preventive strategies, including vaccination, should be promoted to avoid community-acquired bacterial meningitis.

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Data Availability. The datasets (aggregated and anonymised), analysed for this specific

analysis, are available (on reasonable request) from the corresponding author.

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