Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Induced Hypothermia in Severe Bacterial Meningitis
A Randomized Clinical Trial

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IMPORTANCE Despite advances in care, mortality and morbidity remain high in adults with acute bacterial meningitis, particularly when due to *Streptococcus pneumoniae*. Induced hypothermia is beneficial in other conditions with global cerebral hypoxia.

OBJECTIVE To test the hypothesis that induced hypothermia improves outcome in patients with severe bacterial meningitis.

DESIGN, SETTING, AND PATIENTS An open-label, multicenter, randomized clinical trial in 49 intensive care units in France, February 2009–November 2011. In total, 130 patients were assessed for eligibility and 98 comatose adults (Glasgow Coma Scale [GCS] score of ≤8 for <12 hours) with community-acquired bacterial meningitis were randomized.

INTERVENTIONS Hypothermia group received a loading dose of 4°C cold saline and were cooled to 32°C to 34°C for 48 hours. The rewarming phase was passive. Controls received standard care.

MAIN OUTCOMES AND MEASURES Primary outcome measure was the Glasgow Outcome Scale score at 3 months (a score of 5 [favorable outcome] vs a score of 1-4 [unfavorable outcome]). All patients received appropriate antimicrobial therapy and vital support. Analyses were performed on an intention-to-treat basis. The data and safety monitoring board (DSMB) reviewed severe adverse events and mortality rate every 50 enrolled patients.

RESULTS After inclusion of 98 comatose patients, the trial was stopped early at the request of the DSMB because of concerns over excess mortality in the hypothermia group (25 of 49 patients [51%]) vs the control group (15 of 49 patients [31%]; relative risk [RR], 1.99; 95% CI, 1.05-3.77; P = .04). Pneumococcal meningitis was diagnosed in 77% of patients. Mean (SD) temperatures achieved 24 hours after randomization were 33.3°C (0.9°C) and 37.0°C (0.9°C) in the hypothermia and control group, respectively. At 3 months, 86% in the hypothermia group compared with 74% of controls had an unfavorable outcome (RR, 2.17; 95% CI, 0.78-6.01; P = .13). After adjustment for age, score on GCS at inclusion, and the presence of septic shock at inclusion, mortality remained higher, although not significantly, in the hypothermia group (hazard ratio, 1.76; 95% CI, 0.89-3.45; P = .10). Subgroup analysis on patients with pneumococcal meningitis showed similar results. Post hoc analysis showed a low probability to reach statistically significant difference in favor of hypothermia at the end of the 3 planned sequential analyses (probability to conclude in favor of futility, 0.977).

CONCLUSIONS AND RELEVANCE Moderate hypothermia did not improve outcome in patients with severe bacterial meningitis and may even be harmful. Careful evaluation of safety issues in future trials on hypothermia are needed and may have important implications in patients presenting with septic shock or stroke.

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A mong adults with bacterial meningitis, the case fatality rate and frequency of neurologic sequelae are high, especially among patients with pneumococcal meningitis.[1-3] Although adjunctive dexamethasone therapy has been shown to benefit adults with pneumococcal meningitis,[4,5] case fatality remains 20%, stressing the need for new therapeutic approaches.[6] In animal models of meningitis, moderate hypothermia has favorable effects, such as lowering intracranial pressure, modulating nuclear factor-κB activation, preventing apoptosis, and possibly reducing cerebral injury.[7-10] Therapeutic hypothermia[11] is widely applied in global cerebral hypoxemia, such as postcardiac arrest, following evidence of beneficial effects in controlled prospective trials.[12-15] By contrast, hypothermia is less commonly used in traumatic brain injury, where studies have shown conflicting results.[16,17] Clinical trials of patients with trauma have shown a decrease of intracranial pressure in those patients treated with hypothermia, stressing the potential benefit of this technique in bacterial meningitis. Randomized trials on the efficacy and safety of moderate hypothermia in meningitis are lacking, but favorable results of experimental studies and case reports have encouraged clinicians to perform hypothermia in the most severe cases.[18] Lepur et al[19] reported hypothermia in 10 patients with severe bacterial meningitis. In this study, core temperature of patients was lowered between 32°C and 34°C for 72 to 96 hours, with 8 patients having favorable outcomes.

We hypothesized that treatment with hypothermia (32°C-34°C for 48 hours) would improve the functional outcome at 3 months compared with standard care without systemic hypothermia in comatose patients (defined as having a Glasgow Coma Scale[GCS] score of ≤8 for <12 hours) with bacterial meningitis.

Methods

Patients and Sites

We conducted this sequential, open-label, multicenter, randomized controlled trial at 49 intensive care units in France. All sites are routinely using hypothermia for patients after cardiac arrest. Patients were eligible if they were aged at least 18 years and had a suspected or proven bacterial meningitis by either (1) cerebrospinal fluid (CSF) white blood cell count of more than 100/μL and glucose CSF/blood ratio of less than one-third, (2) a CSF protein concentration of more than 2.2 g/L or microorganisms observed in CSF Gram stain, (3) a positive soluble antigen test or polymerase chain reaction for *Streptococcus pneumoniae* or *Neisseria meningitidis*, or (4) positive CSF cultures. All patients had a score on the GCS of 8 or lower for less than 12 hours and had received appropriate antimicrobial therapy. Appropriate antimicrobial therapy was defined as intravenous cefotaxime (200-300 mg/kg/d) or ceftriaxone (100 mg/kg/d); in case of suspicion of listeriosis, amoxicillin was added.

Patients were excluded if they were pregnant, had a positive cryptococcal test, brain abscess, purpura fulminans, or complications requiring therapeutic hypothermia, such as cardiac arrest. Patients were also excluded if the physician in charge decided to limit life support, if the patient had no medical insurance, or if they were included in another interventional study.

The study received ethics approval by CPP Ile de France I, Paris-Hôtel Dieu, Paris, France. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices and adhered to the French regulatory requirements. Written informed consent was obtained from patient surrogates before study inclusion. However, according to French law, in the case of impaired decision making capacity without any surrogate at the time of inclusion, the patient's written informed consent could be obtained after enrollment.

Randomization and Patient Care

Randomization was centralized via the trial website, balanced by blocks of variable and undisclosed size, and stratified on the hypothermia technique (intravascular cooling vs other cooling techniques). In the hypothermia group, patients received a loading dose of 4°C cold saline. We used the protocol previously published by Polderman et al,[20] in which 1500 mL of refrigerated (4°C-6°C) fluids were infused over a 30-minute period. If temperatures had decreased to 33.5°C or lower, no additional refrigerated fluids were infused. If temperatures remained at more than 33.5°C, an additional 500 mL of refrigerated fluid was infused over a 10-minute period. This was repeated until temperatures had reached levels of 33.5°C or higher.[20] All centers were used to routine hypothermia techniques. Esophageal temperature was maintained between 32°C and 34°C for 48 hours with the technique that was used routinely by that particular center. The rewarming phase was strictly passive.

All patients were treated according to guidelines established according to published guidelines and expert opinions.[2,21,22] These recommendations (see eAppendix 1 in the Supplement) included appropriate antimicrobial therapy, mean arterial pressure maintained at more than 70 mm Hg, normocapnia, glycemia of less than 8 mmol/L, natremia between 140 to 145 mmol/L, magnesemia in normal range (0.75-1.00 mmol/L), and phosphoremia of more than 0.6 mmol/L.

We documented baseline characteristics and other parameters during the first week, including nosocomial infections, hemorrhage, cardiovascular complications, and hyperglycemia (eAppendix 2 in the Supplement). Routine electroencephalography was performed after 24 or 48 hours.

Study Outcome Measures

The primary outcome measure was the score on the Glasgow Outcome Scale (GOS) 3 months after randomization[23] as assessed by an independent physician blinded from the treatment regimen (Prospective Randomized Open Blinded Endpoint methodology)[24] by means of a telephone structured interview.[25,26] A score of 1 indicated death; score of 2, a vegetative state; score of 3, severe disability; score of 4, moderate disability; and score of 5, mild or no disability.[25,26] As previously reported in meningitis,[3,4] favorable outcome was defined as a score of 5, and an unfavorable outcome as a score of 1 to 4.

Figure 1. Flow Diagram of Patients
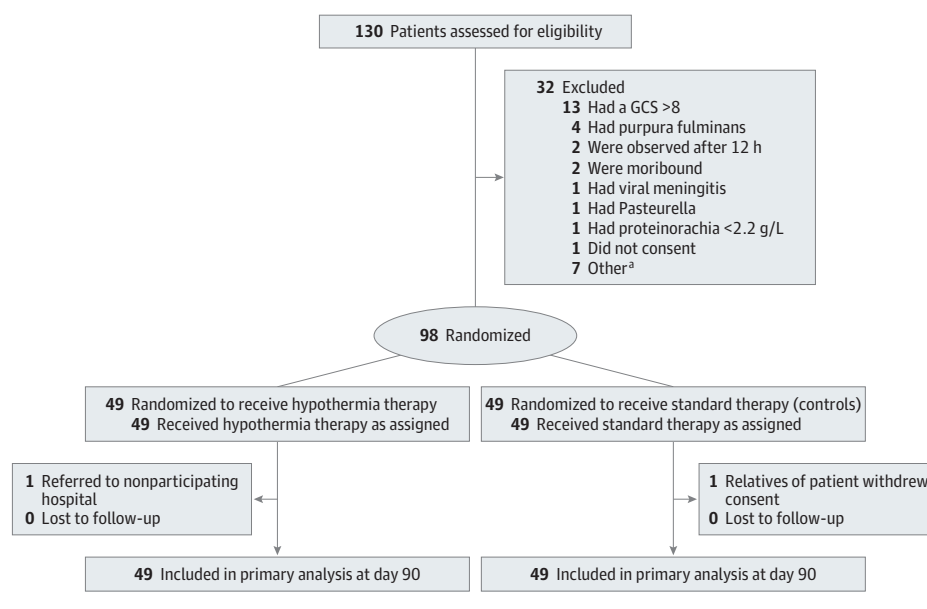
GCS indicates Glasgow Coma Scale.
[a]Other reasons for exclusion were pregnancy, positive cryptococcal test result, brain abscess, or complications requiring therapeutic hypothermia, such as cardiac arrest. Patients were also excluded if the physician in charge decided to limit life support, if the patient had no medical insurance, or if the individual was included in another interventional study. Among these 7 excluded, 2 patients were missed.

Secondary end points were overall mortality at 3 months, hearing impairment at 3 months using the whispered voice test,[27] muscle strength assessed by the Medical Research Council score at intensive care discharge and 3 months posttreatment, complications during the first 7 days after randomization and weekly afterwards over 28 days, and GOS at 6 months. Three investigators (B.M., D.v.d.B., and M.W.), who were masked to the randomization assignment, reviewed all patient charts who died and determined causes of death by consensus, as described previously.[28]

Statistical Analysis

The trial was designed as a triangular sequential study.[29] Unfavorable outcome was expected in 35% of patients with severe meningitis.[1,3] We expected a 15% absolute risk reduction based on previous results of hypothermia after cardiac arrest[5] and dexamethasone in bacterial meningitis.[3] With a 2-sided $\alpha = .05$ and a statistical power of 80%, a total sample size of 276 patients was required. This hypothesis involved a relatively small number of meningitis cases. If a larger sample size had been planned, trial completion would have taken an unrealistically long time with excessive costs. As severe meningitis is a relatively rare disease, 3 interim analyses were planned after 106, 212, and 318 patients were enrolled, respectively. Preset boundaries would permit termination of the trial if the hypothermia group was found to be better than, less than, or equal to the control group.

To address potential safety issues for this new indication of therapeutic hypothermia, the data and safety monitoring board (DSMB) asked to review severe adverse events and mortality rate in both groups for every 50 enrolled patients. Because the number of patients required for the first interim analysis had not been reached, the proportion of patients with an unfavorable outcome was compared between groups by a χ^2 test, according to the intention-to-treat principle. For 1 patient included in the hypothermia group, the GOS score at 3 months was not available because the patient was transferred to a nonparticipating center; therefore, data at 6 months was used (GOS score, 4). Health care proxy withdrew consent after 2 days for 1 patient in the control group who died on day 6. Data from the first 2 days and outcome were kept for analysis. These 2 patients were included in the final analysis. In addition, the primary favorable outcome at 3 months was analyzed with a double triangular sequential design.[29] Post hoc analysis, given observed data from the 98 randomized patients and preplanned assumptions, provided the probabilities to conclude in favor of the hypothermia group, in favor of the control group, and the probability to conclude in favor of futility if the trial had proceeded to completion.

Secondary analyses regarding survival were performed with the Cox proportional hazards regression model. We determined survival curves according to the Kaplan Meier method. Serum sodium concentrations over time were analyzed by using linear mixed models with patient as a random variable. We tested the effect of the interaction of time × treatment group to test sodium concentrations over time by treatment groups. Because we anticipated that pneumococcal meningitis would represent 80% of the total number of enrolled patients, a subgroup analysis of these patients was planned a priori. Analyses were performed with a 2-sided significance level of .05 with R software version 15.1.

Results

Between February 2009 and November 2011, 130 patients were evaluated for inclusion and 32 were excluded from the study (Figure 1). After randomization of 98 patients (49 in each group), the trial was stopped early by the DSMB because of a higher mortality at 3 months in the hypothermia group than in the

control group (25 patients [51%] vs 15 patients [31%] died, respectively; relative risk, 1.99; 95% CI, 1.05-3.77; P = .04). Mortality difference was not a prespecified stopping rule. Interim analyses were planned on the main outcome criterion only. The first interim analysis was planned after 106 patients were enrolled. The DSMB analysis revealed that the difference in mortality at 3 months between the 2 groups was statistically significant (univariate Cox proportional hazards regression model, P = .04). Post hoc analysis, given observed data from the 98 randomized patients and preplanned assumptions, showed that the probability to reach statistical significance in favor of hypothermia was very low if the trial had proceeded to completion (probability to conclude in favor of hypothermia group, 0.023; probability to conclude in favor of control group, <.001; and probability to conclude in favor of futility, 0.977), supporting the DSMB decision (eAppendix 3 in the Supplement).

No significant differences between treatment groups with respect to baseline characteristics was observed (**Table 1**). All patients received mechanical ventilation and were severely ill as reflected by a median score of 7 on the GCS in both groups and high median Simplified Acute Physiology Score II (SAPS II) scores (53 in the control group and 57 in the intervention group). The Simplified Acute Physiology Score ranged from 0 to 154, with higher SAPS II scores indicating more severe illness. A causative bacterium was detected in 90 of 98 patients (92%) and *S pneumoniae* was the most common pathogen, causing disease in 75 of 98 patients (77%). Eight patients presented with coexisting pneumonia. Septic shock at baseline occurred in 18 patients (37%) in the hypothermia group and 10 patients (20%) in the control group (P = .14). Sepsis in these 28 patients was considered to be caused by the microorganism responsible for meningitis. The study included 49 centers, but only 34 centers were active, with a median of randomized patients of 1.

Intervention
Cooling began in the hypothermia group immediately after randomization. Patients reached the goal temperature within a median (interquartile range [IQR]) time of 4.4 hours (2-8 hours) (**Figure 2**) after a median (IQR) cold saline volume of 2401 mL (1500-3125 mL). None of the patients assigned to the control group was treated with hypothermia. We compared patients who received a loading volume of lesser than the median with those who received volumes higher than the median. Mortality (14 of 49 patients [29%] vs 11 of 49 patients [22%]; by t test, P = .34) and scores on the GOS (by Fisher test, P = .90) at 3 months did not differ between patients who received high vs low loading volumes.

Mean (SD) temperatures achieved 24 hours after randomization were 33.3°C (0.9°C) in the hypothermia group and 37.0°C (0.9°C) in the control group. In the hypothermia group, 13 patients were cooled with intravascular technique, 11 with ice packs and cooling air, 10 with ice packs alone, 7 with cooling air alone, 4 with cooling pads, 3 with cooling mattress, and 1 with internal cooling. Hypothermia was stopped before 48 hours after randomization in 7 patients because of death (n = 2), acute myocardial infarction (n = 1), severe bradycardia (n = 1), anisocoria (n = 1), a head computed tomography scan (n = 1),

and referral to a nonparticipating center for neurosurgery (n = 1). The body temperature of the patient for whom hypothermia was stopped because of a head computed tomography scan remained within the 32°C to 34°C range. Overall, median (IQR) time of passive rewarming to a body temperature of more than 36°C was 14 hours (8-111 hours).

Table 1. Baseline Characteristics of the Patients

Characteristics	Hypothermia Group (n = 49)	Control Group (n = 49)
Age, mean (SD), y	59 (18)	59 (17)
Male sex, No. (%)	28 (57)	31 (63)
GCS score on ICU admission, median (IQR), h[a]	7 (4-8)	7 (6-8)
SAPS II score, mean (SD)[b]	57 (16)	53 (17)
SOFA score, mean (SD)[c]	9 (3)	8 (4)
Mechanical ventilation, No. (%)	49 (100)	49 (100)
Septic shock, No. (%)	18 (37)	10 (20)
Pneumonia, No. (%)	3 (6)	5 (10)
CSF leukocyte count, /µL		
Mean (SD)	4342 (9601)	3678 (5457)
Median (range)	890 (6-60 000)	1150 (4-23 400)
Protein, mean (SD), g/L	5.8 (4)	7 (4)
Glucose, median (IQR), mg/dL	0.22 (0.01-0.78)	0.10 (0.00-1.18)
Lactate, mean (SD), mg/dL	139.64 (90.09)	144.14 (54.05)
CSF culture results, No. (%)		
Streptococcus pneumoniae	37 (76)	38 (78)
Streptococcus bovis	1 (2)	0
Neisseria meningitidis	2 (4)	6 (12)
Listeria monocytogenes	1 (2)	2 (4)
Enterobacteriaceae	3 (6)	0
Mycobacterium tuberculosis	1 (2)	0
None	5 (10)	3 (6)
Positive soluble antigen, No. (%)[d]	19 (40)	24 (50)
Positive culture, No. (%)[d]	23 (48)	20 (42)
Positive PCR, No. (%)[d]	6 (13)	4 (8)
Corticosteroids, No. (%)	43 (88)	42 (87)
Dexamethasone, No. (%)	38 (78)	39 (81)
Time, median (IQR), h		
Hospital admission to first antibiotic dose	3.0 (1.1-4.8)	2.6 (1.4-4.9)
Hospital admission to first dose of corticosteroid[e]	5.8 (2.5-8.8)	4.3 (2.3-7.9)
Sedative drugs, No. (%)	14 (29)	13 (27)

Abbreviations: CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; ICU, intensive care unit; IQR, interquartile range; PCR, polymerase chain reaction; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

SI conversions: To convert glucose to mmol/L, multiply by 0.0555; to convert lactate to mmol/L, multiply by 0.111.

[a] Scores on the GCS range from 3 to 15, with 15 indicating a normal level of consciousness.

[b] Scores on the SOFA range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction.

[c] Scores on the SAPS range from 0 to 154, with higher SAPS II scores indicating more severe illness.

[d] Number of patients evaluated was 96 (48 in each group).

[e] Number of patients evaluated was 95 (43 in the hypothermia group and 42 in the control group).

Efficacy and Safety

At 3 months, unfavorable outcome occurred in 42 of 49 patients (86%) in the hypothermia group and 36 of 49 patients (73%) in the control group (risk ratio, 1.17; 95% CI, 0.95-1.43; $P = .13$) (Table 2).

The distribution of scores on the GOS is shown in Table 2 and Figure 3. At 3 months, mortality was significantly higher in the hypothermia group (hazard ratio [HR], 1.99; 95% CI, 1.05-3.77; log-rank $P = .04$) (eTable 1 in the Supplement). In a

multivariable Cox proportional hazards regression analysis after adjustment for age, score on GCS at inclusion, and the presence of septic shock at inclusion, mortality remained higher, although not significantly, in the hypothermia group (HR, 1.76; 95% CI, 0.89-3.45; $P = .10$) (Table 3). Figure 4 shows survival data for patients treated with hypothermia and patients in the control group. Variables used in the Cox proportional hazards regression model were selected a priori because they were clinically relevant and after examination

Figure 2. Body Temperature of Patients With Severe Meningitis During First 48 Hours After Randomization Between Hypothermia and Standard Therapy

No. of patients												
Controls	46	45	45	46	45	46	44	45	44	44	44	42
Hypothermia therapy	47	46	46	46	45	43	43	43	42	42	41	41	40
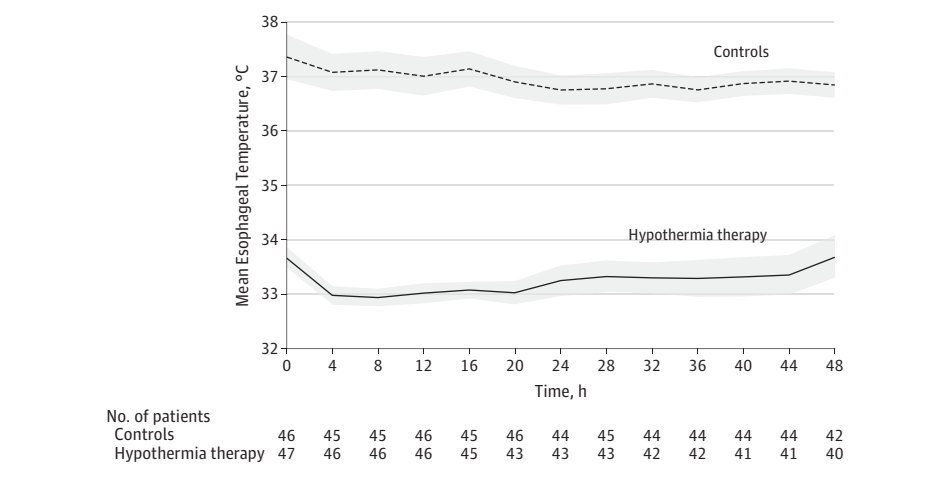
Table 2. Primary and Secondary Outcomes at 3 Months in the Hypothermia and Control Groups (N=98)

Outcome	No. (%) of Patients		Risk Ratio (95% CI)	P Value
	Hypothermia Group (n = 49)	Control Group (n = 49)		
Unfavorable outcome (score on GOS <5)	42 (86)	36 (74)	1.17 (0.95-1.43)	.13
GOS score				
5 = mild or no disability	7 (14)	13 (27)	1 [Reference]	
4 = moderate disability	10 (20)	6 (12)	1.49 (0.69-3.23)	
3 = severe disability	7 (14)	15 (31)	0.23 (0.13-0.44)	.04
2 = vegetative state	0	0		
1 = death	25 (51)	15 (31)	1.90 (1.29-2.81)	
Causes of death[a]				
Neurologic	14 (56)	8 (62)	1 [Reference]	
Systemic	11 (44)	5 (38)	4.23 (1.87-9.58)	.99
MRC score at 3 mo, median (IQR)[b]	60 (53.50-60)	60 (47.50-60)		.95
Hearing impairment at 3 mo[b]	8 (42)	3 (20)	3.38 (1.08-10.57)	.27
Aspiration pneumonia[c]	4 (8)	4 (8)	1.02 (0.27-3.85)	>.99
Hemorrhage[d]	4 (8)	2 (4)	2.00 (0.38-10.41)	.68
Cardiac arrhythmia[d]	12 (25)	7 (15)	1.72 (0.74-3.98)	.31
Nosocomial pneumonia[d]	9 (19)	11 (23)	0.82 (0.37-1.79)	.80

Abbreviations: GOS, Glasgow Outcome Scale; IQR, interquartile range; MRC, Medical Research Council.

[a] Causes of death could be determined in 40 patients (25 in the hypothermia group and 15 in the control group).

[b] The MRC score and hearing impairment data were available for 34 survivors (19 in the hypothermia group and 15 in the control group). The MRC scale assesses strength in 3 muscle groups in each arm and leg. The score for each

muscle group ranges from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60. Comparisons were made with the Wilcoxon test.

[c] Aspiration pneumonia was evaluated in 97 patients (49 in the hypothermia group and 48 in the control group).

[d] Hemorrhage, cardiac arrhythmia, and nosocomial pneumonia were evaluated in 96 patients (48 in the hypothermia group and 48 in the control group).

of the data. Unfavorable outcome at 3 months accounted for 10 of 13 patients (77%) who were cooled with intravascular technique vs 31 of 36 patients (86%) who were cooled with other techniques (*P* = .36). Mortality at 3 months occurred in 6 of 13 patients (46%) who were cooled with intravascular technique vs 14 of 36 patients (40%) who were cooled with other techniques (*P* = .46). Predefined subgroup analysis on patients with pneumococcal meningitis showed similar results (**Table 4**).

There were no differences in occurrence of infections, hemorrhage, cardiovascular effects, and hyperglycemia between treatment groups (Table 2 and eFigures 1 and 2 in the Supplement). When evaluated at intensive care unit discharge in 60 of 67 evaluable patients (90%), and at 3 months in 34 of 58 evaluable patients (59%), hearing loss was similar between groups. Intensive care unit and hospital length of stay were longer in the hypothermia group than in the control group (median [IQR], 15 [9-25] days vs 7 [6-15] days; *P* = .006; and 33 [21-42] days vs 20 [14-30] days; *P* = .03; respectively).

Repeated lumbar punctures 3 days after randomization were performed in 14 patients (29%) in the hypothermia group and 11 patients (22%) in the control group, and all cultures were negative; however, CSF leukocyte counts, protein, and glucose concentrations between treatment groups were similar. Patients showing no activity were 6 (17%) in the control group and 3 (9%) in the hypothermia group. For low-amplitude waves, those proportions were 27 (79%) and 29 (88%), respectively, and for spikes and sharp waves were 1 (3%) for each treatment group. No statistical difference on proportions of those abnormal electroencephalography were found (by Fisher test, *P* = .73). For serum sodium concentration, the overall effect of 0.527 (95% CI, −0.003 to 1.06) of the evolution of concentrations on time, evaluated using linear mixed models, was significant between treatment groups (*P* = .0497) (eFigure 3 in the Supplement). No significant difference between the 2 groups with respect to infusion of osmotic agents was found.

Antibiotic and Anti-inflammatory Treatment

Ninety-seven patients received microbiologically appropriate antibiotic treatment. The median time between arrival in the emergency department and intravenous administration of antibiotics was 3.0 hours in the hypothermia group and 2.6 hours in the control group. In the hypothermia group, 1 patient had confirmed tuberculous meningitis (positive CSF cul-

Figure 3. Three-Month Scores on Glasgow Outcome Scale of Patients With Severe Bacterial Meningitis Treated With Hypothermia or Standard Therapy
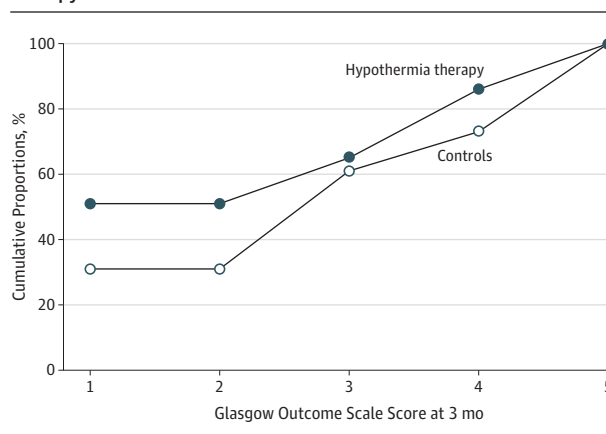
Table 3. Results of the Cox Proportional Hazards Regression Model

Variables	Hazard Ratio (95% CI)	P Value
Treatment group		
Control	1 [Reference]	.10
Hypothermia	1.76 (0.89-3.45)	
Age, per 10-y increment	1.25 (1.01-1.55)	.04
Glasgow Coma Scale score at inclusion	0.89 (0.77-1.02)	.08
Septic shock		
No	1 [Reference]	.006
Yes	2.54 (1.31-4.94)	

Figure 4. Kaplan-Meier Estimates of Survival of Patients With Severe Bacterial Meningitis Treated With Hypothermia or Standard Therapy
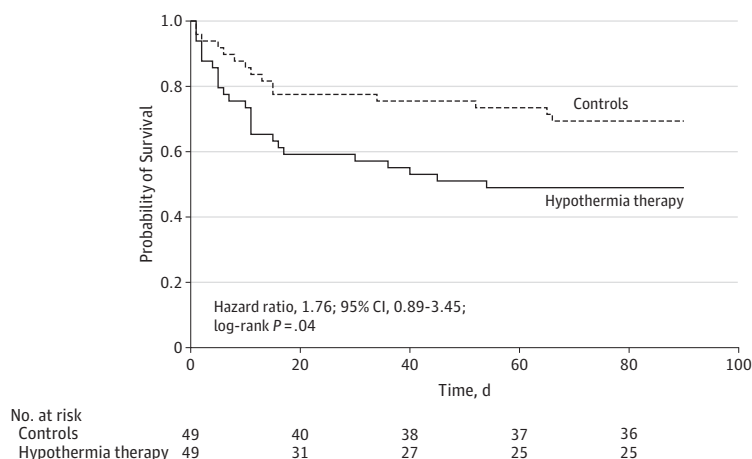
Three-month survival curves were compared with a univariate Cox proportional hazards regression model.

Table 4. Outcomes for Patients With Pneumococcal Meningitis at 3 Months (N=75)

Outcome	No. (%) of Patients		Risk Ratio (95% CI)	P Value
	Hypothermia Group (n = 37)	Control Group (n = 38)		
Unfavorable outcome (score on GOS <5)	32 (86)	30 (79)	1.04 (0.84-1.28)	.58
Score on GOS				
5 = mild or no disability	5 (14)	8 (21)	1 [Reference]	
4 = moderate disability	7 (19)	6 (16)	1.00 (0.47-2.16)	
3 = severe disability	5 (14)	13 (34)	0.18 (0.09-0.37)	.07
2 = vegetative state	0	0		
1 = death	20 (54)	11 (29)	2.39 (1.56-3.68)	
Causes of death[a]				
Neurologic	12 (60)	8 (80)	1 [Reference]	
Systemic	8 (40)	2 (20)	8.00 (2.07-30.88)	.42
MRC score at 3 mo, median (IQR)[b]	60.00 (48.00-60.00)	59.50 (42.50-60.00)		.53
Hearing impairment at 3 mo	7 (54)	2 (20)	4.55 (1.19-17.34)	.20
Aspiration pneumonia[c]	2 (5)	3 (8)	0.65 (0.12-3.67)	>.99
Hemorrhage[d]	3 (8)	1 (3)	2.84 (0.31-26.08)	.35
Cardiac arrhythmia[d]	8 (22)	4 (11)	1.90 (0.62-5.75)	.22
Nosocomial pneumonia[d]	4 (11)	9 (24)	0.42 (0.14-1.25)	.22

Abbreviations: GOS, Glasgow Outcome Scale; IQR, interquartile range; MRC, Medical Research Council.

[a] Causes of death could be determined in 30 patients (20 in the hypothermia group and 10 in the control group).

[b] The MRC score and hearing impairment data were available for 23 survivors (13 in the hypothermia group and 10 in the control group). The MRC scale assesses strength in 3 muscle groups in each arm and leg. The score for each

muscle group ranges from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60. Comparison was made with the Wilcoxon test.

[c] Aspiration pneumonia was evaluated in 76 patients (37 in the hypothermia group and 39 in the control group).

[d] Hemorrhage, cardiac arrhythmia, and nosocomial pneumonia were evaluated in 74 patients (36 in the hypothermia group and 38 in the control group).

ture) and received specific medication after 26 days. This patient died 40 days after randomization because of persistent vegetative state and life support withdrawal. Eighty-seven percent of the patients received corticosteroids in both groups. Thirty-eight patients (78%) in the hypothermia group and 39 patients (81%) in the control group received adjunctive dexamethasone at the recommended dose of 40 mg/d for a maximal duration of 4 days. Hydrocortisone (200 mg/d) was administered in 3 and 5 patients in the hypothermia and control groups, respectively.

Discussion

In our study on adults with severe bacterial meningitis, which was stopped early by the DSMB, therapeutic hypothermia did not improve outcome in patients with severe bacterial meningitis. Although there was a trend toward higher mortality and rate of unfavorable outcome in the hypothermia group, early stopping of clinical trials is known to exaggerate treatment effects,[30,31] precluding firm conclusions about harm of therapeutic hypothermia in bacterial meningitis.

Potential mechanisms behind this clinically relevant mortality difference remain unclear. We found no difference in nosocomial infections, hemorrhage, cardiovascular effects, or hyperglycemia between the treatment groups. There was a difference in median serum sodium concentrations between the treatment groups. Hypernatremia on admission has been described to be associated with unfavorable outcome in bacte-

rial meningitis,[32] but, in our study group, order changed after 2 days and the influence of median sodium levels on outcome of bacterial meningitis over time is unknown. The relatively small difference between serum sodium concentrations found between groups over time more likely results from the detrimental condition of patients included in the hypothermia group than from rapid cold saline infusion. However, outcomes between patients receiving higher vs lower volume cold saline to induce hypothermia were similar. In addition, because each center included a small number of patients, it was difficult to identify any center effect in the statistical analysis.

Septic shock has been associated with unfavorable outcome in bacterial meningitis,[1] and the proportion of this condition was somewhat higher in the hypothermia group than in the control group (47% vs 32%, respectively). The relative low dose of corticosteroids, recommended by several experts,[2] administered to patients with septic shock, could introduce a bias toward a higher mortality in the hypothermia group because early treatment with high-dose dexamethasone reduces the mortality in adults with bacterial meningitis.[4] The proportion of patients treated with high-dose corticosteroids between treatment groups in our study was similar, indicating that a difference in corticosteroid therapy did not confound the results. The use of high-dose corticosteroids in patients with meningitis and septic shock is in line with a recent advisement, stating that the survival benefit in patients with pneumococcal meningitis who were administered adjunctive dexamethasone out-

weighs the risks associated with high-dose corticosteroids in this population.[6]

The results of our study are in contrast with those concerning global cerebral hypoxia, in which beneficial effects of hypothermia were reported.[12-14] Studies in animals have also demonstrated therapeutic value of hypothermia in bacterial meningitis,[7,9,10,33,34] and observational studies reported favorable effects of hypothermia in adults with severe pneumococcal meningitis.[19] In bacterial meningitis, the actual time of the assault is difficult to assess, which might result in a more heterogeneous cerebral disorder than in cardiac arrest or neonatal hypoxic-ischemic encephalopathy.[35] Our findings are more in line with traumatic brain injury, where the effect of hypothermia is controversial.[11,16] Our study is one of the few randomized controlled studies in critically ill patients with bacterial meningitis. The mortality rate among patients in the control group (31%) was consistent with previously reported studies,[4,5,36] indicating that selection bias was not a matter of great concern.

Post hoc futility analysis showed how small the likelihood was of the study finding a results favoring hypothermia if it had proceed to completion, thereby supporting the advice of the DSMB to terminate the study early. Terminated early, our study has low statistical power, precluding robust subgroup analysis and assertion of a smaller harm effect of hypothermia.[37,38] For hypothermia treatment, total blinding was not feasible, but a physician who was blinded for treatment regimens assessed the primary end point, according to the Prospective Open Blinded Endpoint methodology. Although associated with high mortality and morbidity, bacterial meningitis is a relatively rare disease in high-income countries.[39] Because only the most severely ill patients with bacterial meningitis could be included in our study, many centers were needed to include our intended number of patients. We advised to treat all enrolled patients according to guidelines and many clinicians followed these recommendations (eAppendix 1 in the Supplement).

A limitation of our study is the heterogeneity of timeline from disease onset to treatment. This onset is much more difficult to determine compared with cardiac arrest and traumatic brain injury. Moreover, although the median time to target temperature was relatively short (4.4 hours), the timeline was quite variable among patients. Because each enrolling hospital performed cooling in their local method of choice, there was some heterogeneity of targeted hypothermia. However, to date, no technique has been proved to be associated with a better outcome in cardiac arrest. In our study, we did not observe any differences on outcome according to cooling techniques (endovascular vs other techniques, such as ice packs, cooling blanket, cooling pads, or cooling mattress).

Traumatic brain injury studies have evaluated duration of hypothermia ranging from 24 hours to 7 days. We chose to treat patients with hypothermia for 48 hours because the majority of hypothermia studies used this time frame, and CSF cultures in patients with pneumococcal meningitis have been reported to be negative after 24 hours of treatment.[2] The complexity of the patient population and relatively limited funding precluded confirmation that CSF inflammatory biomarker reduction was consistent with animal studies. We also did not evaluate intracranial pressure because this is not considered standard practice.[6]

Conclusion

In conclusion, our trial does not support the use of hypothermia in adults with severe meningitis. Moderate hypothermia did not improve outcome in patients with severe bacterial meningitis and may even be harmful. Our results may have important implications for future trials on hypothermia in patients presenting with septic shock or stroke. Careful evaluation of safety issues in these future and ongoing trials are needed.

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