ORIGINAL ARTICLE

Corticosteroids for Bacterial Meningitis in Adults in Sub-Saharan Africa

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ABSTRACT

BACKGROUND

In sub-Saharan Africa, bacterial meningitis is common and is associated with a high mortality. Adjuvant therapy with corticosteroids reduces mortality among adults in the developed world, but it has not been adequately tested in developing countries or in the context of advanced human immunodeficiency virus (HIV) infection.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial of dexamethasone (16 mg twice daily for 4 days) and an open-label trial of intramuscular versus intravenous ceftriaxone (2 g twice daily for 10 days) in adults with an admission diagnosis of bacterial meningitis in Blantyre, Malawi. The primary outcome was death at 40 days after randomization.

RESULTS

A total of 465 patients, 90% of whom were HIV-positive, were randomly assigned to receive dexamethasone (233 patients) or placebo (232 patients) plus intramuscular ceftriaxone (230 patients) or intravenous ceftriaxone (235 patients). There was no significant difference in mortality at 40 days in the corticosteroid group (129 of 231 patients) as compared with the placebo group (120 of 228 patients) by intention-to-treat analysis (odds ratio, 1.14; 95% confidence interval [CI], 0.79 to 1.64) or when the analysis was restricted to patients with proven pneumococcal meningitis (68 of 129 patients receiving corticosteroids vs. 72 of 143 patients receiving placebo) (odds ratio, 1.10; 95% CI, 0.68 to 1.77). There were no significant differences between groups in the outcomes of disability and death combined, hearing impairment, and adverse events. There was no difference in mortality with intravenous ceftriaxone (121 of 230 patients) as compared with intramuscular ceftriaxone (128 of 229 patients) (odds ratio, 0.88; 95% CI, 0.61 to 1.27).

CONCLUSIONS

Adjuvant therapy with dexamethasone for bacterial meningitis in adults from an area with a high prevalence of HIV did not reduce mortality or morbidity. In this setting, intramuscular administration was not inferior to intravenous administration of ceftriaxone for bacterial meningitis. (Current Controlled Trials number, ISRCTN31371499.)

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Bacterial meningitis ranks 10th as a cause of death from infectious diseases worldwide[1] and is common in the developing world.[2] Its incidence in Malawi, where most adult medical inpatients have advanced human immunodeficiency virus (HIV) infection, is 50 per 100,000 adult person-years,[3] more than 10 times the incidence seen in industrialized countries.[4] *Streptococcus pneumoniae* is the most common causative organism, with a mortality of 65%[5] as compared with 26 to 34%[6,7] in industrialized countries before the introduction of adjuvant therapy with corticosteroids.

The host inflammatory response in bacterial meningitis contributes to neuronal injury[8] and can be modulated by corticosteroids.[9] In Europe, corticosteroids given as adjuvant therapy reduce mortality among adults, particularly in pneumococcal meningitis,[7] and reduce hearing loss in children after *Haemophilus influenzae* type b meningitis.[10] Consequently, corticosteroids have been incorporated into therapeutic guidelines[11,12] and are recommended particularly for pneumococcal meningitis.[13] Data from developing countries or from areas of high prevalence of HIV regarding the use of corticosteroids in bacterial meningitis are scarce. In Egypt, an open-label trial that included adults and children suggested a reduction in mortality for patients with pneumococcal meningitis.[14] A pediatric trial in Malawi showed no benefit from corticosteroids in children with bacterial meningitis.[15] Trials restricted to adults in developing countries have either shown no benefit or lacked sufficient power.[16-19] Corticosteroids are inexpensive, safe, and accessible, and they would therefore be appropriate for such patients if they prove to be effective. We conducted a double-blind, randomized, placebo-controlled trial of adjuvant therapy with dexamethasone in adults with bacterial meningitis in Malawi.

In many parts of sub-Saharan Africa, intravenous therapy cannot be easily administered. Intramuscular ceftriaxone therapy has been assessed in bacterial meningitis in children but not in adults.[20,21] If intramuscular therapy is shown to be effective, it may facilitate early antibiotic therapy in remote areas. Thus, patients also were randomly assigned in a factorial design to receive antibiotic therapy either intramuscularly or intravenously.

METHODS

The study was conducted between May 2002 and January 2005 in Queen Elizabeth Central Hospital in Blantyre, Malawi. This hospital offers free care to 10,000 adult medical inpatients per year, 70% of whom have HIV infection. All patients who had a lumbar puncture were referred immediately to a member of the trial staff for assessment of eligibility. Inclusion criteria were a clinical suspicion of bacterial meningitis and either positive cerebrospinal fluid on microscopy (defined as organisms seen on Gram's stain or more than 100 white cells per cubic millimeter, of which more than 50% were neutrophils) or cloudy cerebrospinal fluid when immediate microscopy was unavailable. Exclusion criteria were age younger than 16 years, corticosteroids received in the previous 48 hours, cryptococcus detected in cerebrospinal fluid specimens by means of microscopy, or contraindications to study drugs. Patients or their legal guardians provided written informed consent or, if they were unable to read or write, independently witnessed verbal consent before recruitment. The study design and data collection were conducted by members of the University of Malawi College of Medicine. The funding body (Meningitis Research Foundation) and the pharmaceutical companies donating drugs (Emcure Pharmaceuticals and Cipla) played no part in the design, conduct, analysis, or reporting of the results, nor were they involved in the writing or approval of the manuscript. The study was approved by the research ethics committees of the University of Malawi College of Medicine and the Liverpool School of Tropical Medicine.

Patients were randomly assigned to receive either dexamethasone (Dexacip, Cipla) at a dose of 16 mg in 4 ml of sterile water twice daily or placebo (buffered sterile water, Cipla) at a dose of 4 ml twice daily intravenously for 4 days, and either intramuscular or intravenous ceftriaxone (C-Tri, Emcure Pharmaceuticals) at a dose of 2 g twice daily for 10 days. Dexamethasone or placebo was administered immediately before the administration of ceftriaxone. Patients received care in the general medical wards. When necessary, patients were transferred to a high-dependency unit and antibiotic therapy was modified according to antimicrobial-sensitivity patterns and clinical progress.

Randomization was performed by computer-generated blocks of eight in a two-way factorial design. Notification of treatment allocation was provided in sealed, opaque envelopes assigned to consecutively recruited patients; opening the envelope constituted entry to the trial. Dexamethasone and placebo were presented as clear, colorless fluid in identical packaging labeled only with the randomization number; the corticosteroid component of the trial was therefore conducted in a double-blind fashion.

Cerebrospinal fluid specimens were examined by means of microscopy for cell and differential counts, and by staining with India ink. A Gram's stain procedure was performed if the sample was turbid or had more than 10 white cells per cubic millimeter. Centrifuged cerebrospinal fluid deposits were incubated on sheep-blood agar in a candle-extinction jar at 37°C for 48 hours and isolates were identified by means of standard techniques.[22] Blood was cultured at 37°C for a minimum of 48 hours (BacT/Alert, bioMérieux). In the first 51 consecutive cerebrospinal fluid specimens for which Gram's stain and culture were negative, polymerase chain reaction (PCR) for meningococcus and pneumococcus was performed.[23] Antibiotic sensitivity was assessed by means of disk diffusion.[24]

For patients who survived to discharge, HIV testing with pretest and post-test counseling was performed after consent was obtained. In patients who died, HIV testing was performed at least 3 months after death. Testing was performed by means of two enzyme-linked immunosorbent assay tests (Vironostika, Organon Teknika, and HIV-1/HIV-2 Go EIA, Abbott); discordant results were tested by means of a third test (Uni-Gold, Trinity Biotech).

Patients were treated in the hospital for a minimum of 10 days and were evaluated at 40 days and at 6 months. Clinically evident adverse events were recorded systematically throughout the trial period. At follow-up, patients had a standardized neurologic examination and a hearing assessment. Patients who did not return for follow-up appointments were visited at home. Details regarding hearing and disability assessment are presented in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

The predefined primary outcome was mortality at 40 days from randomization by intention-to-treat analysis. Secondary outcomes were time to death, combined disability and death as defined by the Glasgow Outcome Score[25] at day 40, hearing impairment at day 40, death at 10 days, and death at 6 months.

Subgroup analyses were performed for patients with proven or probable bacterial meningitis, proven bacterial meningitis alone, and proven pneumococcal meningitis. Proven bacterial meningitis was defined as identification of an organism from a cerebrospinal fluid specimen by means of microscopy, culture, or PCR or from blood culture in the context of a cerebrospinal fluid specimen containing a white-cell count of more than 100 per cubic millimeter with more than 50% neutrophils. Probable bacterial meningitis was defined as a cerebrospinal fluid specimen containing a cell count of more than 100 per cubic millimeter with more than 50% neutrophils without identification of an organism. The analytic plan was approved by the data and safety monitoring board and the trial steering committee before unblinding. A planned interim analysis was performed by the data and safety monitoring board after 100 deaths.

On the basis of a background mortality of 56% and an ability to detect a 20% or greater difference in mortality, the initial sample size of 660 patients was modified to 420 patients to detect a 30% difference after publication of the results of a European trial that showed a relative risk of death of 0.59 for corticosteroid treatment.[7] For the primary outcome, a P value less than 0.05 was considered to indicate statistical significance. All P values are two-sided. Odds ratios and 95% confidence intervals were calculated and adjusted for predefined prognostic factors in a logistic-regression model. The difference in time to death through 40 days between the groups was tested with the use of Cox proportional-hazard ratios. Data were analyzed with the use of Stata software, version 8.2.

RESULTS

Of 522 consecutive patients who met the entry criteria, 465 (89.0%) underwent randomization. Of those who underwent randomization, 233 patients (50.1%) received corticosteroids and 232

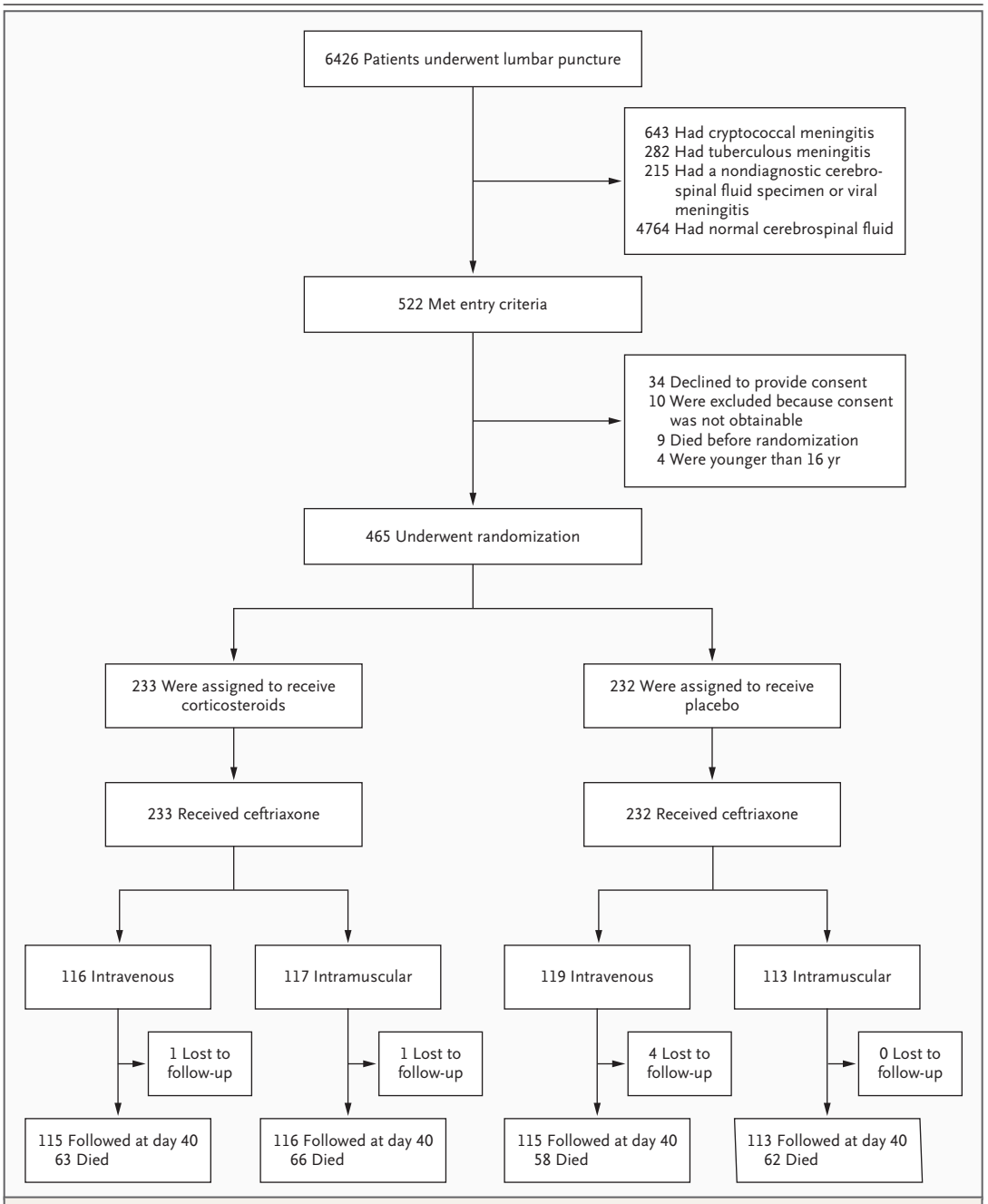

Figure 1. Enrollment, Randomization, and Analysis of Patients.

(49.9%) received placebo (Fig. 1). HIV serologic status was available for 434 patients (93.3%), of whom 389 (89.6%) were HIV-positive. Four patients were known to be HIV-positive at the time of admission; none were receiving antiretroviral therapy or prophylaxis against opportunistic infections. The median CD4 cell count on admission in 101 consecutively recruited HIV-positive patients was 102 per cubic millimeter (interquartile range, 51 to 169). Further details on CD4 cell count testing and HIV aftercare are included in the Supplementary Appendix.

Clinical characteristics and results of laboratory tests were similar in the comparison groups (Table 1). A total of 325 patients (70%), 158 of whom were in the corticosteroid group, had mi-

crobiologically proven bacterial meningitis. A total of 102 patients (22%), 52 of whom were in the corticosteroid group, had probable bacterial meningitis. A total of 38 patients (8%), 23 of whom were in the corticosteroid group, underwent randomization but were subsequently found to have diagnoses other than bacterial meningitis; 20 had cryptococcal meningitis (12 of whom were in the corticosteroid group), 7 had tuberculous meningitis (6 of whom were in the corticosteroid group), and 11 had traumatic lumbar puncture (5 of whom were in the corticosteroid group). Four patients underwent randomization in error; two were younger than 16 years of age, one had a cerebrospinal fluid specimen with a white-cell count of 92 per cubic millimeter, and one had received oral

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Corticosteroid (N=233)	Placebo (N=232)	Intramuscular Ceftriaxone (N=230)	Intravenous Ceftriaxone (N=235)
Age — yr	32.3±10.1	32.6±11.4	32.4±10.9	32.6±10.6
Male sex — no. (%)	122 (52)	108 (47)	115 (50)	115 (49)
Glasgow Coma Scale score†	10.7±3.5	10.8±3.3	11±3.4	10.4±3.4
Hemoglobin — g/dl	10.4±2.8	10.7±3.1	10.5±3.0	10.7±2.8
Median time to presentation — hr (interquartile range)	72 (48–120)	72 (48–144)	72 (48–144)	72 (48–120)
Previous treatment with antimicrobial agents — no. (%)‡				
Oral	35 (15)	42 (18)	34 (15)	43 (18)
Parenteral	48 (21)	47 (20)	49 (21)	46 (20)
Not known	4 (2)	8 (3)	6 (3)	6 (3)
Microbiologic diagnosis — no. (%)				
Proven bacterial	158 (68)	167 (72)	155 (67)	170 (72)
Streptococcus pneumoniae	130 (56)	145 (62)	131 (57)	144 (61)
Neisseria meningitidis	10 (4)	10 (4)	13 (6)	7 (3)
Other gram-negative organisms§	15 (6)	10 (4)	9 (4)	16 (7)
Other¶	3 (1)	2 (1)	2 (1)	3 (1)
Probable bacterial (no organism identified)	52 (22)	50 (22)	56 (24)	46 (20)
Not bacterial meningitis	23 (10)	15 (6)	19 (8)	19 (8)
Cryptococcal meningitis‖	12 (5)	8 (3)	8 (3)	12 (5)
Mycobacterium tuberculosis	6 (3)	1 (0.4)	5 (2)	2 (1)
Not meningitis	5 (2)	6 (3)	6 (3)	5 (2)
Positive blood culture — no. (%)**	82 (35)	68 (29)	69 (30)	81 (34)
Blood culture unavailable — no. (%)	6 (3)	5 (2)	3 (1)	8 (3)
HIV-positive — no./total no. tested (%)	194/216 (90)	195/218 (89)	191/215 (89)	198/219 (90)
HIV status not known — no. (%)	17 (7)	14 (6)	15 (7)	16 (7)
Randomly assigned to receive intramuscular ceftriaxone — no. (%)	117 (50)	113 (49)		
Randomly assigned to receive corticosteroids — no. (%)			117 (51)	116 (49)

* Plus–minus values are means ±SD.
† The Glasgow Coma Scale ranges from 3 to 15, with 3 indicating that the patient is unresponsive and 15 indicating that the patient is fully alert.
‡ Details regarding pretreatment antibiotics are available in Table S1 in the Supplementary Appendix.
§ Other gram-negative organisms were *Escherichia coli* (in 11 patients), non-typhi salmonella (in 7), *Haemophilus influenzae* (in 3), klebsiella species (in 3), and *Enterobacter gergoviae* (in 1).
¶ Other bacteria were *Staphylococcus aureus* (in 2 patients) and α-hemolytic streptococci (in 3).
‖ Of 20 patients, 10 were categorized as having probable bacterial meningitis on the basis of the cell and differential counts from the cerebrospinal fluid specimen but were found to have cryptococcal meningitis either after prolonged incubation or after repeated lumbar puncture.
** Of 150 positive blood cultures, 7 were positive for *Cryptococcus neoformans*.

prednisolone within 48 hours before recruitment. All patients were included in the intention-to-treat analysis.

Organisms were seen on Gram's stain in 263 of 452 specimens (58%). A total of 39 patients had a positive cerebrospinal fluid culture without a positive Gram's stain, and 6 patients had a positive blood culture with a cerebrospinal fluid specimen showing neutrophil pleocytosis but a negative Gram's stain and culture. Of 51 consecutive culture-negative cerebrospinal fluid specimens tested by means of PCR, 17 were positive for either pneumococcus (in 12 patients) or meningococcus (in 5) and were classified as proven bacterial meningitis. Reclassification of these cases as probable bacterial meningitis did not affect the interpretation of the effect of corticosteroids in any subgroup. Ten patients had microbiologically proven dual infection; all had pneumococcal meningitis with concurrent non-typhi salmonella septicemia (in seven patients), *Enterococcus faecalis* septicemia (in one patient), or cryptococcemia (in two patients).

All patients who underwent randomization received at least one dose of the assigned treatment. All 437 patients who met the criteria for proven or probable bacterial meningitis on the basis of findings from cerebrospinal fluid specimens received corticosteroids or placebo for 4 days or until death and ceftriaxone for 10 days or until death. Of the remaining 28 patients who underwent randomization, 5 received corticosteroids or placebo for 4 days or until death and 3 received ceftriaxone for 10 days or until death. Corticosteroids were added to therapy after the completion of the initial 4 days of therapy for three patients; two patients had cerebral edema (one of whom was in the corticosteroid group), and one patient in the corticosteroid group had a presumed drug rash. The results for these patients were analyzed according to the initial randomization.

The outcome at 40 days from recruitment was available for 459 patients (98.7%). Of six patients lost to follow-up (including two in the corticosteroid group), two did not have bacterial meningitis and one was withdrawn from the trial therapy because of age (14 years). Overall mortality was 249 of 459 (54.2%). The association between baseline factors and mortality is shown in Table 2.

Mortality at 40 days from enrollment was 129 of 231 patients in the corticosteroid group (55.8%) and 120 of 228 patients in the placebo group (52.6%) (odds ratio, 1.14; 95% confidence interval [CI], 0.79 to 1.64; P=0.49). The adjusted odds ratio was 1.13 (95% CI, 0.73 to 1.76). An on-treatment analysis, censoring events after premature discontinuation of the study drug, shows a similar mortality of 125 of 222 patients in the corticosteroid group (56.3%) and 117 of 223 patients in the placebo group (52.5%). Given the 80% power of this study, a one-sided test excludes a reduction in 40-day mortality in the corticosteroid group of 23% or greater. Time to death was similar in both groups (hazard ratio, 1.07; 95% CI, 0.84 to 1.38) (Fig. 2). When an interaction term for the comparison of intravenous versus intramuscular ceftriaxone is included, the odds ratio for mortality

Table 2. Association between Baseline Characteristics and Mortality at 40 Days.

Characteristic	Univariate Analysis		Multivariate Analysis*	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Male sex	1.09 (0.75–1.57)	0.67	0.98 (0.62–1.55)	0.94
Age ≥32 yr†	1.92 (1.32–2.79)	0.001	1.96 (1.24–3.10)	0.004
Glasgow Coma Scale score <12‡	2.77 (1.90–4.06)	<0.001	4.10 (2.51–6.69)	<0.001
Hemoglobin <10 g/dl§	1.82 (1.23–2.69)	0.003	2.19 (1.39–3.45)	0.001
>48-hr history¶	1.64 (1.07–2.50)	0.02	1.48 (0.87–2.49)	0.14
Pneumococcal infection	0.76 (0.52–1.10)	0.15	0.56 (0.34–0.93)	0.02
Previous treatment with antibiotics	1.19 (0.81–1.75)	0.364	0.93 (0.58–1.49)	0.76
HIV-positive	1.96 (1.05–3.69)	0.035	1.35 (0.67–2.72)	0.40

* All factors in this table were included in the final model.
† The mean age was 32.5 years.
‡ The Glasgow Coma Scale ranges from 3 to 15, with 3 indicating that the patient is unresponsive and 15 indicating that the patient is fully alert. The median Glasgow Coma Scale score on admission was 11.
§ The median hemoglobin level on admission was 10.4 g per deciliter.
¶ A history of >48 hours was considered to indicate late presentation.

at day 40 in the corticosteroid group becomes 1.09 (95% CI, 0.64 to 1.83).

The results of the intention-to-treat analysis and the predefined analyses for patients with proven and probable bacterial meningitis, proven bacterial meningitis, and pneumococcal meningitis in the corticosteroid trial are shown in Table 3. There were no differences in the rates of death, disability and death, or clinically detectable hearing loss at 40 days or in mortality at 10 days or at 6 months. Further exploratory analyses showed no evidence that corticosteroids were effective in any subgroup (Table S2 in the Supplementary Appendix). Patterns of hearing loss and of disability among survivors are shown in Tables S3A and S3B in the Supplementary Appendix. As compared with patients who received placebo, the temperatures of patients in the corticosteroid group were lower during treatment (mean difference, 0.49°C at day 4; P<0.001) (Fig. S1 in the Supplementary Appendix).

In the trial concerning the route of antibiotic administration, mortality at 40 days was 121 of 230 patients in the intravenous group (52.6%) and 128 of 229 patients in the intramuscular group (55.9%) (odds ratio, 0.88; 95% CI, 0.61 to 1.26) (Table 4). An on-treatment analysis, censoring events after premature discontinuation of ceftriaxone, shows a similar mortality of 119 of 225 patients in the intravenous group (52.9%) and 124 of 219 patients in the intramuscular group (56.6%). Given the actual 80% power of this study, a two-sided test excludes an increase or decrease in 40-day mortality in the intramuscular group of 25% and 24%, respectively. When an interaction term for the comparison of corticosteroid and placebo administration is included, the odds ratio for mortality at 40 days in the intravenous group becomes 0.84 (95% CI, 0.5 to 1.14). In seven patients, pain during intramuscular injection was sufficiently distressing for clinicians to switch to intravenous treatment. Only one isolate (*S. pneumoniae*) showed reduced susceptibility to ceftriaxone (Table S4 in the Supplementary Appendix).

There were no differences in the rates of adverse events potentially related to corticosteroid therapy and none resulted in withdrawal of patients from the trial (Table S5 in the Supplementary Appendix). Nineteen patients had adverse events that were more likely to be due to antibiotics than corticosteroids; nine patients had late fever (including seven patients in the corticosteroid group), five had rash (including two in the corticosteroid group), three had diarrhea (including one in the corticosteroid group), and two had jaundice (both of whom were in the corticosteroid group).

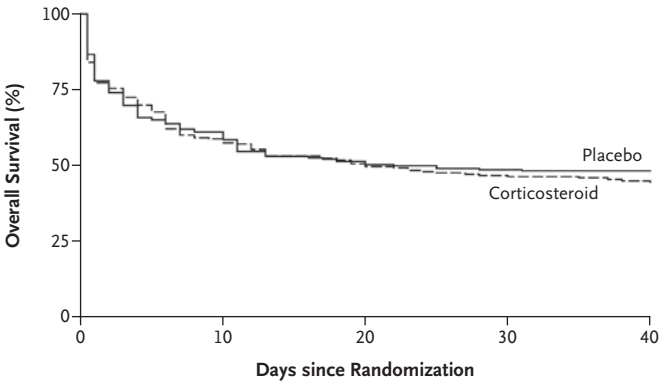

Figure 2. Kaplan–Meier Estimates of Survival for 459 Patients through Day 40.

DISCUSSION

The greatest burden of bacterial meningitis in adults occurs in developing countries where mortality rates are high. If effective, corticosteroids as adjuvant therapy would represent an affordable and appropriate intervention. The results of our study show that, in a setting where the majority of patients are likely to have advanced HIV infection, where presentation tends to be late, and where *S. pneumoniae* is the predominant pathogen, adjuvant therapy with dexamethasone for bacterial meningitis in adults confers no advantage with regard to mortality or morbidity at 40 days.

In our study, mortality was substantially higher than in it is in industrialized settings, but it was typical for a low-resource setting in sub-Saharan Africa. It was lower than in previous studies in Malawi,[3,5] probably due to the use of ceftriaxone (rather than penicillin plus chloramphenicol) and the effect of improved care as a result of the patients' inclusion in a clinical trial.

The negative findings from this study, predominantly in patients with advanced HIV disease, contrast with those of a European trial of corticosteroids involving 301 adults with meningitis.[7] The European trial showed an overall reduction of mortality from 15% to 7% at 8 weeks (P=0.04), and the benefit of corticosteroids was most marked in patients with pneumococcal meningitis. The current findings are similar to those of a large

Table 3. Outcome for Patients Who Received Corticosteroid versus Placebo.

Outcome	Corticosteroid	Placebo	Odds Ratio (95% CI)*	
			Unadjusted	Adjusted
	no./total no. (%)			
Intention-to-treat population				
Death, day 40	129/231 (56)	120/228 (53)	1.14 (0.79–1.64)	1.13 (0.73–1.76)
Disability or death, day 40†	150/227 (66)	146/224 (65)	1.04 (0.71–1.54)	1.01 (0.64–1.60)
Hearing loss, day 40	30/96 (31)	36/99 (36)	0.80 (0.44–1.44)	0.76 (0.37–1.54)
Death, day 10	99/232 (43)	96/230 (42)	1.04 (0.72–1.50)	1.01 (0.65–1.57)
Death, 6 mo	140/204 (69)	127/205 (62)	1.34 (0.89–2.02)	1.26 (0.77–2.06)
Proven or probable bacterial meningitis‡				
Death, day 40	120/216 (56)	114/217 (53)	1.13 (0.77–1.65)	1.11 (0.71–1.73)
Disability or death, day 40	140/213 (66)	139/216 (64)	1.06 (0.71–1.58)	1.01 (0.63–1.60)
Hearing loss, day 40	30/90 (33)	35/97 (36)	0.86 (0.47–1.56)	0.82 (0.40–1.68)
Death, day 10	94/217 (43)	93/217 (43)	1.04 (0.71–1.51)	1.04 (0.66–1.63)
Death, 6 mo	130/194 (67)	120/194 (62)	1.25 (0.83–1.90)	1.25 (0.75–2.02)
Proven bacterial meningitis				
Death, day 40	82/157 (52)	80/165 (48)	1.16 (0.75–1.80)	1.13 (0.67–1.90)
Disability or death, day 40	99/155 (64)	99/164 (60)	1.16 (0.74–1.83)	1.04 (0.60–1.79)
Hearing loss, day 40	26/72 (36)	30/79 (38)	0.92 (0.48–1.79)	0.87 (0.39–1.93)
Death, day 10	70/158 (44)	71/166 (43)	1.06 (0.69–1.65)	1.08 (0.64–1.84)
Death, 6 mo	91/143 (64)	84/148 (57)	1.33 (0.83–2.14)	1.37 (0.77–2.41)
Proven pneumococcal meningitis				
Death, day 40	68/129 (53)	72/143 (50)	1.10 (0.68–1.77)	1.09 (0.62–1.93)
Disability or death, day 40	81/128 (63)	89/142 (63)	1.03 (0.63–1.68)	0.96 (0.53–1.73)
Hearing loss, day 40	22/59 (37)	28/65 (43)	0.79 (0.38–1.62)	0.81 (0.35–1.88)
Death, day 10	61/130 (47)	65/144 (45)	1.07 (0.67–1.73)	1.04 (0.58–1.85)
Death, 6 mo	74/118 (63)	76/127 (60)	1.13 (0.67–1.89)	1.25 (0.67–2.32)

* The adjusted odds ratios are adjusted for age, sex, HIV status, time from onset of symptoms to presentation at the hospital, previous exposure to antibiotics, Glasgow Coma Scale score, hemoglobin level, pneumococcal or nonpneumococcal disease, and route of antibiotic administration. Age, length of history, Glasgow Coma Scale score, and hemoglobin level are continuous variables.

† Eight patients (four in each group) were known to be alive, but the investigators were unable to verify whether they had a disability.

‡ This category includes 10 patients classified as having probable bacterial meningitis (>100 white cells per cubic millimeter, of which >50% were neutrophils) but who subsequently were found to have cryptococcal disease after prolonged culture or repeated lumbar puncture.

trial involving children with meningitis in Malawi,[15] which showed no survival advantage with corticosteroids.

Several differences in the study populations, alone or in combination, may explain the disparity between the results from Malawi and elsewhere. In the current trial, of 434 patients for whom serologic status was known, 90% were HIV-positive and the majority were likely to have had advanced disease. Although HIV status was not reported in the European study, it is likely that the proportion of HIV-positive patients was much lower. HIV is a risk factor for the development of invasive pneumococcal disease[26] and, although our study suggests that HIV is a predictor of mortality, it has previously been suggested that the outcome from meningitis in HIV-infected patients is better than that in HIV-negative patients.[27] Since patients with HIV already have an attenuated host response, corticosteroids may not

Table 4. Mortality at 40 Days for Intravenous versus Intramuscular Ceftriaxone.

Group	Intravenous Ceftriaxone	Intramuscular Ceftriaxone	Odds Ratio (95% CI)*	
			Unadjusted	Adjusted
	no./total no. (%)			
Intention-to-treat population	121/230 (53)	128/229 (56)	0.88 (0.61–1.27)	0.84 (0.54–1.30)
Proven and probable bacterial meningitis	115/221 (52)	119/212 (56)	0.85 (0.58–1.24)	0.79 (0.51–1.23)
Proven bacterial meningitis	87/168 (52)	75/154 (49)	1.13 (0.73–1.75)	0.92 (0.55–1.56)
Pneumococcal meningitis	74/142 (52)	66/130 (51)	1.06 (0.66–1.70)	0.87 (0.49–1.54)

* These odds ratios were adjusted for age, sex, HIV status, time from the onset of symptoms to presentation at the hospital, previous exposure to antibiotics, Glasgow Coma Scale score, hemoglobin level, receipt of corticosteroid or placebo, and pneumococcal or nonpneumococcal disease. Age, length of history, Glasgow Coma Scale score, and hemoglobin level are continuous variables.

confer any additional advantage. Since only 45 patients in the current trial were known to be HIV-negative, we were unable to test this hypothesis, although it would be consistent with the point estimates for mortality among HIV-negative as compared with HIV-positive patients.

There are many barriers to accessing health care in sub-Saharan Africa, and presentation is often delayed. The median length of history in the current study was 72 hours, as compared with 24 hours in the European study. Delayed presentation was associated with a poorer outcome in the current trial, although adjusting for this factor in the analysis had no effect. The general health of participants was likely to be substantially lower in the current study (e.g., a mean hemoglobin level of 10.4 g per deciliter at admission) as compared with the European study, and the intensity of medical assistance was inevitably lower. Such factors almost certainly contributed to the higher mortality reported here, but they cannot explain the lack of benefit from corticosteroids.

A total of 36% of the patients in the European study had pneumococcal meningitis, and these patients received the greatest benefit from corticosteroids as adjuvant therapy. In the current trial, 59% of the patients had pneumococcal disease, but they did not benefit from corticosteroid therapy. It seems unlikely, therefore, that the organism mix explains the difference between the results of the two studies. We had insufficient numbers of patients to perform a reliable subgroup analysis for other organisms, but comparable trials have not shown a benefit of corticosteroids in patients with meningococcal meningitis. Recent exposure to antibiotic therapy was not an exclusion criterion, since this would have made the study nonrepresentative of African practice. The majority of patients did not receive antibiotics before recruitment, and analysis restricted to these patients did not show any advantage of corticosteroid therapy.

Given the mean weight of men in Malawi (60.0 kg)[28] as compared with that of men in Europe (80.6 kg),[29] the dosing schedule used for dexamethasone (16 mg twice daily, vs. 10 mg every 6 hours in the European study) reflects an equivalent total daily dose for weight. Thus, considering the long biologic half-life of dexamethasone, the difference in dosing regimens between the studies is unlikely to account for differences in the results.

We consider that the results of this study based on 249 deaths, as compared with 32 deaths in the European study, are unlikely to be a chance finding. The negative results of the current study suggest that the evidence of the benefit of corticosteroids from a European trial cannot be extrapolated to the very different setting of a high prevalence of HIV infection in sub-Saharan Africa. The implications for HIV-positive adults with pneumococcal meningitis outside Africa or those receiving antiretroviral therapy are unclear. The results from this study suggest that the intramuscular administration of ceftriaxone is an effective therapy for bacterial meningitis in areas where access to intravenous therapy is limited.

This trial does not provide support for the routine inclusion of corticosteroids in the management of adult bacterial meningitis in resource-poor areas where pneumococcus is the primary pathogen and where a substantial proportion of patients are likely to have advanced HIV disease. Until alternative adjuvant therapies prove effective or appropriate vaccines become widely available,[30] mor-

tality from bacterial meningitis in such settings is likely to remain unacceptably high.

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