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DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

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ABSTRACT

Background Mortality and morbidity rates are high among adults with acute bacterial meningitis, especially those with pneumococcal meningitis. In studies of bacterial meningitis in animals, adjuvant treatment with corticosteroids has beneficial effects.

Methods We conducted a prospective, randomized, double-blind, multicenter trial of adjuvant treatment with dexamethasone, as compared with placebo, in adults with acute bacterial meningitis. Dexamethasone (10 mg) or placebo was administered 15 to 20 minutes before or with the first dose of antibiotic and was given every 6 hours for four days. The primary outcome measure was the score on the Glasgow Outcome Scale at eight weeks (a score of 5, indicating a favorable outcome, vs. a score of 1 to 4, indicating an unfavorable outcome). A subgroup analysis according to the causative organism was performed. Analyses were performed on an intention-to-treat basis.

Results A total of 301 patients were randomly assigned to a treatment group: 157 to the dexamethasone group and 144 to the placebo group. The baseline characteristics of the two groups were similar. Treatment with dexamethasone was associated with a reduction in the risk of an unfavorable outcome (relative risk, 0.59; 95 percent confidence interval, 0.37 to 0.94; P=0.03). Treatment with dexamethasone was also associated with a reduction in mortality (relative risk of death, 0.48; 95 percent confidence interval, 0.24 to 0.96; P=0.04). Among the patients with pneumococcal meningitis, there were unfavorable outcomes in 26 percent of the dexamethasone group, as compared with 52 percent of the placebo group (relative risk, 0.50; 95 percent confidence interval, 0.30 to 0.83; P=0.006). Gastrointestinal bleeding occurred in two patients in the dexamethasone group and in five patients in the placebo group.

Conclusions Early treatment with dexamethasone improves the outcome in adults with acute bacterial meningitis and does not increase the risk of gastrointestinal bleeding. (N Engl J Med 2002;347:1549-56.)

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THE mortality rate among adults with acute bacterial meningitis and the frequency of neurologic sequelae among those who survive are high, especially among patients with pneumococcal meningitis.[1,2] Unfavorable neurologic outcomes are not the result of treatment with inappropriate antimicrobial agents, since cerebrospinal fluid cultures are sterile 24 to 48 hours after the start of antibiotic therapy.[3] Studies in animals have shown that bacterial lysis, induced by treatment with antibiotics, leads to inflammation in the subarachnoid space, which may contribute to an unfavorable outcome.[4,5] These studies also show that adjuvant treatment with antiinflammatory agents, such as dexamethasone, reduces both cerebrospinal fluid inflammation and neurologic sequelae.[4,5]

Many controlled trials have been performed to determine whether adjuvant corticosteroid therapy is beneficial in children with acute bacterial meningitis. The results, however, do not point unequivocally to a beneficial effect. A meta-analysis of randomized controlled trials performed since 1988 showed a beneficial effect of adjunctive dexamethasone therapy in terms of severe hearing loss in children with *Haemophilus influenzae* type b meningitis and suggested a protective effect in those with pneumococcal meningitis if the drug was given before or with parenteral antibiotics.[6] There are few data on the use of adjunctive dexamethasone therapy in adults with bacterial meningitis. One large, prospective, randomized trial (neither placebo-controlled nor double-blind) showed a benefit of dexamethasone therapy in a subgroup of patients with pneumococcal meningitis.[7] The paucity of data precludes a recommendation that dexamethasone be ad-

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*The investigators who participated in the European Dexamethasone in Adulthood Bacterial Meningitis Study are listed in the Appendix.

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ministered routinely in adults with bacterial meningitis.[8,9] We conducted a study to determine whether adjunctive dexamethasone treatment improves the outcome in such patients.

METHODS

Eligible Patients

Patients referred to one of the participating centers (listed in the Appendix) were eligible for the study if they were 17 years of age or older, had suspected meningitis in combination with cloudy cerebrospinal fluid, bacteria in cerebrospinal fluid on Gram's staining, or a cerebrospinal fluid leukocyte count of more than 1000 per cubic millimeter. Patients were excluded if they had a history of hypersensitivity to β-lactam antibiotics or corticosteroids; if they were pregnant; if they had a cerebrospinal shunt, had been treated with oral or parenteral antibiotics in the previous 48 hours, had a history of active tuberculosis or fungal infection, or had a recent history of head trauma, neurosurgery, or peptic ulcer disease; or if they were enrolled in another trial.

The study protocol was approved by the institutional review board of each participating hospital. All patients or their legally authorized representatives gave written informed consent before enrollment. Patients were enrolled between June 1993 and December 2001. The study was designed, conducted, and analyzed independently of any companies.

Treatment

Patients were randomly assigned to receive dexamethasone sodium phosphate (Oradexon), at a dose of 10 mg given every six hours intravenously for four days, or placebo that was identical in appearance to the active drug. The study medication was given 15 to 20 minutes before the parenteral administration of antibiotics. After the interim analysis, the protocol was amended to allow administration of the study medication with the antibiotics.

Balanced treatment assignments within each hospital were achieved with the use of a computer-generated list of random numbers in blocks of six. The code was not broken until the last patient to be enrolled had completed eight weeks of follow-up. Treatment assignments were concealed from all investigators, but in an emergency, investigators had access to the sealed, opaque envelopes containing the assignments; two emergencies occurred. Patients were initially treated with amoxicillin (2 g given intravenously every four hours) for 7 to 10 days, depending on the cause of the meningitis and the clinical response. This regimen was based on the available data on susceptibility to antibiotics of cerebrospinal fluid isolates in the Netherlands.[10] The initial antibiotic treatment was maintained or changed according to the results of Gram's staining of cerebrospinal fluid.

Laboratory Studies

Routine examination and cultures of blood and cerebrospinal fluid were performed before the initiation of antibiotic treatment. On day five, routine blood chemical tests were performed, including measurement of glucose and hemoglobin levels. As part of routine surveillance, the Netherlands Reference Laboratory for Bacterial Meningitis performed in vitro testing of cerebrospinal fluid isolates for susceptibility to penicillin.[11]

Assessment of Outcome

The primary outcome measure was the score on the Glasgow Outcome Scale eight weeks after randomization, as assessed by the patient's physician. A score of 1 indicates death; 2, a vegetative state (the patient is unable to interact with the environment); 3, severe disability (the patient is unable to live independently but can follow commands); 4, moderate disability (the patient is capable of living independently but unable to return to work or school); and 5, mild or no disability (the patient is able to return to work or school).[12] A favorable outcome was defined as a score of 5, and an unfavorable outcome as a score of 1 to 4. The Glasgow Outcome Scale has frequently been used in trials involving stroke and other brain injuries. It is a well-validated scale with good interobserver agreement.[13,14]

Secondary outcome measures were death, focal neurologic abnormalities (defined as aphasia, cranial-nerve palsy, monoparesis, hemiparesis, and severe ataxia), hearing loss, gastrointestinal bleeding (clinically relevant bleeding with a decreased serum hemoglobin level), fungal infection, herpes zoster, and hyperglycemia (a blood glucose level higher than 144 mg per deciliter [8.0 mmol per liter]). Audiologic examination was performed in patients with clinical hearing loss. Subgroup analyses were performed for patients with prospectively defined causes of meningitis: *Neisseria meningitidis*, *Streptococcus pneumoniae*, other bacteria, and an unidentified cause (indicated by a negative cerebrospinal fluid culture).

Statistical Analysis

Calculation of the required sample size was based on the assumption that dexamethasone would reduce the proportion of patients with an unfavorable outcome from 40 to 25 percent. With a two-sided test, an alpha level of 0.05, and a power of 80 percent, the analysis required 150 patients per group. The analysis of outcomes was performed on an intention-to-treat basis with the use of a last-observation-carried-forward procedure. An additional analysis in which data for patients lost to follow-up were defined as missing was also performed. The results of these two analyses were similar.

Proportions of patients in the two groups were compared with Fisher's exact test. Two-tailed P values of less than 0.05 were considered to indicate statistical significance. Parametric and nonparametric values were tested with Student's t-test and the Mann–Whitney U test, respectively. The results are expressed as relative risks for the dexamethasone group as compared with the placebo group, with a relative risk of less than 1.0 indicating a beneficial effect. Logistic-regression analysis of base-line variables (sex; age; duration of symptoms; presence or absence of seizures, coma, and hypotension on admission; results of blood culture; cerebrospinal fluid white-cell count; and causative organism) was performed to identify risk factors for an adverse outcome other than the group assignment. Ninety-five percent confidence intervals, calculated with the use of Confidence Interval Analysis, are reported.[15]

A three-member independent data-monitoring committee performed an interim analysis after 150 patients had been enrolled. The study would have been stopped if any significant differences in efficacy or safety had been found. On January 10, 1997, the data-monitoring committee recommended early termination of the trial because the enrollment rate was too slow for completion within a reasonable time. The committee subsequently reconsidered its decision and recommended that the trial be restarted if the enrollment rate could be improved. To increase the enrollment rate, two amendments of the protocol were made. First, the protocol was amended to allow administration of the study medication with the antibiotics. This decision was based on the results of a meta-analysis of trials of dexamethasone in children with acute bacterial meningitis.[6] Second, the protocol was amended to allow investigators to follow local guidelines for administering empirical antibiotic therapy. This change was made because of the participation of centers in countries where highly resistant pneumococcal strains are more common than they are in the Netherlands.[10]

RESULTS

A total of 301 patients were randomly assigned to a study group: 157 to the dexamethasone group and 144 to the placebo group. Two patients (one in each group) did not meet the inclusion criteria because they were too young. Seven patients in the dexameth-

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asone group and nine in the placebo group each met one exclusion criterion; one patient in the dexamethasone group met two exclusion criteria. Eleven patients in each group were withdrawn from treatment early, but all 301 patients received the assigned treatment, at least initially (Fig. 1). Four patients were withdrawn because they did not meet the inclusion criteria (three in the dexamethasone group and one in the placebo group), and five because of adverse events (four in the dexamethasone group and one in the placebo group). Thirteen patients were withdrawn for other reasons: four were accidentally not treated for four days (two in each group; all four received the assigned study medication the first day or the first two days), one patient in the placebo group withdrew consent, and eight had clinical deterioration and were treated with corticosteroids (two in the dexamethasone group and six in the placebo group). The reasons for corticosteroid treatment were brain herniation (in three patients), pulmonary problems (in three), disseminated intravascular coagulation (in one), and acute disseminated encephalomyelitis (in one). Cranial computed tomography (CT) showed diffuse brain swelling in the patients with herniation and hypodense lesions in the patient with acute disseminated encephalomyelitis.

Eight weeks after admission, neurologic examinations were performed in 262 of 269 patients (97 percent). Seven patients were lost to follow-up, three in the dexamethasone group and four in the placebo group. At discharge, six of these seven patients had a score of 5 on the Glasgow Outcome Scale, and one had a score of 4. These last-observation scores were carried forward to eight weeks, so that all 301 patients were included in the analyses of the primary outcome and mortality.

Base-Line Characteristics of the Patients

Classic symptoms and signs of meningitis were present in a large proportion of the patients (headache in 94 percent, fever in 81 percent, and neck stiffness in 94 percent). At base line, the clinical characteristics and the results of laboratory tests were similar in the dexamethasone and placebo groups, although a higher percentage of patients in the dexamethasone group had seizures (Table 1). The mean cerebrospinal fluid pressure was also similar in the two groups, as was

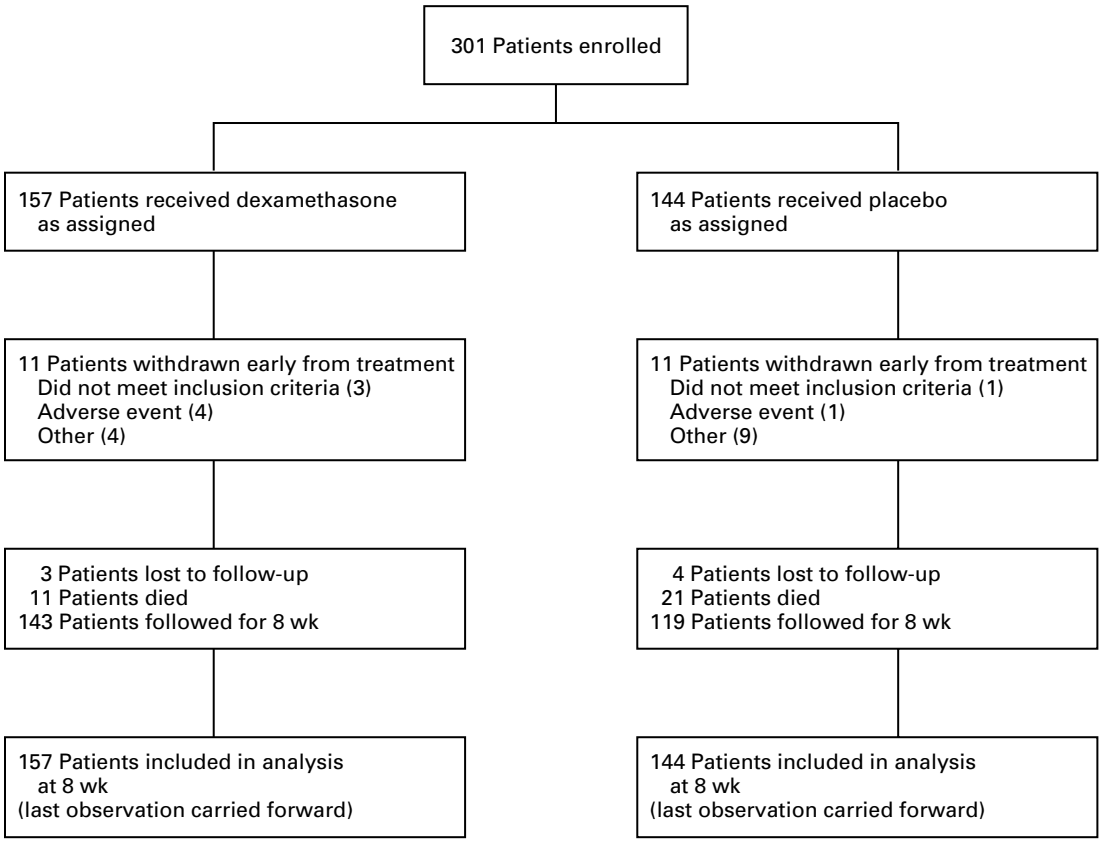

Figure 1. Random Assignment to Treatment, Withdrawal from Treatment, and Follow-up among 301 Adults with Bacterial Meningitis.

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TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY POPULATION.*

CHARACTERISTIC	DEXAMETHASONE GROUP (N=157)	PLACEBO GROUP (N=144)
Age — yr	44±18	46±20
Male sex — no. (%)	89 (57)	80 (56)
Basis for eligibility — no. (%)		
Bacteria in CSF on Gram's staining	116 (74)	99 (69)
No bacteria in CSF on Gram's staining but CSF white-cell count >1000 per mm³	38 (24)	42 (29)
Cloudy CSF only	3 (2)	3 (2)
Duration of symptoms before admission — hr		
Median	24	24
Range	1–336	1–167
Seizures — no. (%)	15 (10)	7 (5)
Findings on admission		
CSF pressure — cm of water†	37±13	34±14
Score on Glasgow Coma Scale‡		
Median	12	12
Range	3–14	3–14
Score <8, indicating coma — no. (%)	25 (16)	23 (16)
Papilledema — no. (%)§	6 (7)	9 (10)
Cranial-nerve palsy — no. (%)	14 (9)	18 (12)
Hemiparesis — no. (%)	10 (6)	12 (8)
CSF culture — no. (%)¶		
Streptococcus pneumoniae	58 (37)	50 (35)
Neisseria meningitidis	50 (32)	47 (33)
Other bacteria	12 (8)	17 (12)
Negative bacterial culture	35 (23)	30 (21)
Indexes of CSF inflammation		
White-cell count — per mm³		
Mean ±SD	8185±12,541	7438±10,688
Median	3667	3498
Range	7–123,000	3–76,000
Protein — g/liter	4.3±3.0	4.7±3.2
Glucose — mg/dl‖	27±31	27±29
Positive blood culture — no. (%)**	72 (53)	60 (47)

*Plus–minus values are means ±SD. CSF denotes cerebrospinal fluid.

†CSF pressure was measured in 157 patients (81 in the dexamethasone group and 76 in the placebo group).

‡Scores on the Glasgow Coma Scale range from 3 to 14, with 14 indicating a normal level of consciousness (abnormal flexion was omitted from the scale).

§A total of 86 patients in the dexamethasone group and 89 in the placebo group were examined for papilledema.

¶CSF cultures were performed in 155 patients in the dexamethasone group and 144 in the placebo group. The category of other bacteria included various streptococcal species other than *S. pneumoniae* in 12 patients, *Listeria monocytogenes* in 6, *Haemophilus influenzae* in 4, *Staphylococcus aureus* in 3, *Escherichia coli* in 1, *Klebsiella pneumoniae* in 1, corynebacterium species in 1, and *Capnocytophaga canimorsus* in 1.

‖To convert the values for glucose to millimoles per liter, multiply by 0.05551.

**Blood culture was performed in 264 patients (136 in the dexamethasone group and 128 in the placebo group).

the proportion of patients in the two groups who had very high pressure (40 cm of water or higher). Gram's staining of cerebrospinal fluid specimens, performed in 290 patients, showed bacteria in 215 patients (74 percent). Cerebrospinal fluid culture yielded bacteria in 234 of 299 patients (78 percent). Forty-three of the 65 patients (66 percent) with negative cerebrospinal fluid cultures had at least one individual cerebrospinal fluid finding that was predictive of bacterial meningitis (a glucose level below 34 mg per deciliter [1.9 mmol per liter], a glucose ratio [the ratio of glucose in the cerebrospinal fluid to that in blood] below 0.23, a protein level above 220 mg per deciliter, a white-cell count above 2000 per cubic millimeter, or a neutrophil count above 1180 per cubic millimeter).[16]

Efficacy

Eight weeks after enrollment, the percentage of patients with an unfavorable outcome was significantly smaller in the dexamethasone group than in the pla-

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cebo group (15 percent vs. 25 percent; relative risk, 0.59; 95 percent confidence interval, 0.37 to 0.94; P=0.03) (Table 2); the absolute reduction in the risk of an unfavorable outcome was 10 percent. Predictors of an unfavorable outcome were coma on admission (P=0.002), hypotension (P=0.03), and meningitis due to *S. pneumoniae* (P=0.02). The benefit of dexamethasone remained substantial in an analysis adjusted for other risk factors (adjusted odds ratio, 0.45; P=0.02). Among the patients with pneumococcal meningitis, 26 percent in the dexamethasone group had an unfavorable outcome, as compared with 52 percent in the placebo group. Among the patients with meningitis due to *N. meningitidis,* however, adjuvant treatment with dexamethasone did not provide a significant benefit.

The proportion of patients who died was significantly smaller in the dexamethasone group than in the placebo group (7 percent vs. 15 percent; relative risk, 0.48; 95 percent confidence interval, 0.24 to 0.96; P=0.04). Among the patients with pneumococcal meningitis, 14 percent of those who received dexamethasone and 34 percent of those who received placebo died. Adjuvant treatment with dexamethasone did not have a significant beneficial effect on neurologic sequelae, including hearing loss. During admission, audiologic examination was performed in 28 patients, 14 of whom had severe hearing loss (60 dB or more in one or both ears). At eight weeks, 27 patients had hearing loss. The distribution of scores on the Glasgow Outcome Scale is shown in Table 3. The lower mortality in the dexamethasone group did not result in an increased rate of severe neurologic sequelae in this group.

Table 4 shows the relative risk of an unfavorable outcome according to the severity of disease (as indicated by the score on the Glasgow Coma Scale on admission). Dexamethasone appeared to be most beneficial in patients with moderate or severe disease.

Adverse Events

Adverse events resulted in the early withdrawal of four patients in the dexamethasone group and one in the placebo group (Fig. 1). In the dexamethasone group, two patients were withdrawn because of severe hyperglycemia, one because of suspected stom-

TABLE 2. OUTCOMES EIGHT WEEKS AFTER ADMISSION, ACCORDING TO CULTURE RESULTS.*

OUTCOME AND CULTURE RESULTS	DEXAMETHASONE GROUP	PLACEBO GROUP	RELATIVE RISK (95% CI)†	P VALUE
	no./total no. (%)			
Unfavorable outcome				
All patients	23/157 (15)	36/144 (25)	0.59 (0.37–0.94)	0.03
Streptococcus pneumoniae	15/58 (26)	26/50 (52)	0.50 (0.30–0.83)	0.006
Neisseria meningitidis	4/50 (8)	5/47 (11)	0.75 (0.21–2.63)	0.74
Other bacteria	2/12 (17)	1/17 (6)	2.83 (0.29–27.8)	0.55
Negative bacterial culture‡	2/37 (5)	4/30 (13)	0.41 (0.08–2.06)	0.40
Death				
All patients	11/157 (7)	21/144 (15)	0.48 (0.24–0.96)	0.04
S. pneumoniae	8/58 (14)	17/50 (34)	0.41 (0.19–0.86)	0.02
N. meningitidis	2/50 (4)	1/47 (2)	1.88 (0.76–20.1)	1.00
Other bacteria	1/12 (8)	1/17 (6)	1.42 (0.10–20.5)	1.00
Negative bacterial culture	0/37	2/30 (7)	—	0.20
Focal neurologic abnormalities				
All patients	18/143 (13)	24/119 (20)	0.62 (0.36–1.09)	0.13
S. pneumoniae	11/49 (22)	11/33 (33)	0.67 (0.33–1.37)	0.32
N. meningitidis	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	3/11 (27)	3/16 (19)	1.45 (0.36–5.92)	0.66
Negative bacterial culture	1/37 (3)	5/26 (19)	0.14 (0.02–1.13)	0.07
Hearing loss				
All patients	13/143 (9)	14/119 (12)	0.77 (0.38–1.58)	0.54
S. pneumoniae	7/49 (14)	7/33 (21)	0.67 (0.25–1.69)	0.55
N. meningitidis	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	2/11 (18)	1/16 (6)	2.91 (0.30–28.3)	0.55
Negative bacterial culture	1/37 (3)	1/26 (4)	0.70 (0.05–10.7)	1.00

*The analyses of unfavorable outcome and death included all patients and were performed with a last-observation-carried-forward procedure. The analyses of neurologic abnormalities and hearing loss included all surviving patients who underwent neurologic examination at eight weeks.

†CI denotes confidence interval.

‡Included in this category are two patients in whom cerebrospinal fluid culture was not performed.

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TABLE 3. DISTRIBUTION OF SCORES ON THE GLASGOW OUTCOME SCALE AT EIGHT WEEKS.

SCORE	DEXAMETHASONE GROUP (N=157)	PLACEBO GROUP (N=144)
	no. of patients (%)	
1 (death)	11 (7)	21 (15)
2 (vegetative state)	0	0
3 (severe disability)	4 (3)	3 (2)
4 (moderate disability)	8 (5)	12 (8)
5 (mild or no disability)	134 (85)	108 (75)

ach perforation (which was not the case), and one because of agitation and flushing. One patient in the placebo group was withdrawn because of suspected cerebral abscess. Overall, treatment with dexamethasone did not result in an increased risk of adverse events (Table 5). In one patient in the dexamethasone group, gastrointestinal bleeding was complicated by stomach perforation, which required surgery.

Clinical Course

Impairment of consciousness was significantly less likely to develop in the patients who received dexamethasone than in those who received placebo (18 of 157 patients [11 percent] vs. 36 of 144 [25 percent], P=0.002). The patients in the dexamethasone group were also significantly less likely to have seizures (8 [5 percent] vs. 17 [12 percent], P=0.04) and cardiorespiratory failure (16 [10 percent] vs. 29 [20 percent], P=0.02).

Antibiotic Treatment and Susceptibility Testing

The most frequently prescribed initial antibiotics were amoxicillin and penicillin (in 77 percent of the patients), third-generation cephalosporin (in 8 percent), and penicillin or amoxicillin combined with a cephalosporin (in 8 percent). The Reference Laboratory for Bacterial Meningitis received cerebrospinal fluid isolates from 78 of 108 patients with *S. pneumoniae* meningitis (72 percent); all the isolates were susceptible to penicillin (minimal inhibitory concentration, less than 0.1 μg per milliliter). Isolates from 80 of the 97 patients with meningococcal meningitis (82 percent) were tested by the reference laboratory; only 1 showed intermediate resistance to penicillin (minimal inhibitory concentration, between 0.1 and 1.0 μg per milliliter). The initial antibiotic regimen provided adequate microbiologic coverage in 116 of the 120 patients (97 percent) with positive cerebrospinal fluid cultures in the dexamethasone group and in 112 of the 114 (98 percent) in the placebo group.

DISCUSSION

The results of our controlled prospective trial show that early treatment with dexamethasone improves the outcome in adults with acute bacterial meningitis. Adjunctive treatment with dexamethasone reduced the risks of both an unfavorable outcome and death. Dexamethasone did not have a beneficial effect on neurologic sequelae, including hearing loss. However, neurologic sequelae were seen predominantly in the most severely ill patients, and the proportion of severely ill patients who survived to be tested was larger in the dexamethasone group than in the placebo group.

The beneficial effect of dexamethasone was most

TABLE 4. UNFAVORABLE OUTCOME AT EIGHT WEEKS ACCORDING TO THE SCORE ON THE GLASGOW COMA SCALE ON ADMISSION.*

COMA SCORE AND CULTURE RESULTS	DEXAMETHASONE	PLACEBO	RELATIVE RISK (95% CI)	P VALUE
	no./total no. (%)			
Score of 12 to 14				
All patients	8/80 (10)	8/80 (10)	1.00 (0.40–2.53)	1.00
Streptococcus pneumoniae	1/15 (7)	2/11 (18)	0.37 (0.04–3.55)	0.56
Neisseria meningitidis	3/27 (11)	4/34 (12)	0.94 (0.23–3.87)	1.00
Score of 8 to 11				
All patients	7/52 (13)	14/41 (34)	0.39 (0.18–0.89)	0.03
S. pneumoniae	6/27 (22)	12/23 (52)	0.43 (0.19–0.95)	0.04
N. meningitidis	1/17 (6)	0/9 (0)	—	1.00
Score of 3 to 7				
All patients	8/25 (32)	14/23 (61)	0.53 (0.27–1.02)	0.08
S. pneumoniae	8/16 (50)	12/16 (75)	0.67 (0.38–1.17)	0.27
N. meningitidis	0/6	1/4 (25)	—	0.40

*Higher scores indicate a better level of consciousness. CI denotes confidence interval.

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TABLE 5. ADVERSE EVENTS.

EVENT	DEXAMETHASONE GROUP (N=157)	PLACEBO GROUP (N=144)	P VALUE
	no. (%)		
Gastrointestinal bleeding	2 (1)	5 (3)	0.27
Blood transfusion required	2 (1)	4 (3)	0.43
Stomach perforation	1 (1)	0	1.00
Hyperglycemia	50 (32)	37 (26)	0.24
Herpes zoster	6 (4)	4 (3)	0.75
Fungal infection	8 (5)	4 (3)	0.38

apparent in the patients with pneumococcal meningitis. However, a beneficial effect in the patients with meningococcal meningitis cannot be ruled out, since the number of patients in this subgroup was small. Therefore, we recommend dexamethasone treatment for all patients with acute bacterial meningitis.

The possibility of selection bias was a matter of concern in the study. To control for selection bias, we compared the base-line characteristics of patients enrolled in the study with prospective data from our nationwide cohort of 634 adults with acute bacterial meningitis. Patients in that cohort, for whom data were collected in the period from 1998 to 2002, were not included in the present study. There were no significant differences between the two groups with respect to the score on the Glasgow Coma Scale on admission. Furthermore, mortality rates among patients in the placebo group in this study and the nationwide cohort were similar. Therefore, we conclude that selection bias did not confound the results.

A delay in initiating antibiotic therapy was also a matter of concern. Informed-consent procedures can delay the initiation of antimicrobial therapy, which may lead to a poor outcome.[17] In addition, cranial CT should be performed before lumbar puncture in order to rule out brain shift in patients with coma, papilledema, or hemiparesis in whom meningitis is suspected. Lumbar puncture increases the risk of brain herniation if an intracranial mass is present.[18,19] In this setting, empirical antibiotic therapy should be started before cranial CT is performed.[18,19] In our study, treatment may have been delayed in patients who underwent cranial CT before lumbar puncture, because the study medication was administered before or with the first dose of antibiotics and the inclusion of patients in the study depended on the presence of cerebrospinal fluid abnormalities. Since early therapy reduces morbidity and mortality,[17] treatment with dexamethasone and antibiotics should be initiated before lumbar puncture in all patients with suspected meningitis who must undergo cranial CT first.

Two important issues are the duration and timing of dexamethasone therapy. Although data suggest that two-day and four-day regimens are equally effective,[20,21] the four-day regimen has been used in most clinical trials involving children with bacterial meningitis.[6] Dexamethasone has been shown to have a beneficial effect in children with pneumococcal meningitis only if it is given before or with the first dose of antibiotics.[6] In our study, we used the four-day regimen and also started it early. Therefore, a four-day regimen is recommended, with dexamethasone therapy started before or with the first dose of antibiotics.

Most patients initially received monotherapy with amoxicillin. In the first half of the study, amoxicillin was standard treatment in all patients. Rates of antibiotic resistance among meningococcal and pneumococcal isolates were very low. Similar rates were found in nationwide studies in the Netherlands.[10,11] In a prospective audit of empirical therapy in adults with bacterial meningitis in the Netherlands, monotherapy with amoxicillin or penicillin appeared to be prescribed most frequently.[11] Although dexamethasone is not associated with adverse events, concern has been expressed that because the drug reduces blood–brain permeability, it may impede the penetration of vancomycin into the subarachnoid space.[9,22] With the worldwide increase in the prevalence of penicillin-resistant pneumococci, combination therapy that includes vancomycin has become more important.[8] In children with bacterial meningitis, treatment with dexamethasone did not reduce vancomycin levels in cerebrospinal fluid.[23] However, treatment failures have been reported in adults who received standard doses of vancomycin and adjunctive dexamethasone.[24] Therefore, patients with pneumococcal meningitis who are treated with vancomycin and dexamethasone should be carefully observed throughout therapy.

Cognitive impairment occurs frequently in adults who survive bacterial meningitis.[25] Because corticosteroids may potentiate ischemic injury to neurons, it is important to know whether dexamethasone prevents death but worsens cerebral cortical functioning.[26] Although in our study the reduction in mortality among the patients treated with dexamethasone did not result in an increased rate of neurologic sequelae, a cognitive evaluation of adults treated with dexamethasone and those treated without it is needed.

The results of our study show that adjunctive dexamethasone therapy improves the outcome in adults with acute bacterial meningitis. Dexamethasone (10 mg every six hours for four days) should be given to all such adults, and the regimen should be initiated before or with the first dose of antibiotics. This treatment does not increase the risk of gastrointestinal bleeding.

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APPENDIX

The following centers and investigators participated in the European Dexamethasone in Adulthood Bacterial Meningitis Study: **the Netherlands** — Academisch Medisch Centrum, Amsterdam: J. de Gans, D. van de Beek, R.H. Enting; Medisch Centrum Alkmaar, Alkmaar: R. ten Houten; Flevoziekenhuis, Almere: G.N. Mallo; Bovenij Ziekenhuis, Amsterdam: P.M.S. Gerkens; Sint Lucas Andreas Ziekenhuis, Amsterdam: J. Vos, J.A.L. Vanneste; Onze Lieve Vrouwe Gasthuis, Amsterdam: H.K. van Walbeek; Slotervaartziekenhuis, Amsterdam: J.J. van der Sande; Gelre Ziekenhuizen, Apeldoorn: R.B. van Leeuwen; Ziekenhuis Rijnstate, Arnhem: Q.H. Leyten; Stichting Ziekenhuisvoorzieningen Gelderse Vallei, Ede: M.G. Smits; Ziekenhuis Leijenburg, Den Haag: R.W.M. Keunen, J. Blankevoort; Medisch Centrum Haaglanden, Den Haag: W.V.M. Perquin, P. Bienfait; Ziekenhuis Bronovo, Den Haag: P.C.L.A. Lambregts; Albert Schweitzer Ziekenhuis, Dordrecht: L.I. Hertzberger, Ziekenhuis Nij Smellinghe, Drachten: J.A. Hilbers, H.L. van der Wiel; Catharina Ziekenhuis, Eindhoven: J.N. Berendes; Diaconessenhuis, Eindhoven: A.J. Vermeij; Medisch Spectrum Twente, Enschede: G. Hageman; Oosterscheldeziekenhuizen, Goes: A.M. Boon; Beatrixziekenhuis, Gorinchem: R.B. Alting van Geusau; Academisch Ziekenhuis Groningen, Groningen: A. Bollen, H.J.G. Dieks, A.E.J. de Jager; Atrium Medisch Centrum, Heerlen: M.J. Wennekes; Westfries Gasthuis, Hoorn: F.E.A.M. Bussemaker; Atrium Medisch Centrum, Kerkrade: A.J.H. van Diepen; Diaconessenhuis, Leiden: P.E. Briët; Rijnland Ziekenhuis, Leiderdorp: R.J.W. Witteveen; Medisch Centrum Haaglanden, Leidschendam: R.J. Groen; IJsselmeerziekenhuizen, Lelystad: J.P. Geervliet; Ziekenhuis Canisius–Wilhelmina, Nijmegen: C.W.G.M. Frenken; Academisch Ziekenhuis Nijmegen Sint Radboud, Nijmegen: P.E. Vos, A.J.M. Keyser; Amphia Ziekenhuis, Oosterhout: A.H. Temmink; Medisch Centrum Rijnmond-Zuid, Rotterdam: C.A. van Donselaar; Academisch Ziekenhuis Rotterdam Dijkzigt, Rotterdam: D. Hasan; Sint Elisabeth Ziekenhuis, Tilburg: C.C. Tijssen; Universitair Medisch Centrum Utrecht, Utrecht: A. Elderson, G. van Dijk; Mesos Medisch Centrum, Utrecht: R.P.M. Bruyn; Sint Joseph Ziekenhuis, Veldhoven: B.J. van Kasteren; Vlietland Ziekenhuis, Vlaardingen: J.J.M. Driesen; Reinier de Graaf Groep, Voorburg: J.L. van Doorn; Sint Lucas Ziekenhuis, Winschoten: M.C. Wittebol; Hofpoort Ziekenhuis, Woerden: R. Wielaard, E.J. Wieringa; Kennemer Gasthuis, IJmuiden: J.A. Don; Gelre Ziekenhuizen, Zutphen: H.J.D. de Zwart; Isala Klinieken, Zwolle: P.L.J.M. Bos; **Belgium** — Algemeen Ziekenhuis Sint-Jan, Brugge: M. D'Hooghe; Sint Blasius Ziekenhuis, Dendermonde: E. Van Buggenhout; Universitair Ziekenhuis Leuven, Leuven: A. Govaerts; Algemeen Ziekenhuis Middelheim, Antwerp: R. Crols; **Germany:** Städtisches Klinikum St. Georg, Leipzig: B.R. Ruf, S. Fischer, T. Grünewald; Universitäts-Krankenhaus Eppendorf, Hamburg: K. Kunze, H.C. Hansen; **Denmark** — Odense Universitetshospital, Odense: S. Stenvang Pedersen; **Austria** — Universitätsklinik für Neurologie, Innsbrück: E. Schmutzhard, H.K. Spiss. **Steering Committee:** J. Dankert, J. de Gans, L. Spanjaard, P. Speelman, M. Vermeulen. **Data Monitoring Committee:** H. van Crevel (chairman), P. Speelman, J.G.P. Tijssen. **Clinical Epidemiology and Biostatistics:** R. de Haan. **Writing Committee:** J. de Gans, D. van de Beek, M. Vermeulen.

REFERENCES

1. Bohr V, Hansen B, Jessen O, et al. Eight hundred and seventy-five cases of bacterial meningitis. I. Clinical data, prognosis, and the role of specialized hospital departments. J Infect 1983;7:21-30.
2. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults: a review of 493 episodes. N Engl J Med 1993;328:21-8.
3. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. N Engl J Med 1992;327:864-72.
4. Scheld WM, Dacey RG, Winn HR, Welsh JE, Jane JA, Sande MA. Cerebrospinal fluid outflow resistance in rabbits with experimental meningitis: alterations with penicillin and methylprednisolone. J Clin Invest 1980;66:243-53.
5. Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. J Infect Dis 1985;151:528-34.
6. McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis: a meta-analysis of randomized clinical trials since 1988. JAMA 1997;278:925-31.
7. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J 1989;8:848-51.
8. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. N Engl J Med 1997;336:708-16.
9. Saez-Llorens X, McCracken GH Jr. Antimicrobial and anti-inflammatory treatment of bacterial meningitis. Infect Dis Clin North Am 1999;13:619-36.
10. Enting RH, Spanjaard L, van de Beek D, Hensen EF, de Gans J, Dankert J. Antimicrobial susceptibility of *Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae* isolates causing meningitis in the Netherlands, 1993-1994. J Antimicrob Chemother 1996;38:777-86.
11. van de Beek D, de Gans J, Spanjaard L, Vermeulen M, Dankert J. Antibiotic guidelines and antibiotic use in adult bacterial meningitis in the Netherlands. J Antimicrob Chemother 2002;49:661-6.
12. Jennett B, Teasdale G. Management of head injuries. Vol. 20 of Contemporary neurology. Philadelphia: F.A. Davis, 1981.
13. Wilson JTL, Pettigrew LEI, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15:573-85.
14. Wade DT. Measurement in neurological rehabilitation. Oxford, England: Oxford University Press, 1992.
15. Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. Br Med J (Clin Res Ed) 1986;292:746-50.
16. Spanos A, Harrell FE Jr, Durack DT. Differential diagnosis of acute meningitis: an analysis of the predictive value of initial observations. JAMA 1989;262:2700-7.
17. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med 1998;129:862-9.
18. van Crevel H, Hijdra A, de Gans J. Lumbar puncture and the risk of herniation: when should we first perform CT? J Neurol 2002;249:129-37.
19. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med 2001;345:1727-33.
20. Syrogiannopoulos GA, Lourida AN, Theodoridou MC, et al. Dexamethasone therapy for bacterial meningitis in children: 2- versus 4-day regimen. J Infect Dis 1994;169:853-8.
21. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J. Dexamethasone therapy for bacterial meningitis in children. Lancet 1993;342:457-61.
22. Coyle PK. Glucocorticoids in central nervous system bacterial infection. Arch Neurol 1999;56:796-801.
23. Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant *Streptococcus pneumoniae* in cerebrospinal fluid of children with acute bacterial meningitis. Antimicrob Agents Chemother 1995;39:1988-92.
24. Viladrich PF, Gudiol F, Linares J, et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. Antimicrob Agents Chemother 1991;35:2467-72.
25. 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;186:1047-52.
26. Sapolsky RM, Pulsinelli WA. Glucocorticoids potentiate ischemic injury to neurons: therapeutic implications. Science 1985;229:1397-400.

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