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Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis

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ABSTRACT

BACKGROUND

We conducted a nationwide study in the Netherlands to determine clinical features and prognostic factors in adults with community-acquired acute bacterial meningitis.

METHODS

From October 1998 to April 2002, all Dutch patients with community-acquired acute bacterial meningitis, confirmed by cerebrospinal fluid cultures, were prospectively evaluated. All patients underwent a neurologic examination on admission and at discharge, and outcomes were classified as unfavorable (defined by a Glasgow Outcome Scale score of 1 to 4 points at discharge) or favorable (a score of 5). Predictors of an unfavorable outcome were identified through logistic-regression analysis.

RESULTS

We evaluated 696 episodes of community-acquired acute bacterial meningitis. The most common pathogens were *Streptococcus pneumoniae* (51 percent of episodes) and *Neisseria meningitidis* (37 percent). The classic triad of fever, neck stiffness, and a change in mental status was present in only 44 percent of episodes; however, 95 percent had at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. On admission, 14 percent of patients were comatose and 33 percent had focal neurologic abnormalities. The overall mortality rate was 21 percent. The mortality rate was higher among patients with pneumococcal meningitis than among those with meningococcal meningitis (30 percent vs. 7 percent, $P<0.001$). The outcome was unfavorable in 34 percent of episodes. Risk factors for an unfavorable outcome were advanced age, presence of otitis or sinusitis, absence of rash, a low score on the Glasgow Coma Scale on admission, tachycardia, a positive blood culture, an elevated erythrocyte sedimentation rate, thrombocytopenia, and a low cerebrospinal fluid white-cell count.

CONCLUSIONS

In adults presenting with community-acquired acute bacterial meningitis, the sensitivity of the classic triad of fever, neck stiffness, and altered mental status is low, but almost all present with at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. The mortality associated with bacterial meningitis remains high, and the strongest risk factors for an unfavorable outcome are those that are indicative of systemic compromise, a low level of consciousness, and infection with *S. pneumoniae*.

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THE EPIDEMIOLOGY OF BACTERIAL MENingitis has changed. Meningitis due to *Haemophilus influenzae* type b has been nearly eliminated in the Western world since vaccination against *H. influenzae* type b was initiated,[1] and the introduction of conjugate vaccines against *Streptococcus pneumoniae* is expected to reduce the burden of childhood pneumococcal meningitis significantly.[2] Although vaccination with a pneumococcal conjugate vaccine is producing herd immunity among adults, the age distribution of meningitis has now shifted to older age groups.[2,3] Several studies of clinical features and prognostic factors in adults with bacterial meningitis have been performed; however, all were retrospective and relatively small in size.[4-23] We performed a nationwide prospective study of clinical features and prognostic factors in adults with community-acquired bacterial meningitis in the Netherlands.

METHODS

We identified adults (defined as patients older than 16 years of age) who had bacterial meningitis and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis from October 1998 to April 2002. This laboratory receives cerebrospinal fluid and blood isolates from approximately 85 percent of all patients with bacterial meningitis in the Netherlands (population, 16.2 million).[3,24] The laboratory provides daily updates of the names of hospitals where patients with bacterial meningitis have been admitted in the preceding two to six days and the names of physicians, usually neurologists. Physicians were informed about the study by telephone. Subsequently, patients or their legal representatives received written information concerning the study and were asked to give written informed consent for participation; only patients for whom consent was obtained were enrolled. Case-record forms were used to collect data on patients' history, symptoms and signs on admission, laboratory findings at admission, clinical course, outcome and neurologic findings at discharge, and treatment.

Patients were categorized as having either community-acquired or hospital-acquired meningitis (the latter was defined as meningitis that occurred during hospitalization or within one week after discharge). Patients with an altered immune status owing to the use of immunosuppressive drugs or splenectomy, diabetes mellitus, or alcoholism were considered immunocompromised, as were patients infected with the human immunodeficiency virus. At discharge, all patients underwent a neurologic examination performed by a neurologist, and the outcome was graded according to the Glasgow Outcome Scale. A score of 1 on this scale indicates death; a score of 2, a vegetative state (the patient is unable to interact with the environment); a score of 3, severe disability (the patient is unable to live independently but can follow commands); a score of 4, moderate disability (the patient is capable of living independently but unable to return to work or school); and a score of 5, mild or no disability (the patient is able to return to work or school). 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 is a well-validated instrument with good interobserver agreement.[25]

The susceptibility of meningococci to penicillin was determined by inoculating strains onto chocolate agar containing 0.1 mg of penicillin per liter. A 1-μg oxacillin disk was used to identify penicillin-resistant strains of pneumococci. Whenever a strain showed antibiotic resistance, the E rosette assay was used to determine the minimal inhibitory concentration of the antibiotic. The inoculation procedure and susceptibility testing were performed as described elsewhere.[26] Parts of this cohort study have been reported previously.[7,26-28]

This observational study used patient data that had been rendered anonymous and was carried out in accordance with Dutch privacy legislation. The study was announced in the journal of the Dutch Neurologic Society, followed by periodic reminders. Before the study, all Dutch neurologists received information about the study, including a case-record form.

Parametric and nonparametric tests were used to identify differences between groups in continuous outcomes, and chi-square tests were used to compare categorical outcomes. We used logistic regression to examine the association between potential predictors and the likelihood of an unfavorable outcome. Odds ratios and 95 percent confidence intervals were used to quantify the strength of these associations. On the basis of previous research and pathophysiologic interest, 20 potentially relevant predictors were chosen.

Despite the low median percentage of missing values for individual variables (2 percent), only 320 of the 696 patients had complete data on all predictors — which presented a considerable

limitation for multivariate models. Therefore, we used multiple imputation techniques to reduce this loss.[29] All predictors together were used to impute missing values on the basis of multivariate normal distributions. The coefficients of five rounds of imputation were combined to obtain the final estimates for the multivariate model. The low rate of missing values per variable, the large number of predictors, and the large sample size maximized the benefits of the multiple imputation methods.[30] All statistical tests were two-tailed, and P values of less than 0.05 were considered to indicate statistical significance.

Statistical analyses were performed with use of SAS software, version 8.02 (SAS Institute). The study was designed, conducted, and analyzed independently of the sponsor.

RESULTS

A total of 1108 episodes of bacterial meningitis were identified by the reference laboratory. A total of 994 case-record forms were sent out, and the response rate was 76 percent (754 of 994) (Fig. 1). The demographic characteristics of patients with meningitis identified by the laboratory and those included in the analysis were similar for each causative organism. Fifty-eight patients were excluded — 50 patients with hospital-acquired meningitis, 3 patients with a recent history of neurosurgery, and 5 patients with a neurosurgical device — leaving a total of 696 episodes of community-acquired meningitis in 671 patients. The annual incidence of community-acquired bacterial meningitis was 2.6 cases per 100,000 adults.

Characteristics of the study population are shown in Table 1. Seizures occurred before admission in 32 of 666 episodes (5 percent). Predisposing conditions were present in 48 percent of episodes, the most common of which were otitis or sinusitis in 25 percent, pneumonia in 12 percent, and an immunocompromised state in 16 percent. Patients with pneumococcal meningitis were more likely to have distant foci of infection than were patients with meningococcal meningitis (62 percent vs. 9 percent, P<0.001).

Classic symptoms and signs of bacterial meningitis were present in a large proportion of patients (Table 1). Headache occurred in 87 percent of episodes, neck stiffness in 83 percent, fever in 77 percent, and a change in mental status (defined by a Glasgow Coma Scale score below 14) in 69 percent. Only 44 percent of episodes were characterized by the classic triad of fever, neck stiffness, and a change in mental status. At least two of four signs (the classic triad plus headache) were present in

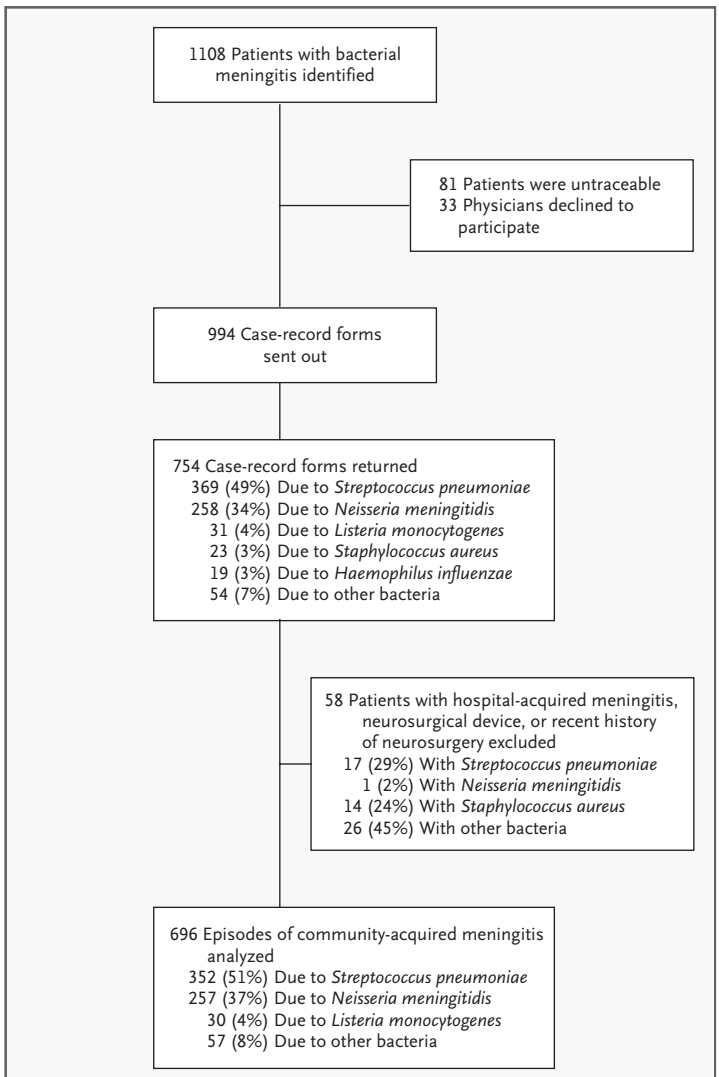

Figure 1. Selection of Patients.

Among the 19 strains of *Haemophilus influenzae*, 16 were nontypeable, 1 was type b, 1 was type e, and 1 was type f. Neurosurgery and neurosurgical devices included ventriculostomy, ventriculoperitoneal or ventriculoatrial shunt, lumbar epidural catheter, and a dorsal-column stimulator. Among the 57 of 696 episodes of meningitis due to bacteria other than *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria monocytogenes*, 14 were due to *H. influenzae*, 9 to *Staphylococcus aureus*, 6 to group A streptococcus, 5 to group B streptococcus, 4 to *Streptococcus suis*, 4 to *Escherichia coli*, 2 to *Streptococcus salivarius*, 1 to group C streptococcus, 1 to group G streptococcus, 1 to *H. parainfluenzae*, 1 to *Klebsiella pneumoniae*, 1 to *Streptococcus bovis*, 1 to *Streptococcus mitis*, 1 to *Streptococcus oralis*, 1 to *Streptococcus constellatus*, 1 to *Staphylococcus epidermidis*, and 1 merely to "streptococci"; 3 specimens were not viable.

Table 1. Characteristics of the Study Population.*

Characteristic	Episodes of Meningitis (N=696)	Characteristic	Episodes of Meningitis (N=696)
Age — yr	50±20	Triad of fever, neck stiffness, and change in mental status — no. (%)	305 (44)
Male sex — no. (%)	345 (50)	Focal neurologic deficits — no. (%)	233 (33)
History of meningitis — no. (%)	37 (5)	Cranial-nerve palsy — no./no. evaluated (%)	
Duration of symptoms <24 hr — no./no. evaluated (%)	317/661 (48)	3rd nerve	24/648 (4)
Seizures — no./no. evaluated (%)	32/666 (5)	6th nerve	21/641 (3)
Pretreated with antibiotics — no. (%)	64 (9)	7th nerve	12/651 (2)
Predisposing conditions — no. (%)		8th nerve	36/550 (7)
Otitis or sinusitis	176 (25)	Aphasia — no./no. evaluated (%)	121/532 (23)
Pneumonia	83 (12)	Hemiparesis — no./no. evaluated (%)	49/682 (7)
Immunocompromise†	114 (16)	Papilledema — no./no. evaluated (%)	13/386 (3)
HIV-positive‡	4 (1)	Indexes of CSF inflammation	
Symptoms on presentation		Opening pressure — mm of water¶	370±130
Headache — no./no. evaluated (%)	544/626 (87)	White-cell count‖	
Nausea — no./no. evaluated (%)	449/610 (74)	Mean — cells/mm³	7753±14,736
Neck stiffness — no./no. evaluated (%)	569/685 (83)	<100/mm³ — no./no. evaluated (%)	47/645 (7)
Rash — no./no. evaluated (%)	176/683 (26)	100–999/mm³ — no./no. evaluated (%)	93/645 (14)
Systolic blood pressure — mm Hg	144±33	>999/mm³ — no./no. evaluated (%)	505/645 (78)
Diastolic blood pressure — mm Hg	79±20	Protein — g/liter	4.9±4.5
Body temperature		CSF:blood glucose ratio	0.2±0.2
Mean — °C	38.8±1.2	Positive blood culture — no./no. evaluated (%)**	404/611 (66)
≥38°C — no./no. evaluated (%)	522/678 (77)	Blood chemical tests	
Score on Glasgow Coma Scale§		ESR — mm/hr††	46±37
Mean	11±3	C-reactive protein — mg/liter‡‡	225±132
<14 (indicating change in mental status) — no. (%)	477 (69)	Thrombocyte count — platelets/mm³§§	198,000±100,000
<8 (indicating coma) — no. (%)	96 (14)		

* The study included 671 patients who had a total of 696 episodes of community-acquired meningitis. Plus–minus values are means ±SD. CSF denotes cerebrospinal fluid.
† Immunocompromise was defined by the use of immunosuppressive drugs, a history of splenectomy, or the presence of diabetes mellitus or alcoholism, as well as patients infected with the human immunodeficiency virus (HIV).
‡ The number of patients tested for HIV infection is unknown.
§ Scores on the Glasgow Coma Scale can range from 3 to 15, with 15 indicating a normal level of consciousness. Glasgow Coma Scale scores were evaluated in 694 patients; 1 patient with pneumococcal meningitis and 1 with meningococcal meningitis were not evaluated.
¶ The CSF pressure was measured in 216 patients.
‖ The CSF leukocyte count was determined in 659 patients; CSF specimens from 14 patients had too many leukocytes for an exact count to be performed.
** Blood culture was performed in 611 patients.
†† The erythrocyte sedimentation rate (ESR) was determined in 549 patients.
‡‡ C-reactive protein levels were determined in 394 patients.
§§ The thrombocyte count was determined in 653 patients.

664 episodes (95 percent), only one in 28 episodes (4 percent), and none in 4 episodes (1 percent). The classic triad was significantly more likely to be present in patients with pneumococcal meningitis than in those with meningococcal meningitis (58 percent vs. 27 percent, P<0.001).

Rash was present in 176 of 683 episodes (26 percent); the causative species was *Neisseria meningitidis* in 162 episodes, *S. pneumoniae* in 8, *Staphylococcus aureus* in 2, group B streptococcus in 2, *H. influenzae* in 1, and *Listeria monocytogenes* in 1. The rash was petechial in 157 of these 176 episodes (89 per-

cent). The rash was petechial in 13 of 14 episodes that were characterized by a rash and a nonmeningococcal cause of meningitis.

In 14 percent of episodes, the patients were comatose on admission, and in 33 percent of episodes, focal neurologic deficits were present on admission. Patients with pneumococcal meningitis had more severe disease than did patients with meningococcal meningitis, as reflected by a higher frequency of seizures (P=0.001) and focal neurologic deficits (P<0.001) and a lower level of consciousness (P<0.001). Results of funduscopic examination were recorded for 386 episodes; 13 episodes were characterized by papilledema (3 percent).

Lumbar puncture was performed in all patients. The time between admission and lumbar puncture was not recorded. Cerebrospinal fluid pressure was evaluated in 216 episodes. Opening pressures were normal (less than 200 mm of water) in 38 episodes (18 percent) and exceeded 400 mm of water in 85 (39 percent). Patients with opening pressures of more than 400 mm of water were more likely to be admitted in a coma than were those with lower opening pressures (14 of 131 [11 percent] vs. 20 of 85 [24 percent], P=0.01). However, the percentage of patients with an unfavorable outcome was similar in the two groups (30 percent and 35 percent, respectively). The mean opening pressures were similar among patients with papilledema and those without papilledema. At least one individual cerebrospinal fluid finding predictive of bacterial meningitis (a glucose level of less than 34 mg per deciliter [1.9 mmol per liter], a ratio of cerebrospinal fluid glucose to blood glucose of less than 0.23, a protein level of more than 220 mg per deciliter, or a white-cell count of more than 2000 per cubic millimeter)[31] was present in 567 of 645 episodes (88 percent).

Cranial computed tomography (CT) was performed on admission in 496 episodes (71 percent); the results were normal in 325. Abnormalities were recorded in 171 episodes (34 percent): cerebral edema was identified in 48 of 496 episodes (10 percent), sinusitis or otitis in 48 (10 percent), evidence of recent infarction in 30 (6 percent), and hydrocephalus in 15 (3 percent). Thirty-eight episodes involved other abnormalities on cranial CT: old vascular lesions in 12, cerebral atrophy in 6, skull fracture in 5, pneumatocephalus in 5, arachnoid cyst in 3, vascular aneurysm in 2, subarachnoid hemorrhage in 1, brain-parenchyma hemorrhage in 1, subdural empyema in 1, meningioma in 1, and Dandy–Walker malformation in 1; in 8 episodes, two abnormalities were identified.

Cranial CT was performed before lumbar puncture in 337 of 696 episodes (48 percent). Focal neurologic deficits (not including cranial-nerve abnormalities), a score of less than 10 on the Glasgow Coma Scale, or both were present in 313 of 696 episodes (45 percent), and cranial CT was performed before lumbar puncture in 197 of these 313 episodes (63 percent). Therapy was initiated before CT in 35 percent of episodes in which CT was performed before lumbar puncture.

The most common microorganism was *S. pneumoniae*, accounting for 51 percent of isolates cultured from cerebrospinal fluid (Fig. 1). The distribution of serotypes among 352 pneumococci is shown in Table 2. *N. meningitidis* was responsible for 37 percent of the episodes, with group B identified in 173 episodes, group C in 79, group Y in 3, group H in 1, and group W135 in 1. Gram's staining of cerebrospinal fluid revealed the microorganism in 524 of 652 episodes (sensitivity, 80 percent; specificity, 97 percent). The yield of Gram's staining was similar in patients who had previously received antimicrobial therapy and those who had not. Antibiotic susceptibility was tested in 351 pneumococcal and 256 meningococcal strains; 2 pneumococcal and 4 meningococcal strains showed intermediate resistance to penicillin; all other strains were sensitive to penicillin. Initial antibiotic treatment consisted of penicillin or amoxicillin in 43 percent of episodes, third-generation cephalosporins in 16 percent, and a combination of penicillin or amoxicillin with a third-generation cephalosporin in 25 percent; other regimens were used in 16 percent of episodes.

During the clinical course, focal neurologic abnormalities were found in half the episodes (Table 3); most were present on admission. Seizures occurred in 15 percent of episodes, and cardiorespiratory failure in 29 percent. Complications were significantly more likely to develop among patients with pneumococcal meningitis than among patients with meningococcal meningitis (P<0.001).

The mortality rate was 21 percent (Table 3) and varied depending on the causative organism; it was 30 percent for pneumococcal meningitis, as compared with 7 percent for meningococcal meningitis (P<0.001) (Table 3) and 20 percent for meningitis due to other pathogens (P=0.05). Thirty-four percent of episodes had an unfavorable outcome. A neurologic examination was performed at dis-

Table 2. Capsular Pneumococcal Serotypes from 352 Adults with Meningitis.

Serotype	No. of Patients (%)
3	36 (10)
14*	34 (10)
19F*	29 (8)
7F	28 (8)
9V*	27 (8)
6B*	21 (6)
10A	21 (6)
8	16 (5)
4*	16 (5)
23F*	14 (4)
6A	10 (3)
19A	10 (3)
12F	10 (3)
Other†	80 (23)

* This serotype is included in the seven-valent conjugated vaccine (coverage, 149 of 352 isolates [42 percent]).
† Other types were as follows: 22F in eight patients, 18C (included in the seven-valent conjugated vaccine) in eight, 35F in six, 1 in five, 9N in five, 17F in five, 38 in four, 15B in four, 16F in four, 18B in four, 33F in four, 23B in four, 24F in three, 34 in three, 5 in two, 15A in two, 15C in two, 20 in two, 22A in two, 9A in one, 18F in one, and 23A in one.

charge in 550 of 553 surviving patients (99 percent); the most common abnormalities identified were hearing loss (14 percent) and hemiparesis (4 percent).

Corticosteroids were administered in 118 episodes (17 percent), and episodes involving corticosteroid therapy were more likely to have an unfavorable outcome than were episodes that did not involve corticosteroid therapy (51 of 118 [43 percent] vs. 186 of 578 [32 percent], P=0.03). Episodes in which corticosteroids were administered before antibiotics were less likely to have an unfavorable outcome than episodes in which corticosteroids were administered after antibiotics (3 of 24 [12 percent] vs. 48 of 94 [51 percent], P=0.001). Opening pressures of more than 400 mm of water were recorded in 46 percent of patients who received corticosteroids and 38 percent of those not receiving corticosteroids.

In the multivariate model several characteristics were significantly associated with an unfavorable outcome (Table 4): advanced age, the presence of otitis or sinusitis, the absence of rash, a heart rate of more than 120 beats per minute, a low score on the Glasgow Coma Scale, a cerebrospinal fluid white-cell count of fewer than 1000 per cubic millimeter, a positive blood culture, an elevated erythrocyte sedimentation rate, and a reduced platelet count. Six other characteristics tended toward statistical significance: the presence of symptoms for less than 24 hours before admission, seizures, pneumonia, an immunocompromised state, a heart rate below 60 beats per minute, and hypotension (defined as a diastolic blood pressure of less than 60 mm Hg).

The causative organism had an independent effect when it was added to the multivariate model. The odds of an unfavorable outcome was six times as high (95 percent confidence interval, 2.61 to 13.91; P<0.001) among patients infected with *S. pneumoniae* as among patients infected with *N. meningitidis*, even after adjustment for other clinical predictors.

During episodes of meningococcal meningitis, hypotension was more common among patients with a cerebrospinal fluid white-cell count of fewer than 100 cells per cubic millimeter than among patients with a higher cerebrospinal fluid white-cell count (8 of 18 [44 percent] vs. 24 of 211 [11 percent], P<0.001). This association was absent during episodes of pneumococcal meningitis.

DISCUSSION

We found that the prevalence of the classic triad of fever, neck stiffness, and an altered mental status is low among adults with community-acquired bacterial meningitis. However, almost all patients (95 percent) presented with at least two of the four symptoms of headache, fever, neck stiffness, and an altered mental status. In addition, a high percentage of patients (33 percent) were admitted with focal neurologic deficits. These percentages are similar to those found in retrospective studies; however, we found an exceptionally high prevalence of aphasia.[4-6,9-23]

The majority of patients who presented with moderate or severe impairment of consciousness, neurologic deficits (not including cranial-nerve abnormalities), or both, which are contraindications to performing lumbar puncture, underwent CT before lumbar puncture (63 percent). However, a large number of patients without these "red flags" also underwent CT first, and many patients with such red flags did not undergo CT before lumbar punc-

Table 3. Clinical Course, Outcome, and Neurologic Findings at Discharge.*

Characteristic	All Episodes of Meningitis (N=696)	Episodes of Pneumococcal Meningitis (N=352)	Episodes of Meningococcal Meningitis (N=257)
		number of episodes (percent)	
Clinical course			
Focal neurologic deficits	351 (50)	227 (65)	85 (33)
Seizures	107 (15)	85 (24)	12 (5)
Cardiorespiratory failure	201 (29)	134 (38)	45 (18)
Mechanical ventilation	160 (23)	109 (31)	36 (14)
Score on Glasgow Outcome Scale			
1 (death)	143 (21)	107 (30)	19 (7)
2 (vegetative state)	3 (<1)	3 (1)	0
3 (severe disability)	24 (3)	17 (5)	4 (2)
4 (moderate disability)	67 (10)	50 (14)	7 (3)
5 (mild or no disability)	459 (66)	175 (50)	227 (88)
Neurologic findings at discharge		*number/number evaluated (percent)*†	
Cranial-nerve palsy			
3rd nerve	7/550 (1)	6/243 (2)	0/237
6th nerve	14/550 (3)	6/243 (2)	1/237 (<1)
7th nerve	8/550 (1)	4/243 (2)	2/237 (1)
8th nerve	78/550 (14)	53/243 (22)	18/237 (8)
Aphasia	11/550 (2)	8/243 (3)	1/237 (<1)
Hemiparesis	24/550 (4)	18/243 (7)	2/237 (1)
Quadriparesis	6/550 (1)	4/243 (2)	2/237 (1)

* The study included 671 patients with a total of 696 episodes of community-acquired meningitis.
† Neurologic examination was performed at discharge in 550 of 553 surviving patients: 243 of 245 patients after pneumococcal meningitis, 237 of 238 patients after meningococcal meningitis, and 70 of 70 patients after other types of meningitis.

ture. In most patients who underwent CT before lumbar puncture, therapy was not initiated before CT was performed. Cranial CT has been recommended as a precaution before lumbar puncture to predict the likelihood and avoid the possibility of brain herniation.[9,32,33] The withdrawal of cerebrospinal fluid removes counterpressure from below, thus increasing the effect of compression from above and exacerbating the brain shift already present.[33]

In patients with red flags indicating space-occupying lesions and in those with moderate or severe impairment of consciousness (as indicated by a score of less than 10 on the Glasgow Coma Scale), lumbar puncture should be preceded by cranial CT. However, a delay in the initiation of antimicrobial therapy may lead to a poor outcome, especially in patients with clinical deterioration.[8] Therefore, in patients with suspected meningitis in whom cranial CT is performed before lumbar puncture, CT should be preceded by blood cultures and the initiation of antibiotic therapy and corticosteroids.[33]

Community-acquired bacterial meningitis has a high rate of an unfavorable outcome in adults (34 percent). Our multivariate model identified several unfavorable prognostic factors, most of which pointed to systemic compromise. A low level of consciousness on admission was predictive of an unfavorable outcome, as was a low cerebrospinal fluid white-cell count. Finally, factors predictive of pneumococcal infection were associated with an unfavorable outcome (advanced age; presence of otitis or sinusitis, pneumonia, or immunocompromised status; and absence of rash).

In our cohort, one of every six patients received corticosteroids. The European Dexamethasone Study showed adjunctive treatment with dexamethasone to be beneficial in adults with bacterial men-

Table 4. Multivariate Analysis of Factors Associated with an Unfavorable Outcome.*

Characteristic	Favorable Outcome (N=459)	Unfavorable Outcome (N=237)	Odds Ratio (95% CI)†	P Value
Age — yr	45±20	60±18	1.19 (1.06–1.35)	0.005‡
Duration of symptoms <24 hr — no./no. evaluated (%)	222/440 (50)	95/221 (43)	0.70 (0.46–1.07)	0.10
Seizures — no./no. evaluated (%)	19/453 (4)	13/213 (6)	0.44 (0.17–1.12)	0.09
Pretreated with antibiotics — no./no. evaluated (%)	41/455 (9)	23/237 (10)	0.61 (0.31–1.21)	0.16
Coexisting conditions — no. (%)				
Otitis or sinusitis	100 (22)	76 (32)	1.80 (1.13–2.84)	0.01
Pneumonia	37 (8)	46 (19)	1.76 (0.96–3.21)	0.07‡
Immunocompromise§	51 (11)	63 (27)	1.63 (0.95–2.79)	0.08‡
Symptoms at presentation				
Headache — no./no. evaluated (%)	396/434 (91)	148/192 (77)	1.34 (0.71–2.54)	0.37‡
Nausea — no./no. evaluated (%)	333/429 (78)	116/181 (64)	1.03 (0.61–1.75)	0.91
Neck stiffness — no./no. evaluated (%)	397/455 (87)	172/230 (75)	1.37 (0.70–2.70)	0.36‡
Rash — no./no. evaluated (%)	146/451 (32)	30/232 (13)	0.46 (0.25–0.86)	0.01‡
Heart rate — no./no. evaluated (%)				
<60 beats/min	6/430 (1)	9/222 (4)	4.05 (0.95–17.24)	0.06‡
60–90 beats/min	166/430 (39)	49/222 (22)	1.00 —¶	—‡
>90–120 beats/min	190/430 (44)	91/222 (41)	1.42 (0.85–2.36)	0.18
>120 beats/min	65/430 (15)	76/222 (34)	2.67 (1.46–4.89)	0.002‡
Diastolic blood pressure <60 mm Hg — no./no. evaluated (%)	39/443 (9)	22/227 (10)	1.99 (0.95–4.20)	0.07
Body temperature ≥38°C — no./no. evaluated (%)	333/448 (74)	189/230 (82)	1.26 (0.67–2.37)	0.48‡
Score on Glasgow Coma Scale‖	10±3	12±3	0.83 (0.76–0.90)	<0.001‡
Triad of fever, neck stiffness, and change in mental status — no. (%)	186 (41)	119 (50)	0.58 (0.30–1.15)	0.12‡
Cerebral abnormality — no. (%)**	79 (17)	78 (33)	1.07 (0.56–2.04)	0.84‡
Cranial-nerve palsy — no. (%)	47 (10)	42 (18)	1.50 (0.81–2.80)	0.20‡

ingitis.[27] Dexamethasone reduced the rate of an unfavorable outcome from 25 percent to 15 percent (relative risk, 0.59; 95 percent confidence interval, 0.37 to 0.94; P=0.03). A post hoc analysis showed that the beneficial effect of dexamethasone on pneumococcal meningitis was attributable to a reduction in systemic rather than neurologic complications.[34] A systemic review showed that adjunctive corticosteroid therapy also reduced the frequency of neurologic sequelae among survivors.[35] The increased likelihood of an unfavorable outcome among those receiving corticosteroids in our cohort was probably due to the fact that corticosteroids were used more frequently in patients with clinical deterioration or those with factors associated with a poorer prognosis.

A low cerebrospinal fluid white-cell count was associated with an adverse outcome. This association has been described before.[22,36] In patients with meningococcal meningitis, a low cerebrospinal fluid white-cell count may be found in those with sepsis and early meningitis. Studies of animals with pneumococcal meningitis showed a relation among a large bacterial cerebrospinal fluid load, lack of response of cerebrospinal fluid leukocytes, and intracranial complications.[37] It probably indicates excessive bacterial growth and lack of a leukocyte response in the cerebrospinal fluid.

In our study, patients with pneumococcal meningitis were at risk for an unfavorable outcome, even after correction for other clinical predictors. Thus, for clinicians, knowledge of the causative organism of meningitis is important in predicting the risk of an unfavorable outcome. Gram's staining of cerebrospinal fluid permits rapid and accurate identification of the causative bacteria in patients with bacterial meningitis and should therefore be routine.[4-7,9]

Table 4. (Continued.)

Characteristic	Favorable Outcome (N=459)	Unfavorable Outcome (N=237)	Odds Ratio (95% CI)†	P Value
Indexes of inflammation in the CSF				
White-cell count — no./no. evaluated (%)††				
<100/mm³	23/428 (5)	39/217 (18)	3.43 (1.64–7.20)	0.001‡
100–999/mm³	56/428 (13)	66/217 (30)	2.82 (1.59–4.78)	<0.001‡
1000–10,000/mm³	238/428 (56)	87/217 (40)	1.00 —¶	—
>10,000/mm³	111/428 (26)	25/217 (12)	0.55 (0.30–1.01)	0.05‡
Protein — g/liter	4.8±4.7	5.4±3.9	1.03 (0.99–1.07)	0.17‡
CSF:blood glucose ratio — mg/dl	0.18±0.2	0.15±0.2	0.91 (0.70–1.17)	0.44‡
Positive blood culture — no./no. evaluated (%)‡‡	238/403 (59)	166/208 (80)	2.24 (1.24–4.03)	0.009‡
Blood chemical tests				
ESR — mm/hr§§	42±37	56±37	1.20 (1.03–1.40)	0.02‡
Thrombocyte count — platelets/mm³¶¶	208,000±100,000	180,000±97,000	0.92 (0.88–0.97)	0.003

* Plus–minus values are means ±SD. CI denotes confidence interval and CSF cerebrospinal fluid.
† Odds ratios are calculated in 10-year increments for age, in increments of 20 mm per hour for the erythrocyte sedimentation rate (ESR), and in increments of 100,000 per cubic millimeter for thrombocyte count.
‡ The P value indicates a significant univariate association with an unfavorable outcome (two-tailed P value <0.05 by the Mann–Whitney U test or Fisher's exact test, as appropriate).
§ Immunocompromise was defined by the use of immunosuppressive drugs, a history of splenectomy, or the presence of diabetes mellitus or alcoholism.
¶ This group served as the reference group.
‖ Scores on the Glasgow Coma Scale can range from 3 to 15, with 15 indicating a normal level of consciousness. Glasgow Coma Scale scores were evaluated in 694 patients; 1 patient with pneumococcal meningitis and 1 with meningococcal meningitis were not evaluated.
** A cerebral abnormality was defined as aphasia, hemiparesis, or monoparesis.
†† The CSF leukocyte count was determined in 659 patients; CSF specimens from 14 patients had too many leukocytes for an exact count to be performed.
‡‡ Blood culture was performed in 611 patients.
§§ The ESR was determined in 549 patients.
¶¶ The thrombocyte count was determined in 653 patients.

Several studies of prognostic factors in bacterial meningitis have been performed; however, all were retrospective and relatively small in size.[4-6,10-22] Our study was nationwide and, therefore, we were able to study a representative sample of adults with acute bacterial meningitis. Furthermore, our prospective approach allowed us to collect comprehensive data on signs and symptoms, clinical course, and outcome. In addition, our large sample gave us the statistical power to perform multivariate analysis.

Our study has one important limitation: only patients who underwent lumbar puncture and who had a positive cerebrospinal fluid culture were included. Negative cerebrospinal fluid cultures occur in 11 to 30 percent of patients with bacterial meningitis.[4-23] No significant differences in clinical presentation have been reported between patients with culture-positive bacterial meningitis and those with culture-negative bacterial meningitis.[4,5,9] Therefore, it is unlikely that this factor confounded our results. Patients with space-occupying lesions on cranial CT do not undergo lumbar puncture,[32,33] and patients with meningitis and a florid rash or septic shock also may not undergo lumbar puncture initially. Thus, an unknown number of such patients were excluded from the cohort, which may have resulted in an underestimation of the mortality rate, especially among patients with meningococcal meningitis.

Rates of antibiotic resistance among meningococcal and pneumococcal isolates were very low. Similar rates have been found in other studies in the Netherlands.[26,38] In the United States, France, Spain, and other countries, antibiotic-resistant *S. pneumoniae* strains are highly prevalent and have emerged as a major problem in the treatment of patients with bacterial meningitis.[39] In response

to this epidemiologic trend, treatment recommendations for suspected and confirmed cases of bacterial meningitis continue to evolve.[40] In areas with high rates of pneumococci that are resistant to broad-spectrum cephalosporins, a combination of a third-generation cephalosporin and vancomycin should be the initial choice for patients with acute bacterial meningitis.[40] Treatment failures in patients with meningitis due to multidrug-resistant bacterial isolates have been described.[9,41,42] The outcome was not significantly influenced by the presence of antibiotic-resistant pneumococcal isolates in several studies[20,23,41,42]; however, the relationship of antibiotic resistance to the outcome of meningitis remains to be elucidated.

Despite the fact that the case fatality rate is decreased by the use of adjunctive dexamethasone, there is still room for improvement. Prompt use of dexamethasone and appropriate antibiotics, together with optimal supportive care, can further reduce the mortality and morbidity associated with bacterial meningitis. Most risk factors for an unfavorable outcome that we identified indicated the presence of systemic compromise, a low level of consciousness, and infection with *S. pneumoniae*. Therefore, aggressive supportive care of patients with bacterial meningitis and systemic complications, preferably in specialized care units, is needed.

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CORRECTION

Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis

Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis . On page 1853, in the right-hand column, lines 5 through 8 of the second full paragraph should have read, ``*N. meningitidis* was responsible for 37 percent of the episodes, with group B identified in 174 episodes, group C in 79, group Y in 3, and group W135 in 1,'' rather than, ``with group B identified in 173 episodes, group C in 79, group Y in 3, group H in 1, and group W135 in 1,'' as printed.