Open access • Journal Article • DOI:10.1056/NEJM199301073280104

Acute Bacterial Meningitis in Adults -- A Review of 493 Episodes

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Published on: 07 Jan 1993 - The New England Journal of Medicine (Massachusetts Medical Society)

Topics: Recurrent bacterial meningitis, Meningitis and Neisseria meningitidis

ACUTE BACTERIAL MENINGITIS IN ADULTS

A Review of 493 Episodes

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Abstract *Background and Methods.* To characterize acute bacterial meningitis in adults, we reviewed the charts of all persons 16 years of age or older in whom acute bacterial meningitis was diagnosed at Massachusetts General Hospital from 1962 through 1988. We included patients who were admitted after initial treatment at other hospitals.

Results. During the 27-year period, 445 adults were treated for 493 episodes of acute bacterial meningitis, of which 197 (40 percent) were nosocomial. Gram-negative bacilli (other than *Haemophilus influenzae*) caused 33 percent of the nosocomial episodes but only 3 percent of the community-acquired episodes. In the 296 episodes of community-acquired meningitis, the most common pathogens were *Streptococcus pneumoniae* (37 percent), *Neisseria meningitidis* (13 percent), and *Listeria monocytogenes* (10 percent); these organisms accounted for only 8 percent of the nosocomial episodes. Only 19 of the 493 episodes of meningitis (4 percent) were due to *H. influenzae*. Nine percent of all patients had recurrent meningitis; many had a cerebrospinal fluid leak. Seizures occurred in 23 percent of patients with community-acquired meningitis, and 28 percent had focal central nervous system findings. Risk factors for death among those with single episodes of community-acquired meningitis included older age (≥60 years), obtunded mental state on admission, and seizures within the first 24 hours. Among those with single episodes, the in-hospital mortality rate was 25 percent for community-acquired and 35 percent for nosocomial meningitis. The overall case fatality rate was 25 percent and did not vary significantly over the 27 years.

Conclusions. In our large urban hospital, a major proportion of cases of acute bacterial meningitis in adults were nosocomial. Recurrent episodes of meningitis were frequent. The overall mortality rate remained high. (N Engl J Med 1993;328:21-8.)

FEW studies of bacterial meningitis have focused on the clinical and pathologic features of the illness in adults.[1-5] Most large series have included both children and adults, with children accounting for 45 to 87 percent of cases.[6-16] Results have rarely been reported according to age group in these studies. To characterize acute bacterial meningitis in adults, we reviewed our experience at Massachusetts General Hospital over a 27-year period, from 1962 through 1988. We focused on several questions of particular current interest: What are the differences between nosocomial and community-acquired meningitis, and has the relative frequency of each type changed? How do patients with recurrent meningitis differ from other patients with meningitis? What are the bacteriologic causes of meningitis in adults, and have these causes changed? What is the frequency of seizures or focal neurologic findings, and what are their neuroanatomical correlates? What has been the role of computed tomography (CT) in the evaluation of community-acquired meningitis? What are the risk factors for death in adults with meningitis? Has the mortality rate changed?

METHODS

We reviewed the charts of all patients 16 years of age or older in whom acute bacterial meningitis was diagnosed at Massachusetts General Hospital from January 1962 through December 1988. Patients who were initially treated at other hospitals but were transferred to this hospital for further therapy were also included. Only those with acute illness (less than seven days of symptoms) and a definite or probable bacterial cause were included. A nosocomial infection was defined according to the 1988 guidelines of the Centers for Disease Control.[17] Although these guidelines do not specify a length of hospitalization before the onset of meningitis, in our study meningitis developed in 97 percent of the patients with nosocomial episodes after more than 48 hours of hospitalization or within one week of discharge.

The diagnosis of meningitis caused by a specific bacterial pathogen, made in 421 episodes, was based on a compatible clinical picture and one of the following: a positive cerebrospinal fluid culture (n = 367); confirmation at autopsy (n = 14); or a negative cerebrospinal fluid culture with a finding of neutrophilic pleocytosis and one of the following: a positive cerebrospinal fluid antigen test (n = 1) or quellung test (n = 2), a positive blood culture (n = 28), identification of gram-negative diplococci on Gram's staining of cerebrospinal fluid (n = 7), or sputum or throat cultures positive for *Neisseria meningitidis* in patients with a petechial or purpuric rash and a fulminant course (n = 2). In addition, 72 episodes of "culture-negative" bacterial meningitis were included in our analysis. These episodes were diagnosed on the basis of a compatible clinical picture and pleocytosis of at least 100 neutrophils per cubic millimeter (0.1×10^9 per liter) despite negative blood and cerebrospinal fluid cultures and results of cerebrospinal fluid Gram's staining that were negative (n = 52), positive for organisms other than gram-negative diplococci (n = 10), or not available (n = 10). Most patients (97 percent) with culture-negative meningitis had more than 300 leukocytes per cubic millimeter of cerebrospinal fluid (0.3×10^9 per liter), and 96 percent had more than 50 percent neutrophils. Diphtheroids, coagulase-negative staphylococci, or propionibacteria isolated from cerebrospinal fluid were considered etiologic agents only if found repeatedly or if cultured from the tip of an indwelling neurosurgical device. Almost one third of culture-negative episodes (22 of 72) occurred in patients with recurrent meningitis.

A second episode of meningitis was considered a recurrence if it was due to a different organism from the first, or if it was due to the same organism but occurred more than three weeks after the completion of therapy for the initial episode. A relapse of meningitis due to the same organism within three weeks of the completion of therapy for the initial episode (as occurred in six patients) was not counted separately. A total of 404 patients had single episodes of meningitis. Forty-one patients (9 percent) had more than 1 episode; all 89 episodes in these patients (including the 30 initial episodes) treated

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at Massachusetts General Hospital between 1962 and 1988 are included in the category "recurrent meningitis." Of these 41 patients, 12 were known to have had additional episodes, not included in this review, that were treated before 1962 or treated entirely at other hospitals.

Antibiotic therapy was considered inadequate if, of the antibiotics available in that era, those chosen were given at an insufficient dose, had poor central nervous system penetration, or were directed against a resistant organism. Mortality was classified as meningitis-related if death was due to meningitis or its complications, but not if it was due to a preexisting serious illness after bacteriologic cure and clinical recovery from meningitis.

The chi-square and Fisher's exact tests were used for statistical analysis.

Results

Classification of Cases

Community-Acquired Meningitis

There were 296 episodes of community-acquired meningitis in 275 patients; 253 patients had single episodes of meningitis, 17 patients had more than 1 episode of community-acquired meningitis (38 episodes), and each of 5 patients had an episode of community-acquired meningitis and an episode of nosocomial meningitis. Of the 17 patients with recurrent community-acquired meningitis, 10 had three or more episodes (not all of which were treated at Massachusetts General Hospital); 1 patient had seven episodes over a period of 11 years. The length of time between recurrences was usually months or years.

In 56 percent of the episodes of community-acquired meningitis, the patients were 50 years of age or older (range, 16 to 88).

Nosocomial Meningitis

There were 197 episodes of nosocomial meningitis in 175 patients; 5 of these patients also had an episode of community-acquired meningitis. A total of 151 patients had single episodes, and 19 had recurrent meningitis (41 episodes); initial and recurrent episodes usually occurred during the same hospitalization. Only three patients had more than one recurrence.

The relative frequency of nosocomial meningitis increased after the 1960s, from 28 percent in 1962 through 1970 to 45 percent from 1971 through 1979 and 48 percent from 1980 through 1988 ($P<0.01$).

Predisposing Factors

The frequency of 13 predisposing factors for single episodes of meningitis is shown in Table 1. Of the 17 patients with recurrent community-acquired meningitis, 8 had a remote history of head trauma or neurosurgery (occurring more than one month before the onset of meningitis), 13 had a cerebrospinal fluid leak, and 7 had one or more episodes of meningitis even after repair of the leak. In recurrent nosocomial meningitis, a neurosurgical procedure preceded either the initial episode or a recurrent episode in all 19 patients, and 9 patients had cerebrospinal fluid leaks. The frequency of cerebrospinal fluid leaks was significantly higher among patients with recurrent meningitis, either community-acquired or nosocomial, than among patients with single episodes of meningitis ($P<0.001$).

Table 1. Predisposing Factors in 404 Single Episodes of Bacterial Meningitis.

Factor	Community-Acquired (N = 253)	Nosocomial (N = 151)
	percent	
Acute otitis media	19	1
Chronic otitis media	7	0
Sinusitis	12	4
Pneumonia	15	8
Endocarditis	7	1
Head injury*		
Recent	5	13
Remote	4	0
Recent neurosurgery*	0	68
Neurosurgical device†	1	32
Altered immune state	19	31
Diabetes mellitus	10	6
Alcoholism	18	5
Cerebrospinal fluid leak	8	13
None of the 13 factors	25	8

*Recent denotes head injury or neurosurgery within one month of the onset of meningitis; remote, more than one month before the onset of meningitis.

†Neurosurgical devices included ventriculostomy, ventriculoperitoneal or ventriculoatrial shunt, lumbar epidural catheter, lumboperitoneal catheter, and dorsal-column stimulator.

Bacteriologic Findings

Streptococcus pneumoniae was the most common pathogen overall (causing 24 percent of the 493 episodes); gram-negative bacilli other than *Haemophilus influenzae* caused 17 percent of the episodes, whereas *N. meningitidis*, streptococci, *Staphylococcus aureus*, and *Listeria monocytogenes* caused 7 to 8 percent each. *H. influenzae* caused only 4 percent of the episodes. In 15 percent of the cases, no pathogen was identified. A higher percentage of patients with culture-negative episodes had received antibiotics before the initial lumbar puncture than was the case for patients with culture-positive episodes (50 percent vs. 36 percent, $P<0.05$).

Significant changes in the frequency of cases caused by several bacterial species (Fig. 1) included peaks in the relative frequency of meningitis caused by *N. meningitidis* in the 1960s and that caused by *L. monocytogenes* in the 1970s ($P<0.05$ for the comparison of these peaks with the other periods shown in Figure 1). These peaks may have been due to unrecognized outbreaks in the Boston area. Our cluster of listeria meningitis cases occurred four years earlier than the previously reported outbreak in Boston.[18] The increase in the relative frequency of gram-negative bacilli as a cause of meningitis (from 11 percent of cases in the 1960s to 24 percent in the 1980s, $P<0.01$) and the concomitant decline in pneumococcal meningitis (from 36 percent to 21 percent, $P<0.01$) may be related to the increase in the relative frequency of nosocomial meningitis. Gram-negative bacillary meningitis

made up 39 percent of all nosocomial episodes in our study, and this frequency did not vary significantly over time.

Strep. pneumoniae, *N. meningitidis*, and *L. monocytogenes* caused 64 percent of all single episodes of community-acquired bacterial meningitis but less than 10 percent of single episodes of nosocomial meningitis (Table 2). Patients with recurrent community-acquired meningitis also had a high frequency of pneumococcal infection (Table 3). Gram-negative bacilli were the predominant organisms in single-episode and recurrent nosocomial meningitis (Tables 2 and 3) but caused only 3 percent of all community-acquired cases (in nine patients). Eight of these nine patients had underlying illnesses (e.g., acquired immunodeficiency syndrome, cirrhosis, leukemia, and diabetes); five also had urinary tract infections. *Escherichia coli* and klebsiella caused almost half of all episodes of nosocomial gram-negative bacillary meningitis and seven of the nine cases of community-acquired disease.

H. influenzae caused meningitis in 19 patients, ranging from 21 to 79 years of age. In 6 patients *H. influenzae* meningitis developed after neurosurgery, and 13 had community-acquired episodes. A cerebrospinal fluid leak was identified in nine patients with *H. influenzae* meningitis.

Clinical Features

The clinical features of 279 episodes of community-acquired meningitis in 259 patients were reviewed (17 episodes treated at other hospitals for more than 24 hours before transfer were excluded from this analysis).

Clinical Findings

On presentation, only two thirds of the patients had the classic triad of fever, nuchal rigidity, and change in mental status, but all had at least one of these findings.

Ninety-five percent of patients had fever (temperature, ≥37.7°C [100°F]) at presentation; another 4 percent became febrile during the next 24 hours. Fever was the only presenting sign in six patients, but three of these had severe headache. Of the 227 patients who survived through defervescence for whom data on the duration of fever were available, 19 percent had prolonged fever (10 or more consecutive days), but most had other possible causes of continued fever. Patients with no identifiable cause of fever other than meningitis had an average of 4 consecutive days of fever (range, 0 to 14).

Neck stiffness was present in 88 percent of patients on initial physical examination. This incidence was not significantly lower among elderly patients (≥70 years of age), in contrast with other reports.[6] Neck stiffness persisted for more than seven days in some patients, despite overall improvement.

A rash was noted on admission in 30 patients (11 percent), of whom 22 had meningococcal meningitis. Although a petechial rash was characteristic of this infection (occurring in 16 patients), it was also seen in pneumococcal meningitis (2), staphylococcal meningitis (2), and culture-negative meningitis (1). Purpura was observed in meningococcal meningitis (six patients) and culture-negative cases (one). A maculopapular rash was seen in three patients with meningococcal meningitis and two patients with pneumococcal meningitis.

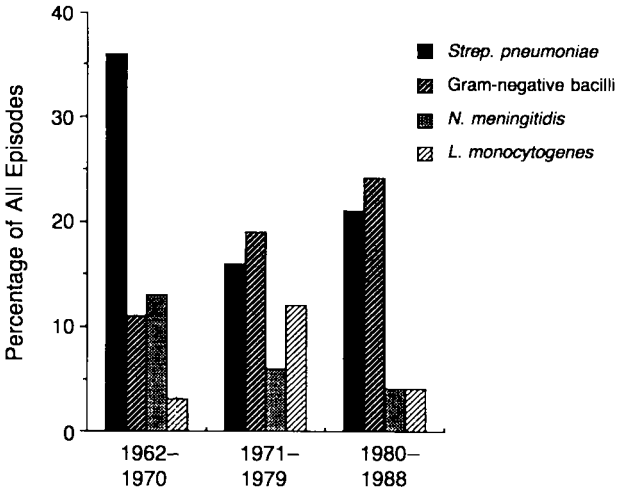

Figure 1. Relative Frequency of Major Bacterial Pathogens in Cases of Meningitis in Adults.

The bars represent the percentage of episodes caused by each pathogen in each period. There were 172 episodes in 1962 through 1970, 186 episodes in 1971 through 1979, and 135 episodes in 1980 through 1988.

Neurologic Findings

Most patients had an abnormal mental status on presentation: 51 percent were confused or lethargic, 22 percent were responsive only to pain, and 6 percent were unresponsive to all stimuli. However, 22 percent were normally alert. On presentation or during the first 24 hours, 29 percent of patients had focal seizures or focal neurologic findings (other than an isolated Babinski reflex or hearing loss) that were not present before the onset of meningitis.

Findings on Funduscopic Examination at Admission

Although the results of a funduscopic examination were not recorded for many patients, "blurred optic-disk margins," "early papilledema," or "papilledema" was recorded for 12 patients (4 percent of 279 episodes) and confirmed by a neurologist or ophthalmologist in 10. Only 3 of these 10 had very high cerebrospinal fluid opening pressures (≥440 mm of water); opening pressures for 5 were near 300 mm of water and were not recorded for 2 others. One patient had cavernous-sinus thrombosis. All 10 patients survived.

Seizures

Seizures occurred in 23 percent of the episodes of meningitis; they were focal in 7 percent, generalized in 13 percent, and not further characterized in 3 percent.

Table 2. Causative Organisms in Single Episodes of Meningitis, 1962 through 1988.*

Organism	Community-Acquired (N = 253)	Nosocomial (N = 151)
	no. (%)	
Strep. pneumoniae	97 (38)	8 (5)
Gram-negative bacilli†	9 (4)	57 (38)
N. meningitidis	35 (14)	1 (1)
Streptococci‡	17 (7)	13 (9)
Enterococcus	0	4 (3)
Staph. aureus	13 (5)	13 (9)
L. monocytogenes	29 (11)	5 (3)
H. influenzae	9 (4)	6 (4)
Mixed bacterial species	6 (2)	10 (7)
Coagulase-negative staphylococci	0	13 (9)
Other§	4 (2)	5 (3)
Culture negative	34 (13)	16 (11)

*Percentages do not always total 100 because of rounding.

†In community-acquired meningitis, the causative organisms were *Escherichia coli* (4 episodes), klebsiella (3), enterobacter (1), and proteus (1); in nosocomial meningitis, *E. coli* (17), klebsiella (13), pseudomonas (6), acinetobacter (6), enterobacter (5), serratia (5), citrobacter (2), proteus (1), "coliform" bacteria (1), and "nonenteric gram-negative rods" (1).

‡In community-acquired meningitis, the causative organisms were group A (4 episodes), group B (1), nonenterococcal group D (3), group D, not further identified (1), other groups (5), and nonhemolytic, nongrouped (3); in nosocomial meningitis, the causative organisms were group B (4), nonenterococcal group D (3), other groups (2), alpha-hemolytic, nongrouped (3), and nonhemolytic, nongrouped (1).

§In community-acquired meningitis, the causative organisms were anaerobes (3 episodes) and diphtheroids (1); in nosocomial meningitis, the causative organisms were micrococci (2), neisseria species (1), propionibacteria (1), and diphtheroids (1).

In two thirds of the cases seizures occurred within 24 hours of admission; more than one third of patients with such early-onset seizures had a history of alcoholism. *Strep. pneumoniae* was the causal agent in a higher percentage of patients who had seizures than of patients who did not (58 percent vs. 30 percent, $P<0.001$), but alcoholism was a confounding factor.

Cranial-Nerve Palsies

Although cranial-nerve palsies accompanied focal central nervous system findings in several patients, they were the only focal neurologic findings in 12 patients (4 percent). Nine patients had such findings on admission; they developed in three more than 24 hours later. Two patients with cavernous-sinus thrombosis had involvement of cranial nerves III, IV, and VI. Three patients had transient unilateral or bilateral sixth-nerve palsies alone, a finding associated with increased intracranial pressure that has been observed in meningitis in children.[19] In other patients, including three with peripheral facial-nerve palsies, a neuropathologic basis for the palsies could not be determined from the information available.

Focal Central Nervous System Dysfunction

Seventy-seven patients (28 percent) had focal central nervous system findings other than focal seizures alone (Table 4). In most, these findings were apparent on admission. Of the 29 patients with gaze preference, the most common early finding, 17 had concurrent evidence of a hemispheric defect (hemiparesis, aphasia, or visual-field defect). Hemiparesis occurred sometime during hospitalization in 37 patients (13 percent), but it persisted until discharge in only 7 of the 25 survivors. Seizures heralded the onset of hemiparesis in three patients. In 13 patients with hemiparesis, intracranial abnormalities (cortical-vein or sagittal-sinus thrombosis, cerebral-artery spasm, subdural empyema, hydrocephalus, cerebral infarct, abscess, or edema) were eventually demonstrated by radiologic studies or at autopsy. The two patients with brain abscess (of the temporal lobe) had chronic otitis media, which suggests that the abscess predated the meningitis.

Cerebrospinal Fluid Findings

Community-Acquired Meningitis

In almost one fifth of the 296 episodes, patients with community-acquired meningitis had opening pressures of 400 mm of water or more (Table 5); 55 percent of these patients were alert or lethargic on presentation. Only half of all patients had hypoglycorrhachia, although 96 percent had elevated protein levels (>45 mg per deciliter). Ten percent of positive

Table 3. Causative Organisms in Recurrent Meningitis, 1962 through 1988.*

Organism	Community-Acquired (N = 38)	Nosocomial (N = 41)
	no. (%)	
Strep. pneumoniae	13 (34)	1 (2)
Gram-negative bacilli†	0	19 (46)
N. meningitidis	3 (8)	0
Streptococci‡	4 (11)	1 (2)
Staph. aureus	1 (3)	6 (15)
H. influenzae	4 (11)	0
Mixed bacterial species	0	2 (5)
Coagulase-negative staphylococci	0	3 (7)
Other§	2 (5)	1 (2)
Culture negative	11 (29)	8 (20)

*Both initial and recurrent episodes in the 17 patients who had more than one episode of community-acquired meningitis and the 19 patients who had more than one episode of nosocomial meningitis are included. Not included are five patients, each of whom had one episode of community-acquired meningitis and one episode of nosocomial meningitis. The community-acquired episodes in these patients were caused by group A streptococcus (1), *N. meningitidis* (1), and *Staph. aureus* (1); 2 episodes were culture-negative. The nosocomial episodes were caused by *Staph. aureus* (2), *klebsiella* (1), and *Strep. pneumoniae* (1); 1 episode was culture-negative. Percentages do not total 100 because of rounding.

†The causative organisms were as follows: pseudomonas (5 episodes), klebsiella (4), enterobacter (3), acinetobacter (2), serratia (1), *E. coli* (1), proteus (1), citrobacter (1), and "gram-negative rods" (1).

‡In community-acquired meningitis: alpha-hemolytic, nongrouped (3 episodes), and group D, not further identified (1); in nosocomial meningitis: nonhemolytic (1).

§In community-acquired meningitis: anaerobes (1 episode) and *Campylobacter fetus* (1); in nosocomial meningitis: *Propionibacterium acnes* (1).

cerebrospinal fluid smears were misinterpreted. The most frequent error (occurring in 7 of 17 cases) was misidentification of listeria as *Strep. pneumoniae*.

CT Scanning

A cranial CT scan was performed in 87 of the 122 adults treated for community-acquired bacterial meningitis after 1975. Of these 87 patients, 13 percent had findings on CT scanning that were consistent with a disruption of the dural barrier (eroding retrobulbar mass, pneumocephalus, or mastoid or sinus-wall defect), and 31 percent had abnormalities related to meningitis or its complications: ventriculomegaly or hydrocephalus (13 patients), cerebral edema (5), meningeal enhancement (4), cerebral infarct (4), subdural effusion (2), abscess (2), lesions consistent with septic emboli (2), cavernous-sinus thrombosis (1), and subdural empyema (1). Only two patients with hydrocephalus required a shunting procedure. Infarcts that were not apparent on the admission CT scan were seen on later CT scans (>72 hours after admission) in four patients. All had persistent focal deficits (hemiparesis in three and triplegia in one). Nineteen of the 39 patients with focal neurologic findings or focal seizures had evidence on CT scanning of an intracranial abnormality related to meningitis, whereas only 8 of the 48 patients with nonfocal findings had such evidence ($P<0.01$).

Treatment

Once the results of cultures were known, appropriate antibiotic agents were used in nearly all 223 episodes of community-acquired meningitis with an identifiable cause that were treated initially at Massachusetts General Hospital (and in which the patients survived for at least 24 hours). However, in 17 episodes patients received inadequate parenteral antibiotic therapy during the first 24 hours. The mortality rate among these patients was higher than that among the other patients (41 percent vs. 19 percent), but the difference was not significant ($P>0.05$).

Adrenocorticosteroids were given within 24 hours of presentation in 8 percent of the 279 episodes of community-acquired meningitis that were treated initially at Massachusetts General Hospital, and this percentage did not vary significantly between the three nine-year study periods.

Cerebral Herniation

Autopsy records, available for 27 of the 40 patients with community-acquired meningitis who died within seven days of presentation, contained evidence of herniation in 8 cases. All had temporal-lobe herniation; four also had cerebellar herniation. All had cerebral edema; two also had dural-sinus or cortical-vein thrombosis, and one had an infarct from a septic embolus. In five, clinical signs of herniation developed within a period ranging from several minutes to several hours after a lumbar puncture (including two patients given intrathecal penicillin in 1962); opening pressures were recorded for four patients and were greater than 500 mm of water.

Table 4. Focal Central Nervous System Findings in 279 Episodes of Community-Acquired Meningitis.*

Time of Onset of Focal Findings	No. of Patients	Findings†				
		Hemiparesis	Aphasia	Visual-field defect	Gaze preference	Other‡
Early (≤24 hr)	67	25	18	8	29	15
Late (>24 hr)	10	6	3	1	0	3
Total	77	31§	21	9	29	18

*The 17 episodes treated at other hospitals for more than 24 hours before transfer have been excluded.

†Aphasia or visual-field defects were noted only when a patient was normally alert or lethargic but responsive to voice. Eleven of the 25 patients with early onset of hemiparesis were normally alert or only lethargic; 5 of these 11 had aphasia or a homonymous hemianopia in association with hemiparesis.

‡Eighteen patients had only the following findings: nystagmus (in 6 patients), central seventh-nerve palsy (4), monoparesis (4), ataxia (1), dysmetria (1), hemianesthesia and cranial-nerve findings (1), and diplopia (1).

§This does not represent the total number with hemiparesis. In 6 of the 42 patients with early focal findings other than hemiparesis, hemiparesis developed later. Therefore, the total number in whom hemiparesis developed at some point during hospitalization was 37.

Mortality

We found no significant difference in mortality rates between periods for any given bacterial pathogen (Table 6), although meningitis-related mortality in episodes of gram-negative bacillary meningitis decreased from 21 percent in 1962 through 1970 and 34 percent in 1971 through 1979 to 13 percent in 1980 through 1988. Overall mortality rates (computed per patient, rather than per episode) were 25 percent for single episodes of community-acquired meningitis, 6 percent for recurrent community-acquired meningitis, 35 percent for single episodes of nosocomial meningitis, and 16 percent for recurrent nosocomial meningitis. None of the 17 patients with recurrent community-acquired meningitis died of meningitis, even though several had four or more episodes.

According to the univariate analysis, three factors were associated with a significantly higher overall mortality rate among patients with single episodes of community-acquired meningitis: an age of 60 years or more (mortality rate, 37 percent vs. 17 percent for patients <60 years of age; $P<0.001$); obtunded mental state on admission (49 percent among patients who were unresponsive or responsive only to pain vs. 16 percent among those normally alert or lethargic, $P<0.001$); and onset of seizures within 24 hours of admission (72 percent vs. 18 percent among those without early-onset seizures, $P<0.001$). The relative risk of death among patients with single episodes of community-acquired meningitis was 2.1 (95 percent confidence interval, 1.4 to 3.3) for patients 60 years of age or older, 3.0 (2.0 to 4.5) for those with obtunded mental status on admission, and 4.0 (2.8 to 5.8) for those in whom seizures began within 24 hours of admission. Ninety-eight percent of the 63 patients who died had at least one of these three risk factors. Risk factors that did not reach statistical significance in this

Table 5. Initial Cerebrospinal Fluid Values in 493 Episodes of Bacterial Meningitis.*

VARIABLE	COMMUNITY-ACQUIRED (N = 296)	NOSOCOMIAL (N = 197)
	percent	
Opening pressure (mm of water)		
0–139	9	23
140–299	52	52
300–399	20	11
≥400	19	15
White-cell count per mm³†		
0–99	10 (13)	17 (19)
100–4999	61 (59)	65 (62)
5000–9999	15 (15)	11 (12)
≥10,000	13 (13)	7 (8)
Percent neutrophils		
0–19	2	2
20–79	19	31
≥80	79	66
Total protein (mg/dl)		
0–45	4	6
46–199	40	42
≥200	56	52
Glucose <40 mg/dl	50	45
Gram-positive	60	46
Culture positive	73	83

*The values shown are percentages of all the episodes in which the results of a given study were reported on initial examination of cerebrospinal fluid. Of the 296 community-acquired episodes, opening pressure was reported in 205, the white-cell count in 286, percent neutrophils in 271, protein level in 263, glucose level in 269, results of Gram's staining in 272, and culture results in 289. Of the 197 nosocomial episodes, opening pressure was reported in 102, white-cell count in 167, percent neutrophils in 163, protein level in 159, glucose level in 164, results of Gram's staining in 126, and culture results in 180. Percentages do not always total 100 because of rounding.

†Because the data for pleocytosis may be biased by our criteria for culture-negative episodes, the percentages of culture-positive episodes alone are given in parentheses.

analysis included an absence of nuchal rigidity, focal central nervous system findings, late-onset seizures (>24 hours after admission), and highly abnormal cerebrospinal fluid values (opening pressure, ≥450 mm of water; glucose level, <40 mg per deciliter; or protein level, ≥300 mg per deciliter).

DISCUSSION

The most striking finding in this study of acute bacterial meningitis in adults was the high frequency of recurrent and nosocomial meningitis (which occurred in 9 percent and 39 percent of patients, respectively). It is difficult to compare these numbers with the results of other studies. The frequency of recurrent meningitis is unknown.[20] Two studies reported a lower frequency,[6,21] but these studies included a substantial proportion of cases in children and reviewed an earlier period. The frequency of nosocomial meningitis among adults is also unknown, although it has been reported as 28 percent among those 50 years of age or older.[22] We would expect the frequency of nosocomial and recurrent meningitis to be lower at community hospitals than at tertiary care centers such as ours.

In studies that include all age groups, typically with a majority of the cases occurring among children, *H. influenzae*, *N. meningitidis*, and *Strep. pneumoniae* cause 70 to 87 percent of all cases.[6-11,23,24] In our study, in contrast, these pathogens caused fewer than 40 percent of cases. At our hospital, pneumococcal meningitis decreased and gram-negative bacillary meningitis nearly doubled in frequency over the 27 years we reviewed, reflecting the increase in the incidence of nosocomial episodes. The number of inpatient neurosurgical procedures at our hospital also increased by 25 percent after the 1960s, a fact that may partly explain these changes. The importance of gram-negative bacillary meningitis in adults has been noted in other studies,[3,25] although the 17 percent frequency that we found was comparatively high. Analysis of data from a population-based study of bacterial meningitis[24] showed that gram-negative bacillary meningitis accounted for 11 percent of 426 culture-positive cases in patients 16 years of age or older (Wenger JD: unpublished data).

When Gram's staining of the cerebrospinal fluid is negative, the choice of empirical therapy must be guided by knowledge of the frequency of pathogens within each category of meningitis (community-acquired, nosocomial, single-episode, and recurrent). In community-acquired meningitis, *Strep. pneumoniae*, *N. meningitidis*, listeria, and streptococci are the most likely pathogens. Gram-negative bacilli should also be considered in patients with underlying illnesses (particularly those with concurrent urinary tract infections); *H. influenzae* becomes more likely if there is otorhinorrhea. In recurrent community-acquired meningitis, *Strep. pneumoniae* predominates,[13,26] but

Table 6. In-Hospital Mortality Rates According to Pathogen.

ORGANISM	NO. OF EPISODES	CASE FATALITY RATE	
		MENINGITIS-RELATED	TOTAL
		percent	
Strep. pneumoniae	120	25	28
Gram-negative bacilli	86	23	36
N. meningitidis	40	10	10
Streptococci	36	17	25
Enterococcus	4	25	50
Staph. aureus	36	28	39
L. monocytogenes	34	21	32
H. influenzae	19	11	11
Mixed bacterial species	18	39	44
Coagulase-negative staphylococci	16	0	0
Other*	12	0	8
Culture negative	72	7	10
All causes	493	19	25
1962–1970	172	21	24
1971–1979	186	18	26
1980–1988	135	17	24

*Other organisms were as follows: anaerobes (4 episodes), propionibacteria (2), diphtheroids (2), micrococci (2), neisseria species (1), and *Campylobacter fetus* (1).

other streptococci and *H. influenzae* are important causal agents as well. If little information is available, previously healthy patients with acute pyogenic community-acquired meningitis may be treated empirically with ampicillin (or chloramphenicol if the patient is highly allergic to penicillin). It is appropriate to add a third-generation cephalosporin initially in patients who may have an underlying illness or a cerebrospinal fluid leak or who live in geographic areas where penicillin-resistant *Strep. pneumoniae* has been isolated. Other proposed empirical regimens are also reasonable.[27-29] Modifications of these regimens may be required depending on the specific clinical situation.

Most clinical features of community-acquired meningitis in adults are similar to those in children. Twenty-seven percent of adults have initial cranial-nerve palsies or focal central nervous system findings (beginning <24 hours after admission), and 23 percent have seizures during hospitalization. In one study, 16.5 percent of 235 children presented with focal neurologic signs and about 30 percent had seizures during the course of the meningitis.[30] As in several studies of childhood meningitis,[31-33] ventriculomegaly was the most common abnormality identified on CT scanning in our study (in 15 percent), but it rarely required a shunting procedure. Subdural effusions, common among infants with meningitis,[31,32,34,35] occurred in only 2 percent in this study. Cerebral infarcts were a late finding in 5 percent and were associated with hemiparesis, as in pediatric studies.[34,36]

The role of CT scanning in meningitis continues to be debated. A CT scan is indicated before the performance of a lumbar puncture in patients with suspected meningitis and signs of increased intracranial pressure or focal findings on neurologic examination. Patients with meningitis rarely have major abnormalities on CT scanning in the absence of focal neurologic findings.[34] In our study, nearly half the patients with community-acquired meningitis and focal findings who underwent CT scanning had evidence of an intracranial abnormality related to meningitis. It is important to emphasize that antimicrobial therapy should be initiated before any patient with suspected meningitis is sent for a CT scan; to do otherwise risks an average delay of more than an hour in starting therapy,[37] a delay that could be of consequence in such patients.

Though it has been described in children[38-40] and in general studies[7,8,41] of bacterial meningitis, few reports describe cerebral herniation as a complication in adults.[42] In our study, all eight adults with evidence of herniation at autopsy had cerebral edema. There are many causes of cerebral edema and increased intracranial pressure in meningitis,[27] and the role of lumbar puncture in causing herniation is still controversial.[43-47] Herniation has occurred in some patients who have not received a lumbar puncture.[41]

In many studies, as in ours, older age and an obtunded mental state correlate with a poor outcome in patients with meningitis. Other risk factors for death observed in some studies — notably, the absence of nuchal rigidity,[48] elevated cerebrospinal fluid protein levels,[48] and hypoglycorrhachia[6] — were not significant in ours.

Over the past three decades, progress has been made in identifying the bacterial causes of meningitis (by, for instance, the development of antigen detection), identifying complications (such as cerebral edema, infarction, and hydrocephalus) by CT scanning, and localizing cerebrospinal fluid fistulas. Despite the introduction of newer antimicrobial agents, the mortality rate among adults with acute bacterial meningitis has not decreased; the exception may be the rate of mortality among adults with gram-negative bacillary meningitis since the advent of third-generation cephalosporins. Even in the 1980s, almost one quarter of adults with meningitis in our study died. Further progress in improving the outcome of meningitis may stem as much from newer developments in the management of the pathophysiologic consequences of meningeal infection[49] as from the introduction of new generations of antimicrobial agents.

We are indebted to Gregory P. Samsa, Ph.D., for assistance in computer programming and statistical analysis.

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