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Clinical Evaluation of Pneumococcal Meningitis in Adults over a Twelve-Year Period

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A retrospective study was performed to review the clinical features and outcome of 39 episodes of pneumococcal meningitis in 36 adult patients over a 12-year period. Overall mortality was 33.3%. Only a few of the deaths were directly related to the central nervous system disease and most of them were due to cardiorespiratory failure. Univariate analysis showed that death was more likely to occur in patients with advanced age, an absence of neck stiffness, a high pulse rate, an associated pneumonia, internal complications, or a long duration of the disease (> 7 days) before treatment was started. Patients who died had a higher erythrocyte sedimentation rate and serum bilirubin level and a lower serum sodium level than those who survived. Discriminant analysis showed the development of internal complications to be the strongest predictive factor of a poor outcome of illness. Two other important predictors of a poor outcome were the absence of neck stiffness and associated pneumonia. The history of a skull fracture or head surgery was significantly correlated with a better than average prognosis. The incidence of sequelae in survivors at the time of discharge amounted to 72%. None of the clinical features were significantly correlated with the development of sequelae, except a higher cerebrospinal fluid protein content.

Pneumococcal meningitis is the most common bacterial infection of the central nervous system (CNS) in adults. For all age groups, *Streptococcus pneumoniae* ranks third among pathogens causing meningitis in the Netherlands (1), after *Neisseria meningitidis* and *Haemophilus influenzae*. Associated mortality reported in other countries is notably high, ranging from 20% to over 50% (2–14). Furthermore, among those who survive, there is a high rate of sequelae, perceptive hearing impairment being the foremost deficit. These figures seem surprising in an era in which highly effective antimicrobial treatment for *Streptococcus pneumoniae* is available. However, previous investigators did not examine the extent to which mortality was directly related to the infection of the central nervous system, or determine whether improvement of supportive care has changed the outcome. Recent observations suggest that in a small and highly developed country such as the Netherlands, the high case-fatality rate of both pneumococcal meningitis and bacteremia has decreased as compared with other countries (15–16).

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We undertook a retrospective analysis of the clinical features of adult patients who were hospitalized for pneumococcal meningitis between 1975 and 1987 in the Leiden University Hospital. The aim of this study was to examine the outcome of pneumococcal meningitis in terms of both mortality and sequelae, and to determine whether traditional risk factors associated with a poor outcome have changed since the advent of modern antibiotic treatment and supportive care.

Materials and Methods

Inclusion Criteria. The records of adult patients with pneumococcal meningitis hospitalized in the Leiden University Hospital between 1 January 1975 and 1 January 1987 were reviewed. Inclusion criteria were age over 15 years and proof of pneumococcal meningitis as attested by either a positive culture of cerebrospinal fluid (CSF) for *Streptococcus pneumoniae* or the finding of *Streptococcus pneumoniae* antigen in the CSF, or a positive blood culture for *Streptococcus pneumoniae* during a clinical episode of meningitis for which no other cause was identified. Isolates of *Streptococcus pneumoniae* were identified by standard laboratory techniques (17) by the Department of Medical Microbiology. Pneumococcal antigen detection was performed according to a commercial latex agglutination method (Wellcome Laboratories, UK).

Patient Data. Patient data pertaining to the history and physical and neurologic examinations as well as relevant lab-

oratory results were abstracted from the charts. The underlying disease in each case was classified according to McCabe and Jackson (18) as rapidly fatal, ultimately fatal and non-fatal. The number of days of illness before treatment was started were counted from the day on which the first symptoms, presumably related to meningitis, developed. Consciousness levels on admission were graded as follows: alert or slightly depressed (i.e. responding to simple commands but unable to talk rationally), somnolent (i.e. arousable by speech), soporose (i.e. arousable by painful stimuli) and comatose. Focal neurologic deficits included cranial nerve palsies, pyramidal signs, aphasia and oculomotor disturbances. Pneumonia was confirmed by chest X-ray and sinusitis by X-rays of the sinuses. Hearing impairment was established by conventional audiometric methods. Laboratory data obtained on the day of hospitalization and on which the diagnosis of meningitis was based were used for statistical analysis. In some charts laboratory data were missing or not determined, e.g. the number of platelets, but this occurred in only a minority of patients and never exceeded seven episodes of meningitis for a given characteristic.

Patient Groups. For statistical analysis, patients were categorized into two groups: those who died during hospitalization and those who did not. In the latter, neurologic sequelae at the time of discharge were assessed and included in the statistical analysis. The cause of death had been determined either by autopsy or on the basis of the clinical data from the medical records. Data on late sequelae, i.e. neurological deficits present after months or years, were not included.

Statistical Analysis. The results were analyzed with respect to statistical significance ($p \leq 0.05$) using a chi-square test for comparison of dichotomous variables and a Wilcoxon's rank-sum test for comparison of continuous variables. For identification of the risk factors most predictive of a poor outcome of pneumococcal meningitis, selected variables were studied in cross-tabulations against death or survival and with stepwise discriminant analysis, using the SPSS-X programme (19). This selection was carried out on the basis of either statistical significance or medical significance.

Results

Patient Characteristics. In the period studied, 39 episodes of pneumococcal meningitis occurred in 36 adult patients. In one episode, only data of age, sex and the outcome of illness were available for the calculation of incidence and mortality; this episode was excluded from further analysis, leaving 38 episodes for evaluation. Of the 36 patients, 20 were male and 16 female. The median age was 57 years (range 15–89 years). Three patients had two episodes of pneumococcal meningitis. Thirty-five episodes of meningitis developed at home; 25 of these patients were admitted directly to the Leiden University Hospital and the other ten initially to nearby community hospitals and were later transferred to our hospital. In three cases the disease occurred during hospitalization in the Leiden University Hospital for another disease. For an estimated adherence population of about 180,000 adult patients per year, the annual incidence amounts to about 2.1 episodes of pneumococcal meningitis per 100,000 adults. In terms of admissions (average: 17,335 adults per year), the figures are indicative of 0.2 episodes/1,000 admissions.

Clinical Features. For the 38 episodes the clinical signs found on presentation are shown in Table 1. The most important laboratory data and CSF investigations are summarized in Table 2. Gram staining of CSF revealed gram-positive diplococci in 29 of the 34 episodes in which such staining was performed. CSF cultures were done in 36 episodes, and 31 were positive for *Streptococcus pneumoniae*. Of the blood cultures done in 33 episodes, 26 were positive. Of the five episodes in which antibiotics were administered prior to admission, Gram staining was positive in four cases, CSF cultures were positive in all five, and blood cultures were positive in two. All isolated strains of pneumococci were sensitive to penicillin.

Underlying Disease. As is shown in Table 3, most of the patients had a non-fatal underlying disease. Five patients had undergone previous head surgery, whereas nine patients had previous skull contusion or fracture. Two of the patients with a history of skull trauma and one of the patients with prior head surgery had a second episode of pneumococcal meningitis.

Associated Infections. The most common associated infection in patients with pneumococcal meningitis was acute otitis media, followed by sinusitis and pneumonia (Table 4). In 40% of all episodes the portal of entry remained unknown.

Complications. Of the 38 episodes, 15 ran an uncomplicated course. The other 23 episodes were complicated, and of these, seven – including four of the six episodes of meningitis associated with pneumococcal pneumonia – required admission of the patient to the intensive care unit. Of these seven patients, severe respiratory insufficiency developed in five cases, requiring endotracheal intubation and mechanical ventilation. Neurologic complications alone were observed in six episodes, seizures or cranial nerve palsies being the most frequent. No cases of subdural effusion, cranial abscess of cerebral sinus thrombosis had occurred.

Treatment. All but three episodes of pneumococcal meningitis were treated with benzylpenicillin given parenterally, either alone or in combination with another antibiotic. In 29 episodes benzylpenicillin was the initially administered antibiotic. In the remaining six episodes a combination therapy (doxycycline and rifampicin ($n = 1$), amoxycillin alone ($n = 1$) or in combination with kanamycin ($n = 2$), as well as ampicillin and cloxacillin ($n = 2$) was given initially; penicillin was administered in all cases

Table 1: Clinical features on admission in 38 episodes of pneumococcal meningitis, in relation to mortality and sequelae. For continuous variables, means ± SD are reported; for discrete variables, numbers of episodes.

	Outcome in all episodes		Sequelae in survivors	
	Non-fatal (n = 25)	Fatal (n = 13)	Absent (n = 7)	Present (n = 18)
Age (years)	44 ± 18[a]	65 ± 17[a]	40 ± 17	45 ± 19
Sex (no. of episodes)				
Male	14	8	5	9
Female	11	5	2	9
Duration of illness before treatment				
0 or 1 days	13	3	3	10
2 to 7 days	11	4	3	8
8 to 17 days	1[b]	6[b]	1	0
Systolic pressure (mm Hg)	136 ± 22	147 ± 39	130 ± 28	139 ± 20
Pulse rate (min^{-1})	97 ± 19[b]	115 ± 25[b]	111 ± 25	92 ± 15
Temperature (°C)	39.3 ± 0.6	39.3 ± 1.0	39.4 ± 0.3	39.2 ± 0.7
Level of consciousness				
Alert or lethargic	7	3	1	6
Somnolent	10	5	3	7
Soporous	6	3	2	4
Comatose	2	2	1	1
Nuchal rigidity	22[a]	5[a]	5	17
Focal neurologic deficit	11	5	3	8
Cranial nerve palsy	4	4	0	4
Nystagmus	5	1	1	4
Seizures	4	6	2	2

[a] $p \leq 0.01$.
[b] $p \leq 0.05$.

Table 2: Laboratory data on admission in 38 episodes of pneumococcal meningitis in relation to mortality and sequelae. Values are means ± SD.

	Outcome in all episodes		Sequelae in survivors	
	Non-fatal (n = 25)	Fatal (n = 13)	Absent (n = 7)	Present (n = 18)
ESR (mm/1st h)	36 ± 32[a]	84 ± 39[a]	21 ± 22	41 ± 34
Leukocytes (X 10^9/l)	20 ± 9	19 ± 6	20 ± 11	19 ± 3
Band forms (%)	17 ± 12	20 ± 13	19 ± 9	16 ± 14
Platelets (X 10^9/l)	205 ± 186	180 ± 77	190 ± 122	210 ± 209
Serum sodium level (mmol/l)	137 ± 4[b]	133 ± 6[b]	137 ± 6	136 ± 4
Serum bilirubin level (μmol/l)	15 ± 16[b]	56 ± 102[b]	12 ± 5	17 ± 21
Serum LDH level (U/l)	250 ± 203	298 ± 147	282 ± 316	229 ± 96
CSF cell count (X 10^9/l)	7.5 ± 6.6	14.9 ± 28.9	10.5 ± 8.8	6.4 ± 5.6
CSF protein level (g/l)	4.9 ± 2.2	4.1 ± 3.1	3.5 ± 1.9[b]	5.4 ± 2.1[b]
CSF glucose level (mmol/l)	1.3 ± 1.7	1.4 ± 1.2	1.1 ± 1.6	1.4 ± 1.8

[a] $p \leq 0.001$.
[b] $p \leq 0.05$.
LDH = lactic acid dehydrogenase.

following results of culture. Benzylpenicillin was given as 2 x 10^6 U six times daily to all except three patients, who received higher dosages (range: 6 times 3 x 10^6 to 12 times 2 x 10^6 U daily). Intrathecal penicillin (single dose of 10,000 U on admission) was administered concomitantly in ten episodes. Antibiotics were withheld in three episodes for various reasons. All of these untreated patients died.

Mortality. Of the total series of 39 episodes, 13 ended fatally; thus, the overall case-fatality rate was 33.3%. Eight fatal episodes occurred in men and five in women ($p = 1.0$). The mean age at death was 65 years, versus the mean age of 44 years for the survivors ($p = 0.002$). Only two patients were considered to have died from the direct effects of pneumococcal meningitis on the CNS. Both of them died within 24 hours after ad-

mission. In both cases a deliberate decision not to treat was made on admission. Two patients were judged to have died from the combined effects of meningitis and cardiopulmonary failure and one patient was considered to have died from the combination of neurologic damage due to severe brain contusion after a car accident and meningitis. In most of the fatal cases the patient died from cardiorespiratory failure later in the course of the disease (median interval between admission and death, 12 days; range, 3–30 days). Non-neurologic complications such as congestive heart failure, respiratory insufficiency (all 5 patients died), gastrointestinal bleeding and thromboembolic phenomena were significantly associated with a poor outcome ($p = 0.0001$) and occurred predominantly in patients with pneumonia or in those without a detectable primary focus. One patient died of overwhelming pneumococcal sepsis from an undiagnosed endocardial focus.

Table 3: Underlying disorders in relation to mortality and sequelae.

	Outcome in all episodes		Sequelae in survivors	
	Non-fatal (n = 25)	Fatal (n = 13)	Absent (n = 7)	Present (n = 18)
Underlying disease				
Rapidly fatal	2	2	1	1
Ultimately fatal	1	2	0	1
Non-fatal	22	9	6	16
Prior head trauma/ skull surgery	14[a]	2[a]	6	8[b]
Prior meningitis	3	0	2	1
Splenectomy	3	0	0	3
Alcoholism	3	4	0	3

[a] p value between the non-fatal and fatal groups ≤ 0.05.
[b] In two patients who developed meningitis soon after head trauma, it could not be established whether sequelae were due to trauma or to meningitis.

There was no significant difference in mortality between patients transferred from other hospitals and patients primarily admitted to the Leiden University Hospital (30% vs. 32%; $p = 0.46$). Outcome was not affected by concurrent pneumococcal bacteremia ($p = 0.96$). A relatively good prognosis was associated with prompt treatment with penicillin (mortality 24%), whereas prompt treatment with another antibiotic had a poorer (mortality 50%) though not significantly different ($p = 0.19$) prognosis. There was no statistical difference ($p = 0.40$) between the combination of intravenous penicillin and intrathecal administration of penicillin versus intravenous penicillin alone (mortality 32% and 10%, respectively).

Discriminant analysis was performed for the following selected variables: age, prior skull trauma, number of days of illness before treatment was started, pneumonia, administration of penicillin, level of consciousness on admission, serum sodium concentration and presence of nuchal rigidity. The results showed that a fatal outcome was predicted best by the following factors, in descending order: development of internal complications, absence of nuchal rigidity on admission and the presence of pneumonia on admission. Episodes during which antibiotics had not been administered were not included in this analysis. The combination of these variable factors predicted outcome correctly in 80% of the fatal episodes and in 96% of the non-fatal episodes.

Neurologic Sequelae. Various neurologic sequelae were observed in 18 of the 25 survivors (72%) at the time of discharge. These included sensorineural hearing loss (9 patients), cranial nerve palsies (5 patients), focal deficits other than cranial nerve palsies (5 patients), radicular syndromes (3 patients) and dementia (2 patients). The sex ratio in this group was 1 (9 men, 9 women), the median age was 57.5 years (range 18–79 years) and the median number of days of hospitalization of all survivors was 27 days (range 15–108 days). Eight patients recovered with 1 sequela, 6 patients with 2 sequelae, 3 patients with 3 sequelae, and 1 patient with 4 sequelae.

Table 4: Focus of infection in 38 episodes of pneumococcal meningitis, in relation to outcome of the disease. Results are given as number of episodes for each type of infection.

	All episodes			Sequelae in survivors		
	Non-fatal (n = 25)	Fatal (n = 13)	P value[a]	Absent (n = 7)	Present (n = 18)	P value[b]
Pneumonia	1	5	0.02	0	1	1.00
Sinusitis	7	1	0.24	3	4	0.48
Otitis media/mastoiditis	8	1	0.51	2	6	0.81
Unknown	9	6	1.00	2	7	0.50

[a] Values in this column pertain to statistical differences between fatal and non-fatal episodes per category indicated.
[b] Values in this column pertain to differences between episodes with and without sequelae.

Seven patients recovered without any sequelae (28%). Eight of the patients with neurologic sequelae had antecedent skull trauma or head surgery (temporal relationship between the two events varied between 2 days and 12 years); in two patients in which only a few days transpired between the skull trauma and the onset of meningitis, the development of sequelae either due to trauma or meningitis could not be established (Table 3).

To determine whether the presence of sequelae was related to the documented clinical features, we divided survivors of pneumococcal meningitis into two groups: group I, showing no sequelae (n = 7), and group II, showing one or more sequelae (n = 18). The results of this analysis are presented in Tables 1–4. Only the CSF protein level in patients with sequelae was higher than in those who recovered without any sequelae.

Discussion

The incidence of pneumococcal meningitis observed in this study, i.e. 2.1 episodes per 100,000 adults, does not diverge from that found in other studies in Western Europe and the USA (6, 10, 14), but is slightly higher than that estimated for registration systems in the Netherlands (15, 20), probably due to underreporting of meningitis episodes to the central registration office here. The present retrospective study showed that one-third of the adult patients with pneumococcal meningitis admitted to a university hospital in a given period had died here, which does not differ substantially from previous reports from Western countries (2–6, 9–14).

The strongest predictive factor for a poor outcome was the development of non-neurologic complications. Absence of nuchal rigidity was the second most predictive factor of a poor outcome of the disease, a finding not previously reported for pneumococcal meningitis. Discriminant analysis showed the presence of pneumonia as the third strongest prognostic factor for a fatal outcome. The last factor indicates the graver prognosis of those who present with systemic pneumococcal disease (14). Although patients who presented in coma or with severe underlying disease, i.e. ultimately fatal or rapidly fatal disease, had a more unfavorable prognosis than those who did not, statistical significance was not reached. Since the number of episodes analyzed in this series was limited, a type II error could have been made. Withholding of antimicrobial treatment was invariably associated with a fatal outcome. Treatment with penicillin tended to be associated with a better prognosis than treatment with other antibiotics. Furthermore, our findings do not support the view that intrathecal penicillin improves survival percentages or prevents the development of neurologic abnormalities. It must be stressed, however, that influence of therapy on outcome should be interpreted with great caution in retrospective studies, because many confounding variables may play a role.

Our findings show that in 47% of all episodes of pneumococcal meningitis one or more sequelae were present at the time of discharge. This proportion was previously believed to be much lower, i.e. in the range of 13–27% (4, 11, 21, 22). The study done by Bohr et al. (11) showed clearly that neurologic sequelae must be interpreted with caution because of their potentially dynamic character. On re-examination of 94 patients who had survived pneumococcal meningitis for four to 14 years, these authors found that at discharge, 13 of the 22 patients still suffered from severe neurologic abnormalities. Furthermore, six of the 24 patients without sequelae at discharge showed pronounced sequelae years later (11, 21). Seizures, a frequent complication in the acute and early post-meningitic phases, did not recur (11, 22, 23). The resolution of deficits holds particularly for cranial nerve palsies, which are probably associated with exudate within the arachnoidal sheaths (22, 23). However, sensorineural hearing loss is usually permanent (24), which means that one-third of the survivors in our study will be permanently deaf.

Unfortunately, apart from the CSF protein level, we were not able to find clinical features present on admission that were predictive of the development of neurologic sequelae. This absence of correlation, too, is probably due to the small number of episodes analyzed. No data are available concerning the use of systemic corticosteroids as adjunctive therapy for bacterial meningitis in adults. A recent study done in children showed a significantly reduced frequency of sensorineural hearing loss in the patients who received dexamethasone as compared with the placebo group (25). However, the follow-up period in these patients was short (26).

It has been suggested from results of both experimental models and clinical studies that complications in bacterial meningitis are due mainly to inflammatory reactions in the CNS and can be prevented by anti-inflammatory therapy (25, 27, 28). In our study, however, death due to CNS damage early in the course of the disease was limited to a minority of the fatal cases. Most patients died of cardiorespiratory insufficiency later in the course of the disease. Therefore, besides prescribing antibiotic and anti-inflammatory therapy, the clinician should concentrate on the prevention and treatment of the non-neurologic complications responsible for a fatal outcome of pneumococcal meningitis.

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