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Pneumococcal meningitis in adults
Spectrum of complications and prognostic factors in a series of 87 cases

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Summary
Studies on the incidence and spectrum of complications and prognostic factors in adults with pneumococcal meningitis are scarce. Therefore, we analysed 87 consecutive cases who were treated in our department between 1984 and 2002. Meningitis-associated intracranial complications developed in 74.7% and systemic complications in 37.9% of cases. Diffuse brain oedema (28.7%) and hydrocephalus (16.1%) developed more frequently than previously reported. The incidences of arterial (21.8%) and venous (9.2%) cerebrovascular complications were also very high. Furthermore, 9.2% of cases developed spontaneous intracranial haemorrhages (two patients with subarachnoid and two with subarachnoid and intracerebral bleedings, all in association with vasculitis; one subject with intracerebral haemorrhage due to sinus thrombosis; and three cases with intracerebral bleedings of unknown aetiology). Other new findings were the incidence of acute spinal cord dysfunction due to myelitis (2.3%) and that of hearing loss (19.5% of all patients and 25.8% of survivors). The in-hospital mortality was 24.1%. Only 48.3% of the patients had a good outcome at discharge [Glasgow Outcome Scale Score (GOS) = 5]. Outcome did not change during the study period, as mortality and GOS were similar for patients treated between 1984 and 1992 and for those treated between 1993 and 2002. Factors associated with a bad outcome (GOS $\leqslant$ 4) were chronic debilitating diseases, low Glasgow Coma Scale Score and focal neurological deficits on admission, low CSF leucocyte counts, pneumonia, bacteraemia and meningitis-associated intracranial and systemic complications. Low CSF leucocyte counts were also associated with the development of meningitis-associated intracranial complications. Age $\geqslant$60 years was associated with a higher mortality (36.7 versus 17.5%), but the GOS of the survivors was comparable to that of the surviving younger patients. The causes of death were mostly systemic complications in the elderly and cerebral complications in the younger patients. A haematogenous pathogenesis seemed likely in asplenic patients, while contiguous spread from sinusitis or otitis was the major cause of meningitis in non-asplenic individuals. Furthermore, asplenic patients had a raised incidence of meningitis-associated intracranial complications, but their outcome was similar to that of non-asplenic subjects. The morbidity and mortality of pneumococcal meningitis in adults are still devastating. We report higher incidences (diffuse brain swelling, hydrocephalus, cerebrovascular complications) or new incidences (myelitis, hearing loss, subarachnoid bleeding) of intracranial complications. Our detailed analysis of prognostic factors may help clinicians to identify patients at risk and may also be helpful in the design of clinical trials.

Keywords: meningitis; subarachnoid haemorrhage; myelitis; hearing loss; prognosis

Abbreviations: CT = computed tomography; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; HIV = human immunodeficiency virus; ICH = intracerebral haemorrhage

Introduction
The leading cause of acute bacterial meningitis in adults is *Streptococcus pneumoniae*, with a mortality of 20–30% despite highly effective antibiotic therapy and modern intensive care facilities (Durand *et al*., 1993; Schuchat *et al*.,

1997). Many fatalities are due to cerebral complications (e.g. brain oedema, hydrocephalus, ischaemic infarction and septic sinus or venous thrombosis) or systemic complications (e.g. septic shock, disseminated intravascular coagulation and adult respiratory distress syndrome) (Pfister *et al*., 1993; Schuchat *et al*., 1997). Most studies of acute bacterial meningitis in adults have included cases due to different causative bacteria (Durand *et al*., 1993; Pfister *et al*., 1993; Sigurdardottir *et al*., 1997; Hussein and Shafran, 2000; McMillan *et al*., 2001). Few studies have included only adults with pneumococcal meningitis (Fiebush *et al*., 1952; Olsson *et al*., 1961; Bruyn *et al*., 1989; Kragsbjerg *et al*., 1994; Auburtin *et al*., 2002). In many studies [in particular those which were performed completely or in part before the introduction of computed tomography (CT)], mortality and sequelae (neurological deficits) were reported as outcome measures. Still, detailed information about the underlying meningitis-associated intracranial complications was seldom reported.

Therefore, in the present study we included only adults with pneumococcal meningitis and chose a time period when CT was readily available in our hospital. Eighty-seven consecutive cases, who were all treated in our neurological intensive care unit (ICU) between 1984 and 2002, were analysed in order to characterize the spectrum and incidence of meningitis-associated intracranial and systemic complications and to identify factors prognostic of clinical outcome.

Patients and methods

We retrospectively identified all adults (patients $\geqslant$16 years old) who were treated for pneumococcal meningitis in the neurological ICU of the Klinikum Grosshadern (a 1400-bed tertiary medical centre) between January 1984 and April 2002 (87 episodes of pneumococcal meningitis in 87 subjects). In our department, as a rule, patients with acute bacterial meningitis are treated in the ICU at least during the first days of their illness, when most complications occur. The diagnosis of pneumococcal meningitis was based on the presence of clinical signs and symptoms of meningitis and identification of pneumococci in the CSF by culture, Gram stain, or antigen detection using latex particle agglutination and/or growth of pneumococci from blood cultures. All patients were treated with antibiotics. For empirical therapy of community-acquired meningitis, the combination of ceftriaxone and ampicillin is usually used in our department; after identification of the pathogen, the antibiotic therapy is chosen according to the antibiogram. Penicillin-resistant pneumococci were not detected during the study period. Patient data were obtained from the charts. The duration of disease until admission was counted from the first day of meningitis-related symptoms until admission to our hospital. All patients were initially examined neurologically and physically and had a cranial CT [the analysis of the initial CT findings of most patients from this cohort was part of a previous study (Kastenbauer *et al*., 2002)], consultation by an ear, nose and throat specialist, and a chest X-ray in order to detect underlying or associated infections, CSF fistulae and/or meningitis-associated complications. During their stay in the neurological ICU, the patients were examined neurologically and physically every day and, on suspicion of a complication, the indicated technical examinations (e.g. CT, MRI, cerebral angiography, Doppler sonography, audiometry) were performed. We systematically analysed the following meningitis-associated intracranial and systemic complications: seizures, arterial and venous cerebrovascular complications, diffuse brain swelling, hydrocephalus, acute spinal cord dysfunction, cerebritis, cranial nerve palsies, hearing loss, septic shock, disseminated intravascular coagulation, acute renal failure and adult respiratory distress syndrome (Pfister *et al.*, 1992, 1993; Roos 1998; Kastenbauer *et al*., 2001). Hearing was classified as in a previous publication on meningitis-associated hearing loss in children (Dodge *et al*., 1984); in brief, hearing levels <30 dB were classified as normal, 30–55 dB as mild, 55–70 dB as moderate, 70–90 dB as severe and >90 dB as profound loss (deafness). The clinical status on the day of discharge from the intensive care unit was evaluated with the Glasgow Outcome Scale (GOS): 1, death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; 5, good recovery. Dichotomous variables were compared by the χ^2 test. Continuous variables were compared by the Mann–Whitney *U* test. Correlation analyses were performed according to Spearman. All statistical tests applied were two-tailed. $P < 0.05$ was considered significant. Unless otherwise stated, data are given as mean $\pm$ standard deviation.

Fifty-two patients (59.8%) were referred from other hospitals (regional hospitals in Upper Bavaria). However, there were no significant differences between referred patients and those who presented directly to the Klinikum Grosshadern (see below) except for a longer duration of disease until admission to our hospital in the referred patients (2.2 $\pm$ 1.7 versus 1.2 $\pm$ 1.0 days, $P = 0.005$). In particular, there were no differences between referred and non-referred patients with regard to age (49 $\pm$ 17 versus 53 $\pm$ 17 years, $P = 0.216$), clinical presentation [e.g. Glasgow Coma Score (GCS) 10.2 $\pm$ 3.4 versus 10.9 $\pm$ 3.7, $P = 0.346$], underlying or associated diseases (e.g. asplenia in 6 of 52 versus 5 of 35 patients, $P = 0.750$; chronic debilitating conditions in 15 of 52 versus 12 of 35 cases, $P = 0.641$; ear or sinus infection in 33 of 52 versus 17 of 35 subjects, $P = 0.190$), incidence and spectrum of meningitis-associated intracranial (40 of 52 versus 25 of 35 patients, $P = 0.620$) or systemic complications (19 of 52 versus 14 of 35 cases, $P = 0.823$) and outcome (GOS 3.7 $\pm$ 1.5 versus 3.5 $\pm$ 1.9, $P = 0.864$).

Results

Patient characteristics

The patients' age was 50 $\pm$ 17 years (range 16–87 years) and the sex ratio (male : female) was 41 : 46. The duration of

disease until admission was 1.8 ± 1.5 days. Eighty-four patients (96.6%) presented with fever (temperature >38°C) and 83 (95.4%) with neck stiffness. The GCS on admission was 10.5 ± 3.5 (range 3–15). Focal neurological deficits were present in 25 patients (28.7%): pyramidal signs (17 patients), dilated or poorly reactive pupils (4 patients), other cranial nerve palsies (4 patients), gaze palsy (5 patients) and aphasia (3 patients) (the total exceeds 25 due to the presence of multiple signs in several patients).

The initial lumbar CSF findings were not available for all patients, because in four patients a lumbar puncture could not be performed due to suspected increased intracranial pressure, and in others the CSF parameters were incomplete (mostly because the volume of CSF collected was too small). In the initial lumbar CSF, the leucocyte count was 3936 ± 5699 cells/μl (n = 81, range 3–33 334 μl), the protein concentration 458 ± 391 mg/dl (n = 75, range 33–1710 mg/dl) and the glucose concentration 22 ± 23 mg/dl (n = 71, range 0–92 mg/dl). The CSF leucocyte counts correlated positively with the glucose level ($r = 0.337$, $n = 70$, $P = 0.004$) but not with the protein concentration ($r = –0.023$, $n = 74$, $P = 0.846$). Furthermore, the protein concentration correlated negatively with the glucose level ($r = –0.455$, $n = 69$, $P < 0.001$).

CSF cultures were performed initially in 83 patients; they were positive in 63 cases (75.9%). Blood cultures were performed initially in 76 patients; they were positive in 49 cases (64.5%). Thirty-nine patients had positive CSF and blood cultures, 16 patients had positive CSF cultures and negative blood cultures, and in 8 patients with positive CSF cultures no blood cultures were performed. Seven of the patients with negative CSF cultures had positive blood cultures (all of these patients also had a positive Gram stain or antigen test in the CSF). Of the 4 patients in whom a lumbar puncture could not be performed initially, 3 had positive blood cultures and 1 with a negative blood culture had a positive Gram stain in ventricular CSF. Of the remaining 13 patients with negative cultures or lacking cultures, 8 tested positive for pneumococcal antigen in the CSF and in 5 subjects the diagnosis was based only on the detection of Gram-positive diplococci in the CSF.

Table 1 *Underlying and associated conditions in 87 adults with pneumococcal meningitis*

Underlying/associated conditions[a]	*n* (%)
Asplenia	11 (12.6)
Chronic debilitating conditions	27 (31.0)
Chronic alcoholism	14 (16.1)
Malignancies not in remission[b]	6 (6.9)
Diabetes mellitus	5 (5.7)
Chronic immunosuppressive therapy	3 (3.4)
Terminal renal failure	2 (2.3)
Chronic hepatitis with liver cirrhosis	2 (2.3)
Ear or sinus infection	50 (57.5)
CSF fistula	18 (20.7)
Pneumonia	19 (21.3)
Endocarditis	2 (2.3)

[a]Underlying and/or associated conditions were present in 80 patients (92.0%) (the total exceeds 80 because of the presence of multiple conditions in several patients); [b]Four patients had plasmocytoma and two had metastatic carcinoma.

Underlying conditions (predisposition for invasive pneumococcal infection) or associated infections were present in 80 patients (92.0%) (Table 1). Details about the asplenic patients are given in Table 2.

Of the 87 patients, 9 (10.3%) had recurrent bacterial meningitis (the episode under study was the second in 4, the third in 3, the fifth in 1 and the sixth in 1 patient). In 5 of them, a CSF fistula was diagnosed and treated surgically; 3 patients had chronic or relapsing sinusitis or otitis and 1 patient suffered from terminal renal insufficiency.

Spectrum of complications and clinical outcome

Sixty-five patients (74.7%) had meningitis-associated intracranial complications.

Twenty-four subjects (27.6%) developed seizures. In 9 patients, the seizures were clearly focal in origin (secondarily generalized tonic–clonic seizures occurred in 4 of them). In 6 of the 9 patients, a corresponding focal brain lesion could be detected neuroradiologically. Of the 15 patients in whom only primarily generalized tonic–clonic seizures were observed, no clear cerebral pathology was evident at the time of the first seizure in 11 patients; however, 4 of the patients had CT findings suggesting intracranial hypertension [brain oedema in 3 patients, hydrocephalus and multiple intracerebral haemorrhages (ICHs) in 1].

Arterial cerebrovascular complications were detected in 19 patients (21.8%) (Table 3) and venous complications in 9 (10.3%, Table 4). Eight patients (9.2%) suffered from intracranial bleedings: 4 had a subarachnoid haemorrhage (all had angiographic evidence of vasculitis, 2 also had ICHs) (Table 3), 1 had an ICH due to sinus thrombosis (Table 4), and in 3 patients the cause of their ICHs remained unclear (2 patient had multiple ICHs and a normal angiography; in a third patient with a frontal ICH no angiography was performed). In 2 additional patients, frontal ICHs were probably due to external ventricular drainages.

Diffuse brain swelling was observed in 25 patients (28.7%) and hydrocephalus in 14 (16.1%). Permanent CSF drainage of hydrocephalus was required in only 2 of the surviving 66 patients (3.3%). Hearing loss developed in 17 patients (19.5%). It was detected exclusively in survivors probably because audiometry was performed only on clinical suspicion of hearing loss after recovery from the critical stage of meningitis. Thus, 17 of 66 survivors (25.8%) suffered from meningitis-associated hearing loss. The hearing loss was symmetrical in 11 patients (mild in 6, moderate in 2, severe in 1 and profound in 2 cases) and asymmetrical in 6 (mild/normal in 2, moderate/normal in 1, moderate/severe in 2 and profound/mild in 1).

Table 2 *Characteristics of 11 splenectomized patients with pneumococcal meningitis*

Gender, age (years)	Cause of splenectomy	Years between splenectomy and meningitis	Previous pneumococcal vaccination	Intracranial/CNS complications of meningitis	GOS
M, 50	Trauma	36	No	Intracerebral haemorrhage	5
F, 33	Trauma	16	No	Brain swelling	5
M, 47	Trauma	29	Yes	Mild bilateral hearing loss	5
F, 34	Trauma	28	No	Brain swelling, suspected cerebritis	5
F, 33	Splenomegaly[a]	29	No	Brain swelling	5
F, 21	Hereditary spherocytosis	11	Yes	Brain swelling	5
F, 69	Gastric carcinoma[b]	5	Yes	Vasculitis, subarachnoid haemorrhage, mild bilateral hearing loss	5
M, 36	Hodgkin's disease[b]	4	n.d.	Profound bilateral hearing loss	4
F, 36	Idiopathic thrombocytopenic purpura	5	Yes	Cerebral ischaemia, profound bilateral hearing loss, paraparesis due to myelitis	3
F, 63	Splenic cyst	4	n.d.	Hydrocephalus, brain swelling	1
M, 42	Hodgkin's disease[b]	10	n.d.	Brain swelling, cerebral herniation	1

[a]The exact diagnosis remained obscure, but she had been healthy since the diagnostic splenectomy in early childhood; [b]in complete remission at the time of meningitis. n.d. = not documented.

Rare CNS complications of meningitis were myelitis and cerebritis. Two patients (2.3%) developed acute spinal cord dysfunction and both had MRI findings consistent with myelitis. In 4 patients (4.6%) the diagnosis of cerebritis was made: 1 had a reversible cortical and subcortical lesion on the MRI without evidence of a vascular cause, and in 3 patients cerebritis was diagnosed neuropathologically post-mortem (*intra vitam*, 2 had diffuse periventricular hypodensities and marked brain swelling and 1 had focal hypodensities on the CT). It should be noted, though, that the incidence of cerebritis was probably higher because it is very difficult to diagnose *intra vitam*. Four patients (4.6%) developed cranial nerve palsies which could not be explained by central lesions: 1 developed complete bilateral internal and external ophthalmoplegia, 1 bilateral abducens nerve palsies, 1 peripheral facial palsy and 1 trochlear and ipsilateral peripheral facial palsy.

Meningitis-associated systemic complications occurred in 33 patients (37.9%): 27 (31%) developed septic shock, 20 (23.0%) disseminated intravascular coagulation, 10 (11.5%) renal failure requiring haemofiltration, and 6 (6.9%) adult respiratory distress syndrome

Fewer than half of the patients made a good recovery (GOS 5) before discharge from the ICU (42 patients, 48.3%). Twenty-one patients (24.1%) died. In 9 patients death was due to cerebral herniation. The other 12 patients succumbed to cardiac/circulatory or multiple organ failure, but 9 of them also had a catastrophic neurological status and neuroradiological evidence of severe and permanent cerebral complications of meningitis at the time of death.

In order to find out whether the patient cohort was homogeneous over the study period, we then compared the patients admitted between 1984 and 1992 ($n = 44$) with those admitted between 1993 and 2002 ($n = 43$). There was no difference in age (49 $\pm$ 17 versus 52 $\pm$ 17 years, $P = 0.510$), disease severity on presentation (GCS 10.1 $\pm$ 3.7 versus 10.8 $\pm$ 3.3, $P = 0.397$; presence of focal neurological deficits, 12 of 44, 27.3% versus 13 of 43, 30.2%, $P = 0.816$), incidence of intracranial complications (32 of 44, 72.7% versus 33 of 43, 76.7%, $P = 0.806$), incidence of systemic complications (13 of 43, 30.2% versus 20 of 43, 46.5%, $P = 0.125$) or outcome (mortality, 11 of 44, 25.0% versus 10 of 43, 25.3%, $P = 1.000$; GOS, 3.52 $\pm$ 1.71 versus 3.67 $\pm$ 1.64, $P = 0.774$).

Prognostic factors

Patients with an adverse outcome (GOS $\leqslant$ 4) differed from those with good a outcome (GOS = 5) (Table 5) in the following respects: on admission they had a lower GCS and more frequently had focal neurological deficits, they had lower CSF leucocyte counts (and tended to have higher CSF protein values), and more frequently had positive blood cultures, chronic debilitating conditions and pneumonia. For the continuous variables, the results were confirmed by correlation analyses: the GOS at discharge correlated with the GCS on admission ($r = 0.487$, $n = 87$, $P < 0.001$), CSF leucocyte counts ($r = 0.482$, $n = 81$, $P < 0.001$) and CSF protein values ($r = –0.291$, $n = 75$, $P = 0.011$). In addition, a correlation of GOS with age ($r = –0.230$, $n = 87$, $P = 0.032$) was observed. GOS was not significantly correlationed with

Table 3 *Spectrum of arterial cerebrovascular complications*

Gender, age (years)	Complication	Location	Probable aetiology	GOS
M, 54	Cerebral perfusion deficit with contralateral hemiparesis	Frontal and parietal lobe	Unclear (normal angiography)	5
F, 68	SAH	Temporal lobe	Vasculitis (CT angiography)	5
M, 41	Ischaemia	Parietal lobe	Unclear (normal angiography)	4
M, 48	Ischaemia	Cerebellar hemisphere	Unclear (normal angiography)	4
F, 52	Ischaemia	Thalamus	Vasculitis (angiography)	4
F, 82	Ischaemia	Parietal lobe	Unclear (normal angiography)	3
F, 36	Ischaemia	Frontal lobe	Probable vasculitis (TCD)	3
F, 69	Cerebral perfusion deficit with contralateral hemiparesis	Frontal, temporal, and parietal lobe	Unclear (normal angiography)	3
F, 57	Ischaemia	Brainstem, thalamus, basal ganglia	Vasculitis (MR angiography)	3
M, 51	Ischaemia, ICH and SAH	Ischaemia in both frontal lobes, ICH in frontal and temporal lobe, prepontine SAH	Vasculitis (angiography)	3
M, 66	Ischaemia	Complete MCA territory	Vasculitis (angiography)	2
M, 56	Ischaemia	Frontal and both temporal lobes and brainstem	Unclear (normal angiography)	2
M, 42	Ischaemia and SAH	Ischaemia in MCA and ACA territory, SAH over frontal and temporal lobes	Vasculitis (angiography)	2
M, 43	Ischaemia	Almost complete MCA territory	Vasculitis (angiography)	1
M, 64	Ischaemia	Both MCA territories	Vasculitis (angiography)	1
F, 71	Ischaemia	Thalamus and basal ganglia (bilaterally)	Unclear (no angiography performed)	1
F, 87	Ischaemia	Pons and thalamus	Vasculitis (angiography)	1
F, 80	Ischaemia	Brainstem, thalamus (bilaterally), temporal lobe	Vasculitis (MR angiography)	1
M, 26	ICH, SAH and ischaemia	Pontine ICH and prepontine SAH, then ischaemia in medulla, pons and complete MCA territory	Vasculitis (angiography)	1

Criteria suggesting vasculitis included arterial narrowing, vessel wall irregularities, focal dilatations and occlusions of distal branches of the middle cerebral artery (Pfister *et al*., 1992). ACA = anterior cerebral artery; ICH = intracerebral haemorrhage; MCA = middle cerebral artery; SAH = subarachnoid haemorrhage; TCD = transcranial Doppler sonography.

CSF glucose level ($r = 0.154$, $n = 71$, $P = 0.200$) or duration of symptoms until admission ($r = 0.025$, $n = 87$, $P = 0.821$). Both meningitis-associated intracranial and systemic complications contributed to the adverse outcome (Table 6): seizures, cerebrovascular complications (arterial and venous), brain swelling and hydrocephalus, as well as septic shock, disseminated intravascular coagulation and acute renal failure, were each more frequent in patients with a GOS $\leqslant 4$.

Because older age was not clearly associated with an adverse outcome (Table 5), although age $\geqslant 60$ years is a known risk factor for mortality from acute bacterial meningitis (Durand *et al*., 1993), we then dichotomized the cohort with respect to age. Eleven of 30 patients aged $\geqslant 60$ years (36.7%) but only 10 of the 57 younger subjects died (17.5%, $P = 0.065$). Systemic complications were the cause of death in 9 of the 11 older patients with a fatal course but in only 3 of the 10 younger patients ($P = 0.030$). Meningitis-associated systemic complications (12 of 30, 40%, versus 21 of 57, 36.8%, $P = 0.819$) and intracranial complications (22 of 30, 73.3%, versus 43 of 57, 75.4%, $P = 1.000$) were equally

Table 4 *Spectrum of venous cerebrovascular complications*

Gender, age (years)	Complication	GOS
F, 53	Thrombosis of frontal superior cerebral veins	5
M, 45	Incomplete thrombosis of the superior sagittal sinus with diffuse brain oedema	4
F, 37	Thrombosis of cavernous sinus with exophthalmos	4
M, 17	Cortical venous thrombosis with ischaemia	4
F, 51	Thrombosis of superior sagittal sinus and transverse sinus with intracerebral haemorrhage	4
M, 51	Thrombosis of internal jugular vein	3
F, 44	Thrombosis of cortical veins and both internal jugular veins with ischaemia	3
M, 25	Thrombosis of cortical veins	1
F, 87	Thrombosis of superior sagittal sinus and frontal superior cerebral veins with ischaemia	1

Venous thrombosis was diagnosed by angiography in 8 patients and by MR angiography in 1 patient.

Table 5 *Patients with good (GOS = 5) and bad (GOS ⩽ 4) outcome of pneumococcal meningitis: demographic data, presenting signs, CSF and microbiological findings, and underlying or associated conditions*

Variable	Patients with GOS = 5 (n = 42)	GOS ⩽ 4 (n = 45)	P
Age, mean ± SD (years)	48 ± 16	53 ± 17	0.121
Males	21 (50.0%)	20 (44.4%)	0.670
Females	21 (50.0%)	25 (55.6%)	
Duration of symptoms, mean ± SD (days)	1.6 ± 1.2	2.0 ± 1.7	0.607
Presenting signs			
Fever (temperature >38°C)	41 (97.6%)	43 (95.6%)	1.000
Neck stiffness	41 (97.6%)	42 (93.3%)	0.617
GCS, mean ± SD	12.2 ± 3.0	8.8 ± 3.2	**<0.001**
Focal neurological deficit	5 (11.9%)	20 (44.4%)	**0.001**
CSF findings, mean ± SD			
Leucocyte count (cells/μl)	5901 ± 7128	2019 ± 2793	**<0.001**
Protein (mg/dl)	378 ± 322	536 ± 439	0.095
Glucose (mg/dl)	27 ± 26	18 ± 20	0.136
Microbiological findings			
Positive CSF culture	29 of 40 (72.5%)	34 of 43 (79.1%)	0.609
Positive blood culture	18 of 36 (50.0%)	31 of 40 (77.5%)	**0.017**
Underlying/associated conditions			
Debilitating conditions	6 (14.3%)	21 (46.7%)	**0.001**
Asplenia	7 (16.7%)	4 (8.9%)	0.342
CSF fistula	11 (26.2%)	7 (15.6%)	0.292
Ear or sinus infection	22 (52.4%)	28 (62.2%)	0.391
Pneumonia	5 (11.9%)	14 (31.1%)	**0.039**

Values in bold type indicate significant differences.

frequent in old and young patients. The surviving old and young patients had a comparable outcome (GOS, 4.4 ± 1.0 versus 4.4 ± 0.9, P = 0.804). Thus, old age seemed to be a risk factor for mortality from pneumococcal meningitis; the outcome of the survivors, however, did not depend on age. Because death in the elderly was mostly due to systemic complications, the incidence of which was not increased, the complications were probably more severe.

We then analysed the cohort with regard to asplenia. In order to minimize confounding variables, we divided the control group (patients without previous splenectomy) into those with chronic debilitating diseases and those who had previously been healthy (patients without previous splenectomy and without any of the debilitating conditions listed in Table 1).

The demographics, duration of symptoms, presenting signs and microbiological findings (rate of positive CSF and blood cultures) of asplenic patients were not different from those of previously healthy subjects (not shown). The CSF leucocyte counts (2167 ± 2328 versus 5432 ± 7077 cells/μl, P = 0.130) and glucose levels (13 ± 15 versus 28 ± 26 mg/dl, P = 0.116) tended to be lower and the protein values higher (445 ± 146

Table 6 *Patients with good (GOS = 5) and bad (GOS ⩽ 4) outcome of pneumococcal meningitis: spectrum of complications*

Complication	Patients with		*P*
	GOS = 5 (*n* = 42)	GOS ⩽ 4 (*n* = 45)	
Meningitis-associated intracranial complications	20 (47.6%)	45 (100.0%)	**<0.001**
Seizures	6 (14.3%)	18 (40.0%)	**0.009**
Cerebral arterial complication	2 (4.8%)	17 (37.8%)	**<0.001**
Cerebral venous complication	1 (2.4%)	8 (17.8%)	**0.019**
Brain swelling	7 (16.7%)	18 (40.0%)	**0.019**
Hydrocephalus	3 (7.1%)	11 (24.4%)	**0.040**
Hearing loss	6 (14.3%)	11 (24.4%)	0.235
Meningitis-associated systemic complications	7 (16.7%)	26 (57.8%)	**<0.001**
Septic shock	4 (9.5%)	23 (51.1%)	**<0.001**
DIC	5 (11.9%)	15 (33.3%)	**0.022**
Acute renal failure	0 (0%)	10 (22.2%)	**0.001**
ARDS	1 (2.4%)	5 (11.1%)	0.204

Values in bold type indicate significant differences. DIC = disseminated intravascular coagulation; ARDS = adult respiratory distress syndrome.

Table 7 *Incidence of complications and outcome depending on the presence of asplenia or debilitating conditions*

	Asplenic patients (*n* = 11)	Patients without previous splenectomy	
		With debilitating conditions (*n* = 27)	Without debilitating conditions (*n* = 49)
Meningitis-associated intracranial complications	11 (100.0%)**	26 (96.3%)***	28 (57.1%)
Meningitis-associated systemic complications	5 (45.5%)	19 (70.4%)***	9 (18.4%)
Glasgow Outcome Score			
Good recovery (GOS 5)	7 (63.6%)	6 (22.2%)**	29 (59.2%)
Moderate disability (GOS 4)	1 (9.1%)	4 (14.8%)	9 (18.4%)
Severe disability (GOS 3)	1 (9.1%)	4 (14.8%)	1 (2.0%)
Vegetative state (GOS 2)	0 (0%)	1 (3.7%)	3 (6.1%)
Death (GOS 1)	2 (18.2%)	12 (44.4%)**	7 (14.3%)

**$P < 0.01$; ***$P < 0.001$ compared with patients without previous splenectomy and without debilitating conditions.

versus 389 ± 341 mg/dl, $P = 0.086$) than those of the previously healthy subjects. There was a marked difference, however, with respect to underlying/associated infections, because ear or sinus infections were rare in asplenic compared with previously healthy patients (1 of 11, 9.1%, versus 34 of 49, 69.4%, $P = 0.001$). The prevalences of cranial CSF leakage and pneumonia, however, were similar (not shown).

Patients with chronic debilitating diseases were older than the previously healthy patients (58 ± 14 versus 48 ± 17 years, $P = 0.025$); the sex ratios and the duration of symptoms were not different (not shown). The clinical presentation was also similar, except that patients with chronic debilitating diseases more often had focal neurological deficits than previously healthy subjects (13 of 27, 48.1%, versus 8 of 49, 16.3%, $P = 0.006$). Their CSF leucocyte counts were lower (2154 ± 2633 versus 5432 ± 7077 cells/μl, $P = 0.007$), the protein values were higher (569 ± 495 versus 389 ± 341 mg/dl, $P = 0.047$) and the glucose levels tended to be lower (17 ± 19 versus 28 ± 26 mg/dl, $P = 0.065$) than those of the previously healthy individuals. The microbiological findings were similar in the two patient groups (not shown). Of the underlying and associated conditions, CSF leakages and ear and sinus infections were similarly frequent, but pneumonia was more prevalent in patients with chronic debilitating diseases (10 of 27, 37.0%, versus 7 of 49, 14.3%, $P = 0.042$).

In a last step, we compared the incidence of complications and the outcome of asplenic patients and of those with chronic debilitating diseases with those of the previously healthy subjects (Table 7). The percentage of asplenic patients who developed meningitis-associated intracranial complications was higher than that of the previously healthy individuals. Meningitis-associated systemic complications ($P = 0.107$), in particular, septic shock (4 of 11, 36.4%, versus

7 of 49, 14.3%, $P = 0.104$) and disseminated intravascular coagulation (4 of 11, 36.4%, versus 5 of 49, 10.2%, $P = 0.50$), tended be more frequent in asplenic patients than in previously healthy subjects. The outcome of asplenic patients, however, was not different from that of previously healthy patients. Subjects with chronic debilitating diseases more frequently developed meningitis-associated intracranial and systemic complications and had a clearly worse outcome than previously healthy individuals.

Discussion

Many previous studies on pneumococcal meningitis have included all age groups (Weiss *et al*., 1967; Tugwell *et al*., 1976; Bohr *et al*., 1984; Hoen *et al*., 1993; Kirkpatrick *et al*., 1994; Stanek and Mufson, 1999), although complications and fatalities are less frequent in children than in adults (Kornelisse *et al*., 1995; Arditi *et al*., 1998). On the other hand, studies on adults have usually included cases of acute meningitis due to various bacterial pathogens (Pfister *et al*., 1993; Durand *et al*., 1993; Sigurdardottir *et al*., 1997; Hussein and Shafran, 2000; McMillan *et al*., 2001). In these studies, mortality has sometimes been analysed separately for the different causative bacteria, but not the incidence and spectrum of complications. Very few of the recent studies have focused on adults with pneumococcal meningitis (Bruyn *et al*., 1989; Kragsbjerg *et al*., 1994; Auburtin *et al*., 2002) and two of these reports have analysed a relatively low number of patients [36 and 31, respectively (Bruyn *et al*., 1989; Kragsbjerg *et al*., 1994)]. Many investigations have reported mortality and/or the presence of sequelae (neurological deficits) as outcome measures; however, the underlying intracranial complications of meningitis have seldom been analysed. The interpretation of previous studies was therefore hampered by heterogeneous cohorts (adults and children and/or different causative bacteria), small sample size, or lack of detailed information on neurological complications. Therefore, we analysed a large cohort consisting only of adults with pneumococcal meningitis. An additional strength of our study was that the sensitivity for the detection of meningitis-associated complications was very high, because the patients were monitored closely in our neurological ICU and neuroradiological diagnostics (in particular CT and angiography) were readily available throughout the whole study period (1984–2002).

Patient characteristics

The composition of our patient cohort appears to be fairly representative with regard to predisposing or associated conditions, as it was relatively similar to the population from another recent paper on pneumococcal meninigitis in adults (Auburtin *et al*., 2002); e.g. in that report 7.5% of the patients were asplenic, 21% suffered from chronic alcoholism, 8.8% had cancer or were on immunosuppressive therapy, 6.3% had diabetes mellitus, 50% had an ear or sinus infection, and 18.8% had recurrent episodes of bacterial meningitis. Furthermore, our analysis revealed that the patient characteristics (e.g. age) and disease severity on presentation (e.g. GOS, incidence of focal neurological deficits) did not change during the study period.

Spectrum of complications and outcome

The mortality of 24.1% is in good agreement with previous work that included or studied exclusively adults with pneumococcal meningitis [mean 26.2%, range 16–33% in seven recent studies (Bruyn *et al*., 1989; Durand *et al*., 1993; Kragsbjerg *et al*., 1994; Sigurdardottir *et al*., 1997; Hussein and Shafran, 2000; McMillan *et al*., 2001; Auburtin *et al*., 2002)]. Also, the incidence of seizures (27.6%) was very similar to that in previous studies on pneumococcal meningitis in adults [22.0% (Sigurdardottir *et al*., 1997), 25.6% (Bruyn *et al*., 1989) and 25.8% (Kragsbjerg *et al*., 1994)].

The high incidence of cerebrovascular complications (19 arterial, 21.8%, and 9 venous, 10.3%), however, is a new finding. Comparable figures were only available from a previous study from our department, which showed cerebrovascular complications in 15.1% of adults with acute meningitis due to various bacteria (Pfister *et al.*, 1992, 1993). Also, the incidence of intracranial bleedings (8 spontaneous haemorrhages, 9.2%, and 2 probably iatrogenic cases due to external ventricular drainages) was surprisingly high, although the arterial blood pressure and blood coagulation parameters were monitored closely and kept within tolerable limits in all patients. Previous studies of intracranial bleeding in adults with acute meningitis due to various bacteria reported much lower incidences, of 1–2% (Pfister *et al*., 1993; Gironell *et al*., 1995). Four of our patients (4.6%) suffered subarachnoid haemorrhages and all of them had angiographic evidence of vasculitis but not of another source of bleeding, such as an aneurysm. Thus, vasculitic destruction of the arterial wall may have been the cause of subarachnoid bleeding in these patients.

The frequencies of brain swelling (28.7%) and hydrocephalus (16.1%) in our study population also clearly exceeded the figures published for adults with acute meningitis due to various bacteria, which were 14.0 and 11.6%, respectively, in a study from our department (Pfister *et al*., 1993) and 5.7 and 14.9% in another report (Durand *et al*., 1993). The high prevalence of hearing loss in survivors of meningitis in our study (25.8%) is in good agreement with the 31% reported for children after pneumococcal meningitis (Dodge *et al*., 1984).

Another new finding of this study is that it gives the first estimate of the incidence of acute spinal cord dysfunction (due to myelitis) during pneumococcal meningitis (2.3%), because it has been described previously only in case reports and not in any larger series on acute bacterial meningitis (Moffett and Berkowitz, 1997; Kastenbauer *et al*., 2001).

Thus, this report confirms previous studies of pneumococcal meningitis in adults with respect to mortality and the

incidence of seizures. Furthermore, we show that loss of hearing was similarly frequent as in children with pneumococcal meningitis. Finally, our study provides much higher or first incidences for complications which can only be diagnosed reliably *intra vitam* by CT, angiography or MRI, namely cerebrovascular complications, brain swelling, hydrocephalus and myelitis.

Prognostic factors

A low GCS on admission, bacteraemia, pneumonia and the development of intracranial and systemic complications were associated with an adverse outcome, confirming previous studies. As in our investigation, the level of consciousness has been identified repeatedly as a strong predictor of outcome in reports on acute meningitis in adults due to pneumococci (Auburtin *et al*., 2002) or various bacteria (Durand *et al*., 1993; Hussein and Shafran, 2000; McMillan *et al*., 2001). Also, the severity of pneumonia-associated pneumococcal meningitis has been demonstrated in studies including all age groups (Carpenter and Petersdorf, 1962; Bohr *et al*., 1985; Hoen *et al*., 1993) and also in a smaller study on adults (Bruyn *et al*., 1989). Bacteraemia was known to be associated with a higher mortality, too (Hoen *et al*., 1993). Finally, the significance of meningitis-associated intracranial and systemic complications confirms an earlier study from our department on acute meningitis in adults due to various bacteria (Pfister *et al*., 1993).

Lower CSF leucocyte counts were clearly associated with an adverse outcome; this is a new finding in pneumococcal meningitis in adults. Similar findings were reported recently in acute meningitis due to various bacteria in adults (McMillan *et al*., 2001). However, previous studies of pneumococcal meningitis in children, adults or all age groups did not [except one investigation (Tugwell *et al*., 1976)] show a significant association (though some reported a tendency) of low CSF leucocyte count with mortality (Carpenter and Petersdorf, 1962; Bohr *et al*., 1984; Bruyn *et al*., 1989; Kornelisse *et al*., 1995; Auburtin *et al*., 2002). Our discrepant result cannot be explained by the outcome measure used, because the CSF leucocyte counts were also different when the patients were dichotomized with respect to mortality instead of GOS (surviving patients versus fatal cases, 4792 ± 6228 versus 1324 ± 2176 cells/μl, $P < 0.001$). Furthermore, the CSF leucocyte counts were lower in patients with meningitis-associated intracranial complications than in those without (2611 ± 3425 versus 7489 ± 8554 cells/μl, $P < 0.001$). Our findings agree well with animal studies of pneumococcal meningitis, which have shown an association of low initial CSF leucocyte counts with high bacterial titres, development of intracranial complications and unfavourable outcome (Giampaolo *et al*., 1981; Tauber *et al*., 1992). Clinically, this may be best illustrated by the extreme cases of 'apurulent meningitis', which carry a dismal prognosis and are characterized by excessive bacterial growth and lack of leucocyte response in the CSF (Felgenhauer and Kober, 1985). This is the first clinical study which demonstrates that a strong initial leucocyte response in the CSF is associated with a lower incidence of intracranial complications and a good prognosis for pneumococcal meningitis. Thus, the CSF leucocytes might be mediators, or at least indicators, of a beneficial host response.

In contrast to our study, focal neurological deficits were not predictive of adverse outcome in previous reports on acute meningitis in adults due to various bacteria (Durand *et al*., 1993; McMillan *et al*., 2001) and in one of the smaller investigations of pneumococcal meningitis (Bruyn *et al*., 1989). Moreover, in many studies focal neurological signs were not analysed as prognostic factors (Sigurdardottir *et al*., 1997; Hussein and Shafran, 2000; Auburtin *et al*., 2002). Our discrepant result cannot be explained by the different outcome measure (GOS instead of mortality), because focal signs were associated with mortality, too (12 of 21 fatal cases, 57.1%, versus 13 of 66 survivors, 19.7%, $P = 0.002$).

Some factors that were clearly predictive of an adverse outcome in other studies were not so in our investigation, in particular old age. Old age was associated with greater mortality in several studies on adults with meningitis due to various bacteria (Durand *et al*., 1993; McMillan *et al*., 2001) or pneumococci (Bruyn *et al*., 1989); only one study of pneumococcal meningitis in adults reported no difference in age between survivors and fatal cases (Auburtin *et al*., 2002). In our investigation, the mean age was not different between patients with good and adverse outcome (GOS $\leqslant 4$). Only after dichotomization with respect to age $\geqslant$60 years did we find a strong trend towards greater mortality in the older patients (36.7 versus 17.5%, $P = 0.065$). However, the GOS of the surviving older patients did not differ from that of the younger survivors. The older patients died from systemic rather than intracranial complications (the opposite was true for the younger patients). The incidence of systemic and intracranial complications, however, did not differ between young and old patients. Thus, the systemic complications were probably more severe. Using the GOS as the outcome measure, we thus demonstrate for the first time that, despite increased mortality, the outcome of the surviving older patients did not differ from the younger ones.

Comorbidity has been shown to be associated with an adverse outcome for adults with acute bacterial meningitis (McMillan *et al*., 2001). However, the definition of comorbidity is difficult. Some studies have combined e.g. pneumonia, head trauma and ear or sinus infections with malignant diseases or immune disorders as underlying or predisposing diseases, and did not find an association with adverse outcome (Hoen *et al*., 1993; Stanek and Mufson, 1999). However, pneumonia is not necessarily an underlying condition but can also be a complication of advanced pneumococcal meningitis due to haematogenous spread of the bacteria from the CNS (Koedel *et al*., 2002). Head trauma or CSF fistulae, on the other hand, are of course underlying or predisposing conditions (facilitating entry of bacteria into the CNS), but were not associated with an adverse outcome in our

study and another study (Auburtin *et al*., 2002), and were even predictive of good outcome in another paper (Bruyn *et al*., 1989). Also, ear or sinus infections were not associated with an adverse outcome in our study and in another (Bohr *et al*., 1984; Bruyn *et al*., 1989). Malignant disease not in remission, immunosuppressive medication, human immunodeficiency virus (HIV) infection and asplenia were often combined in the group of patients with immune disorders in previous studies (McMillan *et al*., 2001; Auburtin *et al*., 2002). Chronic debilitating conditions were strongly associated with an impaired host response (low CSF leucocyte counts), the development of intracranial and systemic complications and an adverse outcome in our study. On the other hand, the prognosis of acute bacterial meningitis has been shown to be even better for HIV-1-positive than for HIV-1-negative patients (Almirante *et al*., 1998). Asplenia is considered by some to be an adverse prognostic factor for bacterial meningitis, although it has not been studied systematically in any of the larger series on acute bacterial meningitis in adults. One reason for this belief may be that case reports with a fatal outcome may be over-represented in the literature. This is probably also the reason why Holdsworth *et al*. (1991), in their review of postsplenectomy infections (which included many single case reports), reported an excessive mortality rate of up to 75% for asplenic adults with pneumococcal meningitis. Therefore, we decided to analyse the role of asplenia in the clinical course of pneumococcal meningitis. The clinical presentation of asplenic patients was not different from that of previously healthy subjects. The long latency between splenectomy and meningitis (4–36 years) in our patients agrees well with previous findings in the literature, that the majority of severe late postsplenectomy infections did not occur within the first 2 years and 42% of infections occurred >5 years after splenectomy (Cullingford *et al*., 1991). Ear or sinus infections were an exception in our asplenic patients (9.1% of cases), whereas they were present in the majority of previously healthy subjects (69.4%). This finding suggests a different main route of infection in these two patient groups, namely contiguous spread of infection from an ear or sinus infection in previously healthy subjects and haematogenous spread to the meninges in the asplenic patients. The similar rate of positive blood cultures in asplenic and non-asplenic patients does not argue against this assumption, because bacteraemia is no proof of a haematogenous pathogenesis of meningitis as it can also be observed within a few hours after intracisternal injection of bacteria in experimental animals (Quagliarello *et al*., 1986). A predominantly haematogenous pathogenesis of pneumococcal meningitis in asplenic subjects is also in agreement with animal experimental studies, which have shown that one of the main functions of the spleen is the clearance of encapsulated bacteria, such as pneumococci, from the blood (Shinefield *et al*., 1966). Furthermore, three of the asplenic patients reported procedures that might have been a cause of transient bacteraemia (1 patient underwent surgery for an ingrown toenail 1 day before and 2 patients received intramuscular injections a few days before onset of meningitis). The clinical course of meningitis in asplenic patients was characterized by an increased incidence of meningitis-associated intracranial complications and also a tendency towards more frequent systemic complications, namely septic shock and disseminated intravascular coagulation. However, in contrast to the occasionally expressed belief that asplenia is predictive of a dismal prognosis, the asplenic patients' outcome was not at all different from that of previously healthy adults.

The present study has two major limitations: the data were collected retrospectively and outcome was determined only at discharge from the neurological ICU. Therefore, the patients did not receive a standardized treatment according to a study protocol and long-term morbidity and mortality could not be assessed. However, our analysis of underlying and associated conditions, meningitis-associated complications, outcome and prognostic factors in a relatively large sample of 87 adults with pneumococcal meningitis will hopefully help clinicians to identify patients at high risk and may also be useful in the design of clinical trials.

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