PNEUMOCOCCAL MENINGITIS IN ADULTS:
A PROSPECTIVE NATIONWIDE COHORT STUDY OVER A 20-YEAR PERIOD

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Summary: Progress has been made in the prevention and treatment of pneumococcal meningitis. The rate of morbidity and mortality is however still high, warranting continuous efforts in identifying new adjunctive treatments and pushing them forward into clinical trials.

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ABSTRACT

Background The epidemiology and treatment of pneumococcal meningitis has changed with the implementation of conjugate vaccines and the introduction of adjunctive dexamethasone therapy.

Methods We analysed episodes of community-acquired pneumococcal meningitis in adults (≥16 years) in the Netherlands, identified by the National Reference Laboratory for Bacterial Meningitis or treating physician between Oct 1, 1998 and Apr 1, 2002 and between Jan 1, 2006 and July 1, 2018. We studied incidence, pneumococcal serotypes and clinical features. Predictors for unfavourable outcome (Glasgow Outcome Scale score 1-4) were identified in a multivariable logistic regression model. Two physicians independently categorized causes of death as neurological or systemic.

Results There were 1816 episodes in 1783 patients. The incidence of 7- and 10-valent pneumococcal conjugate vaccine serotypes decreased (0.42 to 0.06, p=0.001 and 0.12 to 0.03 episodes per 100,000 population per year, p=0.014). Incidence of non-vaccine serotypes increased (0.45 to 0.68, p=0.005). The use of adjunctive treatment with dexamethasone increased and was administered in 85% of patients in 2018. In-hospital death occurred in 363 episodes (20%) and unfavourable outcome in 772 episodes (43%). Delayed cerebral thrombosis occurred in 29 patients (2%) of whom 15 patients (52%) died. Adjunctive dexamethasone therapy was associated with favourable outcome (adjusted odds ratio 2.27, p<0.001), individual pneumococcal serotypes were not.

Conclusion Implementation of conjugate vaccines and adjunctive dexamethasone therapy have changed the incidence and outcome of pneumococcal meningitis in adults over the last two decades. Despite recent advances pneumococcal meningitis remains associated with a residual high rate of mortality and morbidity.

Key words: Bacterial meningitis, Pneumococcal disease, Conjugate vaccines, Dexamethasone, Epidemiology
INTRODUCTION

A pneumococcal conjugate vaccine including seven of the most common and virulent pneumococcal serotypes causing invasive disease at that time (4, 6B, 9V, 14, 18C, 19F, 23F) was recommended for routine use in the US in 2000 [1]. This has been followed by introduction of new vaccines including nine, ten, 11, or 13 serotypes (additional serotypes 1, 3, 5, 6A, 7F, 19A) [2, 3]. Routine use of these vaccines resulted in decreased nasopharyngeal carriage in children and a decreased incidence of invasive pneumococcal disease [4]. The incidence of meningitis in the (non-vaccinated) adult population has also decreased as result of herd-protection [5, 6]. Serotype replacement by non-vaccine serotypes has been reported following the introduction of vaccines and has abolished the overall effect of vaccination on pneumococcal meningitis incidence in some regions [4].

In 2002, a randomized controlled study showed that early treatment with dexamethasone improved outcome in adults with bacterial meningitis [7]. A post hoc analysis showed that dexamethasone decreased death in this subgroup due to a beneficial effect on systemic complications [8]. A meta-analysis of individual patient data however showed that dexamethasone did not seem to reduce death or neurological disability overall [9]. A prospective cohort study including 357 episodes with pneumococcal meningitis in the period 2006-2009 showed that dexamethasone therapy has been implemented on a large scale as adjunctive treatment of adults with pneumococcal meningitis in the Netherlands [10].

Case series on adults with pneumococcal meningitis presented a limited number of patients precluding stratification of pneumococcal serotypes and age groups [11-13]. We studied clinical features, prognostic factors and pneumococcal serotypes of two nationwide prospective cohorts studies on adult pneumococcal meningitis over a 20-year period.

METHODS

Patient inclusion and data collection

We identified adult patients (≥16 years of age) with pneumococcal meningitis from two nationwide prospective cohort studies in the Netherlands, between October, 1 1998 to April, 1 2002, and between January, 1 2006 to July, 1 2018. Methods of patient identification and inclusion have been published previously [6, 14]. Patients were identified by the treating physician or the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) which receives an estimated 85-90% of clinical CSF isolates of patients in the Netherlands (17.3
million population). Extensive data on the patients’ clinical presentation and admission were collected in an online case record form.

**Inclusion and exclusion criteria**

Episodes of bacterial meningitis were included if a bacterial pathogen was cultured from the CSF, or if the CSF chemistry results were indicative of bacterial meningitis according to the Spanos criteria in combination with a positive blood culture, CSF PCR, or CSF antigen test [15]. Episodes in patients with a neurosurgical device, episodes <1 month after complicated head trauma or neurosurgery, and episodes which occurred in hospital or within 1 week after discharge were excluded. Episodes for which the clinical outcome was unknown or without information on the initial clinical presentation were also excluded.

**Procedures and definitions**

Clinical outcome at discharge was scored on the Glasgow Outcome Scale by the treating physician: 1=death, 2=vegetative state (unable to interact with environment), 3=severe disability (unable to live independently), 4=moderate disability (unable to return to work or school), and 5= mild to no disability. A score ≤ 4 was considered as unfavourable outcome. Cause of death was categorized independently by two physicians (DLHK and LtH), unaware of the use of adjunctive dexamethasone, as neurological (brain herniation, cerebral infarction and/or haemorrhage, intractable seizures, withdrawal of care due to poor neurologic prognosis, or other neurological complications) or systemic (septic shock, cardiorespiratory failure, multi-organ dysfunction syndrome, myocardial infarction, or other systemic complications), as described previously [8, 12]. Inconsistencies were resolved after discussion. The interrater agreement was assessed by calculation of the kappa coefficient. The effect of per protocol use of dexamethasone (10mg 4dd for four days, administered before or together with the first dose of antibiotics [16]) was assessed according the intention to treat principle: patients who did not complete the full course due to death, withdrawal of care, or other complications/contraindications were analysed as having received dexamethasone per protocol.

Pneumococcal isolates were serotyped by co-agglutination and capsular swelling (Quellung reaction) using specific antisera (Statens Serum Institute, Denmark). Pneumococcal isolates were screened for penicillin susceptibility by culture on blood agar plates with 1 µg oxacillin discs. Isolates with low susceptibility were assessed by E-test to determine the minimum inhibitory concentration (MIC) for penicillin (susceptible if MIC
≤0.06 mg/L, otherwise resistant) and ceftriaxone (susceptible if MIC ≤0.05 mg/L, intermediate susceptible if MIC >0.05 mg/L and ≤2.0 mg/L, and resistant if MIC >2.0 mg/L; EUCAST norm for meningitis).

Statistical analysis

The cohort was summarized using counts and proportions for categorical variables, and medians with the interquartile range (IQR) describing their 25th to 75th percentile for continuous variables. Differences were tested using chi-square and Mann Whitney U tests as appropriate. Incidences were calculated per epidemiological year (July 1st to June 30th) and compared using incidence rate ratios (epitools package). Trends were analysed using linear regression. The value of prognostic factors previously identified in bacterial meningitis or in pneumococcal meningitis was assessed in univariable and multivariable logistic regression models [6, 14, 17-19]. For the multivariable model, missing values in the selected prognostic factors (median 4.6% per prognostic factor [IQR 0.8–8.9%]) were imputed (mice package), subsequently pooling the results of each dataset (n=8) according to Rubin’s rule [20]. We performed an exploratory analysis of the association between the identified prognostic factors with death due to neurological and systemic causes. We used Kaplan-Meier estimates to assess the effect of dexamethasone on the timing of death due to any cause, and separately for neurological and systemic causes. All statistical analyses were performed using R statistical programming language (version 3.6.1).

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RESULTS

A total of 4126 episodes of bacterial meningitis were reported, 3518 by the reference laboratory and 508 by the treating physician (Figure 1). 228 episodes could not be traced, 1077 episodes were excluded from the cohort, 988 episodes were due to other pathogens, and 17 episodes had insufficient clinical information, leaving 1816 episodes of community-acquired pneumococcal meningitis for the analysis. These episodes occurred in 1783 patients: 27 patients (2%) had 2 episodes and 3 patients had 3 episodes during the study periods.

Median age at presentation was 62 years [IQR 51-70] and 902 episodes (50%) occurred in males (Table 1). Median age increased from 60 years [IQR 47-71] in 1999-2002 to 62 years [IQR 54-70] in 2015-2018 (linear
The triad of fever, neck stiffness, and altered consciousness was present in 842 of the 1661 episodes (51%). At least two of the four signs (triad plus headache) were present in 1335 episodes (96%), 3 of 4 in 1127 episodes (81%), and all four in 621 episodes (45%). Focal neurological abnormalities were present upon admission in 665 of 1804 patients (37%). Patients were comatose in 296 of 1800 episodes (16%).

The mean annual incidence was 0.87 per 100,000 population per year. The reference laboratory received and performed serotyping on isolates of 1711 episodes (94%). After introduction of PCV7 vaccination in June 2006, the incidence decreased from 1.07 to 0.73 (2007 vs. 2017-18, incidence rate ratio 0.69 [95% CI 0.56-0.85], p<0.001), with a decrease in incidence of PCV7 serotypes from 0.42 to 0.06 between 2007 and 2017 (linear regression β=−0.04, p=0.001; Figure 2). The incidence of PCV10-7 serotypes (serotypes targeted by PCV10 (introduced May 2011) but not by PCV7) decreased from 0.12 to 0.03 between 2011 and 2017 (linear regression β=−0.02, p=0.014). Concomitantly, there was an increase in the incidence of non-PCV serotypes from 0.45 to 0.68 between 2007 and 2017 (linear regression β=0.01, p=0.005). PCV13-10 serotypes remained stable (p=0.39). Of the 1697 isolates tested for penicillin susceptibility, 36 isolates (2%) were resistant to penicillin. Of the 34 isolates subsequently tested for ceftriaxone susceptibility, 31 isolates were susceptible and 3 isolates showed intermediate susceptibility.

Initial antibiotic treatment was known for 1714 patients (94%) and consisted of third generation cephalosporin’s in combination with amoxicillin in 752 patients (44%), and in combination with penicillin or ampicillin in 57 patients (3%). Dexamethasone was administered per protocol in 1188 of 1774 episodes (67%), and after the antibiotics or clinical deterioration in 144 episodes, and in a lower dose in 37 episodes. 498 of the 1216 patients (41%) who underwent neuroimaging prior to lumbar puncture received antibiotics prior to neuroimaging. The proportion of patients who underwent neuroimaging prior to lumbar puncture increased over time (192 of 279 (69%) in 1998-2002 to 283 of 315 (90%) in 2015-2018 (p<0.001), as did the proportion of these patients receiving antibiotics before neuroimaging (52 of 192 (27%) in 1998-2002 to 140 of 273 (51%) in 2015-2018 (p<0.001)).

Neuroimaging was performed on and/or during admission in 1679 of 1816 episodes (92%) and revealed abnormalities in 1094 episodes; mastoid and/or sinus opacification in 639 of 1816 episodes (35%),
hypodensities suspect for recent cerebral infarction in 279 (15%), generalized brain oedema in 202 (11%),
hydrocephalus in 105 (6%), cerebral haemorrhage (excluding microbleeds) in 24 (1%), subdural empyema in 23
(1%), venous sinus thrombosis in 22 (1%), and brain abscesses in 14 (1%), or other abnormalities in 142
patients (8%).

Cardiorespiratory failure (circulatory shock or respiratory failure) developed in 578 of 1770 (33%) patients of
whom 469 (74%) patients required mechanical ventilation. Neurological complications occurred in 1149 of
1797 patients (64%), including deterioration of consciousness in 971 of 1693 patients (57%), in-hospital
seizures in 315 of 1744 patients (18%), and focal neurological abnormalities in 364 of 1690 patients (22%).
Clinical outcome at discharge was unfavourable in 772 of 1816 episodes (43%), with in-hospital death occurring
in 363 episodes (20%), vegetative survival occurring in 6 episodes, severe disability in 95 episodes (5%), and
moderate disability in 308 episodes (17%) (Figure 3).

Deaths were attributed to neurological complications in 192 patients and due to systemic complications in 166
patients, with a kappa coefficient for interrater agreement of 0.60 in the Cohort 1, and 0.90 in Cohort 2 (cause of
death missing in 5 episodes). Among the 1044 patients with a favourable outcome (mild to no disability),
hearing loss was identified in 310 of 971 episodes (32%) (153/351 (44%) of cases with severe to moderate
disability had hearing loss), and cognitive impairment in 50 of 692 episodes (7%, only scored in 2006-2018
cohort). Among the 29 patients with delayed cerebral thrombosis, 15 patients died (52%). Two of these patients
(8%) had a favourable outcome (of whom one was restarted on steroids).

Male sex, age, presence of an immunocompromising condition, heart rate, low Glasgow Coma Scale score,
cranial nerve palsy, low CSF leukocyte count, CSF protein, low CSF:blood glucose ratio, low thrombocyte
count, C-reactive protein, and not using dexamethasone were associated with unfavourable outcome in a
multivariable model (Table 2; Table 3). The clinical outcome has improved over the past two decades but the
epidemiological year of infection was not associated with unfavourable outcome when added to this
multivariable model. The use of dexamethasone, a strong predictor for favourable outcome, increased
significantly from 11 of 336 (3%) in 1998-2002 to 1177 of 1438 (82%) between 2006-2018 (p<0.001). In 2018,
73 of 86 patients (85%) received dexamethasone.
Dexamethasone use was associated with a lower rate of cardiorespiratory failure (323 of 1156 (28%) vs. 237 of 575 (41%), p<0.001), lower rate of in-hospital seizures (174 of 1139 (15%) vs. 132 of 569 (23%), p<0.001), and a lower rate of focal neurological abnormalities (214 of 1099 (19%) vs. 142 of 558 (25%), p=0.005), leading to a lower rate of unfavourable outcome (442 of 1188 (37%) vs. 307 of 586 (52%), p<0.001). Dexamethasone was associated with lower mortality rate (178 of 1188 (15%) vs. 175 of 586 (30%), p<0.001), both due to neurological complications (9% vs. 15%, p<0.001) and due to systemic complications (6% vs. 15%, p<0.001; Figure 4). Dexamethasone did not alter the median time to death which was 6 days [IQR 2-13]. The mortality rate among patients who did not receive dexamethasone according to the protocol did not differ between patients in Cohort 1 and Cohort 2 (103 of 325 (32%) vs. 72 of 261 (28%); p=0.294). Delayed cerebral thrombosis occurred in 22 of 1188 episodes (2%) with dexamethasone treatment and in 7 of 586 episodes (1%) without dexamethasone treatment (p=0.30). Patients with delayed cerebral thrombosis more often had symptom onset within 24 hours of presentation (71% vs. 51%, p=0.03) and a low leukocyte count (<1000 cells/µL) in the diagnostic lumbar puncture (58% vs. 32%, p=0.007).

Older patients more often suffered from cardiorespiratory failure and more often died due to these systemic complications (Figure 5A). For neurological deaths, older patients more often died from cerebrovascular complications, while younger patients more often died due to brain herniation (Figure 5B-C). Time to death was 7 days [IQR 3-12] in the 75+ age group and 3 days [IQR 1-9] in the 16-39 age group (p=0.03). There was an interaction between dexamethasone and age ≥75 and their association with unfavourable outcome (interaction term p=0.03 in the multivariable model). Dexamethasone reduced deaths in all age groups (Figure 5D), but was less effective in reducing deaths due to systemic complications in patients ≥75 years of age (relative change -18% in 75+ age group (from 32% to 26%) compared to -70% in other age groups (from 12% to 3%), Figure 5E).

PCV10-7 serotypes, but not PCV7 serotypes, were associated with unfavourable outcome using non-PCV serotypes as reference group in a multivariable model corrected for age group, dexamethasone use, and multiple testing (adjusted odds ratio 1.64 [IQR 1.17-2.31], p=0.004; Figure 6A). None of the individual serotypes were associated with unfavourable outcome in this analysis (Figure 6B).
DISCUSSION

Our study shows that despite advances in vaccination and treatment pneumococcal meningitis is still a severe disease and associated with a residual high rate of mortality and morbidity. The use of pneumococcal conjugate vaccines have led to a decrease in the incidence of pneumococcal meningitis by diminishing the incidence of PCV serotypes causing meningitis. The extent of this decrease has been partly limited by serotype replacement, with a subsequent increase in meningitis caused by non-PCV serotypes. We did not find evidence that this shift towards non-vaccine serotypes has improved clinical outcome following pneumococcal meningitis. Though PCV10 serotypes were significantly associated with unfavourable outcome, the effect size of the association and proportion of cases caused by PCV10 was relatively small, limiting the overall effect. The PCV10 serotypes, 1, 5, 7F have been reported in the literature previously as invasive serotypes, but whether this is a spurious association, or related to the polysaccharide capsule itself, clustering of virulence genes, or other bacterial factors remains unknown [21, 22]. We did not identify individual serotypes to be associated with clinical outcome.

Adjunctive use of dexamethasone was associated with a decreased mortality rate from 30% to 15% and unfavourable outcome from 52% to 37%. This decline in mortality is in accordance with results of the randomized clinical trial, where 14% of patients with pneumococcal meningitis in the dexamethasone group died, compared to 34% in the placebo group [7]. The mortality rate among patients not treated with dexamethasone was similar prior to 2002 and from 2006 onwards (32% vs. 28% respectively), suggesting only a modest positive effect on mortality from improvements of ICU care, more timely clinical presentation and/or administration of antibiotics, or other factors. Of note, in our study, mortality rate was substantially higher than the 5% reported in a German tertiary referral single centre experience following dexamethasone introduction, likely due to the use of prospective surveillance by the reference laboratory [13]. Moribund patients are less likely to be transferred to a tertiary referral centre. Also, physicians are hesitant including moribund patients in clinical studies (demonstrated by the low mortality in patients identified by the treating physician), while 30% of deaths occurred within the first 3 days [23].

Our findings illustrate that age modulates the disease course and effectiveness of adjunctive treatment. For neurological cause of death, young adults mainly died of brain herniation, while older patients died due to cerebrovascular complications or withdrawal of care due to poor prognosis. We found that dexamethasone
mainly reduced the rate of systemic deaths from 15% to 6%. This is concordant with the post-hoc analysis in the randomized clinical trial [8]. Dexamethasone also lowered the rate of neurological deaths from 15 to 9%. Dexamethasone was however not as effective in reducing systemic deaths in the older population. The role of corticosteroids in patients with sepsis has been investigated in several randomized clinical trials with conflicting results and its use in clinical practice is variable. The most recent Cochrane review including 61 studies involving 12,192 patients concluded that corticosteroids probably reduce mortality in patients with sepsis and result in large reductions of ICU and in-hospital stay duration [24]. The lower mortality in critically ill COVID-19 patients treated with adjunctive corticosteroids has generated renewed interest in the use of corticosteroids in other infectious diseases [25]. Clinical trials in promising new treatments for pneumococcal meningitis such as adjuvant complement system intervention could consider post-hoc analyses for systemic and neurological complications and for different age groups [26].

Delayed cerebral thrombosis is a devastating complication that has been associated with poor outcome in 93% and death in 52% in our cohort. This complication defined as the occurrence of multiple cerebral infarctions in patients who initially recover, was not recognized until the implementation of dexamethasone [27]. Although the rate of delayed cerebral thrombosis was higher in patients treated with dexamethasone (2%) this complication also does occur in patients without adjunctive dexamethasone therapy. We hypothesize that the use of dexamethasone may suppress initial cerebral vasculopathy in many patients. However, in some patients vasculopathy may still occur after the 4-day course of adjunctive therapy, stressing the need for evaluation of prolonged or intensified immunosuppressive treatment in bacterial meningitis.

Our study has several limitations. The methods of patient identification and data collection differed to some extent between the Cohort 1 and 2. The categorization of cause of death was based on more elaborate clinical documentation in Cohort 2 resulting in improved interrater agreement compared to Cohort 1, which could have introduced heterogeneity between the time periods. Most importantly, only a small proportion of pneumococcal meningitis cases included in our cohort had negative CSF cultures (4%) as the NRLBM identifies patients with a positive CSF culture. Though not specific to pneumococcal meningitis, a recent study found that 22% of patients with a clinical diagnosis of bacterial meningitis aided by CSF chemistry results had a negative CSF culture [28, 29]. Patients in whom a lumbar puncture is postponed (e.g. anticoagulant therapy or risk of brain herniation), which increased the rate of negative CSF cultures in our cohort, or not undergo lumbar puncture at
all, are thus underrepresented in our cohort. A substantial proportion of identified patients with bacterial meningitis were not included in our cohort.

In conclusion, progress has been made in the prevention and treatment of pneumococcal meningitis over the past two decades. Pneumococcal conjugate vaccines have reduced the incidence of pneumococcal meningitis but serotype replacement highlights that new approaches to prevention are needed. The shift in the pneumococcal population has not significantly altered the clinical course of pneumococcal meningitis. The improved clinical outcome over the past two decades is mainly attributable to the implementation of adjunctive dexamethasone. The rate of morbidity and mortality is however still high, especially in elderly in whom the rate of death due to systemic complications is still high in spite of dexamethasone therapy. This warrants continuous efforts in identifying new adjunctive treatments and pushing them forward into clinical trials.
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CONFLICTS OF INTERESTS

There are no potential conflicts of interest.
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| Features                                      | 1816 patients |
|----------------------------------------------|--------------|
| **Age at presentation (years)**              | 62 [51 – 70] |
| Male                                         | 902/1816 (50) |
| **Medical history**                          |              |
| History of meningitis                        | 120/1809 (7) |
| Cerebrospinal fluid leak                     | 53/1768 (3)  |
| Immunocompromising condition                 | 462/1812 (25) |
| History of cancer                            | 192/1475 (13) |
| **Extra-meningeal focus of infection**       | 959/1811 (53) |
| Otitis or sinusitis                          | 771/1737 (44) |
| Pneumonia                                    | 213/1738 (12) |
| Endocarditis                                 | 13/1712 (1)  |
| **Symptoms <24hr**                           | 877/1722 (51) |
| Pretreatment with antibiotics                 | 194/1768 (11) |
| **Clinical presentation**                    |              |
| Headache                                     | 1242/1535 (81) |
| Nausea                                       | 862/1444 (60) |
| Seizures before or on admission              | 150/1704 (9)  |
| Fever before or on admission (≥38 °C)        | 1508/1743 (87) |
| Heart rate (bpm)                             | 100 [85 – 115] |
| Systolic blood pressure (mmHg)               | 147 [130 – 167] |
| Rash                                         | 50/1639 (3)  |
| Score on Glasgow Coma Scale                  | 10 [8 – 13]  |
| <14 (indicating altered consciousness)       | 1446/1800 (80) |
| <8 (indicating coma)                         | 296/1800 (16) |
| Neck stiffness                                | 1279/1680 (76) |
| Aphasia                                      | 299/929 (32)  |
| Ataxia                                       | 32/808 (4)    |
| Cranial nerve palsy                          | 168/1567 (11) |
| Paresis                                      | 184/1568 (12) |
| Babinski sign                                | 290/1553 (19) |
| **Blood and CSF findings**                   |              |
| C-reactive protein (mg/dL)                    | 20 [9.2 – 31.7] |
| Thrombocyte count (units per µL)             | 199,000 [151,000 – 255,750] |
| Positive blood culture                       | 1288/1590 (81) |
| CSF opening pressure (cm H_2O)               | 44 [31-50]    |
| ≥50 cm H_2O                                  | 284/674 (42)  |
| CSF white cell count (cells per µL)          | 2.570 [561 – 7.063] |
| < 1,000 cells per µL                         | 561/1709 (33) |
| CSF protein concentration (g/dL)             | 0.43 [0.25 – 0.65] |
| CSF:blood glucose ratio                      | 0.03 [0.01 – 0.22] |
| Spanos criteria a                            | 1626/1756 (93) |
| Positive CSF culture                         | 1739/1816 (96) |
| **Neuroimaging on admission**                |              |
| Mastoid or sinus opacification               | 1615/1816 (89) |
| Generalized brain oedema                     | 554/1615 (34)  |
| Recent brain infarction                      | 151/1615 (9)   |
| Hydrocephalus                                | 84/1615 (5)    |
| **Table 1. Clinical presentation and ancillary investigations on admission** |

Data are median [IQR] or n/N (%). CSF=cerebrospinal fluid. Heart rate was obtained in 1727 episodes, systolic blood pressure in 1750 episodes, CSF protein in 1688 episodes, CSF:blood glucose ratio in 1631 episodes, C-reactive protein in 1606 episodes, and thrombocyte count in 1718 episodes. a 1549 of 1679 episodes with positive CSF culture (92%) met the Spanos criteria (at least one of the following: CSF glucose concentration < 34.23 mg/dL (or 1.9 mmol/L; to convert glucose to mmol/L, multiply values by 0.0555), CSF:blood glucose ratio < 0.23, CSF protein concentration > 0.22 g/dL, CSF white cell count > 2,000 cells per µL, or > 1,180 CSF polymorphonuclear leukocytes per µL).
| Prognostic factors | Favorable (n=1044) | Unfavorable (n=772) | Univariable OR | Multivariable aOR | p-value |
|--------------------|--------------------|---------------------|----------------|-------------------|---------|
| Age (years)        |                    |                     |                |                   |         |
| 16-39              | 141/1044 (14)      | 61/772 (8)          | 0.77 [0.55 – 1.09] | 0.88 [0.59 - 1.32] | 0.55    |
| 40-59              | 372/1044 (36)      | 208/772 (27)        | (reference)    | (reference)       |         |
| 60-74              | 458/1044 (44)      | 316/772 (41)        | 1.23 [0.99 – 1.54] | 1.06 [0.81 - 1.38] | 0.67    |
| 75+                | 73/1044 (7)        | 187/772 (24)        | 4.58 [3.33 – 6.30] | 4.03 [2.75 - 5.89] | <0.001  |
| Male               | 502/1044 (48)      | 400/772 (52)        | 1.16 [0.96 – 1.40] | 1.51 [1.20 - 1.90] | <0.001  |
| Immunocompromised  | 223/1041 (21)      | 239/771 (31)        | 1.65 [1.33 – 2.04] | 1.50 [1.13 - 1.99] | 0.005   |
| Alcoholism         | 37/1036 (4)        | 63/776 (8)          | 2.42 [1.59 – 3.67] | 1.42 [0.83 - 2.45] | 0.20    |
| Otitis or sinusitis| 512/1017 (50)      | 259/720 (36)        | 0.55 [0.46 – 0.67] | 0.87 [0.68 - 1.10] | 0.24    |
| Pneumonia          | 86/1017 (8)        | 127/721 (18)        | 2.31 [1.73 – 3.10] | 1.29 [0.91 - 1.82] | 0.15    |
| Heart rate (bpm)   | 100 [84-111]       | 103 [88-120]        | 1.14 [1.09 – 1.19] | 1.08 [1.02 - 1.13] | 0.005   |
| Systolic BP (mmHg) | 146 [130-165]      | 150 [130-170]       | 1.01 [0.98 – 1.05] | 0.99 [0.95 - 1.03] | 0.66    |
| Rash               | 29/951 (3)         | 21/688 (3)          | 1.00 [0.57 – 1.77] | 1.07 [0.54 - 2.12] | 0.85    |
| Glasgow Coma Scale score | 11 [9-13] | 10 [8-12] | 0.86 [0.83 – 0.89] | 0.89 [0.86 - 0.93] | <0.001  |
| Cranial nerve palsy| 49/927 (5)         | 88/640 (14)         | 2.86 [1.98 – 4.12] | 2.39 [1.56 - 3.68] | <0.001  |
| Seizures (baseline)| 74/1012 (7)        | 76/692 (11)         | 1.56 [1.12 – 2.19] | 1.27 [0.83 - 1.94] | 0.27    |
| CSF white cells<100 cells / uL | 65/989 (7) | 125/720 (17) | 3.60 [2.59 – 5.02] | 2.09 [1.38 - 3.15] | <0.001  |
| 100-999 cells / uL | 549/989 (56)       | 197/720 (27)        | 2.09 [1.63 – 2.67] | 1.75 [1.27 - 2.41] | <0.001  |
| 1,000-10,000 cells/ uL >10,000 cells / uL | 177/989 (36) | 293/720 (41) | (reference) | (reference) |         |
| CSF protein (g/dL) | 0.37 [0.22-0.59]   | 0.51 [0.33-0.75]    | 1.11 [1.08 – 1.14] | 1.05 [1.01 - 1.08] | 0.007   |
| CSF:blood glucose ratio < 0.02 | 346/959 (36) | 363/672 (54) | 3.70 [2.80 – 4.90] | 2.49 [1.76 - 3.52] | <0.001  |
| 0.02-0.23 | 306/959 (32)       | 222/672 (33)        | 2.56 [1.91 – 3.44] | 1.83 [1.26 - 2.65] | 0.002   |
| > 0.23 | 307/959 (32)       | 87/672 (13)         | (reference) | (reference) |         |
| Positive blood culture | 744/924 (81) | 544/666 (82) | 1.08 [0.84 – 1.39] | 0.87 [0.64 - 1.18] | 0.37    |
| C-reactive protein (mg/dL)<a> | 15.6 [7.2-26.0] | 26.1 [14.3-37.0] | 1.05 [1.04 – 1.05] | 1.03 [1.02 - 1.04] | <0.001  |
| Thrombocyte count | 188/772 (24)       | 187/772 (24)        | 4.58 [3.33 – 6.30] | 4.03 [2.75 - 5.89] | <0.001  |
|                | n/N (%) | Median [IQR] | aOR [95% CI] | P-value |
|----------------|---------|--------------|--------------|---------|
| <75,000        | 19/993 (2) | 49/725 (7)   | 4.20 [2.44 – 7.22] | 0.01    |
| 75,000-149,000 | 163/993 (16) | 178/725 (25) | 1.78 [1.40 – 2.26] | 0.29    |
| ≥150,000       | 811/993 (82) | 498/725 (69) | (reference) | -       |
| Dexamethasone  | 746/1044 (73) | 442/772 (59) | 0.54 [0.44 – 0.66] | <0.001  |

Table 2 – Baseline variables associated with unfavourable outcome.

The study included 1816 episodes of community-acquired pneumococcal meningitis in 1783 patients; data are median [IQR] or n/N (%), and results of the univariable and multivariable model are represented as the (adjusted) odds ratios (aOR) [95% confidence interval] for unfavourable outcome. P-values are specified for the multivariable model. The multivariable analysis used an imputed dataset with 8 imputation rounds, all variables in the table were entered in the multivariable logistic regression model simultaneously. Abbreviations: BP=blood pressure; CSF=cerebrospinal fluid. Odds ratios are calculated per increment of 10 bpm heart rate, 10 mmHg systolic blood pressure, 0.1g/dL CSF protein, and 1 mg/dL C-reactive protein. Heart rate was obtained in 1727 episodes, systolic blood pressure in 1750 episodes, Glasgow Coma Scale score in 1800 episodes, CSF protein in 1688 episodes, and C-reactive protein in 1606 episodes. *There was a negative correlation between CSF cell count and blood C-reactive protein, in particular in the subgroup of patients with CSF cell counts <1,000 cells per µL: for every additional mg/dL of C-reactive protein, there were 100 fewer white cells in the CSF (linear regression, p<0.001).
| Features                        | Systemic death (n=166) | p-value | Neurological death (n=192) | p-value |
|--------------------------------|------------------------|---------|----------------------------|---------|
| Age                            | 16-39                  | 0.97 [0.37 - 2.55] | 0.94 | 1.66 [0.94 - 2.95] | 0.08 |
|                                | 40-59                  | (reference) | - | (reference) | - |
|                                | 60-74                  | 2.49 [1.46 - 4.24] | <0.001 | 0.93 [0.62 - 1.39] | 0.73 |
|                                | 75+                    | 10.30 [5.79 - 18.34] | <0.001 | 1.28 [0.78 - 2.09] | 0.33 |
| Male                           |                        | 1.84 [1.25 - 2.70] | 0.002 | 1.45 [1.04 - 2.03] | 0.03 |
| Immunocompromising condition   |                        | 1.28 [0.86 - 1.89] | 0.22 | 1.45 [1.01 - 2.08] | 0.04 |
| Heart rate                     |                        | 1.14 [1.05 - 1.24] | 0.001 | 1.01 [0.94 - 1.08] | 0.81 |
| Glasgow Coma Scale score       |                        | 0.96 [0.90 - 1.02] | 0.21 | 0.84 [0.80 - 0.89] | <0.001 |
| Cranial nerve palsy            |                        | 0.92 [0.49 - 1.73] | 0.80 | 1.69 [0.99 - 2.88] | 0.05 |
| CSF white cell count           |                        |                 |     |                 |     |
| <100 cells                     |                        | 1.57 [0.91 - 2.71] | 0.10 | 2.38 [1.41 - 4.02] | 0.001 |
| 100-999 cells                  |                        | 1.23 [0.76 - 2.01] | 0.40 | 1.73 [1.08 - 2.79] | 0.02 |
| 1,000-10,000                   | (reference)            | -        | (reference) | -        |
| >10,000                        |                        | 0.96 [0.53 - 1.73] | 0.89 | 0.76 [0.45 - 1.28] | 0.30 |
| CSF protein (g/dL)             |                        | 1.01 [0.97 - 1.06] | 0.54 | 1.07 [1.03 - 1.11] | <0.001 |
| CSF:blood glucose ratio        |                        |                 |     |                 |     |
| <0.02                          |                        | 1.87 [0.94 - 3.71] | 0.08 | 2.87 [1.52 - 5.42] | 0.01 |
| 0.02-0.23                      |                        | 2.02 [1.02 - 4.01] | 0.04 | 1.73 [0.86 - 3.50] | 0.13 |
| >0.23                          | (reference)            | -        | (reference) | -        |
| C-reactive protein (mg/dL)     |                        | 1.03 [1.02 - 1.05] | <0.001 | 1.02 [1.01 - 1.04] | 0.002 |
| Thrombocytes                   |                        |                 |     |                 |     |
| <75                            |                        | 5.88 [3.11 - 11.12] | <0.001 | 1.14 [0.57 - 2.30] | 0.71 |
| 75-149                         |                        | 1.10 [0.70 - 1.72] | 0.69 | 1.02 [0.69 - 1.52] | 0.91 |
| 150+                           | (reference)            | -        | (reference) | -        |
| Dexamethasone                  |                        | 0.43 [0.30 - 0.63] | <0.001 | 0.59 [0.42 - 0.83] | 0.003 |

Table 3 – Prognostic multivariable model for systemic and neurological cause of death

The study included 1816 episodes of community-acquired pneumococcal meningitis in 1783 patients; data are median [IQR] or n/N (%), and results of the multivariable model are represented as the adjusted odds ratios [95% confidence interval] for systemic and neurological deaths. The multivariable analysis used an imputed dataset with 8 imputation rounds, all variables in the table were entered in the multivariable logistic regression model simultaneously. Odds ratios are calculated per increment of 10 bpm heart rate, 0.1 g/dL CSF protein, and 1 mg/dL C-reactive protein.
FIGURE LEGENDS

Figure 1. Selection of patients. Patients were identified through surveillance of the Netherlands Reference Laboratory for Bacterial Meningitis (n=3518) or by the treating physician (n=508). *Streptococcus pneumoniae* was identified by CSF culture in 1739 episodes, and in the remaining 77 episodes by both blood culture and CSF PCR (n=7), blood culture and CSF antigen (n=7), or only by blood culture (n=42), CSF PCR (n=15), or CSF antigen (n=6). Of the 1480 analysed episodes of community-acquired pneumococcal meningitis in Cohort 2, 1314 episodes were identified by the reference laboratory (mortality rate 18%) and 166 episodes by the treating physician (mortality rate 10%).

Figure 2. Pneumococcal serotype of episodes included in the Netherlands, 1998-2018. Serotype distribution according to pneumococcal conjugate vaccine (PCV) group of included episodes of pneumococcal meningitis in adults per epidemiological year (July-June, represented as year on January 1st). Included episodes were due to serotype (number of episodes): 3§ (187), 8 (158), 7F¶ (148), 22F (108), 19A§ (78), 19F† (75), 10A (68), 12F (67), 23B (62), 23F† (60), 14† (56), 4† (47), 9V† (46), 9N (45), 6B† (39), 11A (37), 18C† (36), 23A (35), 33F (32), 1¶ (31), 6A$ (30), 24F (26), 16F (25), 6C (23), 15B (22), 35F (20), 15A (17), 17F (16), 38 (14), 31 (11), 15C (10), 18B (8), 34 (7), 20 (6), 35B (6), 22A (5), 37 (4), 5¶ (4), 10B (2), 27 (2), 13 (1), 21 (1), 24B (1), 25A (1), 28F (1), 7A (1), 7B (1). Serotyping was not performed or subtyping incomplete in 136 episodes. †PCV7, ¶PCV10-7, §PCV13-10.

Figure 3. Change in clinical outcome over a 20-year period. Histogram showing the clinical outcome as scored on the Glasgow Outcome Scale in 1998-2002, 2006-2011, and 2012-2018. Score 5 indicates mild to no deficits (left), score 1 indicates death (right). Adjunctive dexamethasone was administered between 1992-2002 in 1/104 patients (1%), 0/2 patients (0%), 0/17 patients (0%), 1/48 patients (2%), and 9/165 patients (5%) from GOS 1 to 5 respectively, between 2006-2011 in 77/108 patients (71%), 1/1 patients (100%), 22/29 patients (76%), 87/104 patients (84%), and 305/352 patients (87%) from GOS 1 to 5 respectively, and between 2012-2018 in 100/141 patients (71%), 2/3 patients (67%), 33/44 patients (75%), 118/148 patients (80%), and 432/508 (85%) from GOS 1 to 5 respectively.
Figure 4. Effect of dexamethasone on survival in pneumococcal meningitis. Kaplan Meier estimates stratified for the use of dexamethasone for overall mortality (A), and death due to systemic (B) and neurological complications (C). P-values of the respective log-rank tests were all < 0.0001. Patients discharged within 14 days of admission were not censored but considered to survive. Cause of death was assigned by two independent reviewers. Death due to systemic complications: cardiorespiratory failure (n=72), septic shock (n=42), multi-organ dysfunction (n=21), or myocardial infarction (n=6), or other (n=25); Death due to neurologic complications: brain herniation (n=78), brain infarction and/or haemorrhage (n=56), withdrawal of care due to poor neurological prognosis (n=44), intractable seizures (n=7), or other (n=7).

Figure 5. Age-related differences in pneumococcal meningitis. Rate of cardiorespiratory complications and death due to systemic complications (A), generalized brain oedema and death due to brain herniation (B), and rate of cerebral infarction and/or haemorrhage and resulting death (C) per age group. The effect of dexamethasone use on overall mortality (E), and death due to systemic (E) and neurological complications (F) per age group.

Figure 6. Effect of pneumococcal serotype on unfavourable outcome. Regression coefficients and confidence intervals of a multivariable regression analysis of PCV group (using non-PCV serotypes as reference group) and use of dexamethasone, corrected for age, on unfavourable outcome (D), and the regression coefficients and confidence intervals of a multivariable regression analysis of the 20 most common pneumococcal serotypes (using serotype 3§ as reference group), corrected for dexamethasone use and age, on unfavourable outcome (E). Red dots and confidence intervals represent categories associated with an unfavourable outcome (Glasgow Outcome Scale score ≤4), blue represents categories associated with favourable outcome (Glasgow Outcome Scale score = 5). Dexamethasone was significantly associated with favourable outcome in both models (p <0.001) and remained significant when corrected for multiple testing. * indicates significant results (* = p < 0.05, ** = p < 0.01, *** = p<0.001). • PCV7, † PCV10-7, § PCV13-10.

Abbreviations: PCV = pneumococcal conjugate vaccine.
Figure 1

Cohort 1
Oct 1998 - Apr 2002
1105 episodes notified

1024 episodes retrieved

681 episodes included

1816 episodes of community-acquired pneumococcal meningitis analyzed

Cohort 2
Jan 2006 - Jul 2018
3021 episodes notified

2874 episodes retrieved

228 episodes not retrieved
- hospital without local ethics committee approval (n=114)
- patient untraceable (n=114)

1077 episodes excluded
- physician declined (n=85)
- no informed consent or no case record form returned (n=352)
- patient died prior to consent (n=11)
- nosocomial meningitis (n=344)
- CSF contamination (n=43)
- no pathogen identified (n=213)
- no lumbar puncture performed (n=7)
- no CSF Spans criteria and negative CSF culture (n=22)

2140 episodes included

1005 episodes not analyzed
- episode due to other pathogen:
  Neisseria meningitidis (n=498)
  Listeria monocytogenes (n=154)
  Haemophilus influenzae (n=97)
  other (n=249)
- episodes with insufficient clinical information (n=17)
Figure 4

A Death due to any cause

No dexamethasone
Dexamethasone

No. at risk
Dexamethasone
Death: 1188, 1142, 1124, 1107, 1085, 1072, 1058, 1040
Neurologic: 15, 55, 73, 85, 108, 121, 135, 142
Systemic: 7, 19, 24, 32, 43, 47, 56, 62

No dexamethasone
Death: 583, 541, 522, 492, 479, 469, 462, 457
Neurologic: 8, 28, 40, 50, 55, 59, 64, 69
Systemic: 6, 24, 38, 48, 53, 58, 61, 63

B Death due to neurologic cause

No dexamethasone
Dexamethasone

C Death due to systemic cause

No dexamethasone
Dexamethasone
Complications and resulting deaths per age group

A Systemic complications       B Generalized brain edema       C Cerebrovascular complications

Effect of dexamethasone use on deaths per age group

D Death       E Systemic death       F Neurologic death
