Bacterial meningitis in adults: clinical characteristics, risk factors and adjunctive treatment

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Chapter 7

Nationwide evaluation of implementation and effectiveness of adjunctive dexamethasone in adult pneumococcal meningitis

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Abstract

In this nationwide prospective cohort study we evaluated the implementation and effectiveness of adjunctive dexamethasone therapy in Dutch adults with pneumococcal meningitis. From March 2006 through January 2009, all Dutch patients over 16 years old with community-acquired pneumococcal meningitis were prospectively evaluated. Outcome was classified as unfavorable (defined by a Glasgow Outcome Scale score of 1 to 4 points at discharge) or favorable (a score of 5). Clinical characteristics and outcome were compared with a similar nation-wide cohort of 352 patients with pneumococcal meningitis from a previous period before guidelines recommended dexamethasone therapy (1998-2002). A multivariable prognostic model was used to adjust for differences in case-mix between the two cohorts. We evaluated 357 episodes with pneumococcal meningitis in 2006-2009. Characteristics on admission were comparable with the earlier cohort (1998-2002). Dexamethasone was started with or before the first dose of antibiotics in 84% of episodes in 2006-2009 and 3% in 1998-2002. At discharge, unfavorable outcome was present in 39% in 2006-2009 and 50% in 1998-2002 (odds ratio, 0.63; 95% confidence interval, 0.46 to 0.86; p=0.002). Rates of death (20% vs. 30%; p=0.001) and hearing loss (12% vs. 22%; p=0.001) were lower in 2006-2009. Differences in outcome remained after adjusting for differences in case-mix between cohorts. In conclusion, dexamethasone therapy has been implemented on a large scale as adjunctive treatment of adults with pneumococcal meningitis in the Netherlands. The prognosis of pneumococcal meningitis on a national level has substantially improved after the introduction of adjunctive dexamethasone therapy suggesting a causal effect.

Background

Bacterial meningitis is associated with high mortality and morbidity rates.[1] In 2004, we published a nationwide prospective cohort study in adults with bacterial meningitis from 1998 through 2002.[2] In this study, 696 adults with community-acquired bacterial meningitis confirmed by cerebrospinal fluid culture were included and most common pathogens were *Streptococcus pneumoniae* (51%) and *Neisseria meningitidis* (37%). The mortality rate was 21% and half of surviving patients had neurologic sequelae.[2, 3] The mortality rate was higher among patients with pneumococcal meningitis than among those with meningococcal meningitis (30% vs. 7%, p<0.001). The study was performed before routine dexamethasone therapy was introduced.[2]

Experimental models have shown that outcome in bacterial meningitis is related to the severity of inflammation in the subarachnoid space, and treatment with corticosteroids resulted in a reduction of the inflammatory response and improved outcome.[4, 5] In 2002, a European multicenter randomized clinical trial showed a beneficial effect of adjunctive dexamethasone therapy in adults with bacterial meningitis.[6] In this clinical trial, treatment with dexamethasone was associated with a reduction in the risk of an unfavorable outcome (relative risk, 0.59; 95% confidence interval, 0.37 to 0.94; p=0.03). The effect was most apparent in the pneumococcal subgroup. Among the patients with pneumococcal meningitis, outcome was unfavorable in 26% of the dexamethasone group, as compared with 52% of the placebo group (relative risk, 0.50; 95% confidence interval, 0.30 to 0.83; p=0.006). Guidelines recommend routine use of adjunctive dexamethasone in adults with pneumococcal meningitis in high-income countries.[1, 7, 8] However, three large randomized clinical trials on this topic published in 2007 showed conflicting results.[9-11] In 2008 a multicenter observational study of children with bacterial meningitis showed no association between adjuvant corticosteroid therapy and death or time to hospital discharge.[12] The use of dexamethasone in pneumococcal meningitis therefore remains controversial.

In this nationwide prospective cohort study we assessed the implementation of adjunctive dexamethasone therapy in adults with pneumococcal meningitis and its impact on outcome in the Netherlands.

Methods

Study Patients

We identified adults (defined as patients older than 16 years of age) who had pneumococcal meningitis and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis from March 2006 to January 2009. This laboratory receives cerebrospinal fluid isolates from approximately 85% of all patients with bacterial meningitis in the Netherlands (population, 16.2 million).[13] Daily updates were provided of hospitals where patients with bacterial meningitis have been admitted in the preceding

two to six days. Physicians were informed about the study by telephone. Physicians could also contact investigators 24/7 to include patients, without preceding report of the reference laboratory. Patients or their legal representatives received written information concerning the study and were asked to give written informed consent for participation. The study was approved by all Dutch local ethics committees. Online case-record forms were used to collect data. Patients with negative cerebrospinal fluid cultures or hospital-associated meningitis were excluded. Patients with an altered immune status owing to the use of immunosuppressive drugs or splenectomy, diabetes mellitus, or alcoholism were considered immunocompromised, as were patients infected with human immunodeficiency virus.

Outcomes

Outcome was graded according to the Glasgow Outcome Scale. A score of 1 on this scale indicates death; a score of 2, a vegetative state (the patient is unable to interact with the environment); a score of 3, severe disability (the patient is unable to live independently but can follow commands); a score of 4, moderate disability (the patient is capable of living independently but unable to return to work or school); and a score of 5, mild or no disability (the patient is able to return to work or school). A favorable outcome was defined as a score of 5, and an unfavorable outcome as a score of 1 to 4. The Glasgow Outcome Scale is a well-validated instrument with good interobserver agreement.[14] At discharge, all surviving patients underwent a neurologic examination performed by a neurologist which included the assessment of the Glasgow Outcome Scale.

Cohort 1998-2002

We compared our results with those from a study with similar design that included 352 patients with pneumococcal meningitis from 1998 through 2002, before guidelines recommended routine dexamethasone therapy.[2, 3]

Statistical Analysis

The Mann-Whitney U test (continuous variables) and χ^2 test (categorical variables) were used to identify differences in demographic and clinical characteristics between the two cohorts. In the earlier cohort we developed a prediction model with 18 potentially relevant prognostic factors for unfavorable outcome. We used logistic regression analysis to calculate odds ratios and 95% confidence intervals to assess the strength of the association between potential prognostic factors and the probability of an unfavorable outcome. Missing values were imputed by use of multivariate normal distributions and coefficients of ten rounds of imputation were combined to obtain the final estimates from the multivariate logistic regression model. The coefficients of the multivariable prediction model were applied to obtain a risk score for each patient in the recent cohort. This risk score incorporates all available data on risk factors given an individual profile on clinical and demographic characteristics. We used these risk scores to calculate the expected number of events (if dexamethasone would not have been introduced) and compared

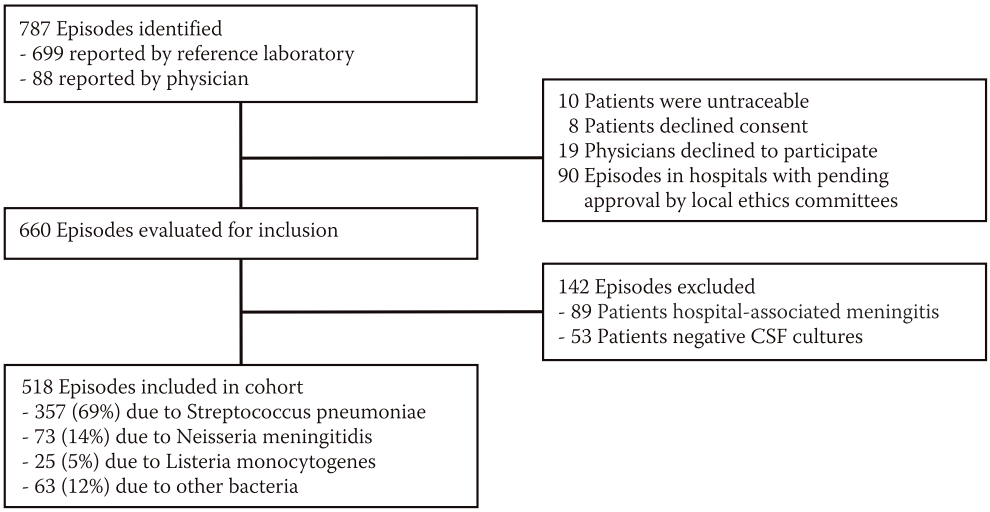
these with the actually observed number patients with unfavorable outcome in the recent cohort. Expected versus observed numbers were calculated for the recent cohort as a whole, across tertiles of predicted risk (i.e., severity of disease), and for various clinical subgroups. All statistical tests were two-tailed, and a p value less than 0.05 was regarded as significant. Analyses were undertaken with SAS software version 9.1.

Results

Study Patients

A total of 787 episodes of bacterial meningitis were identified from March 2006 through January 2009 (Figure 1). The cohort consisted of 518 episodes of community-acquired bacterial meningitis, including 357 episodes of pneumococcal meningitis in 354 patients.

Figure 1. Selection of patients.



Patient Characteristics

Classic symptoms and signs of meningitis were present in a large proportion of the patients (headache in 85%, fever in 81%, and neck stiffness in 76%; Table 1). The classic triad of neck stiffness, fever, and altered mental status (defined as a score on the Glasgow Coma Scale <14) was present in 54% and coma in 18%. At least one individual cerebrospinal fluid finding predictive of bacterial meningitis (a glucose level of less than 34 mg per deciliter [1.9 mmol per liter], a ratio of cerebrospinal fluid glucose to blood glucose of less than 0.23, a protein level of more than 220 mg per deciliter, or a white-cell count of more than 2000 per cubic millimeter)[15] was present in 328 of 348 episodes (94%). At admission, clinical

characteristics and results of laboratory tests between cohorts were similar, although more episodes had positive blood cultures (85 vs. 74%; p=0.002) and less episodes cranial nerve palsies (12 vs. 7%; p=0.02) in 2006-2009.

Cranial computed tomography (CT) was performed on admission in 320 episodes (90%); results were normal in 52%. Abnormalities found were: mastoid or sinus opacification in 37%, generalized brain edema in 18%, recent brain infarction in 7%, and other abnormalities

Table 1. Characteristics of Dutch adults with pneumococcal meningitis in two nationwide cohort studies.[a]

Characteristic	2006-2009 357 Episodes	1998-2002 352 Episodes	Absolute difference (%)
Age - year (means ±SD)	59±15	58±17	
Male sex	167/357 (47%)	171/352 (49%)	-2%
Duration of symptoms longer than 24 hours	177/343 (52%)	162/362 (50%)	2%
Pretreated with antibiotics	40/344 (11%)	44/349 (13%)	-2%
Predisposing conditions			
Otitis or sinusitis	145/357 (41%)	153/352 (43%)	-2%
Pneumonia	56/349 (16%)	62/352 (18%)	-2%
Immunocompromise[b]	83/357 (23%)	76/351 (22%)	1%
HIV positive[c]	2/357 (0.6%)	4/352 (1.1%)	-0.5%
Symptoms on presentation			
Headache	259/305 (85%)	256/305 (84%)	1%
Neck stiffness	260/340 (76%)	280/344 (81%)	-5%
Heart rate ≥120 beats per minute	70/353 (20%)	84/331 (25%)	-5%
Body temperature >38°C	285/354 (81%)	291/345 (84%)	-3%
Diastolic blood pressure <60 mm Hg	33/354 (9%)	18/342 (5%)	4%
Score on Glasgow Coma Scale[d]			
Mean	10±3	10±3	
<14 (indicating altered mental status)	289/357 (81%)	298/351 (85%)	-4%
<8 (indicating coma)	65/357 (18%)	68/351 (19%)	-1%
Triad of fever, neck stiffness, and change in mental status	188/347 (54%)	206/352 (59%)	-5%
Focal neurologic deficits			
Aphasia	63/186 (34%)	79/234 (34%)	0%
Hemiparesis	39/310 (13%)	39/344 (11%)	2%
Cranial nerve palsy (excluding hearing loss)	24/346 (7%)	43/352 (12%)	-5%[e]
Hearing loss	6/346 (2%)	23/243 (9%)	-7%[e]
CSF findings			
Opening pressure - cm H_2O[f]	42 (30-50)	40 (25-50)	
White-cell count[g]	2490 (512-7733)	2530 (531-6983)	
<100 cells/mm^3	37 (11%)	32/320 (10%)	1%
100-999 cells/mm^3	75/343 (22%)	72/320 (23%)	-1%
1000-10 000 cells/mm^3	165/343 (48%)	167/320 (52%)	-4%
>10 000 cells/mm^3	66/343 (19%)	49/320 (15%)	4%
Protein — g/litre[h]	4.1 (2.5-6.1)	4.7 (2.7-7.0)	
CSF: blood glucose ratio[i]	0.02 (0.00-0.16)	0.06 (0.01-0.20)	
Positive gram stain	330/342 (96%)	304/327 (93%)	+3%[e]
Blood findings			
Positive blood culture	261/308 (85%)	230/309 (74%)	+11%[e]
ESR — mm/hr[j]	47 (27-74)	43 (22-74)	
C-reactive protein - mg/litre[k]	215 (104-335)	211 (104-333)	
Thrombocyte count - platelets/mm^3[l]	200 (151-262)	199 (157-250)	

in 16%. Imaging preceded lumbar puncture in 251 episodes (78%). The proportions of patients with a delay in therapy due to cranial CT between cohorts were similar (155 of 357 [43%] vs. 149 of 352 [42%]; p=0.83).

Antimicrobial treatment

Antimicrobial treatment consisted of penicillin or amoxicillin in 33% of episodes, third-generation cephalosporins in 28%, and a combination of penicillin or amoxicillin and third-generation cephalosporins in 34% of episodes; another regimen was used in 5%. Antibiotic treatment was in compliance with Dutch guidelines in 33% of episodes. Guidelines for antibiotic use for meningitis in the Netherlands have not been changed from 1998 to 2009. Adherence to antibiotic guideline between cohorts was similar.[16]

Antibiotic susceptibility testing was performed in 327 episodes; 2 strains showed intermediate susceptibility to penicillin (MIC 1.0 mg/l and 0.125 mg/L). The most common serotypes were type 3 and 14 (each 10%; Table 1 in the supplementary appendix); type 19F, 7F, and 9V (each 8%); type 6B and 10A (each 6%). The proportions of disease caused by the 7-valent pneumococcal conjugate vaccine (PCV7) serotypes between cohorts were similar (42% in 2006-2008 vs. 38% in 1998-2002; p=0.28).

Adjunctive dexamethasone

Adjunctive dexamethasone was administered in 92% of episodes (Table 2). Dexamethasone, 10 mg intravenously, given every six hours for four days was started before or with the first dose of parenteral antibiotics in 276 of 357 episodes (77%). Dexamethasone was given after the first dose of antibiotics in 28 episodes (8%); in 3 episodes this was prompted by clinical deterioration. There were no differences between patients treated with or without early dexamethasone with respect to antibiotic pretreatment (14 vs. 11%; p=0.79), immunocompromised state (22 vs. 29%; P=0.31), diastolic blood pressure (median, 80 vs. 80 mmHg; p=0.61), or heart rate (median, 100 vs. 100 beats per minute; p=0.77). Adjunctive dexamethasone was administered in 59 episodes (17%) in 1998-2002. Eleven of these patients were included in the European dexamethasone in adulthood bacterial meningitis study and received dexamethasone 10 mg intravenously, given every six hours

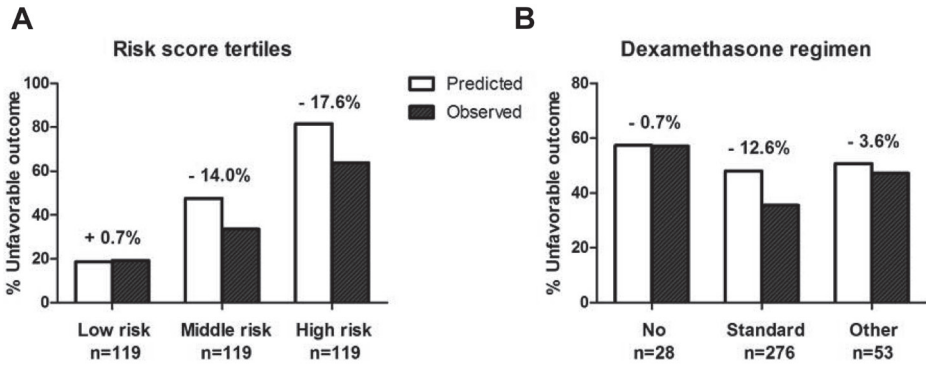
[a]Data are number/number assessed (percent) or median (25th-75th percentile), unless otherwise stated. CSF denotes cerebrospinal fluid. The first cohort study included 343 patients who had a total of 352 episodes of community-acquired meningitis; the second cohort study included 354 patients with 357 episodes. [b] Immunocompromise was defined by the use of immunosuppressive drugs, a history of splenectomy, or the presence of diabetes mellitus or alcoholism, as well as patients infected with the human immunodeficiency virus (HIV). [c] The number of patients tested for HIV infection is unknown. [d] Scores on the Glasgow Coma Scale can range from 3 to 15, with 15 indicating a normal level of consciousness. Glasgow Coma Scale scores were evaluated in 351 patients in 1998-2002 and 357 patients in 2006-2009. [e] p-value for difference between groups <0.05. [f] CSF pressure was measured in 114 patients in 1998-2002 and in 117 patients in 2006-2009. [g] CSF leukocyte count was determined in 320 patients in 1998-2002 and in 343 patients in 2006-2009. [h] CSF protein levels were determined in 316 patients in 1998-2002 and in 342 patients in 2006-2009. [i] Both CSF and blood glucose values were determined in 309 patients in 1998-2002 and in 341 patients in 2006-2009. [j] Erythrocyte sedimentation rate (ESR) was determined in 281 patients in 1998-2002 and in 203 patients in 2006-2009. [k] C-reactive protein levels were determined in 187 patients in 1998-2002 and in 331 in cohort 2006-2009. [l] Thrombocyte count was determined in 326 patients in 1998-2002 and in 344 patients in cohort 2006-2009.

Table 2. Characteristics of intravenous dexamethasone treatment.[a]

Characteristic	2006-2009 357 Episodes	1998-2002 352 Episodes	Absolute difference (%)
Dexamethasone received	329 (92%)	59 (17%)	+75%[b]
Dexamethasone 10 mg every 6 hours for 4 days, started before or with first dose of antibiotics	276 (77%)	11 (3%)	+74%[b]
Dexamethasone started before or with first dose of antibiotics, all dosages and durations	301 (84%)	11 (3%)	+81%[b]
Dexamethasone 10 mg every six hours for 4 days, started at any time	299 (84%)	11 (3%)	+81%[b]

[a] Data are number of episodes (percentage). [b] p-value for differences between cohorts <0.001

Figure 2. Observed and predicted rates of unfavourable outcome in 2006-2009.



Footnote: Panel A shows predicted and observed rates of unfavorable outcome for groups with low, middle, and high risk for unfavorable outcome (groups based on tertiles). Panel B shows predicted and observed rates of unfavorable outcome for patients not treated with dexamethasone, those who received the recommended standard dexamethasone regimen (10 mg intravenously, given every six hours for four days, started before or with the first dose of parenteral antibiotics), and those who received an alternative regimen of dexamethasone. The absolute difference between predicted and observed rates of unfavorable outcome is noted above bars.

for four days, started before or with first dose of parenteral antibiotics; dexamethasone was initiated after clinical deterioration in all other episodes.[6]

Outcome measures

During clinical course, neurologic complications (impairment of consciousness, seizures, or focal neurological abnormalities) and cardiorespiratory failure occurred in 60 and 37% of episodes (Table 3), respectively. Neurologic complications, including epileptic seizures, were less likely to occur in 2006-2008 as compared with 1998-2002 (60 vs. 75%; p<0.001). The rate of cardiorespiratory failure between cohorts was similar.

Table 3. Clinical course, mortality, disability, and neurologic findings at discharge.[a]

Characteristic	2006-2009 357 Episodes	1998-2002 352 Episodes	Difference (%)	p-value
Clinical course				
Neurologic complications[b]	239 (60%)	263 (75%)	-15%	<0.001
Seizures	60/344 (17%)	85/349 (24%)	-7%	0.025
Cardiorespiratory failure	133 (37%)	134 (38%)	-1%	0.823
Score on Glasgow Outcome Scale				
1 (death)	71 (20%)	107 (30%)	-10%	0.001
2 (vegetative state)	0	3 (1%)	-1%	
3 (severe disability)	18 (5%)	17 (5%)	0%	
4 (moderate disability)	50 (14%)	50 (14%)	0%	
5 (no or minor disability)	218 (61%)	175 (50%)	11%	0.002
Neurologic findings at discharge				
Cranial nerve palsy	47/280 (17%)	67/243 (28%)	-11%	0.003
Hearing impairment	33/280 (12%)	55/243 (22%)	-10%	0.001
Focal cerebral deficits	32/280 (11%)	26/243 (11%)	0%	0.791

[a] Neurological examination was performed in 243 of 245 surviving patients of cohort 1998-2002 and 280 of 285 surviving patients of cohort 2006-2009. [b] Neurologic complications were defined as impairment of consciousness, seizures, or focal neurological abnormalities.

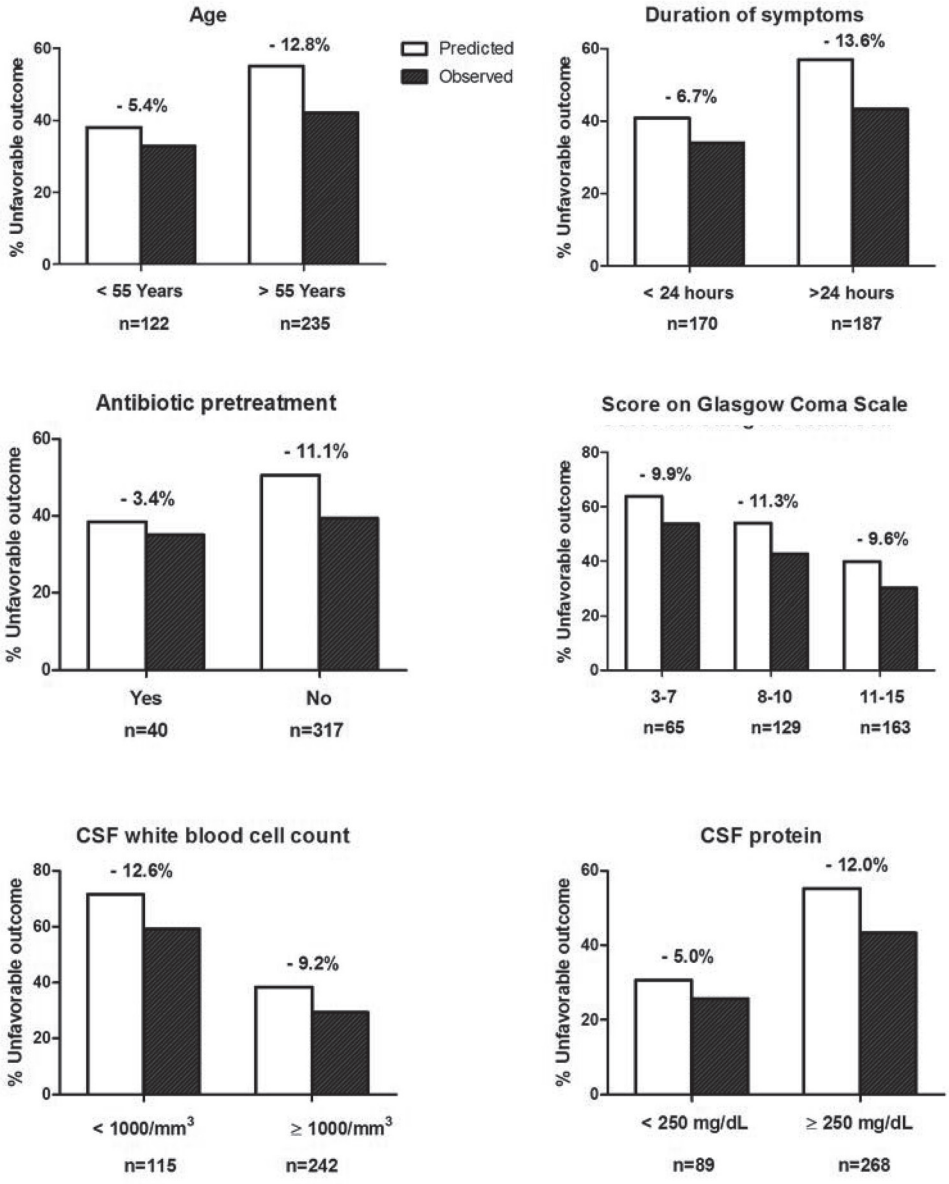
Discussion

The outcome of adults with community-acquired pneumococcal meningitis on a national level has significantly improved over the last few years. We found a decline in unfavorable outcome from 50 to 39%. This observation can not be attributed to a change in disease severity as we corrected for a large set of prognostic factors. The main difference between cohorts was the successful introduction of adjunctive dexamethasone therapy in the Netherlands. The decline in unfavorable outcome that we observed matched the results of a randomized clinical trial that we performed in a comparable population.[6]

Adjunctive dexamethasone was administered in 92% of episodes in 2006-2009. The large majority of physicians adhered to current guidelines recommending a standard regimen of dexamethasone, 10 mg intravenously, given every six hours for four days, started before or with the first dose of parenteral antibiotics. The finding that antibiotic pretreatment, immunocompromised state or signs of septic shock did not influence prescription of dexamethasone is somewhat surprising since guidelines do not recommend high dose adjunctive dexamethasone in these patient groups.[1, 7]

The use of observational data in the evaluation of treatment effects raises fierce debates.[17, 18] The greatest concern with observational studies is the issue known as confounding by indication.[19, 20] Confounding by indication refers to the situation in daily clinical practice that prescribing will be guided by the prognosis of the patient: the worse the prognosis, the more or stronger therapy will be given. This means mixing treatment decisions with prognosis and that correction for important prognostic factors may only remove part of this bias. For several reasons, we believe that our observational data provide valuable evidence about the effectiveness of dexamethasone. First, our key analysis is based on comparing two national cohorts on an intention-to-treat basis (one from a period in

Figure 3. Explorative analysis of differences between observed and predicted outcome.



Footnote: CSF denotes cerebrospinal fluid. The absolute difference between predicted and observed rates of unfavorable outcome is noted above bars.

which hardly any dexamethasone was used, compared to a cohort in which dexamethasone was generally prescribed). The bias due to prescribing dexamethasone to patients that are systematically in poorer or better condition does not apply when comparing two national cohorts as a whole. Second, we applied an extensive adjustment for differences in case mix between the two cohorts based on a large, and independent body of data on prognostic factors in bacterial meningitis.[2, 3] Third, there are no indications of improvements in

other (supportive) treatment options for bacterial meningitis that could explain such a large improvement. Fourth, the treatment benefit observed in our observational study was similar in magnitude as reported in the randomized clinical trial on dexamethasone. The vast majority of patients included in this trial were Dutch patients. Finally, the benefit of dexamethasone was observed across the whole study population, but was more prominent in patients actually receiving dexamethasone (per-treatment analysis).

From 1950 onwards, the introduction of modern hospital facilities, intensive care units, cranial CT, and evidence-based guidelines, may all have contributed to the steady and gradual decrease from 40 to 30% in mortality of community-acquired pneumococcal meningitis.[21] We now observed a further decrease in mortality of 10%, within a 4-year-period, that could not be explained by differences in case-mix. Careful comparison of cohorts did not identify other important factors than the introduction of adjunctive dexamethasone therapy and improved outcome was exclusively seen in dexamethasone-treated patients.

In our randomized clinical trial, dexamethasone appeared to be most beneficial in patients with moderate or severe disease defined on the Glasgow Coma Scale.[6] The current study shows a consistent benefit through categories on the Glasgow Coma Scale. However, observed numbers of patients with unfavourable outcome in 2006-2009 were lower than the expected numbers in the middle and high risk groups, whereas no differences were observed in the low risk group.

The proportions of disease caused by the 7-valent pneumococcal conjugate vaccine (PCV7) serotypes between cohorts were similar. In the Netherlands, PCV7 was introduced for all newborns born after March 31, 2006 without a catch-up program for older children. As the vaccine is administered at 2, 3, 4, and 11 months of age, eligible infants were vaccinated from June 2006 onwards. The 23-valent pneumococcal polysaccharide vaccination is recommended for risk groups but has not been routinely recommended for the elderly thus the uptake has been negligible in the Netherlands. The vaccination status of included adults in the current study is unknown.

Our observations support the use of adjunctive dexamethasone in adult pneumococcal meningitis in high-income countries. Randomized controlled trials in Malawi and Vietnam showed no beneficial effect of adjunctive dexamethasone in adults with suspected bacterial meningitis.[9, 10] The Vietnam trial, however, did support the use of adjunctive dexamethasone in patients with bacteriologically proven meningitis.[10] In the Netherlands, dexamethasone therapy has been implemented on a large scale as adjunctive therapy, and our nation-wide study supports the view that the use of dexamethasone has substantially improved the prognosis of this devastating disease.

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Appendix

List of participating hospitals, local investigators (number of patients enrolled).

Academisch Medisch Centrum (27), Atrium Medisch Centrum, M.J. Wennekes (18), Universitair Medisch Centrum Sint Radboud, R.A.J. Esselink (18), Amphia Ziekenhuis, R.J. de Graaf (17), Medisch Centrum Alkmaar, R. ten Houten (17), Ziekenhuisgroep Twente, J.C. Baart (15), Haga Ziekenhuis, R.W.M. Keunen (14), Meander Medisch Centrum, W.G.H. Oerlemans (14), Westfries Gasthuis, D. Broere (14), Leids Universitair Medisch Centrum, C.S.M. Straathof (13), Groene-Hart ziekenuis, G.A.M. Verheul (13), Slingeland Ziekenhuis, C.J.W. van de Vlasakker (13), Universitair Medisch Centrum Groningen, R.H. Enting (13), OLVG, I.N. van Schaik (12), Tweesteden Ziekenhuis, J.P.L. van der Plas (12), Gelre Ziekenhuis, H.P. Bienfait (11), Diakonessenhuis Utrecht, M.H. Christiaans (10), Rijnstate Ziekenhuis, E.M. Hoogerwaard (10), VU Medisch Centrum, J.C. Reijneveld (10), Beatrix Ziekenhuis, R.B. Alting van Geusau (9), Catharina Ziekenhuis, J.N. Berendes (9), Erasmus Medisch Centrum, B.C. Jacobs (9), Isala Klinieken, J.S.P. van den Berg (9), Rijnland Ziekenhuis, R.J.W. Witteveen (9), Tergooi Ziekenhuizen, M. Stevens, D. Herderschee (9), Boven-IJ Ziekenhuis, M.A. Struys (8), Gelderse Vallei Ziekenhuis, C. Jansen (8), Orbis Medical Concern, H.W.M. Anten (8), Sint Elisabeth Ziekenhuis, G.F.J. Brekelmans (8), Sint Jansdal Ziekenhuis, T.F.M. Fennis (8), StreekZiekenhuis Midden-twente, J.J.W. Prick (8), Viecuri Ziekenhuis, P.H.M. Pop (8), Sint Lucas Andreas Ziekenhuis, E.J. Wouda (7), Sint Franciscus Ziekenhuis, C. Bülens (7), Deventer ziekenhuizen, H.J.M.M. Lohman (6), Flevo Ziekenhuis, J.P. Blankevoort (6), Jeroen Bosch Ziekenhuis, H.F. Visee (6), Koningin Beatrix Ziekenhuis, R.C.F. Smits (6), Ziekenhuis de Lievensberg, P.J.I.M. Berntsen (6), Maasstadziekenhuis, R. Saxena (6), Medisch Spectrum Twente, J.A.G. Geelen (6), Ziekenhuis Bernhoven, P.R. Schiphof (5), Kennemer Gasthuis, M. Weisfelt (5), Reinier de Graaf Ziekenhuis, W.J.H.M. Grosveld (5), Scheper Ziekenhuis, E.V. van Zuilen (5), Slotervaart Ziekenhuis, I.H. Kwa (5), Sint Laurentius Ziekenhuis, P.H.M.F. van Domburg (5), Sint Jansgasthuis, R.H.J. Medaer (5), Zaans Medisch Centrum, A. Koppenaal (5), Medisch Centrum Leeuwarden, W. van der Kamp (5), Antonius Ziekenhuis, R.S. Holscher (4), Bethesda Ziekenhuis, J.P. Schipper (4), Canisius-Wilhelmina Ziekenhuis, G.W. van Dijk (4), Albert Schweitzer Ziekenhuis, H. Kerkhoff (4), Medisch Centrum Haaglanden, M.J.B. Taphoorn (4), Dirksland Ziekenhuis, U.W. Huisman (4), Elkerliek Ziekenhuis, A.J.M.Kok (4), Franciscus Ziekenhuis, A. van Spreeken (4), Gemini Ziekenhuis, P. Admiraal (4), Rivierenland Ziekenhuis, P.J. de Jong (4), Sint Anna Ziekenhuis, H.B.M. van Lieshout (4), Sint Lucas Ziekenhuis, A.N. Zorgdrager (4), Vlietland Ziekenhuis, C.J. Gijsbers (4), Ziekenhuis Zevenaar, A.van de Steen (4), Academisch Ziekenhuis Maastricht, Dr. E.P.M. van Raak (3), Bronovo Ziekenhuis, M. Gerrits (3), Hofpoort Ziekenhuis, E.J. Wieringa (3), IJsselmeerziekenhuizen, E.M. Leenders (3), Maasziekenhuis, R.M.J.A.Roebroek (3), Martini Ziekenhuis Groningen, J.W. Snoek (3), Maxima Medisch Centrum, A.J. Vermeij (3), Mesos Medisch Centrum, P.H. Wessels (3), Oosterschelde Ziekenhuis, A.M. Boon (3), Refaja Ziekenhuis, L. Vrooland (3), Röpcke-Zweers Ziekenhuis, J.G.M. Knibbeler (3), Ruwaard van Putten Ziekenhuis, H.W. ter Spill (3), Spaarne Ziekenhuis, R.J. Meijer (3), Ziekenhuis De Sionsberg, J.P. Krooman (2), IJsselland Ziekenhuis, J. Heerema (2), Waterland Ziekenhuis, J.G.W. Oonk (2), Ziekenhuis Amstelland, D.S.M. Molenaar (2), Ziekenhuis Walcheren, J.P. Koeman (2), Ziekenhuis Zeeuws-Vlaanderen, W. Hoefnagels (2), Ziekenhuis de Tjongerschans, R.F. Duyff (2), Ziekenhuis Delfzicht, J.A. Don (1), Diaconessenhuis Meppel, E.J.V. Keuter (1), Havenziekenhuis, R.J.W. Dunnewold (1), Ziekenhuis Nij Smellinghe, K.D. Beintema (1), Rode Kruis Ziekenhuis, L. Zegerius (1), Sint Antonius Ziekenhuis, H.W. Mauser (1), Wilhelmina Ziekenhuis, A.E. Bollen (1).

Supplementary table 1. Capsular pneumococcal serotypes.

Serotype	2006-2009 cohort N=327[a]	1998-2002 cohort N=352
3	31 (10%)	36 (10%)
14[b]	15 (5%)	34 (10%)
19F[b]	13 (4%)	29 (8%)
7F	39 (12%)	28 (8%)
9V[b]	9 (3%)	27 (8%)
6B[b]	23 (7%)	21 (6%)
10A	10 (3%)	21 (6%)
8	27 (8%)	16 (5%)
4[b]	15 (5%)	16 (5%)
23F[b]	34 (10%)	14 (4%)
6A[c]	7 (2%)	10 (3%)
19A	5 (2%)	10 (3%)
12F	3 (1%)	10 (3%)
22F	19 (6%)	8 (2%)
18C[b]	14 (5%)	8 (2%)
1	12 (4%)	5 (1%)
Other[d]	51 (16%)	63 (18%)
Total PCV7 serotypes	125 (38%)	149 (42%)
PCV7-related serotypes	22 (6%)	26 (7%)

[a] Serotypes were unavailable in 30 of 357 episodes (8%). [b] Serotypes included in the 7-valent pneumococcal conjugate vaccine (PCV7). [c] PCV7 vaccine-related serotypes d Other types in cohort 1 were as follows: in 35F in six, 9Nc in five, 17F in five, 38 in four, 15B in four, 16F in four, 18Bc in four, 33F in four, 23Bc in four, 24F in three, 34 in three, 5 in two, 15A in two, 15C in two, 20 in two, 22A in two, 9Ac in one, 18Fc in one, and 23Ac in one. Other types in cohort 2: 11A in seven, 23Bc in six, 33F in four, 31 in three, 15C in three, 16F in three, 18Bc in three, 23Ac in three, 35F in three, 9Nc in three, 20 in two, 15B in two, 24F in two, 24F in two, 25 in one, 34 in one, 38 in one, 15A in one, 17F in one.

Supplementary table 2. Multivariate analysis model after imputation, cohort 1998-2002

Patient characteristic	Odds ratio (95% confidence interval)	p-value	Missing values
Age (per 10 year)	1.14 (0.98-1.34)	0.093	0
Duration of symptoms (>24hours)	1.53 (0.89-2.64)	0.127	26 (7%)
Seizures before admission	0.79 (0.28-2.26)	0.660	1 (0.3%)
Antibiotics before admission	0.64 (0.29-1.38)	0.251	3 (1%)
Distant focus of infection[a]	1.21 (0.72-2.04)	0.465	0
Immuncompromise[b]	2.03 (1.07-3.82)	0.029	1 (0.3%)
Neck stiffness	0.40 (0.20-0.81)	0.011	8 (2%)
Heart rate >120 beats per minute	1.29 (0.57-2.91)	0.542	21 (6%)
Diastolic blood pressure <60mmHg	1.89 (0.62-5.74)	0.262	8 (2%)
Temperature >38·0 °C	1.47 (0.68-3.17)	0.327	7 (2%
Score on Glasgow Coma Scale	0.90 (0.82-1.00)	0.047	1 (0.3%)
Focal cerebral deficit	1.63 (0.91-2.90)	0.098	0
Cranial nerve palsy (excluding hearing loss)	1.90 (0.95-3.81)	0.071	0
CSF leukocytes count <1000/mm^3	4.74 (2.44-9.21)	<0.001	32 (9%)
CSF protein (per 1g/L)	1.21 (1.09-1.35)	0.001	36 (9%)
CSF to blood glucose ratio (per 0·20)	0.81 (0.58-1.12)	0.201	43 (12%)
Blood culture	0.97 (0.50-1.87)	0.922	43 (12%)
Thrombocyte count (per 100 000)	0.84 (0.64-1.10)	0.201	26 (7%)

[a] Defined as pneumonia, otitis or sinusitis. [b] Immunocompromise was defined by the use of immunosuppressive drugs, a history of splenectomy, or the presence of diabetes mellitus or alcoholism, as well as patients infected with human immunodeficiency virus (HIV).