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

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Chapter 6

Corticosteroids for acute bacterial meningitis

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Abstract

In experimental studies, the outcome of bacterial meningitis has been related to the severity of inflammation in the subarachnoid space. Corticosteroids reduce this inflammatory response.

In this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, issue 1), MEDLINE (1966 to February 2010), EMBASE (1974 to February 2010) and Current Contents (2001 to February 2010). RCTs were scored for methodological quality. Outcomes and adverse effect were collected. Subgroup analyses were performed for children and adults, causative organisms, low-income versus high-income countries, time of administration of steroids and quality of studies.

Twenty-four studies involving 4041 participants were included. Similar numbers of participants died in the corticosteroid and placebo groups (18.0% versus 20.0%; risk ratio (RR) 0.92, 95% confidence interval (CI) 0.82 to 1.04, P = 0.18). There was a trend towards lower mortality in adults receiving corticosteroids (RR 0.74, 95% CI 0.53 to 1.05, P = 0.09). Corticosteroids were associated with lower rates of severe hearing loss (RR 0.67, 95% CI 0.51 to 0.88), any hearing loss (RR 0.76, 95% CI 0.64 to 0.89) and neurological sequelae (RR 0.83, 95% CI 0.69 to 1.00). Subgroup analyses for causative organisms showed that corticosteroids reduced severe hearing loss in *Haemophilus influenzae* (*H. influenzae*) meningitis (RR 0.34, 95% CI 0.20 to 0.59) and reduced mortality in *Streptococcus pneumoniae* (*S. pneumoniae*) meningitis (RR 0.84, 95% CI 0.72 to 0.98). In high-income countries, corticosteroids reduced severe hearing loss (RR 0.48, 95% CI 0.34 to 0.69), any hearing loss (RR 0.57, 95% CI 0.45 to 0.73) and short-term neurological sequelae (RR 0.63, 95% CI 0.47 to 0.85). There was no beneficial effect of corticosteroid therapy in low-income countries. The use of adjunctive corticosteroid treatment was not associated with an increased risk of adverse events (RR 1.13, 95% CI 0.99 to 1.28).

Corticosteroids significantly reduced hearing loss and neurological sequelae. Data support the use of corticosteroids in patients with bacterial meningitis in high-income countries. We found no beneficial effect in low-income countries.

Background

Bacterial meningitis is a severe infection of the meninges, the membrane lining of the brain and spinal cord, associated with high mortality and morbidity rates despite optimal antibiotic therapy and advances in critical care.[1] Late sequelae such as cranial nerve impairment, especially hearing loss, occur in 5 to 40% of patients.[1-5]

In the 1960s two RCTs evaluated the effect of corticosteroids in patients with bacterial meningitis which showed no beneficial effect.[6,7] In the 1980s experimental animal models have shown that outcome in bacterial meningitis is related to the severity of inflammation in the subarachnoid space.[8,9] In these models administration of dexamethasone decreased the inflammatory response, reversed brain edema and improved outcome. New randomized clinical trials were performed in the late 1980's and 1990's with conflicting results.[10-12] Two meta-analyses of RCTs were published showing a reduction of bilateral hearing loss in dexamethasone treated children with *Haemophilus influenzae* meningitis.[13,14]

In the early 1990's the epidemiology of bacterial meningitis changed due to introduction of the *H. influenzae* type B conjugate vaccine that resulted in near elimination of this bacterium as cause of meningitis in high-income countries.[15] New trials were performed in children with bacterial meningitis, most commonly caused by *Streptococcus pneumoniae*. In 1997, a new meta-analysis was published showing adjunctive corticosteroid therapy to prevent prevented hearing loss in patients with *Haemophilus influenzae* meningitis.[16] This meta-analysis also showed a beneficial trend of dexamethasone on neurological sequelae and hearing loss in patients with meningitis due to *Streptococcus pneumoniae*.

In 2000s, 5 large randomized clinical trials have been performed. Two trials in children were performed in Malawi and South-America and three trials in adults were performed in Europe, Vietnam and Malawi.[17-21] The European trial showed a beneficial effect in all patients, with the most apparent effect on mortality and unfavorable outcome in pneumococcal meningitis.[17] The Vietnamese trial showed a beneficial effect only in patients with proven bacterial meningitis.[19] The other trials did not show a beneficial effect. In 2010 an individual patient data meta-analysis was performed with patients from these five trials to determine in which subgroups of patients adjunctive dexamethasone was effective.[22] In this meta-analysis no benefit of adjunctive dexamethasone was found in any of the pre-specified subgroups. However, a post-hoc analysis did show a reduction in any hearing loss in surviving patients treated with dexamethasone.

From 1960 onwards, multiple trials have been published on the role of corticosteroids in bacterial meningitis. The results of many trials were inconclusive and most studies were relatively small. These trials varied greatly in study population, study design, timing and dosage of corticosteroids and results were variable or contradictory. Mortality is substantially higher in low income countries, primarily related to access to care and co-morbidities. This Cochrane systematic review and meta-analysis facilitates an interpretation of these varying results and might identify subgroups that benefit from adjunctive corticosteroid therapy.

Objectives

To examine the efficacy and safety of adjuvant corticosteroid therapy in acute bacterial meningitis.

Methods

Criteria for considering studies for this review

Eligible studies were randomized controlled trials (RCTs) of corticosteroids as an adjuvant therapy in acute bacterial meningitis in participants of any age and in any clinical condition. Participants has to be treated with antibacterial agents and randomized to corticosteroid therapy (or placebo or no therapy) of any type. At least rates of case fatality rate or hearing loss had to be recorded for studies to be included.

Primary outcomes

Primary outcome measures were mortality, severe hearing loss and neurological sequelae. Hearing loss was defined as severe when there was bilateral hearing loss greater than 60 dB or requiring bilateral hearing aids. We analysed any hearing loss and severe hearing loss separately. Neurological sequelae were defined as focal neurological deficits other than hearing loss, epilepsy (not present before meningitis onset), severe ataxia and severe memory or concentration disturbance. Children with isolated speech or language disturbances were not counted as having non-hearing deficits if these problems were associated with severe hearing loss. We analyzed both short- and long-term neurological sequelae, other than hearing loss. Short-term neurological sequelae were defined as sequelae assessed between discharge and six weeks after hospital discharge. Long-term neurological sequelae were defined as sequelae assessed between 6 weeks and 12 months after discharge. Whenever possible, we extracted data for both these outcomes.

Secondary outcomes

Adverse events were a secondary outcome measure. Adverse events were defined as clinically evident gastrointestinal tract bleeding, reactive arthritis, pericarditis, herpes zoster or herpes simplex virus infection, fungal infection, secondary fever (defined as a temperature of 38°C or above occurring after at least one afebrile day during the course of hospitalization) and persistent fever (defined as fever that continued longer than five consecutive days after initiation of appropriate antibiotic therapy). The total number of adverse events in each treatment group was calculated.

Search strategy

In the first publication of this review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2003, issue 1); MEDLINE (1966

to April 2002); EMBASE (1974 to April 2002); HEALTHLINE (1988 to April 2002); CurrentContents for trials published before April 1st 2002, and reference lists of all articles. We also contacted manufacturers and researchers in the field (DvdB).[23]

In a 2006 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, issue 2);MEDLINE (1966 to July 2006); EMBASE (1974 to June 2006); and Current Contents (2001 to June 2006).[24]

In this 2009 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 3); MEDLINE (June 2006 to September 2009); EMBASE (June 2006 to September 2009); Web of Science restricting search results to years published 2006-2009. MEDLINE was searched using keywords and MeSH terms (Appendix 1) in conjunction with the highly sensitive search strategy designed by the Cochrane Collaboration for identifying RCTs.[25] The same strategy was used to search CENTRAL and adapted to search EMBASE (WebSpirs) and Current Contents (OVID). We performed the search without any language restrictions.

Besides the electronic search we identified relevant trials by searching references listed in published studies, handsearching congress abstracts, personal communication with researchers and experts in the field and from literature lists of pharmaceutical companies.

Data collection and analysis

We independently (MB, DvdB) screened the search results and retrieved the full articles of all potentially relevant trials. Each trial report was scrutinized to ensure that multiple publications from the same trial were included only once. We resolved disagreements through discussion and listed the excluded studies and the reasons for their exclusion.

Data were independently (MB, DvdB) extracted according to a pre-specified protocol and included study design, inclusion criteria, patients' characteristics, country in which the study was performed, intervention characteristics, and outcome measures. Scored intervention characteristics were corticosteroid type, daily corticosteroid dose, duration of steroid therapy and timing of corticosteroid therapy initiation (before/with the first dose of antibiotic therapy, or after first dose of antibiotic therapy). We resolved disagreements through discussion and contacted the corresponding publication author in the case of unclear or missing data.

For dichotomous outcomes, we recorded the number of participants experiencing the event and the number randomized in each treatment group. To allow an available-case analysis, we recorded the numbers of participants analyzed in each treatment group and used them in the analyses. However, the number of participants randomized into the treatment arms was also recorded and the discrepancy between the figures used to calculate the loss to follow up. Also, these figures allowed a worst-case scenario analysis to be carried out to investigate the effect of missing data.

For each study a risk of bias table was completed scoring for adequacy of sequence generation, allocation concealment, blinding, if incomplete data were addressed, selective reporting and other sources of bias. Studies without adequate sequence generation were excluded from the meta-analyses.

All outcome measures were dichotomous. We used risk ratios (RR) with 95% confidence intervals (CI) as measure of treatment effect. For studies using multiple treatment groups, only groups receiving corticosteroids or placebo only were included in the meta-analysis. We contacted the corresponding publication author in the case of unclear or missing data. If details were not provided, results used in the analysis were as provided in the publication. We assessed heterogeneity in all analysis with the I-square statistics with a value of >=50% taken to indicate statistical heterogeneity. We conducted visual inspection of the funnel plot of the studies for any obvious asymmetry that could indicate publication bias. We analyzed the data using Review Manager 5. We performed meta-analyses using the Mantel-Haenszel method with a fixed-effect model when heterogeneity was absent. When significant heterogeneity was established we used a random effects model.

We performed subgroup analyses regarding age, causative organism, low-income versus developed countries, time of administration of steroids and study quality. Two age groups were defined: patients younger than 16 years and those of 16 years and older. Three categories of causative organisms were defined: *Haemophilus influenzae* (*H. influenzae*), *Neisseria meningitidis* (*N. meningitidis*) and *Streptococcus pneumoniae* (*S. pneumoniae*). Studies were analyzed in two subsets divided into low-income and high-income countries. Low-income countries had a United Nations Human Development Index of less than 0.7 and high-income countries had an index of 0.7 or higher.[26] Studies were divided in three categories of methodological quality: high, medum and low according to the score in the risk of bias table. If all questions in the risk of bias table were answered positively the study was categorized as high quality, 3 through 5 medium and if less than 3 questions were answered positively as low. In the subgroup analysis the I-square statistic to assess heterogeneity was used with a value of ≥50% taken to indicate statistical heterogeneity.

Missing data in outcome measures severe hearing loss and neurological sequelae were scored for each study if reported. For trials with missing data, we conducted two analyses: an available-case analysis and then a 'worst-case scenario' analysis for trials with missing data. All participants who had dropped out of the corticosteroid group were considered to have an unfavorable outcome whereas those who had dropped out of the control group were considered to have a favorable outcome. We conducted a sensitivity analysis imputing the missing data in this way to determine whether the overall results were sensitive to this assumption.

Results

We identified 39 potentially eligible trials, of which two were described in one paper.[10] Two studies presented data from one trial.[27,28] A total of 24 studies were eligible for inclusion in the meta-analysis (Table 1). These studies included 4041 patients (2024 dexamethasone, 2017 placebo). Subjects over 16 years were included in 7 studies (1517 patients: 756 dexamethasone, 761 placebo).[17-19,29-31] In two studies, patients older than 12 years were considered adults.[29,30] The study intervention consisted of dexamethasone in 21 of 24

studies; dosages ranged from 0.4-1.5 mg/kg/d and duration ranged from 2 to 4 days. In the other studies hydrocortisone, prednisolone or as combination of both were given and duration ranged from 3 to 14 days.[6,7,32] Study medication was administered before or with the first dose of antibiotics in 12 studies, and after the first dose in 8. In 4 studies the time of administration was not stated. A sample size calculation was given in seven studies.[17-21,31,33] Mortality rates ranged from 0 to 54% (Table 1). In one study patients who died during the first 18 hours of admission were excluded;[34] nevertheless, these patients were included in the meta-analysis. Hearing was assessed by audiometry in 7 studies in children and 4 studies in adults; other studies used brainstem evoked potentials (10) or age-specific behavioral measures (8). Three studies assessed both short and long term neurological sequelae.[10,35] Definitions of adverse events were heterogeneous and the number of events was recalculated for each study.

Fifteen trials were excluded (Table 2). Two studies did not randomize between treatment and control group.[36,37] Nine trials did not adequately generate a randomization sequence, and in most of these alternate allocation schemes were used.[38-46] One study compared two dexamethasone regimens,[47] one study was a duplicate study[28] and one study provided insufficient data (communications during scientific meetings only).[48]

Risk of bias in included studies

The sequence generation for patient allocation was adequate in 19 studies (Figure 1 and 2). In 5 studies the method of sequence generation was unclear or not specified.[6,32,34,49,50] In 5 studies the treatment allocation was not concealed,[29,30,32,49,51] and in one study treatment allocation concealment was unclear as patients were paired for placebo or dexamethasone.[34] A multicenter study performed in several South American countries compared two treatments in a 2x2 design, dexamethasone and glycerol with placebo, in four randomization arms (glycerol-dexamethasone, glycerol-placebo, dexamethasone-placebo, placebo-placebo). However, some centers did not include patients in the double placebo group, thereby disturbing the allocation concealment.[21,22] Nevertheless, data were extracted as derived from one study, comparing the glycerol-dexamethasone plus dexamethasone-placebo versus glycerol-placebo plus placebo-placebo groups. Nineteen studies had a double blind design and broke the treatment code after follow-up for the last patient was complete. Five studies did not use blinding.[29,30,32,49,51] Missing data were addressed in 16 studies and were not in 8.[6,29-32,34,52,53] An intention to treat analysis was performed in 6 studies,[17-21,27] comprising 2147 of 4041 patients (53%). In the other 18 studies only per-protocol data were available to be ascertained. The final analysis for mortality is equally based upon per-protocol figures (46% of included patients) and intention to treat figures (54%).

Funnel plots of outcomes (mortality, any hearing loss, short term neurological sequelae and long term neurological sequelae, and adverse events) did not show obvious asymmetry, except for severe hearing loss (Figure 3).

In 10 studies differences in baseline and clinical characteristics between treatment and control groups influenced comparability of groups;[7,11,21,27,30-32,34,51,52] indicating either

Table 1. Characteristics of included studies (in alphabetical order)

Study (year)	Age participants; inclusion criteria
Bademosi (1979)[32]	10-58 year; bacteriologically proven pneumococcal meningitis
Belsey (1969)[34]	0-17 years; purulent meningitis - matching of patients and controls in 48 categories
Bennet (1963)[6]	All ages; life threatening infectious diseases, subgroup meningitis
Bhaumik (1998)[30]	12-75 years; suspected bacterial meningitis with CSF criteria
Ciana (1995)[49]	2 months to 6 years; suspected bacterial meningitis with CSF criteria
de Gans (2002)[17]	Over 16 years; suspected bacterial meningitis with CSF criteria
DeLemos (1969)[7]	1 month to 17 years; diagnosis bacterial meningitis
Girgis (1989)[29]	3 months to 70 years; diagnosis bacterial meningits
Kanra (1995)[52]	To 16 years; bacteriologically proven bacterial meningitis
Kilpi (1995)[51]	3 months to 15 years; suspected bacterial meningitis with CSF criteria – trial also evaluated adjunctive glycerol and combined adjunctive glycerol and DXM therapy
King (1994)[50]	1 month to 18 years; suspected bacterial meningitis with CSF or blood criterion – also patients with suspected meningitis who were too unstable for lumbar puncture
Lebel -1 (1988)[10]	2 months to 16 years; suspected or proven bacterial meningitis
Lebel -2 (1988)[10]	2 months to 16 years; suspected or proven bacterial meningitis
Lebel (1989)[11]	3 months to 16 years; suspected or proven bacterial meningitis
Molyneux (2002)[20]	2 months to 13 years; suspected bacterial meningitis with CSF criteria
Nguyen (2007)[19]	Older than 14 years; culture proven bacterial meningitis or suspected bacterial meningitis with CSF criteria
Odio (1991)[12]	6 weeks to 13 years; culture proven bacterial meningitis or suspected meningitis with CSF inflammations
Peltola (2007)[21]	2 months to 16 years; proven or suspected bacterial meningitis with CSF criteria – trial also evaluated adjunctive glycerol and combined adjunctive glycerol and DXM therapy
Qazi (1996)[33]	2 months to 12 years; suspected bacterial meningitis with CSF criteria
Sankar (2007)[27]	2 months to 12 years; suspected bacterial meningitis with CSF criteria – trial also evaluated adjunctive glycerol and combined adjunctive glycerol and DXM therapy
Scarborough (2007)[18]	Older than 15 years; suspected bacterial meningitis with CSF criteria
Schaad (1993)[53]	3 months to 16 years; suspected or proven bacterial meningitis
Thomas (1999)[31]	18 to 79 years; suspected bacterial meningitis with CSF criteria
Wald (1995)[35]	2 months to 12 years; suspected bacterial meningitis with CSF criteria

insufficient sample size to equal out the random differences between randomization arms or a selection bias. Other indications of a selection bias were found in studies with high numbers of comatose patients or low numbers of culture positive patients.[27,29,33] Nine studies did not present sufficient patient characteristics to determine whether the patients in each randomization arm were comparable.

Intervention – timing	Outcome	Antibiotics
Hydrocortison 100mg; followed by prednisolone 60mg/day, 14 days - before or with AB	Mortality (44%)	sulf/pen
DXM 1.2mg/m2/day,4d - timing unclear	Mortality (3%), hearing loss, adverse events	chlor/sulf/pen
Hydrocortisone scheme, 7d – after AB	Mortality (45%), adverse events	Not specified
DXM 16mg/day, 4d plus 3d scheme – after AB	Mortality (13%), neurological sequelae, adverse events	pen/chlor or ceph
DXM 0.4mg/kg/d, 3d – timing unclear	Mortality (28%), neurological sequelae, adverse events	ampi/chlor
DXM 40mg/day, 4d – before or with AB	Mortality (11%), neurological sequelae, adverse events	various
Metylprednisolone 120mg / day, 3d – after AB	Mortality (3%)	chlor/sulf/pen
DXM 16-24 mg/day, 4d – before or with AB	Mortality (15%), hearing loss, neurological sequelae	ampi/chlor
DXM 0.6 mg/kg/d, 4d – before or with AB	Mortality (5%), hearing loss, neurological sequelae	sulf/ampi
DXM 1.5mg/kg/d, 3d – before or with AB	Mortality (2%), hearing loss, sequelae	ceph
DXM 0.6mg/kg/d, 4d – after AB	Mortality (1%), hearing loss, neurological sequelae, adverse events	various
DXM 0.6mg/kg/d, 4d – after AB	Mortality (2%), hearing loss, neurological sequelae, adverse events	ceph
DXM 0.6mg/kg/d, 4d – after AB	Mortality (2%), hearing loss, neurological sequelae, adverse events	ceph
DXM 0.6mg/kg/d, 4d – after AB	Mortality (2%), hearing loss, neurological sequelae, adverse events	ceph
DXM 0.8mg/kg/d, 2d – before or with AB	Mortality (31%), hearing loss, neurological sequelae	pen/chlor
DXM 0.8mg/kg/d, 4d – before or with AB	Mortality (11%), hearing loss, neurological sequelae, adverse events	various
DXM 0.6mg/kg/d, 4d – before or with AB	Mortality (2%), hearing loss, neurological sequelae, adverse events	ceph
DXM 0.6mg/kg/d, 4d – before or with AB	Mortality (15%), hearing loss, neurological sequelae, adverse events	ceph
DXM 0.6mg/kg/d, 4d – before or with AB	Mortality (19%), hearing loss, neurological sequelae, adverse events	ampi/chlor
DXM 0.9mg/kg/d, 2d – timing unclear	Mortality (4%),neurological sequelae, adverse events	ceph
DXM 32mg/day, 4d – before or with AB	Mortality (19%), hearing loss, neurological sequelae, adverse events	ceph
DXM 0.8 mg/kg/d, 2d – before or with AB	Mortality (19%), hearing loss, neurological sequelae, adverse events	ceph
DXM 40mg/day, 3d – after AB	Mortality (13%), neurological sequelae, adverse events	amox
DXM 0.6 mg/kg/d, 4d – after AB	Mortality (1%), neurological sequelae, adverse events	ceph

Effects of interventions

The overall number of participants who died in the corticosteroid treated group and the placebo group was similar (362 of 2024 (18.0%) versus 392 out of 2017 (20.0%), RR 0.92 95% CI 0.82 to 1.04, p=0.18; Table 3, Figure 4).[6,7,10-12,17-21,27,29-35,49-53] The number of patients with hearing loss was significantly smaller in the corticosteroid treated group

Table 2. Characteristics of excluded studies (in alphabetical order)

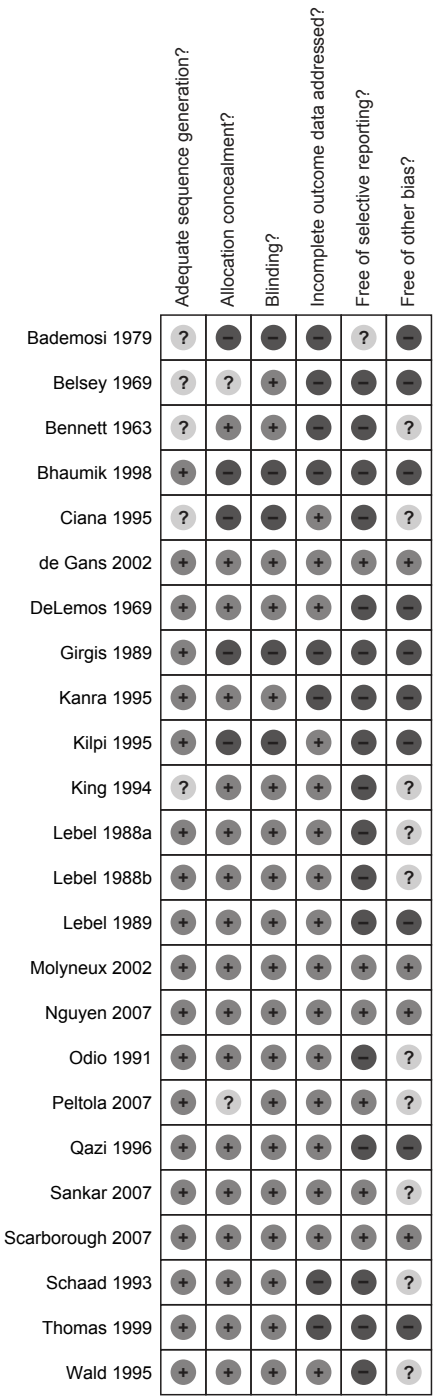
Study (year)	Reason for exclusion
Ayaz (2008)[38]	Inadequate sequence generating
Baldy (1986)[39]	Inadequate sequence generating
Daoud (1999)[40]	Inadequate sequence generating
Farina (1995)[48]	Not enough data for inclusion
Gijwani (2002)[41]	Inadequate sequence generating
Gupta (1996)[42]	Inadequate sequence generating
Jensen (1969)[43]	Inadequate sequence generating
Lepper (1959)[44]	Inadequate sequence generating
Marguet (1993)[36]	No randomisation
Ozen (2006)[37]	No randomisation
Passos (1979)[45]	Inadequate sequence generating
Peltola (2004)[69]	Not enough data for inclusion
Shembesh (1997)[46]	Inadequate sequence generating
Singhi (2008)[28]	Data previously published27
Syrogiannopoulos (1994)[47]	No placebo group, compared 2 to 4 day regimen of dexamethasone

than in the placebo group (any hearing loss: 191 of 1389 (14%) vs. 249 of 1337 (19%), RR 0.76 95% CI 0.64 to 0.89; Figure 5) severe hearing loss: 75 of 1234 (6%) versus 112 of 1203 (9%), RR 0.67 95% CI 0.51 to 0.88; Figure 6).[10-12,17-21,27,29,30,33-35,50-53] Short-term neurologic sequelae (excluding hearing loss) were assessed in 13 studies including 1756 pat ients;[10,11,17,18,20,21,27,30,31,35,49,52] less sequelae were observed in the corticosteroid treated group (161 of 900 (17.9%) vs. 185 of 856 (21.6%), RR 0.83 95% CI 0.69 to 1.00, p=0.05; Figure 7). The occurrence of long term sequelae was not significantly different between corticosteroid treated patients and controls (125 of 836 (15.3%) vs. 136 of 816 (16.7%), RR 0.91 95% CI 0.74 to 1.11; Figure 8).[10-12,19,29,33,35,50-53] Adverse events were recorded in 2619 patients and were equally distributed between treatment and placebo group (RR 1.13, 95% CI 0.99 to 1.28; Figure 9).[6,10-12,17-19,21,27,30,31,33-35,50,52,53]

Subgroup analysis

One hundred and sixty two children out of 1229 (13.2%) in the corticosteroids treated group died, compared to 166 of 1202 (13.8%) in the placebo group (RR 0.95, 95% CI 0.78 to 1.14; Table 3).[7,10,11,20,21,27,29,33,34,49-53] Corticosteroids prevented hearing loss in children: any hearing loss was found in 140 of 966 (14.5%) corticosteroid treated patients, compared to 186 of 936 (19.9%) in the control group (RR 0.74, 95% CI 0.62 to 0.89); severe hearing loss was found in 57 of 783 (7.3%) corticosteroid treated patients, compared to 86 of 765 (11.2%) in the control group (RR 0.67, 95% CI 0.49 to 0.91). For adults, study results on mortality were significantly heterogeneous (I-square=54%). Using the random effects model there was a non significant trend towards protection of corticosteroid therapy against death: 187 of 756 (24,7%) died in the corticosteroid treated group versus 215 of 761 (28.3%; RR 0.74, 95% CI 0.53 to 1.05, p=0.09).[6,17-19,29-31] The rate of hearing loss in adults was lower in corticosteroid-treated patients as compared to controls (68 of 433 (15.7%) versus 90 of 411 (21.9%), RR 0.74 95% CI 0.56-0.98). There was a trend towards fewer short term neurologic sequelae in the corticosteroid treated group (RR 0.72, 95% CI 0.51-1.01, p=0.06).

Figure 1. Methodological quality summary: judgements about each methodological quality item for each included study.



Case-fatality rate varied according to causative micro-organism. Out of 825 patients with *H. influenzae* meningitis, 87 died (10.5%); compared to 371 of 1132 (32.8%) patients with pneumococcal meningitis and 27 of 620 (4.3%) patients with meningococcal meningitis. Corticosteroids protected against death in pneumococcal meningitis (RR 0.84, 95% CI 0.72 to 0.98; Table 3).[6,7,10,12,17-21,29,31,32,35,51-53] In meningococcal meningitis, corticosteroids were associated with a non-significant reduction in mortality (RR 0.71, 95% CI 0.35 to 1.46). For children with meningitis caused by *H. influenzae*, hearing loss was significantly reduced by corticosteroids (RR 0.34, 95% CI 0.20 to 0.59). For children with meningitis caused by bacteria other than *H. influenzae*, no significant beneficial effect was seen (RR 0.95 95% CI 0.65 to 1.39). Studies were analyzed in two subsets divided into high-income[6,7,10-12,17,19,21,31,34,35,50-53] and low-income countries (Table 4).[18,20,27,29,30,32,33,49] The relative risk for mortality in high-income countries was 0.80 (95% CI 0.62 to 1.03; p=0.08) in corticosteroid treated patients and 0.97 (95% CI 0.85-1.10) in low income countries. In high-income, countries the rates of any hearing loss (RR 0.57, 95% CI 0.45 to 0.73), severe hearing loss (RR 0.48, 95% CI 0.34 to 0.69) and short-term neurologic sequelae (RR 0.63, 95% CI 0.47 to 0.85) were significantly lower in corticosteroid treated patients. Subgroup analysis for children in high-income countries showed a decrease in risk of severe hearing loss and neurologic sequelae in the corticosteroid group (severe hearing loss, RR 0.50, 95% CI 0.33 to 0.74; short term sequelae, RR 0.66, 95% CI 0.46 to 0.95), whereas no difference was seen in low-income countries (severe hearing loss, RR 0.94, 95% CI 0.65 to 1.37; short term sequelae, RR 1.07, 95% CI 0.80 to 1.41). For adults in high-income countries, corticosteroids were

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

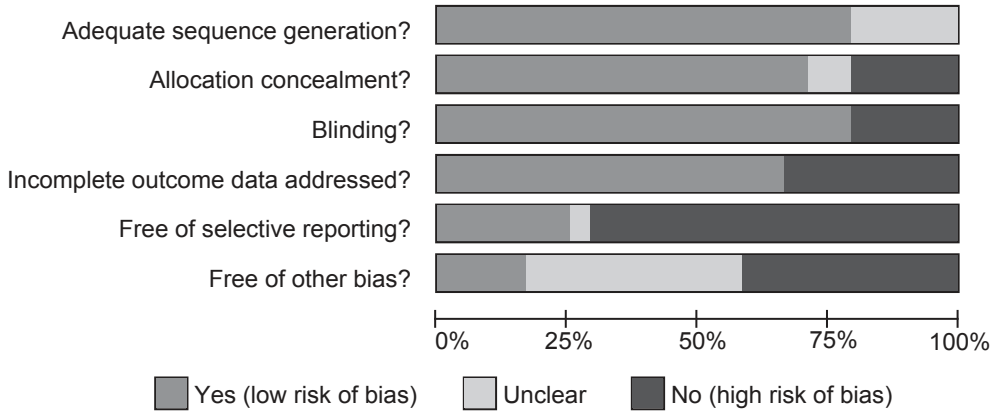


Figure 3. Funnel plots primary outcome measures.

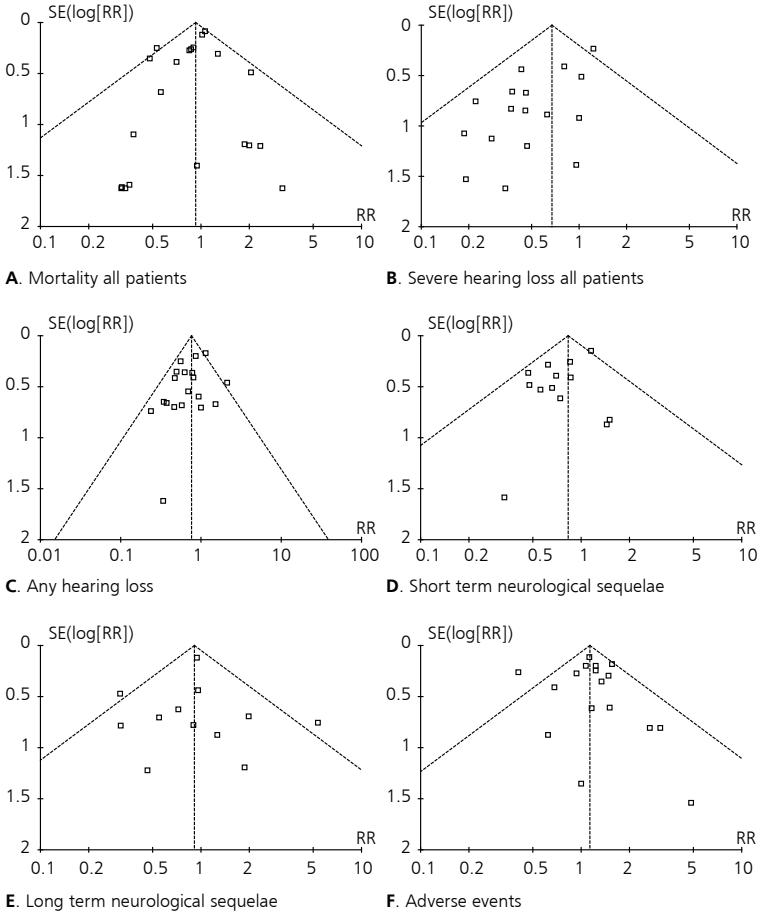


Figure 4. Forest plot of comparison: mortality in all patients

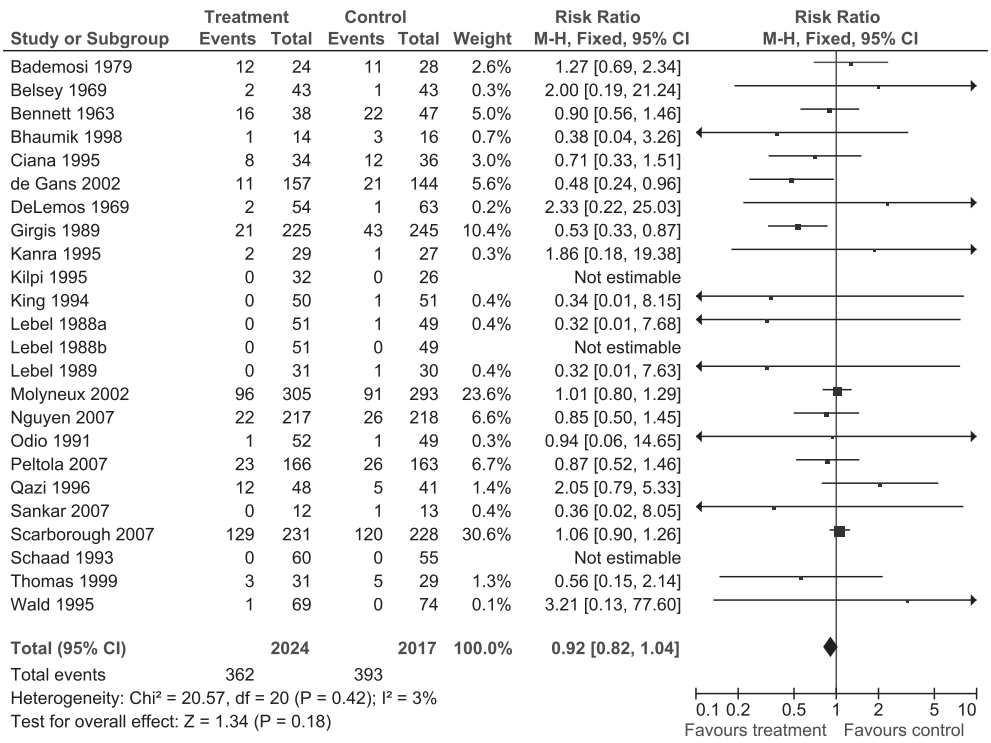


Figure 5. Forest plot of comparison: any hearing loss in all patients.

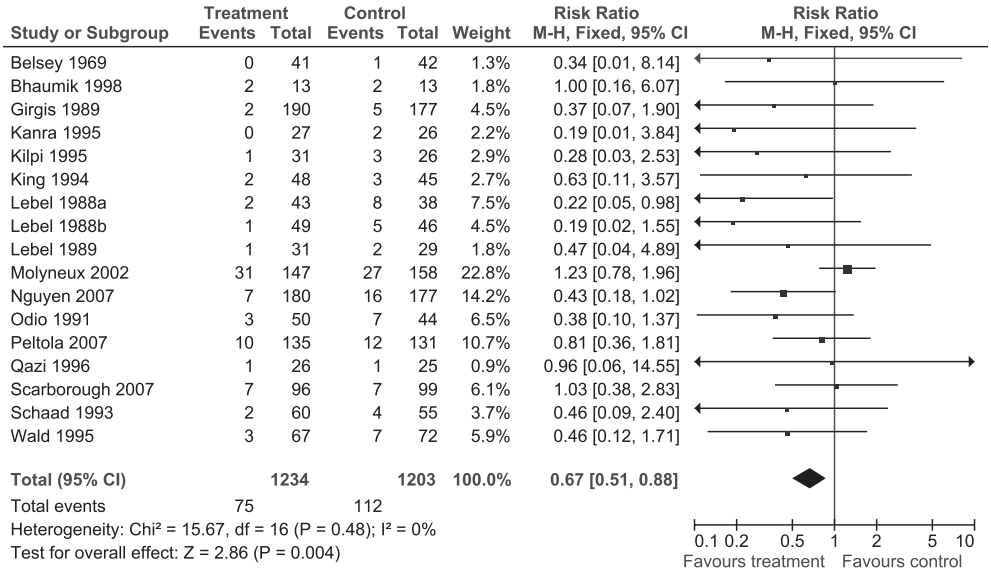


Figure 6. Forest plot of comparison: severe hearing loss in all patients

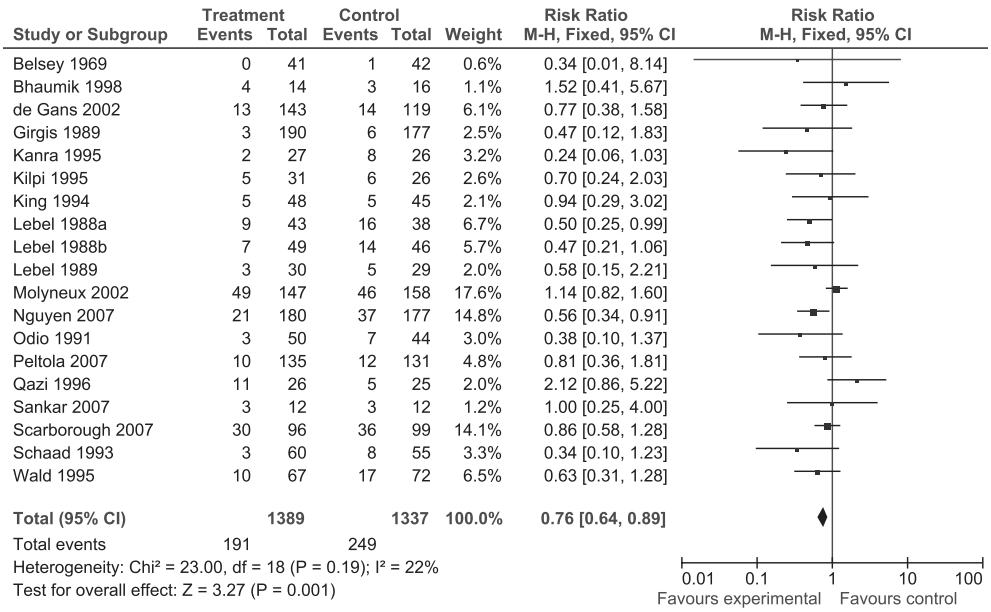
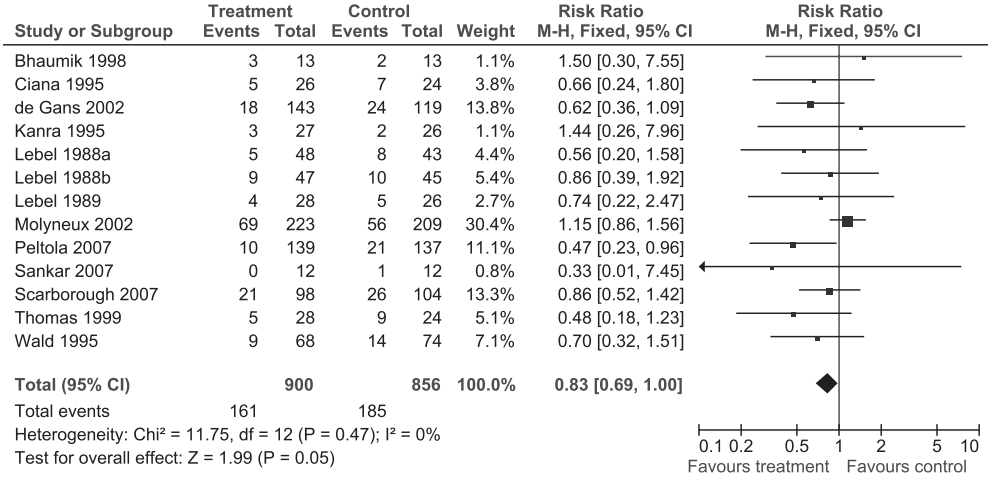


Figure 7. Forest plot of comparison: short term neurological sequelae in all patients.



protective against any hearing loss (RR 0.67, 95% CI 0.45-0.98) and there was a trend towards protection against death (RR 0.76, 95% CI 0.56-1.04).

Subgroup analysis on timing of corticosteroids (before or with the first dose of antibiotics versus after the first dose of antibiotics) showed similar results for mortality (RR 0.94, 95% CI 0.83 to 1.07; RR 0.80, 95% CI 0.52 to 1.22; Table 5). For subgroup-analyses of severe hearing loss and short-term neurological sequelae, administration after the first dose of antibiotics had slightly more favorable point estimates than studies with early administration of corticosteroids, but no statistical significant differences. Studies were analyzed in three

Figure 8. Forest plot of comparison: long term neurological sequelae in all patients.

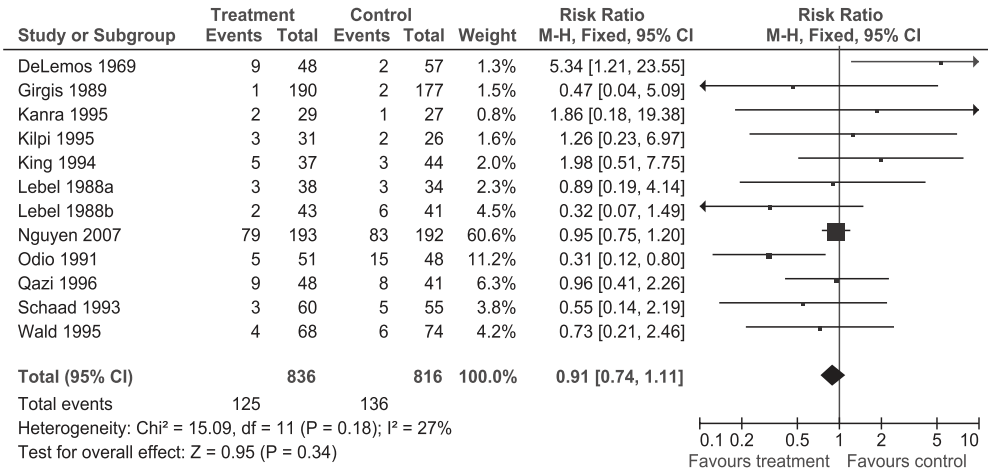
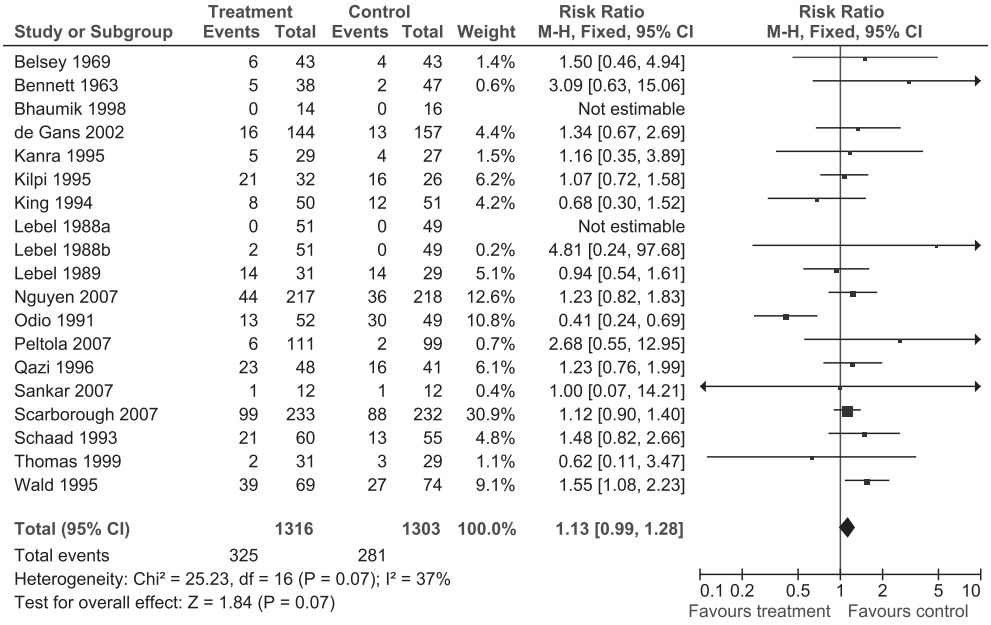


Figure 9. Forest plot of comparison: adverse events in all patients.



categories of study quality according to the studies' score on the risk of bias-table (Figure 1). Four studies including 1793 patients were categorized as high quality,[17-20] 13 studies with 1397patients as median quality[7,10-12,21,27,31,33,35,50,52,53] and 7 studies including 851 patients as low quality.[6,29,30,32,34,49,51] No difference in risk of mortality was found in studies of high and median quality (RR 0.97, 9% CI 0.85 to 1.11; RR 0.98, 95% CI 0.67 to 1.44) while studies of low quality showed a beneficial effect of corticosteroids (RR 0.74, 95% CI 0.56 to 0.97; Table 6). A reduction of hearing loss was found in patients treated with corticosteroids in

Table 3. Overview of primary outcome, secondary outcome and subgroup analysis for age and causative organism.[a]

Category	Studies	Participants	Relative risk (95% CI)
All patients			
Mortality	24	4041	0.92 (0.82-1.04)
Severe hearing loss	17	2438	0.67 (0.51-0.88)
Any hearing loss	19	2782	0.76 (0.64-0.89)
Short term neurological sequelae	13	1756	0.83 (0.69-1.00)
Long term neurological sequelae	12	1652	0.91 (0.74-1.11)
Adverse events	19	2619	1.13 (0.99-1.28)
Children			
Mortality	17	2431	0.95 (0.78-1.14)
Severe hearing loss	14	1545	0.67 (0.49-0.91)
Any hearing loss	15	1958	0.70 (0.59-0.84)
Adults			
Mortality[b]	7	1517	0.74 (0.53-1.05)
Severe hearing loss	4	542	0.72 (0.51-1.01)
Any hearing loss	4	844	0.74 (0.56-0.98)
Causative species			
Mortality			
Haemophilus influenzae	11	825	0.76 (0.53-1.09)
Streptococcus pneumoniae	17	1132	0.84 (0.72-0.98)
Neisseria meningitidis	14	620	0.71 (0.35-1.46)
Severe hearing loss in children – non *H. influenzae* species	13	860	0.95 (0.65-1.39)
Severe hearing loss in children – *H. influenzae*	10	756	0.34 (0.20-0.59)

[a]All statistical analysis were performed with Mantel-Haenszel method, using a fixed effect model unless other wise stated. [b] Random effects model.

studies of median (RR 0.64, 95% CI 0.48 to 0.85), but not in high quality studies (RR 0.84, 95% CI 0.63 to 1.10) or low quality (RR 0.72, 95% CI 0.36 to 1.42).

Sensitivity analysis

Out of 2694 survivors who were included in studies that analyzed severe hearing loss, 216 (8.0%) were not tested or had inconclusive tests (Table 7). Data on any hearing loss were missing in 223 of 2970 (7.5%) surviving patients included in studies that assessed hearing loss. One study provided 46% of missing values in the severe hearing loss analysis and 45% of missing values in the analysis on any hearing loss.[20] In the worst case scenarios, studies were significantly heterogeneous, and therefore, the random effects model was used. Corticosteroid therapy had no effect on severe or any hearing loss in the worst case scenario analyses.

Short term neurological sequelae were assessed in 1695 of 1850 survivors included in studies that scored short term sequelae; data on 155 (8.3%) were missing. Data on long term sequelae were missing in 157 of 1705 (9.2%) of patients. The worst case scenario showed no beneficial effect of corticosteroids for neurological sequelae. None of the worst case scenarios showed evidence of harm with corticosteroid therapy.

Table 4. Subgroup analysis for income of country.

Category	Studies	Participants	Relative risk (95% CI)
Mortality – all patients			
Low income	8	1793	0.97 (0.85-1.10)
High income	16	2248	0.80 (0.62-1.03)
Severe hearing loss – all patients			
Low income	5	965	0.98 (0.71-1.36)
High income	12	1509	0.48 (0.34-0.69)
Any hearing loss – all patients			
Low income	6	992	0.96(0.79-1.16)
High income	13	1810	0.57 (0.45-0.73)
Short term neurological sequelae			
Low income	5	735	1.02 (0.80-1.30)
High income	9	1079	0.63 (0.47-0.85)
Mortality – children			
Low income	4	1039	0.96 (0.78-1.18)
High income	12	1367	0.97 (0.63-1.50)
Severe hearing loss – children			
Low income	3	408	0.94 (0.65-1.37)
High income	11	1152	0.50 (0.33-0.74)
Short term neurological sequelae – children			
Low income	3	506	1.07(0.80-1.41)
High income	7	765	0.66 (0.46-0.95)
Severe hearing loss in children due to non *H. influenzae* species			
Low income[b]	2	297	0.54 (0.05-6.08)
High income[b]	11	565	0.73 (0.41-1.31)
Mortality – adults			
Low income[b]	3	636	0.60 (0.22-1.63)
High income[b]	4	881	0.76 (0.56-1.04)
Any hearing loss – adults			
Low income	1	195	0.86 (0.58-1.28)
High income	3	649	0.67 (0.45-0.98)

[a]All statistical analysis were performed with Mantel-Haenszel method, using a fixed effect model unless other wise stated. [b] Random effects model.

Discussion

This meta-analysis showed a beneficial effect of adjunctive corticosteroids in acute bacterial meningitis. Overall, corticosteroids significantly reduced the rate of hearing loss (RR 0.76, 95% CI 0.64 to 0.89), severe hearing loss (RR 0.67, 95% CI 0.51 to 0.88) and short-term neurological sequelae (RR 0.83, 95% CI 0.69 to 1.00). Use of adjunctive corticosteroids was not associated with a decrease in mortality (RR 0.92, 95% CI 0.82 to 1.04), long-term neurological sequelae (RR 0.91, 95% CI 0.74 to 1.11) or increased adverse events (RR 1.13, 95% CI 0.99 to 1.28).

Subgroup analyses for age showed that in children with bacterial meningitis corticosteroids prevented severe hearing loss (RR 0.67, 95% CI 0.49 to 0.91) and any hearing loss (RR 0.74

Table 5. Timing of steroids.[a]

Category	Studies	Participants	Relative risk (95% CI)
Mortality			
Before or with first dose of antibiotics	12	3063	0.94 (0.84-1.07)
After first dose of antbiotics	9	767	0.80 (0.52-1.22)
Severe hearing loss			
Before or with first dose of antibiotics[b]	10	1887	0.81 (0.62-1.07)
After first dose of antbiotics[b]	6	441	0.65 (0.22-1.96)
Any hearing loss			
Before or with first dose of antibiotics	11	2198	0.62 (0.43-0.89)
After first dose of antbiotics	6	497	0.76 (0.64-0.89)
Short term neurological sequelae			
Before or with first dose of antibiotics[b]	6	1282	0.83 (0.60-1.14)
After first dose of antbiotics[b]	6	457	0.70 (0.47-1.04)

[a]All statistical analysis were performed with Mantel-Haenszel method, using a fixed effect model unless other wise stated. [b] Random effects model.

Table 6. Study quality.[a]

Category	Studies	Participants	Relative risk (95% CI)
Mortality			
High quality	4	1793	0.97 (0.85-1.11)
Median quality	13	1397	0.98 (0.67-1.44)
Low quality	7	851	0.74 (0.56-0.97)
Severe hearing loss			
High quality[b]	3	857	0.89 (0.49-1.60)
Median quality[b]	10	1072	0.47 (0.29-0.75)
Low quality[b]	4	534	0.50 (0.20-1.29)
Any hearing loss			
High quality[b]	4	1119	0.88 (0.71-1.09)
Median quality[b]	11	1091	0.63 (0.50-0.78)
Low quality[b]	4	562	0.72 (0.36-1.42)
Short term neurological sequelae			
High quality	3	896	0.96 (0.76-1.21)
Median quality	8	784	0.62 (0.44-0.88)
Low quality	2	76	0.84 (0.36-1.94)

[a]All statistical analysis were performed with Mantel-Haenszel method, using a fixed effect model unless other wise stated. [b] Random effects model.

Table 7. Sensitivity analysis – worst case scenario dexamethasone.[a]

Category	Studies	Participants	Relative risk (95% CI)
Severe hearing loss[b]	17	2694	1.25 (0.81-1.93)
Any hearing loss[b]	19	2970	1.03 (0.75-1.43)
Short term neurological sequelae	13	1850	0.98 (0.82-1.18
Long term neurological sequelae[b]	12	1797	1.04 (0.66-1.63)

[a]All statistical analysis were performed with Mantel-Haenszel method, using a fixed effect model unless other wise stated. [b] Random effects model.

95% CI 0.62 to 0.89). In adults, the rate of any hearing loss was lower in the corticosteroid-treated group (RR 0.74, 95% CI 0.56-0.98); there also was a trend towards lower mortality in adults receiving corticosteroids (RR 0.74, 95% CI 0.53 to 1.05, p=0.09). Subgroup analysis for causative organism showed that corticosteroids reduce severe hearing loss in patients with meningitis due to *Haemophilus influenzae* (RR 0.34, 95% CI 0.20-0.59); subgroup analysis on *Streptococcus pneumoniae* showed a favorable effect of corticosteroids RR 0.84 (95% CI 0.72 to 0.98). A non-significant trend towards lower mortality was found in the *Neisseria meningitidis* meningitis subgroup (RR 0.71, 95% CI 0.35 to 1.46). Subgroup analysis for high-income and low-income countries showed a trend towards lower mortality in corticosteroid treated patients in high income countries (RR 0.80, 95% CI 0.62 to 1.03; p=0.08) and no apparent decrease in mortality in low income countries (RR 0.97, 95% CI 0.85 to 1.10). Corticosteroids were protective against severe hearing loss (RR 0.48, 95% CI 0.34 to 0.69), any hearing loss (RR 0.57, 95% CI 0.45 to 0.73) and short term neurological sequelae (RR 0.63, 95% CI 0.47 to 0.85) in high income countries. For children in high-income countries, corticosteroids showed a protective effect against severe hearing loss (RR 0.50, 95% CI 0.33 to 0.74) and short-term neurological sequelae (RR 0.66, 95% CI 0.46 to 0.95). A trend towards lower mortality was seen in adults treated with corticosteroids in high-income countries (RR 0.76, 95% CI 0.56 to 1.04; p=0.08).

The sensitivity analysis showed that corticosteroids would have no effect on severe or any hearing loss and short or long term neurological sequelae if all missing data were imputed as unfavorable events in the corticosteroid-treated patients. Corticosteroids were not associated with harm in this worst case scenario.

Overall completeness and applicability of evidence

The available studies do not address two important issues - the minimum duration of corticosteroid therapy or the maximum length of time after parenteral antibiotic therapy for commencement of corticosteroid therapy. In most studies, a four-day regimen of dexamethasone (0.4 or 0.6 mg/kg/day) divided into four daily doses was used. One randomized, prospective study involving 118 children with bacterial meningitis showed a two-day and four-day regimen of dexamethasone to be similarly effective.[47] In this study, physicians were not blinded for treatment groups. Long-term neurological sequelae, or moderate hearing impairment (or both), were found in 1.8 and 3.8% of patients treated with dexamethasone for two and four days, respectively. It is unlikely that a RCT will be performed to answer the question of whether a two-day or four-day should be used in bacterial meningitis; such a clinical trial would need a very large number of patients enrolled to detect significant differences between groups. Since most studies used a four-day regimen (without increase of side-effects) we advice the use of the four-days of corticosteroid therapy.

Subgroup-analyses for timing of corticosteroids (before or with the first dose of antibiotics versus after the first dose of antibiotic) showed no differences in efficacy of corticosteroids. In previous reports, administration of corticosteroids before or with the first dose of

parenteral antibiotics seemed to be more effective than administration after the first dose of antibiotics.[16,50]

A RCT involving 301 adults with bacterial meningitis in European countries showed a beneficial effect of the corticosteroid dexamethasone on unfavorable outcome and mortality.[17] In this European study, dexamethasone or placebo was administered before or with the first dose of antibiotic.[17] The beneficial effect of dexamethasone on mortality was most apparent in patients with pneumococcal meningitis. In a post hoc analysis of this study, the beneficial effect of dexamethasone on mortality in patients with pneumococcal meningitis was attributable to a reduction in systemic complications.[54] Although speculative and not supported by clinical data, one implication of this finding might be that the effect of dexamethasone is not restricted to the first hours after administration.[55]

A meta-analysis of individual patient data was performed of 5 recent large randomized controlled trials on adjunctive dexamethasone therapy in bacterial meningitis.[17-22] Data from 2029 patients from five trials were included and the aim of this analysis was to establish whether any subgroups of patients with acute bacterial meningitis might benefit from adjunctive dexamethasone. Extensive exploration of 15 pre-specified subgroups did not show robust evidence that a particular subgroup would benefit; although there was a benefit in adults aged over 55 years. There were no differences in efficacy of adjunctive dexamethasone with regard to the timing of corticosteroids.

In experimental pneumococcal meningitis, CSF bacterial concentrations appeared to be more important than the timing of dexamethasone therapy in influencing the antibacterial-induced inflammatory response.[56] Hence, there is a time period beyond which corticosteroid loses its effectiveness after the first (parenteral) administration of an antibiotic agents but this time interval has not clearly been defined. On basis of available evidence, dexamethasone should be preferably started before of with the first dose of antibiotic therapy.

Applicability of evidence

In children with acute bacterial meningitis, corticosteroids reduced hearing loss from 20.1 to 13.6% and severe hearing loss from 11.2 to 7.3%. A large proportion of included children had meningitis due to *H. influenzae*, which has virtually been eliminated in high-income countries since routine vaccination of children against this bacterium was started.[15] Nevertheless, sub-analysis in for children in high-income countries showed a protective effect of adjunctive corticosteroids on severe hearing loss overall, and a favorable point estimate for severe hearing loss due to non-*Haemophilus* meningitis. The use of corticosteroids was not associated with harm-full effects. Results of this review support the use of adjunctive corticosteroids in children in high-income countries. None of the studies in this analysis involved children younger than 1 month (neonatal meningitis). Since this is a specific group of patients with specific causative agents,[57] the use of adjunctive corticosteroids is not recommended in neonates with acute bacterial meningitis. A RCT evaluating corticosteroids in neonatal meningitis should be performed.

On the basis of the benefits of corticosteroid therapy in the adult population in high-income countries dexamethasone should be commenced in adults with suspected or proven

community-acquired bacterial meningitis in high-income countries. For adults in low-income countries, the use of corticosteroids is neither beneficial nor harmful.

The use of steroids was associated with only few side effects. However, definitions of adverse events used in the studies were heterogeneous and most studies had no specified criteria in advance, so under ascertainment is possible. Concerns have been raised over the interference by corticosteroids on CSF eradication of meningeal pathogens by reducing the blood brain barrier permeability and thereby the penetration of antibiotics in the subarachnoid space. Therapeutic failures have been described in adults treated with standard doses of vancomycin and adjunctive dexamethasone.[58] However, two studies showed with repeated lumbar punctures that in both adults and children treatment of dexamethasone did not reduce vancomycin levels in the CSF.[59,60] Although these results are reassuring, patients with pneumococcal meningitis who are treated with vancomycin and dexamethasone should still be carefully observed throughout therapy.[1]

In adults who survive acute bacterial meningitis, cognitive impairment occurs frequently.[1,4] As corticosteroids may potentiate ischemic injury to neurons,[61] it is important to know whether corticosteroids have beneficial effects on hearing loss and mortality but worsen cerebral cortical functioning.[55] Neuropsychological outcome was evaluated in patients included in the European Dexamethasone Study who survived pneumococcal or meningococcal meningitis.[62] In 87 out of 99 eligible patients, 46 (53%) of whom were treated with dexamethasone and 41 (47%) of whom received placebo, no significant differences in outcome were found between patients in the dexamethasone and placebo groups (median time between meningitis and testing was eight years). In another recent study on long-term neuropsychological outcome and dexamethasone in children, children who experienced pneumococcal meningitis and were treated with corticosteroids showed better academic achievements compared with children with pneumococcal meningitis who were not treated with adjunctive corticosteroids.[37]

Quality of the evidence

Of the 24 randomized clinical trials included in the meta-analysis 4 were of high quality, 13 of median quality and 7 of low quality. Although the number of high quality studies was low, the number of patients in these studies accounted for 45% of patients included in the meta-analysis. Studies were mostly categorized as median or low quality due to a lack of addressing missing data or because no intention to treat analysis was performed. The results of this meta-analysis should be interpreted with caution as the high quality studies show no effect of corticosteroid treatment.

The sensitivity analysis showed that in a worst case scenario dexamethasone would have no beneficial of harmful effect on hearing loss or neurological sequelae. However, this analysis was heavily influenced by a single study accounting for 46% of missing values. When this study was left out a trend towards benefit of dexamethasone on any hearing loss was found.

Several biases may have diminished the reliability of our results. The first confounding factor is selection bias. Several studies on childhood meningitis had exceptional low mortality rates; nine studies had mortality rates of 3% or less. Mortality rates of childhood

bacterial meningitis in previous reported studies ranged from 8 to 20%.[2,3] Inclusion of studies in the meta-analysis with a less severe illness, as reflected in the very low case fatality rates, will probably underestimate the protective effect of corticosteroids.[63] Five studies had very high mortality rates (over 25%). For patients admitted in a late state of disease, adjuvant corticosteroids are less protective and might even be harmful.[64] Inclusion of such patients might again lead to an underestimation of the treatment effect.

A second bias is introduced when patients are withdrawn.[33,64] The analysis was based upon per-protocol figures, as intention to treat figures were only available for 6 studies (25%) A total of 211 patients were withdrawn after the randomization process, often for unknown reasons. Reasons for withdrawal include ineligibility according to the trial criteria or inability to complete the treatment protocol.[64] Withdrawals on the grounds on ineligibility may have been influenced by knowledge of outcome; if so, this would advantage the corticosteroid regimen. Excluding participants, because of an inability to complete the course of corticosteroids due to side effects (for example, upper gastro-intestinal bleeding) clearly introduces bias in favor of the study medication, whereas withdrawals due to loss to follow up might favor the placebo group. In the Egyptian study, which was not placebo-controlled and not double-blinded, only three pathogens were cultured from the cerebral spinal fluid of enrolled participants, suggesting withdrawal of patients with other bacteria culture from CSF and those with negative CSF cultures.[29]

A third bias is introduced by competitive risks. The comparisons of hearing loss and neurologic sequelae (other than hearing loss) were made excluding all patients who died. Since mortality is possibly a treatment-related outcome, the treatment groups that exclude fatality cases may not be comparable. Competitive risks in this analysis will lead to an underestimation of the treatment effect of corticosteroids.

Finally, the included studies were heterogeneous with respect to study protocol. The first study was published in 1963,[6] the last four in 2007.[18,19,21,27] Several different study interventions were used. Therefore, study population effect-sizes were calculated as relative risks.

Agreements and disagreements with other studies or reviews

Two meta-analyses on the use of adjunctive dexamethasone in adults were published in 2009.[65,66] The first meta-analysis concluded that dexamethasone was associated with a non-significant decrease in mortality, but when the trial from Malawi was left out the decrease in mortality did reach significance.[65] The reasons to exclude the Malawian trial were a HIV positive population, high mortality, poor general status and low human development index (HDI) <0.5. However, other countries that were included had only slightly higher HDI's at the time of inclusion (Egypt 0.53,[29] India 0.53[30] and Malawi 0.49[18]). Several subgroup analyses showed that dexamethasone was most beneficial in patients with definite meningitis, in high and medium income countries and patients with a short duration of symptoms. Out of 4 analyses 8 subgroups consisted of only one or two studies, limiting the value of the meta-analysis. Analyses on mortality and hearing loss in high and medium income countries were similar to our results. The study by Bennett

was not included in this meta-analysis for unknown reasons.[6] The second meta-analysis included four recent trials in adults[17-19,31] and concluded that dexamethasone reduced mortality in high-income countries.[66]

The difference in efficacy of corticosteroids between high and low-income countries was mainly driven by two large studies from Malawi,[18,20] together representing 60% of included patients from low income countries. Patients included in these studies were often HIV-positive, presented late in the disease course or received inappropriate antibiotic therapy.[18,20] There may be several reasons for the difference in efficacy of corticosteroids such as delayed presentation, clinical severity, underlying anemia, malnutrition, the antibiotics used, HIV infection or other, unidentified differences between populations. A study compared characteristics of children with culture positive community-acquired bacterial meningitis in the Children's Unit, Queen Elizabeth Central Hospital, Blantyre, Malawi and in the Royal Liverpool Children's Hospital from time-periods before the introduction of vaccines.[67] Children in Malawi presented later and were more often comatose and malnourished, compared to children in Britain. Mortality from bacterial meningitis in children in Malawi was much higher than in children in Britain (41 versus 7%), even when infected with the same organism.

A recent meta-analysis of individual patient data was performed of 5 recent large randomized controlled trials.[17-22] Data from 2029 patients from five trials were included in the analysis (833 [41.0%] aged <15 years). HIV infection was confirmed or likely in 580 (28.6%) patients and bacterial meningitis was confirmed in 1639 (80.8%). Dexamethasone was not associated with a significant reduction in death (270 of 1019 [26.5%] on dexamethasone vs. 275 of 1010 [27.2%] on placebo; OR 0.97, 95% CI 0.79 to 1.19), death or severe neurological sequelae or bilateral severe deafness (42.3% vs. 44.3%; OR 0.92, 95% CI 0.76 to 1.11), death or any neurological sequelae or any hearing loss (54.2% vs. 57.4%; OR 0.89, 95% CI 0.74 to 1.07), or death or severe bilateral hearing loss (36.4% vs. 38.9%; OR 0.89, 95% CI 0.73 to 1.69). However, dexamethasone reduced hearing loss among survivors (24.1% vs. 29.5%; OR 0.77, 95% CI 0.60 to 0.99, p=0.04). Dexamethasone had no effect in any of the pre-specified subgroups, including specific causative organisms, pre-dexamethasone antibiotic treatment, HIV status, or age. The differences between Malawi and the other clinical settings call into question the appropriateness of summary measures that combine the results, even if statistical tests of heterogeneity are deemed acceptable. Mortality rates in the two studies from Malawi were 3 to 5 fold higher five fold higher than in the studies from Europe, South-America and Vietnam.[17-21] In subgroups of the individual patient data meta-analysis, there were several instances in which the I-square statistic was more than 50%, which indicates at least moderate heterogeneity.[68]

The current Cochrane analysis complies with the beneficial effect of corticosteroids on hearing loss that was found in subgroups of the individual meta-analysis.[22] Treatment with adjunctive corticosteroids was not associated with harm. In order to establish with certainty whether or not dexamethasone has a place in the treatment of bacterial meningitis, a large multinational randomized control trial in that subgroup would be necessary. Such a trial would need to include approximately 13.500 patients to show an odds ratio of 0.9 with a

power of 90% in a population with 27% risk of death in the placebo group, and is therefore unlikely to be performed or finished in the next decade. Meanwhile, results of our analysis support the use of corticosteroids in children and adults with community-acquired bacterial meningitis in high income countries.

Conclusions

In summary, the consistency and degree of benefit identified in this analysis merits the use of corticosteroids in adults and children with acute bacterial meningitis in high-income countries, although the strength of the evidence is not optimal. We recommend a four-day regimen of dexamethasone (0.6mg/kg daily) given before or with the first dose of antibiotics.

Implications for research

1. Although additional evidence from well designed RCTs would be optimal, this is impractical for reasons of cost and logistics.
2. Follow-up studies in countries where dexamethasone has been implemented may provide circumstantial evidence on the effectiveness of adjunctive dexamethasone.
3. Corticosteroids are not recommended in neonatal meningitis due to the different spectrum of causative micro-organisms and the lack of applicable RCT data. RCTs in neonatal meningitis are needed.
4. Case series are needed to determine the effect of adjunctive dexamethasone therapy in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains.

References

1. van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. N Engl J Med 2006; 354: 44-53.
2. Bohr V, Hansen B, Jessen O et al. Eight hundred and seventy-five cases of bacterial meningitis. Part I of a three-part series: clinical data, prognosis, and the role of specialised hospital departments. J Infect 1983; 7: 21-30.
3. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993; 12: 389-94.
4. van de Beek D, Schmand B, de Gans J et al. Cognitive impairment in adults with good recovery after bacterial meningitis. J Infect Dis 2002; 186: 1047-52.
5. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004; 351: 1849-59.

6. Bennett IL, Jr., Finland M, Hamburger M, Kass EH, Lepper M, Waisbren BA. A double-blind study of the effectiveness of cortisol in the management of severe infections. Trans Assoc Am Physicians 1962; 75: 198-207.

7. DeLemos RA, Haggerty RJ. Corticosteroids as an adjunct to treatment in bacterial meningitis. A controlled clinical trial. Pediatrics 1969; 44: 30-4.

8. Scheld WM, Dacey RG, Winn HR, Welsh JE, Jane JA, Sande MA. Cerebrospinal fluid outflow resistance in rabbits with experimental meningitis. Alterations with penicillin and methylprednisolone. J Clin Invest 1980; 66: 243-53.

9. Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. J Infect Dis 1985; 151: 528-34.

10. Lebel MH, Freij BJ, Syrogiannopoulos GA et al. Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. N Engl J Med 1988; 319: 964-71.

11. Lebel MH, Hoyt MJ, Waagner DC, Rollins NK, Finitzo T, McCracken GH, Jr. Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. Am J Dis Child 1989; 143: 301-6.

12. Odio CM, Faingezicht I, Paris M et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med 1991; 324: 1525-31.

13. Geiman BJ, Smith AL. Dexamethasone and bacterial meningitis. A meta-analysis of randomized controlled trials. West J Med 1992; 157: 27-31.

14. Havens PL, Wendelberger KJ, Hoffman GM, Lee MB, Chusid MJ. Corticosteroids as adjunctive therapy in bacterial meningitis. A meta-analysis of clinical trials. Am J Dis Child 1989; 143: 1051-5.

15. Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev 2000; 13: 302-17.

16. McIntyre PB, Berkey CS, King SM et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. JAMA 1997; 278: 925-31.

17. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002; 347: 1549-56.

18. Scarborough M, Gordon SB, Whitty CJ et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med 2007; 357: 2441-50.

19. Nguyen TH, Tran TH, Thwaites G et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med 2007; 357: 2431-40.

20. Molyneux EM, Walsh AL, Forsyth H et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. Lancet 2002; 360: 211-8.

21. Peltola H, Roine I, Fernandez J et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2007; 45: 1277-86.

22. van de Beek D, Farrar JJ, de Gans J, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. Lancet Neurol 2010; 9: 254-63.

23. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids in acute bacterial meningitis. Cochrane Database Syst Rev 2003: CD004405.

24. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2007: CD004405.

25. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. 2009 Available at www.cochrane-handbook.org.

26. United Nations Human Development Index. Human Development Index. 2009. Http://hdr.undp.org/en/statistics/ (accessed 25-11-2009).

27. Sankar J, Singhi P, Bansal A, Ray P, Singhi S. Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis. Indian Pediatr 2007; 44: 649-56.

28. Singhi S, Jarvinen A, Peltola H. Increase in serum osmolality is possible mechanism for the beneficial effects of glycerol in childhood bacterial meningitis. Pediatr Infect Dis J 2008; 27: 892-6.

29. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J 1989; 8: 848-51.

30. Bhaumik S, Behari M. Role of dexamethasone in adjunctive therapy in acute bacterial meningitis in adults. Neurol India 1998; 46: 225-8.

31. Thomas R, Le TY, Bouget J et al. Trial of dexamethasone treatment for severe bacterial meningitis in adults. Adult Meningitis Steroid Group. Intensive Care Med 1999; 25: 475-80.

32. Bademosi O, Osuntokun BO. Prednisolone in the treatment of pneumococcal meningitis. Trop Geogr Med 1979; 31: 53-6.

33. Qazi SA, Khan MA, Mughal N et al. Dexamethasone and bacterial meningitis in Pakistan. Arch Dis Child 1996; 75: 482-8.

34. Belsey MA, Hoffpauir CW, Smith MH. Dexamethasone in the treatment of acute bacterial meningitis: the effect of study design on the interpretation of results. Pediatrics 1969; 44: 503-13.

35. Wald ER, Kaplan SL, Mason EO, Jr. et al. Dexamethasone therapy for children with bacterial meningitis. Meningitis Study Group. Pediatrics 1995; 95: 21-8.

36. Marguet C, Mallet E. [Value of dexamethasone in purulent meningitis in children. Apropos of a comparative study of 85 children]. Arch Fr Pediatr 1993; 50: 111-7.

37. Ozen M, Kanra G, Kara A et al. Long-term beneficial effects of dexamethasone on intellectual and neuropsychological outcome of children with pneumococcal meningitis. Scand J Infect Dis 2006; 38: 104-9.

38. Ayaz C, Celen MK, Geyik MF, Ulug M. The efficacy of dexamethasone treatment in adult patients with acute bacterial meningitis. Neurosciences 2008; 13: 146-50.

39. Baldy JL, Passos JN. Dexamethasone in the treatment of meningococcal meningitis [Dexamethasone no tratamento da meningite meningococcia]. Rev Inst Med Trop Sao Paulo 1986; 104: 61-5.

40. Daoud AS, Batieha A, Al-Sheyyab M, Abuekteish F, Obeidat A, Mahafza T. Lack of effectiveness of dexamethasone in neonatal bacterial meningitis. Eur J Pediatr 1999; 158: 230-3.

41. Gijwani D, Kumhar MR, Singh VB et al. Dexamethasone therapy for bacterial meningitis in adults: a double blind placebo control study. Neurol India 2002; 50: 63-7.

42. Gupta A, Singh NK. Dexamethasone in adults with bacterial meningitis. J Assoc Physicians India 1996; 44: 90-2.

43. Jensen K, Ranek L, Rosdahl N. Bacterial meningitis; a review of 356 cases with special reference to corticosteroid and antiserum treatment. Scand J Infect Dis 1969; 1: 21-30.

44. Lepper MH, Spies HW. Treatment of pneumococcic meningitis; results when penicillin was used alone compared with those when penicillin and streptomycin were used together, with and without hydrocortisone: alternate patient studies. AMA Arch Intern Med 1959; 104: 253-9.

45. Passos JN, Baldy JL. [Evaluation of the use of dexamethasone in the therapeutic schedule for purulent meningitis]. Rev Inst Med Trop Sao Paulo 1979; 21: 90-8.

46. Shembesh NM, Elbargathy SM, Kashbur IM, Rao BN, Mahmoud KS. Dexamethasone as an adjunctive treatment of bacterial meningitis. Indian J Pediatr 1997; 64: 517-22.

47. Syrogiannopoulos GA, Lourida AN, Theodoridou MC et al. Dexamethasone therapy for bacterial meningitis in children: 2- versus 4-day regimen. J Infect Dis 1994; 169: 853-8.

48. Farina JSL, Alencastro R, Dallinga C, Rotta NT. Dexamethasone and bacterial meningitis: a randomized controlled trial in Brazilian children and a meta-analysis. Neurology 1995; 45: 45.

49. Ciana G, Parmar N, Antonio C, Pivetta S, Tamburlini G, Cuttini M. Effectiveness of adjunctive treatment with steroids in reducing short-term mortality in a high-risk population of children with bacterial meningitis. J Trop Pediatr 1995; 41: 164-8.

50. King SM, Law B, Heurter H, Bremner D, Wang E, Gold R. Dexamethasone therapy for bacterial meningitis: better never than late. Can J Inf Dis 1994; 5: 210-5.

51. Kilpi T, Peltola H, Jauhiainen T, Kallio MJ. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. The Finnish Study Group. Pediatr Infect Dis J 1995; 14: 270-8.

52. Kanra GY, Ozen H, Secmeer G, Ceyhan M, Ecevit Z, Belgin E. Beneficial effects of dexamethasone in children with pneumococcal meningitis. Pediatr Infect Dis J 1995; 14: 490-4.

53. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J. Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group. Lancet 1993; 342: 457-61.

54. van de Beek D, de Gans J. Dexamethasone and pneumococcal meningitis. Ann Intern Med 2004; 141: 327.

55. van de Beek D, de Gans J. Dexamethasone in adults with community-acquired bacterial meningitis. Drugs 2006; 66: 415-27.

56. Lutsar I, Friedland IR, Jafri HS et al. Factors influencing the anti-inflammatory effect of dexamethasone therapy in experimental pneumococcal meningitis. J Antimicrob Chemother 2003; 52: 651-5.

57. Saez-Llorens X, McCracken GH, Jr. Bacterial meningitis in children. Lancet 2003; 361: 2139-48.

58. Viladrich PF, Gudiol F, Linares J et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. Antimicrob Agents Chemother 1991; 35: 2467-72.

59. Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant Streptococcus pneumoniae in cerebrospinal fluid of children with acute bacterial meningitis. Antimicrob Agents Chemother 1995; 39: 1988-92.

60. Ricard JD, Wolff M, Lacherade JC et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. Clin Infect Dis 2007; 44: 250-5.

61. Sapolsky RM, Pulsinelli WA. Glucocorticoids potentiate ischemic injury to neurons: therapeutic implications. Science 1985; 229: 1397-400.

62. Weisfelt M, Hoogman M, van de Beek D, de Gans J, Dreschler WA, Schmand BA. Dexamethasone and long-term outcome in adults with bacterial meningitis. Ann Neurol 2006; 60: 456-68.

63. Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. BMJ 1995; 311: 1356-9.

64. Prasad K, Haines T. Dexamethasone treatment for acute bacterial meningitis: how strong is the evidence for routine use? J Neurol Neurosurg Psychiatry 1995; 59: 31-7.

65. Vardakas KZ, Matthaiou DK, Falagas ME. Adjunctive dexamethasone therapy for bacterial meningitis in adults: a meta-analysis of randomized controlled trials. Eur J Neurol 2009; 16: 662-73.

66. Assiri AM, Alasmari FA, Zimmerman VA, Baddour LM, Erwin PJ, Tleyjeh IM. Corticosteroid administration and outcome of adolescents and adults with acute bacterial meningitis: a meta-analysis. Mayo Clin Proc 2009; 84: 403-9.

67. Molyneux E, Riordan FA, Walsh A. Acute bacterial meningitis in children presenting to the Royal Liverpool Children's Hospital, Liverpool, UK and the Queen Elizabeth Central Hospital in Blantyre, Malawi: a world of difference. Ann Trop Paediatr 2006; 26: 29-37.

68. McIntyre P. Adjunctive dexamethasone in meningitis: does value depend on clinical setting? Lancet Neurol 2010; 9: 229-31.

69. Peltola H. Childhood bacterial meningitis relieved better by glycerol than dexamethasone. Abstract, ICAAC 2004, Washington, USA.

Appendix 1 Search strategy

MEDLINE (OVID)

1 exp Meningitis/

2 meningit*:ab,ti

3 or/1-2

4 exp 'corticosteroid'/

5 'adrenal cortex hormones':ab,ti

6 'adrenal cortex hormone':ab,ti

7 corticosteroid*:ab,ti

8 dexameth*:ab,ti

9 exp 'dexamethasone'/

10 steroid*:ab,ti

11 exp 'steroid'

12 or/ 4-11

13 3 and 11