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published in
BMC Infectious Diseases
2010

DOI (link to publisher)
10.1186/1471-2334-10-232

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
de Jonge, R. C. J., van Furth, A. M., Wassenaar, M., Gemke, R. J. B. J., & Terwee, C. B. (2010). Predicting sequelae and death after bacterial meningitis in childhood: A systematic review of prognostic studies. BMC Infectious Diseases, 10, 232. https://doi.org/10.1186/1471-2334-10-232

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Predicting sequelae and death after bacterial meningitis in childhood: A systematic review of prognostic studies

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**Abstract**

**Background:** Bacterial meningitis (BM) is a severe infection responsible for high mortality and disabling sequelae. Early identification of patients at high risk of these outcomes is necessary to prevent their occurrence by adequate treatment as much as possible. For this reason, several prognostic models have been developed. The objective of this study is to summarize the evidence regarding prognostic factors predicting death or sequelae due to BM in children 0-18 years of age.

**Methods:** A search in MEDLINE and EMBASE was conducted to identify prognostic studies on risk factors for mortality and sequelae after BM in children. Selection of abstracts, full-text articles and assessment of methodological quality using the QUIPS checklist was performed by two reviewers independently. Data on prognostic factors per outcome were summarized.

**Results:** Of the 31 studies identified, 15 were of moderate to high quality. Due to substantial heterogeneity in study characteristics and evaluated prognostic factors, no quantitative analysis was performed. Prognostic factors found to be statistically significant in more than one study of moderate or high quality are: complaints >48 hours before admission, coma/impaired consciousness, (prolonged duration of) seizures, (prolonged) fever, shock, peripheral circulatory failure, respiratory distress, absence of petechiae, causative pathogen *Streptococcus pneumoniae*, young age, male gender, several cerebrospinal fluid (CSF) parameters and white blood cell (WBC) count.

**Conclusions:** Although several important prognostic factors for the prediction of mortality or sequelae after BM were identified, the inability to perform a pooled analysis makes the exact (independent) predictive value of these factors uncertain. This emphasizes the need for additional well-conducted prognostic studies.

**Background**

Bacterial meningitis (BM) is a severe infection of the central nervous system which occurs especially in children <5 years of age. Although the occurrence of negative consequences of BM in developed countries is strongly reduced by vaccination strategies, antibiotic treatment and good care facilities, BM is still responsible for substantial morbidity and mortality in both developing and developed countries [1-3].

The mortality rate is approximately 5%, and the long-term morbidity, mainly consisting of persistent neurological sequelae, is 15% [4,6]. Sensorineural hearing loss, seizures, motor problems, hydrocephalus and mental retardation [4,7-10], as well as more subtle outcomes like cognitive, academic and behavioral problems are observed in post-meningitis children [5,11].

In pediatric care, the goal must be to prevent these sequelae as much as possible. Therefore, early recognition of children with BM with high risk for the development of sequelae is mandatory [5,12-15]. For this reason, several studies have developed prediction models or have proposed prognostic factors for mortality or morbidity in children after BM [5-9,12-37]. The aim of the present study was to systematically review the available evidence regarding prognostic factors predicting...
death or sequelae due to BM in children aged 0-18 years in both developing and developed countries.

Methods

Literature selection

A systematic search of MEDLINE and EMBASE until March 20th 2009 was conducted to identify prognostic studies on mortality or various sequelae after BM in children. The search focused on BM using terms for the 10 most common causative pathogens according to the Netherlands Reference Laboratory for Bacterial Meningitis [38]. These pathogens are listed in Appendix 1. Tuberculoid meningitis or rare forms of BM were excluded. The search was refined using MeSH terms and text words on: morbidity, mortality, cause of death, survival rate, survival, prognost*, predict*, course*, cohort* longitudinal, cohort studies, follow-up, followup, follow up, follow-up studies. The search strategies used for Medline and Embase are included in Appendix 2. All abstracts found were screened by two reviewers independently (RdJ and MW). Those potentially eligible for inclusion were read in full text by the same two reviewers independently and subsequently discussed during a consensus meeting. Reference lists of each of the selected publications were checked to retrieve relevant publications which had not been identified by the computerized search.

The publications had to meet the following inclusion criteria, which were defined prior to the search:

- The study aimed to identify prognostic factors on mortality or various sequelae due to BM. Only studies designed as prognosis studies were included. Studies designed to analyze an associative model were excluded.
- The study was designed as a longitudinal cohort study, with at least one follow-up measurement. Both prospective and retrospective studies were included.
- BM had occurred at 0-18 years of age.
- Results were published in English as full report articles in international journals from January 1960 until March 20th 2009.

Quality Assessment

The assessment of the methodological quality was performed using the Quality In Prognosis Studies (QUIPS) tool, designed for systematic reviews of prognostic studies through international expert consensus (Table 1) [39]. This assessment was performed independently by two authors (RdJ and MW). Disagreements between both authors were discussed during a consensus meeting.

| Table 1 Used (adapted) QUIPS list for scoring methodological quality of prognosis studies |
|---------------------------------------------+----------------+----------------+---------|
| Criteria                                    | Score          | +               |
| 1. Study participation                      |                | +/-             | -       |
| • Target population                         | 3              | 1.5             | 0       |
| • Sampling frame                            | 3              | 1.5             | 0       |
| • Inclusion criteria                        | 3              | 1.5             | 0       |
| • Baseline study population                 | 3              | 1.5             | 0       |
| • Adequate study participation              | 3              | 1.5             | 0       |
| 2. Study attrition                          |                | +/-             | -       |
| • Proportion of population available for analysis | 5          | 2.5             | 0       |
| • Outcome and prognostic factor information on those lost to follow up | 5          | 2.5             | 0       |
| • Reasons and potential impact of subjects lost to follow up | 5          | 2.5             | 0       |
| 3. Measurement of prognostic factors        |                | +/-             | -       |
| • Definition of prognostic factor           | 5              | 2.5             | 0       |
| • Valid and reliable measurement of prognostic factor | 5          | 2.5             | 0       |
| • Method and setting of prognostic factor measurement | 5          | 2.5             | 0       |
| 4. Measurement of outcomes                  |                | +/-             | -       |
| • Definition of outcome                     | 5              | 2.5             | 0       |
| • Valid and reliable measurement of outcome | 5              | 2.5             | 0       |
| • Method and setting of outcome measurement | 5              | 2.5             | 0       |
| 5. Statistical analysis and presentation    |                | +/-             | -       |
| • Presentation of analytical strategy       | 5              | 2.5             | 0       |
| • Model development strategy                | 5              | 2.5             | 0       |
| • Reporting of results                      | 5              | 2.5             | 0       |

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http://www.biomedcentral.com/1471-2334/10/232
The QUIPS contains six categories assessing (1) bias due to patient selection, (2) attrition, (3) measurement of prognostic factors, (4) outcome measurement, (5) confounding on statistical analysis, and (6) confounding on presentation. The items on confounding were considered irrelevant for our study because in studies regarding prognosis, the design to predict a specific outcome based on a combination of several possible prognostic factors, confounding is not an issue. The remaining 17 items of the five categories were each scored to assess the quality of the included study. High quality (‘+’) was scored when there was low risk of bias, moderate quality (‘+/−’) with moderate risk, and low quality (‘−’) when there was high risk of bias.

To strengthen the discriminative capacity of the QUIPS we developed a scoring algorithm. All five categories were given a maximum of 15 points each, equally divided over all items per category. For all items we assigned 5 points in case of low risk of bias and 2.5 and 0 in case of moderate and high risk of bias, respectively. Except for category 1 (patient selection bias) which contained five instead of three items. Here we assigned 3 points in case of low risk of bias and 1.5 and 0 in case of moderate and high risk of bias, respectively. A total score, with a maximum of 75 points, was calculated by summing up the scores per item. A priori, we chose to consider ≥60 points (≥80% of the maximum attainable score) as high quality, between 45 and 60 points (≥60% of the maximum attainable score) as moderate/high quality and <45 points as low quality studies.

**Data extraction and analysis**

Of the selected studies, data were extracted regarding study population (age at infection, country), causative pathogen, design (prospective or retrospective), duration of follow-up, method of analysis (uni- or multivariate), outcome measures and independent statistically significant prognostic factors from multivariate analysis or, if not available, from univariate analysis (p < 0.05). To facilitate interpretation and comparison of the results, data were categorized per outcome: (1) hearing loss, (2) mortality, (3) neurological sequelae, or (4) poor outcome when the original study made no distinction between mortality and neurological sequelae. Both short- and long-term outcomes were included.

This review did not aim to analyze original study data, therefore only the data presented in the manuscripts was used. Authors were not approached for insight in their data.

**Analysis of prognostic factors**

Due to heterogeneity in study design, study population and analyses of the included studies, no quantitative analysis was performed. Instead, the prognostic factors predictive for mortality or sequelae after BM were summarized per outcome category. Prognostic factors reported in different papers on the same cohort were counted once. Due to the large variety in proposed factors found, only those factors found significant (p < 0.05) in more than one study of moderate/high quality were presented.

**Results**

**Selection of studies**

Figure 1 presents a flow chart of the study selection. The search strategy yielded 6,963 citations. Of these, 43 articles seemed to fulfill the inclusion criteria and were retrieved in full text. Two additional articles were identified by checking the reference lists. Review of these 45 articles resulted in exclusion of 14 articles not meeting the inclusion criteria. Eleven studies were excluded based on design (one letter, one validation study and nine presenting an association model instead of a prognostic model), one study dealt with diagnosis (prediction of meningitis instead of sequelae), and two studies were excluded because no differentiation was made between viral or aseptic and BM for outcome measurement. Finally, 31 articles were included and assessed on methodological quality.

**Methodological quality**

The results of the quality assessment are presented in Table 2. The overall quality score ranged from 17 to
62.5 points with a median score of 43.5. Based on our cutoff of ≥60 and ≥45 points, respectively, one article was classified as high quality, 14 articles were classified as moderate/high quality and 16 articles as low quality studies.

Studies of moderate/high quality scored well on patient selection, outcome measurement, statistical analysis and presentation, and relatively well on prognostic factor measurement. However, many moderate/high quality studies scored poor on attrition. Studies classified as low quality scored relatively well on patient selection, but poor on all other categories. A poor score on prognostic factor measurement was often due to the fact the studies did not mention all factors considered in their analysis but presented only those factors found significant.

### Study characteristics

Table 3 summarizes the study characteristics of all included publications. Studies were grouped by outcome categories and ranked by quality. Of all 31 included studies, four studies focused on hearing loss, four on mortality, five on neurological sequelae ranging from mild to severe, and another 12 studies focused on poor outcome. The remaining six studies focused on both mortality and neurological sequelae, for which results were presented separately. Therefore, these studies were included more than once. The majority of all studies (n = 21) had a retrospective study design and 22 were conducted in developed countries. Sixteen studies performed a multivariate analysis. Although Klinger et al. [31] performed a multivariate analysis, we reported the prognostic factors based on their univariate analysis,

### Table 2 Results of quality assessment of studies on mortality or sequelae after bacterial meningitis

| Study | Study participation | Study attrition | Measurement of prognostic factors | Measurement of outcomes | Statistical analysis and presentation | Quality score (points) | Quality: + = high +/- = moderate - = low |
|-------|---------------------|-----------------|---------------------------------|-------------------------|--------------------------------------|------------------------|---------------------------------|
| Koomen et al., 2004 [5] | 15 | 12.5 | 10 | 12.5 | 12.5 | 62.5 | + |
| Lovera et al., 2005 [33] | 13.5 | 7.5 | 12.5 | 10 | 12.5 | 56 | +/- |
| Roine et al., 2008 [35] | 15 | 10 | 7.5 | 7.5 | 15 | 55 | +/- |
| Oostenbrink et al., 2002 [21] | 15 | 7.5 | 10 | 10 | 12.5 | 55 | +/- |
| Pelkonen et al., 2009 [6] | 12 | 10 | 12.5 | 7.5 | 12.5 | 54.5 | +/- |
| Forsyth et al., 2004 [18] | 10.5 | 10 | 7.5 | 15 | 10 | 53 | +/- |
| Biesheuvel et al., 2006 [24] | 12 | 7.5 | 10 | 10 | 12.5 | 52 | +/- |
| Pagliano et al., 2007 [19] | 12 | 5 | 12.5 | 10 | 12.5 | 52 | +/- |
| Koomen et al., 2003 [7] | 15 | 7.5 | 10 | 7.5 | 10 | 50 | +/- |
| Woolley et al., 1999 [9] | 12 | 5 | 7.5 | 12.5 | 12.5 | 49.5 | +/- |
| Klinger et al., 2000 [31] | 13.5 | 7.5 | 7.5 | 10 | 10 | 48.5 | +/- |
| Singhi et al., 2007 [15] | 13.5 | 5 | 5 | 12.5 | 12.5 | 48.5 | +/- |
| Kornelisse et al., 1995 [8] | 10.5 | 5 | 10 | 12.5 | 48 | +/- |
| Fakhir et al., 1992 [27] | 12 | 7.5 | 7.5 | 12.5 | 7.5 | 47 | +/- |
| Akpede et al., 1999 [16] | 10.5 | 7.5 | 10 | 10 | 7.5 | 45.5 | +/- |
| Kaarssen et al., 1995 [29] | 13.5 | 7.5 | 7.5 | 5 | 10 | 43.5 | - |
| Kutz et al., 2006 [14] | 13.5 | 5 | 7.5 | 7.5 | 10 | 43.5 | - |
| Pikis et al., 1996 [20] | 13.5 | 7.5 | 7.5 | 7.5 | 7.5 | 43.5 | - |
| Pomeroy et al., 1990 [34] | 15 | 5 | 5 | 10 | 7.5 | 42.5 | - |
| Wasier et al., 2005 [37] | 10.5 | 5 | 7.5 | 7.5 | 10 | 40.5 | - |
| Grimwood et al., 1996 [12] | 7.5 | 5 | 7.5 | 12.5 | 7.5 | 40 | - |
| Edwards et al., 1985 [17] | 10.5 | 7.5 | 7.5 | 10 | 2.5 | 38 | - |
| Letson et al., 1992 [32] | 10.5 | 5 | 5 | 10 | 7.5 | 38 | - |
| Chao et al., 2008 [26] | 12 | 2.5 | 5 | 7.5 | 5 | 32 | - |
| Johnson et al. 2007 [28] | 12 | 2.5 | 5 | 7.5 | 5 | 32 | - |
| Bortolussi et al., 1978 [25] | 10.5 | 5 | 2.5 | 7.5 | 5 | 30.5 | - |
| Antilla et al., 1994 [22] | 7.5 | 2.5 | 7.5 | 7.5 | 2.5 | 27.5 | - |
| Krimi et al., 2003 [30] | 7.5 | 5 | 7.5 | 2.5 | 5 | 27.5 | - |
| Valmari et al., 1987 [36] | 4.5 | 2.5 | 5 | 5 | 7.5 | 24.5 | - |
| Herson et al., 1977 [13] | 4.5 | 2.5 | 5 | 2.5 | 5 | 19.5 | - |
| Bhat et al., 1987 [23] | 4.5 | 2.5 | 2.5 | 2.5 | 5 | 17 | - |
| Study                        | Score (quality) | Design     | Developed or developing (Country) | N   | Age at infection | Pathogen | Follow-up duration | Outcome: Analysis | Significant prognostic factors from multivariate analysis or from univariate analysis with p < 0.05 |
|-----------------------------|-----------------|------------|-----------------------------------|-----|-----------------|----------|--------------------|-------------------|------------------------------------------------------------------|
| Forsyth et al., 2004 [18]  | 53 (+/-)        | Prospective | Developing (Malawi)               | 343 | 2 months - 13 yr | All      | 1 and 6 months after discharge | Hearing loss     | Univariate: Coma, positive CSF Gram stain, a low peripheral WBC count, high CSF protein level, associated neurological sequelae |
| Koome et al., 2003 [7]     | 50 (+/-)        | Retrospective | Developed (The Netherlands)       | 628 | 0 - 95 yr (mean 2.4 yr) | Non Hib | Hearing loss | Multivariate: History of symptoms >2 days, absence petechiae, low CSF glucose level, causative pathogen (S. pneumoniae), ataxia |
| Woolley et al., 1999 [9]   | 49.5 (+/-)      | Retrospective | Developed (UK)                    | 432 | Median 77 months | All      | 6 months intervals for at least 1 yr (range 1-5 yr) | Hearing loss     | Multivariate: Male sex, increased ICP, low CSF glucose level, causative pathogen (S. pneumoniae), presence nuchal rigidity |
| Kutz et al., 2006 [14]     | 43.5 (-)        | Retrospective | Developed (USA)                   | 171 | 3 months 17 yr (mean 3.8 yr) | All      | During hospitalization (longer if necessary) | Hearing loss     | Univariate: Long duration hospitalization, cranial nerve neuropathy, low CSS glucose level, high CSF protein level, seizures (not significant in case of S. pneumoniae) |
| Lovera et al., 2005 [33]   | 56 (+/-)        | Retrospective | Developing (Paraguay)             | 72  | 35 days - 15 yr (mean 48 months) | S. pneumoniae | During hospitalization | Mortality | Univariate: Age <12 months, coma, seizures, prolonged duration of seizures >48 h, low CSS WBC count, high CSS protein (albumin) level, low CSF glucose level, low peripheral WBC count, low Hb |
| Roine et al., 2008 [35]    | 55 (+/-)        | Prospective | Developing (6 countries in Latin America) | 654 total cohort, 332 included in analysis | Median 8 months in patients who died, median 12 months in survivors (not otherwise reported) | All | During hospitalization | Mortality | Multivariate: Impaired consciousness, poor peripheral circulation, high CSF protein level |
| Pelkonen et al., 2009 [6]  | 54.5 (+/-)      | Retrospective | Developing (Angola)               | 403 total cohort, 290 included in analysis | Median 90 months | All | During hospitalization | Mortality | Multivariate: Impaired consciousness, severe dyspnea, convulsions during hospitalization |
| Kornelisse et al., 1995 [8] | 48 (+/-)        | Retrospective | Developing (The Netherlands)      | 83  | 3 days - 123 yr (median 8 months) | S. pneumoniae | During hospitalization | Mortality | Univariate: Coma, level of consciousness, shock, respiratory distress, low peripheral WBC count, low serum sodium level, high CSS protein level |
| Fakhir et al., 1992 [27]   | 47 (+/-)        | Retrospective | Developing (India)                | 247 | 1 month - 14 yr | N. meningitidis | During hospitalization | Mortality | Univariate: Illness duration <12 h, hypotension, peripheral circulatory failure, coma (disturbed sensorium), rash duration <12 h, rash extent widespread, fever >40°C, absent neck rigidity, low peripheral WBC count, low ESR, low platelet count |
| Akpede et al., 1999 [16]   | 45.5 (+/-)      | Prospective | Developing (Nigeria)              | 109 | >1 month - 15 yr | All | During hospitalization (after discharge?) | Mortality | Univariate: Seizures, coma, shock |
Table 3: Study characteristics of studies on prediction of sequelae after bacterial meningitis (Continued)

| Study                          | Score (quality) | Design         | Developed or developing (Country) | N    | Age at infection | Pathogen | Follow-up duration | Outcome: sequelae | Analysis                      | Significant prognostic factors                                                                 |
|-------------------------------|-----------------|----------------|----------------------------------|------|------------------|----------|--------------------|-------------------|-------------------------------|---------------------------------------------------------------------------------------------|
| Wasier et al., 2005 [37]      | 40,5 (-)        | Retrospective  | Developed (France)               | 49   | 1 - 108 months   | S. pneumoniae | 1-12 yr (mean 5 yr) | Mortality          | Multivariate                  | High PRISM II score, low peripheral WBC count, low platelet count                             |
| Chao et al., 2008 [26]        | 32 (-)          | Retrospective  | Developing (Taiwan)              | 37   | 3 months - 11 yr | S. pneumoniae | mortality          | Mortality          | Univariate                    | Coma, shock, mechanical ventilation, endotracheal tube intubation, hyponatremia, low CSF WBC count, low CSF glucose level, low CSF/blood glucose ratio |
| Johnson et al., 2007 [28]     | 32 (-)          | Retrospective  | Developing (Nigeria)             | 71   | <16 yr           | All       | During hospitalization | Mortality          | Univariate                    | Respiratory distress, purulent/turbid CSF appearance, high CSF protein level, low CSF glucose level |
| Bortolussi et al., 1978 [25]  | 30.5 (-)        | Retrospective  | Developed (Canada)               | 52   | Neonates (<1 month) | All       | During hospitalization | Mortality          | Univariate                    | low peripheral WBC count, thrombocytopenia, low birth weight <2500 g                           |
| Koomen et al., 2004 [5]       | 62.5 (+)        | Retrospective  | Developed (The Netherlands)      | 182  | 0 - 95 yr        | Non-Hib   | 4.0 - 10.4 yr post meningitis (average 7.4 yr) | Neurological sequelae | Multivariate                  | male gender, low birth weight ≤3000 g, low educational level father, causative pathogen (S. pneumoniae), low CSF WBC count, delay >6 h start antibiotics, dexamethasone use ≤2 days, anticonvulsive treatment of seizures, prolonged fever >9 days | Univariate sequelae Academic & behavioural limitations                                    |
| Pelkonen et al., 2009 [6]     | 54.5 (+/-)      | Retrospective  | Developing (Angola)              | 403  | Median 90 months | All       | During hospitalization | Severe neurological sequelae | Multivariate                  | History of symptoms >3 days, impaired consciousness, convulsions during hospitalization          |
| Biesheuvel et al., 2006 [24]  | 52 (+/-)        | Retrospective  | Developed (The Netherlands)      | 88   | 0.9 - 5.8 yr     | Non-Hib   | Neurological sequelae | Both mild and severe | Multivariate                  | Seizures (atypical convulsions), absence petechiae/ecchymoses, low body temperature <40°C, high body temperature/fever >40°C, causative pathogen (S. pneumoniae), use of anti epileptic drugs >2 days |
| (derivation) 628 (validation) |                |                |                                  | 628  | (derivation)     | (validation) | (mean 28 yr)          | (mean 9 yr)         |                               |                                                                                              |
| Singhi et al., 2007 [15]      | 48.5 (+/-)      | Prospective    | Developing (India)               | 80   | 2 months - 12 yr | All       | 12-44 months after discharge (mean 27.5 months) | Neurological sequelae | Multivariate                  | coma, cranial nerve palsy, absent deep tendon reflexes                                         |
| (derivation) 123 (validation) |                |                |                                  | 123  | (mean 31.4 months) | All       | (mean 27.5 months) | Both mild and severe | Multivariate                  |                                                                                              |
| Kornelisse et al., 1995 [8]   | 48 (+/-)        | Retrospective  | Developed (The Netherlands)      | 83   | 3 days-123 yr    | S. pneumoniae | Hospital duration | Neurological sequelae | Univariate                    | High clinical severity score (Herson & Todd score), vomiting, shock, low peripheral WBC count, low CSF WBC count, low CSF glucose level |
| de Jonge et al, 2010, 10:232  |                |                |                                  |      |                  |           |                    |                   |                               |                                                                                              |
| Study | Score (quality) | Design | Developed or developing (Country) | N | Age at infection | Pathogen | Follow-up duration | Outcome: poor outcome | Analysis | Significant prognostic factors |
|-------|----------------|--------|----------------------------------|---|-----------------|----------|-------------------|----------------------|----------|--------------------------------|
| Akpede et al., 1999 [16] | 45.5 (+/-) | Prospective | Developing (Nigeria) | 109 | >1 month - 15 yr | All | During hospitalization (after discharge?) | Neurological sequelae: Both mild and severe motor and sensory sequelae | Univariate | Young age ≤2 yr, seizures, coma, prolonged fever >7 days, antibiotic treatment, focal nerve deficits, abnormal posturing, abnormal muscle tone |
| Pikis et al., 1996 [20] | 43.5 (-) | Retrospective | Developed (Greece) | 47 | 1 month - 14 yr (mean 2.6 yr) | S. pneumoniae | 4-23 yr (mean 12.4 yr) | Neurologic sequelae: Both mild and severe | Multivariate | Coma, high peripheral WBC count |
| Pomeroy et al., 1990 [34] | 42.5 (-) | Prospective | Developed (USA) | 185 | 1 month - 14 yr (median 10 months) | All | 1,3,6,12, months after discharge and yearly up to 6 yr | Neurologic sequelae: Both mild and severe | Univariate | Seizures, low CSF glucose level |
| Chao et al., 2008 [26] | 32 (-) | Retrospective | Developing (Taiwan) | 37 | 3 months - 11 yr (mean 37 months) | S. pneumoniae | Neurological sequelae: Both mild and severe lasting >6 months | Univariate | Focal neurological signs, seizures |

| Study | Score (quality) | Design | Developed or developing (Country) | N | Age at infection | Pathogen | Follow-up duration | Outcome: poor outcome | Analysis | Significant prognostic factors |
|-------|----------------|--------|----------------------------------|---|-----------------|----------|-------------------|----------------------|----------|--------------------------------|
| Lovera et al., 2005 [33] | 56 (+/-) | Retrospective | Developing (Paraguay) | 72 | 35 days - 15 yr (mean 48 months) | S. pneumoniae | During hospitalization | Mortality & neurological sequelae | Univariate | Young age <12 months, coma, seizures, seizure duration >48 h, low CSF WBC count, high CSF protein (albumin) level, low CSF glucose level, low peripheral WBC count, low Hb |
| Oostenbrink et al., 2002 [21] | 55 (+/-) | Retrospective | Developed (The Netherlands) | 93 | 1 month - 15 yr (median 28 yr) | Non Hib | 0.6 yr | Mortality & neurological sequelae | Multivariate | Male gender, seizures (atypical convulsions), low body temperature, causative pathogen (S. pneumoniae) |
| Roine et al., 2008 [35] | 55 (+/-) | Prospective | Developing (6 countries in Latin America) | 642 total cohort, 356 included in analysis | Median 7 months in patients with positive outcome measure died, median 14 months in patients without (not otherwise reported) | During hospitalization | Mortality & severe neurological sequelae | Multivariate | Impaired consciousness, history of symptoms >48 h, high CSF protein level, low peripheral WBC count |
Table 3: Study characteristics of studies on prediction of sequelae after bacterial meningitis (Continued)

| Study                        | Country            | Study Design | Population Details | Outcome Measures | Analysis Method | Risk Factors for Mortality & Neurological Sequelae |
|------------------------------|--------------------|--------------|--------------------|------------------|----------------|------------------------------------------------|
| Roine et al., 2008 [35]      | Developing (6 countries in Latin America) | Prospective | Median 7 months in patients with positive outcome measure died, median 18 months in patients without (not otherwise reported) | During hospitalization | Multivariate | Impaired consciousness, convulsions before admission, poor peripheral circulation, low CSF glucose level, low peripheral WBC count |
| Pagliano et al., 2007 [19]   | Developed (Italy)  | Prospective | 1 month -14 yr (median 26 months) | 8 weeks | Mortality & neurological sequelae | ICU admission, low CSF WBC count, penicillin nonsusceptibility |
| Klinger et al., 2000 [31]    | Developed (Canada) | Retrospective | Neonates 1-28 days | 1 yr | Mortality & neurological sequelae | Hypotension, coma, inotrope, seizure duration >12 h, status epilepticus, low CSF/blood glucose level, low peripheral WBC count, abnormal neurological examination at discharge, ventilation, no. of anticonvulsants |
| Akpede et al., 1999 [16]     | Developing (Nigeria) | Prospective | >1 month - 15 yr | All | Mortality & neurological sequelae | Univariate |
| Kaaresen et al., 1995 [29]   | Developed (Norway) | Retrospective | Median 19 yr (range 1 month - 138 yr) | Hospital duration and mean 6 weeks afterwards, or longer if necessary | Mortality & neurological sequelae | *multivariate analysis |
| Grimwood et al., 1996 [12]   | Developed (Australia) | Prospective | 3 months - 14 yr | All | Mortality & neurological sequelae | Young age ≤2 yr, seizures, coma, shock, prolonged fever, >7 days antibiotic treatment, no meningeval signs, focal nerve deficits, abnormal posturing, abnormal muscle tone |
| Edwards et al., 1985 [17]    | Developed (USA)    | Retrospective | Infants (not further described) | Mean 6 yr post meningitis (range 53-93 yr) | Mortality & neurological sequelae | History of symptoms >48 h, seizures, high body temperature >38 °C, peripheral vasoconstriction, low CSF WBC count |
| Letson et al., 1992 [32]     | Developed (USA)    | Retrospective | 3.5 weeks - 30 months (mean 8 months) | Mean 35 months | Mortality & neurological sequelae | Coma, hypotension (BP <40 mm Hg), low peripheral WBC count, low PMN, high CSF protein level |

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* For different time schedules during and after hospital admission not presented here.
### Table 3: Study characteristics of studies on prediction of sequelae after bacterial meningitis (Continued)

| Study                          | Year | Study Design | Region                  | Sample Size | Follow-up Details | Study Duration | Mortality & Neurological Sequelae | Analysis Type | Predictors                                    |
|--------------------------------|------|--------------|--------------------------|-------------|-------------------|----------------|-----------------------------------|---------------|------------------------------------------|
| Anttila et al., 1994 [22]      | 1994 | Prospective  | Developed (Finland)      | 143         | Mean 30 months    | All            | During hospitalization, at discharge and at 2 weeks, 3,6,12 months | Mortality & Neurological sequelae | Univariate Low body temperature, coma, neck rigidity, leaving supine position |
| Kirimi et al., 2003 [30]       | 2003 | Prospective  | Developing (Turkey)      | 48          | 2 months - 13 yr  | All            | Hospital duration                  | Mortality & Neurological sequelae | Univariate Fever >36-48 h after admission, coma 6-48 h after admission, anaemia, prolonged anaemia >3 days, low CSF WBC count, high CRP level, high CSF WBC count >3 days, low CRP level >3 days, antibiotic treatment |
| Valmari et al., 1987 [36]      | 1987 | Retrospective | Developed (Finland)      | 123         | Developing model mean 30 months | All            | Mean 2 months                      | Mortality & Neurological sequelae | Multivariate Male sex, low CSF glucose level, low CSF WBC count, low serum potassium level, positive CSF gram stain, focal neurological signs, low peripheral WBC count, low CSF granulocyte %, low platelet count, neck rigidity, absence petechiae, duration of symptoms >48 h |
| Herson et al., 1977 [13]       | 1977 | Retrospective | Developed (USA)          | 73          | 6 weeks - 5 yr    | H. influenzae b | Hospital duration, Residual morbidity: 3 months - 2 yr | Mortality & Neurological sequelae | Univariate Coma, low body temperature, seizures, shock (BP <60 mm Hg), young age <12 months, low CSF WBC count, low Hb, low CSF glucose level, prolonged symptom duration |
| Bhat et al., 1987 [23]         | 1987 | Prospective  | Developing (India)       | 256         | Non neonatal (not further described) | All            | Mortality & Neurological sequelae | Univariate Duration of illness prior to therapy >7 days, low body temperature, coma, associated illness, low peripheral WBC count, purulent/ turbid CSF appearance, high CSF WBC count, high CSF protein level, low CSF glucose level, neck rigidity, distension of abdomen, no meningeal signs, positive gram stain, positive culture, type of causative pathogen |

Studies are grouped by outcome categories and ranked by quality.
since this study reported several models for different time intervals which was more difficult to compare with other results. There was considerable variation among studies with respect to population size (37 - 716 patients) and follow-up duration (from moment of hospital discharge up to 23 years later). Studies also varied with respect to age at infection (0-17, of which three studies considered specifically neonatal/infant age) and type of causative pathogen studied (varying from describing all types (n = 17), to those only studying a specific microorganism (n = 9; mainly *Streptococcus pneumoniae*) or more than one but not all microorganisms (n = 5; mainly concerning all microorganisms; however, excluding *Haemophilus influenzae type B* (HiB)).

**Prognostic factors**

Table 4 summarizes the most important prognostic factors for sequelae and death after BM per type of outcome. For mortality and various sequelae together, 75 different possible prognostic factors were identified as significant by the included studies. Many of these factors might be of influence for the prediction of sequelae. However, it is implausible that all of them will be (equally) important. And due to poor study quality, factors not predictive for sequelae or death might have been found as prognostic factors. We therefore considered only those factors found significant in more than one study of moderate/high quality as evidence for being potentially important factors. Results from univariate and multivariate analyses are presented.

| Prognostic factor | Moderate/high quality studies with multivariate analysis | Moderate/high quality studies with univariate analysis | Low quality studies with multivariate analysis | Low quality studies with univariate analysis |
|------------------|--------------------------------------------------------|------------------------------------------------------|---------------------------------------------|---------------------------------------------|
|                  | Hearing loss | Mortality | Neurological sequelae | Poor outcome | Hearing loss | Mortality | Neurological sequelae | Poor outcome | All outcomes | All outcomes |
| History of symptoms >48 h | 1x | 1x |
| Coma/impaired consciousness | 2x | 2x | 2x | 1x | 4x | 1x | 3x | 1x | 6x |
| Seizures | 1x | 2x | 2x | | 2x | 1x | 2x | 2x | 4x |
| Shock/ hypotension | 3x | 1x | 2x | | 3x | 1x | 2x | 3x |
| Peripheral circulatory failure | 1x | 1x | | | 1x | | | |
| Severe respiratory distress | 1x | 1x | | | 1x | | | |
| Prolonged fever (>7 days) | | 1x | | | | | 1x | | |
| Seizures >12 h after admission | 1x | 2x | 1x | | 1x | 2x | 1x |
| Low peripheral WBC count | 2x | 1x | 3x | 1x | 2x | 2x | 3x |
| Low CSF WBC count | 1x | 1x | 1x | 1x | 1x | 2x | 3x |
| Low CSF glucose level | 2x | 1x | 1x | 1x | 1x | 2x | 6x |
| High CSF protein level | 1x | 1x | 1x | 2x | 1x | | |
| *S. pneumoniae* as causative pathogen | 2x | 2x | 1x | | | | | |
| Young age | | | | | | | | | |
| <1 year | 1x | 1x | 2x | 1x | 1x | | | |
| <2 years | | | | | | | | | |
| Male gender | 1x | 1x | | | | | | 2x |
| Fever >40°C | | 1x | | | | | | |
| Absence of petechiae | 1x | | | | | | | 1x |
separately. Factors reported in studies of low quality are reported combined and not per type of outcome.

In total, 17 factors were regarded as showing some evidence of importance in the prediction of sequelae or mortality after BM.

- For hearing loss, the factors *S. pneumoniae* as a causative pathogen and a low cerebrospinal fluid (CSF) glucose level showed some evidence of being important (i.e. reported in more than one moderate/high quality study).
- For mortality, coma and seizures were found to be predictive, next to shock, peripheral circulatory failure, severe respiratory distress, a low peripheral white blood cell (WBC) count and a high CSF protein level.
- For neurological sequelae in general, coma, seizures, prolonged fever for at least seven days and a low CSF (WBC) count were considered important risk factors.

Studies reporting on poor outcome, and thereby not differentiating between sequelae or mortality, also reported coma, seizures, shock, a low WBC count both peripheral as well as in CSF and a low CSF glucose level and a high CSF protein level to be important risk factors. Yet they also identified young age (indicated as younger than two years old) and prolonged seizure duration (>12 hours after admission) as important prognostic factors.

When considering all moderate/high quality studies combined, the factors of history of symptoms longer than 48 hours, male gender, fever and absence of petechiae were also found more than once. Although these factors have not been found in more than one study of moderate/high quality for a specific outcome category, they may be important prognostic factors for sequelae or mortality in general.

The 17 identified risk factors were also found in several studies of low quality (see last column of Table 4).

**Discussion**

We identified 31 studies in the literature on prognostic factors predicting sequelae or death due to BM in children 0-18 years of age. The included studies have presented a large number of potentially important prognostic factors. Only those factors reported in more than one moderate/high quality study were considered as showing some evidence of being important. These factors included several clinical parameters: coma/impaired consciousness, seizures, shock, peripheral circulatory failure, severe respiratory distress, (prolonged) fever and prolonged duration of seizures, which are all signs of severity during the acute phase of the disease. In addition, the presented factors also included results from diagnostic tests which are performed during admission of the patient in the hospital: low peripheral WBC and low WBC count in CSF, low CSF glucose level and high CSF protein level. These factors are indicators of an acute severe CNS infection and thus are also parameters of severity of the disease.

The presence of these clinical and diagnostic factors in our study demonstrates that severe illness at admission contributes to BM-related mortality and long-term sequelae. In addition, young age was also considered an important prognostic factor. This might be explained by the immature immune status resulting in more severe infections (especially in neonates and children younger than six months) and the developing (and thus more vulnerable) brain of young children. Although it is thought that young children have a higher capability of neurogenesis than older children and adults which leads to better structural repair of brain tissue, and it is known they have a higher plasticity of the brain that allows intact parts to take over functions of damaged areas, early disruption of the developing brain may leads to more functional damage [40-43]. Further, sequelae of meningitis like epilepsy, cerebral palsy and hearing problems can independently cause developmental problems in the young child.

Another prognostic factor which we also demonstrated to be related to severity was the causative pathogen of BM. *S. pneumoniae* seemed to be an important prognostic factor, suggesting a more pathogenic potency of this species in comparison to other bacteria. This has also been found in other studies presenting association or prognostic models in children or adults [3,10,44]. We also found the absence of petechiae to be a prognostic factor. Since petechiae are strongly related with the causative pathogen (occurring mostly in *Neisseria meningitidis* infections, and much less in *S. pneumoniae* meningitis), it supports the finding that *S. pneumoniae* is responsible for a non favorable outcome. In studies of high and moderate quality that reported the absence of petechiae as a risk factor, *S. pneumoniae* was also a prognostic factor of importance. Finally, male gender was found as an important prognostic factor, for which we do not have an explanation. All of these factors might be important to assess in children with BM when trying to identify those at the highest risk for the development of sequelae.

The main concern about the interpretation of the prognostic factors is the fact that due to limited quality of the included studies and heterogeneity of the data it is impossible to perform a meta-analysis and to construct an overall prediction model.
Limitations
The search strategy was restricted to full report articles published in English, in journals available in the used electronic databases. This might have led to language or publication bias by missing relevant studies.

The quality of studies was assessed using the QUIPS instrument, designed for prognosis studies addressing all common sources of bias. The QUIPS, however, lacks discriminative power. We defined a scoring algorithm for better discrimination of study quality. This scoring algorithm and cutoff points used to qualify the quality of the studies are quite arbitrary. However, all identified prognostic factors found in the included studies are presented in Table 3, allowing readers to draw their own conclusions.

We encountered some problems in interpreting the results of the studies. Only significant prognostic factors of the original studies were presented in our review. However, lack of statistical significance may be due to lack of power. Furthermore, many studies performed only univariate analysis and the presented factors might not have been found significant if multivariate analysis had been performed.

In our overview of prognostic factors we only stratified per type of outcome. We did not compare other subgroups, thereby ignoring the heterogeneity in all other study characteristics (study design, method of analysis, follow-up duration, population, age at infection, pathogen and country of study). We refrained from this since strata would include too few studies of moderate/high quality and too many prognostic factors to discriminate between the groups and draw reliable conclusions.

Finally, due to the limited quality of most studies, and the heterogeneous nature of study characteristics and results, the factors found must only be used with caution.

Conclusions
Several plausible and important prognostic factors for the prediction of sequelae or mortality after BM in childhood were proposed. Because of the limited quality of most studies and the heterogeneous nature of study characteristics and results, findings must be interpreted critically and the prognostic factors found may be used only with caution. This demonstrates that more high quality prognostic studies on factors related to sequelae or death after BM in childhood are clearly needed.

Appendix 1
The 10 most common causative pathogens of BM according to the Netherlands Reference Laboratory for Bacterial Meningitis [38]:
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenzae* type B (HiB)
- *Listeria monocytogenes*
- *Escherichia coli*
- *Streptococcus agalactiae* (Group B Streptococcus, GBS)*
- *Streptococcus pyogenes*
- *Staphylococcus aureus*
- Coagulase-negative *Staphylococcus* (CoNS)
- *Cryptococcus neoformans*

Appendix 2: used search strategies for Medline and Embase
Medline
#1 search terms on "Bacterial meningitis"
"Meningitis, Bacterial"[Mh] OR "Meningitis, Bacterial/complications"[Mh] OR "Meningitis, Bacterial/diagnosis"[Mh] OR "Meningitis, Bacterial/epidemiology"[Mh] OR "Meningitis, Bacterial/physiopathology"[Mh] OR "Meningitis, Bacterial/psychology"[Mh] OR "Meningitis, Meningococcal"[Mh] OR "Meningitis, Meningococcal/complications"[Mh] OR "Meningitis, Meningococcal/diagnosis"[Mh] OR "Meningitis, Meningococcal/mortality"[Mh] OR "Meningitis, Pneumococcal"[Mh] OR "Meningitis, Pneumococcal/complications"[Mh] OR "Meningitis, Pneumococcal/diagnosis"[Mh] OR "Meningitis, Pneumococcal/mortality"[Mh] OR "Meningitis, Escherichia coli"[Mh] OR "Meningitis, Escherichia coli/complications"[Mh] OR "Meningitis, Escherichia coli/diagnosis"[Mh] OR "Meningitis, Escherichia coli/mortality"[Mh] OR "Meningitis, Haemophilus"[Mh] OR "Meningitis, Haemophilus/complications"[Mh] OR "Meningitis, Haemophilus/diagnosis"[Mh] OR "Meningitis, Haemophilus/mortality"[Mh] OR "Meningitis, Listeria"[Mh] OR "Meningitis, Listeria/complications"[Mh] OR "Meningitis, Listeria/diagnosis"[Mh] OR "Meningitis, Listeria/mortality"[Mh] OR meningococcal[tw] AND (bacterial[tw] OR meningococcal[tw] OR pneumococcal[tw] OR Neisseria[tw] OR meningitides[tw] OR Streptococcus[tw] OR pneumonias[tw] OR Haemophilus[tw] OR Hib[tw] OR influenzae[tw] OR Listeria[tw] OR monocytes[tw] OR Escherichia[tw] OR col[tw] OR agalactiae[tw] OR pyogenes[tw] OR Staphylococcus[tw] OR aureus[tw] OR Cryptococcus[tw] OR neoformans[tw])
#2 search terms on "prognosis"
Morbidity[Mh:noexp] OR mortality[Mh:noexp] OR “cause of death”[Mh] OR survival rate [Mh] OR prognosis*[tw] OR predict*[tw] OR course*[tw] OR longitudinal[tw] OR follow-up[tw] OR survival[tw] OR cohort*[tw] OR survival studies[mh] OR follow-up studies[mh]
#3 search terms exclusions
(“addresses”[Pt] OR “biography”[Pt] OR “case reports”[Pt] OR “comment”[Pt] OR “directory”[Pt] OR “editorial”[Pt] OR “festschrift”[Pt] OR “interview”[Pt] OR “lectures”[Pt] OR "lectures"[Pt] OR "lectures"[Pt])
Final search on Bacterial meningitis and prognosis with exclusions
#1 AND #2 NOT #3

Acknowledgements
The authors thank Ricky Levitan for her help with the English language. There was no funding.

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Pre-publication history
The pre-publication history for this paper can be accessed here: http://www.biomedcentral.com/1471-2334/10/232/prepub

doi:10.1186/1471-2334-10-232

Cite this article as: de Jonge et al. Predicting sequelae and death after bacterial meningitis in childhood: A systematic review of prognostic studies. BMC Infectious Diseases 2010 10:232.