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# Risk scores for outcome in bacterial meningitis: Systematic review and external validation study

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**Summary** *Objectives:* To perform an external validation study of risk scores, identified through a systematic review, predicting outcome in community-acquired bacterial meningitis.
*Methods:* MEDLINE and EMBASE were searched for articles published between January 1960 and August 2014. Performance was evaluated in 2108 episodes of adult community-acquired bacterial meningitis from two nationwide prospective cohort studies by the area under the receiver operating characteristic curve (AUC), the calibration curve, calibration slope or Hosmer—Lemeshow test, and the distribution of calculated risks.
*Findings:* Nine risk scores were identified predicting death, neurological deficit or death, or unfavorable outcome at discharge in bacterial meningitis, pneumococcal meningitis and invasive meningococcal disease. Most studies had shortcomings in design, analyses, and reporting. Evaluation showed AUCs of 0.59 (0.57—0.61) and 0.74 (0.71—0.76) in bacterial meningitis, 0.67

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(0.64—0.70) in pneumococcal meningitis, and 0.81 (0.73—0.90), 0.82 (0.74—0.91), 0.84 (0.75—0.93), 0.84 (0.76—0.93), 0.85 (0.75—0.95), and 0.90 (0.83—0.98) in meningococcal meningitis. Calibration curves showed adequate agreement between predicted and observed outcomes for four scores, but statistical tests indicated poor calibration of all risk scores.
*Interpretation:* One score could be recommended for the interpretation and design of bacterial meningitis studies. None of the existing scores performed well enough to recommend routine use in individual patient management.


## Introduction

Bacterial meningitis kills about a fifth of people with the disease and up to half of the survivors suffer debilitating sequelae.[1,2] In bacterial meningitis, clinical deterioration can occur rapidly and is often difficult to predict.[3] Identifying patients at high risk of an unfavorable outcome may be important for counseling patients and their families, as well as deciding upon optimal patient management such as level of care. Accurate prognostic stratification can also be a valuable tool in evaluating and correcting for case mix in clinical research and for targeting intervention strategies.[4,5]

Risk scores can help physicians estimate the likelihood of a particular outcome, by combining multiple predictors from a patient's history, physical examination, or laboratory tests.[4,5] To be useful in clinical practice, the calculated risk has to match observed risk in patients under investigation. To justify treatment or counseling options that differ from standard practice, the calculated risk should differ substantially from baseline risk. A very high (or low) calculated risk should occur often enough to recommend calculation of the score in all patients.

In bacterial meningitis, many risk scores have been developed but few have been externally validated in separate datasets, and their applicability to new patients is not guaranteed.[4,5] After a systematic review of the literature to identify risk scores in community-acquired bacterial meningitis we performed an external evaluation of the performance of existing risk scores, using data collected in a prospective cohort of 2108 Dutch adult patients with community-acquired bacterial meningitis.

## Methods

### Systematic review

We performed a systematic search in MEDLINE and EMBASE to identify scores to predict outcome in adults with community acquired bacterial meningitis (see Electronic Supplementary Material (ESM) Appendix e-1). The search strategy included both MeSH terms and search terms in titles and abstracts. Terms for meningitis and common pathogens of community acquired bacterial meningitis were combined with a previously validated filter for risk scores.[6] We searched for studies report in full in scientific peer-reviewed journals between January first 1960 and August first 2014, without language restrictions.

A risk score was defined as a decision-making tool that provides probabilities, or risk categories, for particular patient outcomes, based on three or more variables obtained from history, physical examination, or simple diagnostic tests.[7] Derivation or validation studies predicting mortality or neurologic deficit in adult patients (defined as 16 years of age or older), or in patients without age restrictions, with community-acquired bacterial meningitis were eligible. We included studies based on cohorts with various pathogens, as well as those on specific pathogens. For invasive meningococcal disease, studies were selected if at least a third of patients in the cohort were reported to have meningitis. Studies focusing on tuberculous meningitis were excluded. If several risk scores had been developed in a single dataset, we only extracted the score with the highest sensitivity and specificity reported in the original publication.

Two reviewers (MWB and MCB) independently screened abstracts. Papers potentially eligible for inclusion bases on the title and abstract were read in full. The risk of bias of included studies was assessed with a list of criteria, based on a number of quality systems for prognostic studies (ESM Table e-1).[8] Disagreement between reviewers (MWB, MCB) was resolved by inviting a third reviewer (DvdB).

### Evaluation of performance

The performance of identified risk scores was evaluated using data from 2108 episodes of community-acquired bacterial meningitis collected in two nationwide prospective cohort studies on community-acquired bacterial meningitis. The Dutch Meningitis Study was performed between 1998 and 2002. It included 696 episodes of community-acquired bacterial meningitis.[1] The most common pathogens were *Streptococcus pneumoniae* (51%) and *Neisseria meningitidis* (37%). Corticosteroids were administered in 17% of episodes. The overall mortality rate was 21%. The MeninGene study is still ongoing[9—12]; we used 1412 episodes included from 2006 to 2014.[13] The most common pathogens were *S. pneumoniae* (72%) and *N. meningitidis* (11%). Adjunctive dexamethasone was administered in 89% of episodes. The overall case fatality rate was 17%.

Both studies have a similar design and methods have been described in detail elsewhere.[1,13] Included patients were older than 16 years, had bacterial meningitis confirmed by cerebrospinal fluid (CSF) culture, or the combination of a positive polymerase chain reaction or antigen test in cerebrospinal fluid for *S. pneumoniae* or *N. meningitidis* with at least one specific cerebrospinal fluid finding predictive of bacterial meningitis.[14] Patients were prospectively identified through continuous surveillance of the Netherlands Reference Laboratory for Bacterial Meningitis.

We evaluated risk scores developed for a specific bacterial pathogen and outcome in the subgroup of patients