Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis
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CRD summary
This review concluded that cerebrospinal fluid lactate may be useful for ruling out bacterial meningitis, but pre-treatment with antibiotics reduced its clinical accuracy. This conclusion reflects the data presented, but should be interpreted cautiously given some limitations in the search strategy and reporting of the review.

Authors' objectives
To assess the diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis.

Searching
MEDLINE and EMBASE were searched from inception to December 2009 for English language studies; search terms were minimally reported. The bibliographies of retrieved articles were screened for additional studies.

Study selection
Studies that measured cerebrospinal fluid lactate in a clinical population of both patients with bacterial meningitis and patients with aseptic meningitis, were eligible for inclusion. Studies were required to report cut-off points for test positivity and sufficient data to populate 2x2 contingency tables (numbers of true positive, false negative, false positive and true negative test results) or sufficient information to derive these values.

Most studies were published in 1970's and 1980's and conducted in Europe or North America. Approximately 40% of studies only included children, whilst approximately 10% only included adults. Most studies measured cerebrospinal fluid lactate using enzymatic methods or gas/liquid chromatography. Reference standard methods used to confirm the diagnosis of bacterial meningitis included culture or microscopic examination, serological test and routine cerebrospinal fluid analysis (cell counts, protein and glucose). All studies performed routine cerebrospinal fluid examination, culture and lactate measurement on the same specimen. Studies considered either the diagnosis of bacterial meningitis only or the diagnosis of bacterial meningitis, tuberculous meningitis and fungal meningitis.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Study methodological quality was assessed independently by two reviewers using the 14-item QUADAS tool; any disagreements were resolved by consensus.

The results of QUADAS assessment were reported in full and were used to generate overall quality scores (maximum 14).

Data extraction
Data were extracted to populate 2x2 contingency tables and used to calculate estimates of sensitivity and specificity with 95% confidence intervals (CIs). Data on the method of cerebrospinal fluid lactate measurement, pathogens of bacterial meningitis assessed (bacteria only, or bacteria fungi and tuberculosis) and whether or not patients were pre-treated with antibiotics, were extracted to inform the exploration of sources of heterogeneity.

Data were extracted independently by two reviewers and any disagreements were resolved by consensus.

Methods of synthesis
Summary receiver operating characteristic curves were generated using a two-level mixed logistic regression model and a hierarchical summary receiver operating characteristic model and a bivariate normal model for the logit transform of sensitivity and specificity between the studies. Pooled estimates of sensitivity and specificity and positive and negative
likelihood ratios, with 95% confidence intervals, were generated using a random-effects model.

Between study heterogeneity was quantified using $I^2$. Potential sources of heterogeneity were assessed using meta-regression and sub-group analyses. Visual examination of funnel plots and Begg's test were used to assess publication bias.

**Results of the review**

Thirty-three studies (with a total of 1,885 participants) were included in the review. The mean QUADAS score was 10.4 (range 8 to 14) and many aspects of study quality were poorly reported. Only nine studies described the selection of participants adequately and collected cerebrospinal fluid samples consecutively.

The hierarchical summary receiver operating characteristic curve gave a pooled estimate of sensitivity of 93% (95% CI 89% to 96%) and a pooled estimate of specificity of 96% (95% CI 93% to 98%). Likelihood ratio positive was 22.9 (95% CI 12.6 to 41.9) and likelihood ratio negative was 0.07 (95% CI 0.05 to 0.12). The diagnostic odds ratio was 313 (95% CI 141 to 698). Pooling using the random-effects model gave similar results.

Subgroup analyses indicated that sensitivity was lower in participants who were pre-treated with antibiotics (49%; 95% CI 23% to 75%; nine studies) compared with those not receiving pre-treatment (98%; 95% CI 96% to 100%; 17 studies).

Meta-analysis indicated that the optimal cut-off value to distinguish bacterial meningitis from aseptic meningitis was around 35 mg/dL.

Begg's test suggested possible publication bias but the authors stated that this test does not provide a valid method of assessing publication bias in reviews of test accuracy studies.

**Authors' conclusions**

The high negative likelihood ratio of cerebrospinal fluid lactate may make it useful for ruling out bacterial meningitis, but pre-treatment with antibiotics reduces clinical accuracy. Cerebrospinal fluid lactate of 35mg/dL could be the optimal cut-off value for distinguishing bacterial meningitis from aseptic meningitis.

**CRD commentary**

The review provided a clearly stated research objective and defined appropriate inclusion criteria. Reporting of the search strategy was limited and inclusion of studies was restricted to English language, raising the possibility of language bias and omission of some relevant studies. Measures to minimise error and/or bias were applied during the data extraction and quality assessment phases of the review, but it was not clear whether similar measures were applied to study selection.

The meta-analytic methods used were well described and appropriate. However, the results of individual studies were not reported (subgroup analysis only).

The authors' conclusions reflect the data presented, but should be interpreted with caution given some limitations in the search strategy and reporting of the review.

**Implications of the review for practice and research**

**Practice:** The authors stated that, for clinical practice, cerebrospinal fluid lactate was reliable in distinguishing bacterial meningitis from aseptic meningitis in combination with other cerebrospinal fluid characteristics. However, pre-treatment with antibiotics reduced its clinical value.

**Research:** The authors did not specify any recommendations for future research.

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