Adenosine deaminase and tuberculous meningitis: a systematic review with meta-analysis
Tuon FF, Higashino HR, Lopes MI, Lirvac MN, Atomiya AN, Antonangelo L, Leite OM

CRD summary
This review found that adenosine deaminase cannot distinguish between bacterial meningitis and tuberculous meningitis, but ranges of adenosine deaminase values could improve tuberculous meningitis diagnosis after bacterial meningitis has been ruled out. These conclusions should be interpreted with some caution due to the possibility of missing studies, unclear study quality and heterogeneity between studies.

Authors' objectives
To evaluate the accuracy of adenosine deaminase as a diagnostic test for tuberculous meningitis.

Searching
MEDLINE, EMBASE, Web of Science, The Cochrane Library and LILACS were searched from inception to May 2007. Search terms were reported. References of retrieved studies were screened to identify additional relevant studies. No language restrictions were applied.

Study selection
Studies that reported total adenosine deaminase values in the cerebrospinal fluid of patients with tuberculous meningitis and controls (patients with other types of meningitis) were eligible for inclusion if they reported sufficient data to produce a 2x2 table of test performance. Cases of tuberculous meningitis had to be defined according to standardised criteria (specified in the article). Patients with other types of infectious meningitis or neoplasms were included as controls. Patients with normal cerebrospinal fluid were excluded.

Studies were conducted in adults and children. Adenosine deaminase measurement assay was Giusti or unknown and thresholds in units per litre (U/L) ranged from 5U/L to 20U/L. Control groups consisted of patients with bacterial meningitis, viral and bacterial meningitis, or viral, bacterial and fungal meningitis and neoplasms. Two studies were conducted in patients with HIV.

Two reviewers independently selected studies for inclusion. Disagreements were resolved through consensus.

Assessment of study quality
Articles were classified as 1, 2, or 3 according to previously described criteria (details were not reported).

The authors did not state how many reviewers assessed studies.

Data extraction
Data were extracted on the adenosine deaminase value of each patient and classified as tuberculosis, meningitis other than tuberculosis and bacterial meningitis. Patients with either bacterial meningitis or non-tuberculous meningitis were classed as controls. Sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio were calculated for each study, together with 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted data.

Methods of synthesis
A summary receiver operating characteristic (SROC) plot was constructed and sensitivity and specificity were pooled (methods not reported) at different adenosine deaminase thresholds. Heterogeneity was assessed using the X² test. Publication bias was assessed using the Egger test.

Results of the review
Thirteen studies (n=380) were included: four prospective and nine retrospective studies. Nine studies enrolled consecutive patients and four studies enrolled a random sample. Test interpretation was blinded in three studies.

Using thresholds defined by the study authors, summary sensitivity was 74% (95% CI 69% to 79%) and summary specificity was 87% (95% CI 85% to 90%). Results were reported for other thresholds. There was substantial heterogeneity between studies (p<0.001).

Mean adenosine deaminase level in patients with tuberculous meningitis was 11.50U/L (standard deviation (SD) 7.90) and 11.80U/L (SD 10.70) in patients with bacterial meningitis. Mean adenosine deaminase level in patients with meningitis other than bacterial types was 3.00 U/L (SD 4.2).

At a threshold of 10U/L the diagnostic odds ratio for tuberculous meningitis compared to bacterial meningitis was 1.10 (95% CI 0.65 to 1.84), which suggested no discriminatory power. The diagnostic odds ratio for tuberculous meningitis compared to other non-bacterial meningitis at the same threshold was 112 (95% CI 88.9 to 145.8), which suggested excellent diagnostic performance.

**Authors’ conclusions**
Adenosine deaminase cannot distinguish between bacterial meningitis and tuberculous meningitis, but using ranges of adenosine deaminase values could be important to improve tuberculous meningitis diagnosis, particularly after bacterial meningitis has been ruled out.

**CRD commentary**
The review addressed a clear question and inclusion criteria were reported. The literature search was adequate for published studies. No specific attempts were made to locate unpublished studies and so there was a possibility of publication bias. Although this was assessed in the review, methods used were not appropriate for diagnostic accuracy studies. Appropriate steps were taken to minimise bias and errors during study selection; it was unclear whether such steps were also taken for data extraction and quality assessment. A formal quality assessment was conducted, but details were lacking and results were simply presented as summary scores which made the results impossible to interpret. Appropriate methods were used to pool studies, but the significant heterogeneity observed was not adequately investigated.

The authors’ conclusions were supported by the results, but should be interpreted with caution due to the possibility of missing studies, unclear study quality and heterogeneity between studies.

**Implications of the review for practice and research**
**Practice:** The authors stated that adenosine deaminase cannot distinguish between bacterial meningitis and tuberculous meningitis. Using ranges of adenosine deaminase values could be important to improve tuberculous meningitis diagnosis, particularly after bacterial meningitis has been ruled out.

**Research:** The authors did not state any implications for practice.

**Funding**
None stated.

**Bibliographic details**

**PubMedID**
20001225
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.