Accuracy of BAL galactomannan in diagnosing invasive aspergillosis: a bivariate metaanalysis and systematic review

Guo YL, Chen YQ, Wang K, Qin SM, Wu C, Kong JL

CRD summary
This review concluded that the bronchoalveolar lavage galactomannan assay was an accurate test for diagnosing proven and probable invasive aspergillosis and was more powerful than serum galactomannan. Some relevant studies may have been missed. The conclusions regarding bronchoalveolar lavage seem appropriate, although the number of patients was small, especially within the subgroup analyses. The authors did not evaluate serum galactomannan.

Authors’ objectives
To determine the overall accuracy of bronchoalveolar lavage galactomannan assay in the diagnosis of invasive aspergillosis.

Searching
MEDLINE and EMBASE were searched for articles published in full in English up to January 2010; search terms were reported. Reference lists of included studies and related publications were searched. Abstracts and meeting proceedings were excluded.

Study selection
Studies that evaluated the accuracy of the galactomannan assay Platelia for diagnosis of invasive aspergillosis in immunocompromised patients using bronchoalveolar lavage were included if they used the original or revised European Organization for Research and Treatment of Cancer/Mycoses as the reference standard. Studies had to include at least 10 patients and provide sufficient data to construct 2x2 tables of test performance.

Most of the studies recruited adults with haematologic malignancy. More than half of the studies used a modified version of the reference standard criteria (modifications varied across studies). Most of the studies administered an antifungal intervention. Most studies required a single bronchoalveolar lavage sample to establish a positive diagnosis. More than half of the studies used a cut-off index value for a positive test of 1 and other studies used 0.5, 1.5 or 2.

Two independent reviewers selected studies for the review; disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
It appeared that two independent reviewers assessed study quality using the adapted 11-point QUADAS tool and the STARD reporting statement. Authors were contacted where there was insufficient information to score a criterion.

Data extraction
Two independent reviewers extracted data to construct 2x2 tables of test performance. Authors were contacted for additional information where required. Sensitivity and specificity were calculated along with 95% confidence intervals (CI). Disagreements were resolved by discussion with a third reviewer.

Methods of synthesis
Pooled estimates of sensitivity and specificity were calculated using the bivariate random-effects model. Summary receiver operating characteristic (SROC) curves were presented. Positive and negative likelihood ratios with 95% CI were calculated from the pooled estimates of sensitivity and specificity. In the primary analyses, results of the reference standard were categorised into proven or probable invasive aspergillosis (positive result) and possible or no invasive aspergillosis (negative result). Classification as proven (positive result) or probable/possible/no invasive aspergillosis (negative result) was also investigated. Where different thresholds for a positive test were reported within a study, the one that offered the best diagnostic performance was included in the meta-analysis. Heterogeneity was assessed using the I² statistic. Heterogeneity was investigated in terms of population, study design, direction of data collection, patient recruitment method, reference standard criteria, blinding, presence of incorporation bias, number of positive samples...
required to make a positive diagnosis and use of an antifungal intervention. Publication bias was assessed using funnel plots. A prevalence of 12% was used for the calculation of post-test probability.

Results of the review
Thirteen datasets across 12 publications met the inclusion criteria (909 participants, range 30 to 116). Four studies were retrospective case-control studies. Eight studies recruited consecutive patients. Four studies were retrospective and four prospective cohort studies. More than 60% of studies were subject to progression bias, did not blind interpreters of the index test and/or reference standard and did not report uninterpretable results. Differential and verification biases and incorporation bias were avoided in approximately 60% to 70% of studies. Approximately 50% of studies had a representative patient spectrum. STARD scores ranged from 12 to 18 (maximum score attainable was not reported).

Across the 13 datasets, sensitivity ranged from 59% to 100% and specificity from 76% to 100%. Pooled sensitivity was 90% (95% CI, 79% to 96%), specificity was 94% (95% CI, 90% to 96%), positive likelihood ratio was 14.87 (95% CI 8.89 to 24.90), and negative likelihood ratio was 0.10 (95% CI 0.04 to 0.24). With a disease prevalence of 12%, the post-test probability of proven or probable invasive aspergillosis was 67% with a positive test and 1% with a negative test. When only proven cases were considered positive on the reference standard (10 studies), pooled sensitivity was 94% (95% CI, 86% to 98%), specificity was 79% (95% CI, 68% to 86%), positive likelihood ratio was 4.41 (95% CI 2.87 to 6.77), and negative likelihood ratio was 0.07 (95% CI 0.03 to 0.19). $I^2$ was more than 50% for each analysis.

Results for subgroup analyses and different cut-off values for the bronchoalveolar lavage galactomannan assay were presented. Sensitivity and specificity were lowered when patients were receiving antifungal treatment. There was no evidence of publication bias.

Authors' conclusions
The bronchoalveolar lavage galactomannan assay was a sensitive and specific test for the diagnosis of proven and probable invasive aspergillosis; it was more powerful than serum galactomannan detection. The assay was likely to be a useful tool for diagnosing invasive aspergillosis.

CRD commentary
The authors addressed a clear research question supported by well-defined reproducible inclusion criteria. Several relevant sources were searched. Inclusion was restricted to studies published in English as full papers so publication and language biases may have been present and relevant studies may have been missed. Each stage of the review process was conducted in duplicate, which reduced risks of error and bias. Study quality was assessed using appropriate criteria. Results of the quality assessment were reported only in summary, but their impact was investigated in the analysis.

Robust and appropriate methods were used to synthesise the data. Heterogeneity was investigated.

Although there may be additional studies that were not identified, this was a generally well-conducted review. The conclusions regarding bronchoalveolar lavage seem appropriate, although the sample size was quite small, especially within the subgroup analyses. The authors did not evaluate serum galactomannan so the comparison with this test is based upon other research of unknown quality.

Implications of the review for practice and research
**Practice**: The authors recommended performing two bronchoalveolar lavage galactomannan samples to rule out diagnoses in at-risk patients if clinical conditions were feasible.

**Research**: The authors stated a need for further studies focused on the impact of treatment agents and neutropenic status.

Funding
None reported.

Bibliographic details
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.