Use of PCR for diagnosis of invasive aspergillosis: systematic review and meta-analysis

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CRD summary
This review found that a single polymerase chain reaction (PCR) negative test result was sufficient to exclude a diagnosis of invasive aspergillosis, but two positive test results were required to confirm the diagnosis. These conclusions were supported by the data presented, but should be interpreted with caution given the possibility of publication bias and failure to investigate heterogeneity.

Authors' objectives
To determine the accuracy of polymerase chain reaction (PCR) tests for the diagnosis of invasive aspergillosis.

Searching
MEDLINE and EMBASE were searched from 1980 to July 2008. Search terms were reported. Bibliographies of retrieved articles were screened. No language restrictions were applied.

Study selection
Studies that enrolled consecutive individuals at high risk for invasive aspergillosis and that assessed polymerase chain reaction (PCR) techniques on blood, serum or plasma samples versus accepted diagnostic criteria as the reference standard, were eligible for inclusion. Accepted criteria for the diagnosis of invasive aspergillosis were defined as those proposed for invasive fungal disease by the European Organisation for Research and Treatment of Cancer and Mycoses Study Group for studies published after 2002. Eligible studies had to report sufficient data to construct a 2x2 table of test performance. Studies that assessed PCR on bronchoalveolar lavage alone were excluded, as were diagnostic case-control studies.

Studies included adults and/or children, most of whom had received chemotherapy for a haematological malignancy or had been given a haemopoietic stem-cell transplant. The prevalence of invasive aspergillosis ranged from 5.4% to 66.7%. Included studies used PCR either to screen patients or as a diagnostic tool. Some studies administered prophylaxis against aspergillosis in all patients. Most included studies performed PCR on whole blood samples, with volumes ranging from 200μL to 10mL. Three studies performed PCR on serum and one on plasma. Twelve variations in PCR technique were used.

Three reviewers independently assessed studies for inclusion; disagreements were resolved through discussion.

Assessment of study quality
The 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to assess study quality.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Data were analysed for two criteria for a positive test result, a single positive sample, or two consecutive positive samples. Pooled sensitivity, specificity and diagnostic odds ratios were calculated together with their 95% confidence intervals (CI). The DerSimonian and Laird random-effects model was used to pool diagnostic odds ratios; sensitivity and specificity were pooled using the bivariate model. Summary positive and negative likelihood ratios were estimated from pooled sensitivity and specificity. Publication bias was assessed using funnel plots and the Egger test. The Moses-Littenberg model was used to estimate summary receiver operating characteristic (SROC) curves. Q* (the point where sensitivity equalled specificity) was calculated. Heterogeneity was assessed using the Cochran Q and I² statistics.
Sensitivity analyses were conducted by excluding individual studies to determine whether quantitative results differed.

**Results of the review**

Sixteen studies (n=1,618 patients) were included. Study quality was generally high, with all studies fulfilling at least 8 of the 14 QUADAS items.

When two consecutive positive samples were required for a positive result, the pooled sensitivity was 75% (95% CI 54 to 88) and pooled specificity was 87% (95% CI 78 to 93). When only a single positive sample was required, the pooled sensitivity was 88% (95% CI 75 to 94%) and the pooled specificity was 75% (95% CI 63 to 84). Data on heterogeneity were not reported. The exclusion of single studies had no effect on the overall diagnostic odds ratio.

**Authors' conclusions**

A single polymerase chain reaction (PCR) negative test result was sufficient to exclude a diagnosis of proven or probable aspergillosis, but two positive tests were required to confirm the diagnosis.

**CRD commentary**

The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was adequate for published studies, but specific attempts were not made to locate unpublished studies, so publication bias was a possibility. This was assessed by the review, but the methods used were not appropriate for diagnostic studies. Appropriate steps were taken to minimise bias and errors in the selection of studies, but it was unclear whether such steps were also taken in the extraction of data or assessment of study quality.

Study quality was assessed using appropriate criteria, but the results of this were not reported in detail or considered in the synthesis of results. Methods used to pool data were appropriate and based on the most robust available models. Based on the summary receiver operating characteristic plots there appeared to have been substantial heterogeneity in both sensitivity and specificity, but results for the statistical assessment of heterogeneity were not reported and heterogeneity was not investigated.

The authors conclusions were supported by the data presented, but should be interpreted with caution given the possibility of publication bias and failure to investigate heterogeneity.

Four of the authors disclosed financial links with pharmaceutical companies.

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

**Practice**: The authors state that a single PCR-negative result is sufficient to exclude a diagnosis of proven or probable aspergillosis, but two positive tests are required to confirm the diagnosis.

**Research**: The authors stated that once a standard for *Aspergillus* species PCR screening has been established (there is currently an ongoing initiative to do this), formal validation may be possible; this might include estimation of its use in patients most likely to benefit and definition of its role in managing invasive aspergillosis.

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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.