Detection of Mycobacterium avium subspecies paratuberculosis from patients with Crohn's disease using nucleic acid-based techniques: a systematic review and meta-analysis

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CRD summary
This review assessed the relationship between presence of Mycobacterium avium subspecies paratuberculosis (MAP) in the gut (as measured my nucleic acid-based assays) and Crohn's disease, using case-control type studies. The authors’ appropriately concluded that although MAP was detected more frequently in Crohn's disease patients than in controls, the association was inconclusive and the pathogenic role of MAP was unclear.

Authors' objectives
To determine the presence of Mycobacterium avium subspecies paratuberculosis (MAP) in patients with Crohn's disease compared with controls, using polymerase chain reaction (PCR) and in situ hybridization (ISH) assays.

Searching
MEDLINE, EMBASE, BIOSIS Previews, The Cochrane library and Web of Science were searched from inception to January 2006. Search terms were reported. Database of Abstracts and Reviews and Conference Proceedings was searched with respect to the following meetings: World Congress of Gastroenterology, British Gastroenterology Society, United European Gastroenterology Week and American College of Gastroenterology. Bibliographies of published articles and reviews were screened for additional studies. Experts in the field were contacted. No language restrictions were applied.

Study selection
Studies that compared frequency of detection of MAP using PCR or ISH assays in patients with Crohn's disease and with controls were eligible for inclusion.

Nearly half of the included studies stated that only adult participants were included. Approximately 25% of studies reported that immunosuppressed patients were included. Most studies used IS900 as the target sequence. Methods used for DNA extraction varied. Methods to enhance MAP detection (mechanical disruption of tissue and use of nested PCR) were not widely used.

The authors did not state how many reviewers performed the inclusion screening.

Assessment of study quality
The authors stated that methodological quality of included studies was assessed using a form adapted from the Berkeley Systematic Reviews Group, but did not specify which tool published on this site was used. Blinding of investigators to the source of tissue or samples was reported in the results tables for included studies.

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

Data extraction
Data were extracted on the proportion of cases and controls testing positive for MAP. The risk difference with 95% confidence interval (CI) was calculated for each included study.

One reviewer extracted data from each study.

Methods of synthesis
Pooled estimates of risk difference and 95% CI were calculated for ISH, PCR and overall using a random effects model where significant heterogeneity (p<0.20) was detected, based on a Χ² test.

Meta-regression was used to investigate sources of heterogeneity. Covariates were specified a priori and included: inclusion of children; study year; inclusion of patients on immunosuppressive therapy; use of nested PCR; mechanical disruption and laser dissection; blinding; use of positive and negative controls; and presence of granulomas in tissue.
samples. Sensitivity analyses were undertaken that excluded single studies, studies with no MAP detected and studies that did not use IS900.

Publication bias was assessed using funnel plots and Begg's test.

**Results of the review**
Forty-seven studies that reported 49 data sets (two studies used both PCR and ISH) were included in the analysis. Forty-three studies used PCR. Six studies used ISH. Median number of participants was 51 (range five to 200). Twelve studies reported blinding of investigators to the source of samples; no further methodological quality data were reported.

All assays: Overall pooled estimate of risk difference was 0.23 (95% CI 0.14 to 0.32; 49 data sets). There was significant between-study heterogeneity. When studies with no MAP (in either cases or controls) were excluded, the pooled estimate of risk difference was 0.33 (95% CI 0.22 to 0.45; 32 data sets).

PCR: Overall pooled estimate of risk difference was 0.20 (95% CI 0.12 to 0.28; 43 data sets). There was significant between-study heterogeneity. Thirteen studies showed a risk difference of zero and three showed a negative risk difference, which suggested greater detection of MAP in controls. Exclusion of the only study that did not use IS900 and exclusion of studies that assessed tissue samples did not significantly affect estimates of risk difference.

ISH: Overall pooled estimate of risk difference was 0.43 (95% CI 0.01 to 0.84; six data sets). There was significant between-study heterogeneity.

Regression analyses suggested that more recent studies, studies that included children and studies that used PCR were more likely to report a positive risk difference (greater MAP in Crohn's disease patients than in controls).

Funnel plots and Begg's test showed evidence of publication bias.

**Authors' conclusions**
Review data confirmed the observation that MAP was detected more frequently in Crohn's disease patients than in controls. However, the association between MAP and Crohn's disease remained controversial and inconclusive, and the pathogenic role of this bacterium in the gut remained uncertain.

**CRD commentary**
This review assessed the relationship between presence of MAP in the gut and Crohn's disease, using case-control type studies. Broad inclusion criteria were stated. Information about control group characteristics was limited, which made the nature of the groups under comparison unclear (for example, were studies of patients with Crohn's disease compared with healthy controls or patients with Crohn's disease compared to patients with other gut pathologies?). A range of sources was searched for relevant studies (including potential sources of unpublished studies) and no language restrictions were applied, which increased the likelihood that a high proportion of relevant studies were retrieved. However, some evidence of publication bias was detected. Data extraction was undertaken by a single author and no details of the rest of the review process were reported, which left potential for error and/or bias. The authors reported that the methodological quality of included studies was assessed, but no details were provided and only the blinding of investigators was reported. The meta-analytic methods used were broadly appropriate, although the value of pooled estimates from data sets with such an apparently high degree of heterogeneity was questionable. The authors' conclusions were appropriately cautious given the weaknesses in the meta-analysis and limitations of the underlying data set.

**Implications of the review for practice and research**
**Practice:** The authors made no recommendations for practice.

**Research:** The authors stated that future studies should determine whether MAP had a pathogenic role in Crohn's disease. Studies should also assess evidence of temporality and specificity of the apparent association between MAP and Crohn's disease.

**Funding**
Not stated.

Bibliographic details
Abubakar I, Myhill D, Aliyu SH, Hunter PR. Detection of Mycobacterium avium subspecies paratuberculosis from patients with Crohn's disease using nucleic acid-based techniques: a systematic review and meta-analysis. Inflammatory Bowel Diseases 2008; 14(3): 401-410

PubMedID
17886288

DOI
10.1002/ibd.20276

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Crohn Disease /complications; DNA, Bacterial /analysis; Diagnosis, Differential; Humans; Mycobacterium avium subsp. paratuberculosis /genetics /isolation & purification; Nucleic Acid Amplification Techniques /methods; Paratuberculosis /complications /diagnosis /microbiology

AccessionNumber
12008103745

Date bibliographic record published
03/02/2009

Date abstract record published
16/06/2010

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.