Oral purified bacterial extracts in chronic bronchitis and COPD: systematic review
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CRD summary
This review found that oral bacteria extracts improve symptoms in patients with chronic bronchitis and chronic obstructive pulmonary disease. There was insufficient evidence to suggest that they prevent exacerbations. Adverse effects such as cutaneous and urologic problems were common. The studies were generally of a poor quality and reported a large variety of outcomes, which weakens the reliability of the authors' conclusions.

Authors' objectives
To quantify the efficacy of oral bacterial extracts in patients with chronic bronchitis and chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, PREMEDLINE, EMBASE, LILACS, BIOSIS Previews, CINAHL, HealthSTAR, Inspec and the Cochrane Controlled Trials Register were searched to July 2003 for reports in any language; the search terms were reported. Manufacturers were contacted for further information and for any available unpublished data. The bibliographies of included reports and relevant reviews were checked manually.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing an oral bacterial (active) extract with a placebo or no treatment were eligible for inclusion. The included studies compared OM-85 BV, LW-50020 and SL-04 with placebo.

Participants included in the review
Studies of adults with chronic bronchitis or COPD were eligible for inclusion. Studies on the prevention of acute respiratory tract infections in otherwise healthy adults were excluded from the review.

Outcomes assessed in the review
Studies reporting on the efficacy or harm of oral bacterial extracts were eligible for inclusion. Studies reporting only on immunological parameters were excluded. The primary outcome was defined as the prevention of exacerbation. Definitions of exacerbation were taken as reported in the original trials. The secondary outcomes included duration of the exacerbation, improvement of symptoms, rate of hospitalisation due to exacerbation and any adverse effects. The included studies followed up patients for 3 to 12 months.

How were decisions on the relevance of primary studies made?
One reviewer screened all retrieved reports to assess eligibility for inclusion in the review.

Assessment of study quality
The studies were assessed, using a 6-point scale, for adequacy of patient enrolment, sequence generation, concealment of allocation, blinding, how drop-outs were handled and whether an intention-to-treat analysis had been performed. The reviewers considered a quality score of 4 or more to be adequate. Four reviewers independently assessed the methodological quality of the included studies. Any disagreements were resolved by discussion.

Data extraction
One reviewer extracted the data from the included studies using standard collection sheets; the other reviewers checked this information. Dichotomous data, i.e. relative risks (RRs) or odds ratios (ORs), on the efficacy or harm of oral bacterial extracts were extracted into 2x2 tables.

**Methods of synthesis**

**How were the studies combined?**

Pooled RRs or ORs, with their associated 95% confidence intervals (CIs), were calculated through combining studies in a meta-analysis using either a fixed-effect or random-effects model.

**How were differences between studies investigated?**

Statistical heterogeneity was assessed visually by examining forest plots and formally by calculating the chi-squared test statistic. Potential causes of any identified heterogeneity and the effect of individual studies on the summary effect estimate were explored.

**Results of the review**

Thirteen RCTs were included in the review (n=2,121 randomised, 1,971 analysed).

The methodological quality of the included studies was generally poor, with a median quality score of 2.

Using a random-effects model, there was no statistically significant difference between the use of active extracts and placebo for the prevention of exacerbation (3 studies); the RR was 0.66 (95% CI: 0.41, 1.08). The presence of statistical heterogeneity was identified (P<0.001).

There was a statistically significant benefit for the average duration of an exacerbation in favour of treatment with active extracts compared with placebo (3 trials); the weighted mean difference was -3.3 days. Significant statistical heterogeneity was detected between the trials.

There was a statistically significant difference in favour of the bacterial extracts, compared with placebo, in improvement assessed by observers (5 studies; RR 0.57, 95% CI: 0.49, 0.66) and patients (2 studies; RR 0.44, 95% CI: 0.31, 0.61).

Skin itching or cutaneous eruptions and urologic problems were experienced significantly more by those receiving bacterial extracts than those receiving placebo. No other significant adverse effects were found, and no significant difference in hospitalisation was identified.

**Authors' conclusions**

Oral bacterial extracts improved symptoms in patients with chronic bronchitis and COPD. There was insufficient evidence to suggest that they prevented exacerbations. Adverse effects such as cutaneous and urologic problems were common.

**CRD commentary**

The review question was clear in terms of the study design, intervention, participants and outcomes. A thorough search strategy, without language restrictions, was employed. Some attempt was made to locate unpublished studies; however, the reviewers did not assess the possibility of publication bias. Only one reviewer selected studies for inclusion in the review, thus creating the possibility for error and bias. Methods were used to minimise bias in the assessment of validity and data extraction.

Adequate information on the included studies was presented. Studies reporting adequate data were combined in a meta-analysis, and forest plots were presented for the primary and some secondary outcomes. Statistical heterogeneity was assessed and briefly discussed where it was identified. The sparse nature of the data prevented any formal sensitivity analyses. The authors' conclusions appear to follow from the evidence presented. The studies were generally of a poor quality and reported on a large variety of outcomes, which weakens the reliability of the authors' conclusions.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future trials should examine whether bacterial extracts are more effective in preventing exacerbations of COPD in high-risk patients with severely impaired lung function. Further relevant end points, such as hospital admission, duration of disease-free intervals, saved days of absence from work and the need for concomitant medications, should be considered.

Funding
Swiss National Research Foundation, Programme for Social Medicine and Preventive and Epidemiologic Research, grant number 3233-051939.97/2.

Bibliographic details

PubMedID
15539739

DOI
10.1378/chest.126.5.1645

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Bacteria; Bronchitis /drug therapy; Chronic Disease; Complex Mixtures /therapeutic use; Humans; Pulmonary Disease, Chronic Obstructive /drug therapy; Randomized Controlled Trials as Topic

AccessionNumber
12005003272

Date bibliographic record published
30/04/2006

Date abstract record published
30/04/2006

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.