Exacerbations of chronic obstructive pulmonary disease: when are antibiotics indicated? A systematic review
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CRD summary
This well-conducted review evaluated the effect of antibiotics on clinical outcomes in patients suffering from exacerbations of chronic obstructive pulmonary disease (COPD). Antibiotics lead to a substantial reduction in treatment failure and mortality rates in COPD patients with severe but not mild to moderate exacerbations. The results of the review are likely to be reliable.

Authors' objectives
To evaluate the effect of antibiotics on clinical outcomes in patients suffering from exacerbations of chronic obstructive pulmonary disease (COPD).

Searching
The Cochrane CENTRAL Register (Issue 4, 2005), PREMEDLINE (1960 to 1965), MEDLINE (1966 to March 2006), EMBASE (1974 to March 2006) and DARE (March 2006) were searched; the search terms were not reported. Bibliographies of included studies and review articles, and conference proceedings of the American Thoracic Society and the European Respiratory Society (2000 to 2006) were handsearched. Six major pharmaceutical companies were contacted for unpublished data. Internet searches of trial registers were made to identify ongoing or recently completed trials. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Mean follow-up ranged from 5 to 35 days.

Specific interventions included in the review
Trials that compared any oral or parenteral antibiotics, given for a minimum of 3 days, with placebo or no antibiotics were eligible for inclusion. In the included trials, patients were treated with one of the following: oxytetracycline, chloramphenicol, penicillin with streptomycin, tetracycline, trimethoprim sulfamethoxazol, amoxicillin (with or without clavulanic acid), doxycycline, cefaclor, co-trimoxazol or ofloxacin. Details of the dosage regimen for each trial were listed in the paper. All of the included trials were placebo-controlled. Patients also received cointerventions including systemic corticosteroids, theophylline, beta-mimetics, gastric ulcer prophylaxis, or ventilation support with or without oxygen.

Participants included in the review
Patients with COPD who were suffering from an exacerbation of symptoms were eligible for inclusion. Studies were only eligible if at least 90% of the patients had a physician-diagnosed or spirometrically-confirmed COPD diagnosis. Studies of patients with acute bronchitis, pneumonia, asthma or bronchiectasis were not eligible for inclusion. COPD exacerbation was defined as the worsening of previously stable COPD, including increased dyspnoea, increased cough, increased sputum volume or change in sputum colour. Exacerbation was categorised as mild to moderate (requiring outpatient treatment) or severe (requiring in-patient treatment). In the included studies, the mean age of the participants ranged from 54 to 71 years (where stated), and between 43% and 100% of the participants were male (where stated). Seven of the trials were based in participants with mild to moderate COPD and six included participants with severe COPD.

Outcomes assessed in the review
The primary outcome was treatment failure, defined as the non-resolution of symptoms or signs or the requirement for more antibiotics. In the included studies, the definition of treatment failure varied, ranging from patient-reported
failure of symptom resolution to the physician's decision to prescribe additional treatment. The secondary outcomes
included duration of hospital stay, admission to an intensive care unit, health-related quality of life, symptoms,
mortality and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers independently made decisions on the relevance of identified trials. Agreement between the two
reviewers was reported as very high (97%), but the authors did not state how any disagreements were resolved.

Assessment of study quality
Two reviewers independently assessed the quality of the included trials using a published checklist, and any
disagreements were resolved by consensus or through discussion with a third reviewer.

Data extraction
One reviewer extracted the data and a second reviewer checked the extraction. Up to three attempts were made to
contact authors of the included studies for further data, where required. Dichotomous data were entered into
contingency tables, while continuous data were recorded using summary statistics of central tendency and variability.
Summary odds ratios (ORs), 95% confidence intervals (CIs) and numbers-needed-to-treat (NNT) were calculated.

Methods of synthesis
How were the studies combined?
Where there was no evidence of statistical heterogeneity (p<0.1) fixed-effect models were used to estimate summary
ORs using the inverse variance method. Publication bias was assessed using Egger's regression-based test.

How were differences between studies investigated?
Statistical heterogeneity between the studies was assessed using the chi-squared statistic. Effect modification by
severity of exacerbation was investigated through subgroup analyses. Reasons for the heterogeneity were investigated
using meta-regression.

Results of the review
Thirteen RCTs (n=1,557) were included in the review.

The quality of the included trials was moderate or good. From an overall score of 10, the quality score ranged from 5 to
8.

There was no evidence of publication bias.

Treatment failure (10 studies, 1,391 participants).

Antibiotics were associated with a lower treatment failure rate than placebo (0.12 versus 0.34), but there was significant
heterogeneity between the studies (p<0.001), so the results were not pooled. This heterogeneity was partly explained by
one study, which was omitted from some subsequent analyses, and partly explained by disease severity. Among
participants with mild to moderate COPD (5 studies, 581 participants), antibiotics were not associated with a treatment
failure rate (OR 1.09, 95% CI: 0.75, 1.59). When the trial mentioned above was included (6 studies, 916 participants),
antibiotics were associated with a lower treatment failure rate than placebo (OR 0.55, 95% CI: 0.41, 0.74); the NNT
was 9 (95% CI: 6, 16). However, there was significant heterogeneity. Among participants with severe COPD (4 studies,
475 participants), antibiotics were associated with a lower treatment failure rate than placebo (OR 0.25, 95% CI: 0.16,
0.390); the NNT was 4 (95% CI: 3, 5).

Mortality. Among participants with severe COPD (4 studies, 475 participants), antibiotics were associated with lower
mortality than placebo (OR 0.20, 95% CI: 0.06, 0.62); the NNT was 14 (95% CI: 12, 30). There was no evidence of
statistical heterogeneity.
Duration of hospital admission (3 studies, 202 participants). Antibiotics were not associated with duration of hospital admission in two of the studies, but were associated with a reduced length of stay in the third study.

Adverse events (6 studies, 1,068 participants). Antibiotics were associated with a higher rate of adverse events than placebo (0.15 versus 0.08), but there was significant heterogeneity between the studies (I-squared 62%), so the results were not pooled.

**Authors' conclusions**
Antibiotics lead to a substantial reduction in treatment failure and mortality rates in COPD patients with severe but not mild to moderate exacerbations.

**CRD commentary**
The review answered a clearly stated research question. Attempts were made to search published and unpublished sources, without any language restrictions, though the search terms were not reported. The authors appear to have tried to minimise errors and bias in the review process. The analysis also considered heterogeneity between the studies and an assessment of study quality was carried out. Overall, it is therefore likely that the results of the review are reliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors recommended a randomised, non-inferiority trial comparing the effectiveness of antibiotics with a watchful-waiting strategy. They also stated that the usefulness of sputum purulence as a guide to antibiotic treatment should be further investigated, as should the long-term effects of antibiotics given for acute exacerbations.

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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.