Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies


CRD summary
The authors concluded that short courses of antibiotic therapy (five days or less) are as effective as conventional courses in the treatment of mild to moderate acute exacerbations of chronic obstructive pulmonary disease and chronic bronchitis. The review was well conducted and these conclusions appear reliable.

Authors’ objectives
To determine whether a short course of antibiotics (five days or less) is as effective as a conventional longer course in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) or chronic bronchitis.

Searching
The following databases were searched from inception to July 2006: the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE. Search terms were reported. The reference lists of included studies were handsearched. The search was restricted to studies published in English.

Study selection
Double-blinded randomised controlled trials (RCTs) of antibiotics for treating acute exacerbation of clinically diagnosed COPD, chronic bronchitis or pulmonary emphysema were eligible for inclusion. Trials had to be conducted on adult patients (at least 18 years old), who were not receiving antimicrobial treatment at the time of diagnosis. Trials had to include treatment for five days or less compared with treatment for over five days. The primary outcome in the review was clinical cure at early follow-up, analysed on an intention-to-treat basis. Secondary outcomes were clinical cure rate at late follow-up and bacteriological cure rate. Indeterminate outcomes for any reason were considered treatment failures. Studies using azithromycin in the short-term arm were excluded.

Most participants in the included trials were outpatients, though some studies included hospital inpatients. Mean participant age was 58 years. The mean percentage of smokers was 72%. Exacerbation was defined in the included studies (where stated) as two out of three of the following: increased cough and /or dyspnoea; increased sputum volume; and increased purulence (i.e. Anthonisen type 1 or 2). The mean duration of treatment was 4.9 days in the short term groups and 8.3 days in the longer term groups. The mean time of early follow-up evaluation was 15 days (range eight to 24 days) and of late evaluation was 31 days (range 17 to 45 days). Antibiotics used in the short term arms were cephalosporins, macrolides and fluoroquinolones. New agents were often used in the short-term treatment arm.

Two reviewers independently selected studies for inclusion, with disagreements resolved by consensus.

Assessment of study quality
Study validity was assessed using the Jadad scale, which measures adequacy of randomisation, double blinding, and management of withdrawals and drop-outs. Each study was awarded a score out of a maximum of 5 points.
Concealment of treatment allocation was also evaluated.

Two reviewers conducted the assessment.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the numbers of events in the control and intervention groups of each study. Where RCTs had more than two treatment arms, the comparison involving the same antibiotic in both arms was chosen for the review.
Two reviewers independently extracted the data for each study.

**Methods of synthesis**
Data were pooled using a fixed effect model to obtain pooled ORs and 95% CIs and subgroup analyses were conducted to assess the impact on outcomes of the antibiotic class used in the short-term arm. Statistical heterogeneity was assessed with the $\chi^2$ test and publication bias was assessed with a funnel plot. Sensitivity analyses were conducted for the primary outcome, excluding trials of lower methodological quality (Jadad score under 4), trials with unknown/inadequate allocation concealment and those comparing different antibiotics.

**Results of the review**
Twenty-one RCTs (n=10,698) were included in the review. Two thirds of studies scored 4 or 5 points on the Jadad scale (mean 3.9 points). Only six studies described a satisfactory method of allocation concealment; the rest gave no information.

Short-term versus longer term antibiotics:
At early follow up, no statistically significant difference between the groups in rates of clinical cure was found (OR 0.99, 95% CI: 0.90, 1.08, 20 RCTs). Nor was there any difference between the groups in rates of bacteriological cure (OR 1.05, 95% CI: 0.87, 1.26, 18 RCTs). Similarly, at late follow up no statistically significant difference between the groups was found in rates of clinical cure (OR 1.0, 95% CI: 0.91, 1.10).

Subgroup analysis by antibiotic type found the odds ratios for early clinical cure were similar among different antibiotic classes. Sensitivity analyses found no statistically significant difference between the groups for the primary outcomes when analysis was restricted to high quality RCTs or RCTs using the same antibiotic in both arms.

No statistically significant heterogeneity was found nor was there any indication of publication bias.

**Authors’ conclusions**
Short courses of antibiotic therapy (five days or less) are as effective as conventional courses in the treatment of mild to moderate acute exacerbations of COPD and chronic bronchitis.

**CRD commentary**
The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies, though no specific efforts were made to retrieve unpublished studies and there was a restriction by language. This means that the review was prone to language and publication biases. However, formal testing showed no indication of publication bias. Adequate details were provided about the primary studies. It should be noted that there was a slight discrepancy in the number of patients analysed between the figure cited in the text and the total number of patients in the included RCT characteristics table. The figure used in this review is taken from the text. Steps were taken to minimise error and bias in the review by having more than one reviewer make decisions independently in the processes of study selection and data extraction. The process of validity assessment was less explicitly described, but two reviewers were involved and relevant criteria were considered. Appropriate statistical methods were used to pool data, to assess for heterogeneity and publication bias and to explore potential clinical and methodological sources of heterogeneity. The primary studies were of relatively good quality, findings were consistent and confidence intervals were relatively tight. The review was generally well conducted and the authors’ conclusions appear reliable.

**Implications of the review for practice and research**
Practice: The authors stated that patients with mild to moderate exacerbations of COPD or chronic bronchitis should receive no more than five days of antibiotic treatment, regardless of antibiotic class, and that guidelines in this area should be revised accordingly.

Research: The authors stated that it would be relevant to carry out studies in this area using amoxicillin-clavulanic acid and tetracycline/doxycycline in the short-term arm.
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