Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis

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CRD summary
This review, which assessed the effectiveness of using systemic corticosteroids, antibiotics, and noninvasive positive pressure ventilation (NPPV) for patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), concluded that all three types of treatment can be effective. The authors' conclusions should be interpreted with some caution in light of language and publication bias issues.

Authors' objectives
To evaluate the effectiveness of systemic corticosteroids, antibiotics and noninvasive positive pressure ventilation (NPPV) for patients with acute exacerbation of chronic obstructive pulmonary disease (COPD).

Searching
The MEDLINE and EMBASE databases were searched from January 1968 to November 2006 for English language articles; search terms were reported. The Cochrane Database of Systematic Reviews was also searched and bibliographies of retrieved papers were checked.

Study selection
Randomised controlled trials (RCTs) of systemic corticosteroids, antibiotics, or NPPV use in adult patients with acute COPD exacerbations (worsening cough or dyspnoea or increased sputum production) were eligible for inclusion. It appeared that placebo or standard therapy (supplemental oxygen, bronchodilators, corticosteroids, antibiotics and diuretics, but not the treatment being studied) were the eligible comparator groups. Studies were excluded when there was clearly an alternative primary diagnosis like asthma, pneumonia, or cardiogenic pulmonary oedema.

The three types of treatment were studied in roughly equal numbers of included trials, with studies of NPPV being slightly more common. Of the treatments used, methylprednisolone was the most commonly studied systemic corticosteroid, NPPV trials used mostly bilevel positive airway pressure (BPAP) via a nasal or face mask, and a wide range of antibiotics were used (mostly β-lactams and tetracycline derivatives). The mean duration of NPPV use was 8.5 hours per day, the mean duration of antibiotic treatment was 8.9 days. The mean age of participants in systemic corticosteroid and NPPV trials was 67 years; the mean age for trials of antibiotics was 63 years. Trials of systemic corticosteroids and antibiotics used placebo as comparators, while NPPV trials used standard therapy. In-hospital mortality was the most common outcome measure used.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The Jadad scale was used to assess study quality (with a maximum possible score of 5).

The authors did not state how the validity assessment was performed.

Data extraction
For dichotomous outcomes, data were extracted and relative risks (RR) and 95% confidence intervals (CI) were calculated; for continuous outcomes, weighted mean differences (WMD) and 95% CI were calculated. Intention-to-treat data were used whenever possible. Trials were categorised by Jadad score, with trials of systemic corticosteroids and antibiotics with a score of 3 or more being eligible for analysis; NPPV trials had to score two or more to be eligible for analysis.

Two reviewers extracted data independently with discrepancies resolved by consensus.

Methods of synthesis
Meta-analyses examining pooled RRs or WMDs were performed using a fixed effect model, or a random effects model when heterogeneity was found. The method of study weighting was not stated. Heterogeneity was assessed using the \( \chi^2 \) test. Studies were sometimes stratified by patient type.

**Results of the review**

Thirty-five RCTs were included in the review (n=2,958). No individual Jadad scores were provided.

Systemic corticosteroids (10 RCTs, n=959, not all eligible for meta-analysis): Use of systemic corticosteroids (compared to placebo) reduced treatment failure by 46%, RR 0.54 (95% CI: 0.41, 0.71), length of hospital stay by 1.4 days, WMD -1.42 (95% CI: -2.18 to -0.65), and improved forced expiratory volume in one second (FEV\(_1\)) by 0.13 litres after 3 days of therapy. However, systemic corticosteroids were associated with an increased risk of hyperglycaemia, RR 5.88 (95% CI: 2.40, 14.41).

Antibiotics (11 RCTs, n=1,020, not all eligible for meta-analysis): Use of antibiotics (compared to placebo) reduced in-hospital mortality by 78%, RR 0.22 (95% CI: 0.08, 0.62), and treatment failure by 46%, RR 0.54 (95% CI: 0.32, 0.92), although statistically significant heterogeneity (p=0.002) was seen. Stratification by patient type showed the treatment effect was significant for hospitalised patients, but not for outpatients.

NPPV (14 RCTs, n=979, not all eligible for meta-analysis): Use of NPPV (compared to standard therapy) reduced in-hospital mortality by 55%, RR 0.45 (95% CI: 0.30, 0.66), reduced length of hospital stay by 1.94 days, WMD -1.94 (95% CI: -3.87, -0.01), although there was significant heterogeneity (p=0.005), and reduced risk of intubation by 65%, RR 0.35 (95% CI: 0.26, 0.47), with the beneficial effect increasing as patient baseline pH decreased.

**Authors’ conclusions**

For acute COPD exacerbations, systemic corticosteroids are effective in reducing treatment failures, while antibiotics reduce mortality and treatment failures in those requiring hospitalisation and NPPV reduces the risk of intubation and in-hospital mortality, especially in those who demonstrate respiratory acidosis.

**CRD commentary**

The review addressed a clear question, although descriptions of inclusion criteria could have been more explicit. Electronic databases and relevant bibliographies were searched, but the exclusion of studies not published in English, coupled with an absence of searches for unpublished studies, means that some relevant trials may have been missed. Suitable methods were employed to minimise the risks of reviewer error and bias for the process of data extraction, although the authors did not report on the methods used to assess study quality or select studies for inclusion. Study quality was assessed using the Jadad scale, although the reporting of these results for individual trials would have made interpretation of the review data easier. Study details were otherwise provided, and appropriate methods were used to pool the data and assess heterogeneity. The authors’ conclusions should be interpreted with some caution in light of the language and publication bias issues.

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

Practice: The authors stated that antibiotic selection should be guided by recent history of antibiotic use and local microbial resistance patterns.

Research: The authors stated that in the future, large clinical trials are needed to clearly determine the role of antibiotics in the management of COPD exacerbations, and to determine their effect on length of hospital stay.

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