Management of acute exacerbations of chronic obstructive pulmonary disease

Authors' objectives
To assess the evidence currently available on the diagnosis, prognosis and management of acute exacerbation of chronic obstructive pulmonary disease (COPD), and on the use of noninvasive positive-pressure ventilation (NPPV) in patients with acute respiratory failure secondary to acute exacerbation of COPD.

Searching
MEDLINE (from 1966 to June 1999), EMBASE (from 1974 to February 1999) and the Cochrane Controlled Trials Register (Issue 4, 1998) were searched. Full details of the search strategies were provided in the report.

Study selection
Study designs of evaluations included in the review
Therapeutics: randomised controlled trials (RCTs) and quasi-randomised or non-randomised prospective controlled trials were eligible, as were retrospective historical or current cohort comparisons.

Diagnosis: studies describing the results of a test (with or without a reference standard test) in a series of patients suspected of having the condition, in two groups of patients, one known to have the condition and the other known to not have the condition, were eligible.

Prognosis: case series or cohort studies providing longitudinal data were eligible.

Adverse effects were obtained from RCTs, non-randomised controlled trials, cohort studies and case series.

Evidence from systematic reviews was also included in the report.

Specific interventions included in the review
The interventions considered for the review were diagnostic or prognostic tests, antibiotics, bronchodilating drugs, corticosteroids, mucous-clearing strategies (including mucolytic drugs and physical treatments) and NPPV.

Participants included in the review
The participants included adults who were likely to have COPD based on clinical diagnosis, spirometry, or known or suspected history; the individuals must have been experiencing an acute exacerbation of respiratory symptoms. Qualifying respiratory symptoms may have included increased dyspnoea, increased quantity or purulence of sputum, or acute respiratory failure. Participants were excluded if they had chronic mechanical ventilation needs, tracheostomies, asthma, bronchiolitis obliterans with organising pneumonia, bronchiolitis obliterans, bronchiectasis, cystic fibrosis, or immunocompromised status.

Outcomes assessed in the review
For efficacy, the authors included studies with outcomes that were measured at least 4 hours after the start of the intervention. The following outcomes were measured and reported in the studies included in the review: mortality; hospitalisation and length of stay; relapse after discharge from out-patient care; relapse after discharge from in-patient care; health-related quality of life (QOL) or QOL; symptom severity or duration; decreased need for intubation; improved breathing mechanics; improved ventilation (in arterial partial pressure of carbon dioxide, PaCO2); decreased need for supplemental oxygen; decreased admissions to the intensive care unit; improved or lack of deterioration of mental status; ability for information at initial workup to predict any of the aforementioned; and side-effects of any intervention mentioned. In summary, the outcomes included: ventilatory function, respiratory symptoms, short-term mortality and health service use.

How were decisions on the relevance of primary studies made?
At least two reviewers selected the studies at the title/abstract and full publication stages, after rigorous efforts were made to preserve the integrity of the selection process.

**Assessment of study quality**
All of the studies were assessed for external and internal validity.

The external validity was assessed using up to four criteria: validity of the underlying COPD diagnosis; validity of the definition of acute exacerbation of COPD; characterisation of severity of acute exacerbation of COPD; and the duration of follow-up (treatment studies only).

The internal validity of the treatment articles was assessed according to the Jadad scale. The internal validity of prognostic studies was assessed according to the levels of evidence defined by the NHS Centre for Evidence Based Medicine. The internal validity of diagnostic studies was assessed using a descriptive approach.

One reviewer assessed the validity of the included studies, while a second reviewer checked the accuracy of the assessment.

**Data extraction**
One reviewer extracted the data from the included studies, while a second reviewer checked the extraction for accuracy and completeness. Data were extracted on study details, design and quality, patient population, study protocol, results and notes. Design and quality covered details of the study design, dates, location, assessment period and quality. Data on the patient population included the number of patients, setting, included patients (COPD and acute exacerbation), excluded patients, smoking history, baseline stable forced expiratory volume in 1 second (FEV1), FEV1 at admission, age, gender and race. Details of the study protocol comprised experimental and control interventions, cointerventions and outcomes.

**Methods of synthesis**
How were the studies combined?
The studies were combined narratively, according to relevant subsections under clinical assessment, treatment and NPPV. The authors stated that where there were sufficiently comparable effectiveness studies, they were combined in a meta-analysis using a fixed-effect model.

How were differences between studies investigated?
Substantive differences between the included studies were discussed in the narrative synthesis. The authors stated that where comparable effectiveness studies were obtained, a statistical test for homogeneity was undertaken to assess whether a meta-analysis was appropriate.

**Results of the review**
A total of 250 studies were included on the review (102 clinical assessment, 84 treatment and 62 NPPV).

The authors presented extensive results regarding the diagnosis of COPD and acute exacerbation of COPD, and the treatment or management of acute exacerbations of COPD, including the use of NPPV. All types of data were only moderately predictive of short-term prognosis. Methylxanthines were associated with a high risk of toxicity. In patients with acute respiratory failure, compared with conservative management, NPPV reduced mortality and the need for endotracheal intubation and mechanical ventilation. The remainder of the authors' main findings were reflected in their conclusions (see below).

**Authors' conclusions**
Patients with acute exacerbation of COPD present with a range of symptoms and severity of illness. Worsening degrees of airway obstruction are associated with a higher likelihood that out-patient management will fail and, as demonstrated
in other illnesses, the presence of co-morbid diseases and worse acute physiological derangements are associated with higher mortality. Blood gas parameters (pH, PaO2, and PaCO2) are closely aligned with decisions to intubate and mechanically ventilate. Ongoing clinical monitoring is necessary for many patients because none of these prognostic factors provides particularly accurate, clinically useful predictions. In terms of treatment, several conservative therapies that were utilised for the management of acute exacerbation showed benefit (i.e. antibiotics, corticosteroids and bronchodilators); however, some therapies (mucolytics and physical therapy) lacked evidence of efficacy. The more aggressive strategy of NPPV may obviate the need for invasive ventilation for some patients with acute exacerbation of COPD and acute respiratory failure, but it is poorly tolerated by many patients.

CRD commentary
This review provided a broad and comprehensive overview of the literature on the diagnosis and management of acute exacerbations of COPD. Multiple databases were searched using various search strategies, all of which were presented in the report. The inclusion and exclusion criteria were developed for each section of the review and appear to have been appropriate for the specific review question in each case. At least two reviewers were involved at the study selection and extraction stages of the review process. Relevant data were extracted from the selected studies and presented in detail in the appendices of the report. The validity of the individual studies was assessed using a mixture of published scales and checklists for the internal validity of treatment articles (Jadad et al.), diagnosis and prognosis articles (Ball et al.), and the authors' own external validity checklist. The data were largely combined in a narrative synthesis, which appears to have been appropriate given the variability between the included studies. The authors’ conclusions appear to follow from the evidence presented.

Implications of the review for practice and research
Practice: The authors stated that antibiotics, corticosteroids and bronchodilators appear to have been of benefit in the conservative treatment of acute exacerbations, though evidence for the efficacy of mucolytics and physical therapies was lacking. NPPV may be of benefit in patients with acute exacerbation of COPD and acute respiratory failure, but is poorly tolerated by many patients.

Research: The authors stated several limitations of the literature included in the report that need to be addressed in future review. For instance: studies were frequently conducted with patients in a period of stable symptoms rather than those experiencing acute exacerbation; there was a lack of a common definition of acute exacerbation; there was a lack of reporting important prognostic factors; there was inconsistent reporting of co-morbid illness or identifiable causes for exacerbation; there was variation amongst the studies in terms of time and geographical location stemming from inconsistency in diagnosis or management; the studies frequently failed to distinguish between patients with asthma and COPD; there was a lack of outcomes relevant to the patients (e.g. symptoms, relapse, health status measures); there was a lack of reporting the strength of association between potential prognostic factors and clinical outcomes; there was a lack of consideration of potential confounding variables; there was a lack of randomised evidence for the older interventions, which form part of current standard care.

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