Management and prevention of exacerbations of COPD

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Acute management of moderate to severe exacerbations of chronic obstructive pulmonary disease

- Supplemental oxygen: titrate to keep oxygen saturation 90-94%
- Short acting β agonist and an anticholinergic bronchodilator
- Oral prednisone 40 mg daily for five days
- Add antibiotics (amoxicillin-clavulinic acid, a respiratory fluoroquinolone, or a macrolide) if the patient has at least two of the following symptoms:
  - Worsening dyspnea
  - Increased sputum volume
  - Increased sputum purulence (particularly if this is one of the symptoms)
- Consider non-invasive ventilation for patients with increased work of breathing and respiratory acidosis (pH <7.35)

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are characterized clinically by worsening dyspnea, cough, sputum production, and airflow obstruction.[1] Such exacerbations are associated with short term and long term reductions in quality of life and lung function, as well as increased risk of death.[2 3] Owing to the considerable impact of these exacerbations on patients' health status, their frequency is now recognized as a key component of the characterization of patients with COPD, and the prevention and treatment of exacerbations has become a primary goal of treatment.[4]

This article aims to review recent evidence, mostly from randomized controlled trials (RCTs), on new drug and non-drug based therapies for the prevention and treatment of COPD exacerbations. Research in this area—both industry driven and academic—has increased greatly over the past decade, and new studies and drugs are rapidly emerging.

SOURCES AND SELECTION CRITERIA

We searched the Cochrane Airways Group register of clinical trials and Medline from 1990 to October 2013 and November 2013, respectively. Search terms included: chronic obstructive pulmonary disease (COPD), or chronic bronchitis, or emphysema, or exacerbations of COPD, and therapy or prevention. Controlled clinical trials and systematic reviews with meta-analyses of interventions or drugs to prevent or treat acute exacerbations of chronic obstructive pulmonary disease were selected for potential inclusion in this article. We excluded observational studies and non-randomized trials.

Definition of an exacerbation of COPD

Exacerbations of COPD are characterized by a sustained worsening of respiratory symptoms from the usual stable state beyond normal day to day variations.[5] Typical symptoms associated with exacerbations include worsening of dyspnea and cough, as well as increased sputum volume and sputum purulence.[1] Exacerbations range in severity from transient reductions in functional status to fatal events.

Definitions of exacerbations vary between clinical studies. Studies that use home based symptom diaries or other symptom monitoring tools—such as the COPD assessment test or the exacerbations of chronic pulmonary disease tool scales—may use symptom based definitions that rely on a sustained worsening of respiratory symptoms for two consecutive days.[6 7] Studies in COPD cohorts suggest that many of these symptom based events may go unreported and untreated.[8 9] About 50% of symptom defined COPD exacerbations are not treated by physicians, and these exacerbations are unlikely to be counted as exacerbation events in most clinical trials.

Causes of COPD exacerbations

COPD exacerbations are caused by complex interactions between the host, respiratory viruses, and airway bacteria, which lead to an increase in the inflammatory burden within the airway.[17]

In general, viral and bacterial infections are the most important triggers of exacerbation.[23-25] Studies suggest that exacerbations are often associated with the isolation of new strains of airway bacteria, with an accompanying host inflammatory response to these new strains.[23 26] Respiratory bacteria and viruses often act in combination.[27]

Recent investigations using cluster analysis suggest that exacerbations can be grouped into four categories: bacterial, viral, predominantly eosinophilic, and a "pauci-inflammatory" category associated with limited changes in the inflammatory profile.[19]

Natural course of exacerbations: onset and recovery

A recent prospective cohort of 212 patients with COPD was monitored using daily symptom diaries for a median of 2.8 years to characterize the time course of the onset of COPD exacerbations.[31] Patients recorded 4439 episodes of worsening respiratory symptoms from baseline; 55% of these events resolved spontaneously and 45% resulted in an exacerbation. In 56% of COPD exacerbations the onset was sudden and the exacerbation threshold was crossed on the same day that respiratory symptoms began. By contrast, in 44% of exacerbations the onset of symptoms was gradual (median duration from symptom onset to exacerbation: four days; fig 3). Patients with sudden onset exacerbations had more intense symptoms but a shorter median recovery time back to baseline health status (11 *v* 13 days; P<0.001). The study concluded that COPD exacerbations exhibit two distinct patterns—sudden and gradual onset—and that sudden exacerbations are associated with increased peak respiratory symptoms but shorter exacerbation recovery times.[31]

Previous data have suggested that the median duration of recovery time after an acute exacerbation is 7-10 days for lung function as measured by peak expiratory flow, although there is wide variation, and a minority (<10%) of patients never recover to their pre-exacerbation lung function.[32] Symptoms may take longer to recover than peak expiratory flow, and the median duration of symptom recovery back to previous baseline is 11-13 days.[31 33]

About a quarter of inpatients treated for an acute COPD exacerbation do not respond to initial treatment and experience an adverse outcome, defined as either death, intubation, or need for readmission or intensification of drug therapy. Similarly, studies suggest that a quarter of outpatients treated for an acute exacerbation either relapse (defined as an unscheduled visit to a physician or the emergency department because of worsening dyspnea) or have a second exacerbation within 30 days of the initial presentation.[33] Many of these patients require readmission to hospital.[33]

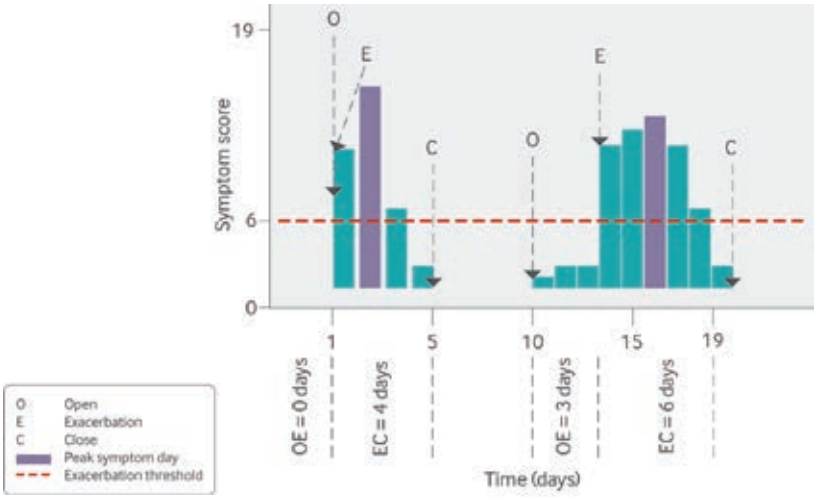

Fig 3| Time course and calculation of the onset and duration of exacerbation intervals: a sudden onset exacerbation is shown on the left, a gradual onset exacerbation on the right. The opening event (O) was defined as the first day of worsening of respiratory symptoms above usual baseline values. An exacerbation (E) was defined as the first of two or more consecutive days during which the patient recorded two or more new or worsening symptoms, at least one of which was a major symptom (a daily symptom score of ≥6 points for two consecutive days (indicated by the dotted line)). A closing (C) was defined as the first of five consecutive days during which symptoms had returned to their usual baseline levels. For sudden onset exacerbations the OE interval is 0 days, indicating that the exacerbation occurs on the first day of worsening of respiratory symptoms. About 55% of exacerbations are sudden onset. The EC represents the duration of the exacerbation—the time from the onset of the exacerbation to recovery back to baseline. Reproduced, with permission, from Papi and colleagues[29]

COPD exacerbations and mortality

A prospective five year cohort study of 304 Spanish men with COPD found that the frequency of exacerbations is independently associated with mortality.[38] When a service based definition of COPD exacerbation (need for emergency department treatment) was used, patients with three or more exacerbations had a survival rate of 30% at five years, whereas those without an exacerbation had a survival rate of 80% (hazard ratio 4.13, 95% confidence interval 1.80 to 9.41). Survival was also influenced by the severity of the exacerbation—exacerbations that necessitated hospital admission or readmission were associated with the poorest survival.[38]

Patients who are admitted for an exacerbation have an in-hospital mortality of about 10%. Patients with an exacerbation and hypercapnic respiratory failure have a two year mortality rate of about 50%.[39] A recent study of 1824 European patients with COPD documented a 45% four year mortality rate after discharge from hospital in those admitted with an exacerbation.[40]

Treatment of acute exacerbations

Corticosteroids

Standard treatment for acute COPD exacerbations includes treatment with bronchodilators, antibiotics, and corticosteroids.[46] Clinical trials have shown that the addition of oral or intravenous corticosteroids to antibiotics significantly decreases treatment failure rates in inpatients with COPD exacerbations[35] and prevents relapse in outpatients with an exacerbation.[34] A recent RCT suggested that, in patients presenting to the emergency department with acute exacerbations of COPD (most of whom were admitted), a five day treatment course with 40 mg of prednisone daily was non-inferior to a 14 day treatment course.[36] Patients treated with five days of prednisone had similar rates of re-exacerbation within six months of follow-up but had significantly reduced exposure to glucocorticoids.[36]

Antibiotics

GOLD guidelines[4] and European Respiratory Society guidelines[49] advocate antibiotics for patients with acute COPD exacerbations who also have worsening dyspnea as well as increased sputum volume and purulence, or if any two of these symptoms, particularly increased sputum purulence, worsen. These recommendations are based on older studies that demonstrated better outcomes in outpatients with COPD exacerbations treated with broad spectrum antibiotics such as trimethoprim-sulfamethoxazole, doxycycline, or amoxicillin.[1] In addition, a clinical trial in patients with severe exacerbations, who needed mechanical ventilation, showed that ofloxacin significantly reduced mortality associated with severe exacerbations.[50]

Two recently published RCTs assessed the use of antibiotics in COPD exacerbations. The first study of 223 inpatients with COPD exacerbations compared the addition of seven days of doxycycline or placebo with treatment with systemic corticosteroids.[51] It found no significant difference in the primary endpoint of clinical success (61% *v* 53%; P=0.32), clinical cure, or lung function at day 30.[51] By contrast, the other RCT studied 310 outpatients with mild to moderate exacerbations, most of whom were not treated with concomitant oral steroids.[20] Amoxicillin-clavulinic acid significantly increased clinical cure rates at the end of treatment (days 9-11) compared with placebo (74% *v* 60%; difference 14.2%, 3.7% to 24.3%). Treatment with amoxicillin-clavulinic acid was also associated with a prolonged time to next exacerbation compared with placebo.[20]

Non-invasive ventilation

Non-invasive ventilation using pressure cycled bilevel positive airway pressure has been studied in several RCTs. It decreases respiratory rate and work of breathing, improves acute respiratory acidosis, and decreases the requirement for intubation and invasive ventilation in patients with COPD exacerbations and respiratory failure.[52] A decrease in the need for invasive ventilation with this treatment has also translated into lower rates of ventilator associated pneumonia, shorter hospital stays, and reduced mortality.[53] GOLD guidelines recommend that patients with severe dyspnea, increased work of breathing, and respiratory acidosis (pH ≤7.35 or arterial carbon dioxide pressure ≥45 mm Hg, or both) should be considered for this treatment, provided they are conscious and able to protect their airway and deal with respiratory secretions.[4]

Influenza vaccine reduces the rate and severity of influenza symptoms, including respiratory ones

Prevention of COPD exacerbations

Given the global health, social, and economic importance of this condition, the prevention of exacerbations is now recognized as a primary goal of maintenance therapy for COPD.[4] Several drug and non-drug based interventions have been studied in clinical trials, with the aim of decreasing the frequency and severity of exacerbations (table).[57]

Vaccinations

Influenza vaccine reduces the rate and severity of influenza symptoms, including respiratory ones. A meta-analysis of 11 trials, including six performed exclusively in patients with COPD, found that, in patients with COPD, influenza vaccine significantly reduced the total number of exacerbations per patient compared with those who received placebo (weighted mean difference −0.37, −0.64 to −0.11; P=0.006).[58]

A meta-analysis of seven trials that assessed the effects of a 23 valent pneumococcal vaccine in patients with COPD found no significant effect on morbidity or mortality.[59]

Long acting bronchodilators

Two classes of bronchodilators are in widespread use for COPD: long acting antimuscarinic agents (LAMAs) and long acting β agonists (LABAs). Bronchodilators clearly have a role in the prevention of COPD exacerbations.

LAMAs

The tiotropium dry powder inhaler is the best studied LAMA.

The most recent systematic review on chronic tiotropium therapy in COPD suggests that, compared with placebo, tiotropium reduces COPD exacerbations by 22% (odds ratio 0.78, 0.70 to 0.87).[60]

Newer LAMAs are becoming available for the treatment of COPD. Tiotropium is available in an aqueous solution inhaler (tiotropium Respimat) in several countries in Europe. An RCT of more than 17 000 patients with COPD compared tiotropium dry powder inhaler with tiotropium aqueous inhaler over a mean of 2.3 years. The mortality rate was non-inferior for aqueous tiotropium compared with standard dry powder inhaler tiotropium. Time to first exacerbation and rates of exacerbation over the entire study period were also equivalent.[13] These data suggest that aqueous tiotropium may have similar efficacy to dry powder tiotropium in preventing exacerbations.

Other new LAMAs include glycopyrronium bromide and aclidinium bromide. An RCT randomized 1066 patients with COPD to glycopyrronium bromide 50 µg per day or to placebo or open label tiotropium. Compared with placebo, glycopyrronium significantly reduced the risk of moderate to severe exacerbations by 34% (P=0.001). This reduction in exacerbations was comparable to that seen with open label tiotropium.[75]

No studies have investigated whether aclidinium bromide reduces exacerbations relative to placebo or to its active comparators.

LABAs

Clinical studies suggest that LABAs can also prevent exacerbations, although the effect size is slightly less than for LAMAs. The TORCH study suggested that salmeterol monotherapy reduces the frequency of exacerbations compared with placebo (0.97 *v* 1.13 exacerbations per year; relative risk 0.85, 0.78 to 0.93; P=0.001).[12] A meta-analysis found that, compared with placebo, LABAs (mainly salmeterol or formoterol) significantly reduced moderately severe COPD exacerbations that necessitated a course of antibiotics or oral steroids (odds ratio 0.73, 0.61 to 0.87) or hospital admission (0.73, 0.56 to 0.95).[60]

A subsequent RCT of 3444 patients with severe COPD and a history of exacerbations compared indicaterol, a new once daily LABA, to tiotropium. Tiotropium was significantly more effective at preventing exacerbations than indicaterol over one year (rate ratio 1.29 in favour of tiotropium).[77]

LABA-LAMA combinations

Several combination LABA-LAMA inhalers are in the final stages of development and should be available for general use within the next 12-24 months.

To date, only one published study has evaluated whether a LAMA-LABA product can prevent COPD exacerbations. The once daily fixed dose combination LABA-LAMA inhaler QVA149 contains both glycopyrronium (50 µg) and indicaterol (110 µg) in a single inhaler. An RCT in patients with severe to very severe COPD and a history of exacerbations showed that QVA149 significantly decreased the rate of moderate to severe exacerbations by 12% compared with glycopyrronium alone, although QVA149 did not significantly reduce exacerbation rates compared with open label tiotropium.[64]

Inhaled corticosteroid-LABA combinations

The largest clinical trial to date of inhaled corticosteroid-LABA combination therapy was the three year TORCH study, which randomized 6112 patients to treatment with fluticasone-salmeterol, either monocomponent, or placebo. Patients treated with fluticasone-salmeterol had an annual rate of 0.85 exacerbations per person compared with 1.13 in the placebo group (rate ratio 0.75, 0.69 to 0.81), and 0.97 in the group treated with salmeterol (0.88, 0.81 to 0.95).[12]

A meta-analysis confirmed that inhaled corticosteroid-LABA combination inhalers significantly reduce COPD exacerbations when compared with placebo (0.73, 0.69 to 0.78).[78] A second meta-analysis confirmed that they also reduced exacerbations when compared with LABA alone (0.76, 0.68 to 0.84).[62]

Pharmacologic treatments for the prevention of acute exacerbations of chronic obstructive pulmonary disease

Pharmacologic treatment	Clinical trial evidence to support efficacy
Influenza vaccination	Efficacy confirmed[58]
Pneumococcal vaccination	Efficacy not confirmed[59]
Long acting antimuscarinic agent bronchodilators (LAMAs)	Efficacy confirmed[60]
Long acting β agonist bronchodilators (LABAs)	Efficacy confirmed[61]
Corticosteroid-LABA combination inhalers	Efficacy confirmed[62]
Triple therapy (inhaled corticosteroid-LABA + LAMA)	Efficacy not confirmed[10 63]
LABA-LAMA combination inhalers	Efficacy not confirmed[64]
Roflumilast	Efficacy confirmed (only in subgroup of patients with chronic bronchitis phenotype)[65]
Pulsed moxifloxacin	Efficacy not confirmed[66]
Azithromycin	Efficacy confirmed[67 68]
Simvastatin	Not effective[69]
N-acetylcysteine	Efficacy not confirmed[70-72]
Vitamin D	Not effective[73]

Guidelines do not currently recommend pulsed antibiotic therapy to prevent exacerbations

Triple therapy (inhaled corticosteroid-LABA plus LAMA)

An RCT randomized of 449 patients to tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone-salmeterol for one year. The primary endpoint was the proportion of patients who experienced a moderate or severe exacerbation over one year. Although tiotropium plus fluticasone-salmeterol did not significantly decrease exacerbations compared with tiotropium plus placebo (0.85, 0.65 to 1.11), it reduced the number of severe exacerbations that necessitated hospital admission by 47% (0.53, 0.33 to 0.86).[10]

Potential increased risk of pneumonia associated with inhaled corticosteroid containing therapies

Although inhaled corticosteroids are not indicated as monotherapy for COPD, products that contain them (corticosteroid-LABA combinations and "triple therapy" combinations) are widely used to treat chronic COPD and prevent exacerbations.

The risk of pneumonia may not be a class effect and may be higher with certain inhaled corticosteroid products than others.

Risk factors for pneumonia in patients with COPD receiving fluticasone furoate-vilanterol include current smoking, a history of pneumonia, a body mass index less than 25, and FEV_1 less than 50% of predicted. It therefore seems reasonable to consider using a budesonide containing inhaled corticosteroid-LABA combination in patients with risk factors that might predispose them to pneumonia. It is also advisable to keep doses of inhaled corticosteroid to the lowest effective dose in patients with COPD and to be vigilant in searching for pneumonia in these patients because symptoms of pneumonia can often overlap with those of an acute exacerbation.[83]

Phosphodiesterase enzyme inhibitors

Clinical trials have shown that the selective phosphodiesterase 4 inhibitor roflumilast reduces COPD exacerbations in a subpopulation of patients with symptoms of chronic bronchitis (chronic cough and sputum production) who have had at least one exacerbation within the past year. In this subgroup, two clinical trials of more than 3000 patients have shown that roflumilast reduces exacerbations by 17% compared with placebo (rate ratio 0.83, 0.75 to 0.92).[65] These effects have not been studied when the drug is added to inhaled corticosteroid-LABA combination therapy or triple therapy. The drug's gastrointestinal side effects, such as nausea, diarrhea, and weight loss, may also limit its effectiveness in some patients.

Antibiotics

Moxifloxacin is a respiratory fluoroquinolone with activity against bacteria that are associated with COPD exacerbations. One RCT randomized stable patients with COPD to oral moxifloxacin 400 mg (n=573) or placebo (n=584) once a day for five days. Treatment was repeated every eight weeks for a total of six courses. At 48 weeks, the odds ratio of having an exacerbation was not significantly lower in the moxifloxacin group in the intent to treat analysis (0.81, 0.645 to 1.008; P=0.059),[65] although it was significantly lower in the per protocol analysis (0.75, 0.565 to 0.994). Guidelines do not currently recommend pulsed antibiotic therapy to prevent exacerbations.[84]

Macrolide antibiotics have pleiotropic immunomodulatory and anti-inflammatory properties in addition to their antibiotic effects. A one year RCT of 1142 patients randomized them to 250 mg of azithromycin once daily or placebo, in addition to their usual drugs for COPD. After one year, the rates of exacerbation were 1.48 per patient year in the azithromycin group and 1.83 per patient year in the placebo group, suggesting a 17% reduction in exacerbations with daily azithromycin (rate ratio 0.83, 0.72 to 0.95).[67] Smaller studies have also shown similar reductions with azithromycin, and a recent meta-analysis of six trials found a 37% relative risk reduction (0.63, 0.45 to 0.87) in COPD exacerbations in patients taking macrolides versus placebo.[68]

Controversies related to azithromycin

Azithromycin is a potent inducer of antimicrobial resistance. In the above RCT, the incidence of macrolide resistance, as measured in nasopharyngeal flora, was significantly higher in those treated with azithromycin versus placebo (81% *v* 41%).[67] The impact of the widespread use of macrolides to prevent COPD exacerbations on bacterial flora in the wider community is hard to quantify, and there is concern that widespread outpatient use of azithromycin may induce macrolide resistance in communities.[68]

Azithromycin has very occasionally been associated with prolongation of the Q-T interval and ventricular arrhythmias.[85]

Given the uncertainties related to antibiotic resistance and potential cardiac toxicity, the most recent 2013 GOLD guidelines do not recommend once daily azithromycin to prevent COPD exacerbations.[4]

Mucolytics

Data on the use of mucolytics, such as N-acetylcysteine, to prevent COPD exacerbations are contradictory.

Vitamin D

An RCT of 182 patients with moderate to severe COPD and a history of exacerbations explored whether high dose vitamin D, given once monthly over 12 months, could reduce the incidence of exacerbations. The median time to first exacerbation did not differ significantly between vitamin D treated and placebo groups (hazard ratio 1.1, 0.82 to 1.56; P=0.41), and neither did exacerbation rates or hospital admissions.[73]

Disease self management for prevention of exacerbations

Several RCTs have evaluated disease self management strategies and the effects of these strategies on rates of exacerbation, emergency department visits, hospital admissions, and death. A systematic review has shown that action plans, in the absence of disease education and self management, do not reduce the use of urgent healthcare for exacerbations.[90] The provision of such action plans is therefore not recommended in the absence of a disease self management strategy.

Several large RCTs have studied the provision of education on disease self management in addition to treatment action plans.

However, this subject is controversial. The safety of disease self management and exacerbation action plans needs further assessment before this strategy can be recommended for all patients.