Strategies for Avoiding Hospitalization of Patients with AECOPD

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Abstract COPD is increasing in prevalence worldwide and results in substantial social and economic burdens. Exacerbations of COPD lead to accelerated decline of lung function, increased morbidity and mortality, and account for a substantial portion of the costs associated with this disease. Both pharmacologic and nonpharmacologic interventions can reduce exacerbation and hospitalization due to COPD. Safe alternatives to hospitalization for AECOPD are being developed but are not yet widely available.

Keywords COPD · AECOPD · Hospitalization · Inhaled corticosteroids · Exacerbation · Bronchodilator

Introduction

COPD is a leading cause of morbidity and mortality worldwide and is an increasing and substantial economic and social burden [1, 2]. The prevalence of COPD is expected to increase in the coming decades as exposure to tobacco smoke, indoor and outdoor air pollution, and the burning of wood or other biomass fuels continues [3]. The economic burden of COPD in the US is estimated at direct costs of \$29.5 billion and indirect costs of \$20.5 billion [4]. Acute exacerbation of COPD (AECOPD) is marked by an acute increase in symptoms beyond normal day to day variation. Acute exacerbation affects the burden of COPD by accelerating the decline in lung function, reducing the

ability to perform daily physical activities, and reducing quality of life [5, 6, 7•, 8]. AECOPD is responsible for as much as 35–84 % of COPD-related healthcare expenses [9–11]. Patient outcomes after COPD exacerbation requiring hospitalization are also dismal, with a two year mortality of 26 % and five year mortality of 55 % [12].

AECOPD results in over 1.5 million emergency department (ED) visits in the US each year. Here the decision must be made regarding inpatient or outpatient treatment, and increasing effort is being made to reduce expensive inpatient care [13]. Once in the ED, no intervention has been shown to reduce hospitalization but common therapy includes increased use of bronchodilators, corticosteroids, and antibiotics [14]. Indications for hospital admission include shortness of breath unresponsive to initial treatment, hypoxemia, worsening hypercapnia, altered mental status, significant comorbid illnesses, symptoms severe enough to prevent necessary activities of daily life, and poor home social support mechanisms [15].

Current Research

Prevention of AECOPD and the hospitalization associated with it are extremely important. Strategies to reduce exacerbation and hospitalization can be divided into pharmacologic and non-pharmacologic methods.

The most rigorous and comprehensive data available on the topic of preventing exacerbation and hospitalization for AECOPD are those for pharmacologic intervention. Given the heterogeneity of the patient population, with some patients having frequent exacerbation and others none, the best methods for reporting and analyzing the effect of intervention on reduction of AECOPD are controversial [16, 17]. The methods used to measure AECOPD outcome must be analyzed and taken into account when interpreting

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the findings of individual studies. The Global Initiative for Chronic Obstructive Lung Disease [7•], or GOLD, is an organization which has brought together international experts and organizations, for example the National Heart, Lung, and Blood Institute and the World Health Organization, to increase awareness of and to provide consensus guidelines for the prevention and management of COPD.

Inhaled corticosteroids (ICS) have been examined in COPD, given the contribution of airway inflammation to the disease process. Numerous studies have revealed significant reductions in AECOPD with ICS use but the statistical methods used to determine the magnitude of this reduction have often been criticized [18]. ICS have also often been included with other bronchodilator agents in studies of incidence AECOPD and many of these studies allowed patients to be on ICS before enrollment as long as they stopped them before study entry. This can affect study results given the increased risk of AECOPD when patients taking ICS for stable COPD discontinue them [19]. In the ISOLDE study, 751 patients were randomized to inhaled fluticasone or placebo, after both a washout period for those already on ICS, and a 14 day course of systemic prednisolone, and followed for the next three years. The TORCH trial compared a combination of fluticasone and salmeterol with fluticasone alone, salmeterol alone, or placebo for 875 patients over a three-year period. The ISOLDE study reported a 25 % reduction and the TORCH trial reported a 19 % reduction in AECOPD with ICS [20, 21]. A Cochrane review in 2012 concluded that ICS are effective in reducing AECOPD by from 8 to 30 % compared with placebo [22]. Hospitalization for COPD was not significantly reduced in any of the ICS trials. Concern over reports of an increased incidence of pneumonia in patients using ICS have been tempered by other studies showing no increase [23] or at least reassurances that pneumonia-related mortality and overall mortality are not increased [24]. From available evidence, use of ICS can help reduce exacerbation but, alone, does not seem to clearly reduce hospitalization for AECOPD.

Long-acting beta agonists have been evaluated for reduction of AECOPD, with conflicting results. The TORCH trial demonstrated that annual exacerbation was 15 % lower when patients used salmeterol compared with placebo. The TRISTAN study was a randomized, double-blinded study in which 1,465 patients received a combination of fluticasone and salmeterol, fluticasone alone, salmeterol alone, or placebo. In this study, salmeterol was shown to reduce AECOPD by 20 % and to reduce the number of patients requiring systemic corticosteroids [25]. Previous studies evaluating formoterol use with placebo did not reveal a reduction in overall AECOPD or severe exacerbation requiring systemic corticosteroids [26, 27]. The studies of formoterol suffered from high dropout in the

placebo and treatment arms and were small studies, which limits their conclusions.

The combination of an inhaled corticosteroid with a long-acting beta agonist has been shown to be more advantageous in reducing AECOPD. In the TRISTAN study, fluticasone and salmeterol reduced AECOPD by 25 % and reduced the number of patients requiring systemic corticosteroids by 39 % [27]. Despite these impressive reductions in exacerbation, hospitalization was not reduced, possibly because of the small size of the study and low exacerbation observed. In the TORCH trial, the combination of fluticasone with salmeterol reduced AECOPD by 25 % and hospitalization was reduced by 17 % compared with placebo or either fluticasone or salmeterol alone [21].

The effect of long-acting antimuscarinic agents in reducing AECOPD has also been examined. Tiotropium and aclidinium are the two agents currently available in the US. To date, the only study whose primary endpoint was reduction in AECOPD was conducted by Niewoehner et al. [28] among 1,879 patients with moderate to severe COPD. A reduction in acute exacerbation (27.9 vs 32.3 %) was seen, but a trend toward lower hospitalization (7.0 vs 9.4 %) did not reach statistical significance. ($p = 0.056$). The understanding potential long-term impacts on function with tiotropium (UPLIFT) study was the largest study to date, with nearly 6,000 patients enrolled and randomized to either placebo or tiotropium. Patients were allowed to use any other inhaled medications except other anticholinergics. This study demonstrated a 14 % reduction in AECOPD but mean hospitalization was not significantly reduced [29]. Aclidinium has shown equivalence with tiotropium in improvement in FEV₁ and can improve symptoms in COPD, but has not been evaluated for reduction of AECOPD or hospitalization as a result of AECOPD.

Several studies have examined which agent best reduces the incidence of AECOPD. In the INSPIRE trial, 1,323 patients with a previous exacerbation and predicted FEV₁ less than 50 % were randomized to either tiotropium or fluticasone with salmeterol. This study demonstrated no significant difference in either acute exacerbation or hospitalization because of COPD, although more antibiotics were used in the fluticasone with salmeterol group and more systemic steroids were used in the tiotropium group [30]. In the POET-COPD trial, tiotropium was compared with salmeterol alone among 7,376 patients with moderate to severe COPD. Tiotropium reduced overall AECOPD and reduced the number of patients who required hospitalization by 27 % [31]; it was not a pure head-to-head comparison, because many patients also were also taking ICS. Use of triple therapy has also been examined. Aaron et al. demonstrated that the use of tiotropium, fluticasone, and

salmeterol together, compared with tiotropium alone, reduced hospitalization for AECOPD among 449 patients with moderate to severe COPD. The overall proportion of patients experiencing an exacerbation of COPD was no different among the treatment groups, which included tiotropium alone, tiotropium plus salmeterol, and tiotropium, salmeterol, and fluticasone, but this study suggests that triple therapy can help reduce severe exacerbation which require hospitalization [32].

Phosphodiesterase-4 (PDE-4) is the main enzyme involved in cAMP metabolism in immune and inflammatory cells, and inhibition of this enzyme inhibits the pro-inflammatory actions of most of these cell types [33–35]. Inconsistent clinical performance and significant side effects, mainly gastrointestinal, have limited mainstream use of these agents for COPD. Recently, roflumilast, a PDE-4 inhibitor with a more favorable benefit-to-side effect ratio has become available. The first randomized, controlled study compared placebo with roflumilast at either 250 or 500 µg dose, and showed that 500 µg roflumilast reduced the risk of AECOPD, but exacerbation requiring systemic steroids or hospitalization was no different, although the study was not powered to investigate this outcome [36]. A subsequent study by Caverley et al. randomized 1,514 patients with COPD to roflumilast 500 µg or placebo and followed them for a year. Although mean incidence of moderate to severe exacerbation was not statistically different, use of systemic corticosteroids was 18 % lower in the roflumilast group [37]. On the basis of subgroup analysis in this study suggesting a larger benefit to patients with more severe airflow limitation and frequent exacerbation, a prospective randomized trial was conducted among 3,091 patients with GOLD III/IV disease with bronchitic symptoms and exacerbation in the previous year; it was found that moderate to severe exacerbation was reduced by 17 % [38]. Hospitalization for AECOPD was not reduced, however. The ongoing REACT (roflumilast in the prevention of COPD exacerbation while taking appropriate combination therapy) study is evaluating addition of roflumilast to different combinations of inhalation therapy, including triple therapy [39]. Until complete, the utility of roflumilast lies in reducing exacerbation, but not in reducing hospitalization for COPD. Side effects remain troublesome; they include diarrhea, nausea, and weight loss, which can be intolerable for some patients.

Macrolide antibiotics have anti-inflammatory and immune-modulating effects in addition to their antimicrobial effects and have been studied for prevention of AECOPD [40]. Erythromycin has been shown to reduce the incidence of AECOPD, but not hospitalization, in several small studies [41, 42]. Azithromycin 250 mg daily was added to usual care in a large, randomized controlled study of 1,142 patients and reduced AECOPD by 27 % and

was associated with a trend toward lower hospitalization [43]. This came at a price, increased incidence of hearing loss and greater incidence colonization by macrolide-resistant organisms. Thus, macrolides seem to reduce AECOPD but do not clearly reduce hospitalization.

Theophylline is a methylxanthine which has bronchodilator properties. At low doses it is believed to have anti-inflammatory and immunomodulatory action [44]. There are surprisingly few data on its effect on exacerbation frequency in COPD. One large retrospective study showed that users of theophylline had a small reduction in exacerbation frequency compared with users of long-acting beta-2 agonists but more exacerbation than users of ICS [45]. In the only randomized controlled study, conducted by Zhou et al., 110 patients were randomized to either slow-release theophylline, 100 mg by mouth twice daily, or placebo over the course of a year; the study showed that theophylline could reduce the frequency and duration of exacerbation. Before study enrollment the patients enrolled were primarily being treated with short-acting beta-agonists alone for COPD control. Theophylline was attractive because of ease of administration and low cost [46]. GOLD guidelines for the treatment of COPD note this reduction in exacerbation frequency but the guidelines do not recommend theophylline when other bronchodilators are available because of its poor action as a bronchodilator and higher potential for toxicity [5].

Mucolytics have also been examined for treatment of COPD. *N*-Acetylcysteine, a mucolytic agent with direct and indirect anti-inflammatory and antioxidant properties, is the most widely studied mucolytic in COPD. A Cochrane analysis in 2012 demonstrated that mucolytics can slightly reduce AECOPD and in the two studies that have examined this secondary outcome hospitalization decreased (OR 0.70, CI 0.49–1.01). Also, for hospitalized patients, duration of hospitalization might be reduced [47–49]. Mucolytics remain controversial and cannot be universally recommended, but side effects seem to be minimal and future studies might reveal subgroups of COPD patients, for example those with frequent exacerbation, who might benefit most.

Pulmonary rehabilitation can improve quality of life in COPD and its effect on exacerbation and hospital admission has been examined with mixed results. Six weeks of pulmonary rehabilitation was compared with placebo in one randomized controlled study of 200 patients, and showed that although respiratory-related hospitalization was no different overall, the incidence of exacerbation per patient in the rehabilitation group was significantly reduced and duration of hospitalization decreased by half [50]. A smaller study among 60 Spanish patients who received one year of pulmonary rehabilitation versus usual care revealed a significant reduction in the number of exacerbations per

patient. Although a trend toward less hospitalization was seen, it was not significant [51]. A Cochrane analysis in 2011 reviewed nine studies on 432 patients who had recently experienced exacerbation of COPD showed that pulmonary rehabilitation programs after AECOPD could reduce subsequent hospital admissions significantly with an odds ratio of 0.22 and number needed to treat of four. It also significantly reduced mortality [52•]. A more recent study of 60 patients in China was unable to reproduce these results and, despite an improvement in health-related quality of life, pulmonary rehabilitation did not reduce emergency room visits or hospital admissions for COPD [53]. It has been proposed that the effect on ED visits and hospital admissions was not seen because this program was limited to exercise and did not include education and access to action plans [54].

Mortality in AECOPD has been most closely linked to significant hypercapnia with respiratory acidosis, and to the presence of co-morbidities at hospital admission [52•, 55, 56]. Managing patients without these risk factors at home has gained more attention with initial studies showing promise in reducing ED visits and hospitalization. Patients often delay reporting acute exacerbation to their physicians, which can lead to longer exacerbation and more frequent hospitalization [57]. Evidence indicates that early reporting of AECOPD to medical practitioners can reduce duration of symptoms, and that failure to report AECOPD symptoms early can lead to increased hospitalization [58]. Bourbeau et al. randomized 190 patients with at least one AECOPD within the past year to either usual care or a self management program. The program included a series of teaching modules, undertaken at home, which included education about the disease, energy conservation and relaxation techniques, healthy lifestyle counseling, which included a section on tobacco cessation, an action plan to be used for acute exacerbation, and a basic exercise program. Patients had telephone access to case managers with expertise in COPD throughout the study. A 39.8 % reduction in hospitalization for AECOPD was noted in the intervention group. Intervention patients were also 41 % less likely to have an ED visit or to have to see another physician at an urgent visit [59]. Casas et al. [60] showed that patients randomized during a hospitalization for AECOPD to either a disease-management program, including a combination of education sessions, home visits, follow-up telephone calls, and access to an action plan for acute exacerbation, had a significantly fewer readmissions to the hospital for COPD during the next year without any difference in mortality. Rice et al. demonstrated, among a larger cohort of VA patients, that a simpler self management plan could lead to a similar dramatic reduction in hospitalization for AECOPD. The intervention group in this study received a one page handout on important topics

in COPD management, attended a 1–1.5 h teaching session conducted by a case manager with respiratory expertise, and had an action plan combined with prewritten prescriptions for corticosteroids and antibiotics, monthly phone calls from a case manager, and 24 h access to a VA telephone hotline. Again, the intervention group was 31 % less likely to be hospitalized and 51 % less likely to visit an emergency room for an AECOPD [61]. Not all studies have shown such promise. Studies have varied in the quality of the self management program, patient population, and duration of follow-up; no reduction in hospitalization had been observed for the largest previous cohort [62]. A recent study by Fan et al. was stopped early, after fewer than half its intended patients had been enrolled, because of a finding of excess mortality in the intervention group. This intervention included patient education sessions designed to address key behavioral and environmental behavior which would help best contribute to patient well being and again focused on smoking cessation, breathing, and cough techniques to conserve energy, self-monitoring of symptoms, and prescriptions to have antibiotics and corticosteroids on hand to begin at the sign of an exacerbation. This study was designed to study the incidence of hospitalization in the two groups, with secondary outcomes including quality of life and mortality. Although the incidence of comorbid cardiovascular disease was higher in the intervention group, it was unclear whether this was responsible for the increased mortality. At the time the trial was stopped, no difference in hospitalization for COPD was noted [63]. Although self-management programs seem to hold promise, they are not universally available and require significant investment in time and resources in outpatient pulmonary specialty clinics; they may become more widespread as reimbursement models change.

Previous reviews of wide-ranging medical conditions suggested that so-called “Hospital at home” programs could provide equivalent outcomes with reduced cost and improved patient experience [64]. These programs involve patients treated at home directly from an urgent care center or ED or those discharged quickly from an inpatient area. A recent Cochrane review of hospital at home programs for AECOPD revealed that among the studies included there was a significant improvement in hospital readmission, with no difference, or perhaps a small reduction, in mortality [65]. Health-related quality of life, lung function, and patient satisfaction also did not seem to differ, although the confidence in the quality of data for these secondary outcomes was limited. These studies randomized patients with AECOPD to either early discharge from the hospital or ED to home or to usual inpatient care within 72 h of presentation. The home intervention included frequent home visits by nursing staff, inhaled bronchodilators, systemic corticosteroids and antibiotics, and additional telephone follow-up.

Direct economic costs reported in three studies suggested overall reduction in cost, even when not taking into account health savings from reduced exacerbation, quality of life, and absence from work. Again, the evidence was of poor quality and is likely to vary significantly between countries, so no direct conclusion can be made with available evidence. Management of appropriate patients at home is feasible, is potentially equally safe and satisfactory for patients, and could reduce costs associated with COPD, but access to such intensive home-management programs is very limited.

Summary and Conclusions

Available evidence suggests that pharmacologic intervention, for example long-acting beta-agonists, long-acting muscarinic antagonists, and ICS can reduce the frequency of exacerbation in COPD. Long-acting beta-agonists and long-acting antimuscarinic antagonists seem to reduce hospitalization for AECOPD. Guidelines for the use of macrolide antibiotics, PDE-4 inhibitors, mucolytics, and theophylline are evolving. Pulmonary rehabilitation has great benefits in COPD overall and seems to reduce hospitalization. Self-management and hospital at home programs also hold promise for preventing hospitalization but are not yet widely available.

Compliance with Ethics Guidelines

Conflict of Interest Sean P. O'Reilly declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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