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# Preventing COPD exacerbations: new options for a crucial and growing problem

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## INTRODUCTION

Your 66 year old patient with chronic obstructive pulmonary disease (COPD) starts her clinic visit by asking: *"How can we prevent another year like the last one?"* Her disease is spirometrically-moderate ($FEV_1$ 64% predicted), but in the past 12 months she had four ER visits and a hospitalization for "breathing problems", each requiring antibiotics and oral steroids. She feels she never really recovered from the last attack. She asks, *"Will I become dependent on oxygen, like my uncle was before he died?"* She is faithfully taking her inhalers, a long-acting beta agonist (LABA)/potent inhaled corticosteroid (ICS) combination, and a long-acting muscarinic antagonist (LAMA). You confirm that she still not smoking, and that her immunizations are current. What can you recommend?

In the 21st century, preventing acute exacerbations of COPD (AECOPD) is as crucial a Primary Care goal as controlling hypertension and dyslipidemias. COPD incidence surpassed stroke in 2008, making it the third leading cause of death in the USA [1]. COPD is more prevalent in Veterans than in the age-matched general population, and is markedly under-diagnosed [2,3], especially in women [4]. Since 2000, more woman than men died of COPD in the USA [5]. With significant latency plus frequent progression even after smoking cessation, COPD prevalence will continue to increase for decades.

Recent advances offer tailored therapies for selected COPD patients. This article explains the importance of preventing AECOPD, summarizes risk factors for frequent AECOPD, and outlines approaches to their prevention.

### Importance of preventing AECOPD

In a longitudinal study of 101 patients (mean $FEV_1$ 42% predicted), AECOPD not requiring hospitalization significantly impaired both lung function and symptoms, with median recovery times of 6 days and 7 days, respectively [6]. But even by 35 days, recovery was incomplete in 25% of patients (by spirometry) and in 14% (by symptoms) [6]. Frequent AECOPD accelerate declines in $FEV_1$ that can be permanent [7,8]. AECOPD warranting

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hospitalization are even worse. They account for most of the estimated $30 billion in direct health care expenditures for COPD treatment in the USA in 2010 [9], and markedly impair quality of life for the following 6–24 months [10–12].

AECOPD requiring hospitalization are surprisingly lethal: recent in-hospital all-cause mortality rates were 5–7% [13,14], and are much greater in those needing mechanical ventilation. This risk persists for survivors; AECOPD requiring hospitalization significantly and independently predict increased all-cause mortality over the next five years (Figs. 1 & 2) [15]. The impact of AECOPD on all-cause mortality is generally underappreciated, as the final cause of death is more often cardiovascular disease than respiratory failure [16,17]. COPD itself has long been known from Framingham data to be an independent risk for cardiovascular events. Recent studies show a surge in cardiovascular inflammatory mediators early during AECOPD [18], which is blunted in those on anti-inflammatory treatment [19].

Clearly, it is incredibly crucial to prevent AECOPDs, and especially to break the cycle of frequent episodes as in the patient described above. The impact of AECOPD on prognosis has led to their inclusion in the most recent staging system of the Global Initiative for Obstructive Lung Disease (GOLD) (http://www.goldcopd.org).

## AECOPD are inflammatory events associated with infectious agents

Due to the variability in COPD symptoms, controversy persists about what constitutes an AECOPD [20]. A definition used in clinical trials is based on the classic Anthonisen criteria[21]: “the increase from baseline of at least two of the most common symptoms (dyspnea, cough, sputum, wheezes or chest tightness), with acute onset but at least two to three-day duration”. If the patient was seen elsewhere, the combination of symptoms and a prescription for antibiotics and/or steroids can be accepted [22], but multiple events must be separated by at least two weeks after treatment completion. Because more objective identification of AECOPD onset and duration would aid advances in treatment, there is intense interest in survey instruments measuring patient-reported outcomes [23,24]. As yet, none have been rigorously validated.

AECOPD can be precipitated by medication non-compliance or air pollution [25], but the overwhelming majority (~80%) are associated with airway pathogens, roughly one-third each bacterial, viral or both [26]. Increased AECOPD risk is predicted by greater degrees of lower respiratory tract colonization (as determined by culture-dependent techniques) by Gram-negative bacteria, especially non-typeable *Haemophilus influenzae* and *Pseudomonas* species. Colonization with those organisms, in turn, correlates roughly with worsening spirometry. Culture-independent techniques depending on next-generation DNA sequencing are still a research technique, but may soon become practical due to falling sequencing costs and faster bioinformatic analysis [27].

Biomarkers to predict risk and to use as prognostic tools during AECOPD are also being scrutinized. Exacerbations themselves are associated with marked increase in a wide variety of markers of inflammation, but none are yet well-validated for clinical use.

## Risk Factors for AECOPD

The most significant predictor of AECOPD risk is a history of previous AECOPD, with risk increasing with numbers of previous exacerbations [28]. The average patient with severe COPD has one exacerbation per year requiring medical attention. “Frequent exacerbations” is usually taken to denote ≥ two AECOPD annually. There are clear associations of AECOPD frequency with greater age, worse spirometry and home oxygen use. Other risk factors include hypercapnia, pulmonary hypertension and low body mass index (reviewed in [15]). The ‘Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints’ (ECLIPSE) study identified frequent exacerbations as a relatively stable phenotype persisting for years [28].

Specific findings on quantitative computed tomography may be novel predictors of AECOPD. Data from the COPDGene cohort showed independent correlations of annual exacerbation frequency with not only airways diseases, as anticipated, but also emphysema severity, not previously considered a predisposition [29]. In another recent paper that raised more questions than it answered [30], enlargement of the pulmonary artery (PA) relative to the aorta (Ao), expressed as a PA:Ao ratio >1, was associated with severe AECOPD in both derivation and validation cohorts [31]. At present, CT scanning cannot be advocated solely to estimate AECOPD risk outside a research setting. However, because many COPD patients will be scanned for other reasons, including lung cancer screening [32], the clinician should be aware of these frequently overlooked imaging characteristics.

Importantly, the “frequent exacerbator phenotype” is not limited to those with advanced COPD. In the ECLIPSE cohort, ≥ two AECOPD occurred in the first year of follow-up in 22% of subjects with spirometrically-moderate COPD (50% predicted ≥ $FEV_1$ >80% predicted) [28]. Hence, many patients, some not even diagnosed, are at risk for the morbidity and deterioration in health status triggered by AECOPD. Non-pulmonary factors consistently associated with frequent AECOPD include reflux disease and cardiovascular disease [28]. The “chronic bronchitis COPD phenotype” has also been associated with more frequent AECOPD [33,34]. Fortunately, there are now both pharmacological and non-pharmacological approaches to preventing AECOPD, some complimentary or indicated for specific groups of patients.

## Pharmacological interventions to prevent AECOPD

**Long-acting Beta Agonists (LABAs) & Inhaled corticosteroids (ICS)—**When used alone, LABAs reduce AECOPD frequency by 20–25% (relative risk 0.79, 95% CI 0.69–0.90) [35]. Although there is no solid evidence of increased cardiac risk with this class of drugs, due to that concern in asthma, many practitioners avoid LABA monotherapy without concurrent ICS use. Data from direct comparison show that the impact on exacerbations is similar for ICS and LABAs [36]. Fortunately, the effect of ICS/LABA combinations on AECOPD frequency is greater than when either is used as monotherapy; several different pairs of agents consistently reduced exacerbation frequency in four large clinical trials [37–40]. As noted in a systematic review [35], this beneficial effect is greater with lower levels of $FEV_1$. However, ICS use increased the risk of pneumonia in both the TORCH and INSPIRE studies [41,42]. A Cochrane review of long-term studies (6235 participants) found an odds-

ratio for pneumonia of 1.56 (95% CI 1.30–1.86) in subject on ICS, relative to placebo, a figure that needs to be individually weighted against the potential benefit demonstrated in the same meta-analysis, with the ICS/LABA combination providing an odds-ratio to reduce AECOPD of 0.76 (95% CI 0.68–0.84) [43,44]

**LAMAs—**In a multi-center trial conducted exclusively in Veterans, addition of tiotropium to usual care significantly reduced the frequency of AECOPD (absolute reduction 4.4%, relative reduction 14.0%) and of hospitalizations for COPD over a six-month study period [45]. Secondary analyses also found longer time to first exacerbation and reductions in unscheduled clinic visits and days of antibiotics in those on tiotropium [45]. Similar results were seen in five other randomized controlled trials comparing tiotropium to either placebo or ipratropium (reviewed in [35]).

Because of the larger effect on $FEV_1$ of tiotropium relative to LABAs [46,47], an attractive option is to start patients with newly-diagnosed COPD of moderate or greater severity on this agent first. In our experience, this strategy often convinces patients of the drug's value more readily than if tiotropium is added after LABAs, which have faster onset of action. Moreover, a pre-specified post hoc analysis [48] of the 'Understanding Potential Long-Term Impacts on Function with Tiotropium' (UPLIFT) study [49], which compared tiotropium to placebo over a 4-year period in 5,993 patients, suggests a greater reduction in AECOPD frequency in those with less severe disease (i.e., the opposite of ICS/LABA combinations). However, systematic reviews have revealed that in patients with history of exacerbations, the positive effect of tiotropium is evident regardless of spirometric severity, and perhaps stronger in more advanced disease [50].

As a class, LAMAs have generally favorable side-effect profiles, but they must be used with some caution in patients with prostatic hypertrophy and are contraindicated in narrow angle glaucoma. Several novel LAMA formulations are in the pipeline, typically in combination with an ICS or a LABA. Together with novel LABAs such as indecaterol [51], they will soon make it feasible to treat stable COPD with once-daily inhalers, which should improve compliance and patient satisfaction.

**Azithromycin—**In a multicenter NIH-sponsored clinical trial, addition of azithromycin (250 mg daily) to usual therapy of 1142 patients at increased risk of exacerbation significantly reduced AECOPD frequency (hazard ratio 0.73, 95% CI, 0.63–0.84) [52]. Multiple measures improved in subjects randomized to azithromycin, including time to first exacerbation (median, 95% CI) (azithromycin 266 days, 227–313 vs. placebo 174 days, 143–215 $p<0.001$); annual AECOPD frequency (azithromycin 1.48 vs. 1.83, $p = 0.01$); and health status as determined by St. George's Respiratory questionnaire.

Importantly, no benefits of scheduled azithromycin were seen in active smokers. Side effects were generally matched between groups, but in this elderly cohort there was more frequent hearing loss in those randomized to azithromycin (25% vs. 20%, $p = 0.04$). Likely due to careful exclusion of those with risk factors for QTc interval prolongation, there were no adverse cardiac events [52]. In clinical practice, similar precautions are recommended before starting this preventive therapy: careful evaluation of hearing function and review of the

electrocardiogram and cardiovascular risk factors. Daily dosing was chosen to avoid a negative result due to inadequate levels. Although untested, there is widespread belief that less frequent dosing (e.g., Monday, Wednesday, Friday) will be effective with an even lower chance of adverse events. The mechanism of action is uncertain, and rather than bactericidal effect, may include inhibition of biofilm formation and quorum-sensing by lung bacteria and modulation of the host immune response [53]. Emergence of drug resistant organisms is a theoretical concern not seen in this study, or in similar use in cystic fibrosis patients.

**Roflumilast—**Roflumilast is a selective phosphodiesterase 4 (PDE4) inhibitor, FDA-approved for severe COPD associated with significant chronic bronchitis and a history of exacerbations. It is both a bronchodilator and has anti-inflammatory properties distinct from those of steroids. In randomized trials, roflumilast reduced AECOPD frequency and improved lung function, even with concomitant LABA or ICS use [54]. Hence, roflumilast might be considered in the hypothetical patient at the start of this article.

However, it is currently unproven that the different mechanism of action of roflumilast will result in further reductions in AECOPD frequency when added to LABA/ICS combination (without or with stable LAMA therapy). That question is being tested in an ongoing study entitled ‘Roflumilast in the Prevention of COPD Exacerbations While Taking Appropriate Combination Treatment’ (REACT) (clinicaltrials.gov identifier NCT01329029, results expected to be available in 2015).

Careful patient selection for roflumilast therapy is crucial. No benefit was seen in earlier studies not restricted to those with daily sputum production. Roflumilast has significant potential adverse effects, including insomnia, gastrointestinal intolerance, and weight loss that averages 10 kg, making it impractical in slender patients. Practitioners should be careful with use in patients with mood disorders, especially depression, as it has been associated with suicidal ideation and increased anxiety, and is also contraindicated in liver disease of moderate or greater severity (Child-Pugh B–C). There are multiple drug interactions (Table 1), but package insert data indicates lack of interaction with LABAs, montelukast, sildenafil or digoxin. Roflumilast should not be used concurrently with theophylline. Because hepatic cytochromes are not inhibited by azithromycin [55] (as they are by erythromycin), concurrent use of roflumilast with azithromycin should not cause toxicity. Roflumilast is not currently on the VA National Formulary, although criteria for non-formulary usage have been published (www.pbm.va.gov).

## Non-pharmacological interventions to prevent AECOPD

Lung volume reduction surgery (LVRS) is known to reduce mortality in patients with upper-zone predominant emphysema and low baseline exercise tolerance after pulmonary rehabilitation [56]. It is less well appreciated that LVRS also reduces AECOPD frequency [57].

Pulmonary rehabilitation following hospitalization for AECOPD can prevent readmissions (OR, 0.22; 95% CI, 0.08–0.58, NNT 4) [58], but it is far less certain that admissions can be prevented by pulmonary rehabilitation in the stable state (reviewed in [59]). Regardless, the current GOLD guidelines recommend rehabilitation programs for the majority of patients with COPD, based either on the presence of persistent symptoms or frequent AECOPD, and

the criterion of low pulmonary function should not be the main determinant to select this treatment.

Finally, as COPD starts to be recognized as a systemic disease, which can be one component of the multi-morbidities common to the elderly, there is interest in developing disease management programs [60], including emphases on the management of the coexistent diseases related to frequent AECOPD.

## What to tell your patient

To return to the case, you or your treatment team should review your patient's technique with inhaled medications. If she cannot properly use them, even with reinstruction, consider switching delivery devices; individual patients prefer and hence better comply with either metered dose inhalers with spacers or with dry powder inhalers. The overwhelming majority of patient with less than end-stage COPD can be managed without resorting to nebulizers. VA national policy prudently discourages home nebulizer use, based on the risks of tachyphylaxis to short-acting beta agonists, drug-resistant infection and worsening of ventilation-perfusion relationships with hypoxemia. You should encourage her to engage in formal pulmonary rehabilitation, which will almost certainly improve her exercise tolerance and quality of life [61]. And you should, of course, congratulate her on getting immunized against seasonal influenza and pneumococcus, and for sustained smoking cessation, which remains the only intervention that both slows the rate of lung function decline in COPD [62] and reduces all-cause mortality

If continued purulent sputum is a problem, consider resistant organisms. It might be reasonable to use an antibiotic with greater spectrum, especially a respiratory fluroquinolone or amoxicillin/clavulanate. And don't forget atypical mycobacterial infection, now recognized to be increased by ICS use [63]. Investigating that possibility might warrant a CT scan followed be induced sputums or even Pulmonary referral for consideration of bronchoscopy, as therapy for *M. avium*, in particular, is difficult and should be based on a firmly established diagnosis.

It would be reasonable to discuss with your patient the risks and benefits of scheduled azithromycin or of roflumilast (if she makes sputum daily and is not under-weight). Her lung function is not sufficiently reduced to warrant work-up for LVRS (typically $FEV_1 < 35\%$ predicted) and certainly not for lung transplant. It would be unexpected that she would require home oxygen for continuous hypoxemia at that level of $FEV_1$. Whether supplemental oxygen improved survival in COPD patients with only transient hypoxemia with exertion is unsubstantiated, and the subject of an ongoing NHLBI trial (Long-term Oxygen Treatment Trial, LOTT) [64]. Her inquiry about the need for oxygen in the context of a family member's terminal illness may indicate inadequate understanding of her disease severity, or possibly anxiety disorders or depression, which are much more common in COPD than other chronic illnesses [65].

In summary, options are steadily improving to prevent AECOPD and thus alleviate the havoc that exacerbations cause your patients. COPD should be seen as an important and

treatable, rather than hopeless, chronic disease in which Primary Care providers can make a major difference.

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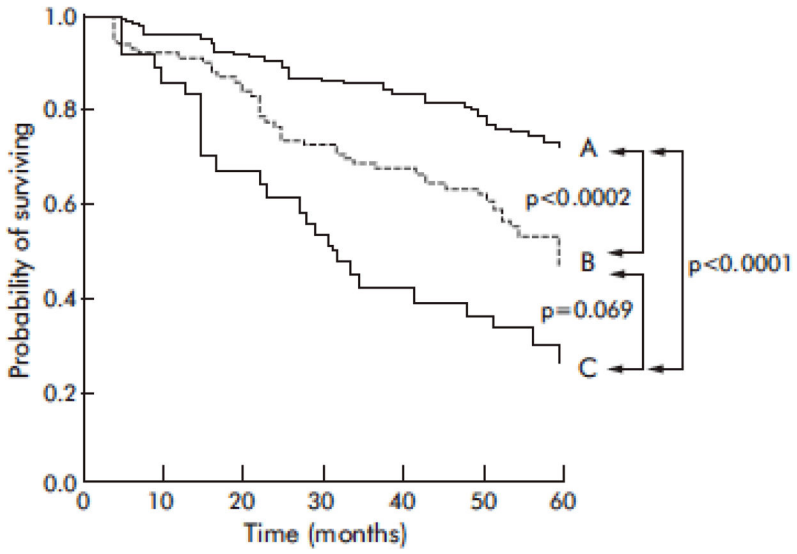


**Figure 1.**

Kaplan-Meier survival curves by frequency of exacerbations in patients with COPD: group A, patients with no acute exacerbations of COPD; group B, patients with 1–2 acute exacerbations of COPD requiring hospital management; group C, patients with >3 acute exacerbations of COPD. Reproduced with permission from [15].

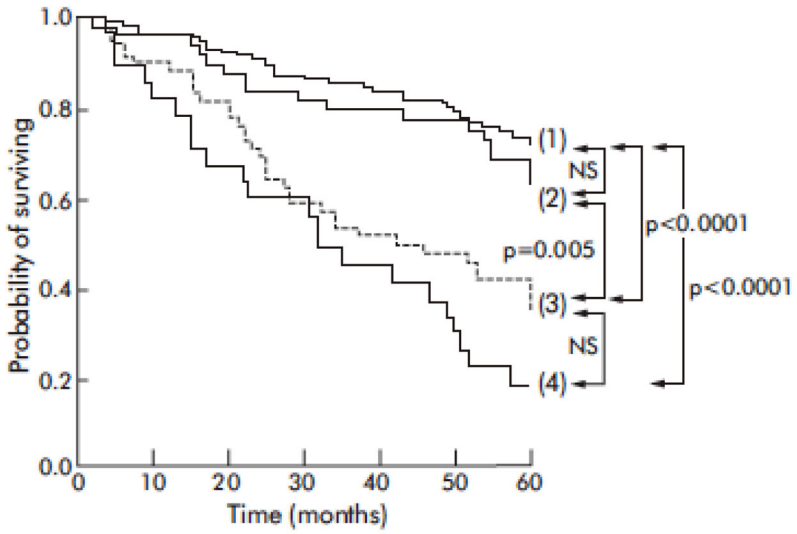


**Figure 2.**

Kaplan-Meier survival curves by severity of exacerbations in patients with COPD: (1) no acute exacerbations of COPD; (2) patients with acute exacerbations of COPD requiring emergency service visits without admission; (3) patients with acute exacerbations of COPD requiring one hospital admission; (4) patients with readmissions. Reproduced with permission from [15].

**Table 1**

Known drug interactions with roflumilast *

| | | |
|---|---|---|
| Cimetidine | increases roflumilast levels | use with caution |
| Enoxacin | increases roflumilast levels | use with caution |
| Erythromycin | increases roflumilast levels | use with caution |
| Fluvoxamine | increases roflumilast levels | use with caution |
| Minulet oral contraceptive (Gestodene/Ethinyloestradiol) | increases roflumilast levels | use with caution |
| Rifampin | markedly decreases roflumilast levels | not recommended |

* data from manufacturer package insert