



**EDUCATIONAL OBJECTIVE:** Readers will recognize, manage, and try to prevent acute exacerbations of chronic obstructive pulmonary disease

**UMUR S. HATIPOGLU, MD**

Quality Improvement Officer, Respiratory Institute, Cleveland Clinic

**LOUTFI S. ABOUSSOUAN, MD**

Respiratory Institute, Cleveland Clinic; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Treating and preventing acute exacerbations of COPD

## ABSTRACT

Acute exacerbations of chronic obstructive pulmonary disease (COPD)—characterized by shortness of breath, increased sputum production, increased purulence, or a combination of these signs—are costly and can have major impacts on the patient’s health. Corticosteroids, antibiotics, and bronchodilators are the cornerstones of prevention and therapy, with mucolytics, oxygen supplementation, and ventilatory support also advisable for some patients. Treatment should be evidence-based and tailored to the patient’s history and present needs.

## KEY POINTS

COPD exacerbations usually start with an infection.

A short course of corticosteroids (eg, prednisone 40 mg daily for 5 to 7 days) improves outcomes with low risk.

The choice of antibiotic depends on severity and frequency of exacerbations and the patient’s age and condition.

Inhaled albuterol 2.5 mg, every 1 to 4 hours, should be prescribed with or without a nebulized anticholinergic.

Ventilation support is important for patients with acute respiratory acidosis (pH < 7.35).

Exacerbations can be prevented with some combination of inhaled agents (long-acting beta-2 agonist, corticosteroid, long-acting antimuscarinic), roflumilast (an oral phosphodiesterase inhibitor), and a mucolytic, depending on the patient’s needs.

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**I**N CONTRAST TO STABLE chronic obstructive pulmonary disease (COPD),<sup>1</sup> acute exacerbations of COPD pose special management challenges and can significantly increase the risk of morbidity and death and the cost of care.

This review addresses the definition and diagnosis of COPD exacerbations, disease burden and costs, etiology and pathogenesis, and management and prevention strategies.

## DEFINITIONS ARE PROBLEMATIC

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines a COPD exacerbation as “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.”<sup>2</sup> It further categorizes acute exacerbations by severity:

- Mild—treated with increased frequency of doses of existing medications
- Moderate—treated with corticosteroids or antibiotics, or both
- Severe—requires hospital utilization (either emergency room treatment or admission).

Although descriptive and useful for retrospective analyses, this current definition poses ambiguities for clinicians. Day-to-day variation in symptoms is not routinely assessed, so deviations from baseline may be difficult to detect. Although clinical tools are available for assessing symptoms in stable and exacerbated states (eg, the COPD assessment test<sup>3</sup> and the Exacerbations of Chronic Pulmonary Disease Tool [EXACT]<sup>4</sup>), they have not been widely adopted in daily practice. Also, according to the current definition, the severity of an exac-

erbatation can be classified only after the course of action is determined, so the severity is not helpful for forming a management strategy at bedside. In addition, physicians may have different thresholds for prescribing antibiotics and corticosteroids.

An earlier definition categorized a COPD exacerbation by the presence of its three cardinal symptoms (ie, increased shortness of breath, sputum volume, and purulence):

- Type I—all three symptoms present
- Type II—two symptoms present
- Type III—one symptom present, accompanied by at least one of the following: upper respiratory tract infection within the past 5 days, unexplained fever, increased wheezing or cough, or 20% increased respiratory rate or heart rate from baseline.

This older definition was successfully used in a prospective clinical trial to identify patients who benefited most from antibiotics for COPD exacerbations.<sup>5</sup>

Despite these caveats regarding a definition, most clinicians agree on the clinical presentation of a patient with COPD exacerbation: ie, having some combination of shortness of breath, increased sputum volume, and purulence. By the same token, patients with COPD who present with symptoms not typical of an exacerbation should be evaluated for another diagnosis. For instance, Tillie-Leblond et al<sup>6</sup> reported that 49 (25%) of 197 patients hospitalized with an “unexplained” exacerbation of COPD were eventually diagnosed with pulmonary embolism.

### ■ EXACERBATIONS ARE COSTLY

The care of patients with COPD places a great burden on the healthcare system. Using multiple national databases, Ford et al<sup>7</sup> estimated that medical costs in the United States in 2010 attributable to COPD and its complications were \$32.1 billion.

The largest component of direct healthcare costs of COPD is exacerbations and subsequent hospitalizations.<sup>8</sup> Data from a predominantly Medicare population indicate that the annualized mean COPD-related cost for a patient with no exacerbations was \$1,425, compared with \$12,765 for a patient with severe exacerbations.<sup>9</sup> The investigators

estimated that reducing exacerbations from two or more to none could save \$5,125 per patient per year.

### ■ EXACERBATIONS AFFECT HEALTH BEYOND THE EVENT

COPD exacerbations are associated with a faster decline in lung function,<sup>10</sup> reduced quality of life,<sup>11</sup> and lost workdays.<sup>7</sup> A single exacerbation may cause a decline in lung function and health status that may not return to baseline for several months, particularly if another exacerbation occurs within 6 months.<sup>12,13</sup> COPD exacerbations have also been linked to poor clinical outcomes, including death.

In a prospective study in 304 men with COPD followed for 5 years, those who had three or more COPD exacerbations annually were four times as likely to die than patients who did not have an exacerbation.<sup>14</sup> Nevertheless, the relationship with mortality may not be causal: Brusselle pointed out in an editorial<sup>15</sup> that established mortality predictors for COPD do not include exacerbations, and symptomatic patients with COPD without any history of exacerbations are at greater risk of death than those who are asymptomatic but at high risk for exacerbations.

### ■ INFECTION + INFLAMMATION = EXACERBATION

An acute COPD exacerbation can be viewed as an acute inflammatory event superimposed on chronic inflammation associated with COPD. Inflammation in the airways increases resistance to air flow with consequent air trapping. Increased resistance and elastic load due to air trapping place respiratory muscles at a mechanical disadvantage and increase the work of breathing.

#### Infection starts the process

Infections, particularly bacterial and viral, are thought to be the major instigators of COPD exacerbation, although environmental factors such as air pollution may also play a role.<sup>16</sup>

Airway inflammation is markedly reduced when bacterial infection is eradicated. But if bacterial colonization continues, inflammatory markers remain elevated despite clinical resolution of the exacerbation.<sup>17</sup> Desai et al<sup>18</sup>

**COPD exacerbation: an acute worsening of respiratory symptoms**

found that patients with COPD and chronic bronchitis with bacterial colonization had a larger symptom burden than patients without colonization, even without an exacerbation.

**Allergic profile increases risk**

Although most studies indicate that infection is the main cause of exacerbations, clinicians should consider other mechanisms of inflammation on an individual basis. COPD exacerbations may be phenotyped by measuring inflammatory markers, perhaps as a starting point for tailored therapies.

Bafadhel et al<sup>19</sup> studied 145 patients with COPD over the course of a year and recorded various biomarkers at baseline and during exacerbations. Exacerbations had an inflammatory profile that was predominantly bacterial in 37%, viral in 10%, and eosinophilic in 17%, and had limited changes in the inflammatory profile in 14%. The remaining episodes were combinations of categories. In another study,<sup>20</sup> multivariate analysis conducted in two cohorts with COPD found that patients who had an allergic phenotype had more respiratory symptoms and a higher likelihood of COPD exacerbations.

Frequent COPD exacerbations are increasingly recognized as being associated with an asthma-COPD overlap syndrome, consisting of symptoms of increased airflow variability and incompletely reversible airflow obstruction.<sup>21</sup>

**Inflammation as a marker of frequent exacerbations**

Evidence is accumulating that supports systemic inflammation as a marker of frequent exacerbations. The Copenhagen Heart Study tested for baseline plasma C-reactive protein, fibrinogen, and white blood cell count in 6,574 stable patients with COPD.<sup>22</sup> After multivariable adjustment, they found a significantly higher likelihood of having a subsequent exacerbation in patients who had all three biomarkers elevated (odds ratio [OR] 3.7, 95% confidence interval [CI] 1.9–7.4), even in patients with milder COPD and those without previous exacerbations.

**Past exacerbations predict risk**

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study<sup>23</sup> found that a history of acute COPD exacerbation

was the single best predictor of future exacerbations. This risk factor remained stable over 3 years and was present across the severity of COPD, ie, patients at lower GOLD stages who had a history of frequent exacerbations were likely to have exacerbations during follow-up.

■ **EXACERBATION INCREASES CARDIOVASCULAR RISK**

COPD exacerbations increase the risk of cardiovascular events, particularly myocardial infarction.<sup>24</sup> During hospitalization for acute exacerbation of COPD, markers of myocardial injury and heart failure may be elevated and are a predictor of death.<sup>25</sup>

Patel et al<sup>26</sup> measured arterial stiffness (aortic pulse wave velocity, a validated measure of cardiovascular risk) and cardiac biomarkers (troponin and N-terminal B-type natriuretic peptide) at baseline in 98 patients and longitudinally during and after a COPD exacerbation. In addition to increased levels of cardiac biomarkers, they found a significant rise in arterial stiffness during the exacerbation event without return to baseline levels over 35 days of follow-up. The arterial stiffness increase was related to airway inflammation as measured by sputum interleukin 6, particularly in patients with documented lower respiratory tract infection.

Retrospective analysis suggests a reduced all-cause mortality rate in COPD patients who are treated with beta-blockers.<sup>27</sup>

**Recommendation.** We recommend that patients already taking a selective beta-blocker continue to do so during a COPD exacerbation.

■ **OUTPATIENT MANAGEMENT**

Treatment with a combination of a corticosteroid, antibiotic, and bronchodilator addresses the underlying pathophysiologic processes of an acute exacerbation: inflammation, infection, and airway trapping.

**Short course of a corticosteroid improves outcomes**

A 10-day systemic course of a corticosteroid prescribed for COPD exacerbation before discharge from the emergency department was found to offer a small advantage over placebo

**Patients with symptoms atypical of an exacerbation should be evaluated for an alternative diagnosis**

for reducing treatment failure (unscheduled physician visits, return to emergency room for recurrent symptoms) and improving dyspnea scores and lung function.<sup>28</sup> Even just a 3-day course improved measures of respiration (forced expiratory volume in the first second of expiration [FEV<sub>1</sub>] and arterial oxygenation) at days 3 and 10, and reduced treatment failures compared with placebo.<sup>29</sup>

Corticosteroid prescription should not be taken lightly, because adverse effects are common. In a systematic review, one adverse effect (hyperglycemia, weight gain, or insomnia) occurred for every five people treated.<sup>30</sup>

Identifying subgroups of patients most likely to benefit from corticosteroid treatment may be helpful. Corticosteroids may delay improvement in patients without eosinophilic inflammation and hasten recovery in those with more than 2% peripheral eosinophils.<sup>31</sup> Siva et al<sup>32</sup> found that limiting corticosteroids to patients with sputum eosinophilia reduced corticosteroid use and reduced severe exacerbations compared with standard care.<sup>32</sup>

**Recommendation.** For an acute exacerbation, we prescribe a short course of corticosteroids (eg, prednisone 40 mg daily for 5 to 7 days). Tapering dosing is probably unnecessary because adrenal insufficiency is uncommon before 2 weeks of corticosteroid exposure. Clinicians should weigh the merits of tapering (reduced corticosteroid exposure) against patient inconvenience and difficulty following complicated instructions.

### **Antibiotics help, but exact strategy uncertain**

Although antibiotic therapy is one of the three pillars of COPD exacerbation management, the optimal antimicrobial agent, duration of therapy, and which patients will benefit remain areas of controversy and research. Thus far, large trials have been unable to definitely show the superiority of one antibiotic over another.<sup>33,34</sup>

A 1987 randomized controlled trial<sup>5</sup> of antibiotic therapy in acute exacerbation of COPD found the greatest benefit to patients who had all three cardinal symptoms (ie, increased shortness of breath, sputum volume, and purulence), with less marked but still significant improvement in patients with two

symptoms. In a 2012 multicenter trial<sup>35</sup> patients with mild to moderate COPD experiencing an exacerbation were treated with either combined amoxicillin and clavulanate or placebo if they had one of the three cardinal symptoms. The antibiotic group had a significantly higher clinical cure rate at days 9 to 11 (74.1% vs 59.9%) as well as a longer time until the next exacerbation (233 vs 160 days).

**Recommendation.** Optimal antibiotic management of COPD exacerbations may also depend on risk factors. For patients with at least two cardinal symptoms, we favor a scheme akin to one proposed for treating community-acquired pneumonia (Table 1).<sup>16,36</sup>

## ■ INPATIENT MANAGEMENT

### **Corticosteroids improve outcomes**

A Department of Veterans Affairs cooperative trial<sup>37</sup> randomized 271 patients hospitalized with COPD exacerbation to receive either corticosteroids (intravenous followed by oral) or placebo for either 2 weeks or 8 weeks. Corticosteroid recipients had lower rates of treatment failure at 30 and 90 days, defined as death from any cause, need for mechanical ventilation, readmission, or intensification of pharmacologic therapy. Corticosteroid therapy also reduced hospital length of stay and improved the rate of recovery. The longer corticosteroid course was associated with a higher rate of adverse effects.

### **Oral corticosteroids not inferior to intravenous**

Using the same end point of treatment failure as the Veterans Affairs cooperative trial, deJong et al<sup>38</sup> demonstrated that prednisone 60 mg by mouth was not inferior to intravenous prednisone. Neither trial demonstrated a difference in mortality between corticosteroid use and placebo.

### **Short course of a corticosteroid not inferior to a long course**

In 2013, the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial<sup>39</sup> randomized 314 patients presenting with an acute COPD exacerbation (92% requiring hospital admission) to oral prednisone 40 mg daily for either 5 days or 14 days. They found that the short course was noninferior in

**A single exacerbation may worsen health status for several months**

**TABLE 1**  
**Antibiotic choice for COPD exacerbations**

Clinical presentation	Risk factors	Suggested antibiotic
<b>Uncomplicated exacerbation</b> (determined by risk factors)	Age < 65	Macrolide
	FEV <sub>1</sub> > 50%	or
	No cardiac disease	2nd- or 3rd-generation cephalosporin
	< 3 exacerbations per year	
<b>Complicated exacerbation</b>	Age ≥ 65	Respiratory fluoroquinolone
	FEV <sub>1</sub> ≤ 50%	or
	Comorbidity	Combined amoxicillin and clavulanic acid
	≥ 3 exacerbations per year	
<b>At risk for <i>Pseudomonas</i> infection</b>	FEV <sub>1</sub> ≤ 50%	Antipseudomonal fluoroquinolone
	Known infection with <i>Pseudomonas</i>	
	Bronchiectasis	
	Prior antibiotic and steroid use	

Information based on Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359:2355–2365 and Anzueto A. Primary care management of chronic obstructive pulmonary disease to reduce exacerbations and their consequences. *Am J Med Sci* 2010; 340:309–318.

**Infections are thought to be the major instigators of COPD exacerbation**

preventing exacerbations over the ensuing 6 months in terms of death and the need for mechanical ventilation.

**Recommendation.** Our threshold for initiating systemic corticosteroid therapy is lower in hospitalized patients than in outpatients. We recommend the regimen of the REDUCE trial: prednisone 40 mg daily for 5 days.

**Corticosteroids for patients on ventilatory support**

Severe COPD exacerbations requiring admission to intensive care are a significant source of morbidity and mortality, and the strategy of corticosteroid treatment is still under investigation.

**Intravenous corticosteroids are effective.** A multicenter trial<sup>40</sup> in 354 patients requiring either invasive or noninvasive mechanical ventilation randomized them to treatment with either intravenous methylprednisolone (tapered) or placebo. Treatment was associated with fewer mechanical ventilation days and a

lower rate of noninvasive ventilation failure.

**Low-dose oral corticosteroids ineffective.** In contrast, an open-label trial<sup>41</sup> of patients requiring ventilatory support and randomized to either oral prednisone (1 mg/kg for up to 10 days) or usual care found no difference in intensive care length of stay or noninvasive ventilation failure. This study used the oral route and smaller doses, and its open-label design might have introduced bias.

**Lower-dose steroids better than high-dose.** A 2014 cohort study of 17,239 patients admitted to the ICU with acute exacerbations of COPD evaluated outcomes of treatment with high methylprednisolone dosages (> 240 mg per day) vs lower dosages, using propensity score matching.<sup>42</sup> No mortality difference was found between the groups. The lower dosage group (median methylprednisolone dose 100 mg per day) had shorter hospital and intensive care unit stays, shorter duration of noninvasive positive pressure ventilation, less need for insulin therapy, and fewer fungal infections.

### Antibiotics for hospitalized patients

Only scarce data are available on the use of antibiotics for patients hospitalized with COPD exacerbation. In a study of patients hospitalized with COPD exacerbations, adding doxycycline to corticosteroids led to better clinical success and cure rates at 10 days compared with placebo, but the primary end point of clinical success at 30 days was not different between the two groups.<sup>43</sup>

### ■ BRONCHODILATORS: A MAINSTAY OF COPD TREATMENT

Bronchodilators are an important part of treatment of COPD exacerbations in inpatient and outpatient settings.

**Nebulized beta-2 agonists** are given every 1 to 4 hours. Albuterol at a 2.5-mg dose in each nebulization was found to be as effective as 5 mg for length of hospital stay and recovery of lung function in patients with an acute exacerbation of COPD.<sup>44</sup>

**Adding an anticholinergic may help.** Nebulized anticholinergics can be given alone or combined with beta-2 agonists. Whether long-acting bronchodilators should be used to manage COPD patients hospitalized with an exacerbation requires further inquiry. In an observational study with historical controls, Drescher and colleagues<sup>45</sup> found cost savings and shorter hospital stays if tiotropium (a long-acting anticholinergic) was added to the respiratory care protocol, which also included formoterol (a long-acting beta-2 agonist).

### ■ OXYGEN: TITRATED APPROACH SAFER

Oxygen should be supplied during a COPD exacerbation to ensure adequate oxyhemoglobin saturation. Caution is needed to avoid hyperoxemic hypercapnia, particularly in patients with severe COPD and propensity to ventilatory failure. The routine administration of oxygen at high concentrations during a COPD exacerbation has been associated with a higher mortality rate than with a titrated oxygen approach.<sup>46</sup> Long-term oxygen treatment started at discharge or as outpatient therapy is associated with reduced hospital admissions and shorter hospital stays for acute exacerbations of COPD.<sup>47</sup>

### ■ VENTILATION SUPPORT

**Noninvasive positive-pressure ventilation** is a useful adjunct to treatment of COPD exacerbations with evidence of ventilatory failure (ie, acute respiratory acidosis), helping to offset the work of breathing until respiratory system mechanics improve. Keenan et al<sup>48</sup> reviewed 15 randomized controlled trials, involving 636 patients, of noninvasive positive-pressure ventilation in the setting of COPD exacerbation. They concluded that noninvasive positive-pressure ventilation reduced the in-hospital mortality rate and length of stay compared with standard therapy. Noninvasive positive-pressure ventilation is most useful in patients with severe COPD exacerbations and acute respiratory acidosis (pH < 7.35).<sup>49</sup>

**Intubation and mechanical ventilation.** Although no standards exist for determining which COPD exacerbations may be too severe for noninvasive positive-pressure ventilation, intubation is clearly indicated for impending respiratory failure or hemodynamic instability. Other factors to consider include the greater likelihood of noninvasive positive-pressure ventilation failure in patients with severe respiratory acidosis (pH < 7.25 is associated with a > 50% failure rate) and in those with no improvement in acidosis or respiratory rate during the first hour after initiation of noninvasive positive-pressure ventilation.<sup>50</sup>

### ■ PREVENTING EXACERBATIONS

Recent data indicate that COPD exacerbations can often be prevented (Table 2).

#### Inhaled pharmacotherapy

Inhaled pharmacotherapeutic agents, singly or in combination, reduce the frequency of COPD exacerbations.

**Combined long-acting beta-2 agonist and corticosteroid is better than single-agent therapy.** In 2007, the Towards a Revolution in COPD Health (TORCH) trial<sup>51</sup> evaluated outpatient therapy in more than 6,000 patients worldwide with either an inhaled long-acting beta-2 agonist (salmeterol), an inhaled corticosteroid (fluticasone), both drugs in combination, or placebo. Patients had baseline prebronchodilator FEV<sub>1</sub> of less than 60% and were followed for 3 years. No difference

**A history of exacerbation is the best predictor of future exacerbations**

was found between the groups in the primary end point of deaths, but the annualized rate of moderate to severe exacerbations was reduced by 25% in the group that received combination therapy vs placebo. Combination therapy showed superior efficacy over individual drug therapy in preventing exacerbations. Treatment with the inhaled corticosteroid, whether alone or in combination with salmeterol, increased the risk of pneumonia.

**A long-acting antimuscarinic agent is better than placebo.** In 2008, the Understanding Potential Long-Term Impacts on Function With Tiotropium (UPLIFT) trial<sup>52</sup> randomized nearly 6,000 patients with COPD and a postbronchodilator FEV<sub>1</sub> of less than 70% to placebo or tiotropium, a long-acting antimuscarinic agent. Tiotropium reduced the exacerbation rate by 14% compared with placebo and improved quality of life.

**Antimuscarinics may be better than beta-2 agonists.** Head-to-head comparisons suggest that long-acting antimuscarinic agents are preferable to long-acting beta-2 agonists for preventing COPD exacerbations.<sup>53,54</sup>

**Triple therapy: evidence is mixed.** For patients with severe symptomatic COPD and frequent exacerbations, triple therapy with a combination of an inhaled long-acting antimuscarinic agent, an inhaled long-acting beta-2 agonist, and an inhaled corticosteroid has been suggested.

Data to support this practice are limited. In the Canadian Optimal Trial,<sup>55</sup> the rate of exacerbations was not different between tiotropium alone, tiotropium plus salmeterol, and triple therapy. However, the rate of hospitalization for severe exacerbation was lower with triple therapy than tiotropium alone. A large, retrospective cohort study also supported triple therapy by finding reduced mortality, hospitalizations, and need for oral corticosteroid bursts compared to combination therapy with an inhaled long-acting beta-2 agonist and an inhaled corticosteroid.<sup>56</sup>

The drawback of triple therapy is an increased incidence of pneumonia associated with combined beta-2 agonist and corticosteroids, most likely due to the corticosteroid component.<sup>51</sup> The risk appears to be higher for higher potency corticosteroids, eg, fluticasone.<sup>57</sup>

TABLE 2

**Preventing COPD exacerbations**

**Inhaled therapy**

- Long-acting beta-2 agonist + inhaled corticosteroid
- Long-acting antimuscarinic agent
- Long-acting antimuscarinic agent + long-acting beta-2 agonist

**Phosphodiesterase-4 inhibitors**

- Roflumilast

**Mucolytics**

- N-acetylcysteine 600 mg oral twice daily
- Carbocysteine (not available in United States)

**Antibiotics**

- Azithromycin 250 mg daily or 500 mg 3 times weekly

**Pulmonary rehabilitation**

**Vaccinations**

- Influenza
- Pneumococcal

**Smoking cessation**

- Seize the opportunity!

In 2014, the Withdrawal of Inhaled Steroids During Optimised Bronchodilator Management (WISDOM) trial<sup>58</sup> randomized nearly 2,500 patients with a history of COPD exacerbation receiving triple therapy consisting of tiotropium, salmeterol, and inhaled fluticasone to either continue treatment or withdraw the corticosteroid for 3 months. The investigators defined an annualized exacerbation rate of 1.2 (ie, a 20% increase) as the upper limit of the confidence interval for an acceptable therapeutic margin of noninferiority. The study showed that the risk of moderate to severe exacerbations with combined tiotropium and salmeterol was noninferior to triple therapy.

Nevertheless, caution is advised when removing the corticosteroid component from triple therapy. The trial demonstrated a worsening in overall health status, some reduction in lung function, and a transient increase in severe exacerbations in the withdrawal group. Patients with increased symptom burden at baseline and a history of severe exacerbations may not be optimal candidates for this strategy.

**Caution is needed to avoid hyperoxemic hypercapnia in patients on oxygen**

### Roflumilast is effective but has side effects

Roflumilast, an oral phosphodiesterase 4 inhibitor, is an anti-inflammatory drug without bronchodilator properties. In randomized controlled trials, the drug was associated with a 17% reduction in acute exacerbations compared with placebo.<sup>59</sup>

Adding roflumilast to either a long-acting beta-2 agonist or a long-acting antimuscarinic agent resulted in a 6% to 8% further reduction in the proportion of patients with exacerbation.<sup>60,61</sup> Martinez et al<sup>61</sup> found that roflumilast added to a regimen of a long-acting beta-2 agonist plus an inhaled corticosteroid reduced moderate to severe exacerbations by 14.2%, even in the presence of tiotropium. Compared with placebo, roflumilast treatment reduced exacerbations necessitating hospitalizations by 23.9%.

The FDA has approved oral roflumilast 500 µg once daily to prevent COPD exacerbations.

Roflumilast is frequently associated with side effects, including gastrointestinal symptoms (chiefly diarrhea), weight loss, and psychiatric effects. A benefit-to-harm study in 2014 concluded that using the drug is only favorable for patients who have a high risk of severe exacerbations, ie, those who have a greater than 22% baseline risk of having at least one exacerbation annually.<sup>62</sup>

**Recommendation.** Roflumilast should be reserved for patients who have severe COPD with a chronic bronchitis phenotype (ie, with cough and sputum production) and repeated exacerbations despite an optimal regimen of an inhaled corticosteroid, long-acting beta-2 agonist, and long-acting antimuscarinic agent.

### Macrolide antibiotics: Role unclear

Macrolide antibiotics have anti-inflammatory and immunomodulatory activities.

**Azithromycin: fewer exacerbations but some side effects.** A multicenter trial<sup>63</sup> in 1,142 COPD patients randomized to either oral azithromycin 250 mg daily or placebo found a 27% reduction in the risk of COPD exacerbation in the intervention arm. No differences were found between the groups in mortality, hospitalizations, emergency department visits, or respiratory failure. Hearing loss

and increased macrolide resistance were noted in the intervention arm. In a secondary subgroup analysis,<sup>64</sup> no difference in efficacy was found by sex, history of chronic bronchitis, oxygen use, or concomitant COPD treatment.

The COPD: Influence of Macrolides on Exacerbation Frequency in Patients trial<sup>65</sup> helped refine patient selection for macrolide therapy. In this single-center study, 92 patients with COPD and at least three exacerbations during the year prior to enrollment were randomized to receive either azithromycin 500 mg three times weekly or placebo. Exacerbations in the intervention group were markedly reduced (42%) with no difference in hospitalization rate.

The place of macrolide antibiotics in the treatment strategy of COPD is unclear, and they are not currently part of the GOLD guidelines. Still unknown is the incremental benefit of adding them to existing preventive regimens, cardiovascular safety, side effects, and potential effects on the resident microbial flora.

Other antibiotics have also been investigated for efficacy in preventing exacerbations.

**Moxifloxacin: fewer exacerbations.** The Pulsed Moxifloxacin Usage and Its Long-term Impact on the Reduction of Subsequent Exacerbations study<sup>66</sup> randomized more than 1,000 patients with stable COPD to receive either moxifloxacin 400 mg or placebo daily for 5 days repeated every 8 weeks for six courses. Frequent assessment during the treatment period and for 6 months afterward revealed a reduced exacerbation rate in the intervention group but without benefit in hospitalization rate, mortality, lung function, or health status.

**Recommendation.** Azithromycin (either 250 mg daily or 500 mg three times weekly) can be considered for patients who have repeated COPD exacerbations despite an optimal regimen of an inhaled corticosteroid, inhaled long-acting beta-2 agonist, and inhaled long-acting antimuscarinic agent. The need to continue azithromycin should be reassessed yearly.

### Mucolytics

**Greatest benefit to patients not taking inhaled corticosteroids.** Mucolytic agents help clear airway secretions by reducing viscos-

**Mucolytics:  
for control  
of thick  
and copious  
phlegm**

ity. N-acetylcysteine and carbocysteine (not available in the United States) also have antioxidant properties that may counteract oxidant stress associated with acute COPD exacerbations.

The Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS)<sup>67</sup> randomized 523 COPD patients to N-acetylcysteine 600 mg daily or placebo. After 3 years of follow-up, no differences were found in the rate of exacerbations, lung function decline, and quality of life. Subgroup analysis suggested a reduction in exacerbations for patients who were not taking inhaled corticosteroids.

The Effect of Carbocysteine on Acute Exacerbation of Chronic Obstructive Pulmonary Disease (PEACE) study randomized more than 700 patients from multiple centers in China who had COPD and a recent history of exacerbations; they found a 25% lower exacerbation rate over 1 year with carbocysteine vs placebo.<sup>68</sup> Most of the patients (83%) were not on inhaled corticosteroids, which complemented findings of the BRONCUS trial.

The Effect of High Dose N-acetylcysteine on Air Trapping and Airway Resistance of COPD (HIACE) study randomized 120 patients with stable COPD in a hospital in Hong Kong to either oral N-acetylcysteine (600 mg twice daily) or placebo and found a reduced exacerbation rate of exacerbations. Patients were matched at baseline for inhaled corticosteroid use.<sup>69</sup>

In 2014, the Twice Daily N-acetylcysteine 600 mg for Exacerbations of Chronic Obstructive Pulmonary Disease (PANTHEON) study<sup>70</sup> randomized 1,006 patients from multiple hospitals in China with a history of moderate to severe COPD and exacerbations to receive either N-acetylcysteine 600 mg twice daily or placebo for 1 year. They found a 22% reduction in exacerbations in the treatment group vs placebo.

GOLD guidelines<sup>2</sup> recommend mucolytics for patients with severe COPD and exacerbations when inhaled corticosteroids are not available or affordable.

**Recommendation.** Mucolytics may be useful for patients with difficulty expectorating and with a history of exacerbations despite appropriate inhaled therapy.

■ OTHER INTERVENTIONS CAN HELP

**Pulmonary rehabilitation provides multiple benefits**

Pulmonary rehabilitation increases exercise tolerance and reduces symptom burden in patients with stable COPD. It is also a multidisciplinary effort that may help reinforce adherence to medications, enhance COPD education, and provide closer medical surveillance to patients at high risk for recurrent exacerbations.

A small randomized controlled trial<sup>71</sup> prescribed pulmonary rehabilitation on discharge for a COPD exacerbation and found sustainable improvements in exercise capacity and health status after 3 months.

In a later study,<sup>72</sup> the same group started pulmonary rehabilitation within a week of hospital discharge and found reduced hospital readmissions over a 3-month period.

**Smoking cessation is always worth advocating**

A large observational cohort study concluded that current smokers were at a higher risk for COPD exacerbations compared with former smokers.<sup>73</sup> Although there are no randomized controlled trials that assess the effects of smoking cessation at the time of COPD exacerbation, we recommend seizing the opportunity to implement this important intervention.

**Vaccinations: Influenza and pneumococcal**

Influenza vaccination is associated with reduced incidence of hospitalization among patients with cardiopulmonary disease.<sup>74</sup> A meta-analysis of randomized clinical trials of influenza vaccination for patients with COPD<sup>75</sup> reported significantly fewer exacerbations from vaccination, mostly owing to fewer episodes occurring after 3 to 4 weeks, coinciding with anticipated vaccine-induced immune protection. Furumoto and colleagues<sup>76</sup> reported an added benefit of combined vaccination with 23-valent pneumococcal polysaccharide vaccine and influenza vaccine in reducing hospital admissions over influenza vaccination alone. We also recommend providing the 13-valent pneumococcal conjugate vaccine to patients with COPD, particularly for those older than 65, consistent with CDC recommendations.<sup>77</sup>

**Pulmonary rehabilitation increases exercise tolerance and reduces symptoms**

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**ADDRESS:** Umur S. Hatipoglu, MD, Respiratory Institute, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; [hatipou@ccf.org](mailto:hatipou@ccf.org)



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