ABSTRACT: Acute exacerbations of chronic obstructive pulmonary disease are associated with significant morbidity and mortality. Clinicians should begin by considering epidemiological aspects of acute exacerbations, including precipitating factors and risk factors. Affected individuals should be assessed using accepted criteria and then offered appropriate pharmacological and nonpharmacological therapy. In addition, prevention strategies should always be discussed with patients prone to acute exacerbations.

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. Today it is the fourth leading cause of death in the world and in Canada. The prevalence of COPD in Canada has been on the rise in both sexes, with a more significant rise in prevalence in men.

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) account for over 1.5 million physician visits annually in Canada and are the most frequent cause of medical visits, hospital admissions, and death among patients with COPD. In Canada COPD was the seventh most common cause of hospitalization for men (2.3%) and the eighth for women (2.0%), excluding childbirth, in 2000–2001. The economic impact of the disease in Canada exceeds $1.67 billion and is likely underestimated. In addition, frequent exacerbations are an important determinant of quality of life and contribute to accelerated rates of decline in lung function.

Mortality among those who are admitted to hospital with exacerbations varies depending on the severity of the underlying COPD. Patients with mild to moderate disease have a 4% short-term mortality if admitted to hospital, but mortality rates can be as high as 24% if patients with acute respiratory failure are admitted to an intensive care unit. Patients requiring ICU admission have a 1-year mortality rate as high as 46%.

The figure also shows the number of deaths expected from 2000 to 2016.

Precipitating factors
Acute exacerbations of COPD are most commonly precipitated by bacterial or viral infection and environmental factors such as air pollution or cold temperatures. It is estimated that 50% to 60% of exacerbations are due to respiratory infections, 10% are due to environmental pollution, and 30% are of unknown cause.

The likelihood of a patient having more than one exacerbation per year

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increases with advanced age and chronic mucus hypersecretion. Co-morbid conditions such as ischemic heart disease, chronic heart failure, or diabetes mellitus increase the risk of an exacerbation severe enough to require hospitalization. A high FEV₁ (forced expiratory volume in 1 second) is protective. COPD exacerbations may also be more common among patients with gastroesophageal reflux that occurs weekly.

Assessment

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines an acute exacerbation of COPD as “an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.” Another widely accepted definition of AECOPD was provided by Anthonisen and colleagues, who proposed the following three clinical criteria to define acute exacerbations: increased sputum volume, increased sputum purulence, and increased dyspnea. Based on these criteria, an exacerbation can be classified as one of three types (Table 1).

The type of exacerbation along with other clinical features will determine if hospitalization is required. Not all those who suffer an exacerbation require hospital admission. (Table 2)

Management

Controlled oxygen therapy. This is almost always the first treatment given to patients with AECOPD, mainly to prevent life-threatening hypoxemia and optimize oxygen delivery to peripheral tissues and alleviate symptoms, namely dyspnea. Supplemental oxygen should be titrated, preferably via Venturi masks, to increase PaO₂ adequately in order to maintain optimal values above 60 mm Hg and ensure adequate SaO₂ levels (greater than 90%) without carbon dioxide retention and acidosis.

Bronchodilators. Short-acting inhaled β₂ agonists and anticholinergic agents play an important role in treating COPD exacerbations by reducing symptoms and improving

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Table 1. Anthonisen classification of AECOPD

<table>
<thead>
<tr>
<th>Type I (most severe)</th>
<th>Type II</th>
<th>Type III</th>
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</thead>
<tbody>
<tr>
<td>All three symptoms (i.e., increased sputum volume, increased sputum purulence and increased dyspnea).</td>
<td>Any two symptoms present</td>
<td>One symptom present plus at least one of the following:</td>
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<tr>
<td></td>
<td></td>
<td>• An upper respiratory tract infection in the past 5 days</td>
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<tr>
<td></td>
<td></td>
<td>• Increased wheezing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fever without an obvious source</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A 20% increase in respiratory rate</td>
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<tr>
<td></td>
<td></td>
<td>• Heart rate above baseline</td>
</tr>
</tbody>
</table>

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Table 2. Criteria suggesting need for hospitalization.

- High-risk comorbidities, including pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, renal failure, or liver failure
- Inadequate response of symptoms to outpatient management
- Marked increase in dyspnea
- Inability to eat or sleep because of symptoms
- Worsening hypoxemia
- Worsening hypercapnia
- Changes in mental status
- Inability to care for self (i.e., lack of home support)
- Uncertain diagnosis

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airflow obstruction. There is no evidence of a difference between classes of short-acting β₂ agonists (SABAs) in terms of bronchodilatation. Combining SABAs with anticholinergics remains controversial. However, it is recommended that anticholinergics be added to a patient’s therapy if a prompt response to SABAs does not occur. Bronchodilator therapy can be delivered with a handheld metered-dose inhaler or a nebulizer, as there appears to be no difference in changes achieved in FEV₁ whether one or the other is used.

**Systemic corticosteroids.** There is very good evidence that systemic corticosteroids shorten recovery time from an acute exacerbation of COPD and improve lung function in terms of FEV₁ and hypoxemia (PaO₂). This group of drugs also reduces the risk of early relapse, treatment failure, and length of hospital stay. Studies have not found corticosteroids to cause a significant reduction in rates of hospitalization when compared with placebo or to significantly reduce risk of readmission. However, it is unclear if the studies in question had the power to determine this. Systemic corticosteroid therapy should be considered in addition to bronchodilator therapy if the patient’s baseline FEV₁ is less than 50% of predicted. A dose of 30 to 40 mg of prednisone per day for 7 to 10 days is recommended.

**Antibiotics.** Whereas prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD, antibiotic use in the management of an acute exacerbation has been shown to reduce short-term mortality and treatment failure rates, mainly in those with moderate to severe COPD exacerbation. The Canadian guidelines for management of AECOPD recommend antibiotics for patients with types I and II exacerbations as determined by the Anthonisen criteria, but not for those with type III. Those requiring antibiotics can be divided into two groups based on the presence of risk factors that either increase the likelihood of treatment failure or have an association with more virulent or resistant bacterial pathogens.

**Noninvasive positive pressure ventilation.** Noninvasive positive pressure ventilation (NIPPV) should be considered in patients presenting with moderate to severe exacerbation of COPD. It should be administered in a setting that allows close cardiopulmonary monitoring. Patients with milder exacerbations do not benefit from NIPPV, and there is no evidence that supports the use of NIPPV for stable COPD patients with chronic hypercapnia.

### Table 3. Antibiotic treatment recommendations for purulent AECOPD.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Symptoms and risk factors</th>
<th>Most likely pathogens</th>
<th>First-choice antibiotics</th>
<th>Alternative antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple</strong> (COPD without risk factors)</td>
<td>• Increased cough</td>
<td>• Haemophilus influenzae</td>
<td>• Amoxicillin</td>
<td>• Beta-lactam/beta-lactamase inhibitor</td>
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<tr>
<td></td>
<td>• Increased sputum volume</td>
<td>• Moraxella catarrhalis</td>
<td>• Sulfamethoxazole</td>
<td>• Fluoroquinolone</td>
</tr>
<tr>
<td></td>
<td>• Increased sputum purulence</td>
<td>• Streptococcus pneumoniae</td>
<td>• Doxycycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased dyspnea</td>
<td></td>
<td>• Trimethoprim/sulphamethoxazole</td>
<td></td>
</tr>
<tr>
<td><strong>Complicated</strong> (COPD with risk factors)</td>
<td>Same as above, plus at least one of the following:</td>
<td></td>
<td>Antibiotics from above combined with oral steroids may suffice. If not, consider one of the following:</td>
<td>May require parenteral therapy</td>
</tr>
<tr>
<td></td>
<td>• FEV₁* less than 50% predicted</td>
<td>• Klebsiella spp</td>
<td>• Beta-lactam/beta-lactamase inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• More than four exacerbations per year</td>
<td>• Gram-negative spp</td>
<td>• Fluoroquinolone</td>
<td></td>
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<tr>
<td></td>
<td>• Ischemic heart disease</td>
<td>• Increased probability of beta-lactam resistance</td>
<td></td>
<td>Consider referral to a specialist or hospital</td>
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<tr>
<td></td>
<td>• Use of home oxygen</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chronic oral steroid use</td>
<td></td>
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<tr>
<td></td>
<td>• Antibiotic use in the past 3 months</td>
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</tbody>
</table>

*FEV₁: Forced expiratory volume in 1 second
NIPPV is cost-effective compared with usual therapeutic care alone.27

**Invasive mechanical ventilation.**

This modality is reserved for those with life-threatening episodes of AECOPD (Table 5). The survival is relatively good, with mortality ranging between 11% and 49%.9,28,29 A number of factors need to be considered before using invasive ventilation, such as the likely reversibility of the precipitating event, the patient’s wishes, and the availability of intensive care facilities.

**Prevention**

Preventive strategies are of paramount importance in managing COPD patients with acute exacerbations, given the costs and the consequences of these events. Smoking cessation, appropriate use of maintenance medication, pulmonary rehabilitation, and immunizations all have important roles to play (see Part I of this theme issue).

**Conclusions**

Acute exacerbations of COPD are a significant cause of morbidity and mortality. They should be treated with bronchodilators as well as oral corticosteroids. If the patient has acute bronchitis, antibiotic therapy should be considered. The clinician should also take the opportunity to discuss prevention strategies, to reassess maintenance treatment, and to consider long-term prognosis and potential end-of-life management issues.

**References**

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