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Acute exacerbation of chronic obstructive pulmonary disease

Bronchodilators, oral corticosteroids, and antibiotics may all be needed to manage an acute exacerbation of COPD.

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[1] and in Canada.[2] The prevalence of COPD in Canada has been on the rise in both sexes, with a more significant rise in prevalence in men.[2]

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.[3,4] 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[2] and is likely underestimated.[5] In addition, frequent exacerbations are an important determinant of quality of life[6] and contribute to accelerated rates of decline in lung function.[7]

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,[8] but mortality rates can be as high as 24% if patients with acute respiratory failure are admitted to an intensive care unit.[9-12] Patients requiring ICU admission have a 1-year mortality rate as high as 46%.[9,10,12] The **Figure** shows the number of COPD deaths in Canada that occurred between 1987 and 1999.

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.[13] 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.[14]

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

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increases with advanced age and chronic mucus hypersecretion. Comorbid conditions such as ischemic heart disease, chronic heart failure, or diabetes mellitus increase the risk of an exacerbation severe enough to require hospitalization.[4] A high FEV_1 (forced expiratory volume in 1 second) is protective.[15] COPD exacerbations may also be more common among patients with gastroesophageal reflux that occurs weekly.[16]

Assessment

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)[17] 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."[17] Another widely accepted definition of AECOPD was provided by Anthonisen and colleagues,[18] 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**)[19]

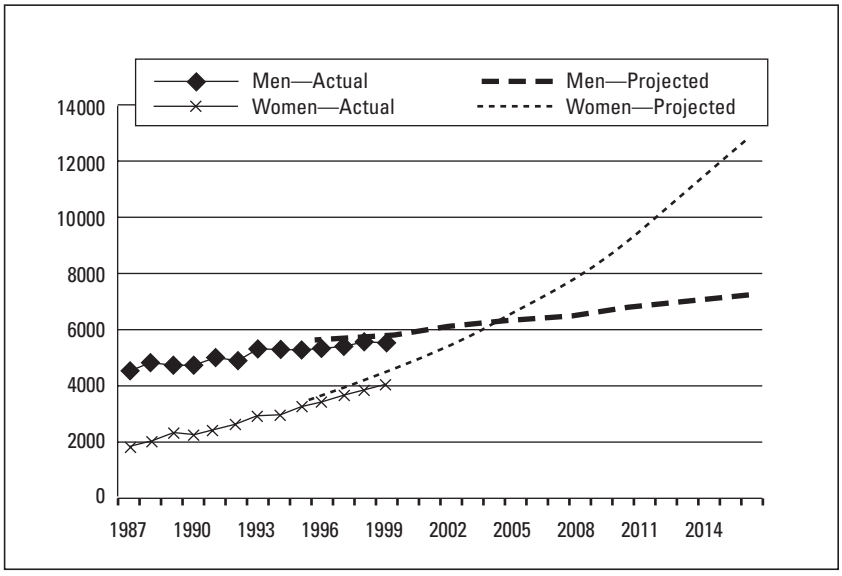

Figure. Actual and projected deaths resulting from chronic obstructive pulmonary disease in Canada, 1987 to 2016.

Source: Adapted from Canadian Thoracic Society recommendations.[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 Pa_{O_2} adequately in order to maintain optimal values above 60 mm Hg and ensure adequate Sa_{O_2} levels (greater than 90%) without carbon dioxide retention and acidosis.[19]

Bronchodilators. Short-acting inhaled ß$_2$ agonists and anticholinergic agents play an important role in treating COPD exacerbations by reducing symptoms and improving

Table 1. Anthonisen classification of AECOPD

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

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

Table 3. Antibiotic treatment recommendations for purulent AECOPD.[2]

Treatment group	Symptoms and risk factors	Most likely pathogens	First-choice antibiotics	Alternative antibiotics
Simple (COPD without risk factors)	• Increased cough • Increased sputum volume • Increased sputum purulence • Increased dyspnea	• *Haemophilus influenzae* • *Moraxella catarrhalis* • Streptococcus pneumoniae	• Amoxicillin • Sulfamethoxazone • Doxycycline • Trimethoprim/sulphamethoxazole • Second- or third-generation cephalosporins • Extended spectrum macrolides	• Beta-lactam/beta-lactamase inhibitor • Fluoroquinolone
Complicated (COPD with risk factors)	Same as above, plus at least one of the following: • FEV_1* less than 50% predicted • More than four exacerbations per year • Ischemic heart disease • Use of home oxygen • Chronic oral steroid use • Antibiotic use in the past 3 months	Same as above, plus the following: • *Klebsiella* spp • Gram-negative spp • Increased probability of beta-lactam resistance	Antibiotics from above combined with oral steroids may suffice. If not, consider one of the following: • Beta-lactam/beta-lactamase inhibitor • Fluoroquinolone	May require parenteral therapy Consider referral to a specialist or hospital

*FEV_1: Forced expiratory volume in 1 second

airflow obstruction. There is no evidence of a difference between classes of short-acting $ß_2$ agonists (SABAs) in terms of bronchodilatation. Combining SABAs with anticholinergics remains controversial.[20] However, it is recommended that anticholinergics be added to a patient's therapy if a prompt response to SABAs does not occur.[17] 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 FEV_1 whether one or the other is used.[21]

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 FEV_1 and hypoxemia (PaO_2). This group of drugs also reduces the risk of early relapse, treatment failure, and length of hospital stay.[2,22,23] Studies have not found corticosteroids to cause a significant reduction in rates of hospitalization when compared with placebo[22] or to significantly reduce risk of readmission.[23] 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 FEV_1 is less than 50% of predicted. A dose of 30 to 40 mg of prednisone per day for 7 to 10 days is recommended.[17]

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.[24,25] 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.[26] 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 (**Table 3**).[2]

Noninvasive positive pressure ventilation. Noninvasive positive pressure ventilation (NIPPV) should be considered in patients presenting with moderate to severe exacerbation of COPD (**Table 4**). 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.[2] NIPPV used as an adjunct to standard medical care improves alveolar ventilation, decreases the need for endotracheal intubation, reduces treatment failure, and reduces mortality. It also shortens the length of hospital stay by more than 3 days and decreases complications associated with treatment. Last but not least,

Table 4. Indications and relative contraindications for noninvasive ventilation.

Indications for NIPPV	Relative contraindications for NIPPV
• Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion	• Respiratory arrest
• Moderate to severe acidosis (pH ≤ 7.35) and/or hypercapnia ($Paco_2$ > 6.0 kPa, 45 mm Hg)	• Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
• Respiratory frequency > 25 breaths per minute	• Impaired mental status
	• High aspiration risk
	• Viscous or copious secretions
	• Recent facial or gastroesophageal surgery
	• Craniofacial trauma
	• Fixed nasopharyngeal abnormalities
	• Burns
	• Extreme obesity

Source: Adapted from Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[17]

Table 5. Indications for invasive mechanical ventilation.

- Inability of patient to tolerate NIPPV or NIPPV failure
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Respiratory frequency > 35 breaths per minute
- Life-threatening hypoxemia
- Severe acidosis (pH > 7.25) and/or hypercapnia ($Paco_2$ > 8.0 kPa, 60 mm Hg)
- Respiratory arrest
- Somnolence, impaired mental status
- Cardiovascular complications (hypotension, shock)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)

Source: Adapted from Global Strategy for the Diagnosis Management, and Prevention of Chronic Obstructive Pulmonary Disease[17]

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 1 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.

Competing interests

Dr FitzGerald has received honoraria for consulting and providing continuing medical education as well as being an investigator on research projects which have been funded by research grants provided to the University of British Columbia from pharmaceutical companies who manufacture therapies for use in chronic obstructive lung disease.

References

1. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: Data from the Third National Health and Nutrition Examination. Am J Med 2003;114:758-762.
2. O'Donnell DE, Aaron S, Bourbeau J, et al. State of the Art Compendium: Canadian Thoracic Society recommendations for the management of chronic obstructive pulmonary disease, Can Respir J 2004; 11(suppl B):7B-59B.
3. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: A prospective study of 200 patients. N Engl J Med 1969;280:397-404.
4. FitzGerald JM, Haddon J, Bradley-Kennedy C, et al. Resource use study in COPD (RUSIC): A prospective study to quantify the effects of COPD exacerbations on health care resource use among COPD patients. Can Resp J 2007;14:145-152.
5. FitzGerald JM, Mittmann N, Kuramoto L, et al. Economic burden of moderate and severe COPD exacerbations in Canada [abstract]. Am J Respir Crit Care Med 2007;175:A135.
6. Seemungal TA, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418-1422.
7. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV_1 decline in current smokers but not ex-smokers with mild chronic obstructive

pulmonary disease: Results from the lung health study. Am J Respir Crit Care Med 2001;164:358-364.
8. Mushlin AI, Black ER, Connolly CA, et al. The necessary length of hospital stay for chronic pulmonary disease. JAMA 1991; 266:80-83.
9. Connors AF, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996; 154:959-967.
10. Burk RH, George RB. Acute respiratory failure in chronic obstructive pulmonary disease. Immediate and long-term prognosis. Arch Intern Med 1973;132:865-868.
11. Portier F, Defouilloy C, Muir JF. Determinants of immediate survival among chronic respiratory insufficiency patients admitted to an intensive care unit for acute respiratory failure. A prospective multicenter study. The French Task Group for Acute Respiratory Failure in Chronic Respiratory Insufficiency. Chest 1992; 101:204-210.
12. Seneff MG, Wagner DP, Wagner RP, et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 1995;274: 1852-1857.
13. Barnes PJ. Chronic obstructive pulmonary disease. N Engl J Med 2000;343: 269-280.
14. Sapey E, Stockley RA. COPD exacerbations. 2: Aetiology. Thorax 2006;61:250-258.
15. Miravitlles M, Guerrero T, Mayordomo C, et al. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: A multiple logistic regression analysis. The EOLO Study Group. Respiration 2000;67:495-501.
16. Rascon-Aguilar IE, Pamer M, Wludyka P, et al. Role of gastroesophageal reflux symptoms in exacerbations of COPD. Chest 2006;130:1096-1101.
17. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-555.
18. Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
19. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-946.
20. Scott S, Walker P, Calverley PMA. COPD exacerbations. 4: Prevention. Thorax 2006;61:440-447.
21. Turner MO, Patel A, Ginsburg S, et al. Bronchodilator delivery in acute airflow obstruction. A meta-analysis. Arch Intern Med 1997;157:1736-1744.
22. Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med 2003; 348:2618-2625.
23. Wood-Baker RR, Gibson PG, Hannay M, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;(1):CD001288.
24. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006; (2):CD004403.
25. Puhan MA, Vollenweider D, Latshang T, et al. Exacerbations of chronic obstructive pulmonary disease: When are antibiotics indicated? A systematic review. Respir Res 2007;8:30.
26. Balter MS, La Forge J, Low DE, et al; Canadian Thoracic Society; Canadian Infectious Disease Society. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Can Respir J 2003;10(suppl B):3B-32B.
27. Rodríguez-Roisin R. COPD exacerbations. 5: Management. Thorax 2006;61:535-544.
28. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. Eur Respir J 2005; 26:234-241.
29. Breen D, Churches T, Hawker F, et al. Acute respiratory failure secondary to chronic obstructive pulmonary disease treated in the intensive care unit: A long term follow up study. Thorax 2002;57: 29-33. BCMJ