Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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A 68-year-old former heavy smoker with a history of chronic obstructive pulmonary disease (COPD) presents to the emergency room with a two-day history of worsened dyspnea and increased purulence and volume of phlegm. Chest radiography shows hyperinflation and no acute infiltrates. Measurement of arterial blood gases while the patient is breathing room air shows acute respiratory acidosis. How should this patient be treated?

The Clinical Problem

COPD, which is characterized by a fixed obstruction of the airway caused by emphysema, chronic bronchitis, or both, is a common and growing clinical problem that is responsible for a substantial worldwide health burden.[1-6] COPD affects 16.4 million persons in the United States and at least 52 million worldwide, and it accounted for 2.74 million deaths in 2000.[2,3] In the United States, COPD is now the fourth leading cause of death[2-4] and is the only leading cause of death for which the mortality rate is currently increasing. COPD has been estimated to account for more than 16 million office visits and 500,000 hospitalizations annually in the United States. Costs attributable to this condition totaled $30.4 billion in 1995, with $14.7 billion spent directly on health care.[2,3,7]

Acute exacerbations of COPD are variously defined but are characterized by worsened dyspnea and increased volume of phlegm, purulence of phlegm, or both. They are often accompanied by hypoxemia and worsened hypercapnia.[8-10] Available series data suggest that patients have such exacerbations regularly (e.g., median rates of 2.4 and 3 episodes per year in two recent series[10,11]). Furthermore, active smokers have more frequent exacerbations than nonsmokers; stopping smoking can reduce the frequency by approximately one third.[12] Data reported in 1996 on 1016 patients who were hospitalized for acute exacerbations,[13] half of whom required intensive care, demonstrated an in-hospital mortality rate of 11 percent, and six-month and one-year mortality rates of 33 percent and 43 percent, respectively. Those who survived the first hospitalization had a 50 percent rate of rehospitalization within six months after discharge.

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Strategies and Evidence

Overview

The optimal treatment of an outpatient with an acute exacerbation of COPD involves diagnostic assessment and use of bronchodilators, systemic corticosteroids, and antibiotics; for patients who are sick enough to be hospitalized, oxygen and mechanical ventilation may also be used. The types and dosages of some commonly used medications for an acute exacerbation of COPD are presented in Table 1.

Diagnostic Assessment

For patients assessed in the emergency department or hospital, chest radiography is recommended because it reveals abnormalities that prompt a change in short-term treatment in 16 percent[15] to 21 percent[16] of cases. Spirometry is infrequently performed in hospitalized patients with acute exacerbations of COPD,[13] although observational studies of patients in the emergency department suggest that a forced expiratory volume in one second (FEV_1) that is less than 40 percent of the predicted value has a sensitivity of 96 percent for predicting relapse or the need for hospitalization[17]; hypercapnia is unlikely when the FEV_1 exceeds 35 percent of the predicted value.[18]

Oxygen

Although it has been relatively unstudied (perhaps because of its evident benefit), supplemental oxygen should be included in the initial therapy for a flare of COPD associated with hypoxemia; oxygen is usually administered by nasal cannula or through a face mask equipped to control the inspired oxygen fraction. Target oxygen saturation values are 90 to 92 percent, with corresponding target values for partial pressure of arterial oxygen (PaO_2) of 60 to 65 mm Hg. These targets ensure near-maximal hemoglobin saturation while lessening the likelihood of the hypercapnia that can

TABLE 1. SOME COMMONLY USED MEDICATIONS FOR ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

DRUG	MODE OF DELIVERY	DOSE	FREQUENCY
Bronchodilators			
Beta-adrenergic agonist			
Albuterol	Metered-dose inhaler	100–200 μg	4 times daily
	Nebulizer	0.5–2.0 mg	4 times daily
	Pill	4 mg	Twice daily
Fenoterol	Metered-dose inhaler	12–24 μg	Twice daily
Metaproterenol	Nebulizer	0.1–0.2 mg	4 times daily
	Pill	10–20 mg	3 to 4 times daily
Terbutaline	Metered-dose inhaler	400 μg	4 times daily
	Subcutaneous injection	0.2–0.25 mg	Every 15–30 min (maximum, two times)
	Pill	2.5–5 mg	4 times daily
Anticholinergic agent			
Ipratropium bromide*	Metered-dose inhaler	18–36 μg	4 times daily
	Nebulizer	0.5 mg	4 times daily
Methylxanthines			
Aminophylline†	Intravenous	0.9 mg/kg of body weight/hr	Infusion
Theophylline	Pill (sustained-release preparations)	150–450 mg‡	Twice daily
Corticosteroids			
Methylprednisolone succinate (for inpatients)§	Infusion, then	125 mg	Every 6 hours for 3 days, then
	Pill	60 mg	Daily for 4 days
		40 mg	Daily for 4 days
		20 mg	Daily for 4 days
Prednisone (for outpatients)	Pill	30–60 mg	Daily for 5 to 10 days, for example,
		40 mg	Daily for 2 days
		30 mg	Daily for 2 days
		20 mg	Daily for 2 days and
		10 mg	Daily for 2 days
Limited-spectrum antibiotics¶			
Trimethoprim–sulfamethoxazole	Pill	160 mg and 800 mg	Twice daily for 5 to 10 days
Amoxicillin	Pill	250 mg	4 times daily for 5 to 10 days
Doxycycline	Pill	100 mg	2 tablets first day, then 1 tablet/day for 5 to 10 days

*Quaternary ammonium anticholinergic agents (e.g., ipratropium, glycopyrrolate) are preferred to tertiary ammonium compounds (e.g., atropine) because they have fewer side effects.

†Aminophylline is sometimes administered after a loading dose; the dose should be determined on the basis of serum levels of theophylline.

‡The dose varies among and within patients.

§Recommendations are according to Saint et al.[14]

¶According to Anthonisen et al.,[8] all should be 10-day courses.

accompany the use of supplemental oxygen.[19] Although the cause of such hypercapnia can be multifactorial, increased inhomogeneity of ventilation and perfusion accompanied by increased dead-space ventilation appears to be more important than decreased alveolar ventilation caused by the suppression of the hypoxic drive.

Bronchodilators

Substantial evidence shows that both inhaled beta-adrenergic agonists (for example, albuterol, fenoterol, metaproterenol, and terbutaline) and anticholinergic agents (including ipratropium bromide and glycopyrrolate) can improve airflow during acute exacerbations of COPD. Specifically, the administration of a bronchodilator can increase the FEV_1 and the forced vital capacity (FVC) by 15 to 29 percent over a period of 60 to 120 minutes.[20-23] Beta-adrenergic agonists have not been shown to be superior to anticholinergic agents.[7,20-23] Factors such as the time to peak effect (which is slightly more rapid with beta-adrenergic agonists) and the frequency of adverse effects (which are generally fewer and milder with ipratropium bromide) may influence the choice of agent for a given patient.

Data from randomized clinical trials have not shown a benefit of the combined use of beta-adrenergic agonists and anticholinergic agents over therapy with either class alone. A recent meta-analysis[22] supports a

strategy of initial use of an inhaled anticholinergic agent, with subsequent addition of a beta-adrenergic agonist only if it is needed despite the use of maximal doses of the anticholinergic medication. However, this approach remains controversial.

The benefits of using a methylxanthine drug such as aminophylline as an additional bronchodilator remain unclear. In three randomized, controlled trials,[7,20,24-26] the addition of intravenous aminophylline did not result in improvements on tests of pulmonary function, produce apparent clinical benefit, or reduce the likelihood of a return to the emergency department during the succeeding week. Furthermore, aminophylline was associated with an increased rate of adverse effects, especially nausea and vomiting.[25] However, in one study, patients treated with aminophylline in the emergency department had a hospitalization rate that was 70 percent lower than that in a control group.[24]

Equivalent bronchodilation appears to be achieved with the use of metered-dose inhalers or nebulizers.[27] Because metered-dose inhalers cost less than nebulizers, but are frequently ineffective during respiratory distress, it is reasonable to initiate therapy with nebulizers and then switch to metered-dose inhalers when clinically feasible.[7,28]

Antibiotics

Bacterial infection may contribute to acute exacerbations of COPD. Two recent meta-analyses of 11 randomized, placebo-controlled trials of antibiotics for acute exacerbations of COPD support their use when there is purulent sputum.[14,20] Pooled data from six trials that evaluated peak expiratory flow rates showed a mean increase in the peak expiratory flow rate of 10.75 liters per minute, in contrast to the decrease in peak expiratory flow rate that has been observed during an acute flare.[11] In the largest trial from which the results are available, symptoms resolved within 21 days in 68 percent of the patients who received antibiotics, as compared with 55 percent of those given placebo.[8]

Antibiotics appear to be most useful in patients with severe exacerbations. For example, in a randomized trial involving 173 patients who were assigned to a 10-day course of doxycycline, trimethoprim–sulfamethoxazole, or amoxicillin,[8] patients with more severe exacerbations (as assessed in terms of worsened dyspnea and the purulence and volume of phlegm) received greater benefit from treatment than those with milder exacerbations.

Although concern about resistant flora has prompted some to advocate the initial use of broader-spectrum antibiotics, there have been no definitive studies supporting the first-line use of newer, more expensive antibiotics. Gram's staining of sputum has generally not been useful,[8] and sputum culture has generally been reserved for patients with no response to initial empirical therapy directed at the common causal pathogens (e.g., *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae*). Without definitive data regarding the optimal duration of therapy, most clinicians prescribe courses of 5 to 10 days.

Corticosteroids

Several randomized, placebo-controlled trials[7,19] have demonstrated that systemic corticosteroids accelerate improvement in airflow, gas exchange, and symptoms and reduce the rate of treatment failure. In the largest of these trials,[29] 271 hospitalized veterans were randomly assigned to receive a 3-day course of intravenous methylprednisolone (125 mg every six hours) or placebo, and the recipients of corticosteroids were further assigned to have the dose of oral prednisone tapered over the course of either 15 days or 8 weeks. Patients who received corticosteroids had an FEV_1 that was slightly but significantly higher (by 0.1 liter) than that in the placebo group on day 1. Other benefits associated with corticosteroid use were a lower rate of treatment failure at 30 and 90 days and a shorter hospital stay. The difference in FEV_1 between the corticosteroid group and the placebo group was no longer significant at 2 weeks, and outcomes were no better with an 8-week course of corticosteroids than with a 15-day course.

The optimal duration of corticosteroid therapy for an acute exacerbation of COPD remains uncertain, but recent data support a course of 5 to 10 days.[30-32] Specifically, in a randomized trial comparing oral prednisolone (a two-week regimen of 30 mg per day) with placebo, the FEV_1 improved through day 5 more in the corticosteroid group than in the placebo group.[30] In a more recent study comparing a 3-day regimen with a 10-day regimen of intravenous methylprednisolone in hospitalized patients,[31] improvements in FEV_1 and PaO_2 were evident after 3 days of therapy, but the 10-day course was associated with greater improvement in FEV_1, FVC, and PaO_2, as well as with more rapid resolution of symptoms. No difference was observed in the rate of recurrence at six months.

Noninvasive Positive-Pressure Ventilation

Enhancing ventilation by unloading fatigued ventilatory muscles is an important treatment goal in the case of an acute exacerbation of COPD that is complicated by respiratory failure. In six of seven randomized, controlled trials of positive-pressure ventilation without intubation, patients who received this type of therapy had better outcomes than those who did not.[33-35] Benefits included lower rates of intubation, lower in-hospital mortality rates, accelerated symptomatic and physiological improvement, and shorter hospital stays.

Noninvasive positive-pressure ventilation[33,36-38] should be considered when there is a need for ventilatory assistance, as indicated by such symptoms as worsened dyspnea, acute respiratory acidosis, and worsened oxygenation (e.g., a ratio of PaO_2 to the fraction of inspired oxygen of less than 200). Patients unlikely to benefit from noninvasive positive-pressure ventilation include those with respiratory arrest, medical instability (e.g., hypotensive shock or uncontrolled cardiac ischemia), an inability to protect the airway, excessive secretions, agitation or uncooperativeness, or conditions that preclude the placement of a mask or the achievement of a proper fit. Although there has been some concern to the contrary, management of noninvasive positive-pressure ventilation does not require more of health care providers' time and does not cost more than the treatment of intubated patients.[36-40]

AREAS OF UNCERTAINTY

Better methods are needed to encourage smoking cessation, since smoking is a key causative factor in COPD. More attention to detecting and treating $alpha_1$-antitrypsin deficiency is also needed.[41] In addition, standards are needed for the definition of an acute exacerbation of COPD and for the stratification of risk. The optimal bronchodilator regimen and route of delivery remain uncertain, especially with the advent of new drugs (e.g., tiotropium). The role of broader-spectrum antibiotics and guidelines for their use, and the indications for noninvasive positive-pressure ventilation, especially outside the intensive care unit, remain to be defined.

GUIDELINES

Five sets of guidelines for managing acute exacerbations of COPD have been issued by five widely recognized professional societies and health organizations since 1994: the European Respiratory Society,[5] the British Thoracic Society,[6] the American Thoracic Society,[1] a joint panel of the American College of Chest Physicians and the American College of Physicians–American Society of Internal Medicine,[20-22] and a joint panel of the National Heart, Lung, and Blood Institute and the World Health Organization (known as the Global Initiative for Chronic Obstructive Lung Disease, or GOLD).[2] These guidelines, summarized in Table 2, are similar in many respects; most (including those proposed by GOLD) endorse a short course of systemic corticosteroids and antibiotics for severe exacerbations and the use of noninvasive ventilation for exacerbations complicated by acute ventilatory failure. Unlike some of the guidelines, those from GOLD favor beta-adrenergic agonists as first-line bronchodilator therapy, recommend adding an anticholinergic agent if there is no response to the beta-adrenergic agonist, and endorse consideration of a methylxanthine drug.

SUMMARY AND RECOMMENDATIONS

My approach to treating the patient with an acute exacerbation of COPD is as follows. For patients who present to the emergency department or who are deemed sick enough to be hospitalized, diagnostic assessment includes chest radiography and, if the patient's distress or somnolence prompts concern about acute respiratory acidemia, measurement of arterial blood gases. Initial therapy includes supplemental oxygen, usually through a face mask to ensure an oxyhemoglobin saturation, measured by pulse oximetry, of 90 to 92 percent. For both inpatients and outpatients, combined bronchodilator therapy should be used, with ipratropium bromide and albuterol administered every four to six hours initially; nebulizers are recommended whenever the patient's distress level raises doubt about the effective use of a metered-dose inhaler. As the condition improves and the distress level is reduced, metered-dose inhalers can be used in place of nebulizers. Since many patients do not use their inhalers appropriately, spacer devices should be prescribed and appropriate techniques should be reviewed.

On the basis of data from a randomized trial,[8] a 10-day course of a narrow-spectrum antibiotic (e.g., trimethoprim–sulfamethoxazole, doxycycline, or amoxicillin) should be prescribed when there is increased dyspnea and increased purulence and volume of phlegm. Sputum staining and cultures are reserved for cases that are refractory to antibiotic therapy. Oral systemic corticosteroids are prescribed both for outpatients (tapering over the course of eight days, beginning with 40 mg per day and decreasing the dose by 10 mg every other day) and for inpatients (Table 1).[29] Given the lack of evidence to support the usefulness of chest physiotherapy or mucokinetic drugs, neither of these should be routinely prescribed.

For eligible patients with acute respiratory acidemia, bilevel noninvasive positive-pressure ventilation should be implemented for multiple-hour stretches, with occasional interruption, during the first several days of hospitalization. Such ventilation is initially administered in the intensive care unit to ensure close monitoring and ready access to intubation and mechanical ventilation, should the trial of noninvasive positive-pressure ventilation fail.

For patients who present for the first time with an exacerbation of underlying COPD, recovery from the acute episode provides an opportunity to discuss smoking cessation, to explore the possibility of $alpha_1$-antitrypsin deficiency, to vaccinate the patient against pneumococcus and influenza, and to consider referral to a pulmonary rehabilitation program. For patients who require hospitalization, an outpatient follow-up visit should be scheduled for four to eight weeks after hospital discharge. Spirometry should be performed

TABLE 2. RECOMMENDATIONS BY PROFESSIONAL SOCIETIES REGARDING THE MANAGEMENT OF ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.*

VARIABLE	BRITISH THORACIC SOCIETY[6]	AMERICAN COLLEGE OF CHEST PHYSICIANS AND AMERICAN COLLEGE OF PHYSICIANS–AMERICAN SOCIETY OF INTERNAL MEDICINE[18-20]	EUROPEAN RESPIRATORY SOCIETY[5]	AMERICAN THORACIC SOCIETY[1]	GOLD[2]
Date of statement	1997	2001	1995	1995	2001
Type of statement	Consensus	Evidence-based systematic review	Consensus	Consensus	Evidence-based review
Diagnostic testing	Recommended for patients being admitted: chest radiography, arterial blood gases, complete blood count, electrolytes, blood urea nitrogen, electrocardiography, and FEV_1, peak flow, or both; sputum culture and sensitivity	Recommended for patients admitted from emergency department: chest radiography Not recommended: spirometry	Recommended for hospitalized patients: FEV_1, arterial blood gases, chest radiography, complete blood count, sputum Gram's stain and culture, electrolytes, electrocardiography	Recommended: determine the cause of exacerbation; sputum culture in severe exacerbations, if condition has worsened despite use of antibiotics, or for residents of a nursing home	Recommended: chest radiography, electrocardiography, arterial blood gases, sputum culture and sensitivity testing (if no response to initial antibiotics), electrolytes, hematocrit
Bronchodilator therapy	Recommended: For outpatients: beta-adrenergic agonists, anticholinergic agents, or both For inpatients: beta-adrenergic agonists and anticholinergic agents; add IV aminophylline if no response	Recommended: anticholinergic agent in maximal dose as first-line agent; then add beta-adrenergic agonist Not recommended: methylxanthines	Recommended: beta-adrenergic agonists, anticholinergic agents, or both in increased dose or frequency; consider IV aminophylline in severe exacerbations	Recommended: beta-adrenergic agonist as first-line agent, possibly in combination with anticholinergic agent; IV aminophylline if aerosol therapy cannot be given or proves inadequate	Recommended: beta-adrenergic agonist as first-line agent; add anticholinergic agent if prompt response not evident; consider oral or IV methylxanthine in severe exacerbation
Bronchodilator delivery	For outpatients: metered-dose inhaler (with instruction) For inpatients: nebulizer	Insufficient evidence for a preferred delivery device	Metered-dose inhaler can generally achieve good response; some patients prefer nebulizer during exacerbations	No preference	Not discussed
Antibiotics	Recommended for moderate or severe exacerbations: oral route; "common" antibiotic (e.g., tetracycline, amoxicillin) as first-line agent; broader-spectrum cephalosporin or macrolide if no response	Optimal duration of therapy unclear	Recommended: 7-to-14-day course of inexpensive antibiotic (e.g., amoxicillin or tetracycline)	Recommended for abnormal mucus: "simple" antibiotic (e.g., doxycycline or amoxicillin) unless severe exacerbation, in which case consider extended-spectrum penicillin or cephalosporin	Recommended with increased sputum volume and purulence: choice should reflect local sensitivity for *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*
Corticosteroids	Not recommended for outpatients unless already receiving, known response, or failure to achieve response to increased bronchodilator dose Recommended for inpatients: e.g., 30 mg of prednisone daily for 7 to 14 days	Recommended for patients not receiving long-term oral corticosteroids: systemic corticosteroids for up to 2 wk	Recommended: 0.4–0.6 mg/kg/day of oral corticosteroids for outpatients; IV for severe exacerbation in hospitalized patients	Recommended: reassess use after 1–2 wk	Recommended: 30–40 mg of oral or IV prednisolone per day for 10–14 days
Supplemental oxygen	Recommended: to achieve PaO_2 $\geq$50 mm Hg without pH <7.26; initial treatment with face mask with FIO_2 $\leq$0.28	Recommended	Recommended: to raise PaO_2 $\geq$60 mm Hg without raising $PaCO_2$ by $\geq$10 mm Hg	Recommended: to raise PaO_2 just above 60 mm Hg	Recommended: target PaO_2 >60 mm Hg or SaO_2 >90%; measure arterial blood gases 30 min after the initiation of oxygen
Chest physiotherapy and clearance of secretions	Not recommended	Not recommended	Recommended: coughing to clear sputum; physiotherapy at home	Recommended for hospitalized patients with $\geq$25 ml of sputum/day	Manual or mechanical chest percussion and postural drainage possibly beneficial for patients with lobar atelectasis or >25 ml of sputum/day; facilitate sputum clearance by stimulating coughing

Mucokinetic drugs	Not recommended	Not recommended	Not recommended	Not recommended	Not discussed
Mechanical ventilation	Recommended: when pH <7.26 and no response to other treatment; initial trial of NIPPV, IV doxapram, or both	Recommended: NIPPV in severe exacerbations	Recommended: intermittent positive-pressure ventilation or continuous positive airway pressure; doxapram may have a positive effect	Recommended: when criteria met (e.g., ample experience, adequate staffing, hemodynamic stability, patient awake without copious secretions)	Recommended when ≥2 of the following present: severe dyspnea with accessory muscle use or paradoxical abdominal motion; pH, 7.30–7.35, and $PaCO_2$, 45–60 mm Hg; respiratory rate >25
Other	Diuretics for raised jugular venous pressure and peripheral edema				Diet; low-molecular-weight heparin; fluids

*GOLD denotes the Global Initiative for Chronic Obstructive Lung Disease (a joint panel of the National Heart, Lung, and Blood Institute and the World Health Organization), FEV_1 forced expiratory volume in one second, IV intravenous, PaO_2 partial pressure of arterial oxygen, FIO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, SaO_2 arterial oxygen saturation, and NIPPV noninvasive positive-pressure ventilation.

after the administration of a bronchodilator, and the patient's need for supplemental oxygen both while at rest and during activity should be reassessed. Bronchodilator therapy should be continued over the long term, with the addition of an inhaled corticosteroid reserved for patients in whom the obstruction of airflow has been demonstrated to be reversible (e.g., those who have an increase of at least 12 percent and 200 ml in the FEV_1 after the use of a bronchodilator) and patients who have frequent exacerbations.

Given this approach, the short-term treatment of the patient described in the vignette should include admission to the hospital because of acute respiratory acidemia, and the administration of a combination of bronchodilators, a limited-spectrum antibiotic, and intravenous corticosteroids. Unless there is rapid reversal of acidemia, bilevel noninvasive positive-pressure ventilation should be initiated.

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