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Bartolome R. Celli

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Update on the Management of COPD*

Bartolome R. Celli, MD, FCCP

COPD is highly prevalent and will continue to be an increasing cause of morbidity and mortality worldwide. COPD is now viewed under a new paradigm as preventable and treatable. In addition, it has become accepted that COPD is not solely a pulmonary disease but also one with important measurable systemic consequences. Patients with COPD have to be comprehensively evaluated to determine the extent of disease so that therapy can be adequately individualized. We now know that smoking cessation, oxygen for hypoxemic patients, lung reduction surgery for selected patients with emphysema, and noninvasive ventilation during severe exacerbations have an impact on mortality. The completion of well-planned pharmacologic trials have shown the importance of decreasing resting and dynamic hyperinflation on patient-centered outcomes and the possible impact on mortality and rate of decline of lung function. In addition, therapy with pulmonary rehabilitation and lung transplantation improve patient-centered outcomes such as health-related quality of life, dyspnea, and exercise capacity. Rational use of single or multiple therapeutic modalities in combination have an impact on exacerbations and hospitalizations. This monograph presents an integrated approach to patients with COPD and updates their management incorporating the recent advances in the field. The future for patients with COPD is bright as primary and secondary prevention of smoking becomes more effective and air quality improves. In addition, current research will unravel the pathogenesis, clinical, and phenotypic manifestations of COPD, thus providing exciting therapeutic targets. Ultimately, the advent of newer and more effective therapies will lead to a decline in the contribution of this disease to poor world health. ***(CHEST 2008; 133:1451–1462)***

Key words: BODE index; COPD; management; pharmacotherapy; therapy

Abbreviations: BODE = body mass index, airflow obstruction, dyspnea, exercise capacity; ICS = inhaled corticosteroids; LABA = long-acting β-agonist; LVRS = lung volume reduction surgery; MDI = metered-dose inhaler; NIPPV = noninvasive positive pressure ventilation; TORCH = Towards a Revolution in COPD Health

COPD is defined as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. Airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.[1,2] This definition changes the paradigm that characterized older definitions[3,4] in two important aspects. First, it presents a positive attitude toward the disease; and second, it highlights a salient feature of COPD: its frequent expression of systemic manifestations. This monograph summarizes the recent advances in the management of this disease, provides the evidence that patients with COPD respond to treatment, and shows that treatment is effective in multiple outcomes of importance to patients.

*From Pulmonary and Critical Care, Caritas St. Elizabeth's Medical Center, Boston. MA.
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Correspondence to: Bartolome R. Celli, MD, FCCP, Chief, Pulmonary and Critical Care Medicine, Caritas St. Elizabeth's Medical Center, 736 Cambridge St, Boston, MA 02135-2997; e-mail: bcelli@copdnet.org
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COPD Is Highly Prevalent, Underdiagnosed, Undertreated, and Underperceived

COPD affects millions of individuals, limits the functional capacity of many, and has become an

important cause of death worldwide. Although preventable, COPD has a long subclinical phase. The previously accepted thought that COPD develops in only 15% of smokers is an underestimation of the actual number that is now known to be much larger. Once dyspnea develops, it occurs at ever lower levels of exercise. With disease progression, gas exchange becomes compromised and patients may have respiratory failure.[1–4] In the end, death can occur either from respiratory failure or from frequently associated comorbidities such as heart disease and lung cancer.[5–7] The estimated prevalence of COPD varies from 7 to 19% in several well-conducted studies[8–13] around the world. It is a disease that is increasing in women, and if we assume the lowest prevalence, the total number of cases of COPD in the world approximates 280 million persons. Unfortunately, COPD remains largely underdiagnosed.[14,15] Finally, due to many possible reasons, patients underperceive the magnitude of their problem and accept the limitations associated with disease progression as natural for a person who has smoked.[16]

COPD, a Multicomponent Disease

The airflow obstruction of COPD, as expressed by FEV_1, is by definition only partially reversible.[1,2] In a paradoxical way, this defining physiology has been used as the outcome to determine the effectiveness of interventions. It is no surprise that the lack of large response in FEV_1 to different therapies[17–26] has resulted in an undeserved nihilism. There is increasing evidence that independent of the degree of airflow obstruction, lung volumes are important in the genesis of the symptoms and limitations of patients with more advanced disease. A series of studies[27–31] have demonstrated that dyspnea perceived during exercise, including walking, more closely relates to the development of dynamic hyperinflation than to changes in FEV_1. Further, the improvement in exercise brought about by several therapies including bronchodilators, oxygen, lung volume reduction surgery (LVRS), and even rehabilitation is more closely related to delaying dynamic hyperinflations than by improving the degree of airflow obstruction.[27–30,32] Casanova et al[33] showed that hyperinflation, expressed as the inspiratory capacity/total lung capacity ratio, predicted survival better than FEV_1. The importance of lung volume as determinant of outcomes provides us not only with new insights into pathogenesis, but also opens the door for new imaginative ways to alter lung volumes and perhaps impact on disease progression.

It is now accepted that COPD may be associated with important systemic expressions in patients with more advanced disease.[1,5,34] Perhaps as a consequence of a persistent systemic inflammatory state or due to other yet unproven mechanisms such as imbalanced oxidative stress or abnormal immunologic response, the fact is that many patients with COPD may have decreased fat-free mass, impaired systemic muscle function, anemia, osteoporosis, depression, pulmonary hypertension, and cor pulmonale, all of which are important determinants of outcome. Indeed, dyspnea measured with simple tools such as the modified Medical Research Council scale,[35] the body mass index,[36,37] and the timed 6-min walk distance[38,39] are all better predictors of mortality than FEV_1. The incorporation of these variables into the multidimensional BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) index predicts survival even better.[5] The BODE index, also responsive to exacerbations,[40] and more importantly acts as a surrogate marker of future outcome after interventions,[41] may better help clinicians determine the comprehensive severity of disease.

Based on the multidimensional nature of the disease and the availability of multiple effective therapies, the proposed approach shown in Figure 1 may help clinicians evaluate patients comprehensively and choose therapies other than the current approach using primarily the percentage of predicted FEV_1 from reference values.

COPD, a Treatable Disease

Current evidence suggests that smoking cessation,[6] long-term oxygen therapy in hypoxemic patients,[42,43] noninvasive mechanical ventilation in some patients with acute-on-chronic respiratory failure,[44–46] and LVRS for patients with upper-lobe emphysema and poor exercise capacity[47] improve survival. The TORCH (Towards a Revolution in COPD Health) study[48] of $>$ 6,000 patients showed that the combination of salmeterol and fluticasone not only improved lung function and health status, but that the relative risk of dying over the 3 years decreased by 17.5% over the 3 years of the study. Other therapies such as pulmonary rehabilitation and lung transplantation improve symptoms and the quality of life once the diagnosis has been established.[1,2,49,50] The overall goals of treatment of COPD are to prevent further deterioration in lung function, improve symptoms and quality of life, treat complications, and prolong a meaningful life.[1,3]

Therapy Is Effective for the Respiratory Manifestations of COPD

Once COPD is diagnosed, the patient should be encouraged to actively participate in disease manage-

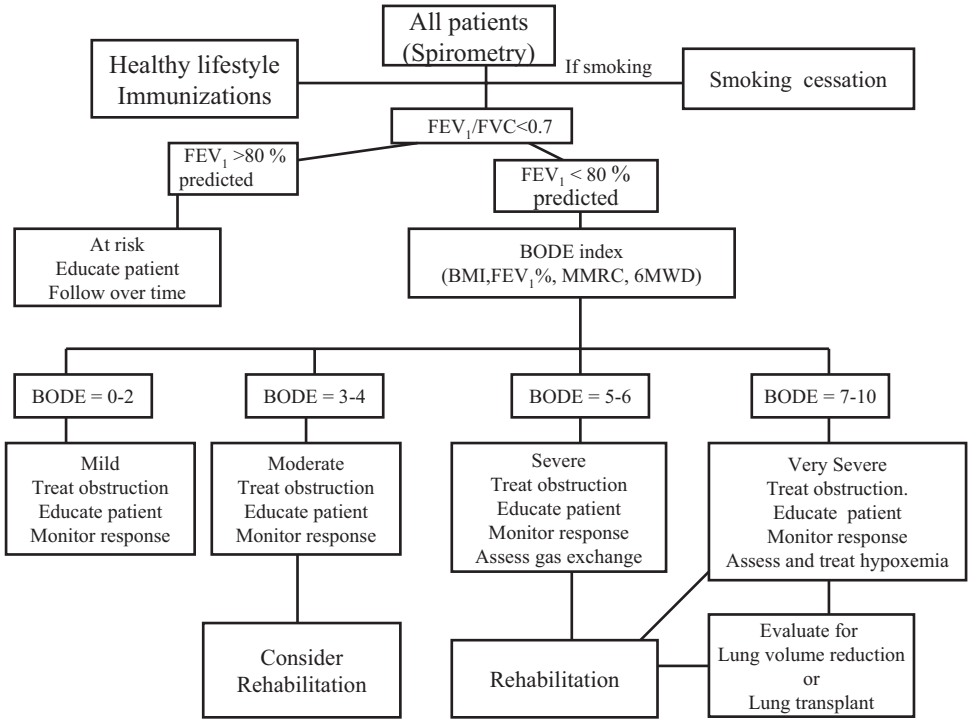

FIGURE 1. Schematic algorithm to approach patients with COPD. The evaluation of the multiple domains using simple validated tools can better help stage the global severity of the disease. BMI = body mass index; FEV_1% = percentage of predicted FEV_1; MMRC = modified Medical Research Council scale; 6MWD = 6-min walk distance.

ment. This concept of "collaborative management" may improve self-reliance and esteem. All patients should be encouraged to lead a healthy lifestyle and exercise regularly. Preventive care is extremely important at this time, and all patients should receive immunizations including pneumococcal vaccine and yearly influenza vaccinations.[1,3] This comprehensive approach is summarized as a proposal in Figure 1. It directs action according to the multidimensional evaluation of the patient.

Smoking Cessation and Decreased Exposure to Biomass Fuel Combustion Fumes

As smoking is the major cause of COPD, smoking cessation is the most important component of therapy for patients who still smoke.[1,3] Because secondhand smoking is known to damage lung function, limitation of exposure to involuntary smoke, particularly in children, should be encouraged. The factors that cause patients to smoke include the addictive potential of nicotine; conditional responses to stimuli surrounding smoking; psychosocial problems such as depression, poor education, and low income; and forceful advertising campaigns. As the causes that drive the patient to smoke are multifactorial, smoking cessation programs should also involve multiple interventions. The clinician should always participate in the treatment of smoking addiction because a physician's advice and intervention and use of the appropriate medications including nicotine patch, gum or inhalers, bupropion, and verenicline help determine successful results.[51–54] The significant burden of COPD in patients exposed to the fumes of biomass fuel consumption in certain areas of the world should improve by changing to more efficient and less polluting sources of energy.

Pharmacologic Therapy of Airflow Obstruction

Many patients with COPD require pharmacologic therapy. This should be organized according to the severity of symptoms (dyspnea and functional capacity), the degree of lung dysfunction, and the tolerance to specific drugs.[1,3] A step-wise approach similar in concept to that developed for systemic hypertension may be helpful because medications alleviate symptoms, improve exercise tolerance and quality of life, and may decrease mortality. Tables 1 and 2 provide a summary of the evidence supporting the effect of individual and combined pharmacologic agents on outcomes of importance to patients with COPD.

Table 1—*Effect of Individual Pharmacologic Agents on Important Outcomes of Patients With COPD

Agents	FEV_1	Lung Volume	Dyspnea	Quality of Life	Adverse Events	Exercise Endurance	Disease Modifier by FEV_1	Mortality
Albuterol	Yes (A)	Yes (B)	Yes (B)	NA	NA	Yes (B)	NA	NA
Ipratropium bromide	Yes (A)	Yes (B)	Yes (B)	No (B)	Yes (B)	Yes (B)	No	NA
LABAs	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	No	NA
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	NA	NA
ICS	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	No	No
Theophylline	Some (A)	Yes (B)	Yes (A)	Yes (B)	NA	Yes (B)	NA	NA

*Yes supports an improvement in outcome, Some supports an improvement in outcome, and No supports no improvement in outcome. Level of evidence: A = more than one randomized trial; B = limited randomized trials. NA = not available. Modified from Celli and MacNee.[1]

Bronchodilators

Several important concepts guide the use of bronchodilators. In some patients, the changes in FEV_1 may be small and the symptomatic benefit may be due to other mechanisms such as a decrease in lung hyperinflation.[55,56] Some older COPD patients cannot effectively activate metered-dose inhalers (MDIs), and we should work with the patient to achieve mastery of the MDI. If this is not possible, use of a spacer or nebulizer to facilitate inhalation of the medication will help achieve the desired results. The advent of once-daily or twice-daily nebulized bronchodilators such as formoterol offers an interesting alternative to the MDI in those patients unable to activate them effectively. Mucosal deposition in the mouth can result in local side effects (*ie*, thrush with inhaled steroids) or general absorption and its consequences (*ie*, tremor after β-agonists). Finally, the inhaled route is preferred over the oral administration,[1,3] and long-acting bronchodilators are more effective than short-acting bronchodilators.[1,2]

Currently Available Bronchodilators

β-Agonists: These drugs increase cyclic adenosine monophosphate within many cells and promote airway smooth-muscle relaxation. Other nonbronchodilator effects have been observed, but their significance is uncertain. In patients with mild intermittent symptoms, it is reasonable to initiate drug therapy with an MDI of a short-acting β-agonist as needed for relief of symptoms.[1,2] In patients with persistent symptoms, it is indicated to use long-acting β-agonists (LABAs)[1,2,57–60] at a dose of one or two puffs bid. LABAs prevent nocturnal bronchospasm, increase exercise endurance, and improve quality of life. The safety profile of salmeterol in the TORCH trial[48] is reassuring to clinicians who frequently prescribe selective LABAs to their patients with COPD. The advent of longer-acting agents and preparations that can be provided via nebulizer will increase our choices and perhaps help increase compliance.

Anticholinergics: These drugs act by blocking muscarinic receptors that are known to be effective in COPD. The appropriate dosage of the short-acting ipratropium bromide is two to four puffs tid or q6h, but some patients require and tolerate larger doses.[1,3] The therapeutic effect is a consequence of a decrease in exercise-induced dynamic hyperinflation.[28] The long-acting tiotropium is very effective in inducing prolonged bronchodilation[18,21] and decreasing hyperinflation[55] in patients with COPD. In addition, it improves dyspnea, decreases exacerbations,[61] and improves health-related quality of life when compared to placebo and even to ipratroprium bromide.[62,63] The results of the large Understanding Potential Long Term Impacts on Function With Tiotropium trial[64] evaluating the potential role of tiotropium as a disease-modifying agent will deter-

Table 2—*Effect of Some Combined Pharmacologic Agents on Important Outcomes of Patients With COPD

Agents	FEV_1	Lung Volume	Dyspnea	Quality of Life	Adverse Events	Exercise Endurance	Disease Modifier by FEV_1	Mortality
Salmeterol plus theophylline	Yes (B)	NA	Yes (B)	Yes (B)	NA	NA	NA	NA
Formoterol plus tiotropium	Yes (A)	NA	Yes (B)	Yes (B)	NA	NA	NA	NA
Salmeterol plus fluticasone	Yes (A)	Yes (B)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	Yes	Some
Formoterol plus budesonide	Yes (A)	NA	Yes (A)	Yes (A)	Yes (A)	NA	NA	NA
Tiotropium plus salmeterol plus fluticasone	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	NA	NA

*See Table 1 for expansion of abbreviations and definition of terms. Modified from Celli and MacNee.[1]

mine its place in the overall armamentarium of treatments for patients with COPD. Currently, tiotropium represents a first-line agent for patients with persistent symptoms.

Phosphodiesterase Inhibitors: Theophylline is a nonspecific phosphodiesterase inhibitor that increases intracellular cyclic adenosine monophosphate within airway smooth muscle. Bronchodilator effects are best seen at high doses, where there is also a higher risk of toxicity. The potential for toxicity of theophylline has led to a decline in its popularity. Theophylline is of particular value for less-compliant or less-capable patients who cannot use aerosol therapy optimally. The previously recommended therapeutic serum levels of 15 to 20 mg/dL are too close to the toxic range and are frequently associated with side effects. Therefore, a lower target range of 8 to 13 mg/dL is safer and still therapeutic.[1,3] The combination of two or more bronchodilators (theophylline, albuterol, and ipratropium) has some rationale because they seem to have additive effects and can result in maximum benefit in stable COPD.[2,65] A possible action of theophylline on the expression of genes central to inflammation in COPD[66] deserves further investigation.

The specific phosphodiesterase E4 inhibitors cilomilast and roflumilast may have an antiinflammatory and bronchodilator effect but less GI irritation, and this could prove extremely useful if these theoretical benefits are clinically confirmed. Data from the first 6-month studies[67,68] show modest bronchodilation effects and some benefits on quality of life.

Nonsteroidal Antiinflammatory Therapy: In contrast to their value in asthma, nonsteroidal antiinflammatory drugs have not been documented to have a significant role in the treatment of patients with stable COPD.[1,2] Cromolyn and nedocromil could possibly be helpful if the patient has associated respiratory tract allergy. One study[69] using monoclonal antibody against interleukin-8 and another study[70] using an antibody against tumor necrosis factor-α failed to detect any response. However, patients were selected according to the degree of airflow obstruction and not based on the presence or increased level of the specific targeted molecules. Groups of leukotriene inhibitors that have proven useful in asthma have not been adequately tested in COPD, so that final conclusions about their potential use cannot be drawn at this time.

Corticosteroids: Glucocorticoids act at multiple points within the inflammatory cascade, although their effects in COPD appear more modest compared with bronchial asthma. In outpatients, exacerbations necessitate a course of systemic corticosteroids as will be discussed later in this monograph, but it is important to wean patients quickly because the older COPD population is susceptible to complications such as skin damage, cataract development, diabetes, osteoporosis, and secondary infection. These risks do not accompany standard doses of inhaled corticosteroid (ICS) aerosols, which may cause thrush but pose a negligible risk for other outcomes such as development of cataracts and osteoporosis. Several large multicenter trials[23,24,71–73] evaluated the role of ICS in preventing or slowing the progressive course of symptomatic COPD; the results of these earlier studies showed minimal if any benefits in the rate of decline of lung function. However, in the one study[23] in which it was evaluated, inhaled fluticasone decreased the rate of loss of health-related quality of life and frequency of exacerbations. Recent retrospective analyses[74,75] of large databases suggesting a possible effect of ICS on improving survival were not confirmed in the TORCH trial,[48] in which the combination of ICS and LABAs was superior to ICS alone with regard to all outcomes evaluated, including survival. This coupled with the more frequent development of pneumonia (described as an adverse event but not precisely diagnosed with chest radiography, sputum cultures, or laboratory confirmation) in the patients receiving ICS suggests that in patients with COPD, ICS should not be prescribed alone but rather in combination with an LABA.[48]

Combination Therapy: Most studies that have explored the value of combination therapy have shown significant improvements over single agents alone, and it may be time to think of combination therapy as first-line therapy. Initially, the inhaled combination of ipratroprium and albuterol proved effective in the management of COPD.[26] More recently, the combination of tiotropium once daily and formoterol twice daily was better than either agent alone. In that study,[62] the administration of once-daily tiotropium and once-daily formoterol was very effective, suggesting that once-daily dosing of combinations may offer a viable option to the more complex twice-daily therapy. In another trial,[22] the combination of theophylline and salmeterol was significantly more effective than either agent alone in lung function and health status. The TORCH study[48] showed the benefits of the salmeterol/fluticasone combination on survival, FEV_1, exacerbation rate, and quality of life compared with placebo and either of the single components, confirming earlier studies[76–78] evaluating the combination of β-agonists and corticosteroids. A recent trial[79] comprising >400 patients with

symptomatic COPD compared the effectiveness of therapy using tiotropium in all patients combined with placebo in group 1, with salmeterol in group 2, and with the combination of salmeterol and fluticasone in the third group. Although the primary outcome, the exacerbation rate, was similar among the groups, the number of hospitalizations, health-related quality of life, and lung function was significantly better in the group receiving tiotropium plus salmeterol and fluticasone compared with tiotropium plus placebo and tiotropium plus salmeterol. Based on these results, it is reasonable to propose the approach shown in Figure 2. Once symptoms become persistent, therapy should begin with a long-acting antimuscarinic agent such as tiotropium or LABAs twice daily. Once a patient reaches an $FEV_1 < 60\%$ of predicted, and continues to be symptomatic, the evidence from the TORCH trial supports the addition of the combination of ICS and LABAs. Continuation of tiotropium is reasonable, given its effectiveness and safety record. I believe that all of the trials support the concept that intense and aggressive therapy does modify the course of the disease, including rate of decline of FEV_1, as was shown in the TORCH study.[48] The results of the 4-year Understanding Potential Long Term Impacts on Function With Tiotropium trial,[62] in which trough FEV_1 is the primary outcome, should help clarify the disease-modification effect of the currently available medications.

Mucokinetic Agents: These drugs aim to decrease sputum viscosity and adhesiveness in order to facilitate expectoration. The only controlled study[80] in the United States suggesting a value for these drugs in the long-term management of bronchitis was a multicenter evaluation of organic iodide. This study[80] demonstrated symptomatic benefits. Oral acetylcysteine is favored in Europe for its antioxidant effects. A large trial[81] failed to document any substantial benefit, but patients were not selected by the presence or absence of increased oxidative stress. Genetically engineered ribonuclease seems to be useful in cystic fibrosis but is of no value in COPD.[1,2]

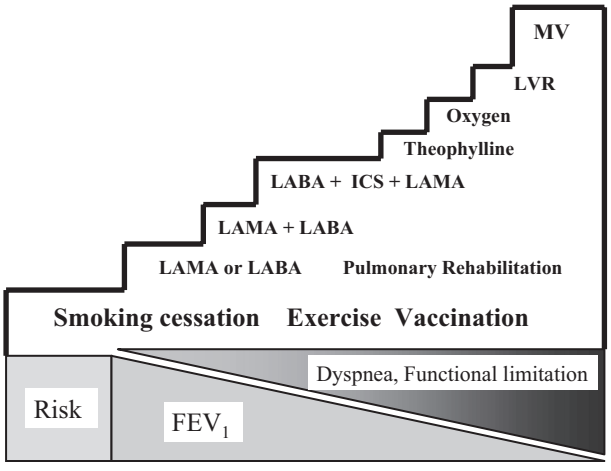

FIGURE 2. Schematic representation of the possible therapeutic options for patients at risk for COPD and those with established disease. The progressive decrease in FEV_1 is represented by the horizontal decrease of the surface of the triangle. However, the increase of the size of the opposing triangle reflects worsening of dyspnea, exercise capacity, and development of systemic compromise. As COPD progresses (decreasing airflow and worsening of symptoms), the number of therapeutic options increases. No predefined thresholds of lung function or symptoms have been placed because the therapy is determined by the assessment of a particular patient condition. LAMA = long-acting muscarinic agent; LVR = lung volume reduction; MV = mechanical ventilation.

Antibiotics: In patients with evidence of respiratory tract infection, such as fever, leukocytosis, and a change in chest radiographic findings, antibiotics have proven effective.[82–85] If recurrent infections occur, particularly in winter, continuous or intermittent prolonged courses of antibiotics may be useful.[86] The major bacteria to be considered are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, although patients with more severe airflow limitation appear to have a higher prevalence of Gram-negative bacteria such as *Pseudomonas aeruginosa*. The antibiotic choice will depend on local experience, supported by sputum culture and sensitivities if the patient is moderately ill or needs to be admitted to hospital.[1,2]

α_1-Antitrypsin: Although supplemental weekly or monthly administration of this enzyme may be indicated in nonsmoking, younger patients with genetically determined enzyme deficiency and emphysema, in practice such therapy is difficult to initiate because of its cost and need of long-term weekly or monthly IV administration. α_1-Antitrypsin is relatively safe.[1,3,87,88] Although not entirely clear, the best candidates for replacement therapy would be patients with mild-to-moderate COPD for whom progression of the disease can be stalled.

Vaccination: Ideally, infections of the respiratory tract should be prevented in patients with COPD by using effective vaccines. Thus, routine prophylaxis with pneumococcal and influenza vaccines is recommended.[12,89,90]

Lung Volume Reduction: Multiple operations have been tried in patients with COPD.[91] For patients with localized large bullae and relatively preserved lung function, bullectomy has proven useful. In patients with diffuse severe emphysema, lung transplantation results in normalization of pulmonary function, and improvement in exercise capacity and quality of life, but its effect on survival remains controversial.[92–95] Several issues must be considered

when evaluating a candidate for lung transplantation, including pulmonary disability, projected survival without transplantation, comorbid conditions, and patient preferences. General guidelines include that the patient be < 65 years old without any other medical condition that could shorten predicted survival. The presence of a high BODE index helps facilitate the selection of candidates for transplant because they have a very poor prognosis if left untreated.[96]

The other surgical procedure that has received recent attention is pneumoplasty, or LVRS.[47,97–103] It is an alternative for selected patients with severe inhomogeneous emphysema who remain symptomatic after optimal comprehensive medical therapy. LVRS improves FEV_1 by close to 10%, with larger improvements in exercise tolerance, dyspnea, and health-related quality of life.[47,101–103] The effect on survival is larger in patients with inhomogeneous upper-lobe disease and limited exercise performance after rehabilitation.[47,104] The ideal candidate should have an FEV_1 between 20% and 35% of predicted, a diffusion capacity of the lung for carbon monoxide no lower than 20% of predicted, hyperinflation, and limited comorbidities. Reports[104–106] evaluating techniques capable of achieving lung volume reduction without the surgical risk open exciting new avenues. Indeed, the bronchoscopic placement of one-way valves[107] or biological substances[108–110] capable of inducing closure of emphysematous areas may add to an already exciting armamentarium to treat selected patients with advanced COPD.

Therapies That Are Effective for the Nonrespiratory Manifestations of COPD

The most exciting changes in the way we conceptualize COPD is the recognition of the extrapulmonary manifestations of COPD.[5,111,112] Some of the most important advances in the therapy of COPD center on our capacity to impact on the disease without having to necessarily alter lung function. Two of the proven forms of therapy for COPD fall within this category: pulmonary rehabilitation and oxygen therapy. If we add mechanical ventilation during exacerbations, the field is wide open to explore even more exciting therapies.

Pulmonary Rehabilitation

Pulmonary rehabilitation is an essential component of the comprehensive management of patients with symptomatic COPD.[1,2,113–120] Patients with moderate-to-moderately severe disease are the best candidates for treatment, for whom the disabling effects of end-stage respiratory failure can be prevented. The rehabilitation program should have resources available to teach and supervise respiratory therapy techniques such as oxygen, use of inhalers and nebulizers, physical therapy (breathing techniques, chest physical therapy, postural drainage), exercise conditioning (upper and lower extremity), and activities of daily living (work simplification, energy conservation). Also desirable are services to evaluate and advise on nutritional needs, psychological, and vocational counseling. Exercise training is the most important component of a pulmonary rehabilitation program. Maltais et al[121] documented that the muscle biopsy samples in trained patients, but not control subjects, manifested significant increases in all enzymes responsible for oxidative muscle function. Pulmonary rehabilitation can change outcomes that predict survival.[122] Indeed, in an observational study, Cote and Celli[123] showed that rehabilitation improved the BODE score, and the 3-month change in the BODE index predicted survival. Reimbursement for pulmonary rehabilitation treatment remains a hurdle to its widespread application.

Supplemental Oxygen Therapy

The results of the Nocturnal Oxygen Therapy Trial[42] and Medical Research Council study[43] showed that supplemental oxygen improves survival in patients with hypoxemic COPD. Other beneficial effects of long-term oxygen include reductions in polycythemia, pulmonary artery pressures, dyspnea, hypoxemia during sleep, and reduced nocturnal arrhythmias. Importantly, oxygen can also improve neuropsychiatric testing[124,125] and exercise tolerance.[126–128] Oxygen supplementation to patients who desaturate during exercise improves exercise performance. Currently, exercise-induced oxygen desaturation is an accepted indication to provide supplemental oxygen therapy.[1,2] The beneficial effects of oxygen without necessarily changing the degree of airflow obstruction provide evidence that the disease can be modified without changing the decline of the FEV_1.

Exacerbations

An exacerbation is an event in the natural course of the COPD characterized by a change in the patient's baseline dyspnea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in management.[1,3,129,130] Care must be taken to rule out heart failure, myocardial infarction, arrhythmias, and pulmonary embolism, all of which may present with clinical signs and symptoms similar to

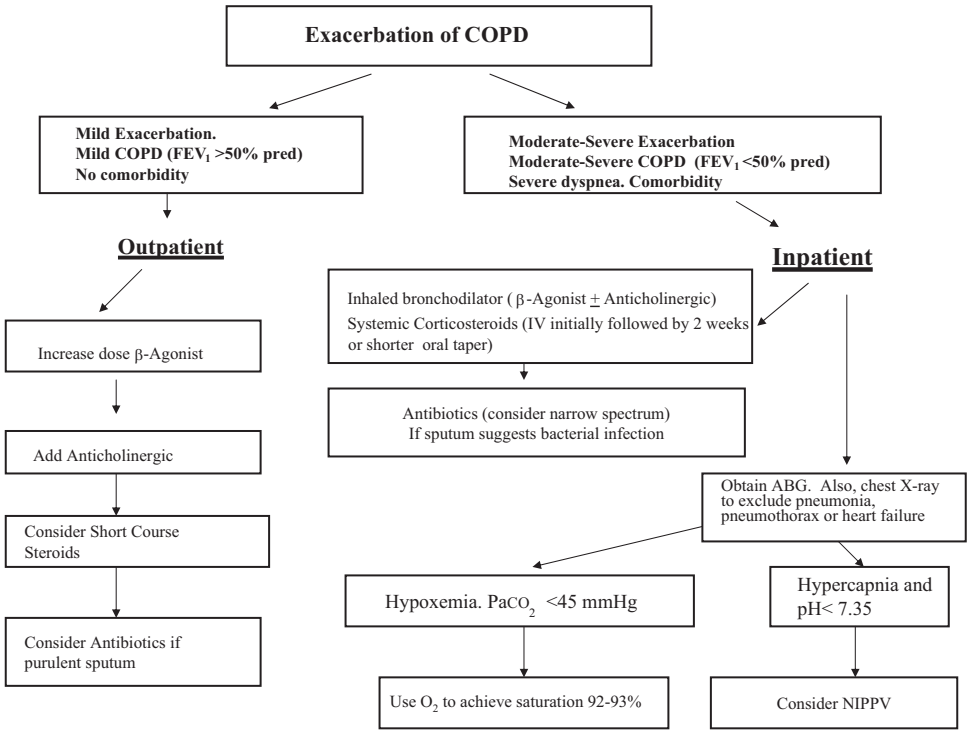

FIGURE 3. Algorithm describing the approach to patients with COPD with exacerbations characterized by increased dyspnea, cough, or change in the color or volume of sputum. pred = predicted; ABG = arterial blood gas; see Figure 1 legend for expansion of abbreviation.

exacerbation of COPD. An algorithm describing a rational approach to exacerbations is shown in Figure 3.

The pharmacologic therapy of exacerbations is initiated with the same therapeutic agents available for the long-term management of COPD.[1,3] The most important agents include anticholinergic and β-agonists aerosols by nebulization. Several trials[131–133] have proven the usefulness of systemic corticosteroids. It is important to avoid prolonged (> 2 weeks) or high-dose therapy because older patients are susceptible to severe complications such as psychosis, fluid retention, and a vascular necrosis of bones. Antibiotics have been helpful in purulent exacerbations of COPD.[134] The antibiotics used in severe exacerbation have to be guided by knowledge of the prevalent pathogens in that area.[1,2] Exacerbations are to be prevented and treated aggressively because they have a prolonged and intense effect on health-related quality of life and can result in accelerated loss of lung function.[40,135–137] Besides pharmacologic therapy, some patients may need temporary administration of supplemental oxygen.[1,2]

Ventilatory support should be considered if patients have persistent hypoxemia and/or hypercapnia with low pH (< 7.35) despite maximal medical therapy.[1] Several randomized trials[40–43] have shown that noninvasive positive pressure ventilation (NIPPV) is beneficial in selected patients with respiratory failure, decreasing the need for invasive mechanical ventilation and its complications, and possibly improving survival. Certain conditions would make patients less likely to respond to NIPPV. These conditions include respiratory arrest, medical instability (shock, cardiac ischemia), inability to protect the airway, excessive secretions, agitation or uncooperativeness, craniofacial trauma, or deformity. Despite the usefulness of NIPPV in acute-on-chronic respiratory failure, its use in patients with stable COPD remains debatable and is not routinely recommended.[138,139]

CONCLUSION

Over the years, our knowledge about COPD and the capacity to treat it have increased significantly. We now know that COPD is not just a disease affecting the lungs,[140] but that it has important systemic consequences.[141] Smoking cessation campaigns have resulted in a decrease in smoking prevalence in the United States. Similar efforts in the rest of the world should have the same impact. The widespread application of long-term oxygen therapy for hypoxemic patients has resulted in increased

survival. During this time, we have expanded our pharmacologic armamentarium to effectively improve lung function and alter its rate of decline, exercise capacity, dyspnea, quality of life, and even survival. Several studies[113–123] have documented the benefits of pulmonary rehabilitation. Noninvasive ventilation has benefited patients with acute-on-chronic failure. The revival of surgery for emphysema or, in the immediate future, endobronchial lung volume reduction should provide an alternative to lung transplantation for those patients with severe COPD who are still symptomatic on maximal medical therapy. With all these options, a nihilistic attitude toward the patient with COPD is not justified. The evidence supports a positive and aggressive attitude.

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Errata

In the June 2008 supplement, in the article by Hirsh et al, "Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]:71S–109S), on page 99S, in column one, Recommendation 2.5.2, the text should read "For patients with acute ST-segment elevation myocardial infarction receiving fibronolytic therapy who have preserved renal function (< 2.5 mg/dL [220 μmol/L] in males and < 2.0 mg/dL [175 μmol/L] in females), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A)." The online version has been corrected, and that version should be used.

In the June 2008 supplement, in the article by Goodman et al, "Acute ST-Segment Elevation Myocardial Infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]:708S–775S), on page 710S, in column one, Recommendation 2.5.2 (and on page 739S column one), the text should read "For patients with acute ST-segment elevation myocardial infarction receiving fibronolytic therapy who have preserved renal function (< 2.5 mg/dL [220 μmol/L] in males and < 2.0 mg/dL [175 μmol/L] in females), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A)." The online version has been corrected and that version should be used.

In the June 2008 supplement, in the article by Kearon et al, "Antithrombotic Therapy for Venous Thromboemobolic Disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]: 454S–545S), the conflict of interest disclosures from the authors were inadvertently left out. They are as follows: Dr. Kearon discloses that he has received grant monies from the Canadian Institutes for Health Research and the Heart and Stroke Foundation of Canada. He is also on an advisory committee for GlaxoSmithKline and Boehringer Ingelheim. Dr. Agnelli reveals no real or potential conflicts of interest or commitment. Dr. Goldhaber discloses that he has received grant monies from Mitsubishi, Boehringer Ingelheim, Sanofi-Aventis, Eisai, GlaxoSmithKline, and AstraZeneca. He has also received consultant fees from Sanofi-Aventis, Eisai, Bristol-Myers Squibb, and Boehringer Ingelheim. Dr. Raskob discloses that he has served on the speaker bureau and advisory committees and has received consultant fees from Bayer, BMS, Daiichi-Sankyo, Pfizer, Sanofi-Aventis, Takedo and Boehringer Ingelheim. Dr. Comerotta discloses that he is on the speaker bureaus of Sanofi-Aventis, Bristol-Myers Squibb, and GlaxoSmithKline and serves on an advisory committee for ConvaTec, and Bacchus Vascular. He is also a shareholder of LeMaitre Vascular.

In the September 2008 supplement by Tarlo et al, "Diagnosis and Management of Work-Related Asthma: American College of Chest Physicians Consensus Statement" (Chest 2008; 134:1S–41S), some of the subheadings are misleading in the print version. The online version has been corrected and should be used. There is no change to the text, but the level of headings shown on pages 7S–9S, 17S, and 31S–32S is more clear. Also, on the Table of Contents pages the Endorsements should read "The Canadian Society of Allergy and Clinical Immunology and The Canadian Thoracic Society".

In the July 2008 issue, in the correspondence by BaHammam et al, "Positive Airway Pressure Therapy and Daytime Hypercapnia in Patients With Sleep-Disordered Breathing" (Chest 2008; 134:218–219), the first author's surname was misspelled. It is BaHammam. It has been corrected in the online edition.

Correction

I have come to realize that I neglected to provide as full a potential conflict of interest statement as I could have in my review article, "Update on the Management of COPD" (Chest 2008; 133:1451–1462). I wish to disclose the following: Bartolome R. Celli has been reimbursed by GSK, BI, Pfizer, AZ, Almirall, and Esteve for participating in advisory boards and spoken at different meetings. The division that Dr. Celli heads has been awarded research grants for different medication trials by the same companies and for the discovery of new biomarkers in COPD, and has received grants for the participation in the development of biological lung volume reduction surgery from the company AERIS. Bartolome R. Celli, MD, FCCP, Pulmonary and Critical Care Medicine, Caritas St. Elizabeth's Medical Center, Boston, MA.

Update on the Management of COPD*

Bartolome R. Celli

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