ABSTRACT

Major quality-of-life complaints voiced by patients with chronic obstructive pulmonary disease (COPD) include chronic fatigue, overwhelming hopelessness, physical immobility, and dyspnea. Beyond the usual symptomatic treatments of bronchodilators and corticosteroids, clinicians should employ a full range of “symptomatic” treatments to attack the specific complaints that combine to produce such a poor quality of life in so many patients with COPD. Specifically, targeted interventions can be aimed at preventing exacerbations, decreasing mucus, treating hypoxemia, decreasing hyperinflation, enhancing sleep, and improving nutrition and conditioning. This article describes the potential benefits—and the unanswered questions—related to therapeutic approaches involving antibiotics, noninvasive positive pressure ventilation, lung volume reduction surgery, renutrition and reconditioning, nocturnal oxygen therapy, mucus clearance, and lung transplantation. Use of such therapies, alone or in combination, is critical to improving the overall quality of life of patients with COPD. (Adv Stud Med. 2003;3(5B):S400-S407)

Chronic obstructive pulmonary disorder (COPD) is characterized by episodic increases in dyspnea, sputum production, and coughing. The major pharmacological therapies for stable COPD such as bronchodilators and inhaled corticosteroids are aimed mainly at symptomatic relief. Vaccination and rehabilitation are also important components of patient management. For exacerbations of severe COPD, the major therapeutic options expand to include increased doses of bronchodilators, oral corticosteroids, antibiotics, ventilator support, oxygen, and surgical treatment.

A disappointing theme permeates this current range of COPD therapies: none of them modifies the long-term lung function decline that is the hallmark of the disease. Only oxygen has been shown to increase the survival of patients with chronic respiratory failure. Given the immense burden of COPD on society and the individual, this lack of a true disease-modifying treatment is disheartening. However, many clinicians today have interpreted the current lack of curative therapies as a reason to avoid treating patients with COPD. “Symptomatic treatment,” in other words, has taken on a pejorative sense and has produced, in many clinicians, a nihilistic approach to the management of patients with COPD.

This attitude that “nothing works in COPD” must change. While it remains true that current “symptomatic” therapies do not prevent decline of lung function, they can provide measurable and near-term improvements in other key COPD outcomes. Among the most important of these are patient quality-of-life outcomes such as chronic fatigue, overwhelming hopelessness, physical immobility, and dyspnea. These are the palpable day-to-day concerns that can be alleviated by more aggressive therapy with today’s “symptomatic treatments.” In many cases, clinicians will need to combine therapies to help the patient and to prevent complications but—as in cancer therapy or treatment of heart disease—this concept of multimodality therapy is highly appropriate and is finally being applied in COPD. As quality-of-life outcomes and other nonphysiologic endpoints are increasingly monitored in COPD clinical trials, the full value of existing “symptomatic” therapies will emerge and clinicians will become even more aggressive in using these current treatments to improve the everyday lives of their patients.
In this article, a variety of treatments used in COPD exacerbations or moderate-to-severe COPD management are reviewed. [Editor's Note: See the previous Advanced Studies in Medicine issues in this COPD series for a discussion of the management of earlier stages of stable COPD.] These treatments are discussed in the context of the typical vicious cycles of COPD exacerbations that recur in many patients 2 or 3 times every year (Figure 1). From coughing, to infection, to hypoxia, to deconditioning, to sleep loss—the COPD cycle of acute exacerbation takes a tremendous toll on the quality of life in patients with COPD. Aggressive treatment for an individual patient today may not change the expected forced expiratory volume in 1 second (FEV₁) of the average patient 5 or 10 years in the future, but it may make 2 months or more of this year for this patient considerably less miserable. This is why we treat patients with COPD today.

**COPD Exacerbations**

Chronic COPD accounts for an estimated 13.4 million physician office visits in the United States every year, more than 600,000 hospitalizations, and over $30 billion in direct and indirect healthcare costs including at least $9.9 billion for work-related lost productivity. Following an acute exacerbation, most patients experience a transient or permanent decrease in quality of life, and as many as half are readmitted to the hospital within 6 months. Premature hospital discharge related to cost pressure undoubtedly accounts for many of these readmissions.

A recent study monitoring the typical course of symptoms during acute COPD exacerbations confirms that recovery can be prolonged. In this prospective study, 101 outpatients with moderate-to-severe COPD (mean FEV₁ of 42%) were observed over 2.5 years, both during stable periods and during 504 exacerbations. Symptoms and peak expiratory flow rate (PEFR) were serially measured. Before exacerbation onset, there was a 4-day to 7-day prodromal period of dyspnea, cough, sore throat, and common cold symptoms. This symptomatic deterioration leading up to exacerbation was not reflected in lung function tests. On the day of exacerbation onset, there was a sharp increase in these symptoms: 64% of patients had increased dyspnea, 35% had cold-like symptoms, and 20% had increased cough. These suggest that increased patient awareness and self-monitoring of symptoms may assist in earlier therapy initiation.

The study also documented that in the 91 patients with exacerbations, the typical recovery took about 1 week: the median recovery time in PEFR was 6 days and the median recovery in symptoms was 7 days. However, approximately 25% of the patients still had abnormal PEFRs or symptoms at 35 days, and at least 7% had still not fully recovered by 91 days. These data support what many pulmonologists in critical care settings realize intuitively as they send patients with COPD home after a few days: the recovery is fragile in a significant proportion of these patients.

A first step in preventing lengthy and debilitating COPD exacerbations is identifying risk factors associated with hospitalization for COPD. Demographic and historical risk factors associated with COPD hospitalization include 3 or more COPD admissions in the previous year (P<.0005); low FEV₁ (P<.0005); underprescription of long-term oxygen therapy (LTOT) (P=.007); and current smoking (P=.022). In addition, a recent noncontrolled study found that patients hospitalized for COPD often had 1 or more modifiable risk factors, including the lack of an influenza vaccination (seen in 28% of patients); lack of rehabilitation program attendance (86%); nonadher-
Infections are a critical and well-known factor in precipitating COPD exacerbations. Many COPD exacerbations are preceded by symptoms of a cold (eg, 35% in the study described above) and researchers have now tested patients for the specific bacteria and virus associated with such exacerbations. Using polymerase chain reaction methodology, a British group found that exacerbations in 66 of 168 patients (39%) were associated with respiratory viral infections. Rhinovirus accounted for 58% of these infections, followed by respiratory syncytial virus, coronavirus, and influenza. A group in the United States recently recovered nontypeable Haemophilus influenzae (NTHi) in the bronchial wash or brush specimens of 6 of 23 patients (26%) with chronic bronchitis and in 1 of 15 patients (7%) with acute exacerbations; these tests were negative in all 26 healthy controls. These results confirm high levels of NTHi colonization in patients with chronic bronchitis, but even more intriguing were the results of special biopsies and tests for intracellular NTHi. These tests were positive in 13 of 15 acutely ill patients with bronchitis (87%) versus 0 in 7 healthy adults.

These results, which strongly suggest a role for specific strains of bacteria or viruses in the pathogenesis of COPD exacerbation, were recently supported by a recent prospective study of 81 outpatient who had COPD. The patients were tracked with monthly sputum samples and molecular typing of sputum isolates for nonencapsulated H influenzae and other new strains. Over a period of nearly 5 years and 374 total exacerbations (mean: 2.1 per patient per year), findings of new strains were noted at 33% of clinic visits for exacerbations. In contrast, new strains were seen in only 15% of routine clinic visits not involving exacerbations (P<.001). In other words, isolation of a new strain of H influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae was associated with a significantly increased risk of COPD exacerbation.

More study is needed to determine if specific treatments for bacterial or viral pathogens—or for any of the other risk factors associated with exacerbations—will lead to improved outcomes in those patients with COPD who have frequent exacerbations. As such precipitating factors and markers of treatment failure are identified, the timing of antibiotic therapy and the criteria for selection of specific drugs may change.

**MANAGING THE CYCLES OF COPD EXACERBATION**

Several therapies and procedures have been developed to remedy the specific problems of hypoxemia, hyperinflation, undernutrition, deconditioning, and sleep disorders that define the vicious cycle of COPD exacerbations. Studies examining the benefits, risks, and unknowns of these therapies are reviewed here to illustrate the range of management options available to today's clinician. This is not intended to be an exhaustive review of COPD therapy options. Also, the data supporting efficacy of these interventions are frequently inconclusive. Nevertheless, increased awareness and selective use of such evolving techniques can dramatically improve the quality of life of certain patients as they fall into increasingly frequent cycles of exacerbation and despair.

**NONINVASIVE POSITIVE PRESSURE VENTILATION FOR RESPIRATORY FAILURE**

Respiratory failure is an extreme problem seen in COPD exacerbations. Noninvasive positive pressure ventilation (NPPV) may improve vital signs and gas exchange and may relieve dyspnea while reducing the need for intubation in select patients. In a representative study, the need for intubation in patients with COPD was reduced from 67% (8 of 12 patients) in the standard therapy group to 9% (1 in 11 patients) in the NPPV group (P<.05). In a recent analysis of 7 randomized trials of NPPV in patients with COPD, the success rate in avoiding endotracheal intubation and positive pressure ventilation was 83% (n=245), as compared with 61% (n=238) in controls. This reduced need for intubation was recently confirmed along with several additional NPPV benefits—decreased mortality, reduced treatment failure, and rapid improvement in pH during the first hour—in a Cochrane Review in the setting of COPD exacerbations.

In fact, the growing list of potential NPPV benefits (Table 1) is now leading more clinicians to consider the use of this intervention earlier in the course of respiratory failure secondary to COPD. These potential benefits cited in various studies have included not only physiologic and clinical gains but also improved economic outcomes (such as decreased intensive care unit [ICU] stay...
and lower cost per admission). Despite the promise of NPPV, many issues must be resolved before the technique can be taken up in "real-world" settings. Not only are larger studies with improved characterization of appropriate patients required, the optimal NPPV settings and mask interface (eg, nasal or full) must also be defined. Finally, the cost reimbursement structure for COPD-related interventions must also mature to reflect the total value of NPPV. Currently, hospital payments are much less for noninvasive ventilation than for invasive ventilation, with Medicare reimbursement ranging from about $65,000 for tracheotomy and $15,000 for endotracheal intubation to $2,500 for NPPV. This uncoupling of the financial incentive for NPPV from the relative medical value of the procedure hinders wider use.

Lung Volume Reduction Surgery for Dynamic Hyperinflation

Dynamic hyperinflation is a major—but often overlooked—feature of COPD exacerbations and is associated with severe dyspnea. A large component of the breathlessness seen in patients with COPD can be directly related to the degree of dynamic hyperinflation. In a study of patients with moderate-to-severe COPD, for example, researchers used inspiratory capacity to show that 80% of the patients had evidence of dynamic hyperinflation during exercise. Those patients with the most severe emphysema also were shown to have more severe dyspnea and greater abnormalities in measures of inspiratory reserve volume. The inability to expand the peak tidal volume in response to the increased respiratory drive of exercise contributes to exercise intolerance in these patients with moderate-to-severe COPD.

Such studies of dynamic hyperinflation suggest that exercise performance and dyspnea might be improved by therapeutic interventions that reduce the severity of hyperinflation. In our clinic, the LVRS procedure has worked exceedingly well in certain gas-trapped patients but has had no positive impact in others, as indicated by yet-to-be-published comparisons of FEV1 in patients with hyperinflation who were observed for up to 5 years after surgery (Figure 2). The clinicopathological correlates of findings in chest wall mechanics often include shortened diaphragm muscles, decreased diaphragm blood flow, reduced diaphragm curvature, medial rotation of diaphragm fibers, and a decreased area of apposition—all changes that put the diaphragm at a geometric mechanical disadvantage. A study of 37 patients undergoing LVRS and rehabilitation in our clinic showed significant improvements in maximum inspiratory pressure and diaphragm strength.

Thus, the LVRS procedure may produce a variety of physiological and clinical benefits that add up to an improved quality of life for patients—mainly via reduced dyspnea, increased exercise tolerance, and improved sleep patterns (Table 2). As with many other surgical interventions, however, these benefits have yet to be documented in large and convincing studies and many other aspects of the procedure remain to be defined. The National Emphysema Treatment Trial (NETT) is a prospective, randomized, controlled trial comparing optimized medical therapy to LVRS. This multicenter trial has completed enrollment and will shortly present results in over 1200 patients. NETT is designed not only to demonstrate whether LVRS provides a survival advantage over standard care but also to characterize the optimal patient as well as the durability of the treatment effect.

In our clinic, the LVRS procedure has worked exceedingly well in certain gas-trapped patients but has had no positive impact in others, as indicated by yet-to-be-published comparisons of FEV1 in patients with hyperinflation who were observed for up to 5 years after surgery (Figure 2). The clinicopathological correlates of

---

### Table 1. Noninvasive Positive Pressure Ventilation (NPPV) in Chronic Obstructive Pulmonary Disease (COPD)

<table>
<thead>
<tr>
<th>Potential Benefits of NPPV</th>
<th>Unresolved Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased development of nosocomial pneumonia</td>
<td>• Characterization of ideal target patient?</td>
</tr>
<tr>
<td>• Decreased need for tracheotomy</td>
<td>• Optimal settings and mask interface?</td>
</tr>
<tr>
<td>• Decreased ventilator days</td>
<td>• &quot;Real-world&quot; effectiveness?</td>
</tr>
<tr>
<td>• Decreased intensive care unit length of stay and costs</td>
<td>• Efficacy in chronic severe COPD?</td>
</tr>
<tr>
<td>• Decreased mortality</td>
<td>• Appropriate cost reimbursement?</td>
</tr>
</tbody>
</table>
good response to LVRS seem to include less marked interstitial fibrosis, less goblet cell hyperplasia, less peribronchial fibrosis, less chronic fibrosis, less vascular inflammation, and more severe bullous emphysema. Overall, these pathological characteristics indicate that patients with more emphysema and less fibrosis or small airways disease will be most likely to benefit from LVRS.

In select patients, bullectomy may also be helpful in improving lung function, boosting exercise capacity, and relieving dyspnea. However, there are a small number of patients who benefit from bullectomy. Ideal candidates are those with approximately one-third hemithorax occupied by a bulla that compresses otherwise normal or near-normal lung parenchyma without other significant comorbidities.

**Renutrition for Low Body Weight**

The classic image of the “pink puffer” in COPD is rooted in fact, and this weak underweight patient is now known to be especially prone to exacerbations. While low body weight is a problem in approximately 20% of the outpatient population with COPD; it is seen in fully half of all inpatients who have COPD. Low body weight is a concern because of the association with respiratory muscle weakness, gas exchange abnormalities—both hypoxia and hypercapnia—and decreased exercise tolerance. Decreased survival is also linked to low body weight, as indicated most recently in a study of 142 patients with COPD (mean age 65 years) who were observed for about 3 years.17 In those patients with an FEV₁ of less than 50%, a midthigh muscle cross-sectional area (obtained by computed tomography [CT] scan) of less than 70 cm² was strongly linked to increased mortality (odds ratio of 13).

While the prevalence and portentousness of low body weight in patients with COPD are unquestioned, the underlying cause—and therefore the best treatment approach—is still debated. Historically, undernourishment has been cited as the principle cause and is the reason most basic COPD rehabilitation strategies now incorporate a renutrition component among other nonpulmonary goals. The physiologic basis for inadequate nutrition in these patients is thought to involve a decreased oral intake or an

---

**Table 2. Lung Volume Reduction Surgery (LVRS) in COPD**

<table>
<thead>
<tr>
<th>Potential Benefits of LVRS</th>
<th>Unresolved Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved spirometry</td>
<td>True morbidity and mortality?</td>
</tr>
<tr>
<td>Better gas exchange</td>
<td>Survival effect?</td>
</tr>
<tr>
<td>Improved respiratory mechanics</td>
<td>Cost?</td>
</tr>
<tr>
<td>(decreased end expiratory lung volume, increased respiratory muscle strength, improved lung and chest wall recoil)</td>
<td>Characterization of the optimal candidate?</td>
</tr>
<tr>
<td>Improved exercise tolerance and sleep</td>
<td>Durability of the response?</td>
</tr>
<tr>
<td>Improved dyspnea and quality of life</td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 2. Lung Function After Lung Volume Reduction Surgery in COPD Patients: Responders (R) versus Nonresponders (NR)**

FEV₁ = forced expiratory volume in 1 second; LVRS = lung volume reduction surgery.
increased metabolic expenditure (estimated at 20% to 30% higher than normal) due to increased breathing effort. Other possible contributing factors are diet-induced thermogenesis, oropharyngeal dysfunction related to severe hyperinflation, and negative effects of medications.

Evolving data now indicate, however, that wasting of protein and skeletal muscle may play a larger role than poor nutrition in the weight loss of advanced COPD. In the previously described study of thigh cross-section, for example, a decrease in muscle mass correlated better with reduced mortality than did a decrease in body mass index. A potential physiologic reason for such COPD-related muscle wasting involves the potential induction of a systemic inflammatory state (eg, increased tumor necrosis factor, interleukin-6, interleukin-1, or reactive oxygen species). At least 1 study has also documented increased skeletal muscle apoptosis in patients with COPD who have weight loss not attributable to malnourishment while another controversial study has found a reduced muscle redox capacity after endurance training in patients with COPD. The results of this latter study suggest that patients with COPD have abnormal glutathione (GSH) regulation and, therefore, are unable to properly handle the increases in reactive oxygen species that occur following exercise. More data are required to confirm this and the other hypotheses related to weight loss in COPD; continued research into the systemic effects of COPD will contribute to the search for more rational and effective therapies.

PULMONARY REHABILITATION FOR THE DECONDITIONED PATIENT

Pulmonary rehabilitation programs are aimed at ameliorating the muscle wasting and weight loss just discussed, together with the related general deconditioning seen in patients with late-stage COPD. The principle goals of rehabilitation are to reduce symptoms, decrease disability, increase participation in physical and social activities, and improve the overall quality of life. The main methods used to achieve these goals are exercise training, patient and family education, and psychosocial and behavioral interventions. The goals of rehabilitation are laudable, the methods employed have no adverse effects, and over the past 20 years several prospective randomized controlled trials have noted the benefits of respiratory rehabilitation.

In a meta-analysis of 14 such trials, researchers have confirmed favorable effects of rehabilitation on functional exercise capacity and important aspects of patient quality of life such as dyspnea and patient control over COPD. Although many of these trials were small and of brief duration, the overall clinical benefits to patients in terms of increased functional exercise capacity seem clear. Specific rehabilitation-associated benefits as documented in the meta-analysis and in other more recent trials have included improvements in the 4-minute and 6-minute walking distance tests, the shuttle walk test, cycle endurance, dyspnea, maximum oxygen consumption (VO2max), work rate VO2max, and activities of daily living. These indicators of increased exercise tolerance were generally seen after just 8 to 12 weeks of rehabilitation.

Despite the evidence of efficacy for pulmonary rehabilitation in COPD, clinicians still struggle to win reimbursement for such programs. In those patients with 2 or 3 exacerbations each year, repeat training can be critically important in maintaining quality of life, and yet repeat funding can be especially difficult to secure. While the patient risk factors that might allow for more targeted application of such rehabilitation programs are yet to be determined, the available evidence should convince healthcare organizations to increase access to these relatively inexpensive and comprehensive outpatient rehabilitation programs.

IMPROVING SLEEP

Sleep impairment has been recognized for over 25 years as a debilitating component of COPD. One of the first studies addressing this important quality-of-life issue tracked 20 patients with an FEV1 of less than 1 liter and found increased sleep latency, decreased amounts of uninterrupted sleep, and decreased slow-wave sleep and rapid eye movement sleep. More recently, we monitored sleep impairment in 25 of our own patients with COPD (FEV1 28% of predicted) and confirmed significant reductions in total sleep time and sleep efficiency together with increases in the arousal index. About 41% of the sleep time in these patients was spent at arterial oxygen saturation (SaO2) of less than 90% (lowest SaO2 was 83%). A similar reduction in arterial oxygen partial pressure was previously noted in inpatients with COPD during sleep and had suggested the potential benefits of nocturnal oxygen therapy in certain patients.

Research also shows that the magnitude of the desaturation is inversely correlated with the arousal index and with the pulmonary artery pressure measured during the day or night. However, contradic-
tory results have been reported on the effect of chronic nocturnal oxygen supplementation on reducing the mean pulmonary artery pressure and improving patient sleep function.

But is nocturnal oxygen desaturation important to the quality of sleep—or to other outcomes—in patients with COPD? Is this physiologic abnormality a key part of the pathogenesis of right ventricular failure and mortality? Or is it simply a marker of severe disease—a harbinger of poor outcomes but not a direct contributor to patient decline and, therefore, not a component of the disease that warrants therapy?

Long-term trials with continuous oxygen therapy in patients meeting the special needs for treatment have documented an improved survival between 100 days and 500 days. Whether this therapy has a longer-term benefit, or whether patients with less severe COPD would benefit, is still unknown.

**Mucous Clearance**

Mucolytic agents do not help most patients with COPD. As stated in the National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, only a few patients with viscous sputum seem to benefit from mucokinetic or mucoregulator agents. Relief of this symptom should remain a high priority for researchers, however, since mucus is nearly a universal complaint of patients with COPD. Studies related to 2 recent products illustrate the promise associated with improved mucus clearance—and also how such therapies may one day be combined with other modalities targeting completely different aspects of COPD symptomology to provide the best overall outcome.

In one study, the effect of aerosolized uridine 5'-triphosphate (UTP) on mucociliary clearance was tested in patients with mild chronic bronchitis. Following inspiration of the aerosolized UTP, the clearance was acutely improved, a positive change most likely associated with stimulation of ciliary beating and airway hydration of secretions. In another recent study, patients used a new flutter-valve mucus clearance device before inhaling their usual dose of a combination bronchodilator (ipratropium and salbutamol). Use of the simple device immediately before bronchodilator therapy improved results from both spirometry and the 6-minute walk test, as compared to patients using a sham device. Such results indicate that more aggressive efforts aimed at mucus clearance, perhaps even as part of our current rehabilitation programs, may pay further synergistic dividends in exercise tolerance and quality of life.

**Lung Transplant**

Lung transplantation is an option for carefully selected patients with COPD refractory to maximal medical therapy and with an FEV₁ less than 25% of predicted. At least 1 study has demonstrated significant and stable improvements in quality of life after successful lung transplantation. The health dimensions improving in the years after surgery included physical function, role function, social function, mental health, and health perception. These benefits, of course, need to be considered in light of the discouragingly stubborn 3-year to 5-year mortality rates of 55% to 60% seen in this surgical population. Even with improvements in immunosuppressive regimens (eg, sirolimus, interleukin-2 antagonists) long-term survival after lung transplantation has remained at about 50%. Clearly, only selected patients with COPD will be considered for this risky and costly procedure.

**Conclusions**

From helping patients clear their throats to lung transplantation, clinicians have a range of options beyond the usual bronchodilators, corticosteroids, and oxygen to help their patients with moderate-to-severe COPD. By attacking the specific components of the disease that so often wear down and demoralize patients with COPD, clinicians can dramatically improve the quality of life in these individuals. Targeted interventions can be aimed at preventing exacerbations, decreasing mucus, treating hypoxemia, decreasing hyperinflation, enhancing sleep, and improving nutrition and conditioning. As just reviewed, the benefits of many of these therapies remain to be defined. Also, the proper selection of a symptomatic therapy for a given patient who has COPD requires much more study. Nevertheless, clinicians should consider using—and perhaps combining—as many of these therapies as necessary to reduce the symptom-heavy burden of this diverse disease.

**References**


