CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will be aware of major advances in the assessment and treatment of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease: An update for the primary physician

ABSTRACT

Our understanding of how to manage chronic obstructive pulmonary disease (COPD) has advanced significantly over the past decade. Physicians should instill optimism for improved symptoms and quality of life in their patients with COPD, a previously stigmatized condition.

KEY POINTS

A new COPD classification scheme is based on severity, symptoms, and exacerbations.

Azithromycin 250 mg daily prevents exacerbations of COPD in those at high risk.

Long-acting muscarinic antagonists such as aclidinium and tiotropium are first-line therapy.

Relatively new options include roflumilast, an oral phosphodiesterase inhibitor, and indacaterol, an ultra-long-acting beta agonist that is taken once daily.

Nondrug interventions include pulmonary rehabilitation, vitamin D supplementation, noninvasive positive-pressure ventilation, and lung-volume reduction surgery.

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CHRONIC OBSTRUCTIVE pulmonary disease (COPD) has seen several changes in its assessment and treatment in recent years, reflecting advances in our understanding of this common and serious disease.

This review updates busy practitioners on the major advances, including new assessment tools and new therapies.

COMMON AND INCREASING

COPD is the third leading cause of death in the United States, behind heart disease and cancer,[1] and of the top five (the others being stroke and accidents), it is the only one that increased in incidence between 2007 and 2010.[2] The 11th leading cause of disability-adjusted life years worldwide in 2002, COPD is projected to become the seventh by the year 2030.[3]

CHARACTERIZED BY OBSTRUCTION

COPD is characterized by persistent and progressive airflow obstruction associated with chronic airway inflammation in response to noxious particles and gases. Disease of the small airways (inflammation, mucus plugging, and fibrosis) and parenchymal destruction (emphysema) limit the flow of air.

COPD is diagnosed by spirometry—specifically, a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) of less than 0.7 after a bronchodilator is given. The severity of airflow limitation is revealed by the FEV_1 as a percent of the predicted value.

Cigarette smoking is the major cause of COPD, but the prevalence of COPD is 6.6% in people who have never smoked, and one-fourth of COPD patients in the United States have never smoked.[4]

TABLE 1

GOLD: A new classification based on severity, symptoms, and exacerbations

Who it is for: All patients with chronic obstructive pulmonary disease

Impact: Guides management, predicts exacerbations better

Caveats: Exacerbation history and FEV_1 are not equal in predicting risk

GOLDEN GOALS: FEWER SYMPTOMS, LOWER RISK

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) periodically issues evidence-based statements on how to prevent and treat COPD.

In its 2013 update,[5] GOLD suggested two goals: improving symptoms and reducing the risk of death, exacerbations, progression of disease, and treatment-related adverse effects. The latter goal—reducing risk—is relatively new.

Exacerbations are acute inflammatory events superimposed on chronic inflammation. The inflammation is often brought on by infection[6] and increases the risk of death[7] and the risk of a faster decline in lung function.[8]

Smoking is the major cause of COPD, but 1/4 of COPD patients have never smoked

Exacerbations may characterize a phenotype of COPD. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) analyzed the frequency of COPD exacerbations and associated factors in 2,138 patients with COPD over a period of 3 years.[9] Although patients with more severe obstruction tended to have more exacerbations, some patients appeared susceptible to exacerbations irrespective of the severity of obstruction. The best predictor of exacerbations was a history of exacerbations.

HOW DO I ASSESS A PATIENT WITH COPD ON PRESENTATION?

Markers of airflow obstruction such as the FEV_1 do not correlate strongly with exertional capacity and health status in patients with COPD.[10,11]

The BODE index (***b***ody mass index, ***o***bstruction, ***d***yspnea score, and ***e***xercise oximetry) takes into account the multidimensional nature of COPD. It performs better than the FEV_1 in predicting the risk of death.[12] The propensity for exacerbations and comorbidities further modulates outcome.

Assessing symptoms

The modified British Medical Research Council (mMRC) dyspnea scale, based on work by Fletcher in 1952,[13] has five grades, numbered 0 through 4:

- Grade 0—Breathless with strenuous exercise only
- Grade 1—Breathless when hurrying on level ground or walking up a slight hill
- Grade 2—Walks slower than people of the same age on level ground because of shortness of breath or has to stop when walking at own pace on level ground
- Grade 3—Stops for breath after walking about 100 yards or after a few minutes on level ground
- Grade 4—Too breathless to leave the house or breathless when dressing or undressing.

Grade 2 or higher separates symptomatic from asymptomatic COPD.

The COPD Assessment Test (CAT) (www.catestonline.org) is a proprietary questionnaire. Patients use a 6-point scale (numbered 0 though 5) to rate eight symptoms (cough, mucus production, chest tightness, shortness of breath on exertion, limitations in home activities, lack of confidence leaving the home, poor sleep, and lack of energy). A total score of 10 or higher is abnormal.

Four GOLD groups

The new GOLD guidelines (TABLE 1)[5] define four groups of patients according to their severity of airflow obstruction, symptoms, and exacerbation history:

- **Group A—fewer symptoms, low risk:** Fewer symptoms ("less symptoms," as worded in the guidelines) means a CAT score less than 10 or an mMRC grade less than 2; "low risk" means no more than one exacerbation per year and an FEV_1 of at least 50%
- **Group B—more symptoms, low risk:** "More symptoms" means a CAT score of 10 or more or an mMRC grade of 2 or more
- **Group C—fewer symptoms, high risk:** "High risk" means two or more exacerbations per year or an FEV_1 less than 50%
- **Group D—more symptoms, high risk.**

Thus, a patient with an FEV_1 of 60% (moderate airflow limitation) who has had one exacerbation during the past year and a CAT score of 8 would be in group A. In contrast, a patient who has an FEV_1 of 40% (severe airflow limitation), no history of exacerbations, and a CAT score of 20 would be in group D.

Updated GOLD guidelines suggest utilizing a stepwise approach to treatment, akin to asthma management guidelines, based on patient grouping.[5]

How accurate is the new GOLD system?

Although practical and suited for use in primary care, the new GOLD system is arbitrary and has not been thoroughly studied, and may therefore need refinement.

Lange et al[14] compared the new GOLD system with the previous one in 6,628 patients with COPD. As anticipated, the new system was better at predicting exacerbations, as it incorporates a history of exacerbations in stratification. The presence of symptoms (as determined by an mMRC grade ≥ 2) was a marker of mortality risk that distinguished group A from group B, and group C from group D. Surprisingly, the rate of death was higher in group B (more symptoms, low risk) than in group C (fewer symptoms, high risk).

Notably, most patients in group C qualified for this group because of the severity of airflow obstruction, not because of a history of exacerbations. Therefore, patients whose symptoms are out of proportion to the severity of obstruction may be at higher risk of death, possibly because of comorbidities such as cardiovascular disease.[15] Patients who qualified for groups C and D by having both a history of frequent exacerbations (≥ 2 per year) and symptoms rather than either one alone had a higher risk of death in 3 years.

Similarly, the symptom-assessment tool that is used—ie, the mMRC grade or the CAT score—also makes a difference.

The Health-Related Quality of Life in COPD in Europe Study[16] retrospectively analyzed data from 1,817 patients to determine whether the cutoff points for symptoms as assessed by mMRC grade and CAT score were equivalent. Although the mMRC grade correlated well with overall health status, the cutoff mMRC grade of 2 or higher did not correspond to a CAT score of 10 or higher, classifying patients with health status impairment as asymptomatic (mean weighted kappa 0.626). The two tools agreed much better when the cutoff was set at an mMRC grade of 1 or higher (mean weighted kappa 0.792).[16]

Although assessment schemes continue to evolve as data accumulate, we believe the new system is a welcome initiative that reflects the changing notions of COPD.

Comorbidities matter

Another shift is the recognition that certain comorbidities increase the risk of death. In 1,664 patients with COPD who were followed for 51 months, 12 distinct comorbidities were associated with a higher risk of death after multivariate analysis.[17]

The COTE index (COPD-Specific Comorbidity Test) is based on these findings. It awards points as follows:

- 6 points for cancer of the lung, esophagus, pancreas, or breast, or for anxiety
- 2 points for all other cancers, liver cirrhosis, atrial fibrillation or flutter, diabetes with neuropathy, or pulmonary fibrosis
- 1 point for congestive heart failure, gastric or duodenal ulcer, or coronary artery disease.

A COTE index score of 4 or higher was associated with a risk of death 2.2 times higher in each quartile of the BODE index.

We strongly recommend being aware of comorbidities in COPD patients, particularly when symptoms are out of proportion to the severity of obstruction.

The best predictor of exacerbations is a history of exacerbations

SHOULD I USE ANTIBIOTICS TO TREAT ALL COPD EXACERBATIONS?

Infections are thought to cause more than 80% of acute exacerbations of COPD.

Anthonisen et al,[18] in a landmark trial, found broad-spectrum antibiotics to be most helpful if the patient had at least two of the three cardinal symptoms of COPD exacerbation (ie, shortness of breath, increase in sputum volume, and sputum purulence). Antibiotics decreased the rate of treatment failure and led to a more rapid clinical resolution of exacerbation. However, they did not help patients who had milder exacerbations.

Antibiotics may nevertheless have a role in ambulatory patients with mild to moderate

TABLE 2

Azithromycin 250 mg daily to prevent exacerbations

Who it is for: Those with exacerbations and emergency room visits, given emergency steroids, or hospitalized in previous year

Impact: Reduces exacerbations, improves quality of life

Use with other therapies: 80% of participants in trials were already on inhaled corticosteroids, long-acting beta agonists, or long-acting muscarinic antagonists; those on triple therapy did not benefit

Caveats: Hearing decrement, colonization with macrolide-resistant organisms

COPD who present with exacerbations characterized by one or more cardinal symptoms.

Llor et al,[19] in a multicenter randomized double-blind placebo-controlled trial in Spain, concluded that amoxicillin clavulanate (Augmentin) led to higher clinical cure rates and longer time to the next exacerbation in these patients. Most of the benefit was in patients with more symptoms, consistent with the results of the study by Anthonisen et al.[18]

There is also strong evidence to support the use of antibiotics in addition to systemic corticosteroids in hospitalized patients with acute exacerbations of COPD. A 7-day course of doxycycline (Vibramycin) added to a standard regimen of corticosteroids was associated with higher rates of clinical and microbiological cure on day 10 of the exacerbation.[20] In a large retrospective cohort study in 84,621 hospitalized patients with COPD exacerbations, fewer of those who received antibiotics needed mechanical ventilation, died, or were readmitted.[21] Although sicker patients received antibiotics more frequently, their mortality rate was lower than in those who did not receive antibiotics, who were presumably less sick.

Patients with symptoms disproportionate to the severity of obstruction may be at higher risk of death

A meta-analysis confirmed the salutary effect of antibiotics in inpatients and particularly those admitted to the intensive care unit.[22] Mortality rates and hospital length of stay were not affected in patients who were not in intensive care.

Biomarkers such as procalcitonin might help reduce the unnecessary use of antibiotics. Stolz et al[23] conducted a randomized controlled trial in which they based the decision to give antibiotics on a threshold procalcitonin level of at least 1 µg/L in hospitalized patients with COPD exacerbation. The rate of antibiotic use was reduced by more than 40% in the procalcitonin group without any difference in clinical outcomes, 6-month exacerbation rate, or rehospitalization compared with controls. Nonstandardized procalcitonin assays are a possible barrier to the widespread adoption of this threshold.

Comment. In general, we recommend antibiotics for hospitalized patients with COPD exacerbation and look forward to confirmatory data that support the use of biomarkers. For outpatients, we find the Anthonisen criteria useful for decision-making at the point of care.

ARE THERE ANY NEW INTERVENTIONS TO PREVENT COPD EXACERBATIONS?

Macrolides

Macrolides have a proven role in managing chronic suppurative respiratory diseases such as cystic fibrosis[24] and diffuse panbronchiolitis.[25] Since they are beneficial at lower doses than those used to treat infection, the mechanism may be anti-inflammatory rather than antimicrobial.

Albert et al[26] assigned 1,142 patients who had had a COPD exacerbation within a year before enrollment or who were on home oxygen therapy to receive azithromycin (Zithromax) 250 mg daily or placebo.[25] The azithromycin group had fewer acute exacerbations (hazard ratio 0.73, 95% CI 0.63–0.84, $P < .001$), and more patients in the azithromycin group achieved clinically significant improvements in quality of life, ie, a reduction in the St. George's Respiratory Questionnaire (SGRQ) score of at least 4 points (43% vs 36%, $P = .03$). Adverse events that were more common in the azithromycin group were hearing loss (25% vs 20%) and macrolide-resistant strains in nasopharyngeal secretions (81% vs 41%). In subgroup analysis, the benefit in terms of reducing exacerbations was greater in patients over age 65, patients on home oxygen, and patients with moderate or severe obstruction compared with those with very severe obstruction.

Comment. Macrolides are a valuable addition to the agents available for preventing COPD exacerbation (TABLE 2), but their role

is still uncertain. Potential topics of research are whether these drugs have a role in patients already on preventive regimens, whether they would have a greater effect in distinct patient populations (eg, patients who have two or more exacerbations per year), and whether their broader use would lead to a change in the resident flora in the community.

Clinicians should exercise caution in the use of azithromycin in light of recent concern about associated cardiac morbidity and death. All patients should undergo electrocardiography to assess the QTc interval before starting treatment, as in the trial by Albert et al.[26]

Phosphodiesterase inhibitors

Roflumilast (Daliresp) is an oral phosphodiesterase 4 inhibitor approved for treating exacerbations and symptoms of chronic bronchitis in patients with severe COPD (TABLE 3). Phosphodiesterase 4, one of the 11 isoforms of the enzyme, is found in immune and inflammatory cells and promotes inflammatory responses. Roflumilast has anti-inflammatory properties but no acute bronchodilatory effect.[27] Several phase 3 trials found the compound to have beneficial effects.

Calverley et al[28] performed two placebo-controlled double-blind trials in outpatients with the clinical diagnosis of COPD who had chronic cough; increased sputum production; at least one recorded exacerbation requiring corticosteroids or hospitalization, or both; and an FEV_1 of 50% or less. Patients were randomized to receive roflumilast 500 µg once a day (n = 1,537) or placebo (n = 1,554) for 1 year. The rate of moderate to severe exacerbations was 1.17 per year with roflumilast vs 1.37 with placebo ($P < .0003$). Adverse events were significantly more common with roflumilast and were related to the known side effects of the drug, namely, diarrhea, weight loss, decreased appetite, and nausea.

Fabbri et al[29] performed two other placebo-controlled double-blind multicenter trials, studying the combinations of roflumilast with salmeterol (Serevent) and roflumilast with tiotropium (Spiriva) compared with placebo in 1,676 patients with COPD who had postbronchodilator FEV_1 values of 40% to 70% of predicted. The mean prebronchodilator FEV_1 improved by 49 mL ($P < .0001$) in the salmeterol-plus-roflumilast trial and by 80 mL ($P < .0001$) in the tiotropium-plus-roflumilast trial compared with placebo. Fewer patients on roflumilast had exacerbations of any severity in both trials (risk ratio 0.82, $P = .0419$ and risk ratio 0.75, $P = .0169$, respectively).

No trial has yet addressed whether roflumilast is better than the combination of a long-acting muscarinic antagonist and a beta agonist, or whether roflumilast can be substituted for inhaled corticosteroids in a new triple-therapy combination. Clinicians should also be aware of psychiatric side effects of roflumilast, which include depression and, possibly, suicide.

TABLE 3

An oral phosphodiesterase inhibitor[a]

Who it is for: Those with chronic bronchitic phenotype and exacerbations

Impact: Fewer exacerbations, higher FEV_1

Use with other therapies: Fewer exacerbations when added to long-acting beta agonists or long-acting muscarinic antagonists

Caveats: Small effect on quality of life; has limiting side effects (diarrhea, nausea, weight loss, insomnia, headache, depression)

[a] Roflumilast 500 µg daily

ARE THERE ANY NEW BRONCHODILATORS FOR PATIENTS WITH COPD?

Long-acting muscarinic antagonists

Reversible airflow obstruction and mucus secretion are determined by the vagal cholinergic tone in patients with COPD.[30] Antagonism of cholinergic (muscarinic) receptors results in bronchodilation and reduction in mucus production. Consequently, inhaled anticholinergic agents are the first-line therapy for COPD (TABLE 4).

Tiotropium bromide is a long-acting antimuscarinic approved in 2002 by the US Food and Drug Administration (FDA). The UPLIFT trial (Understanding Potential Long-Term Impacts on Function With Tiotropium)[31] enrolled 5,993 patients with a mean FEV_1 of 48% of predicted. Over a 4-year follow-up, significant improvements in mean FEV_1 values (ranging from 87 mL to 103 mL

No trial has addressed whether roflumilast is better than a long-acting muscarinic antagonist plus a beta agonist

TABLE 4

Long-acting muscarinic antagonists[a]

Who they are for: Considered first-line therapy for chronic obstructive pulmonary disease; aclidinium for nocturnal control

Impact: Improve FEV_1 and health-related quality of life, reduce exacerbations

Use with other therapies: In the UPLIFT trial,[31] benefit seen in addition to other respiratory medications

Caveats: Possible risk of urinary retention

[a] Tiotropium 18 µg daily, aclidinium 400 µg twice daily

before bronchodilation and 47 mL to 65 mL after bronchodilation, $P < .001$) in the tiotropium group were observed compared with placebo. The rate of the primary end point—the rate of decline in mean FEV_1—was not different between tiotropium and placebo. However, there were important salutary effects in multiple clinical end points in the tiotropium group. Health-related quality of life as measured by the SGRQ improved in a clinically significant manner (> 4 points) in favor of tiotropium in a higher proportion of patients (45% vs 36%, $P < .001$). Tiotropium reduced the number of exacerbations per patient year (0.73 ± 0.02 vs 0.85 ± 0.02, RR = 0.86 (95% CI 0.81–0.91), $P < .001$) and the risk of respiratory failure (RR = 0.67, 95% CI 0.51–0.89). There were no significant differences in the risk of myocardial infarction, stroke, or pneumonia.

Long-acting beta agonists may increase the risk of death in asthma, but not in COPD

Aclidinium bromide (Tudorza Pressair) is a long-acting antimuscarinic recently approved by the FDA. Compared with tiotropium, it has a slightly faster onset of action and a considerably shorter half-life (29 hours vs 64 hours).[32,33] Its dosage is 400 µg twice daily by inhalation. It provides sustained bronchodilation over 24 hours and may have a favorable side-effect profile, because it undergoes rapid hydrolysis in human plasma.[34]

ACCORD COPD I[35] and ATTAIN,[36] two phase 3 trials in patients with moderate-to severe COPD, found that twice-daily aclidinium was associated with statistically and clinically significant (> 100 mL) improvements in trough and peak FEV_1 compared with placebo. Health status (assessed by SGRQ) and dyspnea (assessed by transitional dyspnea index) also improved significantly. However, improvements beyond minimum clinically significant thresholds were achieved only with 400 µg twice-daily dosing.

To date, no study has evaluated the impact of aclidinium on COPD exacerbation as a primary end point. Fewer moderate to severe exacerbations were reported in an earlier 52-week study of once-daily aclidinium (ACCLAIM COPD II) but not in ACCLAIM COPD I.[37]

Aclidinium may offer an advantage over tiotropium in patients who have nocturnal symptoms. Twice-daily aclidinium 400 µg was associated with superior FEV_1 area-under-the-curve values compared with placebo and tiotropium, the difference mostly owing to improved nocturnal profile.[38]

Long-acting beta-2 agonists

Stimulation of airway beta-2 receptors relaxes smooth muscles and consequently dilates bronchioles via a cyclic adenosine monophosphate-dependent pathway.[39]

Short-acting beta-2 agonists such as albuterol and terbutaline have long been used as rescue medications for obstructive lung disease. Long-acting beta-2 agonists provide sustained bronchodilation and are therefore more efficacious as maintenance medications. Salmeterol, formoterol (Foradil), and arformoterol (Brovana) are long-acting beta-2 agonists in clinical use that are taken twice daily.

Clinical studies indicate that use of long-acting beta-2 agonists leads to significant improvements in FEV_1,[40–42] dynamic hyperinflation, exercise tolerance,[43,44] and dyspnea.[45,46] These drugs have also been associated with significant improvements in health-related quality of life and in the frequency of exacerbations.[47–49]

In patients with asthma, long-acting beta agonists may increase the risk of death.[50] In contrast, in patients with COPD, they appear to offer a survival advantage when used in combination with inhaled corticosteroids,[51] and some argue that this benefit is entirely from the long-acting beta agonist (a 17% reduction in mortality) rather than the inhaled corticosteroid (0% reduction in mortality).[52]

Indacaterol (Arcapta), approved in July

2011, is the first once-daily beta agonist or "ultra-long-acting" beta agonist (TABLE 5). Possibly because it has a high affinity for the lipid raft domain of the cell membrane where beta-2 receptors are coupled to second messengers,[53] the drug has a 24-hour duration of action.

In patients with COPD, inhaled indacaterol 150 µg once daily improved airflow obstruction and health status as measured by SGRQ compared with salmeterol 50 µg twice daily and placebo.[54] At the higher dose of 300 µg daily, the 52-week INVOLVE trial[55] demonstrated early and more sustained improvement in FEV_1 compared with placebo and formoterol. In this study, a lower exacerbation rate than with placebo was also noted. The drug has also shown equivalent bronchodilator efficacy at 150 µg and 300 µg daily dosing compared with tiotropium.[56]

The benefits of a longer-acting bronchodilator such as indacaterol are likely mediated by smoothing out airway bronchomotor tone over 24 hours without the dips seen with shorter-acting agents and by improvement of the FEV_1 trough before the subsequent dose is due, aptly named "pharmacologic stenting."[57] Once-daily dosing should also foster better adherence. The safety profile appears excellent with no increase in cardiovascular or cerebrovascular events compared with placebo.[58]

The FDA approved the 75-µg daily dose instead of the higher doses used in the studies mentioned above. This decision was based on the observation that there appeared to be a flattened dose-response in patients with more severe COPD, with no further improvement in trough FEV_1 at higher doses.[59]

TABLE 5

An ultra-long-acting beta agonist[a]

Who it is for: First line in at least moderate disease not requiring inhaled corticosteroids, combined with inhaled corticosteroids in at least severe exacerbations of chronic obstructive pulmonary disease

Impact: "Pharmacologic stenting" with increased area under the time-airflow curve, increased FEV_1, better bronchodilation over twice-daily long-acting beta agonists, and at least as potent as long-acting muscarinic antagonists

Use with other therapies: A long-acting beta agonist with inhaled corticosteroid and tiotropium may improve lung function and quality of life; compared with tiotropium or twice-daily long-acting beta agonists, greater likelihood in achieving a minimally clinically important difference in dyspnea or quality of life

Caveats: Nasopharyngitis and headache

[a] Indacaterol 75 µg daily

TABLE 6

Oral vitamin D for chronic obstructive pulmonary disease

Who it is for: Those with serum 25-hydroxyvitamin D < 10 ng/mL

Impact: Reduction in exacerbations

Use with other therapies: Benefits seen in addition to usual medications for COPD

Caveats: Benefits in a post hoc analysis only in severe deficiency state

DOES VITAMIN D SUPPLEMENTATION HAVE A ROLE IN COPD MANAGEMENT?

Vitamin D is vital for calcium and phosphate metabolism and bone health. Low vitamin D levels are associated with diminished leg strength and falls in the elderly.[60] Osteoporosis, preventable with vitamin D and calcium supplementation, is linked to thoracic vertebral fracture and consequent reduced lung function.[61,62]

Patients with COPD are at higher risk of vitamin D deficiency, and more so if they also are obese, have advanced airflow obstruction, are depressed, or smoke.[62] Therefore, there are sound reasons to look for vitamin D deficiency in patients with COPD and to treat it if the 25-hydroxyvitamin D level is less than 10 ng/mL (TABLE 6).

Vitamin D may also have antimicrobial and immunomodulatory effects.[63] Since COPD exacerbations are frequently caused by infection, it was hypothesized that vitamin D supplementation might reduce the rate of exacerbations.

In a study in 182 patients with moderate to very severe COPD and a history of recent exacerbations, high-dose vitamin D supplementation (100,000 IU) was given every 4 weeks for 1 year.[64] There were no differences in the time to first exacerbation, in the rate of exacerbation, hospitalization, or death, or in quality of life between the placebo and inter-

TABLE 7

Noninvasive positive-pressure ventilation in the stable setting

Who it is for: Those with hypercapnic chronic obstructive pulmonary disease

Impact: Improved survival, exercise-related dyspnea, daytime $Paco_2$, FEV_1, vital capacity, and health-related quality of life

Use with other therapies: Advantages augment those of pulmonary rehabilitation

Caveats: Benefits may not be seen in patients without hypercapnia

TABLE 8

Pulmonary rehabilitation

Who it is for: Those with severe symptoms; FVC, FEV_1, or diffusing capacity of lung for carbon monoxide < 60%; motivation; and a treatment goal

Impact: Improved exercise capacity, survival and quality of life, reduced hospitalizations

Use with other therapies: Benefits seen in addition to standard COPD medications and often exceed those of medications.

Caveats: Benefits last only as long as exercise lasts

We recommend screening for vitamin D deficiency in patients with COPD

vention groups. However, subgroup analysis indicated that, in those with severe vitamin D deficiency at baseline, the exacerbation rate was reduced by more than 40%.

Comment. We recommend screening for vitamin D deficiency in patients with COPD. Supplementation is appropriate in those with low levels, but data indicate no role in those with normal levels.

WHAT ARE THE NONPHARMACOLOGIC APPROACHES TO COPD TREATMENT?

Noninvasive positive-pressure ventilation

Nocturnal noninvasive positive-pressure ventilation may be beneficial in patients with severe COPD, daytime hypercapnia, and nocturnal hypoventilation, particularly if higher inspiratory pressures are selected (TABLE 7).[65,66]

For instance, a randomized controlled trial of noninvasive positive-pressure ventilation plus long-term oxygen therapy compared with long-term oxygen therapy alone in hypercapnic COPD demonstrated a survival benefit in favor of ventilation (hazard ratio 0.6).[67]

In another randomized trial,[68] settings that aimed to maximally reduce $Paco_2$ (mean inspiratory positive airway pressure 29 cm H_2O with a backup rate of 17.5/min) were compared with low-intensity positive airway pressure (mean inspiratory positive airway pressure 14 cm H_2O, backup rate 8/min). The high inspiratory pressures increased the daily use of ventilation by 3.6 hours per day and improved exercise-related dyspnea, daytime $Paco_2$, FEV_1, vital capacity, and health-related quality of life[66] without disrupting sleep quality.[68]

Caveats are that acclimation to the high pressures was achieved in the hospital, and the high pressures were associated with a significant increase in air leaks.[66]

Comments. Whether high-pressure noninvasive positive-pressure ventilation can be routinely implemented and adopted in the outpatient setting, and whether it is associated with a survival advantage remains to be determined. The advantages of noninvasive positive-pressure ventilation in the setting of hypercapnic COPD appear to augment those of pulmonary rehabilitation, with improved quality of life, gas exchange, and exercise tolerance, and a slower decline of lung function.[69]

Pulmonary rehabilitation

Pulmonary rehabilitation is a multidisciplinary approach to managing COPD (TABLE 8).

Patients participate in three to five supervised sessions per week, each lasting 3 to 4 hours, for 6 to 12 weeks. Less-frequent sessions may not be effective. For instance, in a randomized trial, exercising twice a week was not enough.[70] Additionally, a program lasting longer than 12 weeks produced more sustained benefits than shorter programs.[71]

A key component is an exercise protocol centered on the lower extremities (walking, cycling, treadmill), with progressive exercise intensity to a target of about 60% to 80% of the maximal exercise tolerance,[72] though more modest targets of about 50% can also be beneficial.[73]

Exercise should be tailored to the desired outcome. For instance, training of the upper arms may help with activities of daily living. In one study, unsupported (against gravity) arm training improved upper-extremity function more than supported arm training (by er-

gometer).[74] Ventilatory muscle training is less common, as most randomized trials have not shown conclusive evidence of benefit. Current guidelines do not recommend routine inspiratory muscle training.[71]

Even though indices of pulmonary function do not improve after an exercise program, randomized trials have shown that pulmonary rehabilitation improves exercise capacity, dyspnea, and health-related quality of life; improves cost-effectiveness of health care utilization; and provides psychosocial benefits that often exceed those of other therapies. Although there is no significant evidence of whether pulmonary rehabilitation improves survival in patients with COPD,[71] an observational study documented improvements in BODE scores as well as a reduction in respiratory mortality rates in patients undergoing pulmonary rehabilitation.[75]

A limitation of pulmonary rehabilitation is that endurance and psychological and cognitive function decline significantly if exercise is not maintained. However, the role of a maintenance program is uncertain, with long-term benefits considered modest.[71]

Lung-volume reduction surgery

Lung-volume reduction consists of surgical wedge resections of emphysematous areas of the lung (TABLE 9).

The National Emphysema Treatment Trial[76] randomized 1,218 patients to undergo either lung-volume reduction surgery or maximal medical therapy. Surgery improved survival, quality of life, and dyspnea in patients with upper-lobe emphysema and a low exercise capacity (corresponding to < 40 watts for men or < 25 watts for women in the maximal power achieved on cycle ergometry). While conferring no survival benefit in patients with upper-lobe-predominant emphysema and high exercise capacity, this surgery is likely to improve exercise capacity and quality of life in this subset of patients.

TABLE 9

Lung-volume reduction surgery

Who it is for: Those with upper lobe emphysema, low exercise capacity

Impact: Long-term improvements in dyspnea, quality of life, oxygen use, and survival

Use with other therapies: Advantages seen while patient is on maximal therapy and pulmonary rehabilitation

Caveats: Surgical risk, air leaks, costs more than medical therapy

Importantly, the procedure is associated with a lower survival rate in patients with an FEV_1 lower than 20%, homogeneous emphysema, a diffusing capacity of the lung for carbon monoxide lower than 20%, non-upper-lobe emphysema, or high baseline exercise capacity.

The proposed mechanisms of improvement of lung function include placing the diaphragm in a position with better mechanical advantage, reducing overall lung volume, better size-matching between the lungs and chest cavity, and restoring elastic recoil.[76,77]

Ongoing trials aim to replicate the success of lung-volume reduction using nonsurgical bronchoscopic techniques with one-way valves, coils, biologic sealants, thermal ablation, and airway stents.

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