The management and treatment of chronic obstructive pulmonary disease (COPD) involve both medications and nonpharmacological interventions. There are a variety of national and international management and treatment guidelines available. They include avoiding risk factors, such as cigarette smoking, the appropriate use of medications and supplemental oxygen, pulmonary rehabilitation, and surgery.

Additionally, these guidelines address the treatment of COPD in exacerbation.\textsuperscript{1-3}
Goals of therapy
The goals of COPD management include improving lung function, preventing disease progression, the relief of symptoms, improvement in exercise tolerance, prevention of exacerbations, reduction of complications, minimizing adverse effects from treatment, and reducing mortality. Preferred pharmacological management of chronic COPD has been advocated by evidence-based guidelines. Treatment recommendations are based on a determination of a specific patient’s disease severity. Therefore, spirometry becomes an essential tool in this process. But other factors, such as disease symptoms, frequency of exacerbations, and certain patient preferences and abilities, must be considered.

Spirometry is needed in patients with symptoms of cough, dyspnea on exertion, fatigue, and reduced functionality. Many of these patients are at risk for COPD and already have comorbidities associated with COPD.

COPD treatment goals include improving lung function and symptoms; preventing disease progression, exacerbations, and complications; improving exercise tolerance; and, ultimately, reducing mortality.

These airflow measurements are helpful in determining treatment steps. For example, a forced expiratory volume in 1 second (FEV₁) less than 60% of predicted generally indicates the need for regular maintenance therapy, and values below 30% of predicted signal the need to create a treatment plan for more severe disease. Spirometry generally should not be used to randomly screen for airflow obstruction in individuals without respiratory symptoms.

Pharmacology according to treatment guidelines
Previously, COPD treatment hinged on spirometry results only (Figure 1). The current approach to COPD care is based on disease severity, taking into account airflow measurement, symptoms, and exacerbation history (Figure 2).

Valid questionnaires such as the COPD Assessment Test or the modified Medical Research Council scale are used for symptom assessment; spirometry helps determine the severity of airflow limitation (Table 1), and exacerbations during the last year are recorded and counted.

By considering these components together, a patient can often be placed into a certain category, A through D. Using this process, the clinician can decide on which treatment strategy to use, both nonpharmacological (Table 2) and pharmacological (Table 3). This approach hopefully improves the efficacy of interventions, reduces health care costs by avoiding unnecessary interventions, and minimizes complications.

Initial drug therapy for patients with mild COPD who have preserved lung function and few symptoms is a short-acting inhaled bronchodilator, either albuterol or ipratropium. If the patient...
is more symptomatic and has not had an exacerbation, then either a long-acting anticholinergic or a long-acting beta₂-agonist should be tried. There is convincing evidence that the once-daily anticholinergic, tiotropium, is more effective than twice-daily salmeterol in preventing COPD exacerbations.⁵ For patients with more severe disease, a long-acting beta₂-agonist with an inhaled corticosteroid or a long-acting anticholinergic should be considered.⁶ It may be necessary to use all 3 agents in patients with even more severe COPD.² Certainly, patients with frequent exacerbations tend to have more severe airflow obstruction and they require an inhaled corticosteroid therapy. The combination of a long-acting beta₂-agonist and an inhaled corticosteroid is more effective than its individual components in reducing exacerbations and in improving lung function and exercise capacity.⁵

Roflumilast, a phosphodiesterase type 4 inhibitor, has been shown to prevent corticosteroid-treated exacerbations in patients who have chronic bronchitis and a low FEV₁.⁹ Theophylline therapy has been used to treat COPD for many years. At higher doses, numerous adverse effects have hampered its use, but at lower doses theophylline may have anti-inflammatory effects and likely have value in preventing exacerbations.¹⁰ Even when used at lower dosages, theophylline has been associated with gastrointestinal side effects.

All treatments have the potential for side effects. Beta₂-agonists are associated with palpitations, tremor, and electrolyte imbalances. Patients with existing cardiac disease often have COPD and are at risk for many of the adverse effects associated with these medications. Long-acting anticholinergic medications have been associated with urinary retention, dry mouth, and, rarely, glaucoma. Concerns about cardiac death with long-acting anticholinergic therapy have not been substantiated. Common adverse effects of roflumilast include gastrointestinal upset, weight loss, and depression. A variety of new medications belonging to the long-acting beta₂-agonist, long-acting anticholinergic, and inhaled corticosteroid classes are currently available for once-daily use.

Patients with moderate-to-severe COPD, who have a history of COPD exacerbations despite optimal maintenance therapy, often benefit from the long-term use of an oral macrolide in preventing exacerbations.¹¹ When using macrolide therapies, individual patients should be assessed for prolonged QT interval, hearing loss, and bacterial resistance consequences. To date, there is no consensus on the dose or duration of macrolide therapy. Macrolide antibiotics have been used for years in the management of chronic airway diseases for their antimicrobial, anti-inflammatory, and immune-modulating effects.

Systemic oral corticosteroids for the long-term treatment of COPD should generally not be used beyond the 30 days after an acute exacerbation,¹² unlike their use during an acute attack, for which they can be used routinely.

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**Figure 1. Therapy at each stage of COPD.**

- **I: Mild**
  - FEV₁/FVC > 0.70
  - FEV₁ ≥ 80% predicted
  - Active reduction of risk factor(s); influenza vaccination
  - *Add short-acting bronchodilator (when needed)*

- **II: Moderate**
  - FEV₁/FVC < 0.70
  - 50% ≤ FEV₁ < 80% predicted
  - Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation

- **III: Severe**
  - FEV₁/FVC < 0.50
  - 30% ≤ FEV₁ < 50% predicted
  - Add inhaled glucocorticosteroids if repeated exacerbations

- **IV: Very Severe**
  - FEV₁/FVC ≤ 0.30
  - FEV₁ ≤ 30% predicted or FEV₁ < 50% predicted plus chronic respiratory failure
  - Add long term oxygen if chronic respiratory failure. Consider surgical treatments

*Postbronchodilator FEV₁ is recommended for the diagnosis and assessment of severity of COPD.*

Treatment of acute exacerbation

Acute exacerbations of COPD substantially influence patient mortality and often drive the clinical course of the disease to a higher level of severity. Shortness of breath, the dominant symptom during an exacerbation, is related not only to severe airflow obstruction, but also to both static and dynamic hyperinflation that severely restricts the tidal volume of each breath. In addition to deterioration in respiratory mechanics, pulmonary gas exchange worsens, leading to hypoxemia with or without hypercapnia. Often, the need for supplemental oxygen is imperative, and in the most severe COPD patients, oxygen-induced hypercapnia can develop. An inhaled bronchodilator is the initial medication used because of the speed of onset of action and the minimal risk for severe adverse effects, compared with parenteral bronchodilator therapy. A variety of both inhaled beta₂-agonists and an anticholinergic therapy is used. There are no good data to indicate just how these inhaled bronchodilators should be used. The dose and the frequency of administration of these medications are empiric and selected by the attending physician. Many physicians use albuterol at doses of 2.5 to 5.0 mg by nebulization or 2 to 3 puffs or more by inhaler. The inhaler can be used every 3 to 4 hours and the nebulizer every 4 to 6 hours, but often even more frequent therapy is necessary. Ipratropium bromide 0.5 mg by nebulizer or inhaler is used in combination with albuterol. Continuous inhaled albuterol therapy is also used in many institutions. Frequency of use of these bronchodilators should decrease over 48 to 72 hours as the exacerbation slowly resolves. When using continuous bronchodilator therapy, it is important to monitor the patient for systemic toxicity, including severe tachycardia and other arrhythmias. Hypokalemia is not a particular problem in clinical practice, but induced glaucoma by anticholinergic therapy can occur if the mist of the nebulizer treatment or the spray from the inhaler enters the eyes of a susceptible patient. For years, intravenous aminophylline was used as a principal treatment for acute COPD exacerbation, but with the institution of safer inhaled bronchodilators, this medication is reserved for the most severe patients who are not responding to nebulized bronchodilator therapy. Aminophylline is a weak bronchodilator and has significant potential toxicity. Therefore, it is not commonly used. Parenteral corticosteroids are used in the acute management of COPD. Again, data on how to use these medications are scarce. It does appear that the use of
corticosteroid therapy reduces relapse, treatment failures, and accelerates the rate at which lung function improves and seems to reduce hospital length of stay when hospitalization is necessary.\textsuperscript{16,17} Corticosteroid dose, frequency of administration, and duration of treatment remain empiric and selected by the attending physician, similar to that of bronchodilator therapies. Inpatient corticosteroid therapy is generally handled differently than outpatient therapy. Corticosteroids are initially administered parenterally in the inpatient setting and orally in the outpatient setting. Methylprednisolone 30 to 40 mg every 6 to 8 hours intravenously is a common practice used in hospitalized patients, whereas a tapering daily dose of prednisone therapy 40 to 60 mg a day is used in the outpatient setting. After 1 or 2 days, the parenteral therapy for the inpatient is often switched to oral therapy using prednisone. In both groups, the duration of therapy is generally 7 to 14 days. The way in which daily dose tapering occurs is very physician-specific and generally based on no objective data published in the literature. Hyperglycemia is common in patients treated with corticosteroid therapy. For individuals treated for a prolonged period of time with corticosteroid therapy, one must be aware of the development of muscle weakness, especially if the patient is immobile.\textsuperscript{18} Antibiotic therapy is often used in patients with COPD exacerbation, especially if fever, chills, and purulent sputum are present and also if the patient has severe COPD with little physical reserve.\textsuperscript{19} The choice of treatment often focuses on local antibiotic sensitivities to the 2 predominant causes of bacterial bronchitis during a COPD exacerbation, namely, \textit{Haemophilus influenzae} and \textit{Streptococcus pneumoniae}.\textsuperscript{20} When employed, antibiotics are generally used for 5–7 days. It is important to remember that many individuals with COPD exacerbation do not have bacterial bronchitis and may derive no benefit from using antibiotic therapy. There is some evidence, however, that critically ill patients with COPD exacerbation who receive antibiotics have better outcomes.\textsuperscript{21} Viral infections likely play a significant role in COPD infections, not only as a primary infection, but also by altering the respiratory microbiome and allowing bacterial proliferation.

Table 3. Pharmacologic therapy for stable COPD*

<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>RECOMMENDED FIRST CHOICE</th>
<th>ALTERNATIVE CHOICE</th>
<th>OTHER POSSIBLE TREATMENTS**</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SA anticholinergic prn or SA beta,-agonist prn</td>
<td>LA anticholinergic or LA beta,-agonist or SA beta,-agonist and SA anticholinergic</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LA anticholinergic or LA beta,-agonist</td>
<td>LA anticholinergic and LA beta,-agonist or LA anticholinergic and PDE-4 inhibitor or LA beta,-agonist and PDE-4 inhibitor</td>
<td>SA beta,-agonist and/or SA anticholinergic or Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LA beta,-agonist or LA anticholinergic</td>
<td>LA anticholinergic and LA beta,-agonist or LA anticholinergic and PDE-4 inhibitor or LA beta,-agonist and PDE-4 inhibitor</td>
<td>SA beta,-agonist and/or SA anticholinergic or Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LA beta,-agonist and/or LA anticholinergic</td>
<td>ICS + LA beta,-agonist and LA anticholinergic or ICS + LA beta,-agonist and PDE-4 inhibitor or LA anticholinergic and LA beta,-agonist or LA anticholinergic and PDE-4 inhibitor</td>
<td>Carbocysteine</td>
</tr>
</tbody>
</table>

*Medications in each box are mentioned in alphabetical order and therefore not necessarily in order of preference.

**Medications in this column can be used alone or in combination with other options in the First and Alternative Choice columns


New therapies

Many therapies exist for COPD (Table 4). Several new therapies are now available or under development for use alone or in combination with other agents in the management of COPD. These new medications include once-daily long-acting beta,-agonists indacaterol, vilanterol, and olodaterol as well as long-acting...
muscarinic antagonists umeclidinium, aclidinium, and glycopyrronium. These agents are delivered through novel delivery systems and are dosed once daily. Combinations of once-daily, long-acting beta₂-agonists and long-acting muscarinic antagonists include vilanterol and umeclidinium, tiotropium and olodaterol, glycopyrronium and indacaterol, glycopyrronium and formoterol, and aclidinium and formoterol; the combinations of vilanterol and umeclidinium and of tiotropium and olodaterol are currently available to physicians in the United States. Also available is a once-daily, long-acting beta₂-agonist and an inhaled corticosteroid, fluticasone furoate and vilanterol. At this time, no triple once-daily formulation exists for use. Other novel agents are also being investigated, agents that target airway inflammation in COPD by inhibiting proinflammatory pathways and activating certain

**Figure 2. Combined assessment of COPD**


<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>CAT</th>
<th>mMRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>&lt; 10</td>
<td>0-1</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>≥ 10</td>
<td>≥ 2</td>
</tr>
<tr>
<td>C</td>
<td>High Risk</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>&lt; 10</td>
<td>0-1</td>
</tr>
<tr>
<td>D</td>
<td>High Risk</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>≥ 10</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>


### Table 4. COPD medications

#### BETA₂-AGONISTS

<table>
<thead>
<tr>
<th>Short-acting</th>
<th>Long-acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoterol</td>
<td>Formoterol</td>
</tr>
<tr>
<td>Levosalbuterol</td>
<td>Arformoterol</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Indacaterol</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Salmeterol</td>
</tr>
<tr>
<td></td>
<td>Tulobuterol</td>
</tr>
<tr>
<td></td>
<td>Olodaterol</td>
</tr>
</tbody>
</table>

#### ANTICHOLINERGICS

<table>
<thead>
<tr>
<th>Short-acting</th>
<th>Long-acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium bromide</td>
<td>Aclidinium bromide</td>
</tr>
<tr>
<td>Oxitropium bromide</td>
<td>Glycopyrronium bromide</td>
</tr>
</tbody>
</table>

#### COMBINATION

<table>
<thead>
<tr>
<th>Short-acting beta₂-agonist plus anticholinergic in one inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoterol/Ipratropium</td>
</tr>
<tr>
<td>Salbutamol/Ipratropium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-acting beta₂-agonist plus anticholinergic in one inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indacaterol/Glycopyrronium</td>
</tr>
<tr>
<td>Vilanterol/Umeclidinium</td>
</tr>
</tbody>
</table>

#### METHYLXANTHINES

- Aminophylline
- Theophylline (SR)

#### INHALED CORTICOSTEROIDS

- Beclomethasone
- Budesonide
- Fluticasone

#### COMBINATION

<table>
<thead>
<tr>
<th>Long-acting beta₂-agonist plus corticosteroid in one inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol/Budesonide</td>
</tr>
<tr>
<td>Formoterol/Mometasone</td>
</tr>
<tr>
<td>Salmeterol/Fluticasone</td>
</tr>
<tr>
<td>Vilanterol/Fluticasone furoate</td>
</tr>
</tbody>
</table>

#### SYSTEMIC CORTICOSTEROIDS

- Prednisone
- Methylprednisolone

#### PHOSPHODIESTERASE-4 INHIBITORS

- Roflumilast
Patients with COPD can benefit from certain vaccinations during the course of their illness. It is recommended that the influenza vaccine should be given to all patients with COPD on a yearly basis.

Intrinsic anti-inflammatory pathways, and even some that focus on lung regeneration and mucociliary actions.

Immunizations
Patients with COPD can benefit from certain vaccinations during the course of their illness. It is recommended that the influenza vaccine should be given to all patients with COPD on a yearly basis. Influenza vaccination is associated with a substantial reduction in the risk for hospitalization for pneumonia or influenza as well as for a reduction in the risk for death. On the other hand, there is less evidence for the role of the pneumococcal vaccine in preventing exacerbations. However, vaccination of all COPD patients with 23-valent pneumococcal polysaccharide vaccine is recommended by the Advisory Committee on Immunization Practices.

References

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