Chapter 79: Chronic Obstructive Pulmonary Disease

INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation that is not fully reversible. Two principal conditions (referred to as phenotypes) include:

  ✔ *Chronic bronchitis*: Chronic or recurrent excess mucus secretion with cough that occurs on most days for at least 3 months of the year for at least 2 consecutive years.

  ✔ *Emphysema*: Abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, without fibrosis.

PATHOPHYSIOLOGY

- The most common cause of COPD is exposure to tobacco smoke. Inhalation of noxious particles and gases activates neutrophils, macrophages, and $CD8^+$ lymphocytes, which release chemical mediators, including tumor necrosis factor-α, interleukin-8, and leukotriene B_4. Inflammatory cells and mediators lead to widespread destructive changes in airways, pulmonary vasculature, and lung parenchyma, resulting in chronic airflow limitation.

- Oxidative stress and imbalance between aggressive and protective defense systems in the lungs (proteases and antiproteases) may also occur. Oxidants generated by cigarette smoke react with and damage proteins and lipids, contributing to cell and tissue damage. Oxidants also promote inflammation and exacerbate protease–antiprotease imbalance by inhibiting antiprotease activity.

- The protective antiprotease α_1-antitrypsin (AAT) inhibits protease enzymes, including neutrophil elastase. AAT deficiency increases risk for premature emphysema.

- Inflammatory exudate in airways leads to increased number and size of goblet cells and mucus glands. Mucus secretion increases and ciliary motility is impaired. There is thickening of the smooth muscle and connective tissue in airways. Chronic inflammation leads to scarring, fibrosis, and airflow obstruction.

- Arterial blood gas (ABG) abnormalities result from impaired gas transfer due to parenchymal damage and loss of alveolar-capillary networks. Significant ABG changes are usually not present until airflow limitation is very severe. In such patients, *hypoxemia* (low arterial oxygen tension—Pao_2 45–60 mm Hg [6.0–8.0 kPa]) and *hypercapnia* (elevated arterial carbon dioxide tension—$Paco_2$ 50–60 mm Hg [6.7–8.0 kPa]) can become chronic problems. Hypoxemia is initially associated with exertion but develops at rest as the disease progresses. Hypoxemia results from hypoventilation (V) of lung tissue relative to perfusion (Q) of the area. This low V/Q ratio progresses over several years, resulting in a consistent decline in Pao_2. As gas exchange worsens with disease progression, patients may exhibit chronic hypercapnia and are referred to as CO_2 retainers. In such patients, central respiratory response to chronically increased $Paco_2$ is blunted. Serum pH is usually near normal because the kidneys compensate by retaining bicarbonate. If acute respiratory distress develops (eg, as with pneumonia or COPD exacerbation with respiratory failure) $Paco_2$ may rise sharply, resulting in worsening respiratory acidosis.

- Chronic hypoxemia and changes in pulmonary vasculature lead to increases in pulmonary pressures, especially during exercise. Sustained elevated pulmonary pressures can lead to right-sided heart failure (cor pulmonale) characterized by right ventricle hypertrophy in response to increased pulmonary vascular resistance.

- Chronic airflow obstruction leads to air trapping, resulting in thoracic hyperinflation and flattening of diaphragmatic muscles, making them less efficient muscles of ventilation and predisposing patients to muscle fatigue, especially during exacerbations. Patients with thoracic hyperinflation have increased functional residual capacity (FRC), which is the amount of air left in the lungs after exhalation. Increased FRC limits the amount of air the patient can inhale to fill the lungs and shortens the inhalation time, which may increase complaints of dyspnea.
- Loss of skeletal muscle mass and decline in overall health status can lead to ischemic cardiovascular events, cachexia, weight loss, osteoporosis, anemia, and muscle wasting.

CLINICAL PRESENTATION

- Initial symptoms include chronic cough and sputum production; patients may experience cough for several years before dyspnea develops. Dyspnea is worse with exercise and progressive over time, with decreased exercise tolerance or decline in physical activity. Chest tightness or wheezing may be present.
- Physical examination may be normal in milder stages. When airflow limitation progresses, patients may have shallow breathing, increased resting respiratory rate, “barrel chest” due to lung hyperinflation, pursed lips during expiration, use of accessory respiratory muscles, and cyanosis of mucosal membranes.

DIAGNOSIS

- Diagnosis is based on patient symptoms, history of exposure to risk factors such as tobacco smoke and occupational substances, and confirmation by pulmonary function testing, such as spirometry.
- Spirometry assesses lung volumes and capacities. Forced vital capacity (FVC) is the total volume of air exhaled after maximal inhalation, and FEV_1 is the total volume of air exhaled in 1 second. Postbronchodilator spirometry results should be used to assess lung function in patients with COPD. FEV_1 is measured 10–15 minutes after inhalation of a short-acting β_2-agonist or 30–45 minutes after a short-acting anticholinergic or a combination of the two agents. Airflow limitation is confirmed by a postbronchodilator FEV_1/FVC <70% (0.70).
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest a four-grade classification of airflow limitation based on the FEV_1/FVC <70% (0.70), measured FEV_1 compared to predicted FEV_1 (%), and presence of symptoms: (1) mild, (2) moderate, (3), severe, or (4) very severe.
- Recommended patient assessment questionnaires to assess dyspnea and other measures of health status include the COPD Assessment Test (CAT), modified Medical Research Council (mMRC) Dyspnea Questionnaire, and the COPD Control Questionnaire (CCQ).

TREATMENT

- Goals of Treatment: Prevent or slow disease progression, relieve symptoms, improve exercise tolerance, improve overall health status, prevent and treat exacerbations, prevent and treat complications, and reduce morbidity and mortality.

Nonpharmacologic Therapy

- Educate patients about their disease, treatment plans, and strategies to slow progression and prevent complications.
- Smoking cessation is the most important intervention to prevent development and progression of COPD. Reducing exposure to occupational dust and fumes as well as other environmental toxins is also important.
- Pulmonary rehabilitation programs include exercise training, breathing exercises, optimal medical treatment, psychosocial support, and health education.
- Administer the influenza vaccine annually during each influenza season. The CDC recommends giving the 23-valent pneumococcal polysaccharide

vaccine (PPSV23) for people from ages 2 to 64 who have chronic lung disease, smokers over the age of 18, and all people older than 65 years. The GOLD guidelines recommend the pneumococcal vaccine for COPD patients age ≥65 years of age and for patients <65 years old with comorbidities or FEV_1 <40% predicted.

- Once patients are stabilized as outpatients and pharmacotherapy is optimized, institute long-term oxygen therapy if either of the following conditions is documented twice in a 3-week period: (1) resting Pao_2 <5 mm Hg (7.3 kPa) or Sao_2 <88% (0.88) with or without hypercapnia, or (2) resting Pao_2 55–60 mm Hg (7.3–8.0 kPa) or Sao_2 <88% (0.88) with evidence of right-sided heart failure, polycythemia, or pulmonary hypertension. Oxygen can be delivered by nasal cannula at 1–2 L/min, providing 24%–28% (0.24–0.28) fraction of inspired oxygen (FiO_2) with a goal to raise Pao_2 above 60 mm Hg (8.0 kPa).

Pharmacologic Therapy

- No COPD medication has been conclusively shown to slow lung function decline or prolong survival. The GOLD guidelines recommend that a combined "ABCD" classification system based on symptom severity and risk of future exacerbations be used as a stepwise approach to pharmacotherapy rather than FEV_1 measurements (**Table 79-1**). Symptom assessment should be measured at baseline and then during routine visits using CAT or mMRC. Defined cut points for patients exhibiting "more symptoms" and "less symptoms" have been established for CAT and mMRC. Frequency of exacerbations is assessed by reviewing exacerbation history for the past 12 months. Patients are assigned to an ABCD category based on these two assessments. Patients with at least two exacerbations in the last 12 months, or one exacerbation requiring hospitalization, are considered high risk for future exacerbations (category C or D). Guidelines recommend that initial and escalation therapy be based on ABCD category classification.

- Bronchodilators are the mainstay of drug therapy; classes include short- and long-acting β_2-agonists, short- and long-acting muscarinic antagonists (anticholinergics), and methylxanthines. Short-acting inhaled bronchodilators relieve symptoms (eg, dyspnea) and increase exercise tolerance. Long-acting inhaled bronchodilators relieve symptoms, reduce exacerbation frequency, and improve quality of life and health status. Bronchodilators do not significantly improve measurements of expiratory airflow such as FEV_1.

TABLE 79-1

Recommended Initial and Escalation Pharmacotherapy for Stable COPD

Patient Category	Initial Therapy	Escalation Therapy
A (less symptoms, less exacerbation risk)	Offer either short- or long-acting bronchodilator, depending on symptoms	Continue therapy if beneficial or if re-education needed Stop therapy if intolerable adverse effects and switch to alternate class for symptom control Combine bronchodilator classes for additional symptom control If patient experiences exacerbations, reassess goals (ie, low vs. high risk for exacerbation) and follow escalation therapy as outlined in category C
B (more symptoms, less exacerbation risk)	Start LAMA or LABA for symptom control	Continue therapy if beneficial or if re-education needed Add long-acting bronchodilator if persistent symptoms on monotherapy (LAMA/LABA) If dual bronchodilators do not improve symptoms, consider stepping back to monotherapy AFTER assessing adherence and inhaler technique If patient experiences exacerbations, reassess goals (ie, low vs. high risk for exacerbation) and follow escalation therapy as outlined in category C
C (less symptoms, more exacerbation risk)	Start long-acting bronchodilator for exacerbation prevention; LAMA is preferred over LABA for initial therapy	Continue therapy if beneficial or if re-education needed Add long-acting bronchodilator if persistent symptoms on monotherapy (LAMA/LABA) If persistent exacerbations on long-acting bronchodilator monotherapy and eosinophil count <300/µL (0.3×10^9/L), add additional long-acting bronchodilator (LAMA/LABA); dual bronchodilators are preferred due to better efficacy and lower risk of pneumonia If persistent exacerbations on long-acting bronchodilator monotherapy and eosinophil count ≥300/µL (0.3×10^9/L), consider starting ICS/LABA instead of LAMA/LABA If persistent exacerbations on dual LAMA/LABA and eosinophil count ≥100/µL (0.1×10^9/L), consider adding ICS If persistent exacerbations on dual LAMA/LABA and eosinophil count <100/µL (0.1×10^9/L), consider roflumilast for patients with FEV_1 <50% (0.50) or azithromycin daily (nonsmokers or former smokers only) If persistent exacerbations on triple therapy (LAMA/LABA/ICS), consider roflumilast for patients with FEV_1<50% (0.50) or azithromycin daily (nonsmokers or former smokers only) If recurrent exacerbations or pneumonia, consider withdrawal of ICS over 12 weeks
D (more symptoms, more exacerbation risk)	Start long-acting bronchodilator for exacerbation prevention; LAMA is preferred over LABA for initial therapy If highly symptomatic (ie, CAT >20), consider dual long-acting bronchodilators (LAMA/LABA) If blood eosinophil count ≥300/µL (0.3×10^9/L), consider starting ICS/LABA instead of LAMA/LABA	Continue therapy if beneficial or if re-education needed If persistent exacerbations, follow escalation therapy as outlined in category C If recurrent exacerbations or pneumonia, consider withdrawal of ICS over 12 weeks

CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council questionnaire; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist.

Short-Acting Bronchodilators

- Either a short- or long-acting bronchodilator is recommended initially for patients with occasional symptoms (**Table 79-1**, category A). Short-acting bronchodilators are also recommended for all patients (categories A–D) as rescue or as-needed therapy to manage symptoms. Choices among short-acting bronchodilators include short-acting β_2-agonists (SABAs) or short-acting muscarinic antagonists (SAMAs). Both drug classes have a relatively rapid onset of action, relieve symptoms to a similar degree, and improve exercise tolerance and lung function. Short-acting bronchodilators do not reduce the frequency or severity of COPD exacerbations. If a patient does not achieve adequate symptom control with one agent, combining a SABA with a SAMA is reasonable.

- **Short-acting β_2-agonists (SABAs)** stimulate adenyl cyclase to increase formation of cyclic adenosine monophosphate (cAMP), which mediates relaxation of bronchial smooth muscle. They may also improve mucociliary clearance. SABAs have a rapid onset of effect; they cause only a small improvement in FEV_1 acutely but may still improve symptoms and exercise tolerance. The SABA choices include **albuterol** and **levalbuterol** (**Table 79-2**). Albuterol is most frequently used and is a racemic mixture of (R)-albuterol (responsible for bronchodilation) and (S)-albuterol (which has no therapeutic effect). Levalbuterol is a single-isomer formulation of (R)-albuterol that offers no clear efficacy or safety advantages over albuterol, and it is more expensive. Inhalation is the preferred route for SABAs, and administration via metered-dose or dry powder inhalers (MDIs, DPIs) is at least as effective as nebulization therapy and is more convenient and less costly. Inhaled SABAs are generally well tolerated; they can cause sinus tachycardia and rhythm disturbances rarely in predisposed patients. Skeletal muscle tremors can occur initially but generally subside as tolerance develops. Older patients may be more sensitive and experience palpitations, tremors, and "jittery" feelings.

- **Short-acting muscarinic antagonists (SAMAs)** produce bronchodilation by inhibiting muscarinic receptor subtypes M_1, M_2, and M_3 in bronchial smooth muscle and mucus glands. This blocks acetylcholine, reducing cyclic guanosine monophosphate (cGMP), which normally acts to constrict bronchial smooth muscle, and decreasing mucus secretion. **Ipratropium bromide** is the most commonly prescribed SAMA in the United States (**Table 79-2**). Improvements in pulmonary function are similar to inhaled SABAs, although ipratropium has a slower onset of action (15–20 minutes vs. 5 minutes for albuterol) and more prolonged effect. Because of its slower onset, ipratropium may be less suitable for as-needed use but is often prescribed in this manner. In contrast to albuterol, patients may experience additional symptom improvement with a larger number of inhalations (eg, 6 puffs every 6 hours, maximum 24 puffs/day), whereas no additional improvement occurs with more frequent use than every 6 hours. The most frequent patient complaints are dry mouth, nausea, and occasionally metallic taste. Because it is poorly absorbed systemically, anticholinergic side effects are uncommon (eg, blurred vision, constipation, urinary retention, nausea, and tachycardia). Inhaled anticholinergics may rarely precipitate narrow-angle glaucoma symptoms.

TABLE 79-2

Select Medications Used for Treatment of COPD[a]

Generic (Brand) Name	Dosage Form	Dosage Frequency[b]
Short-acting β_2-agonists		
Albuterol sulfate (Proventil HFA, Ventolin HFA, Proair HFA)	MDI	Every 4–6 hrs PRN
Albuterol sulfate (Proair RespiClick)	DPI	Every 4–6 hrs PRN
Levalbuterol hydrochloride (Xopenex, generic)	NEB solution	Every 6–8 hrs PRN
Levalbuterol tartrate (Xopenex HFA)	MDI	Every 4–6 hrs PRN

Short-acting muscarinic antagonists (SAMAs)		
Ipratropium bromide (Atrovent HFA)	MDI	4 times/day PRN
Ipratropium bromide (generic)	NEB solution	3–4 times/day PRN
Long-acting β_2-agonists (LABAs)		
Arformoterol tartrate (Brovana)	NEB solution	Every 12 hrs
Formoterol fumarate (Perforomist)	NEB solution	Every 12 hrs
Indacaterol maleate (Arcapta Neohaler)	DPI	Once daily
Olodaterol hydrochloride (Striverdi Respimat)	SMI	Once daily
Salmeterol xinafoate (Serevent Diskus)	DPI	Twice daily
Long-acting muscarinic antagonists (LAMAs)		
Aclidinium bromide (Tudorza Pressair)	DPI	Twice daily
Tiotropium bromide (Spiriva Respimat)	SMI	Once daily
Tiotropium bromide (Spiriva Handihaler)	DPI	Once daily
Glycopyrrolate (Lonhala Magnair)	NEB solution	Twice daily
Glycopyrrolate (Seebri Neohaler)	DPI	Twice daily
Umeclidinium bromide (Incruse Ellipta)	DPI	Once daily
Inhaled corticosteroids		
Beclomethasone dipropionate (Qvar 40, 80)	MDI	Twice daily
Budesonide (Pulmicort Flexhaler)	DPI	Twice daily
Flunisolide (Aerospan HFA)	MDI	Twice daily
Fluticasone propionate (Flovent HFA)	MDI	Twice daily
Mometasone furoate (Asmanex Twisthaler)	DPI	Twice daily
Combination inhalers		
SABA/SAMA: albuterol sulfate + ipratropium bromide (Duoneb, generic)	NEB solution	4–6 times/day PRN
SABA/SAMA: albuterol sulfate + ipratropium bromide (Combivent Respimat)	SMI	4–6 times/day PRN
LAMA/LABA: umeclidinium bromide + vilanterol trifenatate (Anoro Ellipta)	DPI	Once daily

LAMA/LABA: tiotropium bromide + olodaterol hydrochloride (Stiolto Respimat)	SMI	Once daily
LAMA/LABA: glycopyrrolate + indacaterol maleate (Utibron Neohaler)	DPI	Twice daily
LAMA/LABA: glycopyrrolate + formoterol fumarate (Bevespi Aerosphere)	MDI	Twice daily
ICS/LABA: budesonide + formoterol fumarate dehydrate (Symbicort)	MDI	Twice daily
ICS/LABA: fluticasone furoate + vilanterol trifenatate (Breo Ellipta)	DPI	Once daily
ICS/LABA: fluticasone propionate + salmeterol xinafoate (Advair Diskus, Airduo RespiClick)	DPI	Twice daily
ICS/LABA: fluticasone propionate + salmeterol xinafoate (Advair HFA)	MDI	Twice daily
ICS/LABA: mometasone furoate + formoterol fumarate (Dulera)	MDI	Twice daily
ICS/LAMA/LABA: fluticasone furoate + umeclidinium bromide +vilanterol trifenatate (Trelegy Ellipta)	DPI	Once daily
Oral medications		
Roflumilast (Daliresp)	Oral tablets	Once daily
Theophylline (Theo-24, generic)	Oral tablets, capsules	Once or twice daily (extended release)

[a]Not all medications are FDA-approved for treatment of COPD.

[b]Consult official product labeling or the medical literature for dosages used for COPD treatment.

DPI, dry power inhaler; hrs, hours; ICS, inhaled corticosteroid; inh, inhalations; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler; NEB, nebulized; PRN, as needed; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SMI, soft mist inhaler.

Long-Acting Bronchodilators

- Long-acting bronchodilators are recommended for patients with persistent symptoms or in whom short-acting therapies do not provide adequate relief (**Table 79-1**, category B). Long-acting agents are also recommended for patients at high risk for exacerbation (categories C and D). Therapy can be administered as an inhaled long-acting β_2-agonist (LABA) or muscarinic antagonist (LAMA). Compared with short-acting agents, long-acting bronchodilators are more convenient for patients with persistent symptoms and are superior in improving lung function, relieving symptoms, reducing exacerbation frequency and need for hospitalization, and improving quality of life. LABAs and LAMAs are equally effective in managing symptoms, but LAMAs are more effective for preventing exacerbations and should be considered first-line monotherapy for patients at high risk for exacerbation. Treatment selection should consider individual patient response, tolerability, adherence, and economic factors.
- The available LABAs differ primarily by dosing frequency and device type (**Table 79-2**). **Arformoterol**, **formoterol**, **indacaterol**, and **olodaterol** have an onset of action similar to albuterol (<5 minutes), whereas **salmeterol** has a slower onset (15–20 minutes); however, none of these agents are recommended for acute relief of COPD symptoms. **Vilanterol** is available in the United States only in combination with an inhaled corticosteroid (fluticasone) or LAMA (umeclidinium). There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

- The available LAMAs differ in dosing frequency and device type (**Table 79-2**). They are more selective than ipratropium at blocking muscarinic receptors and dissociate slowly from M_3 receptors, resulting in prolonged bronchodilation. **Aclidinium**, **glycopyrrolate**, and **umeclidinium** have a faster onset of action (5–15 minutes) than **tiotropium** (80 minutes); however, none of these agents are recommended for acute relief of symptoms. There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

Combination Muscarinic Antagonists and β_2-Agonists

- Combination bronchodilator regimens are often used as symptoms worsen over time. Combining bronchodilators with different mechanisms of action allows use of the lowest possible effective doses and reduces potential adverse effects from individual agents. Short-acting bronchodilators may be combined for patients experiencing persistent symptoms, although step-up to long-acting bronchodilator monotherapy is usually preferred (**Table 79-1**).
- Guidelines recommend combining long-acting bronchodilators (LAMA/LABA) for patients who have persistent symptoms or recurrent exacerbations on bronchodilator monotherapy. The combination provides significant improvement in lung function, symptoms, and quality-of-life measures compared with LABA or LAMA monotherapy. In addition, dual long-acting bronchodilator therapy decreases the frequency of moderate-to-severe exacerbations compared to either LAMA or LABA monotherapy.

Methylxanthines

- **Theophylline** and **aminophylline** may produce bronchodilation by several mechanisms, including inhibition of phosphodiesterase, thereby increasing cAMP levels.
- Chronic theophylline use in COPD may improve lung function and gas exchange. Subjectively, theophylline reduces dyspnea, increases exercise tolerance, and improves respiratory drive.
- Methylxanthines have a limited role in COPD therapy because of the availability of LABAs and LAMAs as well as significant methylxanthine drug interactions and interpatient variability in dosage requirements. Theophylline may be considered in patients intolerant of or unable to use inhaled bronchodilators.
- Sustained-release theophylline preparations are most appropriate for long-term COPD management; they improve adherence and achieve more consistent serum concentrations than rapid-release products. Caution should be used in switching from one sustained-release preparation to another because of variability in sustained-release characteristics.
- Initiate theophylline therapy with 200 mg twice daily and titrate upward every 3–5 days to the target dose; most patients require 400–900 mg daily. Make dose adjustments based on trough serum concentrations. A therapeutic range of 8–15 mcg/mL (44–83 µmol/L) is targeted to minimize risk of toxicity. Once a dose is established, monitor concentrations once or twice a year unless the disease worsens, medications that interfere with theophylline metabolism are added, or toxicity is suspected.
- Common theophylline side effects include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. Arrhythmias and seizures may occur, especially at toxic concentrations.
- Factors that decrease theophylline clearance and lead to reduced dosage requirements include advanced age, bacterial or viral pneumonia, heart failure, liver dysfunction, hypoxemia from acute decompensation, and drugs such as cimetidine, macrolides, and fluoroquinolone antibiotics.
- Factors that may enhance theophylline clearance and result in need for higher doses include tobacco and marijuana smoking, hyperthyroidism, and drugs such as phenytoin, phenobarbital, and rifampin.

Corticosteroids

- Anti-inflammatory mechanisms of corticosteroids in COPD include reducing capillary permeability to decrease mucus, inhibiting release of proteolytic enzymes from leukocytes, and inhibiting prostaglandins.
- The recommended role of inhaled corticosteroid (ICS) therapy is for patients at high risk of exacerbation (**Table 79-1**, categories C and D) who

have recurrent exacerbations despite optimal therapy with inhaled bronchodilators. In order to best target therapy, consensus guidelines propose using blood eosinophil counts to identify patients with COPD who might benefit from chronic ICS treatment.

- The clinical benefits of ICS therapy (including decreased exacerbation frequency and improved lung function and health status) have been observed with combination therapy, primarily as an addition to LABA monotherapy. Given lack of supporting evidence, ICS monotherapy is not recommended for patients with COPD.
- For patients with recurrent exacerbations despite optimal long-acting bronchodilator monotherapy, combination therapy with dual long-acting bronchodilators (LAMA/LABA) is preferred over combination therapy with ICS/LABA (**Table 79-1**). Dual therapy with ICS/LABA may be considered instead of LAMA/LABA for patients with blood eosinophil counts ≥300 cells/μL (0.3×10^9/L).
- For patients with persistent symptoms and recurrent exacerbations on dual inhaled therapy, triple therapy with LAMA/LABA/ICS is recommended as initial escalation therapy (**Table 79-1**). Given the risk of adverse ICS effects, some clinicians avoid triple inhalation therapy for patients with persistent exacerbations and lower blood eosinophil counts (<100 cells/μL [0.1×10^9/L]) in favor of oral alternatives such as roflumilast or azithromycin.
- Short-term systemic corticosteroids may also be considered for acute exacerbations. Chronic systemic corticosteroids should be avoided in COPD because of questionable benefits and high risk of toxicity.
- The moderate-to-high ICS doses used in clinical trials of COPD have been associated with an increased risk of pneumonia and mycobacterial pulmonary infections. Other adverse effects include hoarseness, sore throat, oral candidiasis, and skin bruising. Severe side effects such as adrenal suppression, osteoporosis, and cataract formation occur less frequently than with systemic corticosteroids, but clinicians should monitor patients receiving high-dose chronic inhaled therapy. Treat patients with the lowest effective ICS dose to minimize risk of fracture.

Roflumilast

- **Roflumilast** is a phosphodiesterase 4 (PDE4) inhibitor that relaxes airway smooth muscle and decreases activity of inflammatory cells and mediators such as TNF-α and IL-8. Roflumilast is recommended for patients with recurrent exacerbations despite treatment with triple inhalation therapy (LAMA/LABA/ICS; **Table 79-1**). It may also be considered as escalation therapy for patients with recurrent exacerbations on dual long-acting bronchodilators (LAMA/LABA) who are not candidates for ICS, such as those with low blood eosinophil count (<100 cells/μL [0.1×10^9/L]) or who are at higher risk of adverse effects associated with ICS. Because theophylline and roflumilast have similar mechanisms of action, they should not be used together.
- Major adverse effects include diarrhea, nausea, decreased appetite, weight loss, headache and neuropsychiatric effects such as suicidal thoughts, insomnia, anxiety, and new or worsened depression. Although most symptoms usually resolve over time, a low starting dose (250 mcg orally once daily) is recommended for the first 4 weeks before increasing to the maintenance dose (500 mcg once daily). Caution is advised in patients with a history of depression or suicidality.
- Roflumilast is metabolized by CYP3A4 and 1A2; coadministration with strong CYP P450 inducers is not recommended due to potential for subtherapeutic plasma concentrations. Use caution when administering roflumilast with strong CYP P450 inhibitors due to potential for adverse effects.

Azithromycin

- Chronic **azithromycin** was associated with a lower rate of COPD exacerbation and improved quality-of-life scores in one study, but more patients in the azithromycin group reported hearing deficits (25% vs. 20% in the placebo group), and patients who continued to smoke did not achieve reduction in exacerbation frequency with azithromycin. Azithromycin was also associated with a higher rate of colonization with macrolide-resistant bacteria. In addition, the azithromycin product labeling includes a precaution about QT prolongation after a retrospective study reported increased cardiac events with short courses of azithromycin.
- Based on limited evidence supporting long-term treatment (beyond 1 year), current guidelines recommend to consider adding chronic azithromycin only for patients with recurrent exacerbations despite optimal therapy and who are not active smokers (**Table 79-1**). Clinicians may

consider azithromycin for individual patients at high risk for exacerbations but must carefully weigh the risks and benefits of therapy.

α1-Antitrypsin Replacement Therapy

- For patients with inherited AAT deficiency-associated emphysema, treatment focuses on reduction of risk factors such as smoking, symptomatic treatment with bronchodilators, and augmentation therapy with replacement AAT.
- Several proprietary **alpha$_1$-proteinase inhibitors** are available: Glassia, Prolastin-C, Aralast, Aralast-NP, and Zemaira. Augmentation therapy is intended to maintain serum concentrations above the protective threshold of 10 µmol/L throughout the dosing interval. The recommended dosing regimen is 60 mg/kg IV given once weekly, usually at a rate of 0.08 mL/kg/min (consult individual product labeling), adjusted to patient tolerance. Augmentation therapy can cost over $50,000 annually.

COPD EXACERBATIONS

- A COPD exacerbation is defined as a change in the patient's baseline symptoms (dyspnea, cough, or sputum production) beyond day-to-day variability sufficient to warrant a change in management.
- The primary physiologic change is often a worsening of ABG values due to poor gas exchange and increased muscle fatigue. With severe exacerbations, profound hypoxemia and hypercapnia can be accompanied by respiratory acidosis and respiratory failure.
- Although criteria used to define acute exacerbations vary, most rely on a change in one or more of the following clinical findings: worsening dyspnea, increased sputum volume, or increased sputum purulence (**Table 79-3**).
- Additional symptoms may include chest tightness, increased need for bronchodilators, malaise, fatigue, and decreased exercise tolerance. Physical exam may reveal fever, wheezing, and decreased breath sounds. Obtain a sputum sample for Gram stain and culture and a chest x-ray to evaluate for new infiltrates.
- The diagnosis of acute respiratory failure is made based on an acute change in ABGs: an acute drop in Pao_2 of 10–15 mm Hg (1.3–2.0 kPa) or any acute increase in $Paco_2$ that decreases the serum pH to 7.3 or less. Additional indications of respiratory failure include restlessness, confusion, tachycardia, diaphoresis, cyanosis, hypotension, irregular breathing, miosis, and unconsciousness.
- Goals of Treatment: (1) Minimize the negative consequences of the acute exacerbation (ie, reduce symptoms, prevent hospitalization, shorten hospital stay, prevent acute respiratory failure or death) and (2) prevent future exacerbations.

TABLE 79-3

Staging Acute Exacerbations of COPD

Mild (type 1)	One cardinal symptom[a] plus at least one of the following: upper respiratory tract infection within 5 days, fever without other explanation, increased wheezing, increased cough, increase in respiratory or heart rate >20% above baseline
Moderate (type 2)	Two cardinal symptoms
Severe (type 3)	Three cardinal symptoms

[a]Cardinal symptoms include worsening of dyspnea, increase in sputum volume, and increase in sputum purulence.

Nonpharmacologic Therapy

- Provide oxygen therapy for patients with significant hypoxemia (eg, oxygen saturation <90% [0.90]). Use caution because many COPD patients rely on mild hypoxemia to trigger their drive to breathe. Overly aggressive oxygen administration to patients with chronic hypercapnia may result in respiratory depression and respiratory failure. Adjust oxygen to achieve Pao_2 >60 mm Hg (8.0 kPa) or oxygen saturation (Sao_2) >90% (0.90). Obtain ABG after oxygen initiation to monitor CO_2 retention resulting from hypoventilation.

- Noninvasive positive-pressure ventilation (NPPV) provides ventilatory support with oxygen and pressurized airflow using a face or nasal mask without endotracheal intubation. NPPV is not appropriate for patients with altered mental status, severe acidosis, respiratory arrest, or cardiovascular instability. Intubation and mechanical ventilation may be needed in patients failing NPPV or who are poor candidates for NPPV.

Pharmacologic Therapy

Bronchodilators

- Dose and frequency of bronchodilators are increased during acute exacerbations to provide symptomatic relief. SABAs are preferred because of rapid onset of action. Muscarinic antagonists may be added if symptoms persist despite increased doses of β_2-agonists. LABAs or LAMAs should not be used for quick relief of symptoms or on an as-needed basis.

- Bronchodilators may be administered via MDI, DPI, or nebulization with equal efficacy. Nebulization may be considered for patients with severe dyspnea who are unable to hold their breath after actuation of an MDI.

- Theophylline should generally be avoided due to lack of evidence documenting benefit and the concern for adverse effects.

Corticosteroids

- Treatment with systemic corticosteroids in acute exacerbations improves oxygenation and recovery time, shortens hospitalization, and reduces risk of relapse.

- Although the optimal corticosteroid dose and duration are unknown, prednisone 40 mg orally daily (or equivalent) for 5 days is effective for many patients. If treatment is continued for longer than 2 weeks, employ a tapering oral schedule to avoid hypothalamic–pituitary–adrenal axis suppression.

Antimicrobial Therapy

- In order to limit unnecessary use, antibiotics should be initiated in any of these clinical situations: (1) patients presenting with three cardinal symptoms of acute exacerbation, (2) patients presenting with two cardinal symptoms as long as one is increased sputum purulence, and (3) patients requiring mechanical ventilation regardless of symptoms. Utility of sputum Gram stain and culture is questionable because some patients have chronic bacterial colonization of the bronchial tree between exacerbations. Use of C-reactive protein (CRP) as a biomarker to guide antimicrobial therapy decisions may be reasonable.

- Selection of empiric antimicrobial therapy should be based on the most likely organisms: *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*. Drug-resistant pneumococci, β-lactamase–producing *H. influenzae* and *M. catarrhalis*, and enteric gram-negative organisms, including *Pseudomonas aeruginosa*, may be present in complicated acute exacerbations.

- **Table 79-4** summarizes the most common organisms based on patient presentation and recommended antimicrobial therapy. Continue antimicrobial therapy for at least 5–7 days. If the patient deteriorates or does not improve as anticipated, hospitalization may be necessary, and more aggressive attempts should be made to identify potential pathogens responsible for the exacerbation.

TABLE 79-4

Recommended Antimicrobial Therapy for Acute Exacerbations of COPD

Patient Characteristics	Likely Pathogens	Recommended Therapy
Uncomplicated exacerbations (<4 exacerbations per year, no comorbid illness)	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *H. parainfluenzae* Resistance uncommon	Macrolide (azithromycin, clarithromycin) Second- or third-generation cephalosporin Doxycycline Therapies not recommended[a]: TMP/SMX, amoxicillin, first-generation cephalosporins, erythromycin
Complicated exacerbations (Age ≥65 and >4 exacerbations per year, presence of comorbid illness)	As above plus drug-resistant pneumococci, β-lactamase–producing *H. influenzae* and *M. catarrhalis*	Amoxicillin/Clavulanate Fluoroquinolone with enhanced pneumococcal activity (levofloxacin, gemifloxacin, moxifloxacin)
Presence of risk factors for colonization and infection with multi-drug resistant pathogens: ✔ Need for chronic corticosteroid therapy ✔ Recent hospitalization (90 days) ✔ Recent antibiotic therapy (90 days) ✔ Resident of long-term care facility	Some enteric gram-negatives As above plus *P. aeruginosa*	Fluoroquinolone with enhanced pneumococcal and *P. aeruginosa* activity (levofloxacin) IV therapy if required: β-lactamase–resistant penicillin with antipseudomonal activity, third- or fourth-generation cephalosporin with antipseudomonal activity

[a]TMP/SMX should not be used due to increasing pneumococcal resistance; amoxicillin and first-generation cephalosporins are not recommended due to β-lactamase susceptibility; and erythromycin is not recommended due to insufficient activity against *H. influenzae.*

TMP-SMX, trimethoprim-sulfamethoxazole.

EVALUATION OF THERAPEUTIC OUTCOMES

- In chronic stable COPD, assess pulmonary function tests annually and with any treatment additions or discontinuations. Other outcome measures are symptom scores, quality-of-life assessments, exacerbation rates, emergency department visits, and hospitalizations.
- In acute exacerbations of COPD, assess white blood cell count, vital signs, chest x-ray, and changes in frequency of dyspnea, sputum volume, and sputum purulence at the onset and throughout treatment of the exacerbation. In more severe exacerbations, ABG and Sao_2 should also be monitored.
- Evaluate patient medication adherence, side effects, and potential drug interactions at every encounter.

See Chapter 44, Chronic Obstructive Pulmonary Disease, authored by Sharya V. Bourdet and Dennis M. Williams, for a more detailed discussion of this topic.