CHRONIC OBSTRUCTIVE PULMONARY DISEASE {COPD}

BY

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- **COPD is a chronic inflammatory disease with systemic manifestations that affect airways leading to an IRREVERSIBLE airway obstruction.**

Causes:

- **The most commonly associated noxious agent is cigarette smoke, and cigarette smoking is the single largest risk factor for COPD.. Second hand smoke is a recognized risk factor.**
- **Environmental and occupational air pollutants.**
- **Deficiency of alpha-1-antitrypsin is a treatable cause of abnormal inflammatory response; it can be an important etiologic factor in early onset and severe disease.**

- **Chronic obstructive pulmonary disease (COPD)** is characterized by **progressive airflow limitation that is not fully reversible**. It include **two** principal conditions:

- **A-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**.
- **B-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 inflammatory cells to release inflammatory mediators**. Inflammatory cells and mediators lead to widespread **destructive changes in airways resulting in chronic airflow limitation.**
- **Oxidative stress** and **imbalance between aggressive and protective** defense systems in the lungs (**proteases and antiproteases**) may also occur.

- **If acute respiratory distress develops** (eg, as with pneumonia or COPD exacerbation with respiratory failure) Paco2 may rise sharply, resulting in worsening respiratory acidosis.

- Chronic hypoxemia and changes in pulmonary vasculature lead to increases in pulmonary pressures. **Sustained elevated pulmonary pressures can lead to right-sided heart failure (cor pulmonale)**

- The protective antiprotease **α1-antitrypsin** (AAT) inhibits protease enzymes. AAT deficiency increases risk for premature emphysema.

- **Mucus secretion increases and ciliary motility is impaired**.
- **Arterial blood gas (ABG) abnormalities** result from impaired gas exchange when airflow limitation is very severe. In such patients, **hypoxemia** (low arterial oxygen tension—PaO2) and **hypercapnia** (elevated arterial carbon dioxide tension—Paco2) can become chronic problems.

- Chronic airflow obstruction leads to air trapping, resulting in **thoracic hyperinflation**.
- 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**
- **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.
- When airflow limitation progresses,**shallow breathing**, increased **resting respiratory rate**, **"barrel chest" due to lung hyperinflation**, **pursed lips during expiratio**n, 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**. (**FVC**) and **FEV1**
- **Postbronchodilator spirometry results is confirmed by a postbronchodilator FEV1/FVC <70% (0.70).**
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest a four-grade classif (1) **mild**, (2) **moderate**, (3), **severe**, or (4) **very severe.**

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
- reduce morbidity and mortality.

Nonpharmacologic Therapy

- **Smoking cessation**
- **Reducing exposure to occupational dust and fumes**
- **Pulmonary rehabilitation programs** include exercise training, breathing exercises, and psychosocial support.
- Administer the **influenza vaccine annually** during each influenza season. The CDC recommends giving the **pneumococcal vaccine** 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 FEV1 <40% predicted.**

- **long-term oxygen therapy if either of the following conditions is documented twice in a 3-week period:**
  - (resting PaO2 <5 mm Hg or **SaO2 <88% with or without hypercapnia**.
  - (resting PaO2 55–60 mm Hg or **SaO2 <88% (0.88) with evidence of right-sided heart failure, polycythemia, or pulmonary hypertension**

Pharmacologic Therapy

- The GOLD guidelines recommend that "**ABCD**" classification system based on **symptom severity and risk of future exacerbations be used as a stepwise approach to pharmacotherapy** rather than FEV1 measurements

- 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).**

- **Bronchodilators are the mainstay of drug therapy**; classes include :
- short- and long-acting **β2-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.**

CLASS A

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

CLASS B

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

CLASS 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 $<300/\mu L$ ($0.3 \times 10^9/L$), 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 $\geq 300/\mu L$ ($0.3 \times 10^9/L$), consider starting ICS/LABA instead of LAMA/LABA If persistent exacerbations on dual LAMA/LABA and eosinophil count $\geq 100/\mu L$ ($0.1 \times 10^9/L$), consider adding ICS If persistent exacerbations on dual LAMA/LABA and eosinophil count $<100/\mu L$ ($0.1 \times 10^9/L$), consider roflumilast for patients with FEV_1 <50% (0.50) or azithromycin daily (nonsmokers or former smokers only)

CLASS D

		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

Short-Acting Bronchodilators

- 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 β2-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.**
- The SABA choices include albuterol and levalbuterol. **Albuterol** (Salbutamol) 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 .

- **Inhaled SABAs are generally well tolerated**; **they can cause** sinus tachycardia
- Older patients may be more sensitive and experience palpitations, tremors, and “jittery” feelings.
- **Ipratropium bromide**. 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.**
- 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

Long-Acting Bronchodilators

- Long-acting bronchodilators are recommended for patients with persistent symptoms or in **whom short-acting therapies do not provide adequate relief** (**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 β2-agonist (LABA**) or **muscarinic antagonist (LAMA).**
- There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

- 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.**
- The available LABAs: 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.**
- The available LAMAs :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.

Combination Muscarinic Antagonists and β2-Agonists

- **Short-acting bronchodilators may be combined** for patients experiencing persistent symptoms, although step-up to long-acting bronchodilator monotherapy is usually preferred.

- 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 compared with LABA or LAMA monotherapy.**

Methylxanthines (Theophylline and aminophylline)

- 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.

- **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, hyperthyroidism,drugs such as phenytoin, phenobarbital, and rifampin.

Corticosteroids

- inhaled corticosteroid (ICS) therapy is for patients at high risk of exacerbation (**Categories C and D**) **who have recurrent exacerbations despite optimal therapy with inhaled bronchodilators.**
- 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. **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.**
- 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.
- Given the risk of adverse ICS effects, some clinicians avoid triple inhalation therapy for patients with persistent exacerbations and **lower blood eosinophil counts [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 use of ICS s 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.
- Roflumilast is recommended for patients with recurrent exacerbations **despite treatment with triple inhalation therapy (LAMA/LABA/ICS).**
- 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 × 109/L]) or who are at higher risk of adverse effects associated with ICS.

- Because theophylline and roflumilast have similar mechanisms of action, **they shoul 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. Caution is advised in patients with a history of depression or suicidality.
- 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.**
- azithromycin **reported hearing deficits**
- patients who **continued to smoke did not achieve reduction in exacerbation frequency with azithromycin**.
- Azithromycin **was also associated with a higher rate macrolide resistant bacteria** AND **precaution about QT prolongation.**
- Therefore; the guidelines recommend to consider **adding chronic azithromycin only for patients with recurrent exacerbations despite optimal therapy and who are not active smokers.**

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 alpha1-proteinase inhibitors are available. **Augmentation therapy is given IV once weekly.**

COPD exacerbations

- COPD exacerbation is defined as **a change in the patient's baseline symptoms (dyspnea, cough, or sputum production) (**worsening dyspnea, increased sputum volume, or increased sputum purulence**) sufficient to warrant a change in management**.

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.

- The **diagnosis of acute respiratory failure** is made based on an acute change in ABGs:
- an acute drop in PaO2 of 10–15 mm Hg
- any acute increase in Paco2
- decreases the serum pH to 7.3 or less.
- **Additional indications of respiratory failure include** restlessness, confusion, tachycardia, diaphoresis, cyanosis, hypotension, irregular breathing, 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.

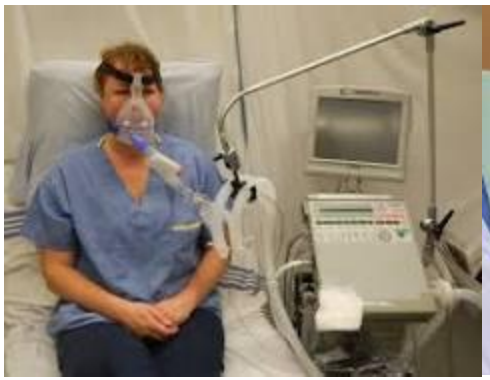
Nonpharmacologic therapy

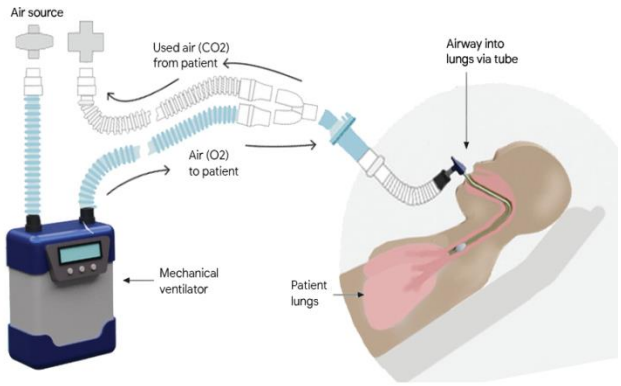
- **Provide oxygen therapy for patients with significant hypoxemia** (eg, oxygen saturation <90% [0.90]).
- **Use caution because many COPD patients rely on mild hypoxemia to trigger their drive to breathe.** Overly aggressive oxygen administration to patients with chronic hypercapnia may result in respiratory depression and respiratory failure.

- Adjust oxygen to achieve PaO2 >60 mm Hg or **oxygen saturation (SaO2) >90%** (0.90).

- 4-Obtain ABG after oxygen initiation to monitor CO2 retention resulting from hypoventilation.

- **Noninvasive positive-pressure ventilation** (**NPPV**) provides ventilatory support with oxygen using a face or nasal mask **without endotracheal intubation**.





- **Intubation and mechanical ventilation** may be needed in patients failing NPPV or who are poor candidates for NPPV (patients with altered mental status, severe acidosis, respiratory arrest, or cardiovascular instability).

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 β2-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:
  - patients presenting **with three cardinal symptoms** of acute exacerbation.
  - patients presenting with **two cardinal symptoms** as long as one is **increased sputum purulence**.
  - patients requiring **mechanical ventilation** regardless of symptoms.
- **Continue antimicrobial therapy for at least 5–7 days**.

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

Evaluation of therapeutic outcomes

- **In chronic stable COPD**, **assess pulmonary function tests annuall**
- **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 SaO2 should also be monitored.
- 5-Evaluate patient medication **adherence**, **side effects**, and **potential drug interactions** at every encounter

COMPARISON BETWEEN ASTHMA & COPD

Factor	ASTHMA	COPD
Age of onset	Less than 30 ys	More than 40 years
Family History	Usual	Uncommon
History of Atopy	Often	Uncommon
Smoking History	Variable	Usual
Main Symptoms	Cough & Wheeze	Dyspnea &Cough
Cough	Nocturnal,with exercise	Early morning
Purulent Sputum	Uncommon	Typical
Bronchodilator Reversibility	Complete	Partial
Lung Function with Therapy	Near normal	Chronically less than normal

Comorbidities	Uncommon	CVS,DM,Osteoporosis, Psychiatric dis.,Cancer
Diagnosis	See before	Spirometry
Hypoxemia	rare	Common
Polycythemia	Rare	Not uncommon
Ig E elevation	Common	Uncommon
Response to Steroids	Strong	Usually weak
Response to LTRBs	Strong	Usually weak
Response to Antibiotics	Poor efficacy	Good efficacy
Progressive deterioration	Uncommon	Typical