Chronic obstructive pulmonary disease (COPD)

COPD is defined as a disease state characterized by progressive airflow limitation that is not fully reversible. Previous definitions of COPD included chronic bronchitis and emphysema. Emphysema, an *anatomically* defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a *clinically* defined condition with chronic cough and sputum.

Differentiating COPD as either chronic bronchitis or emphysema as descriptive subsets of COPD is no longer considered relevant. This is based on the observation that the majority of COPD is caused by a common risk factor (cigarette smoking) and most patients exhibit features of both chronic bronchitis and emphysema.

Epidemiology and etiology:

Current estimates suggest that 80 million people worldwide suffer from moderate to severe disease. COPD commonly occurs in patients who are 40 years of age and older. In most instances, the smoking history is very prominent.

Cigarette smoking represents the most significant risk factor, and the risk of developing COPD relates to both the amount and the duration of smoking. It is unusual to develop COPD with less than 20 cigarettes/day/year. Not all smokers develop the condition, suggesting that individual susceptibility factors are important (Genetic susceptibility is important in this disease because only 20% to 30% of smokers develop the disease).

Pathophysiology of COPD:

When exposed to noxious particles like tobacco smoke, an inflammatory response is initiated to release neutrophils and macrophages into the lungs and airways. This results in the release of chemical mediators like tumor necrosis factor -α and interleukin.

This inflammatory response leads to damage to the airways, pulmonary vasculature, and lung tissue. This state of chronic inflammation causes fibrosis resulting in airflow limitation.

Other processes like oxidative stress and imbalances of proteases and antiproteases may also play a role:

Proteinases *(is an enzyme that catalyzes, increases the rate of, proteolysis, the breakdown of proteins into smaller polypeptides or single amino acids)* and antiproteinases are part of the normal protective and repair mechanisms in the lungs. **Proteinases** are found throughout the body, especially in neutrophils **and** macrophages.

The imbalance of proteinase–antiproteinase activity in COPD is a result of either increased activity of destructive proteinases (e.g. neutrophil elastase) or inactivation of protective antiproteinases.

Oxidative stress: Oxidants (e.g., hydrogen peroxide, and nitric oxide), generated by cigarette smoke react with and damage proteins and lipids, contributing to tissue damage. Oxidants also promote inflammation and exacerbate protease–antiprotease imbalance by inhibiting antiprotease activity.

Clinical presentation:

The three most common symptoms in COPD are cough, sputum production, and exertional dyspnea (often described as increased effort to breathe, heaviness, air hunger).

When airflow limitation becomes severe, patients may have cyanosis of mucosal membranes, development of a "barrel chest" due to hyperinflation of the lungs, increased resting respiratory rate, pursing of lips during expiration, and use of accessory respiratory muscles.

Patients experiencing COPD exacerbation may have worsening dyspnea, increased sputum volume (of thick sputum), and change in sputum color (which is yellow or green in color).

Comparison with asthma:

Cough is usually nonproductive with asthma and productive with COPD. Cough is worse at night and early in the morning with asthma; throughout the day with COPD. Asthma is often related to allergies/environmental triggers; COPD has a common history of smoking.

Asthma is generally not progressive, and symptoms and airflow obstruction are often completely reversible. COPD, on the other hand, is a progressive and often fatal disorder. The degree of bronchodilator reversibility is typically less than that seen in asthma. [[Asthma can be reversible; lung damage from COPD is irreversible].

Patients with asthma respond well to anti-inflammatory medication, including inhaled corticosteroids (ICS). In COPD, the beneficial effects of anti-inflammatory medication, including ICS, are much more modest.

Diagnosis:

1-Clinical Presentation and History

2-Spirometry: Spirometry is the standard for assessing airflow limitation The hallmark of COPD is reduced FEV1: FVC ratio to less than 70%.

The degree of airflow obstruction is an important prognostic factor in COPD and is the basis for the severity classification**.**

3-Arterial blood gases (ABG): ABG is recommended for patients with severe COPD to assess for the presence and severity of hypoxemia and hypercapnia.

Spirometric Classification of Chronic Obstructive Pulmonary Disease (COPD) Severity Based on Postbronchodilator FEV_1

Stage	Classification	Spirometry Results
I	Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
III	Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
IV	Very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure[a]

[a] Respiratory failure is defined as arterial partial pressure of oxygen (Pao_2) <8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($Paco_2$) >6.7 kPa (50 mm Hg) while breathing air at sea level.
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Treatment:

Goals of Treatment:

The goals of COPD management include: Prevent or minimize disease progression, relieve symptoms, prevent and treat exacerbations, and reduce morbidity and mortality.

Nonpharmacologic Therapy:

Smoking cessation slows the rate of decline in pulmonary function in patients with COPD. Stopping smoking can also reduce cough and sputum production and decrease airway reactivity.

Pulmonary rehabilitation programs where a number of interventions are used, including airway clearance techniques for patients with chronic sputum production exercise training, nutritional counseling, and psychosocial support.

Long-term administration of oxygen (more than 15 hours/day) to patients with chronic respiratory failure has been shown to reduce mortality and improve quality of life.

Pharmacologic Therapy:

Short-acting bronchodilators, such as the β2-agonists salbutamol and terbutaline, or the anticholinergic ipratropium bromide, may be used (as needed) for patients with mild disease (intermittent symptoms).

Longer acting bronchodilators, such as the β2-agonists salmeterol, and formoterol, or the anticholinergic tiotropium bromide, are more appropriate for patients with moderate to severe disease (symptoms are more persistent).

Inhaled corticosteroids (ICS) are currently recommended in patients with severe disease (FEV1 < 50%) who report two or more exacerbations requiring antibiotics or oral steroids per year. ICS reduce the frequency and severity of exacerbations.

1. Bronchodilators:

Bronchodilators are the mainstay of treatment for symptomatic COPD. They can be used as needed for symptoms or on a scheduled basis to prevent or reduce symptoms.

Bronchodilator drugs commonly used in COPD include β2-agonists, anticholinergics, and theophylline.

a. β2-Agonists:

The short-acting β2-agonists (Duration of action is 4 to 6 hours) include salbutamol, and terbutaline. They are used as "rescue" therapy for acute symptom relief.

Most COPD patients need continuous bronchodilator therapy on a scheduled (regular) basis every day. For these patients, short acting β2-agonists are inconvenient because of the need for frequent dosing. Salmeterol, and formoterol are LABAs that are dosed every 12 hours on a scheduled basis and provide bronchodilation throughout the dosing interval. Patients treated with long-acting *β*2-agonists should also have a short-acting *β*2-agonist such as salbutamol available for as-needed use ("rescue" medication).

b. Anticholinergics (Long acting muscarinic antagonists LAMAs):

Ipratropium and tiotropium are inhaled anticholinergic medications commonly used for COPD.

Ipratropium bromide is the primary short-acting anticholinergic agent used for COPD. It has a slower onset of action than short-acting *β2*-agonists (15–20 min vs 5 min for salbutamol). It may be less suitable for as-needed use, but it is often prescribed in this manner. It is also available as a solution for nebulization.

Tiotropium bromide is a long-acting agent that protects against cholinergic bronchoconstriction for more than 24 hours. It is given once daily.

Combination of an inhaled anticholinergic and *β*2-agonist is often used, especially as the disease progresses and symptoms worsen. Combination of both short acting *β*2-agonists with ipratropium provides added symptomatic relief and improvements in pulmonary function. (Combivent ® contains salbutamol and ipratropium in an MDI for therapy of COPD).

C. Methylxanthines:

Theophylline and aminophylline produce bronchodilation by inhibiting phosphodiesterase and other mechanisms.

Methylxanthines have a very limited role in COPD therapy because of drug interactions and interpatient variability in dosage requirements. Theophylline should be reserved for patients who cannot use inhaled medications (cannot use inhaled devices efficiently) or who remain symptomatic despite appropriate use of inhaled bronchodilators.

Sustained-release theophylline preparations improve adherence and achieve more consistent serum concentrations than rapid-release products.

2. Corticosteroids:

Appropriate situations for corticosteroids in COPD include (1) short-term systemic use for acute exacerbations and (2) inhalation therapy for chronic stable COPD.

Chronic systemic corticosteroids should be avoided in COPD management because of questionable benefits and high risk of toxicity.

Inhaled corticosteroids (ICS) are currently recommended in patients with severe disease (FEV1 < 50%) who report two or more exacerbations requiring antibiotics or oral steroids per year. ICS reduce the frequency and severity of exacerbations. Side effects of inhaled corticosteroids are mild and include hoarseness, and oral candidiasis.

Combination of inhaled corticosteroids and long-acting bronchodilators (fluticasone plus salmeterol or budesonide plus formoterol) is associated with greater improvements than either agent alone and makes administration of both drugs more convenient.

3.Combination Therapy:

For patients who remain symptomatic on monotherapy, a combination of bronchodilators can be used. (e.g., combining salbutamol plus ipratropium, a long-acting β2-agonist plus theophylline, or a long-acting β2-agonist plus tiotropium).

Triple therapy with inhaled corticosteroid, long-acting β2- agonist, and tiotropium is commonly used (Adding tiotropium to a LABA/ICS combination (triple therapy) improves lung function and health-related quality of life and reduces the number of exacerbation).

Therapy of COPD Exacerbations:

An exacerbation is acute worsening of the patient's symptoms. Common symptoms are worsening of dyspnea, increased sputum production, and change in sputum color.

These exacerbations are commonly precipitated by infection (more often viral than bacterial) and air pollution, but the cause cannot be identified in about one-third of severe exacerbations.

A-Oxygen:

B-Bronchodilators:

Short-acting β2-agonists are preferred because of rapid onset of action. Anticholinergic agents may be added if symptoms persist despite increased doses of β2-agonists .

Acute COPD Exacerbation: "A COPD"
A - Antibiotics if indicated.
C - Corticosteroids.
O - O2
P – Phlegm (sputum) control (Mucolytics)
D - Dilators.

Bronchodilators may be administered via MDIs or nebulization with equal efficacy.

Nebulization may be considered for patients with severe dyspnea (and/or cough) who are unable to hold their breath after actuation of an MDI.

Theophylline should generally be avoided due to lack of evidence documenting benefit. It may be considered for patients not responding to other therapies.

C-Corticosteroids:

Patients with acute COPD exacerbations may receive a short course of IV or oral corticosteroids. [prednisone 40 mg orally daily (or equivalent) for 10 to 14 days can be effective for most patients].

If treatment is continued for longer than 2 weeks; employ a tapering oral schedule because of hypothalamic-pituitary-adrenal axis suppression.

If inhaled corticosteroids are part of the patient's usual treatment regimen; they should be continued during systemic therapy.

D-Antimicrobial Therapy:

Antibiotics are of most benefit and should be initiated if at least two of the following three symptoms are present: 1) increased dyspnea, 2) increased sputum volume, and 3) Increased sputum purulence (Purulent sputum contains pus, and viscous mucus and is typically yellow or green)

First-line antibiotic therapy includes macrolides, doxycycline, and cephalosporins. In case of treatment failure, respiratory fluoroquinolones e.g., levofloxacin, moxifloxacin, gemifloxacin (fluoroquinolones with enhanced activity against the important respiratory pathogen *Streptococcus pneumoniae* relative to earlier fluoroquinolone derivatives like ciprofloxacin) or amoxicillin-clavulanate (Augmentin) are recommended.

Initiate therapy within 24 hours of symptoms to prevent unnecessary hospitalization and generally continue for at least 7 to 10 days. Five-day courses with some agents may produce comparable efficacy.