




# COPD


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- COPD, as a disease state characterized by airflow limitation that is not fully reversible
  - COPD includes *emphysema*, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and *small airways disease*, a condition in which small bronchioles are narrowed. COPD is present only if chronic airflow obstruction occurs; chronic bronchitis without chronic airflow obstruction is not included within COPD.


# RISK FACTORS

- **cigarette smoking** was a major risk factor for mortality from chronic bronchitis and emphysema.
- The historically higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males;
- however, the prevalence of COPD among females is increasing as the gender gap in smoking rates has diminished in the past 50 years.

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- COPD is the fourth leading cause of death and affects >16 million persons in the United States.
  - GOLD estimates suggest that COPD will rise from the sixth to the third most common cause of death worldwide by 2020.

# Airway Responsiveness and COPD

- A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, including **methacholine** and histamine, is one of the defining features of asthma
- However, many patients with COPD also share this feature of airway hyperresponsiveness.

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- increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function.
  - Thus, airway hyperresponsiveness is a risk factor for COPD.

# Respiratory Infections

- **childhood** respiratory infections have also been assessed as potential predisposing factors for the eventual development of COPD.
- The impact of **adult** respiratory infections on decline in pulmonary function is controversial,

## Occupational Exposures

- Increased respiratory symptoms and airflow obstruction have been suggested as resulting from general exposure to **dust at work**. Several specific occupational exposures, including **coal mining**, **gold mining**, and **cotton textile dust**, have been suggested as risk factors for chronic airflow obstruction.
- However, although nonsmokers in these occupations developed some reductions in FEV
- the importance of dust exposure as a risk factor for COPD, independent of cigarette smoking, is not certain.



# Ambient Air Pollution

- Some investigators have reported increased respiratory symptoms in those living in **urban** compared to **rural** areas, which may relate to increased pollution in the urban settings.
- However, the relationship of air pollution to chronic airflow obstruction remains unproven.


## Passive, or Second-Hand, Smoking Exposure

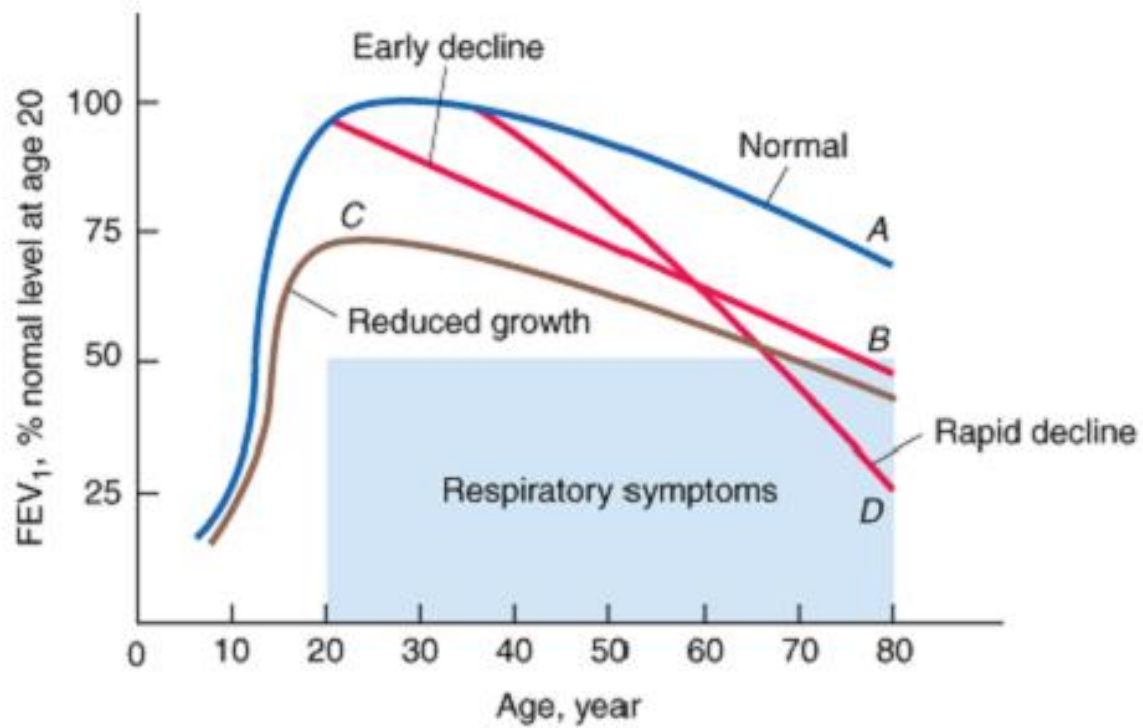
- Exposure of children to **maternal smoking** results in significantly reduced lung growth.
- In utero tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function.


## Genetic Considerations


### $\alpha_1$ ANTITRYPSIN DEFICIENCY

- Individuals with two **Z alleles** or one Z and one null allele are referred to as PiZ which is the most common form of severe  $\alpha_1$ AT deficiency.

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- though only 1–2% of COPD patients are found to have severe  $\alpha$ 1AT deficiency as a contributing cause of COPD,
  - these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD.
  - PiZ individuals often develop early-onset COPD




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- The effects of cigarette smoking on pulmonary function appear to depend on the **intensity** of smoking exposure,
  - the **timing** of smoking exposure during growth,
  - and the **baseline lung function** of the individual




In contrast to asthma, the reduced FEV<sub>1</sub> in COPD seldom shows large responses to inhaled bronchodilators, although improvements **up to 15%** are common.

Asthma patients can also develop chronic (not fully reversible) airflow obstruction.

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- In COPD there is often "air trapping" (increased residual volume and increased ratio of residual volume to total lung capacity) and
  - progressive hyperinflation (increased total lung capacity) late in the disease.





- The PaO<sub>2</sub> usually remains near normal until the FEV<sub>1</sub> is **decreased to ~50%** of predicted, and even much lower FEV<sub>1</sub> is can be associated with a normal PaO<sub>2</sub> at least at rest.
- An elevation of PaCO<sub>2</sub> is not expected until the FEV<sub>1</sub> **is <25%** of predicted and even then may not occur.
- **Pulmonary hypertension** severe enough to cause cor pulmonale and right ventricular failure due to COPD occurs only in those individuals who have marked decreases




in **FEV<sub>1</sub> (<25% of predicted)** together with chronic hypoxemia (Pao<sub>2</sub> <55 mmHg),

- although earlier in the course some elevation of pulmonary artery pressure, particularly with exercise, may occur







Ventilation/perfusion mismatching accounts for essentially all of the reduction in  $P_a$  that occurs in COPD; shunting is minimal.





# PATHOLOGY

- Cigarette smoke exposure may affect the **large** airways, **small airways** (< 2 mm diameter), and **alveolar** space.
- Changes in large airways cause cough and sputum, while changes in small airways and alveoli are responsible for physiologic alterations.

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- Cigarette smoking often results in mucous gland enlargement and goblet cell hyperplasia.
  - These changes are proportional to cough and mucus production that define chronic bronchitis, but these abnormalities are not related to airflow limitation

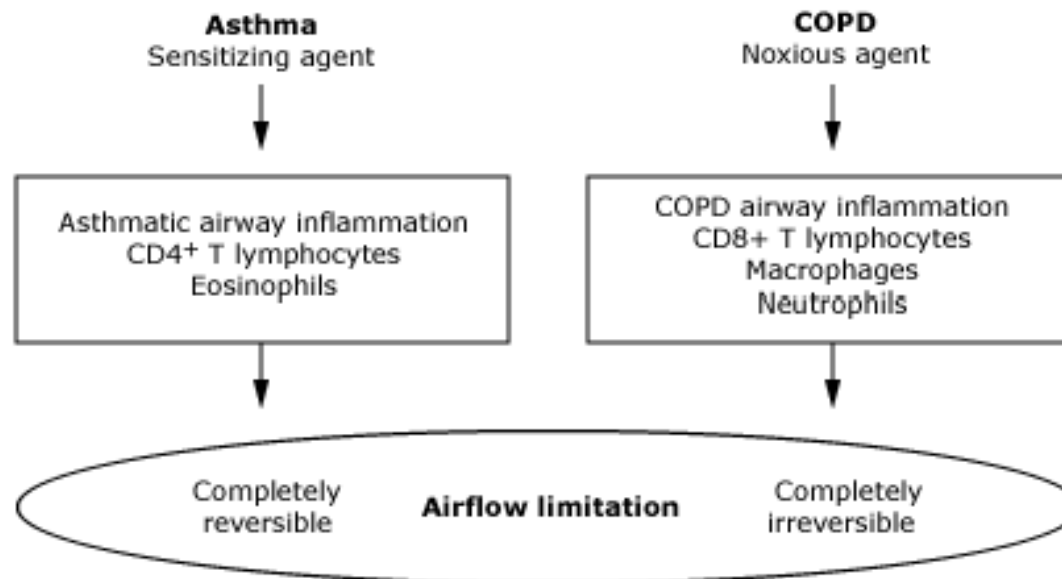
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- The major site of increased **resistance** in most individuals with COPD is in **airways <2 mm** diameter.
  - the concept of decreased alveolar attachments leading to small airway obstruction is appealing because it underscores the mechanistic relationship between loss of elastic recoil and increased resistance to airflow in small airways.


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- **Emphysema** is characterized by destruction of gas-exchanging airspaces, i.e., the respiratory bronchioles, alveolar ducts, and alveoli. Their walls become perforated and later obliterated with coalescence of small distinct airspaces into abnormal and much larger airspaces.

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- In **smokers'** lavage fluid, macrophages comprise >95% of the total cell count, and neutrophils, nearly absent in nonsmokers' lavage, account for 1–2% of the cells. T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers.




## Asthma and COPD




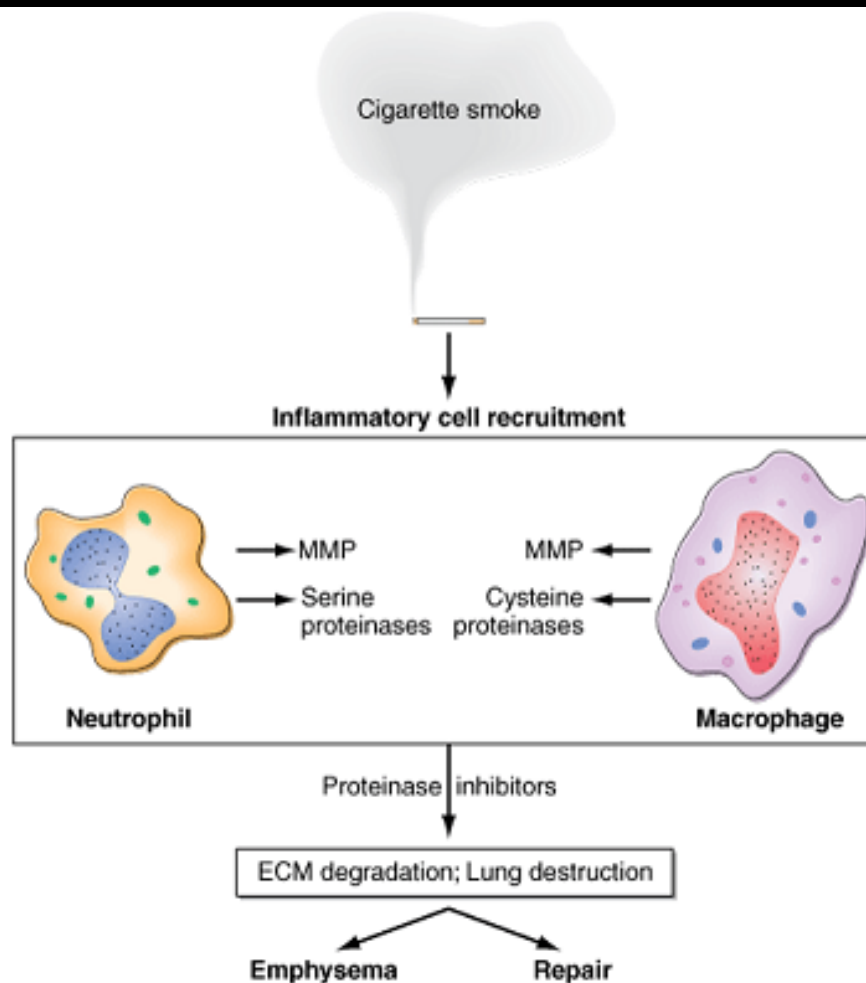
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- Emphysema is classified into distinct pathologic types, the most important being **centriacinar and panacinar**.
  - *Centriacinar emphysema*, the type most frequently associated with cigarette smoking,
  - *Panacinar emphysema* refers to abnormally large airspaces evenly distributed within and across acinar units. Panacinar emphysema is usually observed in patients with  $\alpha_1$ AT deficiency, which has a predilection for the lower lobes.



## PATHOGENESIS

- Airflow limitation, the major physiologic change in COPD, can result from both small airway obstruction and emphysema,
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- (1) Chronic exposure to cigarette smoke may lead to inflammatory cell recruitment within the terminal airspaces of the lung.
  - (2) These inflammatory cells release elastolytic proteinases which damage the extracellular matrix of the lung.
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Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>

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# CLINICAL PRESENTATION

## History

- The three most common symptoms in COPD are cough, sputum production, and exertional dyspnea.




# Physical Findings

- In the early stages of COPD, patients usually have an entirely normal physical examination.
- Current smokers may have signs of active smoking, including an odor of smoke or nicotine staining of fingernails.
- In patients with more severe disease, the physical examination is notable for a prolonged expiratory phase and expiratory wheezing.



# Laboratory Findings


- The degree of airflow obstruction is an important prognostic factor in COPD and is the basis for the GOLD disease classification .
  - More recently it has been shown that a multifactorial index incorporating airflow obstruction, exercise performance, dyspnea, and body mass index is a better predictor of mortality than pulmonary function alone.
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**Table 254-1 Gold Criteria for COPD Severity**


<b>GOLD Stage</b>	<b>Severity</b>	<b>Symptoms</b>	<b>Spirometry</b>
0	At Risk	Chronic cough, sputum production	Normal
I	Mild	With or without chronic cough or sputum production	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted
IIA	Moderate	With or without chronic cough or sputum production	$FEV_1/FVC < 0.7$ and $50\% \leq FEV_1 < 80\%$ predicted
III	Severe	With or without chronic cough or sputum production	$FEV_1/FVC < 0.7$ and $30\% \leq FEV_1 < 50\%$ predicted
IV	Very Severe	With or without chronic cough or sputum production	$FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted with respiratory failure or signs of right heart failure

**Note:** GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease (COPD).

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- **An elevated hematocrit** suggests the presence of chronic hypoxemia, as does the presence of signs of right ventricular hypertrophy.
  - Computed tomography (CT) scan is the current definitive test for establishing the presence or absence of emphysema in living subjects .
  - From a practical perspective, the CT scan does little to influence therapy of COPD except in those individuals considering surgical therapy for their disease

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE: TREATMENT Stable Phase COPD

- Only three interventions—**smoking** cessation, **oxygen** therapy in chronically hypoxemic patients, and **lung volume reduction surgery** in selected patients with emphysema—have been demonstrated to influence the natural history of patients with COPD.

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- It has been shown that middle-aged smokers who were able to successfully stop smoking experienced a significant improvement in
    - the rate of decline in pulmonary function,
    - returning to annual changes similar to that of nonsmoking patients.

# BRONCHODILATORS


- In general, bronchodilators are used for symptomatic benefit in patients with COPD.
- While regular use of ipratropium bromide does not appear to influence the rate of decline of lung function, it improves symptoms and produces acute improvement in FEV<sub>1</sub>
- Tiotropium, a long-acting anticholinergic, has been shown to improve symptoms and reduce exacerbations.

# BETA AGONISTS


- These provide symptomatic benefit.
- The main side effects are tremor and tachycardia.
- Long-acting inhaled agonists, such as **salmeterol**, have benefits comparable to **ipratropium bromide**. Their use is more convenient than short-acting agents. The addition of a agonist to inhaled anticholinergic therapy has been demonstrated to provide incremental benefit.

# INHALED GLUCOCORTICOIDS

- Several trials have failed to find a beneficial effect for the regular use of inhaled glucocorticoids on the rate of decline of lung function, as assessed by FEV<sub>1</sub>
- inhaled glucocorticoids reduce exacerbation frequency by ~25%
- reduce mortality by ~25%




A trial of inhaled glucocorticoids should be considered in patients with

- frequent exacerbations, defined as two or more per year
  - in patients who demonstrate a significant amount of acute reversibility in response inhaled bronchodilators.
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# ORAL GLUCOCORTICOIDS

- The chronic use of oral glucocorticoids for treatment of COPD is not recommended because of an unfavorable benefit/risk ratio.
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# THEOPHYLLINE

- Theophylline produces modest improvements in expiratory flow rates and vital capacity and a slight improvement in arterial oxygen and carbon dioxide levels in patients with moderate to severe COPD. Nausea is a common side effect; tachycardia and tremor have also been reported.
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# OXYGEN

- Supplemental O<sub>2</sub>
- is the only pharmacologic therapy demonstrated to decrease mortality in patients with COPD.
- For patients with resting hypoxemia (resting O<sub>2</sub>saturation <88% or <90% with signs of pulmonary hypertension or right heart failure), the use of O<sub>2</sub> has been demonstrated to have a significant impact on mortality.

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- *N-acetyl cysteine has been used in patients with COPD for both its mucolytic and antioxidant properties*
  - Eligibility for @1AT augmentation therapy requires a serum @1AT level  $<11 M$  (approximately 50 mg/dL). Typically, PiZ individuals will qualify, although other rare types associated with severe deficiency (e.g., null-null) are also eligible. Since only a fraction of individuals with severe @1AT deficiency will develop COPD, @1AT augmentation therapy is not recommended for severely @1AT-deficient persons with normal pulmonary function and a normal chest CT scan.




# Nonpharmacologic Therapies

- Patients with COPD should receive the influenza vaccine annually.
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# PULMONARY REHABILITATION

- In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6–12-month period.
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# LUNG VOLUME REDUCTION SURGERY (LVRS)



- Patients with upper lobe–predominant emphysema and a low postrehabilitation exercise capacity are most likely to benefit from LVRS.
- COPD is the single leading indication for lung transplantation .
- Current recommendations are that candidates for lung transplantation should be <65 years; have severe disability despite maximal medical therapy; and be free of comorbid conditions such as liver, renal, or cardiac disease

# Exacerbations of COPD

- Exacerbations are commonly considered to be episodes of increased dyspnea and cough and change in the amount and character of sputum.
- Self-reported health-related quality of life correlates with frequency of exacerbations more closely than it does with the degree of airflow obstruction.



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- **Bacterial infections** play a role in many, but by no means all, episodes. **Viral respiratory** infections are present in approximately onethird of COPD exacerbations.
  - In a significant minority of instances (20–35%), no specific precipitant can be identified.

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- chronic suppressive or "rotating" antibiotics are not beneficial in patients with COPD.
  - Inhaled glucocorticoids did reduce the frequency of exacerbations by 25–30% in some analyses