Chronic Obstructive Pulmonary disease

KAMRANI RAMIZ MD

PULMONOLOGIST

ASSISTANT PROFESSOR OF ARAK UNIVERSITY OF MEDICAL SCIENCES

INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible .
- COPD includes *emphysema*, an anatomically defined condition characterized by destruction of the lung alveoli with air space enlargement;
- *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and
- *small airway disease*, a condition in which small bronchioles are narrowed and reduced in number.

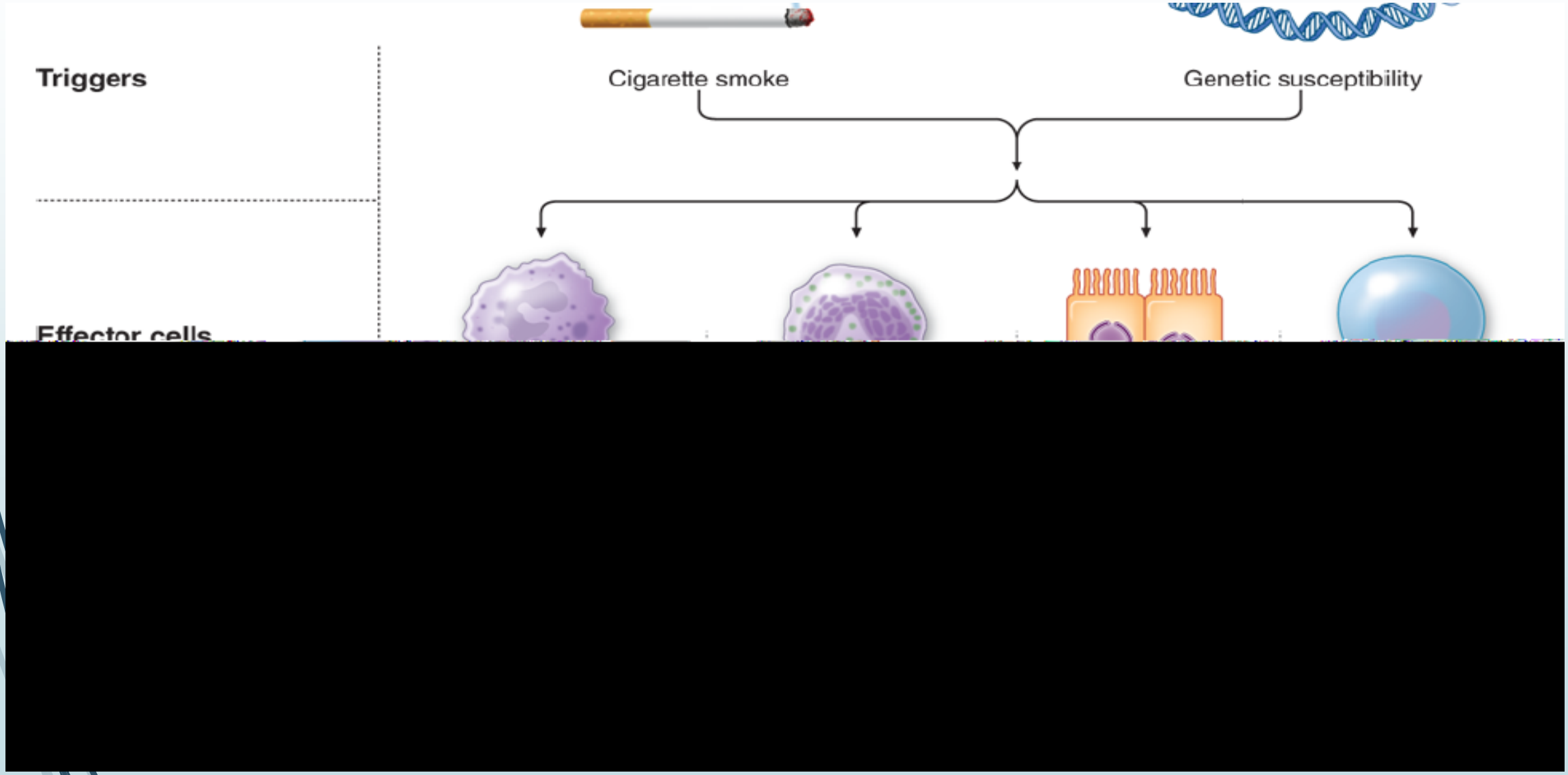
- The classic definition of COPD requires the presence of chronic airflow obstruction, determined by spirometry, that usually occurs in the setting of noxious environmental exposures—most commonly cigarette smoking.
- Emphysema, chronic bronchitis, and small airway disease are present in varying degrees in different COPD patients.
- Patients with a history of cigarette smoking without chronic airflow obstruction may have chronic bronchitis, emphysema, and dyspnea. Although these patients are not included within the classic definition of COPD, they may have similar disease processes.
- Respiratory symptoms and other features of COPD can occur in subjects who do not meet a definition of COPD based only on airflow obstruction determined by spirometric thresholds of normality.

- COPD is the third leading cause of death and affects >10 million persons in the United States. COPD is also a disease of increasing public health importance around the world.

- Estimates suggest that COPD will rise to the third most common cause of death worldwide by 2020.

PATHOGENESIS

- Airflow limitation, a major physiologic change in COPD, can result from small airway disease and/or emphysema. Small airways may become narrowed by cells (hyperplasia and accumulation), mucus, and fibrosis, and extensive small airway destruction has been demonstrated to be a hallmark of advanced COPD.
- Although the precise biological mechanisms leading to COPD have not been determined, a number of key cell types, molecules, and pathways have been identified from cell-based and animal model studies.
- The pathogenesis of emphysema is more clearly defined than the pathogenesis of small airway disease.
- Pulmonary vascular destruction occurs in concert with small airway disease and emphysema.


Triggers
Cigarette smoke
Genetic susceptibility
Effector cells

- **Pathogenesis of emphysema.**
- Upon long-term exposure to cigarette smoke in genetically susceptible individuals, lung epithelial cells and T and B lymphocytes recruit inflammatory cells to the lung. Biological pathways of protease-antiprotease imbalance, oxidant/antioxidant imbalance, apoptosis, and lung repair lead to extracellular matrix destruction, cell death, chronic inflammation, and ineffective repair.

- (1) Chronic exposure to cigarette smoke in genetically susceptible individuals triggers inflammatory and immune cell recruitment within large and small airways and in the terminal air spaces of the lung.
- (2) Inflammatory cells release proteinases that damage the extracellular matrix supporting airways, vasculature, and gas exchange surfaces of the lung.
- (3) Structural cell death occurs through oxidantinduced damage, cellular senescence, and proteolytic loss of cellular-matrix attachments leading to extensive loss of smaller airways, vascular pruning, and alveolar destruction.
- (4) Disordered repair of elastin and other extracellular matrix components contributes to air space enlargement and emphysema.

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

- Elastin, the principal component of elastic fibers, is a highly stable component of the extracellular matrix that is critical to the integrity of the lung.
- The elastase:antielastase hypothesis, proposed in the mid-1960s, postulated that the balance of elastin-degrading enzymes and their inhibitors determines the susceptibility of the lung to destruction resulting in air space enlargement.
- This hypothesis was based on the clinical observation that patients with genetic deficiency in a1 antitrypsin (a1AT), the inhibitor of the serine proteinase neutrophil elastase, were at increased risk of emphysema, and that instillation of elastases, including neutrophil elastase, into experimental animals, results in emphysema.

- A complex network of immune and inflammatory cells and additional proteinases that contribute to emphysema has subsequently been identified.
- Upon exposure to oxidants from cigarette smoke, lung macrophages and epithelial cells become activated, producing proteinases and chemokines that attract other inflammatory and immune cells.
- Oxidative stress is a key component of COPD pathobiology; the transcription factor NRF2, a major regulator of oxidant-antioxidant balance, and SOD3, a potent antioxidant, have been implicated in emphysema pathogenesis by animal models.
- Mitochondrial dysfunction in COPD may worsen oxidative stress.

- One mechanism of macrophage activation occurs via oxidant-induced inactivation of histone deacetylase-2 (HDAC2), shifting the balance toward acetylated or loose chromatin, exposing nuclear factor-kappaB sites, and resulting in transcription of matrix metalloproteinases and proinflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor a (TNF-a);

- this leads to neutrophil recruitment. CD8+ T cells are also recruited in response to cigarette smoke and release interferon-inducible protein-10 (IP-10, CXCL-7), which in turn leads to macrophage production of macrophage elastase (matrix metalloproteinase-12 [MMP-12]).

- Matrix metalloproteinases and serine proteinases, most notably neutrophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction.

- Proteolytic cleavage products of elastin serve as a macrophage chemokine, and proline-glycineproline (generated by proteolytic cleavage of collagen) is a neutrophil chemokine—fueling this destructive positive feedback loop.

- Elastin degradation and disordered repair are thought to be primary mechanisms in the development of emphysema

Autoimmune Mechanisms

- Increased B cells and lymphoid follicles are present around the airways of COPD patients, particularly those with advanced disease.

- Antibodies have been found against elastin fragments as well; IgG autoantibodies with avidity for pulmonary epithelium and the potential to mediate cytotoxicity have been detected.

- Concomitant cigarette smoke–induced loss of cilia in the airway epithelium and impaired macrophage phagocytosis predispose to bacterial infection with neutrophilia.

- In end-stage lung disease, long after smoking cessation, there remains an exuberant inflammatory response, suggesting that cigarette smoke–induced inflammation both initiates the disease and, in susceptible individuals, establishes a chronic process that can continue disease progression even after smoking cessation

Cell Death

- Cigarette smoke oxidant-mediated structural cell death occurs via a variety of mechanisms including excessive ceramide production and Rtp801 inhibition of mammalian target of rapamycin (mTOR), leading to cell death as well as inflammation and proteolysis.

- Involvement of mTOR and other senescence markers has led to the concept that emphysema resembles premature aging of the lung.

- Heterozygous gene-targeting of one of the leading genetic determinants of COPD identified by genome-wide association studies (GWAS), hedgehog interacting protein (*HHIP*), in a murine model leads to aging-related emphysema.

Ineffective Repair

- The ability of the adult lung to replace lost smaller airways and microvasculature and to repair damaged alveoli appears limited.
- Uptake of apoptotic cells by macrophages normally results in production of growth factors and dampens inflammation, promoting lung repair.
- Cigarette smoke impairs macrophage uptake of apoptotic cells, limiting repair. It is unlikely that the intricate and dynamic process of septation that is responsible for alveologenesis during lung development can be reinitiated in the adult human lung.

PATHOLOGY

- Cigarette smoke exposure may affect the large airways, small airways (≤2 mm diameter), and alveoli.
- Changes in large airways cause cough and sputum production, while changes in small airways and alveoli are responsible for physiologic alterations.
- Airway inflammation, destruction, and the development of emphysema are present in most persons with COPD; however, they appear to be relatively independent processes, and their relative contributions to obstruction vary from one person to another.
- The early stages of COPD, based on the severity of airflow obstructionappear to be primarily associated with medium and small airway disease with the majority of Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1 and GOLD 2 subjects demonstrating little or no emphysema.

- Advanced stages of COPD (GOLD 3 and 4) are typically characterized by extensive emphysema, although there are a small number of subjects with very severe (GOLD 4) obstruction with virtually no emphysema.

- The subjects at greatest risk of progression in COPD are those with both aggressive airway disease and emphysema. Thus, finding emphysema (by chest CT) either early or late in the disease process suggests enhanced risk for disease progression.

LARGE AIRWAYS

- Cigarette smoking often results in mucus gland enlargement and goblet cell hyperplasia, leading to cough and mucus production that define chronic bronchitis, but these abnormalities are not related to airflow limitation.
- In response to cigarette smoking, goblet cells not only increase in number but in extent through the bronchial tree.
- Bronchi also undergo squamous metaplasia, predisposing to carcinogenesis and disrupting mucociliary clearance.
- patients may have smooth-muscle hypertrophy and bronchial hyperreactivity leading to airflow limitation.
- Neutrophil influx has been associated with purulent sputum during respiratory tract infections. Independent of its proteolytic activity, neutrophil elastase is among the most potent secretagogues identified.

SMALL AIRWAYS

- The major site of increased resistance in most individuals with COPD is in airways ≤2 mm diameter.
- Characteristic cellular changes include goblet cell metaplasia, with these mucus-secreting cells replacing surfactant-secreting Club cells. Smooth-muscle hypertrophy may also be present.
- Luminal narrowing can occur by fibrosis, excess mucus, edema, and cellular infiltration.

- Reduced surfactant may increase surface tension at the air-tissue interface, predisposing to airway narrowing or collapse.

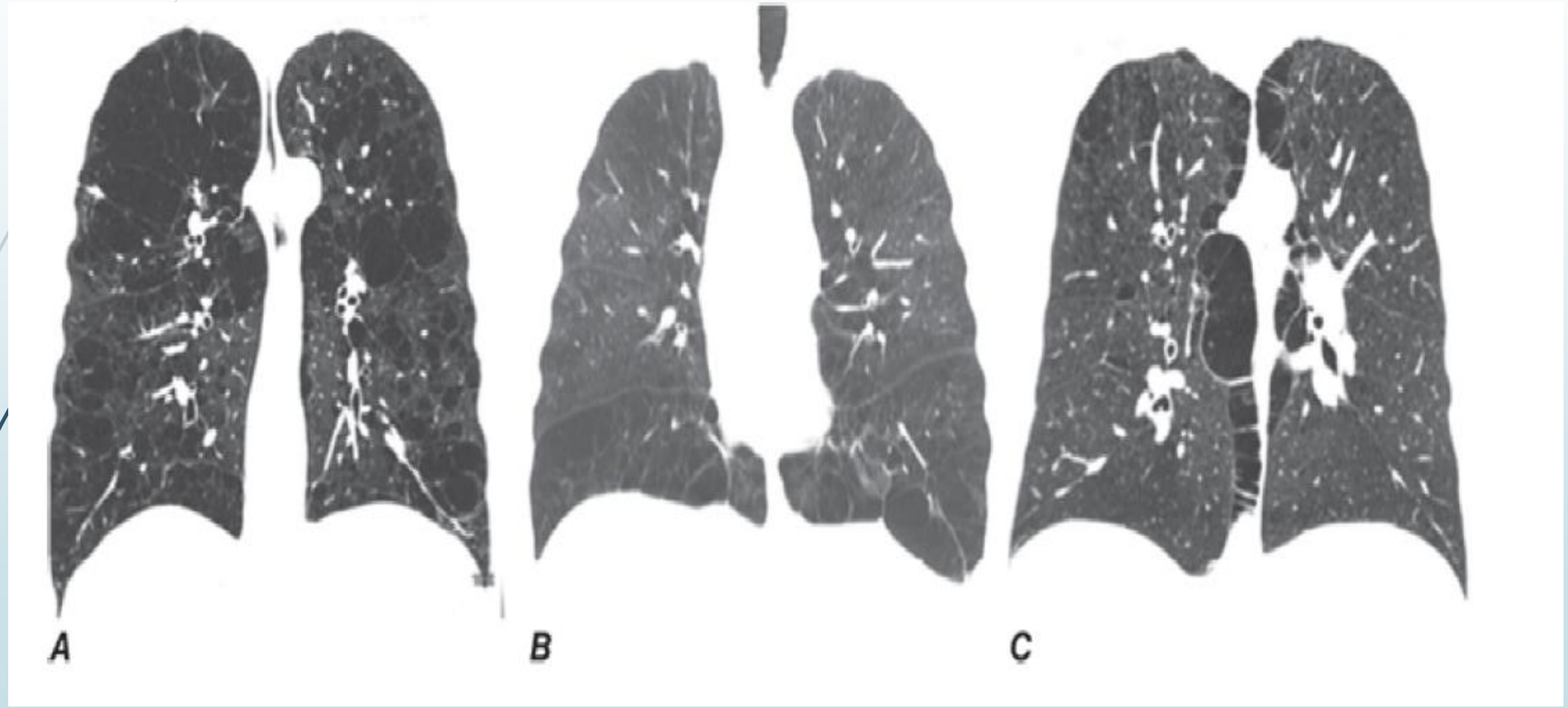
- Respiratory bronchiolitis with mononuclear inflammatory cells collecting in distal airway tissues may cause proteolytic destruction of elastic fibers in the respiratory bronchioles and alveolar ducts where the fibers are concentrated as rings around alveolar entrances.
- Advanced COPD has been shown to be associated with a loss of many of the smaller airways and a similar significant loss of the lung microvasculature.

LUNG PARENCHYMA

- Emphysema is characterized by destruction of gas-exchanging air spaces, i.e., the respiratory bronchioles, alveolar ducts, and alveoli.
- Their walls become perforated and later obliterated with coalescence of the delicate alveolar structure into large emphysematous air spaces.
- Large numbers of macrophages accumulate in respiratory bronchioles of essentially all smokers.
- Bronchoalveolar lavage fluid from such individuals contains roughly five times as many macrophages as lavage from nonsmokers.
- Neutrophils and T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers.

Emphysema is classified into distinct pathologic types

- which include centrilobular, panlobular, and paraseptal .
- *Centrilobular emphysema, the type most frequently associated with cigarette smoking, is characterized by enlarged air spaces found* (initially) in association with respiratory bronchioles. Centrilobular emphysema is usually most prominent in the upper lobes and superior segments of lower lobes and is often quite focal.
- *Panlobular emphysema refers to abnormally large air spaces evenly* distributed within and across acinar units. Panlobular emphysema is commonly observed in patients with a1AT deficiency, which has a predilection for the lower lobes.
- Paraseptal emphysema occurs in 10–15% of cases and is distributed along the pleural margins with relative sparing of the lung core or central regions. It is commonly associated with significant airway inflammation and with centrilobular emphysema.


A
B
C

Copd part 2

PATHOPHYSIOLOGY

- Persistent reduction in forced expiratory flow rates is the most typical finding in COPD.

- Increases in the residual volume and the residual volume/total lung capacity ratio, non-uniform distribution of ventilation, and ventilation-perfusion mismatching also occur

AIRFLOW OBSTRUCTION

- Airflow limitation, also known as airflow obstruction, is typically determined for clinical purposes by spirometry, which involves forced expiratory maneuvers after the subject has inhaled to total lung capacity.

- Key parameters obtained from spirometry include the volume of air exhaled within the first second of the forced expiratory maneuver (FEV1) and the total volume of air exhaled during the entire spirometric maneuver (forced vital capacity [FVC]).

- Patients with airflow obstruction related to COPD have a chronically reduced ratio of FEV1/FVC. In contrast to asthma, the reduced FEV1 in COPD seldom shows large responses to inhaled bronchodilators, although improvements up to 15% are common.

HYPERINFLATION

- Lung volumes are also routinely assessed in pulmonary function testing.
- 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.
- Hyperinflation of the thorax during tidal breathing preserves maximum expiratory airflow, because as lung volume increases, elastic recoil pressure increases, and airways enlarge so that airway resistance decreases.

- Despite compensating for airway obstruction, hyperinflation can push the diaphragm into a flattened position with a number of adverse effects.

- First, by decreasing the zone of apposition between the diaphragm and the abdominal wall, positive abdominal pressure during inspiration is not applied as effectively to the chest wall, hindering rib cage movement and impairing inspiration.

- Second, because the muscle fibers of the flattened diaphragm are shorter than those of a more normally curved diaphragm, they are less capable of generating inspiratory pressures than normal.

- Third, the flattened diaphragm must generate greater tension to develop the transpulmonary pressure required to produce tidal breathing.

- Fourth, the thoracic cage is distended beyond its normal resting volume and during tidal breathing the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation instead of gaining the normal assistance from the chest wall recoiling outward toward its resting volume.

GAS EXCHANGE

- Although there is considerable variability in the relationships between the FEV1 and other physiologic abnormalities in COPD, certain generalizations may be made.

- The partial pressure of oxygen in arterial blood PaO2 usually remains near normal until the FEV1 is decreased to ~50% of predicted, and even much lower FEV1 values can be associated with a normal PaO2, at least at rest.

- An elevation of arterial level of carbon dioxide (PaCO2) is not expected until the FEV1 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 typically occurs in individuals who have marked decreases in FEV1 (<25% of predicted) and chronic hypoxemia (PaO2 <55 mmHg); however, recent evidence suggests that some patients will develop significant pulmonary hypertension independent of COPD severity.

- Non-uniform ventilation and ventilation-perfusion mismatching are characteristic of COPD, reflecting the heterogeneous nature of the disease process within the airways and lung parenchyma .
- multiple parenchymal compartments having different rates of ventilation due to regional differences in compliance and airway resistance.
- Ventilationperfusion mismatching accounts for essentially all of the reduction in PaO2 that occurs in COPD; shunting is minimal.
- This finding explains the effectiveness of modest elevations of inspired oxygen in treating hypoxemia due to COPD and therefore the need to consider problems other than COPD when hypoxemia is difficult to correct with modest levels of supplemental oxygen.

RISK FACTORS
CIGARETTE SMOKING

- studies have shown accelerated decline in FEV1 in a dose-response relationship to the intensity of cigarette smoking, which is typically expressed as pack-years (average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking).

- This dose-response relationship between reduced pulmonary function and cigarette smoking intensity accounts, at least in part, for the higher prevalence rates of COPD with increasing age.
- The historically higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males;
- the prevalence of COPD among females is increasing as the gender gap in smoking rates has diminished in the past 50 years.

- Although the causal relationship between cigarette smoking and the development of COPD has been absolutely proved, there is considerable variability in the response to smoking.

- Pack-years of cigarette smoking is the most highly significant predictor of FEV1 , **but only 15% of the variability in FEV1 is explained by pack-years.**

- **This finding suggests that additional environmental** and/or genetic factors contribute to the impact of smoking on the development of chronic airflow obstruction.

- Although cigar and pipe smoking may also be associated with the development of COPD, the evidence supporting such associations is less compelling, likely related to the lower dose of inhaled tobacco by-products during cigar and pipe smoking.

- The impact of electronic cigarettes (e-cigarettes) on the development and progression of COPD has not yet been determined

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**. In older subjects, there is considerable overlap between persons with a history of chronic asthma and smokers with COPD in terms of airway responsiveness, airflow obstruction, and pulmonary symptoms.

- The origin of asthma is viewed as an allergic disease while COPD is thought to primarily result from smoking-related inflammation and damage; however, they likely share common environmental and genetic factors and the chronic form in older subjects can present similarly.
- This is particularly true for childhood asthmatic subjects who become chronic smokers.

- Asthmatics with reduced lung function early in life were more likely to meet spirometric criteria for COPD in early adulthood.
- Patients with features of both asthma and COPD have been described as the asthma-COPD overlap syndrome.
- Both asthma and airway hyperresponsiveness are risk factors for COPD.
- Increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function.

RESPIRATORY INFECTIONS

- The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long-term reductions in pulmonary function are not typically seen following an individual episode of acute bronchitis or pneumonia.

- However, respiratory infections are important causes of COPD exacerbations, and recent results from the COPDGene and ECLIPSE studies suggest that COPD exacerbations are associated with increased loss of lung function longitudinally, particularly among those individuals with better baseline lung function levels.

- The impact of the effects of childhood respiratory illnesses on the subsequent development of COPD has been difficult to assess due to a lack of adequate longitudinal data, but recent studies have suggested that childhood pneumonia may lead to increased risk for COPD later in life

OCCUPATIONAL EXPOSURES

- Increased respiratory symptoms and airflow obstruction have been suggested to result from exposure to dust and fumes at work.
- Several specific occupational exposures, including coal mining, gold mining, and cotton textile dust, have been implicated as risk factors for chronic airflow obstruction.
- The importance of dust exposure as a risk factor for COPD, independent of cigarette smoking, is not certain for most of these exposures.
- However, among coal miners, coal mine dust exposure was a significant risk factor for emphysema in both smokers and nonsmokers. In most cases, the magnitude of these occupational exposures on COPD risk is likely substantially less important than the effect of cigarette smoking.

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 unproved.
- Prolonged exposure to smoke produced by biomass combustion—a common mode of cooking in some countries—also appears to be a significant risk factor for COPD among women in those countries.
- However, in most populations, ambient air pollution is a much less important risk factor for COPD than cigarette smoking

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.
- Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions often observed in COPD remains uncertain.

GENETIC CONSIDERATIONS

- Severe a1AT deficiency is a proven genetic risk factor for COPD.
- The common M allele is associated with normal a1AT levels. The S allele, associated with slightly reduced a1AT levels, and the Z allele, associated with markedly reduced a1AT levels, also occur with frequencies of >1% in most white populations.
- Rare individuals inherit null alleles, which lead to the absence of any a1AT production through a heterogeneous collection of mutations.
- 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 a1AT deficiency.

- Although only ~1% of COPD patients are found to have severe a1AT deficiency as a contributing cause of COPD, these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD.
- A significant percentage of the variability in pulmonary function among PiZ individuals is explained by cigarette smoking; cigarette smokers with severe a1AT deficiency are more likely to develop COPD at early ages.

- Among PiZ nonsmokers, impressive variability has been noted in the development of airflow obstruction. Asthma and male gender also appear to increase the risk of COPD in PiZ subjects.

- The risk of lung disease in heterozygous PiMZ individuals, who have intermediate serum levels of a1AT (~60% of PiMM levels), has been controversial.

- alpha-1 antitrypsin augmentation therapy is not recommended for use in PiMZ subjects

Other Genetic Risk Factors

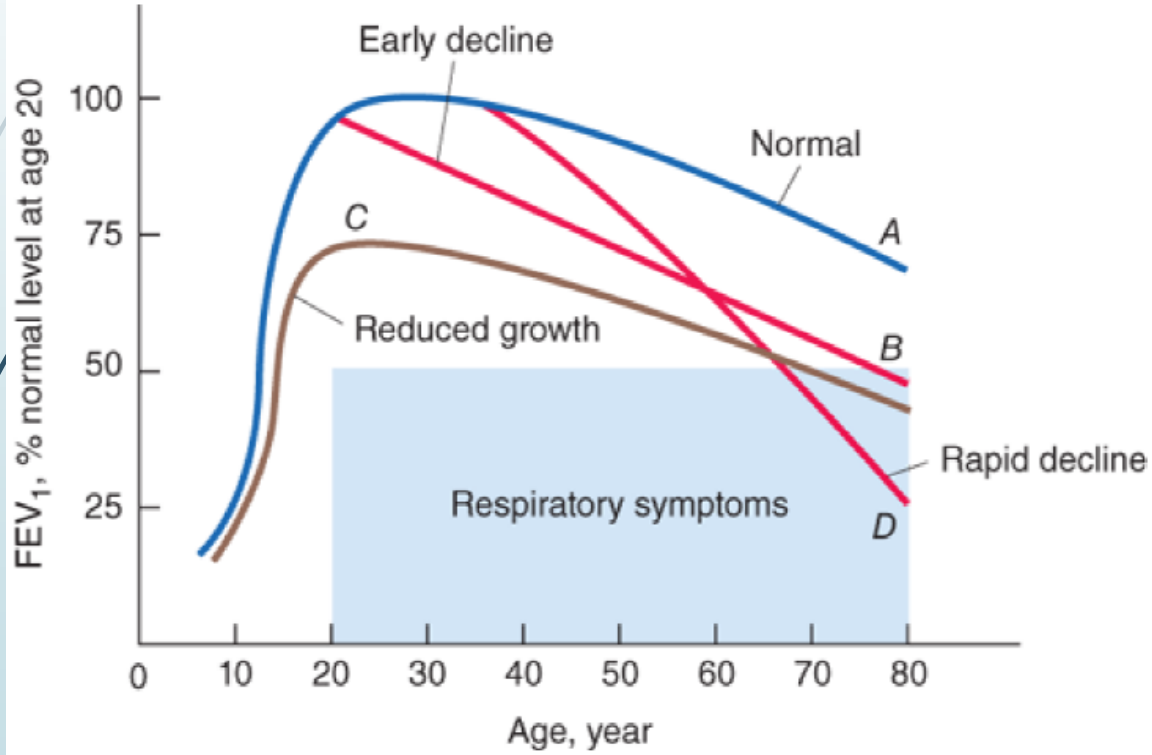
- GWAS have identified >20 regions of the genome that contain COPD susceptibility loci.

- Gene-targeted murine models for *HHIP, FAM13A, and IREB2 exposed to chronic cigarette* smoke had altered emphysema susceptibility, suggesting that those genes are likely to be involved in COPD pathogenesis.

NATURAL HISTORY

- 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;
- Other environmental factors may have similar effects.
- Most individuals follow a steady trajectory of increasing pulmonary function with growth during childhood and adolescence, followed by a plateau in early adulthood, and then gradual decline with aging.

Hypothetical tracking curves of forced expiratory volume in 1 s (FEV_1) for individuals throughout their life spans. The normal pattern of growth and decline with age is shown by curve *A*. Significantly reduced FEV_1 (<65% of predicted value at age 2(can develop from a normal rate of decline after a reduced pulmonary function growth phase (curve *C*), early initiation of pulmonary function decline after normal growth (curve *B*), or accelerated decline after normal growth (curve *D*). *(From B Rijcken: Doctoral dissertation, p 133, University of Groningen, 1991; with permission.)*



- The rate of decline in pulmonary function can be modified by changing environmental exposures (i.e., quitting smoking), with smoking cessation at an earlier age providing a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed.
- The absolute annual loss in FEV1 tends to be highest in mild COPD and lowest in very severe COPD.

- Multiple genetic factors influence the level of pulmonary function achieved during growth; genetic determinants likely also influence the rate of decline in response to smoking and potentially to other environmental factors as well.

COPD
PART 3

CLINICAL PRESENTATION
History

- The three most common symptoms in COPD are cough, sputum production, and exertional dyspnea.
- Many patients have such symptoms for months or years before seeking medical attention.
- Although the development of airflow obstruction is a gradual process, many patients date the onset of their disease to an acute illness or exacerbation.
- A careful history, however, usually reveals the presence of symptoms prior to the acute exacerbation.
- The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious.

- Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for many patients with COPD.
- Conversely, activities that allow the patient to brace the arms and use accessory muscles of respiration are better tolerated. Examples of such activities include pushing a shopping cart or walking on a treadmill.

- As COPD advances, the principal feature is worsening dyspnea on exertion with increasing intrusion on the ability to perform vocational or avocational activities.
- In the most advanced stages, patients are breathless doing simple activities of daily living.

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 of the lungs is notable for a prolonged expiratory phase and may include expiratory wheezing. In addition, signs of hyperinflation include a barrel chest and enlarged lung volumes with poor diaphragmatic excursion as assessed by percussion.

- Patients with severe airflow obstruction may also exhibit use of accessory muscles of respiration, sitting in the characteristic “tripod” position to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles.

- Patients may develop cyanosis, visible in the lips and nail beds.

- Although traditional teaching is that
- patients with predominant emphysema, termed "pink puffers," are thin and noncyanotic at rest and have prominent use of accessory muscles,
- patients with chronic bronchitis are more likely to be heavy and cyanotic ("blue bloaters"),
- current evidence demonstrates that most patients have elements of both chronic bronchitis and emphysema and that the physical examination does not reliably differentiate the two entities.

- Advanced disease may be accompanied by cachexia, with significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue.

- This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines (TNF-a). Such wasting is an independent poor prognostic factor in COPD.

- Some patients with advanced disease have paradoxical inward movement of the rib cage with inspiration (Hoover's sign), the result of alteration of the vector of diaphragmatic contraction on the rib cage as a result of chronic hyperinflation.

- Signs of overt right heart failure, termed *cor pulmonale, are relatively infrequent since the advent of supplemental oxygen therapy.*

- Clubbing of the digits is not a sign of COPD, and its presence should alert the clinician to initiate an investigation for causes of clubbing.

- In this population, the development of lung cancer is the most likely explanation for newly developed clubbing

LABORATORY FINDINGS

- The hallmark of COPD is airflow obstruction (discussed above). Pulmonary function testing shows airflow obstruction with a reduction in FEV1 and FEV1/FVC .
- **With worsening disease severity, lung volumes may increase, resulting in an increase in total lung capacity, functional residual capacity, and residual volume. In patients with emphysema**,
- the diffusing capacity may be reduced, reflecting the lung parenchymal destruction characteristic of the disease.
- The degree of airflow obstruction is an important prognostic factor in COPD and is the basis for the GOLD spirometric severity classification.

- Although the degree of airflow obstruction *generally correlates with the presence and severity of respiratory symptoms, exacerbations, emphysema, and* hypoxemia, the correlations are far from perfect.
- Thus, clinical features should be carefully assessed in each individual patient with COPD to determine the most appropriate therapies.
- It has been shown that a multifactorial index (BODE) incorporating airflow obstruction,
- exercise performance,
- dyspnea, and
- body mass index is a better predictor of mortality rate than pulmonary function
- alone.

TABLE 286-1 GOLD Criteria for Severity of Airflow Obstruction in COPD

GOLD Stage	Severity	Spirometry
I	Mild	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 50\%$ but $< 80\%$ predicted
III	Severe	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 30\%$ but $< 50\%$ predicted
IV	Very severe	$FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted

- Arterial blood gases and oximetry may demonstrate resting or exertional hypoxemia. Arterial blood gases provide additional information about alveolar ventilation and acid-base status by measuring arterial PCO_2 and pH.

- The change in pH with PCO_2 is 0.08 units/10 mmHg acutely and 0.03 units/10 mmHg in the chronic state.

- Knowledge of the arterial pH therefore allows the classification of ventilatory failure, defined as PCO_2 >45 mmHg, into acute or chronic conditions with acute respiratory failure being associated with acidemia.

- The arterial blood gas is an important component of the evaluation of patients presenting with symptoms of an exacerbation.

- An elevated hematocrit suggests the presence of chronic hypoxemia, as does the presence of signs of right ventricular hypertrophy

- Obvious bullae, paucity of parenchymal markings, or hyperlucency on chest x-ray suggests the presence of emphysema.
- Increased lung volumes and flattening of the diaphragm suggest hyperinflation but do not provide information about chronicity of the changes.
- Chest computed tomography (CT) scan is the current definitive test for establishing the presence or absence of emphysema, the pattern of emphysema, and the presence of significant disease involving medium and large airways .
- It also enables the discovery of coexisting interstitial lung disease and bronchiectasis, which are common complications in COPD. (described below).

- Smokers with COPD are at high risk for development of lung cancer, which can be identified on a chest CT scan.

- In advanced COPD, CT scans can help determine the possible value of surgical therapy.

- Recent guidelines have suggested testing for a1AT deficiency in all subjects with COPD or asthma with chronic airflow obstruction.
- Measurement of the serum a1AT level is a reasonable initial test.
- For subjects with low a1AT levels, the definitive diagnosis of a1AT deficiency requires PI type determination.
- This is typically performed by isoelectric focusing of serum or plasma, which reflects the genotype at the PI locus for the common alleles and many of the rare PI alleles as well.
- Molecular genotyping of DNA can be performed for the common PI alleles (M, S, and Z).

TREATMENT

Chronic Obstructive Pulmonary Disease STABLE PHASE COPD

- The two main goals of therapy are to provide symptomatic relief (reduce respiratory symptoms, improve exercise tolerance, improve health status)
- and
- reduce future risk (prevent disease progression, prevent and treat exacerbations, and reduce mortality).
- The institution of therapies should be based on symptom assessment, benefits of therapy, potential risks, and costs.

- Only three interventions
- 1)smoking cessation,
- 2)oxygen therapy in chronically hypoxemic patients, and
- 3) lung volume reduction surgery (LVRS) in selected patients with emphysema
- have been demonstrated to improve survival of patients with COPD.

- There is suggestive, but not definitive, evidence that the use of inhaled corticosteroids (ICS) and muscarinic antagonists may reduce the mortality rate.

PHARMACOTHERAPY
Smoking Cessation

- 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, often returning to annual changes similar to that of nonsmoking patients .
- **In addition, smoking cessation improves survival. Thus, all patients with COPD should be strongly urged to quit smoking and** educated about the benefits of quitting.
- An emerging body of evidence demonstrates that combining pharmacotherapy with traditional supportive approaches considerably enhances the chances of successful smoking cessation.

- There are three principal pharmacologic approaches to the problem:

- nicotine replacement therapy available as gum, transdermal patch, lozenge, inhaler, and nasal spray;
- bupropion; and
- varenicline, a nicotinic acid receptor agonist/antagonist.

- all adult, nonpregnant smokers considering quitting be offered pharmacotherapy, in the absence of any contraindication to treatment.

Bronchodilators

- In general, bronchodilators are the primary treatment for almost all patients with COPD and are used for symptomatic benefit and to reduce exacerbations.
- The inhaled route is preferred for medication delivery, because side effects are less than with systemic medication delivery.
- In symptomatic patients, both regularly scheduled use of long-acting agents and as-needed short-acting medications are indicated.

Anticholinergic Muscarinic Antagonists

- Short-acting ipratropium bromide improves symptoms with acute improvement in FEV1.
- Long-acting muscarinic antagonists (LAMA, including aclidinium, glycopyrrolate, tiotropium, and umeclidinium) improve symptoms and reduce exacerbations.
- In a large randomized clinical trial, there was a trend toward reduced mortality rate in tiotropium-treated patients that approached statistical significance.
- Side effects are minor; dry mouth is the most frequent side effect.

Beta Agonists

- Short-acting beta agonists ease symptoms with acute improvements in lung function.
- Long-acting agents (LABA) provide symptomatic benefit and reduce exacerbations, though to a lesser extent than a LAMA.
- Arformoterol, formoterol, indacaterol, olodaterol, salmeterol, and vilanterol.
- The main side effects are tremor and tachycardia.

Combinations of Beta Agonist — Muscarinic Antagonist

- The combination inhaled β agonist and muscarinic antagonist therapy has been demonstrated to provide improvement in lung function that is greater than either agent alone and reduces exacerbations.

Inhaled Corticosteroids

- The main role of ICS is to reduce exacerbations.
- Although one large trial and a meta-analysis demonstrated an apparent benefit from the regular use of inhaled glucocorticoids on the rate of decline of lung function, a number of other well-designed randomized trials have not.
- Their use has been associated with increased rates of oropharyngeal candidiasis and pneumonia and in some studies an increased rate of loss of bone density.
- A trial of ICS should be considered in patients with frequent exacerbations, defined as two or more per year, and in patients with features of asthma, such as eosinophilia. In stable patients, ICS withdrawal may be considered.
- Although ICS withdrawal does not lead to an increase in exacerbations, there may be a small decline in lung function

Oral Glucocorticoids

- The chronic use of oral glucocorticoids for treatment of COPD is not recommended because of an unfavorable benefit/risk ratio.
- The chronic use of oral glucocorticoids is associated with significant side effects, including osteoporosis, weight gain, cataracts, glucose intolerance, and increased risk of infection.
- A recent study demonstrated that patients tapered off chronic low-dose prednisone (~10 mg/d) did not experience any adverse effect on the frequency of exacerbations, health-related quality of life, or lung function.

Theophylline

- Theophylline produces modest improvements in airflow and vital capacity, but is not first-line therapy due to side effects and drug interactions.

- Nausea is a common side effect; tachycardia and tremor have also been reported. Monitoring of blood theophylline levels is required to minimize toxicity.

PDE4 Inhibitors

- The selective phosphodiesterase 4 (PDE4) inhibitor roflumilast has been demonstrated to reduce exacerbation frequency in patients with severe COPD, chronic bronchitis, and a prior history of exacerbations

- Its effects on airflow obstruction and symptoms are modest.

Antibiotics

- There are strong data implicating bacterial infection as a precipitant of a substantial portion of exacerbations.

- A randomized clinical trial of azithromycin, chosen for both its anti-inflammatory and antimicrobial properties, administered daily to subjects with a history of exacerbation in the past 6 months demonstrated a reduced exacerbation frequency and longer time to first exacerbation in the macrolide-treated cohort (hazard ratio, 0.73).

Oxygen

- Supplemental O2 is the only pharmacologic therapy demonstrated to unequivocally decrease mortality rates in patients with COPD.
- For patients with resting hypoxemia (resting O2 saturation ≤88% in any patient or ≤89% with signs of pulmonary hypertension or right heart failure), the use of O2 has been demonstrated to have a significant impact on mortality.
- Patients meeting these criteria should be on continuous oxygen supplementation because the mortality benefit is proportional to the number of hours per day oxygen is used.
- Various delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.
- A recent study failed to demonstrate significant benefits to COPD patients with moderate hypoxemia at rest or with hypoxemia only with activity.

a1AT Augmentation Therapy

- Specific treatment in the form of IV a1AT augmentation therapy is available for individuals with severe a1AT deficiency. Despite sterilization procedures for these blood-derived products and the absence of reported cases of viral infection from therapy, some physicians recommend hepatitis B vaccination prior to starting augmentation therapy.

- A recent randomized study suggested a reduction in emphysema progression in patients receiving a1AT augmentation therapy.

- Eligibility for a1AT augmentation therapy requires a serum a1AT level <11 µ*M (~50 mg/dL). Typically, PiZ individuals will qualify, although other rare types associated* with severe deficiency (e.g., null-null) are also eligible.

- Because only a fraction of individuals with severe a1AT deficiency will develop COPD, a1AT augmentation therapy is not recommended for severely a1AT-deficient persons with normal pulmonary function and a normal chest CT scan

NONPHARMACOLOGIC THERAPIES

- Patients with COPD should receive the influenza vaccine annually. Pneumococcal vaccines and vaccination for *Bordetella pertussis* are recommended.
- **Pulmonary Rehabilitation**
- This refers to a comprehensive treatment program that incorporates exercise, education, and psychosocial and nutritional counseling. 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- to 12-month period;

Lung Volume Reduction Surgery

- In carefully selected patients with emphysema, surgery to remove the most emphysematous portions of lung improves exercise, lung function, and survival.
- The anatomic distribution of emphysema and post-rehabilitation exercise capacity are important prognostic characteristics.
- Patients with upper lobe–predominant emphysema and a low post-rehabilitation exercise capacity are most likely to benefit from LVRS.

- Patients with an FEV1 <20% of predicted and either diffusely distributed emphysema on CT scan or diffusing capacity of lung for carbon monoxide (DLCO) <20% of predicted have increased mortality after the procedure, and thus are not candidates for LVRS.

Lung Transplantation

- COPD is currently the second leading indication for lung transplantation (.
- **Current recommendations are that** candidates for lung transplantation should have very severe airflow limitation,
- severe disability despite maximal medical therapy,
- be free of significant comorbid conditions such as liver, renal, or cardiac disease.

Copd part 4

EXACERBATIONS OF COPD

- Exacerbations are a prominent feature of the natural history of COPD.
- Exacerbations are episodic acute worsening of respiratory symptoms, including increased dyspnea, cough, wheezing, and/or change in the amount and character of sputum.
- They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat.
- The strongest single predictor of exacerbations is a history of a previous exacerbation

- The frequency of exacerbations increases as airflow obstruction worsens;
- patients with severe (FEV1 <50% predicted) or very severe airflow obstruction (FEV1 <30% predicted) on average have 1–3 episodes per year.
- However, some individuals with very severe airflow obstruction do not have frequent exacerbations.
- Other factors, such as an elevated ratio of the diameter of the pulmonary artery to aorta on chest CT, and gastroesophageal reflux, are also associated with increased risk of COPD exacerbations.

Precipitating Causes and Strategies to Reduce Frequency of Exacerbations

- A variety of stimuli may result in the final common pathway of airway inflammation and increased respiratory symptoms that are characteristic of COPD exacerbations.
- Studies suggest that acquiring a new strain of bacteria is associated with increased near-term risk of exacerbation and that bacterial infection/superinfection is involved in >50% of exacerbations.
- Viral respiratory infections are present in approximately one-third of COPD exacerbations.
- In a significant minority of instances (20–35%), no specific precipitant can be identified

Patient Assessment

- An attempt should be made to establish the severity of the exacerbation as well as the severity of preexisting COPD.
- The more severe either of these two components, the more likely that the patient will require hospital admission.
- The history should include quantification of the degree and change in dyspnea by asking about breathlessness during activities of daily living and typical activities for the patient. The patient should be asked about fever; change in character of sputum; and associated symptoms such as wheezing, nausea, vomiting, diarrhea, myalgias, and chills.
- Inquiring about the frequency and severity of prior exacerbations can provide important information; **the single greatest risk factor for hospitalization with an exacerbation is a history of previous hospitalization**.

- The physical examination should incorporate an assessment of the degree of distress of the patient.
- Specific attention should be focused on tachycardia, tachypnea, use of accessory muscles, signs of perioral or peripheral cyanosis, the ability to speak in complete sentences, and the patient's mental status.

- The chest examination should establish the presence or absence of focal findings, degree of air movement, presence or absence of wheezing, asymmetry in the chest examination (suggesting large airway obstruction or pneumothorax mimicking an exacerbation), and the presence or absence of paradoxical motion of the abdominal wall.

- Patients with severe underlying COPD, who are in moderate or severe distress, or those with focal findings should have a chest x-ray or chest CT scan.
- Approximately 25% of x-rays in this clinical situation will be abnormal, with the most frequent findings being pneumonia and congestive heart failure.
- Patients with advanced COPD, a history of hypercarbia, mental status changes (confusion, sleepiness), or those in significant distress should have an arterial blood-gas measurement.
- The presence of hypercarbia, defined as a PCO_2 >45 mmHg, has important implications for treatment.

- In contrast to its utility in the management of exacerbations of asthma, measurement of pulmonary function has not been demonstrated to be helpful in the diagnosis or management of exacerbations of COPD.

- Pulmonary embolus (PE) should also be considered, as the incidence of PE is increased in COPD exacerbations.

- The need for inpatient treatment of exacerbations is suggested by the presence of respiratory acidosis and hypercarbia, new or worsening hypoxemia, severe underlying disease and those whose living situation is not conducive to careful observation and the delivery of prescribed treatment

TREATMENT OF ACUTE EXACERBATIONS Bronchodilators

- Typically, patients are treated with inhaled β agonists and muscarinic antagonists. These may be administered separately or together.

- Patients are often treated initially with nebulized therapy, as such treatment is often easier to administer in those in respiratory distress. It has been shown, however, that conversion to metered-dose inhalers is effective when accompanied by education and training of patients and staff.

- This approach has significant economic benefits .
- The addition of methylxanthines (theophylline) to this regimen can be considered, although convincing proof of its efficacy is lacking. If added, serum levels should be monitored in an attempt to minimize toxicity.

Antibiotics

- Patients with COPD are frequently colonized with potential respiratory pathogens, and it is often difficult to identify conclusively a specific species of bacteria responsible for a particular clinical event.
- Bacteria frequently implicated in COPD exacerbations include
- *Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.*
- *In addition, Mycoplasma pneumoniae or Chlamydia pneumoniae are found in 5–10% of exacerbations.*
- *The choice of antibiotic should be based on local patterns of antibiotic* susceptibility of the above pathogens as well as the patient's clinical condition. Patients with moderate or severe exacerbations are usually treated with antibiotics, even in the absence of data implicating a specific pathogen

- In patients admitted to the hospital, the use of systemic glucocorticoids reduces the length of stay, hastens recovery, and reduces the chance of subsequent exacerbation or relapse.

- Current recommendations suggest 30–40 mg of oral prednisolone or its equivalent typically for a period of 5–10 days in outpatients.

- Hyperglycemia, particularly in patients with preexisting diagnosis of diabetes, is the most frequently reported acute complication of glucocorticoid treatment

Oxygen

- Supplemental O2 should be supplied to maintain oxygen saturation ≥90%.
- Studies have demonstrated that in patients with both acute and chronic hypercarbia, the administration of supplemental O2 does not reduce minute ventilation.
- It does, in some patients, result in modest increases in arterial PCO2, chiefly by altering ventilation-perfusion relationships within the lung. This should not deter practitioners from providing the oxygen needed to correct hypoxemia.

Mechanical Ventilatory Support

- The initiation of noninvasive positive-pressure ventilation (NIPPV) in patients with respiratory failure, defined as $PaCO_2$ >45 mmHg, results in a significant reduction in mortality rate, need for intubation, complications of therapy, and hospital length of stay.

Contraindications to NIPPV include

- cardiovascular instability,
- impaired mental status,
- inability to cooperate,
- copious secretions or
- inability to clear secretions,
- craniofacial abnormalities or trauma precluding effective fitting of mask, extreme obesity, or
- significant burns

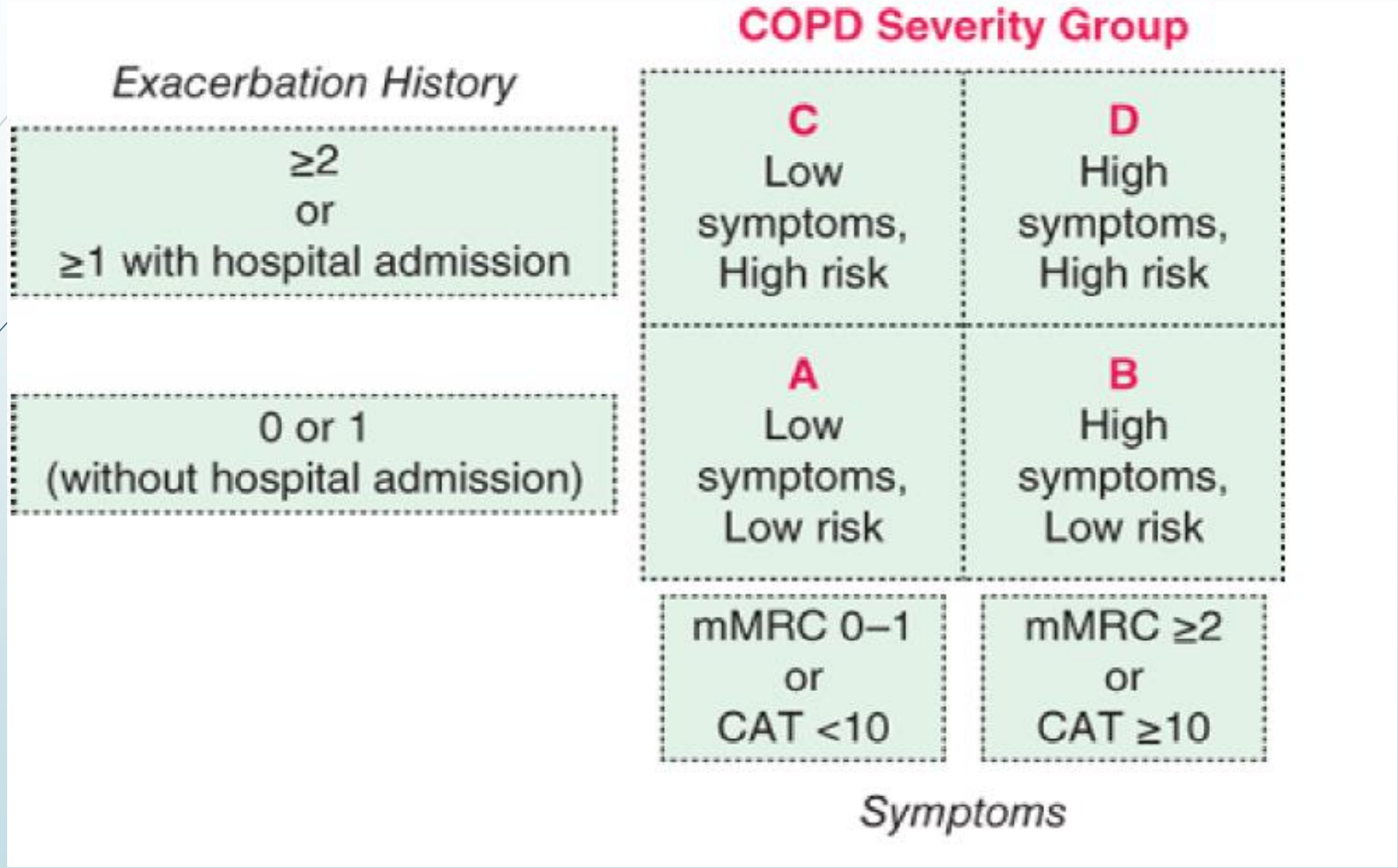
- Invasive (conventional) mechanical ventilation via an endotracheal tube is indicated for patients with severe respiratory distress despite initial therapy, life-threatening hypoxemia, severe hypercarbia and/or acidosis, markedly impaired mental status, respiratory arrest, hemodynamic instability, or other complications.
- The goal of mechanical ventilation is to correct the aforementioned conditions.

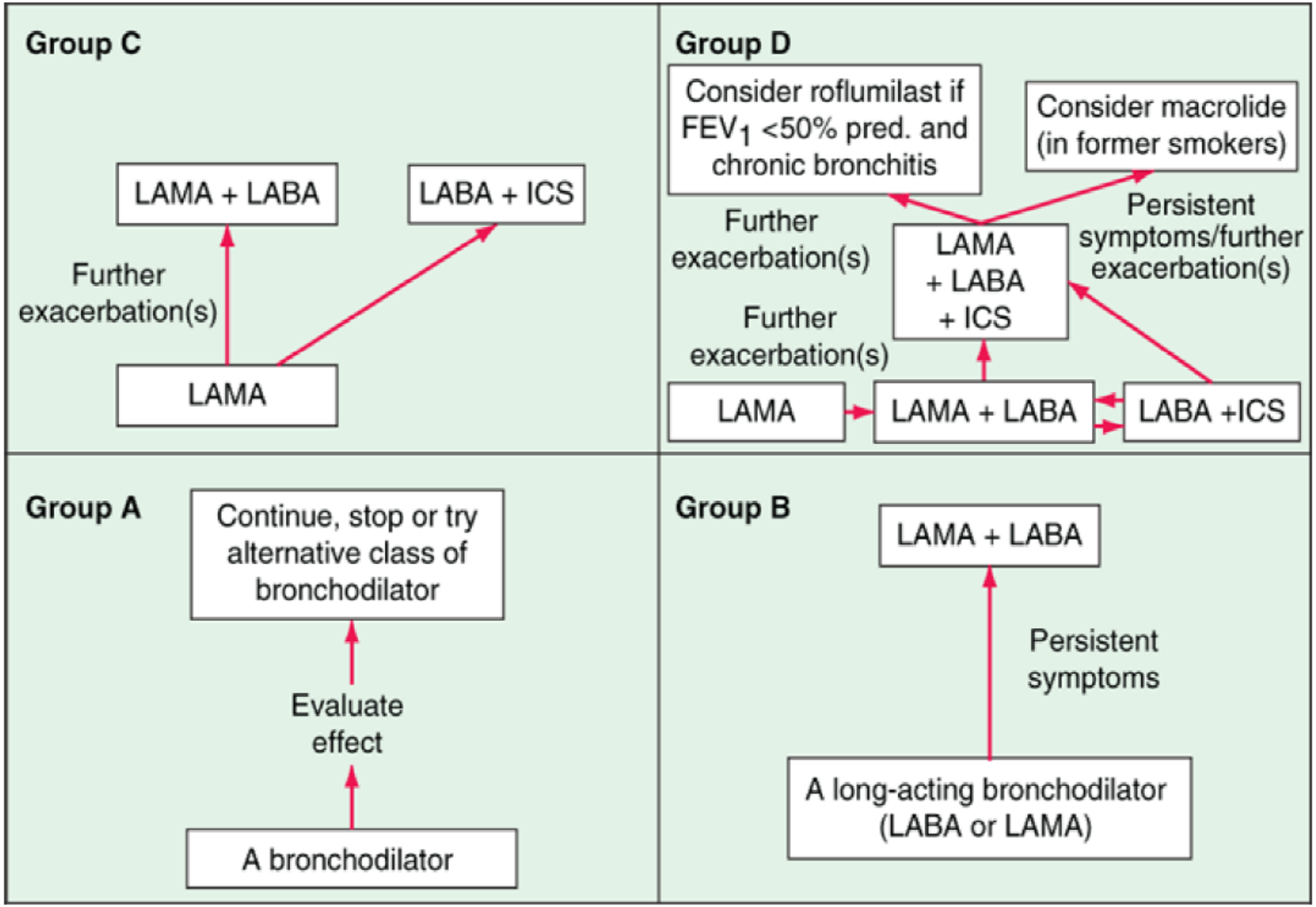
- Factors to consider during mechanical ventilatory support include the
- need to provide sufficient expiratory time in patients with severe airflow obstruction and
- the presence of auto-PEEP (positive end-expiratory pressure), which can result in patients having to generate significant respiratory effort to trigger a breath during a demand mode of ventilation.
- The mortality rate of patients requiring mechanical ventilatory support is 17–30% for that particular hospitalization.
- For patients aged >65 admitted to the intensive care unit for treatment, the mortality rate doubles over the next year to 60%, regardless of whether mechanical ventilation was required.

- Following a hospitalization for COPD, about 20% of patients are re-hospitalized in the subsequent 30 days and 45% are hospitalized in the next year.

- Mortality following hospital discharge is about 20% in the following year.

COPD severity assessment





Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo

- mMRC—Modified Medical Research Council Dyspnea Scale. Provides a single number for degree of breathlessness: 0—only with strenuous activity; 1—hurrying on level ground or walking up a slight hill; 2—walk slower than peers or stop walking at their own pace; 3—walking about 100 yards or after a few minutes on level ground; 4—too breathless to leave the house or when dressing.

- CAT—COPD Assessment Test. An 8-item COPD health status measure with Likert scale responses for questions about cough, phlegm, chest tightness, dyspnea on one flight of stairs, limitation in home activities, confidence in leaving the home, sleep and energy.

Good luck

- THANKS FOR YOUR ATTENTION