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Grasemann H, Ratjen F: Cystic fibrosis. N Engl J Med 389:1693, 2023. Keating D et al: VX-445-tezacaftor-ivacator in patients with cystic fibrosis and one or two Phe508del alleles. N Engl J Med 379:1612, 2018. Manfredi C et al: Making precision medicine personal for cystic fibrosis. Science 365:220, 2019. Middleton PG et al: Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 381:1809, 2019. Ramos KF et al: Survival and lung transplant outcomes for individuals with advanced cystic fibrosis lung disease living in the United States and Canada: An analysis of national registries. Chest 160:843, 2021. Sosnay PR et al: Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet 45:1160, 2013. Stoltz DA et al: Origins of cystic fibrosis lung disease. N Engl J Med 372:351, 2015. VIDEO 302-1 Role of CFTR during airway mucociliary clearance. Initial video sequences depict establishment of the normal periciliary fluid layer bathing the surface airway epithelium, with spheres representing chloride and bicarbonate ions secreted through CFTR and across the apical (mucosal) respiratory surface. Later video describes failure of CFTR anion transport and resulting depletion of the periciliary layer, “plastering” of cilia against the mucosal surface, and accumulation of mucus in the airway with resulting bacterial infection. (Reproduced with permission from Cystic Fibrosis Foundation.) VIDEO 302-2 Pharmacologic modulation of mutant CFTR. Initial video (A) illustrates CFTR encoding an ion transport gating (class III) defect. The cystic fibrosis (CF) gene product is localized to the plasma membrane but incapable of conducting anions (yellow spheres) until a potentiator molecule (shown in green) binds and facilitates channel opening. Later video (B) describes CFTR encoding a maturational processing (protein biogenesis, class II) defect. The mutant protein is misfolded, fails to traffic to the cell surface, and is degraded by the proteasome. Binding of corrector molecules (red spheres) improves folding and facilitates CFTR stabilization and cell surface localization/function. (Reproduced with permission from Cystic Fibrosis Foundation.) Craig P. Hersh, Edwin K. Silverman,

Dawn DeMeo

Chronic Obstructive

Pulmonary Disease Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by persistent respiratory symptoms and airflow obstruction (https://goldcopd.org/2024-gold-report/). COPD includes emphysema, an anatomically defined condition character ized by destruction of the lung alveoli with air space enlargement; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and/or small airway disease, a condition in which small bronchioles are narrowed and reduced in number. The classic defini tion of COPD requires the presence of chronic airflow obstruction, determined by spirometry, that usually occurs in the setting of noxious environmental exposures, most commonly products of combustion, including cigarette smoking in the United States and biomass fuels in some other countries. The increasing prevalence of vaping and use of inhaled cannabis are of increasing concern, especially in adolescent populations. Other factors including abnormal lung development, respiratory infections, asthma, and genetics, can lead to COPD. Emphysema, chronic bronchitis, and small airway disease are present in varying degrees in different COPD patients. Patients with a his tory of cigarette smoking without chronic airflow obstruction may

have chronic bronchitis, emphysema, respiratory symptoms including dyspnea, and acute exacerbations. Although these patients are not included within the classic definition of COPD, they may have similar disease processes. Investigators in the COPDGene study proposed a multidimensional approach to COPD diagnosis, which is based on domains of environmental exposures, respiratory symptoms, imaging abnormalities, and physiologic abnormalities.

COPD is the fourth leading cause of death and affects >15 million persons in the United States. COPD is also a disease of increasing public health importance around the world. Globally, there are an estimated 480 million individuals with COPD, with a projection of 592 million by 2050. Chronic Obstructive Pulmonary Disease CHAPTER 303 PATHOGENESIS AND PATHOLOGY Airflow obstruction, the primary physiologic marker of COPD, can result from airway disease and/or emphysema. Cigarette smoke expo sure 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 physi ologic alterations. Airway inflammation, small airway destruction, and the development of emphysema are present in most persons with COPD; however, their relative contributions to airflow obstruction vary from one person to another. The early development of chronic air flow obstruction is driven by small airway disease. Small airways may become narrowed by cells (hyperplasia and accumulation), mucus, and fibrosis. Advanced stages of COPD are typically characterized by extensive emphysema, although there are a small number of subjects with very severe airflow obstruction with airway disease and virtually no emphysema. The subjects at greatest risk of progression in COPD are those with both aggressive airway disease and emphysema. ■ ■LARGE AIRWAY DISEASE Cigarette smoking often results in mucus gland enlargement and goblet cell hyperplasia, leading to cough and mucus production that define chronic bronchitis. Mucus plugs have been frequently observed on chest computed tomography (CT) scans of COPD patients, and they have recently been associated with increased mortality risk. In response to cigarette smoking or other inhaled exposures, goblet cells increase not only in number but also in extent through the bronchial tree. Bron chi also undergo squamous metaplasia, predisposing to carcinogenesis and disrupting mucociliary clearance. Although not as prominent as in asthma, patients with COPD may have bronchial hyperreactivity leading to airflow obstruction. 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 AIRWAY DISEASE The major site of increased airflow 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 hyper trophy 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 mono nuclear 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. Narrowing and drop-out of small airways precede the onset of emphysematous destruction. 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 PARENCHYMAL DESTRUCTION Emphysema is characterized by destruction of gas-exchanging air spaces, i.e., the respiratory bronchioles, alveolar ducts, and alveoli. Large numbers of macrophages accumulate in respiratory bron chioles of essentially all smokers. Neutrophils, B lymphocytes, and

PART 7 Disorders of the Respiratory System A B C FIGURE 303-1 Computed tomography (CT) patterns of emphysema. A. Centrilobular emphysema with severe upper lobe involvement in a 68-year-old man with a 70-pack-year smoking history but forced expiratory volume in 1 s (FEV1) 81% predicted (Global Initiative for Chronic Obstructive Lung Disease [GOLD] spirometry grade 1). B. Panlobular emphysema with diffuse loss of lung parenchymal detail predominantly in the lower lobes in a 64-year-old man with severe α1antitrypsin (α1AT) deficiency. C. Paraseptal emphysema with marked airway inflammation in a 52-year-old woman with a 37-pack-year smoking history and FEV1 40% predicted. T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers. Alveolar walls become perforated and later obliterated with coalescence of the delicate alveolar structure into large emphysematous air spaces. Emphysema is classified into distinct pathologic types, which include centrilobular, panlobular, and paraseptal (Fig. 303-1). Centri lobular 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. Panlobular emphysema refers to abnormally large air spaces evenly distributed within and across acinar units. Panlobular Cigarette smoke Genetic susceptibility Triggers Effector cells Macrophages Neutrophils Lymphocytes Epithelial cells Biological pathways Protease/Antiprotease Key molecules MMP12 SERPINA1 Neutrophil Elastase SOD3 HDAC2 Ceramide Elastin NF KappaB NRF2 TGFBeta Rtp801 Extracellular matrix destruction Pathobiological result FIGURE 303-2 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. Although most of these biological pathways influence multiple pathobiological results, only a single relationship between pathways and results is shown. A subset of key molecules related to these biological pathways is listed.

emphysema is commonly observed in patients with α1-antitrypsin (α1AT) deficiency, which has a predilection for the lower lobes. Paraseptal emphysema is distributed along the pleural mar gins with relative sparing of the lung core or central regions. Except for α1AT deficiency, pathobiological

mechanisms related to different emphysema patho phenotypes are not well understood. Radiographic imaging can be used to quantify the amount and distribution of emphysema. ■ ■DISEASE MECHANISMS Although the precise biological mecha nisms 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 (shown in Fig. 303-2) is more clearly defined than the pathogenesis of small airway disease. Pulmonary vascular destruction occurs in concert with small airway disease and emphysema. The current dominant paradigm for the pathogenesis of emphysema comprises a series of four interrelated events: (1) Chronic inhaled exposures (typically cigarette smoke) in genetically susceptible indi viduals 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 oxidant-induced Oxidant/Antioxidant Lung repair Apoptosis Chronic inflammation Ineffective repair Cell death

damage, cellular senescence, and proteolytic loss of cellular-matrix attachments leading to extensive loss of smaller airways, vascular prun ing, 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 compo nent 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 α1AT, the inhibitor of the serine proteinase neutrophil elastase, were at increased risk of emphysema, and that instillation of elastases, including neutro phil elastase, into experimental animals resulted in emphysema. The elastase:antielastase hypothesis remains a prevailing mechanism for the development of emphysema. However, a complex network of immune and inflammatory cells and additional biological mechanisms that con tribute to emphysema have subsequently been identified. Both innate and adaptive immune systems are likely involved in COPD pathogen esis. Upon exposure to oxidants from cigarette smoke, lung macro phages and epithelial cells become activated, producing proteinases and chemokines that attract other inflammatory and immune cells. Single-cell transcriptomics revealed that a subset of alveolar type 2 cells is the predominant site of lung gene expression of HHIP, one of the top COPD susceptibility genes identified by genome-wide association studies. 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 dysfunc tion in COPD may worsen oxidative stress. One mechanism of mac rophage activation occurs via oxidant-induced inactivation of histone deacetylase-2 (HDAC2), shifting the balance toward acetylated or open chromatin, exposing nuclear factor-κB sites, and resulting in transcrip tion of matrix metalloproteinases and proinflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor α (TNF-α); 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 macro phage elastase (matrix metalloproteinase-12 [MMP12]). Matrix metalloproteinases and serine proteinases, most notably neu trophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction. Extracellular vesicles induced by

cigarette smoke and expressing neutrophil elastase or MMP12 on their surface have been recently implicated as important sources of these destructive proteinases. Proteolytic cleavage products of elastin serve as a macro phage chemokine, and proline-glycine-proline (generated by proteolytic cleavage of collagen) is a neutrophil chemokine, fueling this damaging positive feedback loop. Elastin degradation and disordered repair are thought to be primary mechanisms in the development of emphysema. There is some evidence that autoimmune mechanisms may promote the progression of disease. Lymphoid follicles composed of B cells and T cells are present around the airways of COPD patients, particularly in patients with advanced disease. TH1 and TH17 lymphocytes may activate innate immune cells (including neutrophils, macrophages, and innate lymphoid cells), contributing to a cycle of chronic inflam mation. 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 smok ing 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 cellular senescence markers has led to the concept that emphysema resembles premature aging of the lung; emphysema has been identified in the lung tissue of lifetime never smokers of advanced age. Heterozygous gene targeting of hedgehog interacting protein (HHIP) in a murine model leads to aging-related emphysema.

Chronic Obstructive Pulmonary Disease CHAPTER 303 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 and other inhaled exposures impair 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 reiniti ated in the adult human lung. PATHOPHYSIOLOGY Persistent irreversible reduction in forced expiratory flow rates is the classic definition of COPD. Hyperinflation with increases in the residual volume and the residual volume/total lung capacity ratio, nonuniform distribution of ventilation, and ventilation-perfusion mis matching also occur. ■ ■AIRFLOW OBSTRUCTION Airflow obstruction, also known as airflow limitation, is typically determined for clinical purposes by spirometry, which involves maxi mal 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 fixed airflow obstruction have a chronically reduced ratio of FEV1/FVC that does not normalize following bronchodilator treatment. ■ ■HYPERINFLATION Lung volumes are also commonly 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) in more advanced disease. Hyperinflation of the thorax during tidal breath ing

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 pres sure 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 normal inspiratory pressures. Third, the flattened dia phragm 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 gen eralizations may be made. The partial pressure of oxygen in arterial blood Pao2 usually remains near normal until the FEV1 is decreased

to below 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 arterial hyper tension 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, some patients develop significant pulmonary arterial hypertension likely due to vascular destruction, independent of COPD severity (Chap. 294).

Nonuniform ventilation and ventilation-perfusion mismatching are characteristic of COPD, reflecting the heterogeneous nature of the disease process within the airways and lung parenchyma. Physiologic studies are consistent with multiple parenchymal compartments having different rates of ventilation due to regional differences in compliance and airway resistance. Ventilation-perfusion 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. PART 7 Disorders of the Respiratory System RISK FACTORS ■ ■CIGARETTE SMOKING By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking was a major risk factor for mortality from chronic bronchitis and emphysema. Subsequent longitudinal studies have shown accelerated decline in FEV1 in a doseresponse relationship to the intensity of cigarette smoking, which is typically expressed as pack-years (average number of packs of ciga rettes smoked per day multiplied by the total number of years of smok ing). 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 histori cally higher rate of smoking among males is the likely explanation for the historically higher prevalence of COPD among males; however, the prevalence of COPD among females has increased to the point that it is the same or exceeds the prevalence of COPD in men. Although the causal relationship between cigarette smoking and the development of COPD has been absolutely proved, there is consider able individual variability in the response to smoking. Pack-years of cigarette smoking is

the most highly significant predictor of FEV1 (Fig. 303-3), but only 15% of the variability in FEV1 is explained by pack-years. This finding suggests that additional developmental, envi ronmental, and/or genetic factors contribute to the impact of smoking on the development of chronic airflow obstruction. Nonetheless, many patients with a history of cigarette smoking with normal spirometry have evidence for worse health-related quality of life, reduced exercise capacity, and emphysema and/or airway disease on chest CT scans; thus, they have not escaped the harmful effects of cigarette smoking and may present with respiratory exacerbations despite normal spi rometry. While they do not meet the classic definition of COPD based on population normals for FEV1 and FEV1/FVC, studies have shown that these subjects overall have a shift toward lower FEV1 values, which is consistent with obstruction on an individual level. 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 and vaping on the development and progression of COPD is a growing area of concern; emerging literature identifies increased risk for pulmonary symptoms. Inhaled cannabis use is increasing in prevalence and may increase risk for cough, sputum production, and wheeze. However, it remains unclear whether there is an elevated risk for COPD from cannabis inhalation. A large study of lung function observed heavy cannabis use associated with steeper decline in FEV1, although other studies have not observed accelerated lung function decline.

–1 S.D. Mean +1 S.D. 0 Pack years (945)

Median

0–20 Pack years (578)

21–40 Pack years (271)

% of Population

41–60 Pack years (154)

61+ Pack years (100)

FEV1 (% predicted) FIGURE 303-3 Distributions of forced expiratory volume in 1 s (FEV1) values in a general population sample, stratified by pack-years of smoking. Means, medians, and ±1 standard deviation of percent predicted FEV1 are shown for each smoking group. Although a dose-response relationship between smoking intensity and FEV1 was found, marked variability in pulmonary function was observed among subjects with similar smoking histories. S.D., standard deviation. (Reproduced with permission from B Burrows: Quantitative relationships between cigarette smoking and ventilatory function. Am Rev Respir Dis 115:195, 1977.) ■ ■AIRWAY RESPONSIVENESS AND COPD A tendency for increased reversible bronchoconstriction in response to a variety of exogenous stimuli, including methacholine and histamine, is one of the defining features of asthma (Chap. 298). However, many patients with COPD also share this feature of airway hyperresponsive ness. In older subjects, there is considerable overlap between persons with a history of chronic asthma and COPD in terms of airway respon siveness, airflow obstruction, and pulmonary symptoms. The origin of asthma is viewed in many patients 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 relevant for childhood asthmatic subjects who chronically smoke throughout adulthood. Longitudinal studies that compared airway responsiveness to subse quent decline in pulmonary function have demonstrated that increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function. A study from the Childhood Asthma Management Program identified four lung function trajectories in chil dren with persistent asthma. Asthmatics with reduced lung function early in life were more likely to develop persistent airflow obstruction in early adulthood. Both asthma and airway hyperresponsiveness are risk factors for COPD. ■ ■RESPIRATORY INFECTIONS The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long-term reductions in pul monary function are not typically seen following an individual episode of acute bronchitis or pneumonia. However, respiratory infections are important causes of COPD exacerbations, and results from the COPDGene and ECLIPSE studies suggest that COPD exacerbations are associated with increased loss of lung function longitudinally, par ticularly 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. Globally, tuberculosis infection has been associated with chronic airflow limitation and may be an important risk factor in the absence of a personal tobacco use history; tuberculosis-associated COPD may present with both emphysematous and fibrotic changes in the lung and with extensive airway remodeling. Infection with human immunodeficiency virus (HIV) leads to an increased risk for COPD and emphysema, especially with lower CD4 cell counts; COPD is fre quently underdiagnosed in this setting. ■ ■OCCUPATIONAL EXPOSURES Increased respiratory symptoms and airflow obstruction have been suggested to result from exposure to vapors, gas, dust, or fumes (VGDF). Several specific occupational exposures, including coal min ing, gold mining, and cotton textile dust, have been implicated as risk factors for chronic airflow obstruction. Although nonsmokers in these occupations can develop some reductions in FEV1, 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. Given general under recognition of VGDF and other occupational drivers and exacerbants of COPD, clinical history taking should include past and current occupational exposures, and referral to occupational health specialists as relevant. ■ ■AIR POLLUTION AND CLIMATE CHANGE Some investigators have reported increased respiratory symptoms in those living in urban compared to rural areas, which may relate to increased ambient air pollution in urban settings, especially fine and ultrafine particulate pollution. However, the relationship of air pollu tion to chronic airflow obstruction remains unproved. Prolonged expo sure to smoke produced by biomass combustion—a common mode of cooking in some countries—is a significant risk factor for COPD, particularly among women. The future impact of global warming on COPD is not clear, although increased extreme hot days are associated with respiratory exacerbations. ■ ■EARLY LIFE PASSIVE SMOKE EXPOSURE Maternal tobacco smoking during in utero lung development con tributes to significant reductions in postnatal lung development and pulmonary function. Exposure of children to environmental smoke related to tobacco and biomass fuel may also result in reduced lung growth and respiratory exacerbations. Early life exposure to

environ mental tobacco smoke has been linked to emphysema in adulthood. ■ ■GENETICS Although cigarette smoking is the major environmental risk factor for the development of COPD, the development of airflow obstruction in smokers is highly variable. Severe α1AT deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist. α1-Antitrypsin Deficiency Many variants of the protease inhibi tor (PI or SERPINA1) gene that encodes α1AT have been described. The common M allele is associated with normal α1AT levels. The S allele, associated with slightly reduced α1AT levels, and the Z allele, associated with markedly reduced α1AT levels, also occur with frequencies of >1% in most white populations. Rare individuals inherit null alleles, which lead to the absence of any α1AT 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 α1AT deficiency. Although only ~1% of COPD patients are found to have severe α1AT 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,

but the ascertainment bias in the published series of PiZ individuals— which have usually included many PiZ subjects who were tested for α1AT deficiency because they had COPD—means that the fraction of PiZ individuals who will develop COPD and the age-of-onset distribu tion for the development of COPD in PiZ subjects remain unknown. Approximately 1 in 3000 individuals in the United States inherits severe α1AT deficiency, but only a small minority of these individuals has been identified. The clinical laboratory test used most frequently to test for α1AT deficiency is measurement of the immunologic level of α1AT in serum (see “Laboratory Findings”).

Chronic Obstructive Pulmonary Disease CHAPTER 303 A significant percentage of the variability in pulmonary function among PiZ individuals is explained by cigarette smoking; cigarette smokers with severe α1AT deficiency are more likely to develop COPD at early ages. However, the development of COPD in PiZ subjects, even among current or ex-smokers, is not absolute. 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. Other genetic and/or environmental factors likely contribute to this variability. Specific treatment in the form of α1AT augmentation therapy is available for severe α1AT deficiency as a weekly IV infusion (see “Treatment,” below). Several recent studies have demonstrated that heterozygous PiMZ subjects (who have intermediate serum levels of α1AT) who smoke are at increased risk for the development of COPD. However, α1AT augmentation therapy is not recommended for use in PiMZ subjects. Other Genetic Risk Factors Studies of pulmonary function measurements performed in general population samples have indi cated that genetic factors other than PI type influence variation in pul monary function. Familial aggregation of airflow obstruction within families of COPD patients has also been demonstrated. Genome-wide association studies (GWAS) have identified >80 regions of the genome that contain COPD susceptibility loci, including a region near the HHIP gene on chromosome 4, a cluster of genes on chromosome 15 (including components of the nicotinic acetylcho line receptor and another gene, IREB2, related to mitochondrial iron regulation), and FAM13A on chromosome 4, which is involved in Wnt/beta-catenin signaling. As with most other complex diseases, the risk associated with individual GWAS loci is modest, but these genetic determinants may identify important biological pathways related to COPD. Gene-targeted murine models for HHIP, FAM13A, and IREB2 exposed to chronic cigarette smoke had altered emphysema suscepti bility, suggesting that those genes are likely to be involved in COPD pathogenesis. An

elevated polygenic risk score, which sums the effects of multiple genetic variants, is associated with increased COPD risk. NATURAL HISTORY The effects of cigarette smoking on pulmonary function appear to depend on the intensity of smoking exposure, the timing of smok ing exposure during lung growth and development, 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 starting in the fourth decade of life. Individuals appear to track in their quantile of pulmonary function based on environmental and genetic factors that put them on different tracks. The risk of eventual mortality from COPD is closely associated with reduced levels of FEV1 and the presence of emphysema. A graphic depiction of the natural history of COPD is shown as a function of the influences on tracking curves of FEV1 in Fig. 303-4. Death or disability from COPD can result from a normal rate of decline after a reduced growth phase (curve C), an early initiation of pulmonary function decline after normal growth (curve B), or an accelerated decline after normal growth (curve D). Although accelerated rates of lung function decline have classically been associated with COPD, analyses of several population-based cohorts demonstrated that many subjects with fixed airflow obstruc tion had reduced growth but normal rates of lung function decline.

Early decline

FEV1, % normal level at age 20 Normal C A

Reduced growth B

Rapid decline Respiratory symptoms

D PART 7 Disorders of the Respiratory System

Age, year FIGURE 303-4 Hypothetical tracking curves of forced expiratory volume in 1 s (FEV1) for individuals throughout their life spans. The normal pattern of growth and decline with age is shown by curve A. Significantly reduced FEV1 (<65% of predicted value at age 20) 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.) The rate of decline in pulmonary function can be modified by changing environmental exposures (i.e., quitting smoking), with smoking cessa tion 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 influ ence the level of pulmonary function achieved during growth. In chronic smokers, a group at risk for COPD (sometimes called pre-COPD) based on substantial chest CT changes (emphysema and airway wall thickening) has been identified in subjects with normal physiology (normal FEV1 and FEV1/FVC). COPD in these subjects commonly progresses in two primary patterns. Subjects with an emphysema-predominant pattern show emphysema early and classi cally progress through COPD severity grades. Subjects with an airway disease–predominant pattern typically show initial evidence of airway inflammation and progress with little emphysema early as FEV1 falls while retaining a normal FEV1/FVC ratio. This is termed preserved ratio–impaired

spirometry (PRISm) physiology. The natural history of patients classified as having PRISm revealed an increased risk of mor tality and respiratory and cardiovascular events. Although advanced age is an important risk factor for COPD, early COPD is an important area of research given advances in understanding cellular and molecu lar features and the importance of slowing lung function decline. CLINICAL PRESENTATION ■ ■HISTORY The three most common symptoms in COPD are cough, sputum pro duction, 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 respira tory 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. It is best elicited by a careful history focused on typical physical activities and how the patient's ability to perform them has changed. Activities involving significant arm work, particularly at or above shoulder level, are par ticularly 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 basic activi ties of daily living. Validated questionnaires such as the COPD Assess ment Test (CAT) and Modified Medical Research Council dyspnea scale may be used to reliably capture symptoms and activity limitations. Accompanying worsening airflow obstruction is an increased fre quency of exacerbations (described below). Patients may also develop resting hypoxemia and require institution of supplemental oxygen. A thorough history must consider symptoms of common comorbidities, such cardiovascular disease, gastroesophageal reflux, osteoporosis, frailty, depression, and anxiety. ■ ■PHYSICAL EXAMINATION In the early stages of COPD, patients usually have an entirely normal physical examination. 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 hyperinfla tion include a barrel chest and enlarged lung volumes with poor dia phragmatic excursion as assessed by percussion. Patients with severe airflow obstruction may also exhibit use of accessory muscles of res piration, 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. Advanced disease may be accompanied by cachexia, with signifi cant weight loss and diffuse loss of subcutaneous adipose tissue. This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines (e.g., TNF-α). Such wasting is an independent poor prognostic factor in COPD. Signs of overt right heart failure, termed cor pulmonale, are relatively infrequent since the advent of supplemental oxygen therapy, but pul monary hypertension must be considered in patients with persistent activity limitations or lower extremity edema. 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 COPD patients, 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 reduc tion in FEV1 and FEV1/FVC (Chap. 296). 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 dis ease. The degree of airflow obstruction is an important prognostic factor in COPD. For spirometric severity grading, the Global Initia tive for Chronic Obstructive Lung Disease (GOLD) has consistently used thresholds of FEV1 as a percentage of predicted value based on population reference equations. The American Thoracic Society and European Respiratory Society have recently advocated grading sever ity of lung function impairment using population-defined Z-scores

(Table 303-1). Pulmonary function interpretation has traditionally used race-specific reference values; however, race-neutral interpreta tion of pulmonary function tests may be preferable. 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 body mass index, airflow obstruction, dyspnea, and exercise performance, is a better predictor of mortality. Exercise capacity can be quantified by the distance a patient is able to walk in 6 min. The GOLD COPD classification system incor porates respiratory symptoms and exacerbation history; these metrics are used to guide COPD treatment (see below). Arterial blood gases and oximetry may demonstrate resting or exer tional hypoxemia. Arterial blood gases provide additional information about alveolar ventilation and acid-base status by measuring arterial

TABLE 303-1 Comparison of GOLD and ATS/ERS Criteria for Severity of Airflow Obstruction GOLD ERS/ATS SEVERITY SPIROMETRY SEVERITY SPIROMETRY Mild FEV1/FVC <0.7 and FEV1 ≥80% predicted a FEV1/FVC <LLN and zFEV1 > –1.645 Moderate FEV1/FVC <0.7 and FEV1 ≥50% but <80% predicted Mild FEV1/FVC <LLN and zFEV1 between –1.65 and –2.5 Severe FEV1/FVC <0.7 and FEV1 ≥30% but <50% predicted Moderate FEV1/FVC <LLN and zFEV1 between –2.51 and –4 Very severe FEV1/FVC <0.7 and FEV1 <30% predicted Severe FEV1/FVC <LLN and zFEV1 < –4.1 aThe ERS/ATS document does not provide a term for this category. Some authors have called it “borderline” or “minimal.” Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; zFEV1, z-score of FEV1. Pco2 and pH. The change in pH with Pco2 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 Pco2 >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. The blood eosinophil count, measured on a complete blood count with differential, is used to guide therapy, with the goal of reducing exacerbation risk Radiographic studies may assist in the classification of the type of COPD. Chest x-ray findings may be consistent with COPD but cannot be used reliably to make the diagnosis. Increased lung volumes and flattening of the diaphragm suggest hyperinflation but do not provide information about chronicity of the changes. Obvious bullae, paucity of parenchymal markings, or hyperlucency on chest x-ray suggests the presence of emphysema. Chest 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 (Fig. 303-1). It also enables the discovery of coexist ing interstitial lung disease and bronchiectasis. Smokers with

COPD are at high risk for development of lung cancer; annual low-dose chest CT scans for lung cancer screening have been demonstrated to reduce mortality in selected current and former smokers. In advanced COPD, CT scans can help determine the possible value of surgical or broncho scopic therapy (described below). Guidelines suggest testing for α1AT deficiency in all subjects with COPD or asthma with chronic airflow obstruction. Measurement of the serum α1AT level is the usual initial test. For subjects with low α1AT levels, the definitive diagnosis of α1AT 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. Mass spec trometry or molecular genotyping can be performed for the common PI variants (M, S, and Z), and DNA sequencing can detect other rare deficiency variants. TREATMENT Chronic Obstructive Pulmonary Disease STABLE COPD The two main goals of COPD therapy are to provide symptomatic relief (reduce respiratory symptoms, improve exercise tolerance, and 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 assess ment, benefits of therapy, potential risks, and costs. Figure 303-5 pro vides the currently suggested assessment of COPD patients based on spirometry, respiratory symptoms and risk for exacerbations. Response to therapy should be assessed, and decisions should be made whether or not to continue or alter treatment. Three interventions—smoking cessation, oxygen therapy in chronically hypoxemic patients, and lung volume reduction surgery

 (LVRS) in selected patients with emphysema—have been demon strated to improve survival of patients with COPD. Evidence is less strong that other nonpharmacologic interventions also reduce mortality, such as pulmonary rehabilitation after a COPD hospital ization, noninvasive positive-pressure ventilation in severe hyper capnia, and possibly lung transplantation. Triple inhaled therapy (long-acting beta-agonist bronchodilator, long-acting muscarinic antagonist bronchodilator, and inhaled corticosteroid) reduces mortality in selected patients with COPD. PHARMACOTHERAPY Smoking Cessation (See also Chap. 465) 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 pul monary function, often returning to annual changes similar to that of nonsmoking patients. In addition, smoking cessation improves survival. Thus, all smokers with COPD should be strongly urged to quit smoking and educated about the benefits of quitting. An emerging body of evidence demonstrates that combining phar macotherapy 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. The use of electronic cigarettes as a harm reduction strategy remains controversial. Current rec ommendations from the U.S. Surgeon General are that all adult, nonpregnant smokers considering quitting be offered pharmaco therapy, in the absence of any contraindication to treatment. Smok ing cessation counseling is also recommended, and free counseling is available through state Smoking Quitlines. Bronchodilators In general, inhaled bronchodilators are the primary treatment for almost all patients with COPD and are used for symptomatic benefit and to reduce exacerbation risk. In symp tomatic patients, both regularly scheduled use of long-acting agents and as-needed short-acting medications are indicated. Figure 303-6 provides suggestions for prescribing inhaled medication therapy based on grouping patients by severity of symptoms and risk of exacerbations. Muscarinic Antagonists Short-acting ipratropium bromide improves symptoms with acute

improvement in FEV1. Long-acting muscarinic antagonists (LAMA; including aclidinium, glycopyrro late, glycopyrronium, revefenacin, tiotropium, and umeclidinium) improve symptoms and reduce exacerbations. Side effects are minor; dry mouth is the most frequent. Beta Agonists Short-acting beta agonists ease symptoms with acute improvements in lung function. Long-acting beta agonists (LABAs) provide symptomatic benefit and reduce exacerbations, though to a lesser extent than a LAMA. Currently available longacting inhaled beta agonists are arformoterol, formoterol, inda caterol, olodaterol, salmeterol, and vilanterol. The main side effects are tremor and tachycardia. Combinations of Beta Agonist–Muscarinic Antagonist Combina tion inhaled LABA and LAMA therapy has been demonstrated to

GOLD ABE Assessment Tool Spirometrically confirmed diagnosis Assessment of airflow obstruction GRADE FEV1 (% predicted) PART 7 Disorders of the Respiratory System GOLD 1 ≥80 ≥2 moderate exacerbations or ≥1 leading to hospitalization E Post-bronchodilator FEV1/FVC <0.7 GOLD 2 50–79 GOLD 3 30–49 0 or 1 moderate exacerbations (not leading to hospitalization) A B GOLD 4 <30 FIGURE 303-5 Chronic obstructive pulmonary disease (COPD) severity assessment. COPD severity categories are defined using respiratory symptoms (based on the Modified Medical Research Council Dyspnea Scale [mMRC] or COPD Assessment Test [CAT]) and annual frequency of COPD exacerbations. The mMRC 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. The CAT is an eight-item COPD health status measure with Likert scale responses for questions about cough, phlegm, chest tightness, dyspnea after climbing one flight of stairs, limitation in home activities, confidence in leaving the home, sleep, and energy. Range of total score is 0–40. Both mMRC and CAT are available from Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024. (Reproduced with permission from 2025 GOLD Report-Global initiative for chronic obstructive lung disease; 2025.) provide improvement in lung function that is greater than either agent alone and reduces exacerbations. Dual bronchodilators are recommended as first-line treatments in patients with symptoms and/or increased exacerbation risk. There are multiple approved drug-device combinations, and some patients may find improved symptoms or increased ease of use for a particular inhaler or nebu lizer device. Inhaled Corticosteroids The main role of inhaled corticosteroids (ICS) is to reduce exacerbations. In population studies, patients with an eosinophil count of <100 cells per microliter do not ben efit, while benefit increases as eosinophil counts rise above 100; ICS are recommended as part of the initial treatment regimen for eosinophil counts above 300. ICS are never used alone in COPD due to little symptomatic benefit but, rather, are combined with a LABA or used with a LABA and LAMA. Triple-therapy inhal ers (LAMA-LABA-ICS) may be preferred over multiple inhalers. ICS use has been associated with increased rates of oropharyngeal candidiasis and pneumonia and, in some studies, an increased rate of loss of bone density and development of cataracts. ICS can

be added when patients with eosinophils counts above 100 continue to have exacerbations despite dual bronchodilator therapy. In stable patients without exacerbations, ICS withdrawal may be considered. Although ICS withdrawal does not lead to an increase in exacerba tions, 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 associ ated with significant side effects, including osteoporosis, weight gain, cataracts, glucose intolerance, and increased risk of infection. A 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.

Assessment of symptoms/risk of exacerbations EXACERBATION HISTORY (PER YEAR) mMRC 0–1 CAT <10 mMRC ≥2 CAT ≥10 SYMPTOMS PDE4 Inhibitors The selective phosphodiesterase 4 (PDE4) inhibi tor 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 respiratory symptoms are modest, and side effects (including nausea, diarrhea, and weight loss) are common. Antibiotics There are strong data implicating bacterial infection as a precipitant of COPD exacerbations. A randomized clinical trial of azithromycin, chosen for both its anti-inflammatory and antimi crobial properties, administered daily to subjects with a history of exacerbation in the past 6 months, demonstrated a reduced exac erbation frequency and longer time to first exacerbation. Azithro mycin was most effective in older patients, former smokers, and milder COPD. Side effects include hearing loss and development of macrolide-resistant organisms; chronic azithromycin should be avoided in the setting of a prolonged QTc interval. Oxygen Supplemental O2 has been demonstrated to unequivo cally decrease mortality in hypoxemic patients with COPD. For patients with resting hypoxemia (resting O2 saturation ≤88% in any patient or ≤89% with signs of pulmonary arterial hyperten sion, right heart failure, or erythrocytosis), the use of O2 has been demonstrated to have a significant impact on mortality. Patients meeting these criteria should be on continuous oxygen supplemen tation because the mortality benefit is proportional to the number of hours per day oxygen is used. Various delivery systems are avail able, including portable systems that patients may carry to allow mobility outside the home. A recent study failed to demonstrate mortality or symptomatic benefits to COPD patients with moderate hypoxemia at rest or with hypoxemia only with activity. Long-term nocturnal noninvasive mechanical ventilation may be beneficial in stable COPD patients with chronic hypercapnia; a sleep study is recommended prior to initiation to exclude concurrent obstructive sleep apnea.

Initial Pharmacological Treatment ≥2 moderate exacerbations or ≥1 leading to hospitalization GROUP E LABA + LAMA* consider LABA+LAMA+ICS* if blood eos ≥300 0 or 1 moderate exacerbations (not leading to hospital admission) GROUP A A bronchodilator mMRC 0–1, CAT <10 mMRC ≥2, CAT ≥10 *Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment Exacerbations refers to the number of exacerbations per year; eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™. A Follow-up Pharmacological Treatment DYSPNEA EXACERBATIONS LABA or LAMA LABA + LAMA* • Consider switching inhaler device or molecules • Implement or escalate non-pharmacological treatment(s) • Consider adding ensifentrine • Investigate (and treat) other causes of dyspnea *Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment. Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥300 cells/µl de-escalation is more likely to be associated with the development of exacerbations. Exacerbations refers to the number of exacerbations per year. B FIGURE 303-6 Medication therapy for stable chronic obstructive pulmonary disease (COPD). Initial pharmacologic therapy (A) is based on both COPD exacerbations and respiratory symptoms

(assessed through the Modified Medical Research Council Dyspnea Scale [mMRC] or the COPD Assessment Test [CAT]). Follow-up pharmacologic therapy (B) is based on response to treatment initiation and reassessment of symptoms and exacerbations. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2024. *For B: Single-inhaler therapy may be more convenient and effective than multiple inhalers. **Consider deescalation of ICS if pneumonia or other side effects occur. Eos, blood eosinophil count in cells per microliter; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist. (Reproduced with permission from 2025 GOLD Report-Global initiative for chronic obstructive lung disease; 2025.) α1AT Augmentation Therapy Specific treatment in the form of IV α1AT augmentation therapy is available for individuals with severe α1AT deficiency. Although biochemical efficacy of α1AT augmen tation therapy has been shown, the benefits of α1AT augmentation

GROUP B LABA + LAMA* Chronic Obstructive Pulmonary Disease CHAPTER 303 LABA or LAMA if blood eos <300 if blood eos ≥300 LABA + LAMA* if blood eos ≥100 if blood eos <100 LABA + LAMA + ICS* if blood eos ≥300 Dupilumab chronic bronchitis Roflumilast FEV1 <50% & chronic bronchitis Azithromycin preferentially in former smokers therapy are controversial. A randomized study suggested a reduc tion in emphysema progression in patients receiving α1AT augmen tation therapy. Eligibility for α1AT augmentation therapy requires a serum α1AT level <11 μM (~55 mg/dL). Typically, PiZ individuals

will qualify, although other rare types associated with severe defi ciency (e.g., null-null) are also eligible. Because only a fraction of individuals with severe α1AT deficiency will develop COPD, α1AT augmentation therapy is not recommended for severely α1ATdeficient persons with normal pulmonary function and a normal chest CT scan.

Other Biologic Therapies Dupilumab is a monoclonal antibody targeting IL-4 and IL-13, delivered by subcutaneous injection. It is approved for use in allergic diseases including asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, and eosino philic esophagitis. A recent study showed that dupilumab injections reduced the exacerbation rate in symptomatic COPD patients with high exacerbation risk and elevated blood eosinophils of at least 300 cells per microliter, when added to triple inhaled therapy. NONPHARMACOLOGIC THERAPIES Patients with COPD should receive the influenza vaccine annually. Pneumococcal, COVID-19, and respiratory syncytial virus (RSV) vaccines are recommended; vaccination for Bordetella pertussis is recommended for those not vaccinated in adolescence. PART 7 Disorders of the Respiratory System Pulmonary Rehabilitation Pulmonary rehabilitation is a compre hensive 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 In carefully selected patients with emphysema, surgery to remove the most emphysematous portions of lung improves exercise capacity, lung function, and survival. The anatomic distribution of emphysema and postrehabilitation exer cise capacity are important prognostic characteristics. Patients with upper lobe–predominant emphysema and a low postrehabilitation 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. Two different endobronchial one-way valves for bronchoscopic lung volume reduction (BLVR) have been approved by the U.S. Food and Drug Administration. The indications are largely similar to those for LVRS, although valves can be used to treat emphysema in any lung lobe. Patients should not have interlobar collateral ventilation, either measured by intact fissures on chest CT scan or a bronchoscopic device. The main postprocedure complication is pneumothorax, which usually occurs within the first 3 days. A small study suggested similar outcomes at 12 months for BLVR compared to LVRS. Lung Transplantation (See Chap. 309) COPD is currently the second leading indication for lung transplantation. Current recom mendations are that candidates for lung transplantation should have very severe airflow obstruction; have severe disability despite maximal medical therapy; be free of significant comorbid condi tions such as liver, renal, or cardiac disease; and not be a candidate for LVRS or BLVR. Currently, there is no cure for COPD except lung transplantation. Current efforts focus on early diagnosis and comprehensive treatment as well as mitigation of environmental risk factors. EXACERBATIONS OF COPD Exacerbations are often a prominent feature of the natural history of COPD. Exacerbations are episodic acute worsening of respira tory symptoms, including increased dyspnea, cough, and/or change in the amount and character of sputum, usually over a period of <14 days. They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat. The stron gest single predictor of exacerbations is a history of a previous exacerbation. The frequency of exacerbations increases as airflow obstruction worsens; patients with severe airflow obstruction (FEV1

<50% predicted) on average have 1–3 episodes per year. However, some individuals with severe airflow obstruction do not have fre quent exacerbations. Other factors, such as current smoking, an ele vated 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. Economic analyses have shown that a majority of the $50 billion annual COPD-related health care expen ditures in the United States are due to COPD exacerbations. Precipitating Causes and Strategies to Reduce Frequency of Exac erbations A variety of stimuli may result in the final common pathway of airway inflammation and increased respiratory symp toms that are characteristic of COPD exacerbations. Viral respira tory infections had been thought to be a less common cause of COPD exacerbations than bacterial infection, although polymerase chain reaction–based studies have shown that viral infections may be a cause of >50% of exacerbations. Studies suggest that acquir ing a new strain of bacteria is associated with increased near-term risk of exacerbation. Other inciting factors include air pollution, allergens, pulmonary embolism, and medication nonadherence. In a significant minority of instances, 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 it is 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 exac erbations 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 pneumo thorax 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, and occasionally pneumo thorax. Patients with advanced COPD, a history of hypercarbia, or mental status changes (confusion, sleepiness) or those in significant distress should have an arterial blood gas measurement. The pres ence of hypercarbia, defined as a Pco2 >45 mmHg, has important implications for treatment (discussed below). In contrast to its util ity 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 because 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 wors ening hypoxemia, severe underlying COPD, significant comor bidities such as heart failure, and those whose living situation is not conducive to careful observation and the delivery of prescribed treatment. COPD exacerbation is a clinical diagnosis. A recent expert consensus has developed more objective criteria to diagnose and stage the severity of COPD exacerbations, based on dyspnea, vital signs, and testing of C-reactive protein and arterial blood

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