COPD

- Disease state characterised by persistent respiratory symptoms and airflow obstruction
- includes
  - ***Emphysema***
    - ***anatomically*** defined condition with 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
- Classic definition
  - requires the presence of chronic airflow obstruction, determined by spirometry
- All 3 forms present in varying degrees in different patients
- May have either of 3 without airflow obstruction so cant be defined as COPD but similar process
- ***COPDGene*** study recently proposed a multidimensional approach to COPD diagnosis, which is based on domains of
  - environmental exposures,
  - respiratory symptoms,
  - imaging abnormalities,
  - physiologic abnormalities.

Pathogenesis

- Airflow obstruction may be from airway disease or emphysema
- Small airways may become narrowed by
  - cells (hyperplasia and accumulation),
  - mucus
  - fibrosis,
- extensive small airway destruction has been demonstrated to be a ***hallmark*** of COPD.
- Pulmonary vascular destruction occurs in concert with small airway disease and emphysema
- Pathogenesis paradigm consists of 4 interrelated events
  - 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.
  - Inflammatory cells release proteinases that damage the extracellular matrix supporting airways, vasculature, and gas exchange surfaces of the lungs
  - Structural cell death occurs through oxidant-induced damage, cellular senescence, and proteolytic loss of cellular-matrix attachments leading to extensive loss of smaller airways, vascular pruning, and alveolar destruction
  - Disordered repair of elastin and other extracellular matrix components contributes to air space enlargement and emphysema.

Inflammation and extracellular matrix proteolysis

- Elastin is principle component of elastic fibres and highly stable, crucial to integrity of lung
- ***elastase:antielastase hypothesis***
  - the balance of elastin-degrading enzymes and their inhibitors determines the susceptibility of the lung to destruction, resulting in air space enlargement
  - Based on genetic deficiency in α1 antitrypsin (***α1AT***), 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

- complex network of immune and inflammatory cells and additional biological mechanisms that contribute to emphysema have subsequently been identified

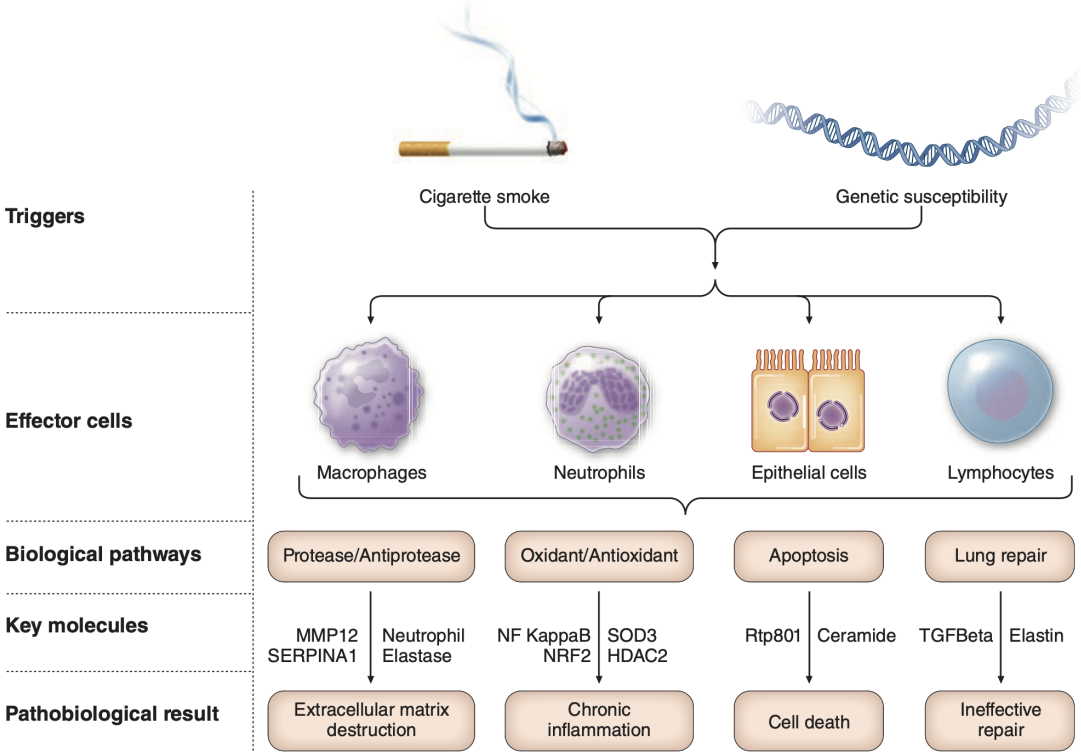

FIGURE 292-1 Pathogenesis of emphysema. Upon long-term exposure to cigarette smoke in genetically susceptible individuals, lung epithelial cells and T and B lymphocytes recruit inflammatory cells to the lung. Biological pathways of protease-antiprotease imbalance, oxidant/antioxidant imbalance, apoptosis, 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.

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- Autoimmune mechanism may promote progression of disease
- In end-stage lung disease, long after smoking cessation, there remains an exuberant inflammatory cells 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
  - variety of mechanism
    - ceramide production
    - Rtp801 inhibition of mTOR
  - Emphysema is premature aging of lung
  - hedgehog interacting protein (HHIP) is gene involved
- Ineffective repair
  - Limited repair ability
  - Cigarette smoke blocks macrophage uptake of apoptotic cells, blocking Growth factor production
  - Septation is responsible for alveologenesis in lung development and cannot be reinitiated

Pathology

- Affects large airway, small airway (<_ 2mm) and alveoli
- Large airway
  - cough
  - sputum production
- Small and alveoli
  - physiological alterations
- airway inflammation , destruction and emphysema are present in most as independent process
- Early COPD has mostly small and medium airway disease
- GOLD 1/2 have almost no emphysema
- GOLD 3/4 have emphysema though maybe absent in some

- greatest risk of progression in COPD are those with both aggressive airway disease and emphysema.
- Emphysema on CT either early or late suggests enhanced disease progression risk

TABLE 292-1 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

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

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large airway

- smoking causes mucus gland enlargement and goblet cell hyperplasia (in number and extent) --> cough and mucus production --> chronic bronchitis
- Squamous metaplasia of bronchi --> carcinogenesis risk + mucociliary clearance disrupted
- smooth muscle hypertrophy + bronchial hypersensitivity leading to obstruction
- Neutrophil influx causes purulent sputum during respiratory tract infections
- neutrophil elastase is among the most potent secretagogue

Small airway (<_ 2mm)

- major site of increased resistance
- goblet cell metaplasia, with these mucus-secreting cells replacing surfactant-secreting Club cells
- Smooth-muscle hypertrophy
- Luminal narrowing by
  - fibrosis,
  - excess mucus,
  - edema,
  - cellular infiltration
  - reduced surfactant increasing surface tension
- Narrowing and drop-out of small airways before emphysematous destruction

Lung parenchyma

- destruction of gas-exchanging air spaces
  - respiratory bronchioles,
  - alveolar ducts,
  - alveoli
- alveolar spaces in smokers have

- macrophage
- neutrophil
- B & T lymphos
- CD8+

- Emphysema types
  - centrilobular
    - m/c with smoke
    - initially close to respiratory bronchioles
    - upper lobe and superior segment of lower
    - focal
  - panlobular
    - evenly within and across acinar units
    - α1AT deficiency,
    - lower lobes
  - paraseptal
    - pleural margins
    - 10-15%
    - sparing of core and central regions

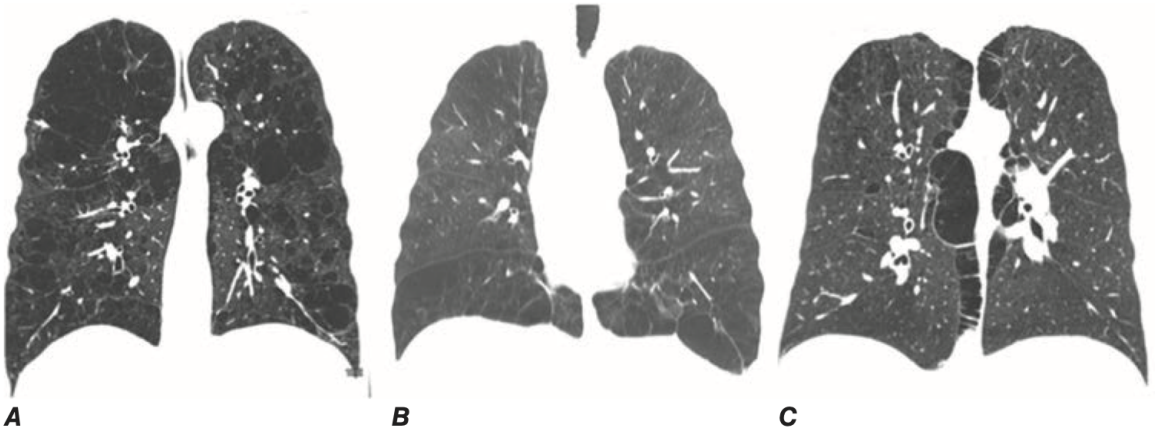

FIGURE 292-2 CT patterns of emphysema. ***A.*** Centrilobular emphysema with severe upper lobe involvement in a 68-year-old man with a 70-pack-year smoking history but forced expiratory volume in 1 s (FEV_1) 81% predicted (GOLD spirometry grade 1). ***B.*** Panlobular emphysema with diffuse loss of lung parenchymal detail predominantly in the lower lobes in a 64-year-old man with severe α_1 antitrypsin (α_1AT) deficiency. ***C.*** Paraseptal emphysema with marked airway inflammation in a 52-year-old woman with a 37-pack-year smoking history and FEV_1 40% predicted.

Hyperinflation

- "air trapping"
  - increased residual volume
  - increased ratio of residual to total lung volume
- Progressive hyperinflation (increased TLC)
- preserves maximum expiratory airflow, because as lung volume increases, elastic recoil pressure increases, and airways enlarge so that airway resistance decreases
- Pushes diaphragm into flat position
  - zone of apposition reduces, positive abdominal pressure during inspiration is not applied as effectively to the chest wall, hindering rib cage movement and impairing inspiration
  - shortens muscle fibres --> less capable of generating inspiratory pressures than normal
  - must generate greater tension to develop the transpulmonary pressure required to produce tidal breathing
  - thoracic cage is distended beyond its normal resting volume, the inspiratory muscles must do work to overcome the resistance of the thoracic cage

Gas exchange

- Pao2 remains normal till FEV1 < 50%
- Paco2 not elevated till FEV1 <25%
- PAH severe to cause cor pulmonale and right ventricular failure due to COPD in FEV1 (<25% of predicted) and chronic hypoxemia (Pao2 <55 mmHg)
- Nonuniform ventilation and ventilation-perfusion mismatching
- multiple parenchymal compartments having different rates of ventilation due to regional differences
- pao2 reduction due to V/Q mismatching
- minimal shunting

Risk Factor

Cigarette smoking

- accelerated decline in FEV1 in a dose-response relationship to the intensity of cigarette smoking
  - accounts for higher prevalence rates of COPD with increasing age
- typically expressed as pack-years
  - average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking
- considerable individual variability in the response to smoking.
- Pack-years of cigarette smoking is the most highly significant predictor of FEV1 (but only 15% impact explained)
- dditional environmental and/ or genetic factors contribute to the impact of smoking
- even if smoker has normal spirometry
  - worse health-related quality of life,
  - reduced exercise capacity,
  - emphysema and/or airway disease on chest CT evaluation
- Cigar and pipe less compelling evidence
  - related to the lower dose of inhaled tobacco by-products

Airway responsiveness

- Many patients share responsiveness with asthma
- considerable overlap between persons with a history of chronic asthma and smokers with COPD in older subjects specially
- share common environmental and genetic factors and the chronic form in older subjects can present similarly.
- increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function

Respiratory infections

- significant long-term reductions in pul- monary function are not typically seen following an individual episode of acute bronchitis or pneumonia
- respiratory infections are important causes of COPD exacerbations
- 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)

occupation exposure

- exposure to dust and fumes
- Specific exposure
  - coal mining,
  - gold mining
  - cotton textile dust

- coal mine dust exposure was a significant risk factor for emphysema in both smokers and nonsmokers
- less important than cigarette

Ambient air pollution

- urban compared to rural areas, more respiratory symptoms
- relationship unproven
- smoke produced by biomass combustion in cooking is seen in women

passive or second hand smoking

- maternal smoking results in significantly reduced lung growth
- In utero, tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function

Genetic

- development of airflow obstruction in smokers is highly variable.
- Severe α1AT deficiency is a proven risk factor
- α1 Antitrypsin Deficiency (1% of COPD)
  - PI or SERPINA1 locus codes
  - M allele is normal
  - S is low level
  - Z is marked reduction
  - Null is absence
  - PiZ is most common with 2 null and one Z
  - develop early-onset COPD
  - measurement of the immunologic level of α1AT in serum
  - α1AT augmentation therapy is available for severe α1AT deficiency as a weekly IV infusion
- Others
  - Familial aggregation of airflow obstruction within families of COPD patients has also been demonstrated
  - > 80 regions of the genome contain COPD susceptibility loci
  - HHIP on chromosome 4

Natural History

- effect of smoking depends on
  - intensity of smoking exposure,
  - the timing of smoking exposure during growth and development
  - baseline lung function of the individual
- Tracking of pulmonary function ++
- FEV1 relates to risk of mortality

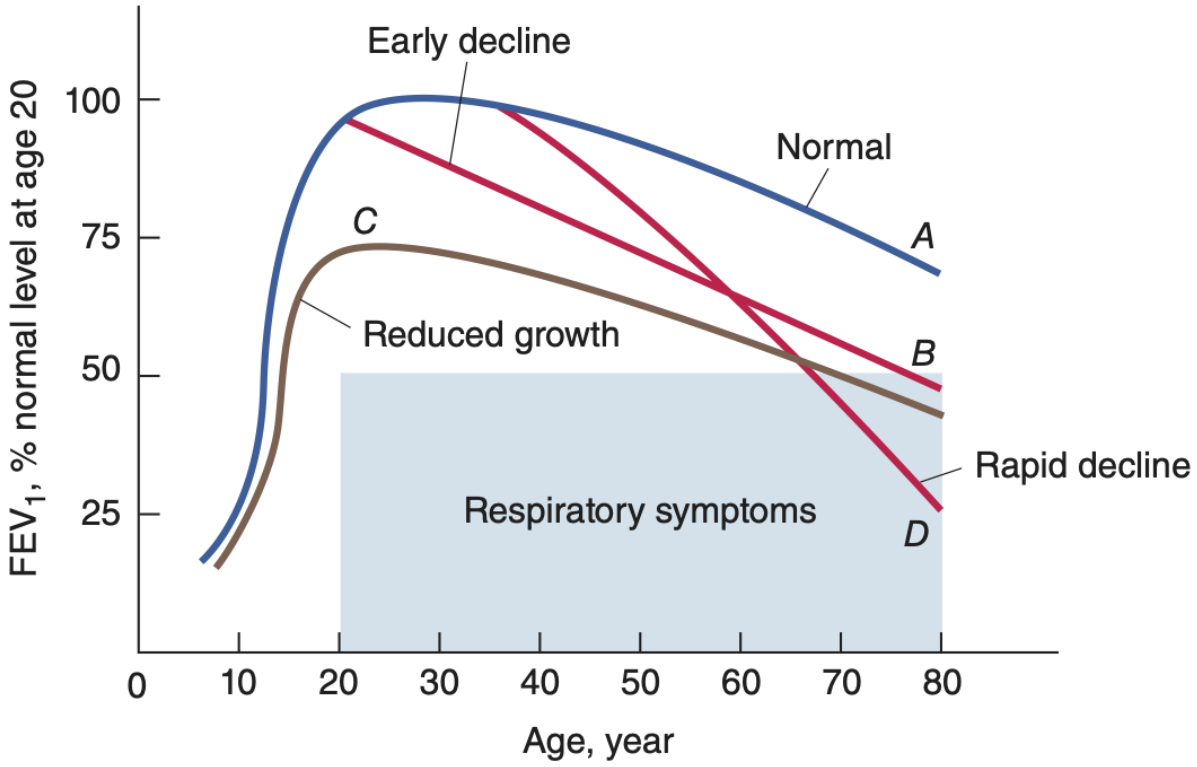

FIGURE 292-4 Hypothetical tracking curves of forced expiratory volume in 1 s (FEV_1) for individuals throughout their life spans. The normal pattern of growth and decline with age is shown by curve *A*. Significantly reduced FEV_1 (<65% of predicted value at age 20) can develop from a normal rate of 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; with permission.)*

-
- smoking cessation at an earlier age providing a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed
- absolute annual loss in FEV1 tends to be highest in mild COPD and lowest in very severe COPD
- In chronic smokers, CT changes maybe present without spirometry change
  - emphysema-predominant pattern show emphysema early and classically progress through GOLD 1 to GOLD 2–4
  - airway disease–predominant pattern initial evidence of airway inflammation and progress with little emphysema early as FEV1 falls while retaining a ***normal FEV1/FVC ratio***
    - preserved ratio–impaired spirometry (***PRISm***) physiology
    - Late emphysema
    - direct to GOLD 3/4

Clinical presentation

History

- symptoms
  - cough,
  - sputum production
  - exertional dyspnea

        - increased effort to breathe, heaviness, air hunger, or gasping
        - insidious onset
        - worsening such that in late stages, day to day activity impacted
        - seek history of physical activity and ability to perform
        - arm work, at or above shoulder level is difficult
        - activity allowing bracing arms and using accessory respiratory muscles better tolerated (shopping cart push or treadmill walk)
- exists for years before seeking medical attention
- Progressive but patients date it to a infection in past while history will give evidence of prior respiratory symptoms

Physical findings

- early stage have normal exam
- Smokers
    - signs of smoking
    - odor of smoke
    - nicotine staining of fingernails
- Severe disease
    - prolonged expiration
    - expiratory wheeze
- Barrel chest, enlargement of lung and poor diaphragm excursion (by percussion)
- use of accessory muscles of respiration,
- sitting in the characteristic “tripod” position to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles
- Cyanosis of lips and nailbeds
- pink puffers (emphysema) vs blue bloaters (chronic bronchitis) not reliable nowadays
- Cachexia in advanced disease
    - weight loss and subcutaneous fat losses
    - low oral intake and TNF-α
    - independent poor prognosis
- Hoovers sign
    - paradoxical inward movement of the rib cage with inspiration
    - due to alteration of the vector of diaphragmatic contraction on the rib cage due to chronic hyperinflation.
- cor pulmonale or sign of RHF infrequent due to supplemental O2
- Clubbing is ***NOT SEEN***, must evaluate for lung cancer

Laboratory findings

- PFT shows airflow obstruction with a reduction in FEV1 and FEV1/FVC
- as worsens
    - lung volumes may increase, resulting in an increase in total lung capacity (TLC) , functional residual capacity (FRC) , and residual volume(RV)
- diffusing capacity may be reduced in emphysema due to parenchymal damage
- airflow obstruction generally correlates with
    - presence and severity of respiratory symptoms,
    - exacerbations,
    - emphysema,
    - hypoxemia
- BODE (better predictor of mortality)
    - BMI

    - obstruction
    - Dyspnea
    - exercise perform
- ABG --> resting or exertional hypoxemia
- high hematocrit and signs of right heart failure suggests chronic hypoxemia
- CXR
    - Obvious bullae, paucity of parenchymal markings, or hyperlucency suggest emphysema
- CT is imaging of choice
    - type and presence of emphysema
    - rule out malignancy
    - identify surgical target
- suggested testing for α AT deficiency
- definitive diagnosis of α1AT deficiency requires PI type determination

Stable phase treatment

- provide symptomatic relief
    - reduce respiratory symptoms,
    - improve exercise tolerance
    - improve health status
- reduce future risk
    - prevent disease progression,
    - prevent and treat exacerbations,
    - reduce mortality

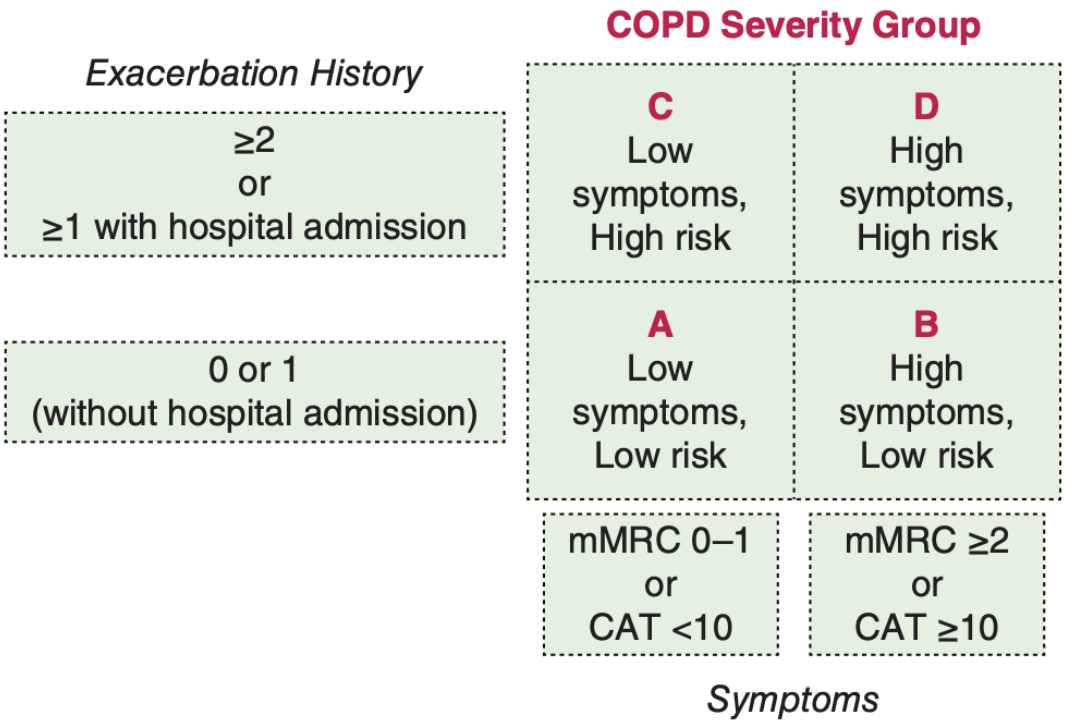

FIGURE 292-5 Chronic obstructive pulmonary disease (COPD) severity assessment. COPD severity categories are based on respiratory symptoms (based on the Modified Medical Research Council Dyspnea Scale [mMRC] or COPD Assessment Test [CAT]) and annual frequency of COPD exacerbations. The mMRC provides a 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 on 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) 2017. *(Reproduced with permission from Global Strategy for Diagnosis, Management and Prevention of COPD 2017, ©.)*

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Pharmacotherapy

Smoking Cessation

- Significant improvement
- Lowers rate of decline to that of non smokers
- combine pharma with supportive
- pharma
  - nicotine replacement
    - gum
    - lozenge
    - patch
    - inhaler, nasal spray

    - bupropion
    - varenicline
        - nicotinic acid receptor agonist/antagonist
- all should be offered pharmacotherapy if nonpregnant and no contraindication

Bronchodilators

- primary treatment
- symptomatic benefit and reduce exacerbations
- inhaled as side effects low
- both long-acting and short-acting

Muscarinic antagonists

- Short-acting ipratropium bromide improves symptoms and acute FEV1
- LAMA
    - aclinidium, glycopyrrolate, glycopyrronium, revefenacin, tiotropium, umeclinidium
    - reduced mortality in tiotropium
- dry mouth is most common side effects

Beta agonists

- Short-acting reduced symptoms
- LABAs provide less benefit than LAMA
- LABAs --> arformetrol, formetrol, indacaterol, olodaterol, salmetrol, vilanterol
- Tremor and tachycardia

Beta agonist-Muscarinic antagonist combination

- greater benefit than either alone

inhaled corticosteroids

- mainly reduce exacerbations
- no benefit in eosinophilic count <100
- never use alone but with LABA or LAMA
- increased oropharyngeal candida and pneumonia , increased loss of bone and cataracts
- trial in patients with frequent exacerbations (>2 per year or 1 causing hospitalization)
- stable without exacerbations consider withdraw
- if smoking +, benefit is low

oral glucocorticoids

- not recommended
- unfavourable side effect to benefit ratio
- side effects
    - osteoporosis
    - weigh gain
    - cataracts
    - glucose intolerance
    - infections

Theophylline

- modest improvement
- not 1st line due to side effects and interaction
- nausea
- tachycardia tremor
- monitor blood levels

PDE4 inhibitors

- Roflumilast (pde4)
- reduces exacerbations in severe COPD , bronchitis and history of exacerbations
- less benefit in lung function
- nausea diarrhea weight loss common

Antibiotic

- bacterial infections precipitates most exacerbations
- azithromycin daily reduce exacerbations
- low benefit in active smokers

oxygen

- only therapy to reduce mortality
- resting hypoxemia
  - resting O2 saturation ≤88% in any patient
  - ≤89% with signs of pulmonary arterial hypertension, right heart failure or erythrocytosis
- benefit proportional to hours of o2 per day

α1AT Augmentation Therapy

- IV
- severe deficiency
- recommend hepatitis B vaccination prior to starting augmentation therapy
- not recommended for severely α1AT-deficient per- sons with normal pulmonary function and a normal chest CT scan.

NON PHARMACOLOGICAL

- influenza vaccine annual
- pneumococcal vaccine
- bordetella pertusis vaccine

Pulmonary rehab

- incorporates
  - exercise, education, and psychosocial and nutritional counseling
- improve health-related quality of life, dyspnea, and exercise capacity.
- reduce rates of hospitalization over a 6- to 12-month period

Lung volume reduction surgery

- remove the most emphysematous portions of lung improves exercise capacity, lung function, and survival.

- prognosis
  - anatomic distribution of emphysema (upper lobe better)
  - postrehabilitation exercise capacity (low better)
- contraindication
  - FEV1 <20% of predicted and either diffusely distributed emphysema on CT scan or diffusing capacity of lung for carbon monoxide (DICO) <20% of predicted
- Bronchoscopic methods also approved now

Lung transplant

- 2nd leading indication
- severe airflow obstruction, severe disability despite maxi- mal medical therapy, and be free of significant comorbid conditions such as liver, renal, or cardiac disease.

Exacerbations Treatment

- part of natural history
- episodic acute worsening of respiratory symptoms, including increased dyspnea, cough, wheezing, and/ or change in the amount and character of sputum
- best predictor
  - history of a previous exacerbations
- exacerbations increases as airflow obstruction worsens;
  - patients with severe (FEV <50% predicted) or very severe airflow obstruction (FEV1 <30% predicted) on average have 1–3 episodes per year
- other factors
  - elevated ratio of the diameter of the pulmonary artery to aorta on chest CT
  - gastroesophageal reflux

Precipitating causes

- New strain of bacteria
- bacterial infections/ superinfection causes >50% exacerbations
- viral in 30%

Patient assessment

- Establish severity of exacerbations and COPD both
- quantification of the degree and change in dyspnea
  - asking about breathlessness during activities of daily living and typical activities for the patient
  - fever; change in character of sputum; and associated symptoms such as wheezing, nausea, vomiting, diarrhea, myalgias, and chills.
- Physical to assess degree of distress
  - tachycardia,
  - tachypnea,
  - use of accessory muscles,
  - signs of perioral or peripheral cyanosis,
  - ability to speak in complete sentences
  - patient’s mental status
- Chest
  - focal findings
  - air movement
  - wheeze

    - asymmetry in chest
        - large airway
        - pneumothorax mimicking exacerbations
    - paradox motion of chest wall
- CXRay / CT
    - severe COPD
    - moderate or severe distress
    - focal findings
- ABG
    - advanced COPD
    - history of hypercarbia
    - mental status changes
    - significant distress
- PFT not useful in exacerbations
- consider PE
- Inpatient
    - presence of respiratory acidosis and hypercarbia,
    - new or worsening hypoxemia,
    - severe underlying disease
    - those whose living situation is not conducive to careful observation and treatment

management

Bronchodilators

- inhaled beta agonist and muscarinic antagonists
- initially with nebuliser
- conversion to MDI is effective
- MDI reduce costs and inpatient burden
- +/- theophylline
    - if added monitor serum levels

Antibiotic

- difficult to establish specific species
- includes
    - Streptococcus pneumoniae
    - Haemophilus influenzae
    - Moraxella catarrhalis
    - Chlamydia pneumoniae
    - viral pathogens
- decide on local patterns
- moderate to severe exacerbations give antibiotic

systemic glucocorticoids

- reduce length of stay
- also lower relapse
- 2 weeks vs 8 weeks results similar
- 30-40 mg oral prednisolone for 5-10 days outpatient
- hyperglycemia is complication

oxygen

- maintain saturation >90%
- supplemental o2 does not reduce minute ventilation
- may modest increase in paco2
  - alters V/Q ratio

Mechanical ventilation

- NIPPV
  - paco2 >45
  - significant reduction in mortality rate, need for intubation, complications of therapy, and hospital length of stay.
  - C/I
    - cardiovascular instability, impaired mental status, inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma precluding effective fitting of mask, extreme obesity, or significant burdens...in
- Invasive
  - 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
- need to provide sufficient expiratory time in patients with severe airflow obstruction
- 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