POLTAVA STATE MEDICAL UNIVERSITY

Department of internal medicine №1

Chronic **O**bstructive **P**ulmonary **D**isease (COPD)

Developed by: Nataliia Prykhodko, ass. prof., PhD
np.prykhodko@gmail.com

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

It define **COPD** as a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development.

Key facts

- Chronic Obstructive Pulmonary Disease (COPD) affects more than 65 million people worldwide, but millions more may have it and not know it.
- 1 in 5 Americans has COPD.
- COPD is the 3-rd leading cause of death worldwide.
- It caused 3.23 million deaths in 2019.
- Over 80% of these deaths occurred in low- and middle-income countries.

Etiology COPD

The risk of developing COPD is related to the following factors:

smoking

- **Tobacco smoke** – cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV_1, and a greater COPD mortality rate than non- smokers. Other types of tobacco (e.g., pipe, cigar, water pipe) and marijuana are also risk factors for COPD, as well as environmental tobacco smoke (ETS).

pollution

- **Indoor air pollution** – resulting from the burning of wood and other biomass fuels used for cooking and heating in poorly vented dwellings, is a risk factor that particularly affects women in developing countries. There is a lack of research about biomass related COPD, although there is limited evidence from an observational study that switching to cleaner cooking fuels or reducing exposure may reduce COPD risk in non-smokers.

- **Outdoor air pollution** – also contributes to the lungs' total burden of inhaled particles, although it appears to have a relatively small effect in causing COPD.

chemical exposure

- **Occupational exposures** – including organic and inorganic dusts, chemical agents and fumes, are under- appreciated risk factors for COPD.

Etiology COPD

- **Genetic factors** – such as severe hereditary deficiency of alpha-1 antitrypsin (AATD); the gene encoding matrix metalloproteinase 12 (*MMP-12*) and glutathione *S*-transferase have also been related to a decline in lung function or risk of COPD.

- **Age and sex** – aging 40+ and female sex increase COPD risk.

- **Lung growth and development** – any factor that affects lung growth during gestation and childhood (low birth weight, respiratory infections, etc.) has the potential to increase an individual's risk of developing COPD.

- **Socioeconomic status** – Poverty is consistently associated with airflow obstruction and lower socioeconomic status is associated with an increased risk of developing COPD. It is not clear, however, whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition, infections, or other factors related to low socioeconomic status.

- **Asthma and airway hyper-reactivity** – asthma may be a risk factor for the development of airflow limitation and COPD.
- **Chronic bronchitis** – may increase the frequency of total and severe exacerbations.
- **Infections** – a history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood.

Pathogenesis COPD

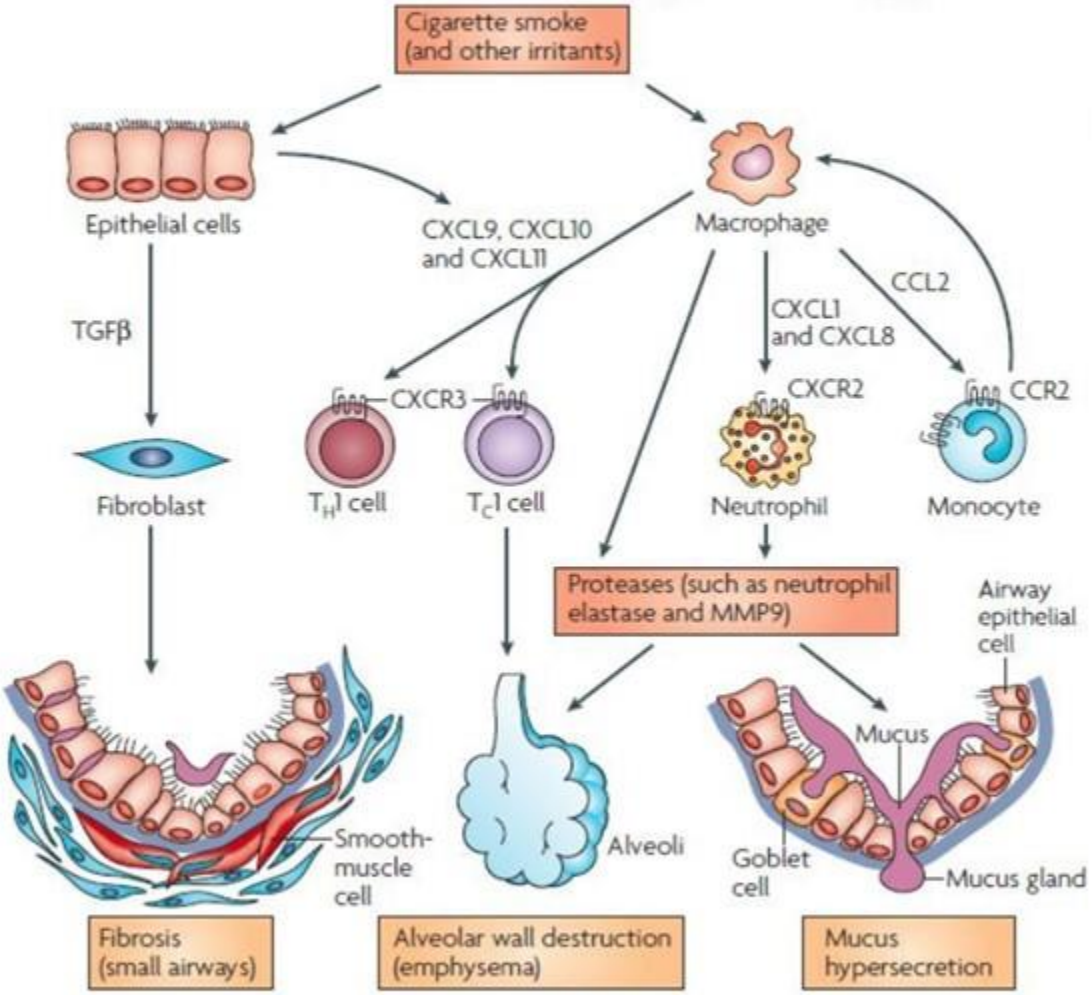
Pathologic changes in COPD occur in the large (central) airways, the small (peripheral) bronchioles, and the lung parenchyma.

Inhaled agents cause chronic inflammation in the airways, which lead to progressive airway obstruction through:

- Damage to endothelial cells → ↓ mucocilliary clearance
- Mucous gland hyperplasia → mucous hypersecretion and plugging
- Airway edema and smooth muscle hyperplasia → luminal narrowing
- Peribronchial fibrosis → bronchial distortion

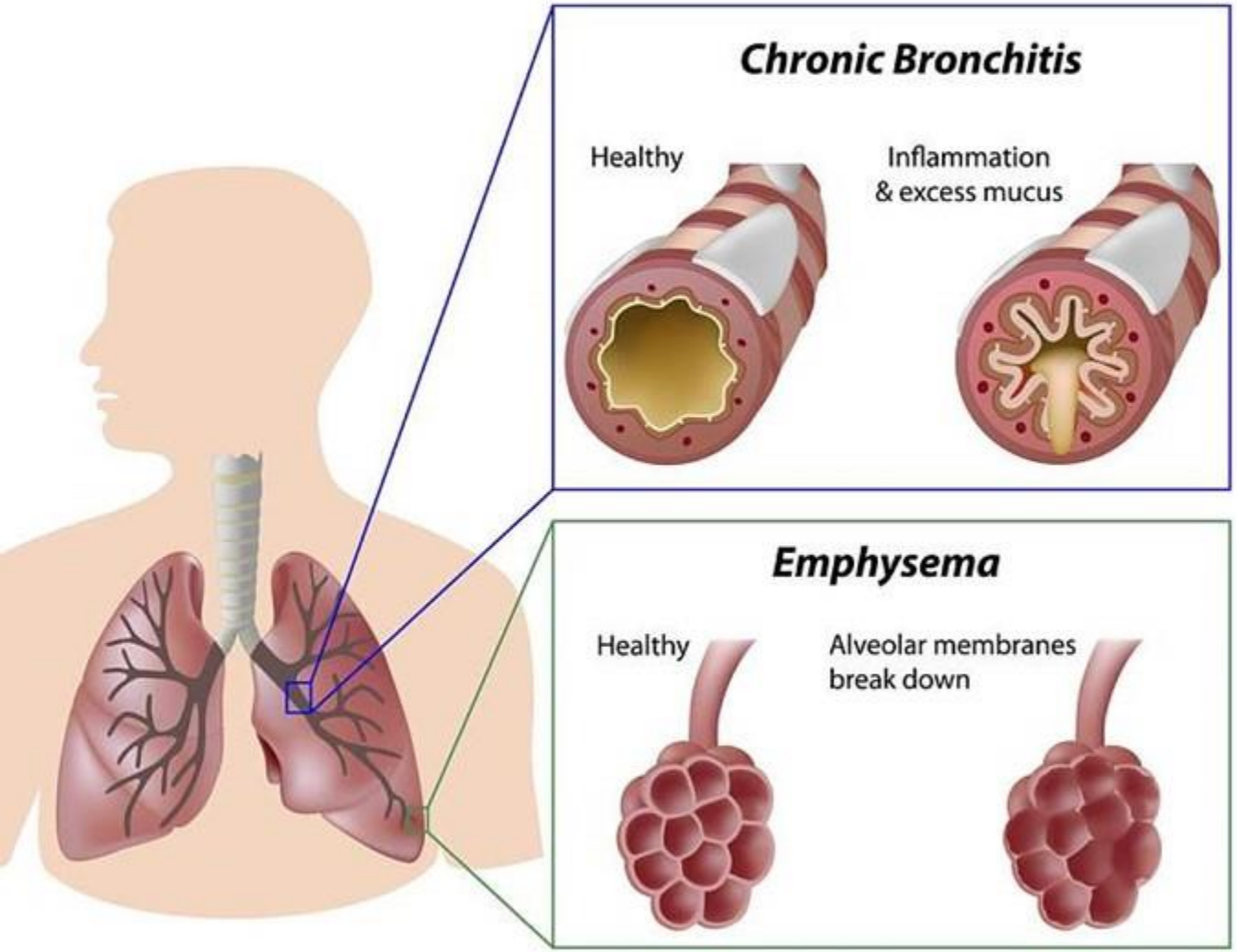
Inflammatory response → activated neutrophils release proteases

- Protease activity exceeds antiprotease activity → tissue destruction
- Alveolar destruction leads to:
  - Enlarged alveoli
  - ↓ Elastic recoil
  - ↑ Compliance
- Consequences:
  - Airway closure during expiration → obstruction
  - Air trapping → lung hyperinflation



Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol. 2008 Mar;8(3):183-92.

Pathogenesis COPD



Chronic bronchitis
- presence of a chronic productive cough for 3 months during each of 2 consecutive years (other causes of cough being excluded)

Emphysema - an abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.

Morphologic patterns:

Centriacinar emphysema (associated with cigarette smoking):

- Destruction of the respiratory bronchioles and a central portion of the acini
- More severe in the apical lung fields

Panacinar emphysema (associated with AAT deficiency):

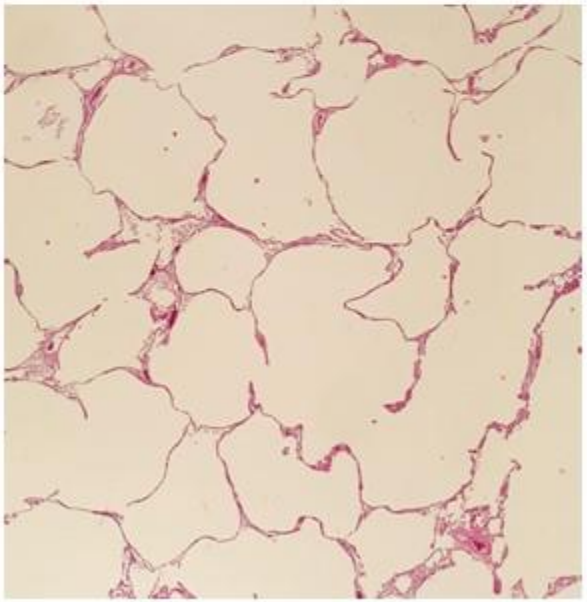
- Destruction of all parts of the acinus
- More severe in the basal lung fields

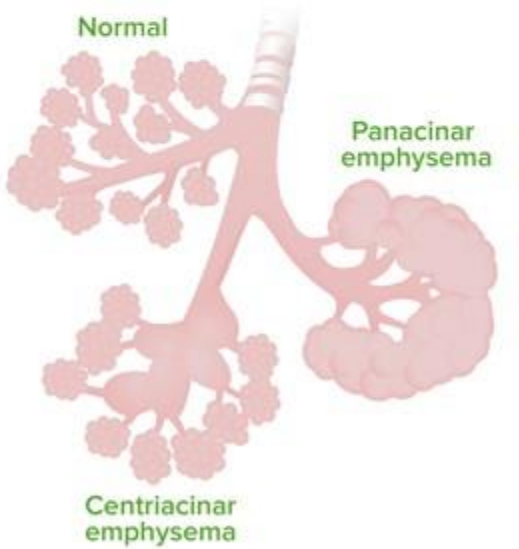
Effects of the pulmonary vasculature

•Tissue destruction → ↓ ability to oxygenate blood

•Hypoxemia → vasoconstriction in small pulmonary arteries → ↑ vascular resistance

•Chronic hypoxemia → vascular remodeling → irreversible pulmonary hypertension





https://www.lecturio.com/concepts/chronic-obstructive-pulmonary-disease-copd

Signs and symptoms

COPD symptoms often don't appear until significant lung damage has occurred, and they usually worsen over time, particularly if smoking exposure continues.

Signs and symptoms of COPD may include:

- Dyspnea that is persistent, progressive over time, characteristically worse with physical activities;
- A chronic cough that may be intermitted and unproductive;
- Chronic sputum production: mucus (sputum) that may be clear, white, yellow or greenish;

Additional symptoms:

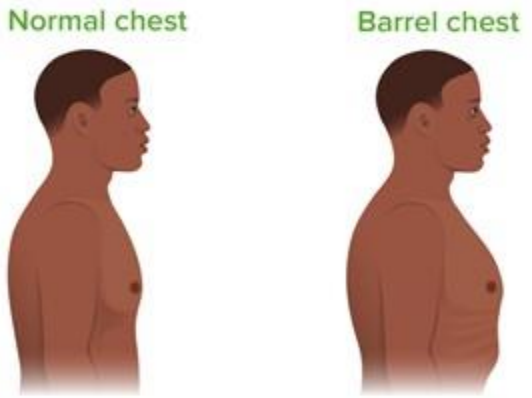
- Wheezing
- Chest tightness
- Frequent respiratory infections
- Lack of energy
- Unintended weight loss (in later stages)

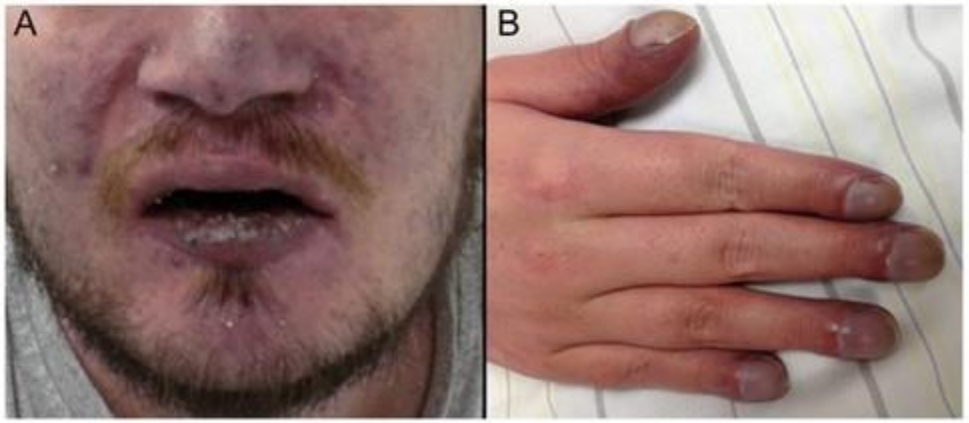
COPD exacerbation:

- Worsening dyspnea
- Increased cough
- Purulent sputum production
- Wheezing
- Fever may or may not be present.

Physical examination for COPD

- **Airflow obstruction**
- Wheezing during auscultation
- Prolongation of forced expiratory time
- **Hyperinflation of lungs**
- Barrel chest
- Low diaphragmatic position
- Decreased intensity of heart and breath sounds
- **Severe disease**
- Pursed-lip breathing
- Use of accessory respiratory muscles
- Retraction of intercostal spaces
- **Extremities:**
- Digital clubbing (B)
- Cyanosis (A)
- **Findings suggestive of "cor pulmonale":**
- Jugular venous distension
- Peripheral edema

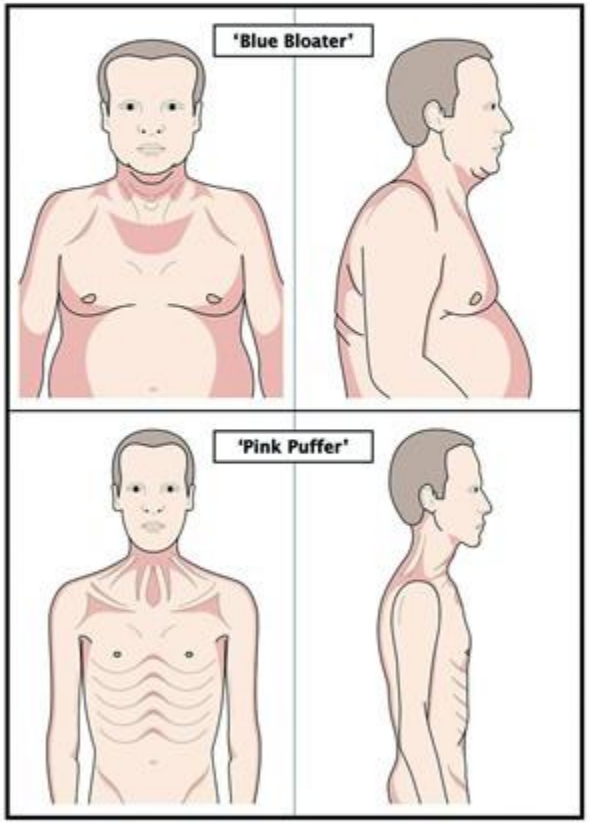




Clinical phenotypes

Signs and symptoms are associated more frequently with either chronic bronchitis or emphysema. However, patients often present with a mixture of features.

- **Chronic bronchitis ("blue bloater"):**
- Patients are generally overweight.
- Frequent, productive cough
- Peripheral edema
- Cyanosis
- **Emphysema ("pink puffer"):**
- Patients are generally thin.
- Barrel chest
- Infrequent cough
- Pursed lip breathing
- Accessory muscle use
- Tripod positioning
- Hyperresonant chest



Pulmonary function tests

Pulmonary function tests are used to confirm COPD diagnosis. Testing is indicative of obstruction, which is largely irreversible.

Spirometry measure different lung volumes and other functional metrics of pulmonary function.

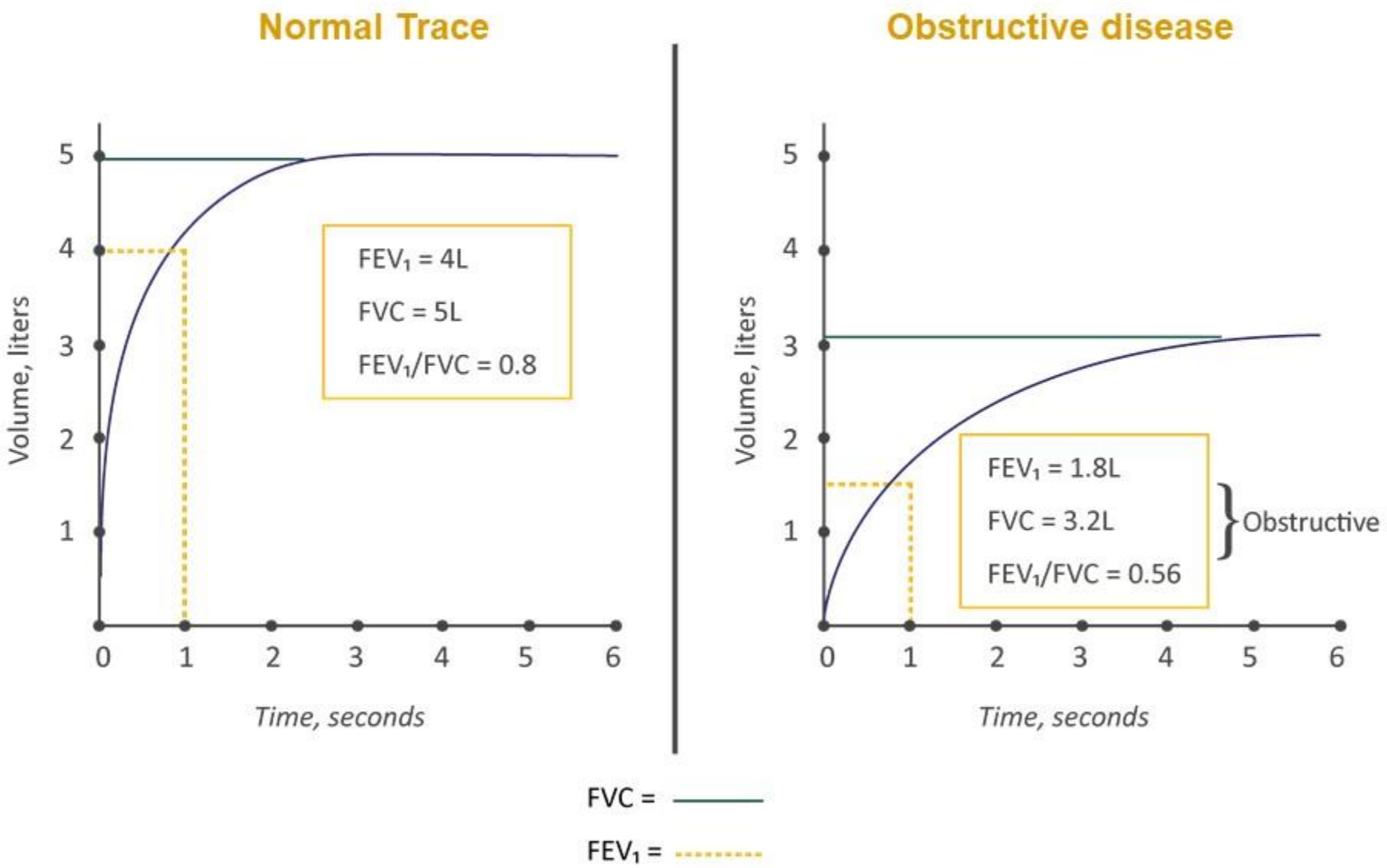
Spirometry changes:

- ↓ Forced expiratory volume in 1 second (FEV_1): maximum volume of air forcefully expired 1 second after maximal inspiration
- ↓ Forced vital capacity (FVC): maximum volume of air forcefully expired after maximal inspiration
- Greater loss of FEV_1 than FVC → ↓ FEV_1/FVC

The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation.

- Bronchodilator reversibility test - absence of increasing of FEV_1 more than 200 mL and 12% of the initial value indicates irreversible airway obstruction/

Spirometry



Supporting evaluation

Laboratory studies:

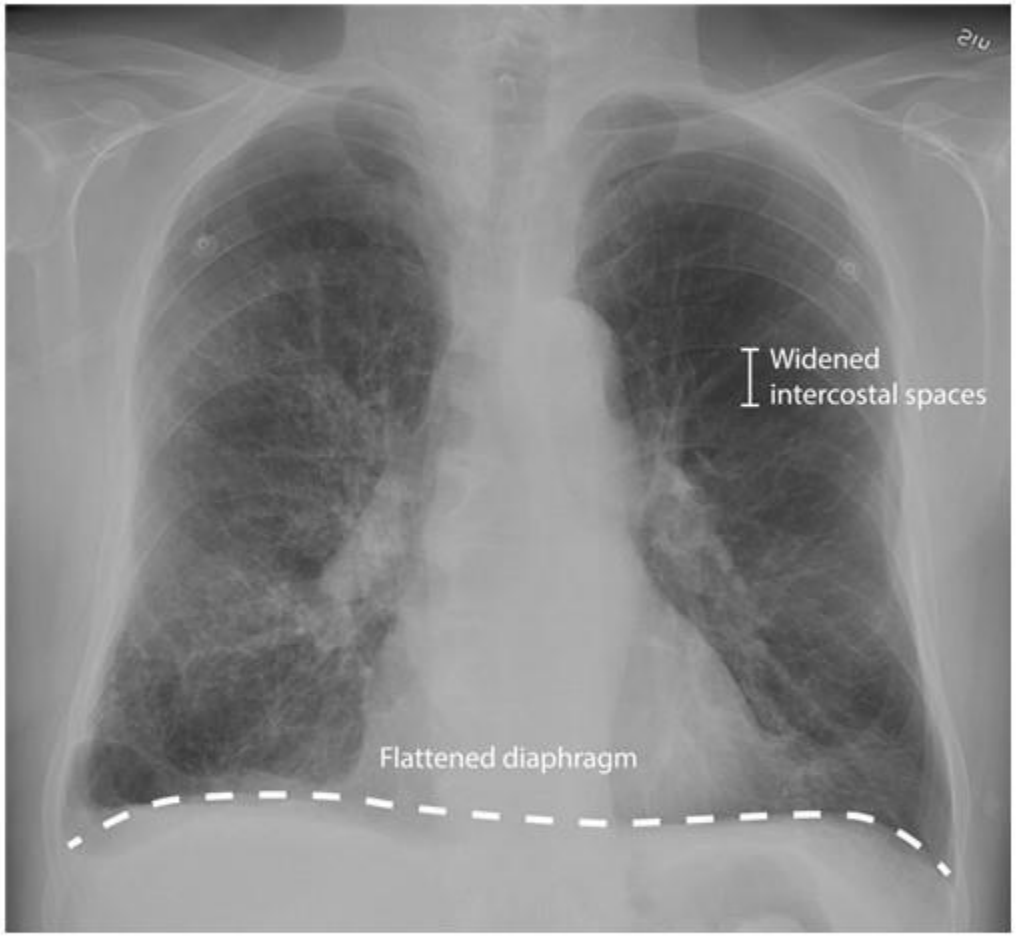
- Arterial blood gas (ABG):
  - Hypoxemia:
    - Progressive
    - Often worse during acute exacerbation
  - Hypercapnia:
    - Develops as FEV_1 falls
    - pH is usually near normal due to renal compensation (↑ serum HCO_3)
- ↑ BNP in cor pulmonale
- AAT testing: Consider if COPD symptoms are present (not in typical demographic):
  - Younger
  - Nonsmoker
  - Concomitant, unexplained liver disease

Supporting evaluation

Chest X-ray:

- Barrel-shaped chest
- Wide intercostal spaces
- Horizontal ribs
- Flattened, low diaphragm
- Hyperlucency
- Attenuated peripheral vascular
- markings

(due to parenchymal destruction)



Classification of airflow limitation severity in COPD

In addition to COPD diagnosis, spirometry results may be used in conjunction with symptoms to help stage severity.
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria are as follows:

GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

based on post-bronchodilator FEV_1 in patients with $FEV_1/FVC < 0.70$

FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity

Assessment of symptoms

To evaluate the symptoms, the GOLD document recommends the use of the modified British Medical Research Council dyspnea scale (mMRC) or the COPD assessment test (CAT) in an equivalent manner.

mMRC Grade 0.	I only get breathless with strenuous exercise.	☐
mMRC Grade 1.	I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2.	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3.	I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4.	I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

[a] Fletcher CM. BMJ 1960; 2: 1662.

Assessment of symptoms

The COPD Assessment Test (CAT) is designed to measure the impact of COPD on a person's life, and how this changes over time. The CAT is simple to administer, and aims to help clinicians, with their patients, better manage COPD.

			SCORE
EXAMPLE: I am very happy	0 (X) 2 3 4 5	I am very sad	
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

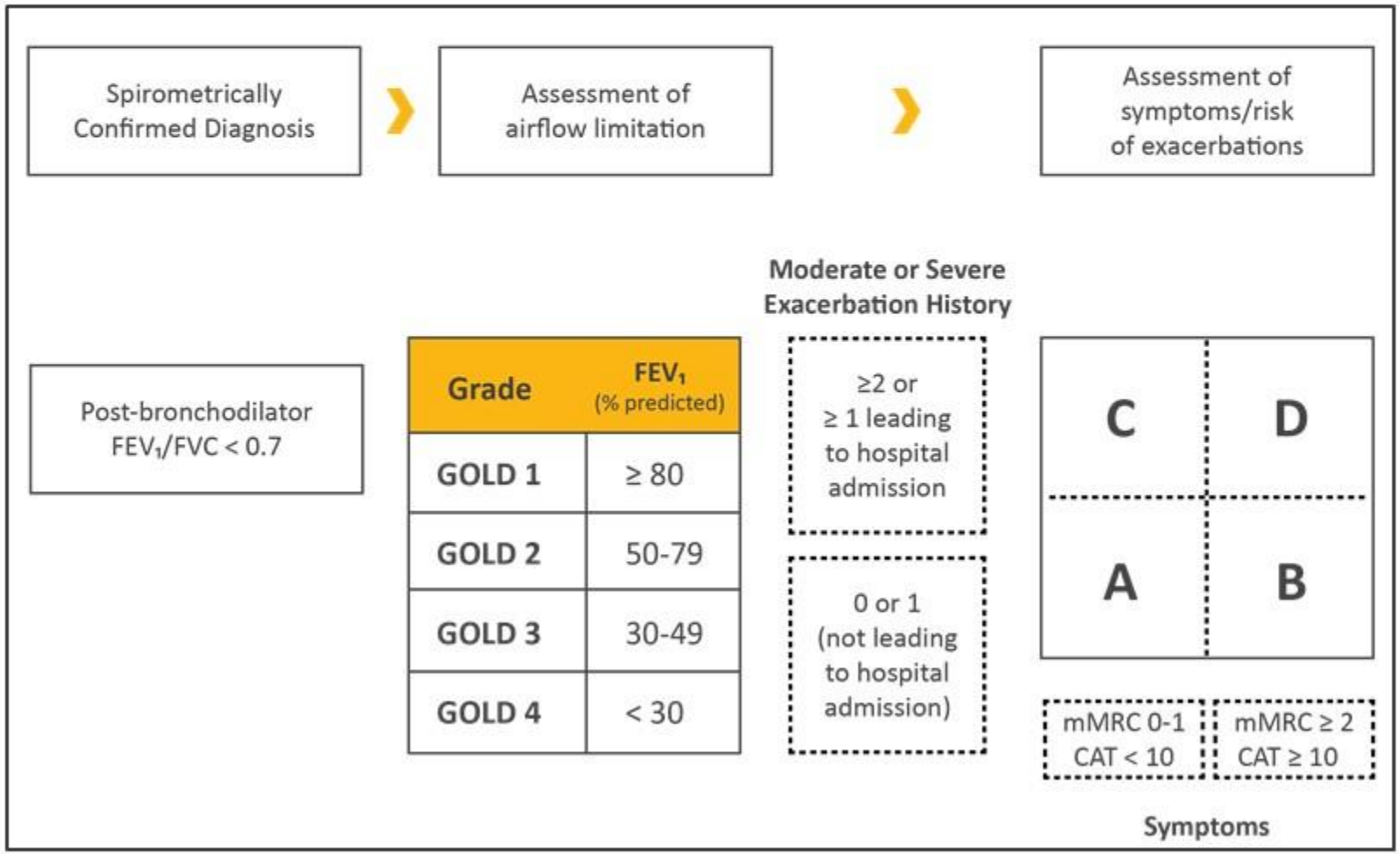
TOTAL SCORE: ◯

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

FIGURE 2.3

Combined COPD assessment

The "ABCD" COPD assessment tool proposed by the GOLD is based on the combination of the patient's level of respiratory symptoms, and future risk of exacerbations.



Differential diagnosis of COPD

Diagnosis	Suggestive features*
COPD	Onset in mid-life; onset in early adulthood should prompt suspicion for alpha-1 antitrypsin deficiency
	Symptoms slowly progressive
	Long smoking history, although can occur in nonsmokers
	Dyspnea during exercise
	Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood)
	Symptoms vary from day to day
	Symptoms at night/early morning
	Allergy, rhinitis, and/or eczema also present
	Family history of asthma
	Largely reversible airflow limitation
Central airway obstruction (eg, bronchogenic or metastatic cancer, lymphadenopathy, scarring from endotracheal tube)	Monophonic wheeze or stridor
	Variable inspiratory or fixed slowing on flow volume loop
	Chest radiograph often normal
	Airway narrowing on three dimensional reconstruction of HRCT scan

Differential diagnosis of COPD

Diagnosis	Suggestive features*
Heart failure	Fine basilar crackles on auscultation
	Chest radiograph shows dilated heart, pulmonary edema
	Pulmonary function tests typically indicate volume restriction, but airflow limitation can sometimes be seen
Bronchiectasis	Large volumes of purulent sputum
	Commonly associated with recurrent or persistent bacterial infection
	Coarse crackles on auscultation, clubbing of digits
	Chest radiograph/HRCT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages
	Chest radiograph shows upper lung zone scarring and/or calcified granulomata
	Positive PPD or IGRA
	High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset in younger age, nonsmokers
	May have history of rheumatoid arthritis or fume exposure
	HRCT on expiration shows hypodense areas, mosaic pattern
Diffuse panbronchiolitis	Most patients are male and nonsmokers
	Highest prevalence in East Asia
	Almost all have chronic sinusitis
	Chest radiograph and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

Management of COPD

Principles

- Improve symptoms.
- Decrease exacerbations.
- Improve patient function.
- Improve quality of life.

General management

- Smoking cessation (critical in slowing lung function decline)
- Vaccinations for:
  - Pneumococcal pneumonia
  - Influenza
- Pulmonary rehabilitation:
  - Guided exercise and behavioral interventions
  - Goal is to improve functional capacity.
- O_2 therapy:
  - If O_2 saturation is < 88% in a stable patient (PO_2 < 55 mm Hg)
  - If concurrent pulmonary hypertension, right-sided heart failure, or polycythemia

Smoking Cessation

Smoking cessation is both extremely difficult and extremely important; it slows but does not halt the rate of FEV1 decline and increases long-term survival

Simultaneous use of multiple strategies is most effective:

- Establishment of a quit date
- Behavior modification techniques
- Group sessions
- Nicotine replacement therapy (by gum, transdermal patch, inhaler, lozenge, or nasal spray)
- Varenicline or bupropion
- Physician encouragement

Quit rates > 50% at 1 year have not been demonstrated even with the most effective interventions, such as use of bupropion combined with nicotine replacement or use of varenicline alone.

Medical therapy

Inhaled bronchodilators are the mainstay of COPD management.

Drugs include:

•Beta-agonists - relax bronchial smooth muscle and increase mucociliary clearance

•Anticholinergics (antimuscarinics) - relax bronchial smooth muscle through competitive inhibition of muscarinic receptors (M1, M2, and M3).

These two classes of drugs are equally effective. Patients with mild (group A) disease are treated only when symptomatic. Patients with moderate to severe (group B, C, or D) COPD should be taking drugs from one or both of these classes regularly to improve pulmonary function and increase exercise capacity.

Medical therapy

Inhaled corticosteroids (ICS)
Corticosteroids are often part of treatment.
ICS seem to reduce airway inflammation, reverse beta-receptor down-regulation, and inhibit leukotriene and cytokine production.
They do not alter the course of pulmonary function decline in patients with COPD who continue to smoke, but they do relieve symptoms and improve short-term pulmonary function in some patients, are additive to the effect of bronchodilators, and diminish the frequency of COPD exacerbations.
They are indicated for patients ***who have repeated exacerbations*** or ***symptoms despite optimal bronchodilator therapy***.

Combinations of a long-acting beta-agonist and an inhaled corticosteroid are more effective than either drug alone in the treatment of chronic stable disease.
Oral or systemic corticosteroids should usually **not be used!** to treat chronic stable COPD.

https://www.msdmanuals.com/professional/pulmonary-disorders/chronic-obstructive-pulmonary-disease-and-related-disorders/treatment-of-stable-copd#v48769078

Medical therapy

Theophylline

Theophylline plays only a small role in the treatment of chronic stable COPD now that safer, more effective drugs are available.
Theophylline decreases smooth muscle spasm, enhances mucociliary clearance, improves right ventricular function, and decreases pulmonary vascular resistance and arterial pressure. Its mode of action is poorly understood but appears to differ from that of beta-2-agonists and anticholinergics. Its role in improving diaphragmatic function and dyspnea during exercise is controversial.

Phosphodiesterase-4 inhibitors

Phosphodiesterase-4 inhibitors are more specific than theophylline for pulmonary phosphodiesterase and have fewer adverse effects.
They have anti-inflammatory properties and are mild bronchodilators.
Phosphodiesterase-4 inhibitors such as roflumilast can be used in addition to other bronchodilators for reduction of exacerbations in patients who have COPD with chronic bronchitis. Roflumilast should be started at a oral dose of 250 mcg once a day and increased to 500 mcg once a day as tolerated.

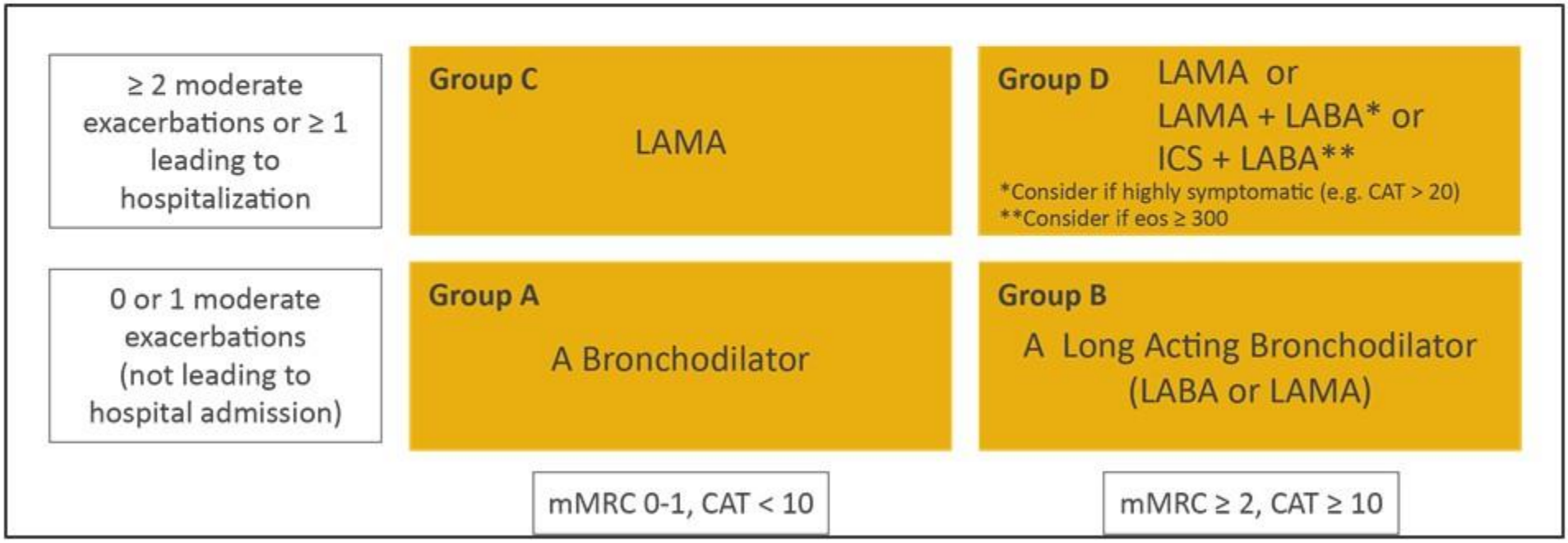
https://www.msdmanuals.com/professional/pulmonary-disorders/chronic-obstructive-pulmonary-disease-and-related-disorders/treatment-of-stable-copd#v48769078

Medical therapy

- **Bronchodilators:**
  - Short acting (used as needed for rescue):
    - Beta-2 adrenergic agonists (e.g., albuterol)
    - Anticholinergics (e.g., ipratropium bromide)
  - Long acting:
    - Beta-2 adrenergic agonists (e.g., salmeterol, formoterol, indacaterol)
    - Anticholinergics (e.g., tiotropium, aclidinium, umeclidinium)
- **Phosphodiesterase-4 inhibitors:**
  - Option: roflumilast
  - Reduces inflammation
  - Can increase FEV_1 and reduce exacerbations
- **Inhaled corticosteroids:**
  - Options: budesonide, fluticasone
  - Can produce both marginal improvements and adverse effects
- **Theophylline** (oral bronchodilator)
- **Mucolytics**

Initial Treatment of COPD

- Avoidance of risk factors (eg, smoking)
- Influenza vaccine annually
- Pneumococcal polysaccharide vaccine and Pneumococcal conjugate vaccine
- Regular, prudent exercise and pulmonary rehabilitation if indicated



ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting anticholinergic; mMRC = Modified British Medical Research Council; PDE4I = phosphodiesterase-4 inhibitor;

Management of acute exacerbations

- **Outpatient or inpatient therapy depending upon severity**
- **Short-acting bronchodilators:**
  - Scheduled every 4–6 hours
  - Continuous nebulization may be needed for severe bronchospasm.

The most widely used drug is **albuterol** 2.5 mg by nebulizer or 2 to 4 puffs (100 mcg/puff) by metered-dose inhaler every 2 to 6 hours. Inhalation using a metered-dose inhaler causes rapid bronchodilation; there are no data indicating that doses taken with nebulizers are more effective than the same doses correctly taken with metered-dose inhalers. In cases of severe unresponsive bronchospasm, continuous nebulizer treatments may sometimes be administered.

Systemic steroids should be begun immediately for all but mild exacerbations. Options include **prednisone** 30 to 60 mg orally once a day for 5 to 7 days and stopped directly or tapered over 7 to 14 days depending on the clinical response. A parenteral alternative is **methylprednisolone** 60 to 500 mg IV once a day for 3 days and then tapered over 7 to 14 days. These drugs are equivalent in their acute effects.

KEY POINTS FOR INHALATION OF DRUGS

- The choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference.
- It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, to ensure that inhaler technique is adequate and re-check at each visit that patients continue to use their inhaler correctly.
- Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy requires modification.

KEY POINTS FOR THE USE OF BRONCHODILATORS

- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea **(Evidence A)**, and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy.

- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator treatment should be escalated to two **(Evidence A)**.

- Inhaled bronchodilators are recommended over oral bronchodilators **(Evidence A)**.

- Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable **(Evidence B)**.

KEY POINTS FOR THE USE OF ANTI-INFLAMMATORY AGENTS

- Long-term monotherapy with ICS is not recommended **(Evidence A)**.
- Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators **(Evidence A)**.
- Long-term therapy with oral corticosteroids is not recommended **(Evidence A)**.
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations the addition of a PDE4 inhibitor to a treatment with long acting bronchodilators with/without ICS can be considered **(Evidence B)**.
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered **(Evidence B)**.
- Statin therapy is not recommended for prevention of exacerbations **(Evidence A)**.
- Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**.

Management of acute exacerbations

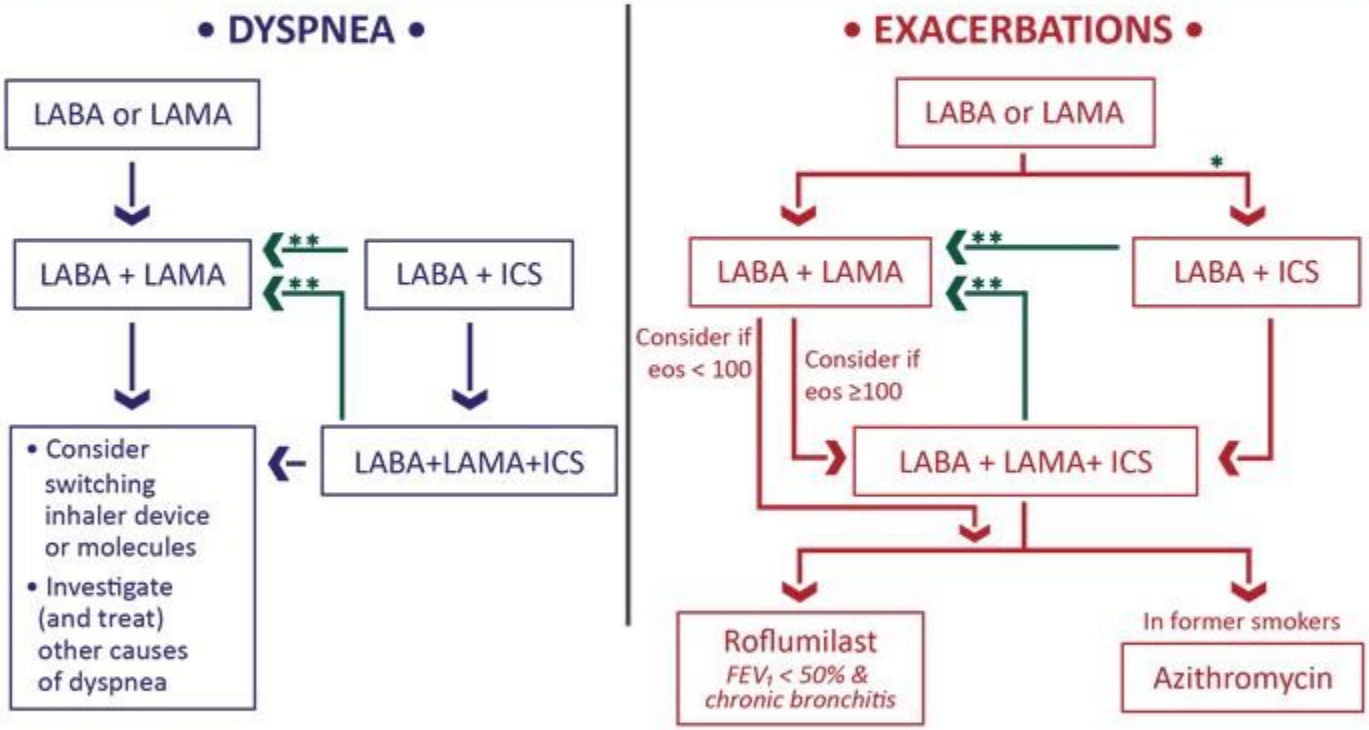
- **Antibiotics are indicated for:**
  - Purulent sputum
  - Evidence of pneumonia
  - Patients requiring hospitalization

✓ Trimethoprim/sulfamethoxazole 160 mg/800 mg orally twice a day
✓ Amoxicillin 250 to 500 mg orally 3 times a day
✓ Doxycycline 50 to 100 mg orally twice a day
✓ Azithromycin 500 mg orally once a day

- **Controlled O_2 therapy for acute respiratory failure:**
  - Nasal cannula
  - Noninvasive ventilation:
    - Hypercapnia and hypoxemia
    - Significant effort to breathe
  - Invasive ventilation:
    - Severe respiratory failure
    - May be difficult to wean patients with severe COPD

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)

** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*

*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

Complications

- Respiratory failure
- Respiratory infections (pneumonia)
- Pulmonary hypertension → cor pulmonale
- Long-term complications of steroids → osteoporosis
- Weight loss or cachexia
- Bullae rupture → secondary spontaneous pneumothorax