Respiratory system (Pharmacology)

- Lecture 1: Treatment of COPD
- Lecture 2: Treatment of Asthma 1
- Lecture 3: Treatment of Asthma 2
- Lecture 4: Treatment of allergic rhinitis + cough
- Lecture 5: Treatment of bacterial respiratory infections 1
- Lecture 6: Treatment of bacterial respiratory infections 2
- Lecture 7: Treatment of tuberculosis (TB)

Lecture 1: Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Respiratory system

Second year

Medical school

Hashemite University

2nd semester 23/24

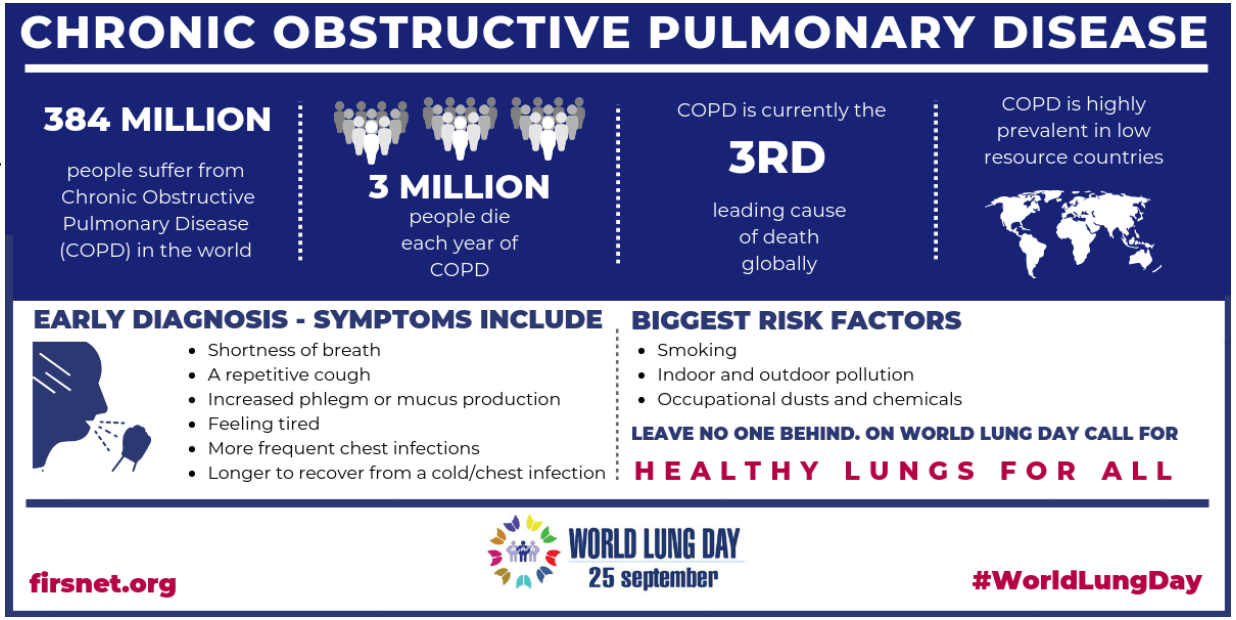
Sofian Al Shboul, MD, PhD.

Lecture objectives

- Review the pathophysiology of COPD
- Understand COPD therapeutic approach
- Describe the mechanisms of action (MOA), pharmacokinetics and side effects of agents used for COPD management

Facts & numbers

- Nearly half COPD patients say it limit their work and social activity
- Known as disease of old age but can occur as young as 35 years
- **SMOKING**
- Approximately 15-20% of the cases occur in nonsmokers.



It is NOT curable but treatable

Definition & sub-types

"an event characterized by dyspnea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways"

Defining "Chronic Obstructive Pulmonary Disease (COPD)"

Author: Yan Yu
Reviewers: Jason Baserman, Jennifer Au, Ciara Hanly, Zesheng Ye (叶泽生), Yonglin Mai (麦泳琳)*, Naushad Hirani*, Juri Janovcik*
* *MD at time of publication*

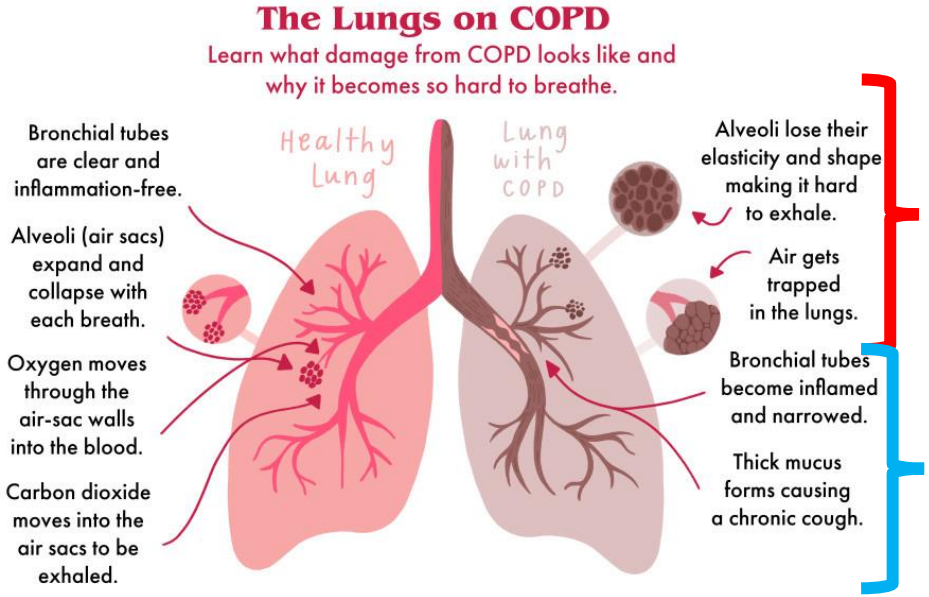
COPD
Systemic disease, largely manifesting as an airflow-obstructing respiratory disorder; can manifest in the form of any of the following disorders:

Emphysema
Lung tissue destruction & abnormal, permanent enlargement of lung acini: airspaces distal to terminal bronchioles

Chronic Bronchitis
Chronic, productive cough for a total duration of 3 months per year, over 2 continuous years

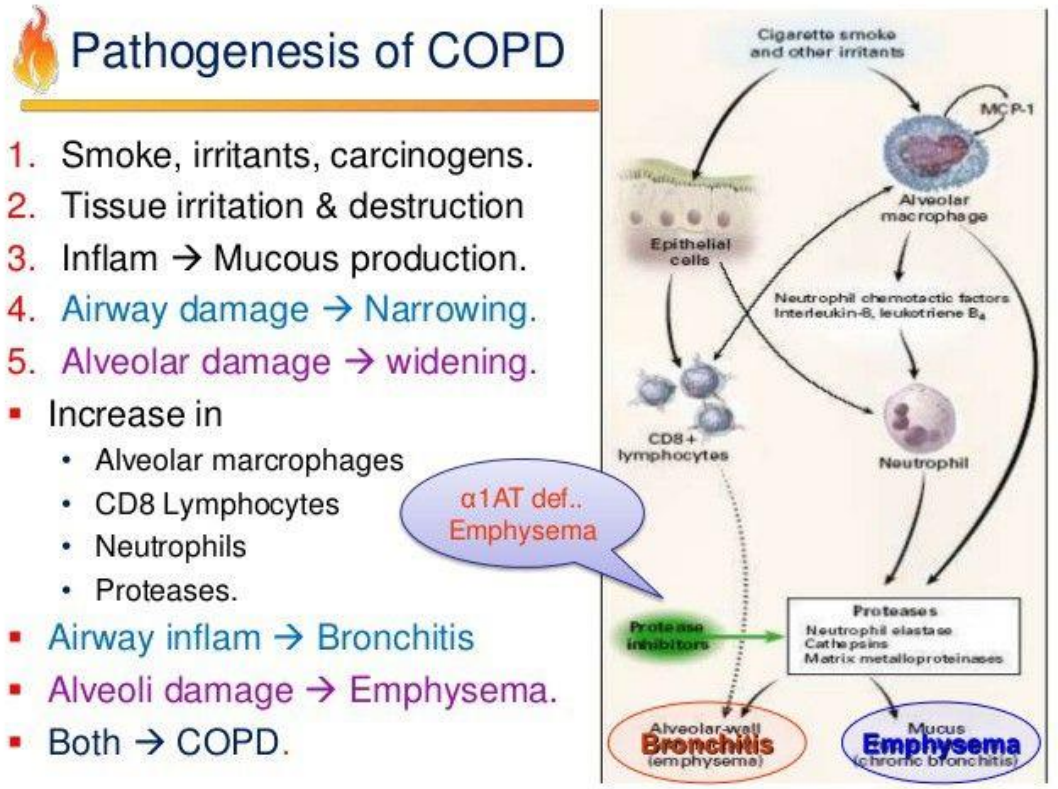
Clinically, COPD is seen as:

- Progressive, irreversible airflow obstruction and lung hyperinflation (causing respiratory symptoms like cough, sputum production, and dyspnea)
- Post-bronchodilator spirometry results: FEV1/FVC ratio <0.7 (FEV1 is not a defining feature of COPD, but a marker of severity)
- ↑ frequency & severity of acute exacerbations
- Systemic manifestations such as deconditioning and muscle weakness



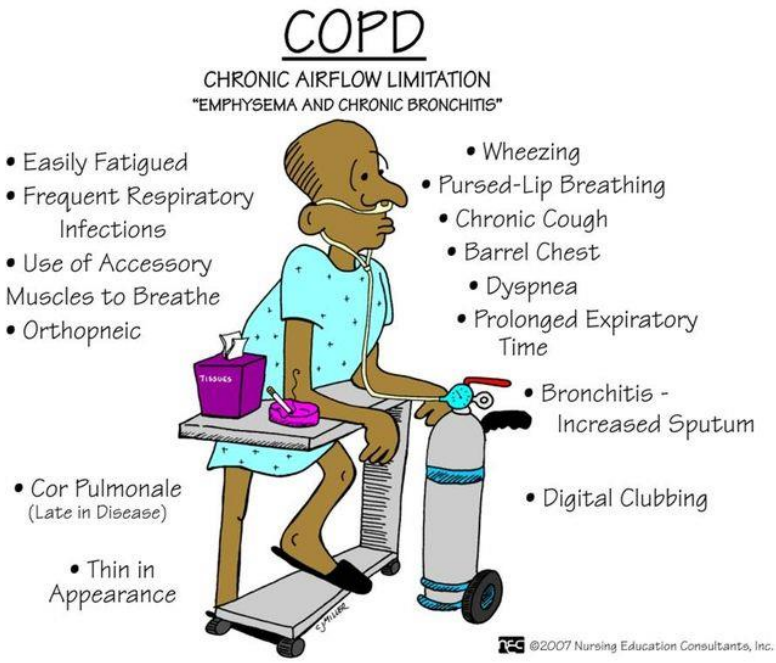
Pathogenesis

- Chronic bronchitis and emphysema: CD8+ T-lymphocytes, neutrophils, and CD68+ monocytes/macrophages in the airways.
- the bronchial inflammation of asthma: presence of CD4+ T-lymphocytes, eosinophils, and increased interleukin (IL)-4 and IL-5.



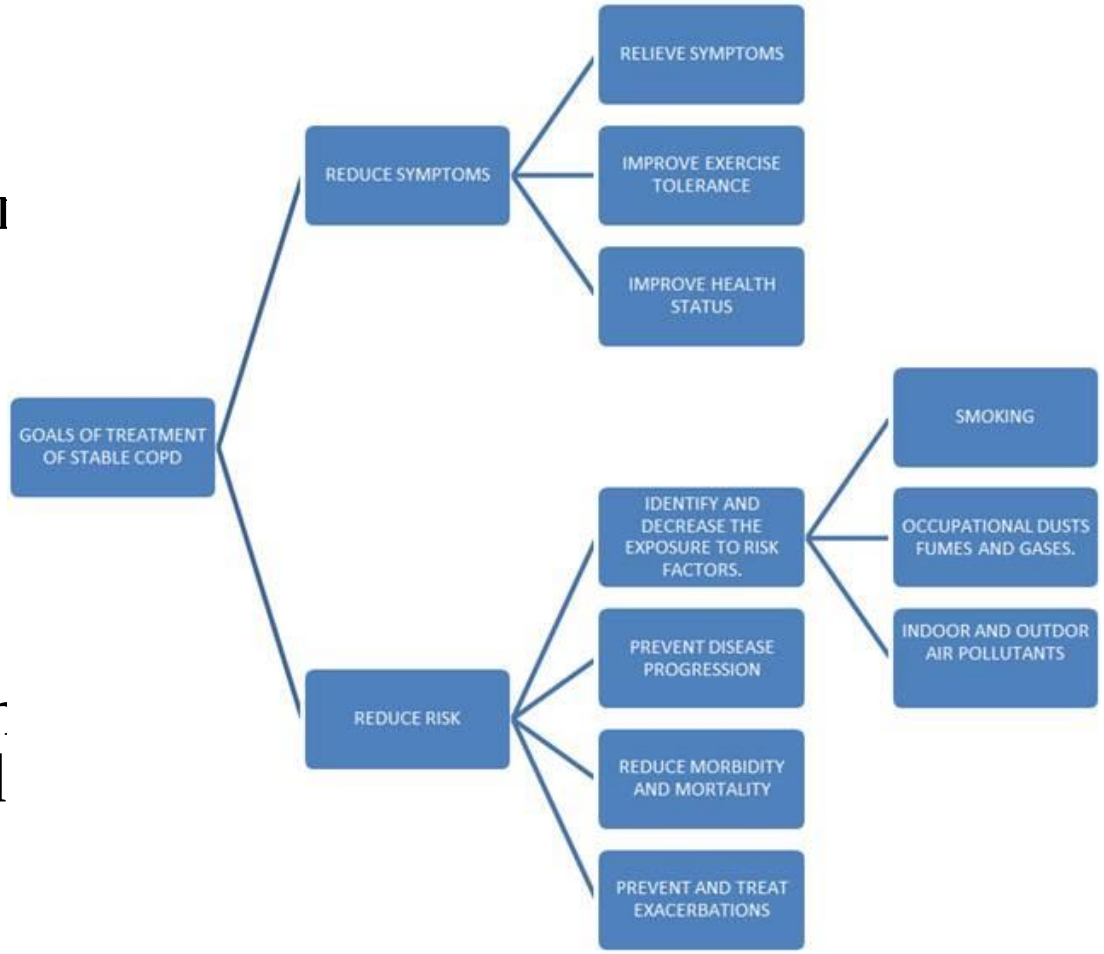
Signs & symptoms

- Dyspnea
- Chronic cough
- Sputum production
- Wheezing and chest tightness
- Breathlessness
- Difficulty sleeping
- Fatigue.



Treatment & management

- Quit smoking
- education and counselling (about COPD ai inhaler techniques).
- Seasonal influenza and COVID-19 vaccinations.
- Diet: no ideal COPD diet but excess weigh can contribute to dyspnea >>> normal bod mass index (BMI).



Pharmacological agents

COPD pharmacological treatment include

1. Short-acting β_2 agonists (SABAs)
2. Long-acting β_2 agonists (LABAs)
3. Short-acting muscarinic antagonist (SAMA)
4. Long-acting muscarinic antagonist (LAMA)
5. Inhaled corticosteroids (ICS)
6. Combinations of these classes
7. Vaccines, antibiotics and other agents

The mainstays of drug therapy for stable symptomatic COPD are inhaled bronchodilators (beta-agonists and muscarinic antagonists).

Pharmacological agents

MEDICATION	IND
SHORT-ACTING β_2 ADRENERGIC AGONISTS (SABAs)	
Albuterol PROAIR, PROVENTIL, VENTOLIN	Asthma, COPD
Levalbuterol XOPENEX	Asthma, COPD
LONG-ACTING β_2 ADRENERGIC AGONISTS (LABAs)	
Formoterol FORADIL, PERFOROMIST	Asthma, COPD
Olodaterol STRIVERDI RESPIMAT	COPD
Salmeterol SEREVENT	Asthma, COPD
INHALED CORTICOSTEROIDS	
Budesonide PULMICORT, RHINOCORT*	Allergic rhinitis, Asthma, COPD
Fluticasone FLONASE*, FLOVENT	Allergic rhinitis, Asthma, COPD
Mometasone ASMANEX, NASONEX*	Allergic rhinitis, Asthma

LONG-ACTING β_2 ADRENERGIC AGONIST/CORTICOSTEROID COMBINATION	
Formoterol/budesonide SYMBICORT	Asthma, COPD
Formoterol/mometasone DULERA	Asthma, COPD
Salmeterol/fluticasone ADVAIR	Asthma, COPD
SHORT-ACTING ANTICHOLINERGIC	
Ipratropium ATROVENT	Allergic rhinitis, Asthma, COPD
SHORT-ACTING β2 AGONIST/SHORT-ACTING ANTICHOLINERGIC COMBINATION	
Albuterol/ipratropium COMBIVENT RESPIMAT, DUONEB	COPD
LONG-ACTING ANTICHOLINERGIC (LAMA)	
Glycopyrrolate SEEBRI NEOHALER	COPD
Tiotropium SPIRIVA	Asthma, COPD
LABA/LAMA COMBINATION	
Formoterol/glycopyrrolate BEVESPI AEROSPHERE	COPD
Olodaterol/tiotropium STIOLTO RESPIMAT	COPD

OTHER AGENTS	
Roflumilast DALIRESP	COPD
Theophylline ELIXOPHYLLIN, THEO-24	Asthma, COPD

SABAs (Short-Acting Beta Agonists)	LABAs (Long-Acting Beta Agonists)	ICS (Inhaled Corticosteroids)	LABAs+ICS	SAMA (Short-Acting Muscarinic Antagonist)	SABA/SAMA	LAMA (Long-Acting Muscarinic Antagonists)	LABA/LAMA	others
Albuterol	Salmeterol	Fluticasone	Salmeterol/ Fluticasone	Ipratropium	Albuterol/Ipratropium	Glycopyrrolate	Formoterol/ Glycopyrrolate	Roflumilast
Levalbuterol	Formoterol	Budesonide	Formoterol/ Budesonide			Tiotropium	Olodaterol/ Tiotropium	Theophylline
	Olodaterol	Mometasone	Formoterol/ Mometasone					

Pharmacological agents

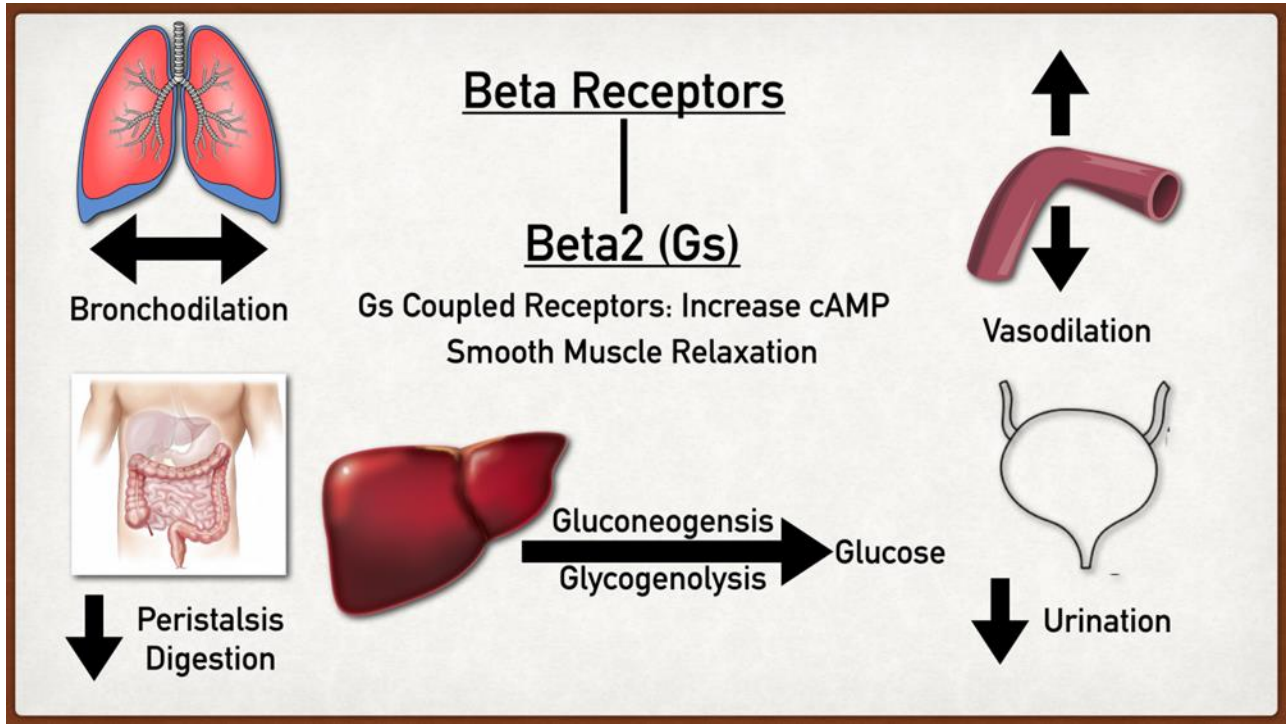
Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities
BETA AGONISTS				
• Albuterol	Selective β_2 agonist	Prompt, efficacious bronchodilation	Asthma, chronic obstructive pulmonary disease (COPD) • drug of choice in acute asthmatic bronchospasm	Aerosol inhalation • duration several hours • also available for nebulizer and parenteral use • *Toxicity:* Tremor, tachycardia • overdose: arrhythmias
• Salmeterol	Selective β_2 agonist	Slow onset, primarily preventive action; potentiates corticosteroid effects	Asthma prophylaxis	Aerosol inhalation • duration 12–24 h • *Toxicity:* Tremor, tachycardia • overdose: arrhythmias
• *Metaproterenol, terbutaline: Similar to albuterol; terbutaline available as an oral drug*				
• *Formoterol: Similar to salmeterol*				
CORTICOSTEROIDS, INHALED				
• Fluticasone	Alters gene expression	Reduces mediators of inflammation • powerful prophylaxis of exacerbations	Asthma • adjunct in COPD • hay fever (nasal)	Aerosol • duration hours • *Toxicity:* Limited by aerosol application • candidal infection, vocal cord changes
• *Beclomethasone, budesonide, flunisolide, others: Similar to fluticasone*				
CORTICOSTEROIDS, SYSTEMIC				
• Prednisone	Like fluticasone	Like fluticasone	Asthma • adjunct in COPD	Oral • duration 12–24 hours • *Toxicity:* Multiple • see Chapter 39
• *Methylprednisolone: Parenteral agent like prednisone*				
METHYLXANTHINES				
• Theophylline	Uncertain • phosphodiesterase inhibition • adenosine receptor antagonist	Bronchodilation, cardiac stimulation, increased skeletal muscle strength (diaphragm)	Asthma, COPD	Oral • duration 8–12 h but extended-release preparations often used • *Toxicity:* Multiple (see text)

Pharmacological agents:

β2-adrenergic agonists (adrenergic β2 receptor agonists):

act on the β2 adrenergic receptor:

- smooth muscle relaxation
- dilation of bronchial passages
- vasodilation in muscle and liver
- relaxation of uterine muscle
- release of insulin.



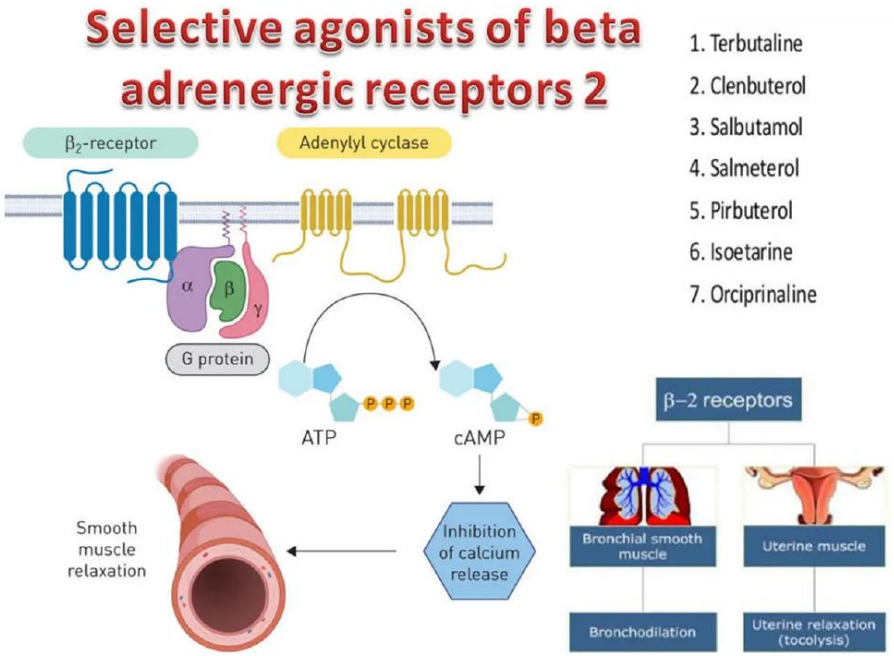
❖**Primarily used to treat asthma and COPD.**

Pharmacological agents:

β2-adrenergic agonists

➢**MOA**:

Receptor activation (G protein (Gs) + adenylyl cyclase) >> increases intracellular cAMP >> activate protein kinase A (PKA) >> reduce intracellular Ca2+ or decrease the sensitivity of Ca2+ >> inhibition of myosin light chain phosphorylation (MLCK) >> preventing airway smooth muscle contraction.



➢Anti-inflammatory effects?

reducing intercellular adhesion molecule-1 (ICAM-1)

reducing granulocyte-macrophage colony-stimulating factors (GM-CSF) release

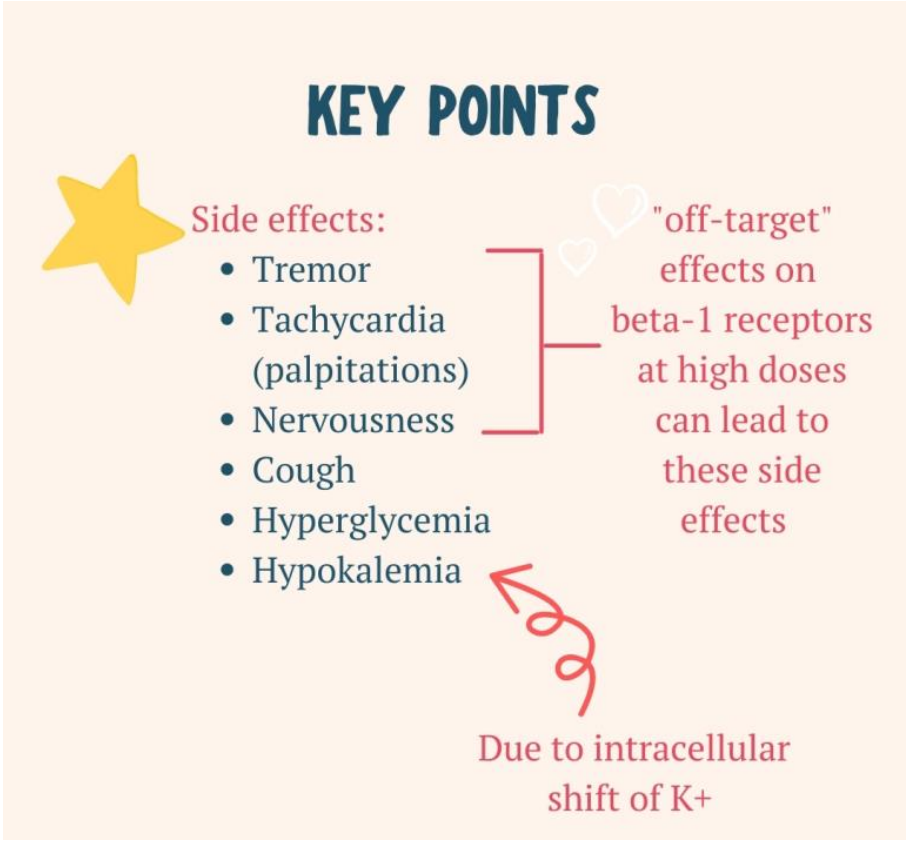
Pharmacological agents:

β2-adrenergic agonists

β2-adrenergic agonists (adrenergic β_2 receptor agonists):

❖Side effects: See the figure

❖All β2 agonists are available in inhaler form: metered-dose inhalers (MDI) or dry powder inhalers (DPI)



Pharmacological agents:
muscarinic antagonist

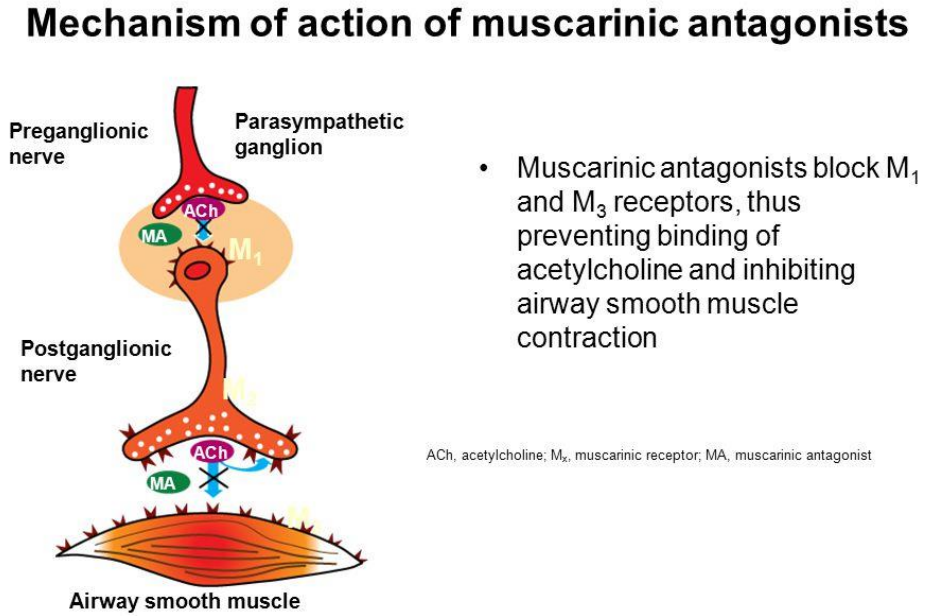
COPD pharmacological treatment include

3. Short-acting muscarinic antagonist (SAMA)
4. Long-acting muscarinic antagonist (LAMA)

Pharmacological agents:

muscarinic antagonist (muscarinic receptor antagonist (MRA):

- ✓Muscarinic receptors are predominately present on glandular cells, smooth muscle cells, and cardiac muscle cells.
- ✓Competitively inhibit the effect of **acetylcholine (ACh)** at muscarinic receptors (M1 and M3)
- ✓M1: CNS
- ✓M3: smooth muscle GI, UT, **airway**, and blood vessels
- ✓Side effects: dry mouth, constipation and urinary retention



Tashkin DP, Fabbri LM, *Respir Res.* 2010;11:149.

Pharmacological agents:

Inhaled corticosteroids (ICS)

COPD pharmacological treatment include

5. Inhaled corticosteroids (ICS)

inhibit the release of arachidonic acid through inhibition of phospholipase A2

Pharmacological agents:

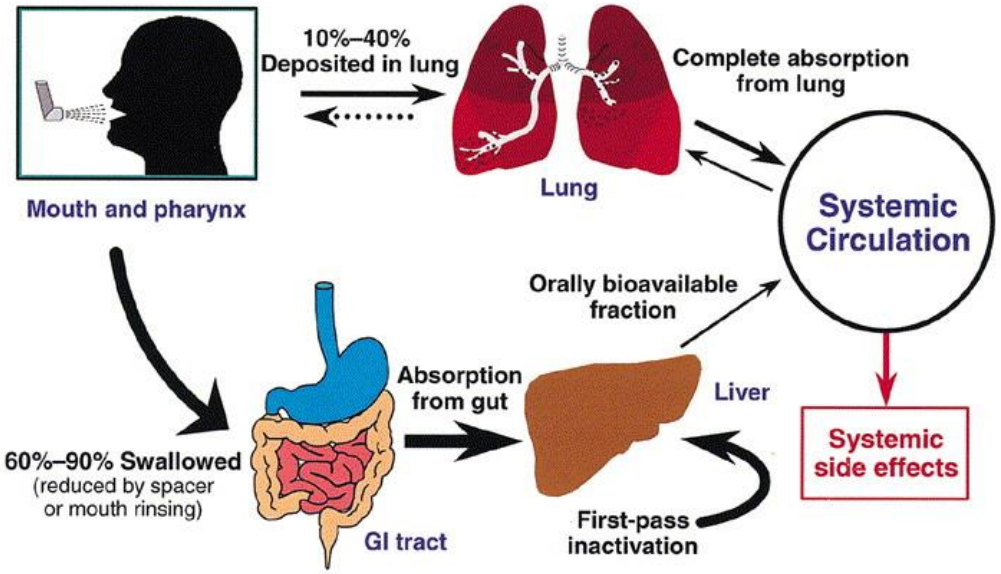
Inhaled corticosteroids (ICS)

Oral glucocorticoids can be effective in treating an acute exacerbation **BUT** generally they are not recommended

- Anti-inflammatory agents that should be reserved for patients with frequent or severe exacerbations and high blood eosinophils (~10% of the COPD population), or those with concomitant asthma

- Do not relax airway smooth muscle directly but reduce bronchial reactivity and potentiate the effects of β-receptor agonists

- Main effect: inhibition of the infiltration of lymphocytes, eosinophils, and mast cells.



Pharmacological agents:

Drug combinations

COPD pharmacological treatment include

6. Combinations of different drug classes

LONG-ACTING β_2 ADRENERGIC AGONIST/CORTICOSTEROID COMBINATION	
Formoterol/budesonide SYMBICORT	Asthma, COPD
Formoterol/mometasone DULERA	Asthma, COPD
Salmeterol/fluticasone ADVAIR	Asthma, COPD
[redacted]	
SHORT-ACTING β2 AGONIST/SHORT-ACTING ANTICHOLINERGIC COMBINATION	
Albuterol/ipratropium COMBIVENT RESPIMAT, DUONEB	COPD
LONG-ACTING ANTICHOLINERGIC (LAMA)	
[redacted]	
LABA/LAMA COMBINATION	
Formoterol/glycopyrrolate BEVESPI AEROSPHERE	COPD
[redacted]	
Olodaterol/tiotropium STIOLTO RESPIMAT	COPD

Pharmacological agents:

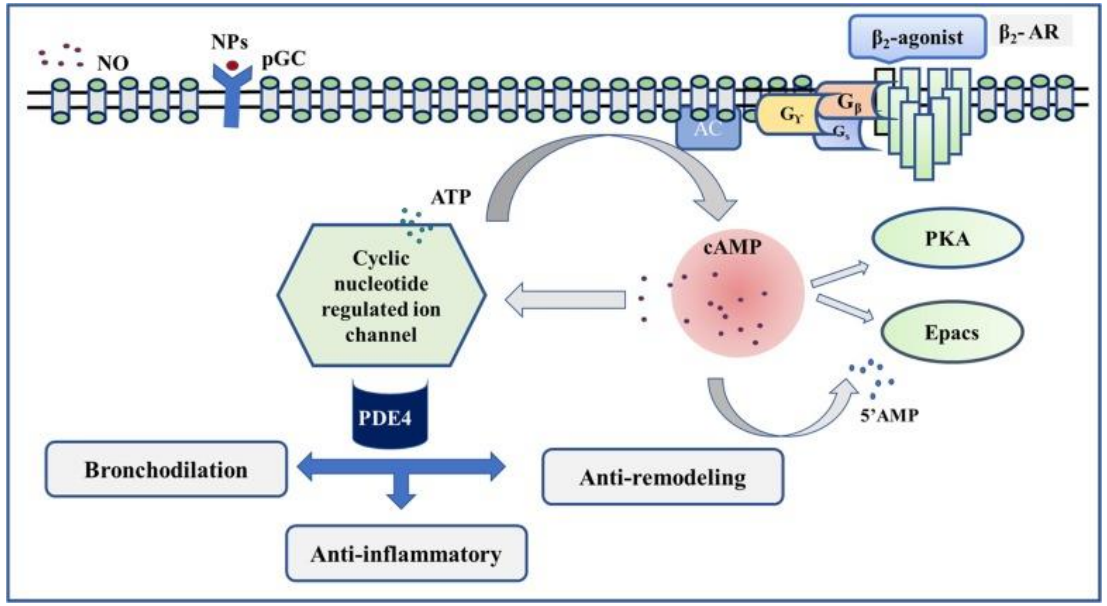
Other agents

Roflumilast

* Oral phosphodiesterase-4 (PDE4) inhibitor

* Reduces exacerbations in patients with severe chronic bronchitis.

* Reduce inflammation by increasing levels of intracellular cAMP in lung cells.



Pharmacological agents:

Other agents

- **Roflumilast**
- **NOT** a bronchodilator and is **NOT** indicated for the relief of acute bronchospasm, it decreases inflammation in lungs
- Used in treating those with chronic bronchitis and a history of exacerbations.
- Use is limited by common adverse effects including weight loss, nausea, diarrhea, and headache. used with caution in those suffering from depression.

Pharmacological agents:

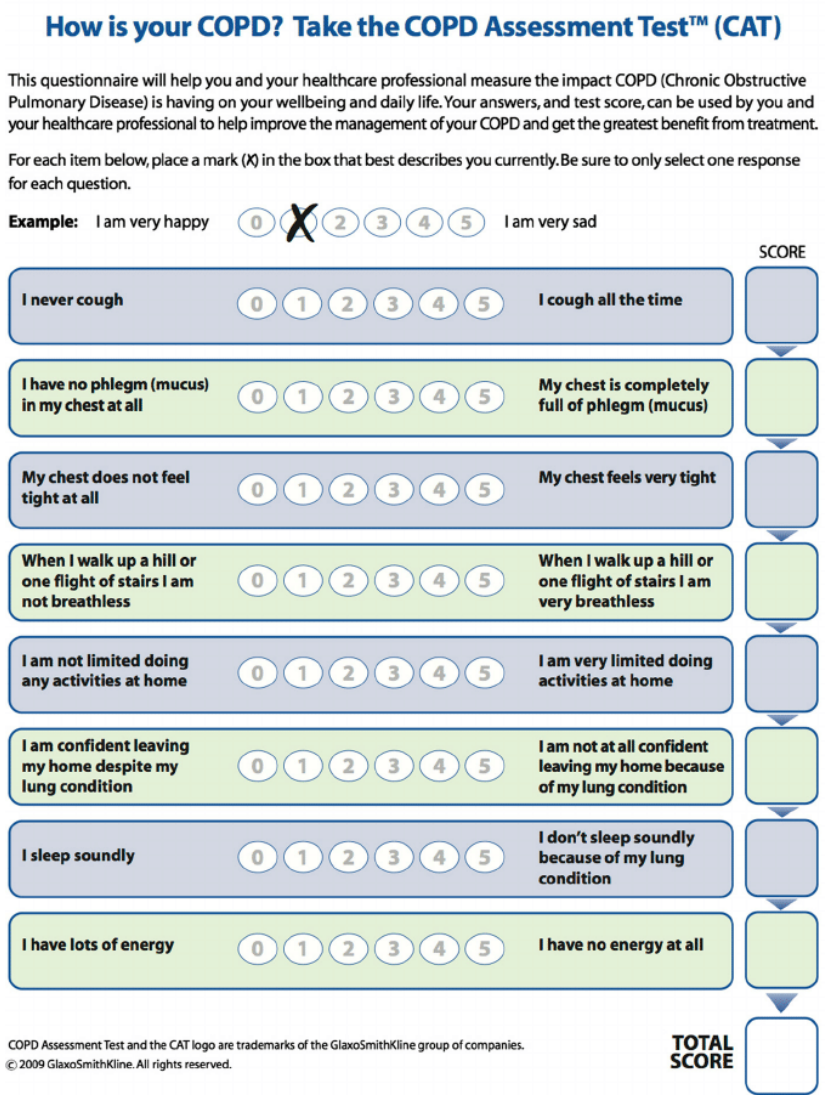
Other agents

- Methylxanthines such as theophylline which has mild bronchodilatory effect in stable COPD. Theophylline is seen to improve breathlessness when used as an add-on to salmeterol. Methylxanthines are not recommended for use in exacerbations due to adverse effects.

- Cough medicines are not recommended. Beta blockers are not contraindicated for those with COPD and should only be used where there is concomitant cardiovascular disease

CAT & mMRC scales

Range of CAT scores from 0–40. Higher scores denote a more severe impact of COPD on a patient's life.



How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

		SCORE
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

Modified Medical Research Council (mMRC) dyspnea scale

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

Treatment plans

Table 1: mMRC dyspnea scale	
Grade	**Description of breathlessness**
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking my own pace
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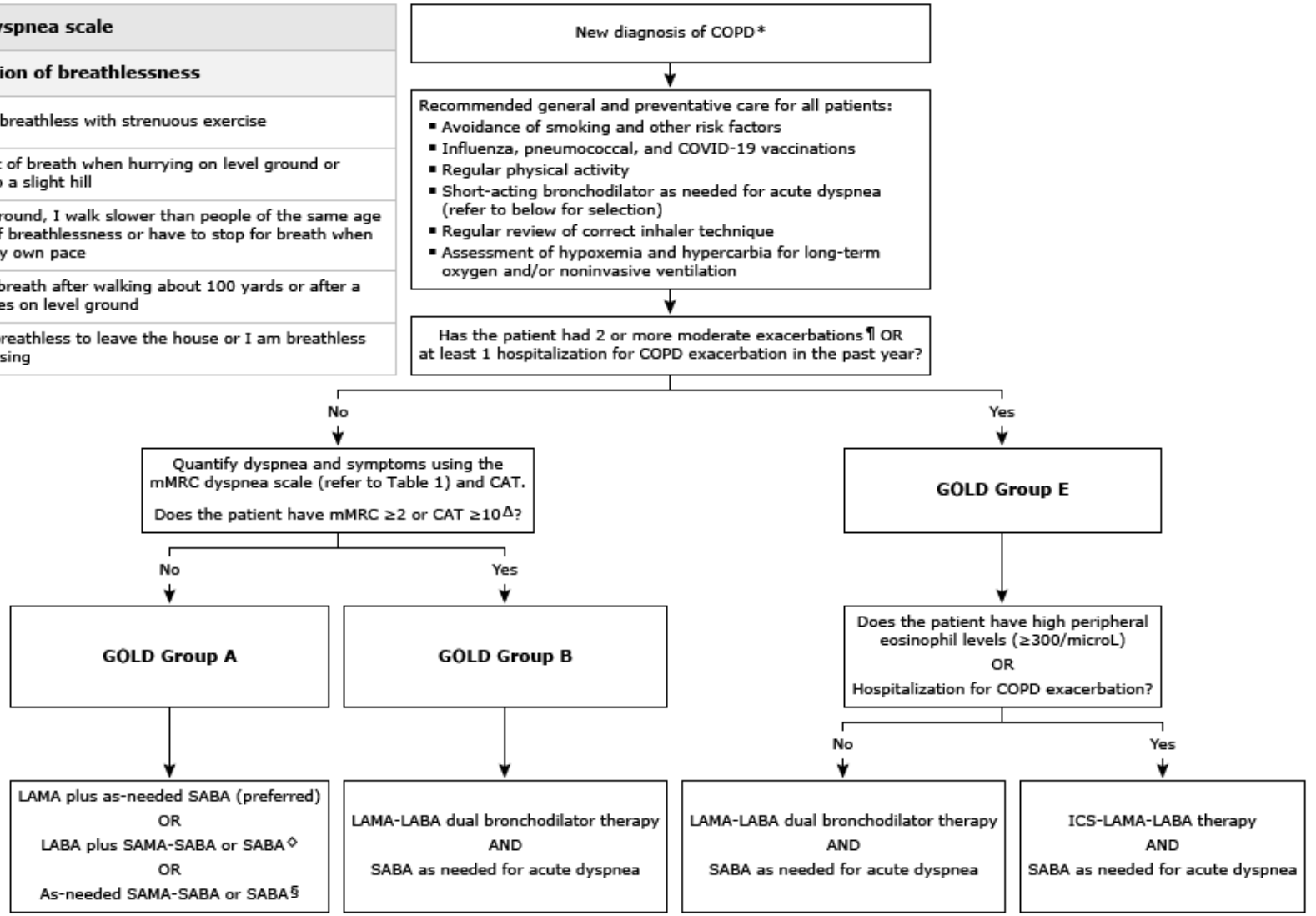
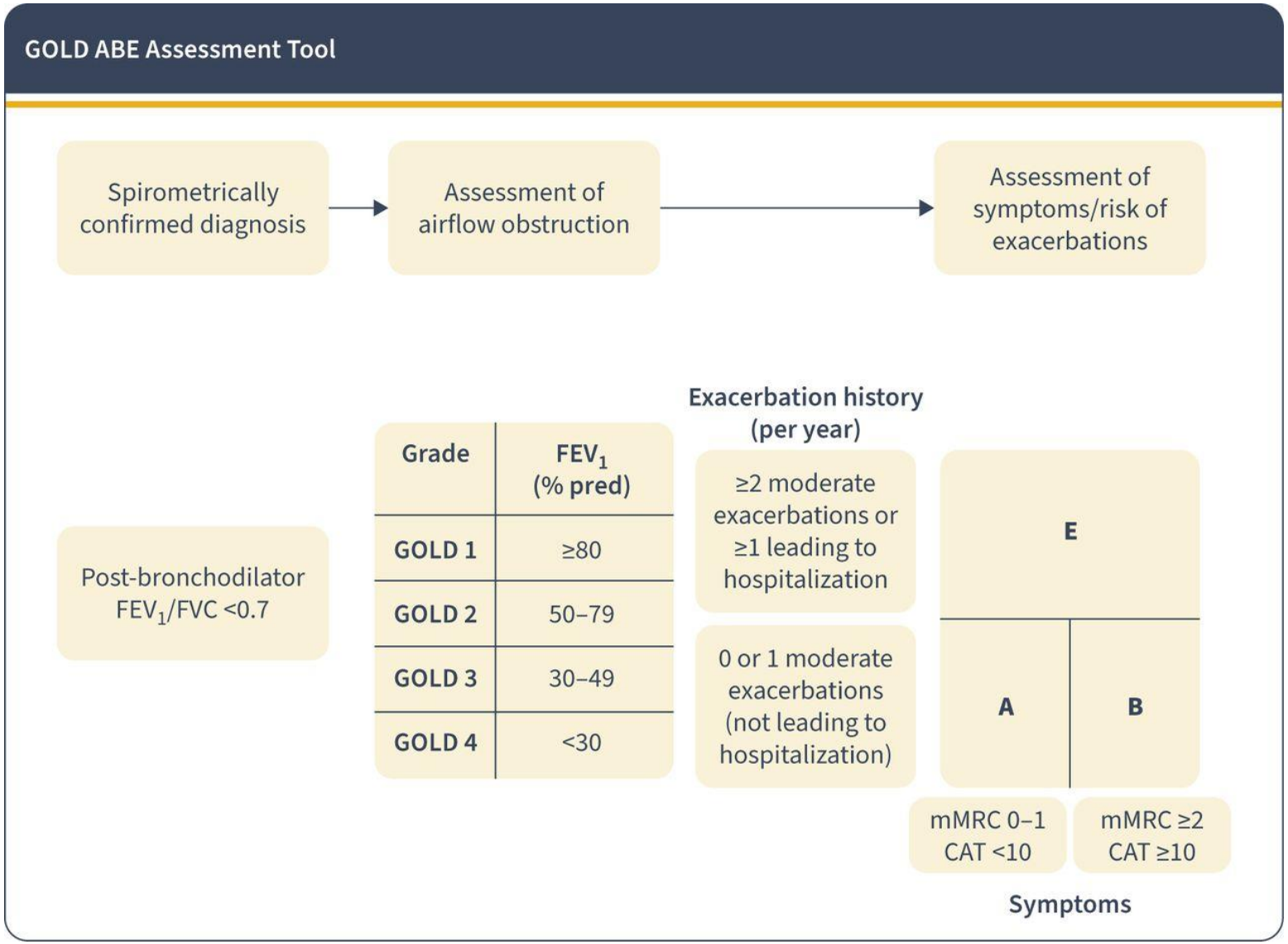


GOLD ABE assessment tool.



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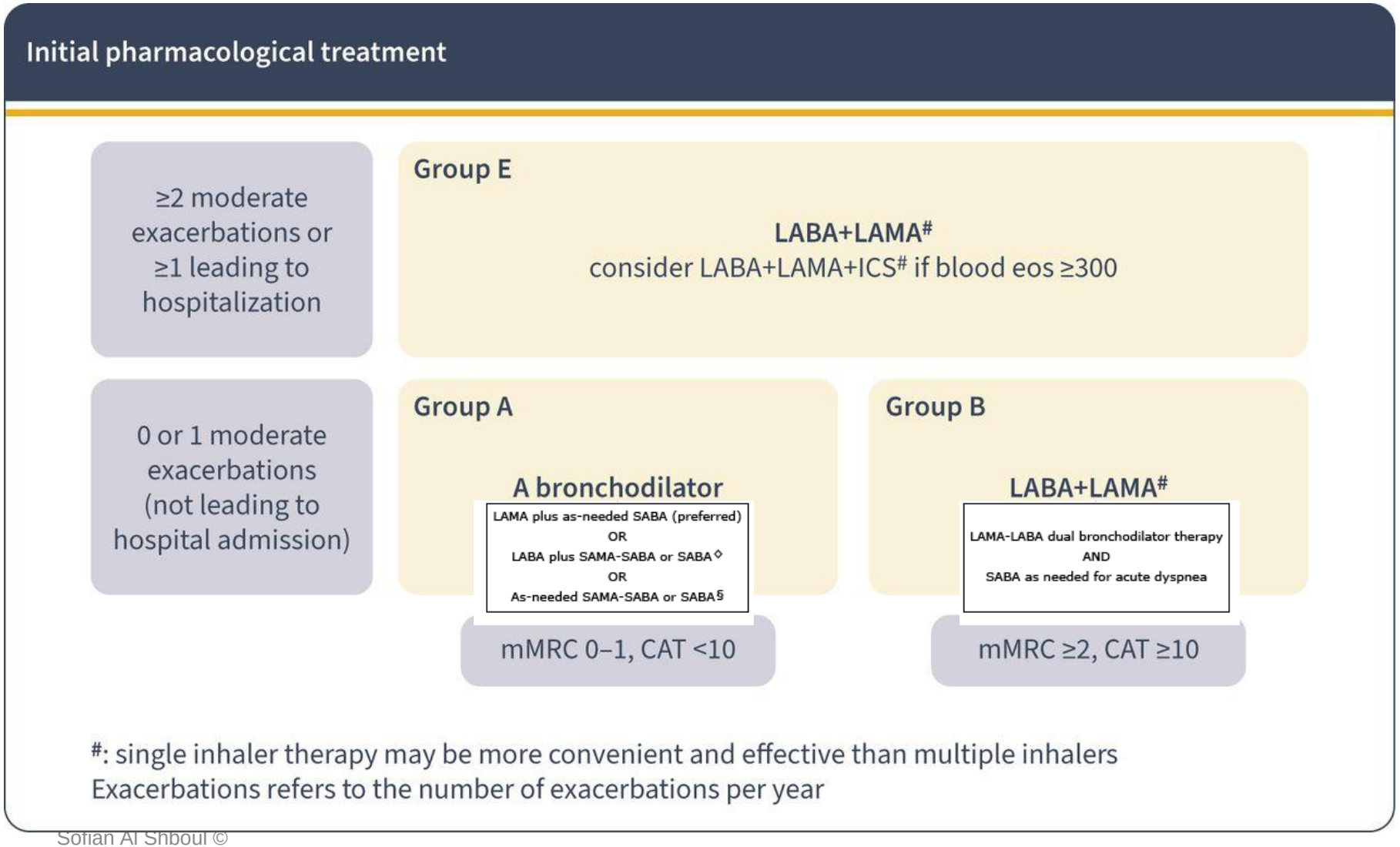
Initial pharmacological treatment



If there is an indication for an ICS, then LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice

The use of LABA+ICS in COPD is no longer encouraged.

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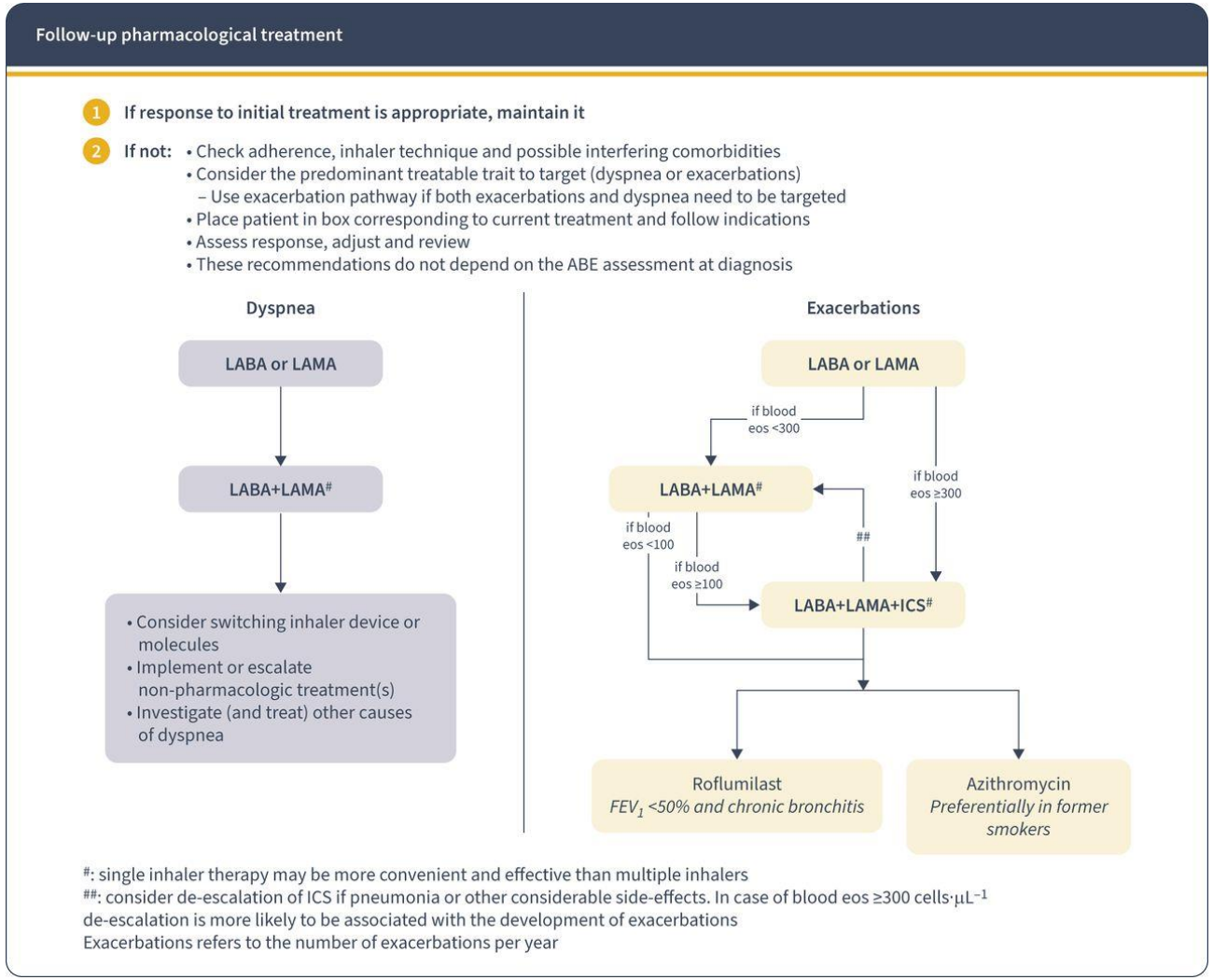
Follow-up pharmacological treatment.



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