Subject | Pharma
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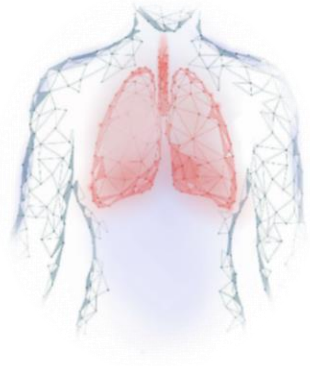


Asthma and COPD:

To start we need to remember some things from pathology: asthma and COPD fall under the umbrella of obstructive lung diseases (difficulty exhaling). Asthma is caused by hypersensitive airways, and COPD is divided into two diseases; chronic bronchitis and emphysema. Chronic bronchitis is having a productive cough for 3 months in 2 consecutive years, and emphysema is a *permanent* enlargement of air spaces without fibrosis. Despite asthma and COPD being distinct, now there are overlaps in the disease, meaning a patient can have both asthma and COPD. This is important because overlap changes the treatment plan for patients, and it has a worse prognosis.

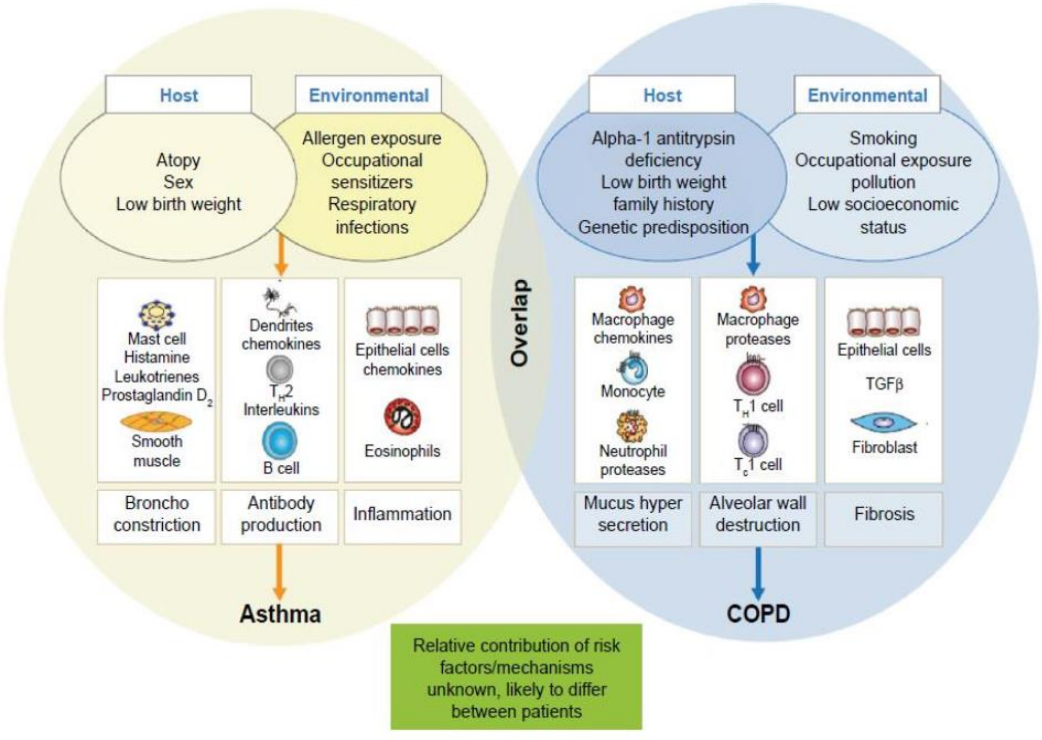


Figure showing the differences in pathophysiology of both diseases.

We need to know that eosinophils, basophils, smooth muscles, and leukotrienes (IL-4, 5, 6, 13) are important in asthma, and that neutrophils, fibroblasts, and TGFβ are important in COPD.

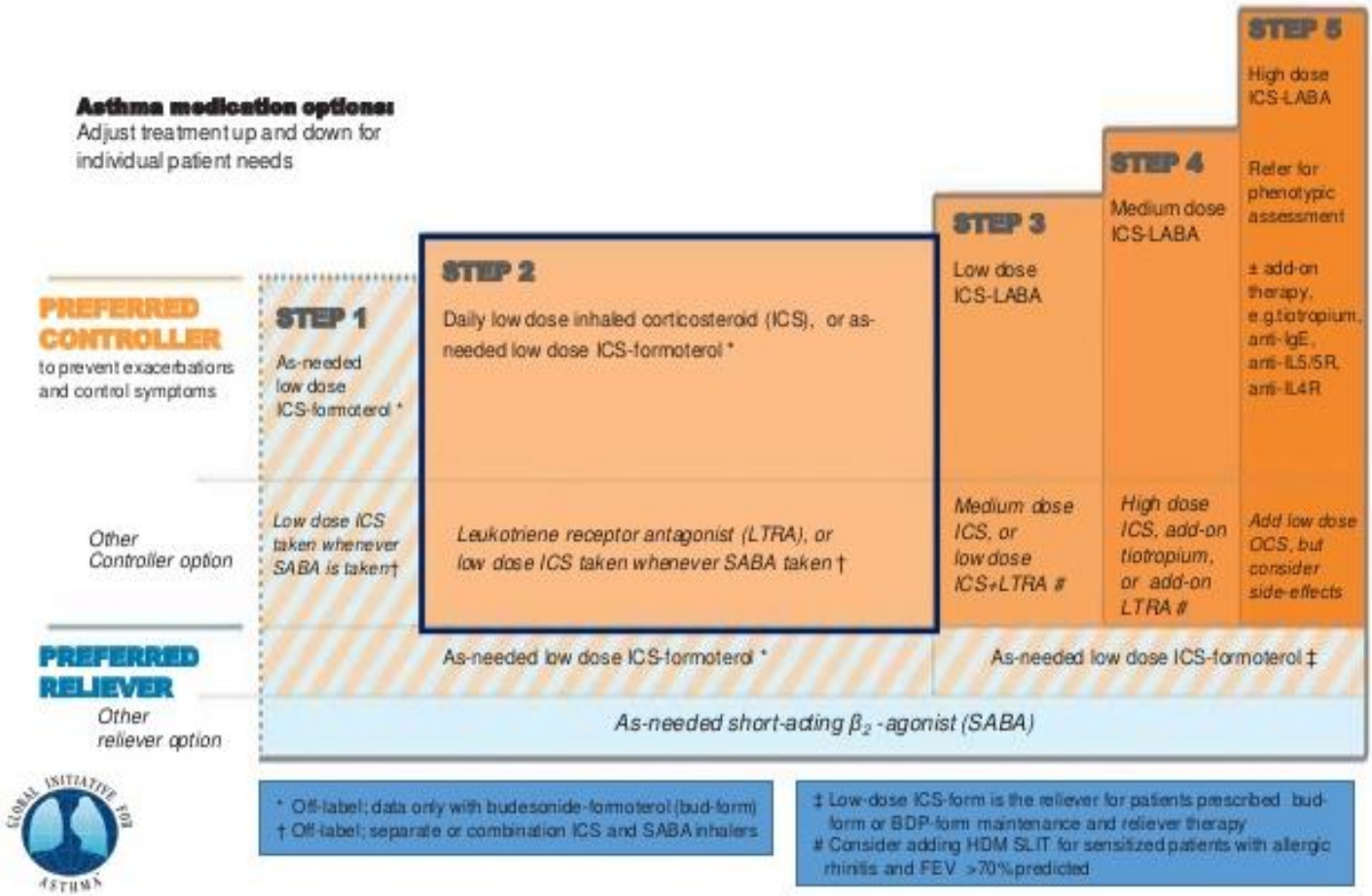
Asthma:

Now that we can distinguish between the two, we need to diagnose the severity of the disease, and this will guide our treatment plan. We do NOT need to know the exact numbers for asthma, but the diagnosis is based on 3 main points: the symptoms, the frequency of nocturnal attacks, and the FEV_1 or PEF. Now that we know our disease and its severity, we need to know the goals of treatment in order tailor our plan for the patient. The goals of asthma treatment: **to avoid troublesome symptoms night and day, use little or no reliever medication (short acting, such as salbutamol inhaler), to have productive and physically active lives, have near normal lung function, and to avoid serious attacks.**

Notice, that a goal is to decrease usage of reliever medication, and we do that by using **controller** medication.

Now on to treatment plans:

New 2019 guidelines provide a step approach to asthma treatment based on severity.



ICS – inhaled corticosteroids

SABA – short acting β2 agonist

LABA – long acting β2 agonist

Notice that initially we start off with low dose drugs, and gradually increase dosage according to severity. If this does not work, we administer add-on drugs. **The cornerstone of asthma treatment is ICS.**

Knowing what drugs that are used for asthma are not enough, as doctors we also need to know when to observe our patients, when to start treatment, and when to stop. Regarding asthma, the patient's condition should be reviewed 1-3 months after treatment starts, then every 3-12 months. For pregnant patients it should be every 4-6 weeks, and 1 week if an attack occurs after beginning treatment. The review process is made to see patients progress and if their condition is getting better or worse. If the patient is getting better we step-down our treatment, if they are getting worse we step-up our treatment. Another factor we must take into account is **adherence.** Is the patient taking their controller medication with the correct technique, at the right times and at the right doses? If not, then this can lead to uncontrolled symptoms and increased risk of attacks.

To summarize, we start off with ICS then add a LABA if the patient doesn't improve.

COPD:

In contrast to asthma patients, the treatment for COPD will not improve their condition, because it is a permanent destruction of airways. Despite this, quitting smoking will prevent more changes from taking place, so it will not improve, but prevent worsening conditions in COPD patients. The goals for COPD treatment are: to relieve symptoms, improve exercise tolerance, and improve health status which all reduce symptoms; and to prevent disease progression, prevent and treat exacerbations, as well as reduce mortality, all of which reduce risk. **The only thing shown to reduce mortality in COPD patients is cessation of smoking.**

The main symptom of COPD is coughing with sputum production. The severity of COPD is based on FEV_1 and it is classified similar to asthma (mild, moderate severe, very severe).

Here is a list of maintenance drugs used in COPD (only highlighted drugs are for memorization).

COMMONLY USED MAINTENANCE MEDICATIONS IN COPD*

Generic Drug Name	Inhaler Type	DELIVERY OPTIONS: *Nebulizer*	*Oral*	*Injection*	Duration Of Action
BETA$_2$-AGONISTS					
SHORT-ACTING (SABA)					
Fenoterol	MDI	√	pill, syrup		4-6 hours
Levalbuterol	MDI	√			6-8 hours
Salbutamol (albuterol)	MDI & DPI	√	pill, syrup, extended release tablet	√	4-6 hours 12 hours (ext. release)
Terbutaline	DPI		pill	√	4-6 hours
LONG-ACTING (LABA)					
Arformoterol		√			12 hours
Formoterol	DPI	√			12 hours
Indacaterol	DPI				24 hours
Olodaterol	SMI				24 hours
Salmeterol	MDI & DPI				12 hours
ANTICHOLINERGICS					
SHORT-ACTING (SAMA)					
Ipratropium bromide	MDI	√			6-8 hours
Oxitropium bromide	MDI				7-9 hours
LONG-ACTING (LAMA)					
Aclidinium bromide	DPI, MDI				12 hours
Glycopyrronium bromide	DPI		solution	√	12-24 hours
Tiotropium	DPI, SMI, MDI				24 hours
Umeclidinium	DPI				24 hours
Glycopyrrolate		√			12 hours
Revefenacin		√			24 hours
COMBINATION SHORT-ACTING BETA$_2$-AGONIST PLUS ANTICHOLINERGIC IN ONE DEVICE (SABA/SAMA)					
Fenoterol/ipratropium	SMI	√			6-8 hours
Salbutamol/ipratropium	SMI, MDI	√			6-8 hours
COMBINATION LONG-ACTING BETA$_2$-AGONIST PLUS ANTICHOLINERGIC IN ONE DEVICE (LABA/LAMA)					
Formoterol/aclidinium	DPI				12 hours
Formoterol/glycopyrronium	MDI				12 hours
Indacaterol/glycopyrronium	DPI				12-24 hours
Vilanterol/umeclidinium	DPI				24 hours
Olodaterol/tiotropium	SMI				24 hours
METHYLXANTHINES					
Aminophylline			solution	√	Variable, up to 24 hours
Theophylline (SR)			pill	√	Variable, up to 24 hours
COMBINATION OF LONG-ACTING BETA$_2$-AGONIST PLUS CORTICOSTEROID IN ONE DEVICE (LABA/ICS)					
Formoterol/beclometasone	MDI, DPI				12 hours
Formoterol/budesonide	MDI, DPI				12 hours
Formoterol/mometasone	MDI				12 hours
Salmeterol/fluticasone	MDI, DPI				12 hours
Vilanterol/fluticasone furoate	DPI				24 hours
TRIPLE COMBINATION IN ONE DEVICE (LABA/LAMA/ICS)					
Fluticasone/umeclidinium/vilanterol	DPI				24 hours
Beclometasone/formoterol/glycopyrronium	MDI				12 hours
PHOSPHODIESTERASE-4 INHIBITORS					
Roflumilast			pill		24 hours
MUCOLYTIC AGENTS					
Erdosteine			pill		12 hours
Carbocysteine†			pill		
N-acetylcysteine†			pill		

TABLE 3.3

*Not all formulations are available in all countries. In some countries other formulations and dosages may be available. † Dosing regimens are under discussion.
MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler.

In asthma treatment the cornerstone was ICS, but in COPD the central component of treatment is **bronchodilators**. In this case the first prescribed drug should be a LAMA or LABA (**tiotropium** or **formoterol**). In the case of asthma, bronchodilators are actually contraindicated because of lumen narrowing.

Because inflammation is the main cause of symptoms in asthma and COPD, we do see use of anti-inflammatory agents. Remember, ICS is the cornerstone of asthma treatment, and we can use oral steroids during and after acute attacks. Combination therapy of steroids has proven successful in COPD, but using it alone *can* increase the risk of pneumonia in patients (increased mortality). The use of PDE4 inhibitors is still being studied and the doctor said that it wasn't necessary for us to know, but he did say it *can* be used in severe chronic bronchitis. Alpha-1 antitrypsin replacement therapy *may* be used in cases of emphysema, but it is not a main-stay treatment.

Table 4.5. 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)**.
- 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)**.

Remember at the beginning of the lecture, we mentioned that some patients have an overlap in asthma and COPD. Because of this, ICS can be used as an add-on treatment for COPD patients that have asthma like symptoms (high eosinophils, exacerbations and admissions, etc.):

FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):

· STRONG SUPPORT ·	· CONSIDER USE ·	· AGAINST USE ·
• History of hospitalization(s) for exacerbations of COPD#	• 1 moderate exacerbation of COPD per year#	• Repeated pneumonia events
• ≥ 2 moderate exacerbations of COPD per year#	• Blood eosinophils 100-300 cells/µL	• Blood eosinophils <100 cells/µL
• Blood eosinophils >300 cells/µL		• History of mycobacterial infection
• History of, or concomitant, asthma		

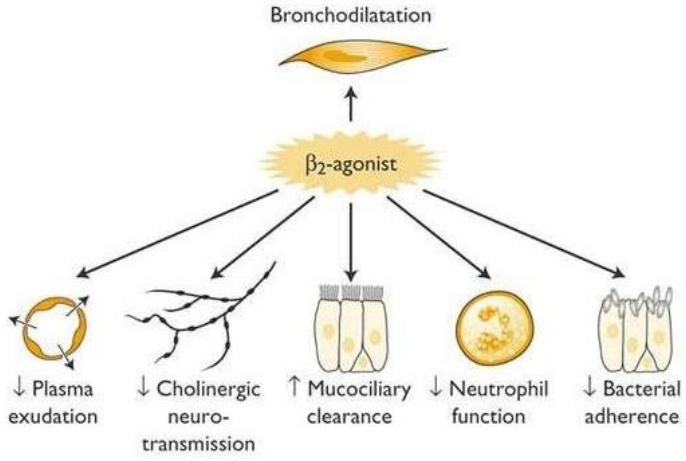
#despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);

*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

FIGURE 3.1

To summarize COPD treatment; after diagnosis you start with a LAMA or LABA, if the patient is coming to the hospital with frequent exacerbations, you add ICS (make sure the patient has no recurring infections because ICS increases the risk of pneumonia).

Although the main therapeutic use of β2 agonists is bronchodilation, they have other actions;



Now onto some real pharmacology, a small review of the distribution and effect of β-receptors

Organ	B1	B2
Heart	+ inotropic and chronotropic	
Vessels		Vasodilation
Bronchi		Bronchodilation
Uterus		Tocolysis
Skeletal muscles		Tremor
Fat tissue	Lipolysis (B3)	
Carb metabolism		Glycogenolysis

The reason we need to know these is because of the main side effects of the β adrenergic drugs. Most patients complain of palpitations and tremors, and it can get so bad that they refuse to continue treatment with the drug. Other adverse effects include insomnia, hypokalemia (only in high doses), paradoxical bronchospasm, and allergic reactions. The last two can happen with any drug.

Examples of β2 agonists:

Short acting: salbutamol, levosalbutamol, terbutaline

Long acting: formoterol, salmeterol

Ultra-long acting: indacaterol, vilanterol

Now, we move onto muscarinic receptors:

Muscarinic receptors

Receptor	Locations	Pharmacological actions
M1 Excitatory	CNS gastric parietal cells	CNS excitation Gastric acid secretion
M2 Inhibitory	Heart	Cardiac inhibition (Bradycardia)
M3 Excitatory	Exocrine glands Smooth muscles (GIT, urinary tract, bronchial muscles) Vascular endothelium	• Secretion of glands • Smooth muscle contraction • Vasodilatation (via nitric oxide)
M4 & M5	CNS	memory, arousal, attention and analgesia

We only care about M3 receptors, as they constrict smooth muscles causing bronchoconstriction.

Because the receptors cause bronchoconstriction, we use muscarinic antagonists (anticholinergic) to treat COPD. The only examples we need to know are ipratropium bromide and tiotropium bromide, as well as the combination drugs. The things we need to know about each:

	Ipratropium	Tiotropium
Onset of action	15 mins	30 mins
Duration	6 hours	24 hours

So in the case of an acute attack, we want to use the rapid onset drug, while the long acting one can be used once a day for management.

Most of the cholinergic drugs are similar to atropine, and all of them have a quaternary amine. This is important to know because of the side effects. The anticholinergics also have little effect on the mucociliary clearance.

Ipratropium: only 10-30% deposited in lungs, and 2% absorbed via GIT, so inhaler technique is very important, renal secretion

Tiotropium: secreted into urinary tract as well as clearance via kidney, patients with renal failure have impaired elimination of drug, available in dry powder form; improve lung function, reduce hyperinflation, reduce symptoms of COPD and dry out secretions; dry mouth, blurry vision (increased intraocular pressure), and urinary retention are most important side effects