Lectures 2-3: Treatment of Asthma

Respiratory system
Second year
Medical school
Hashemite University
2nd semester 23/24
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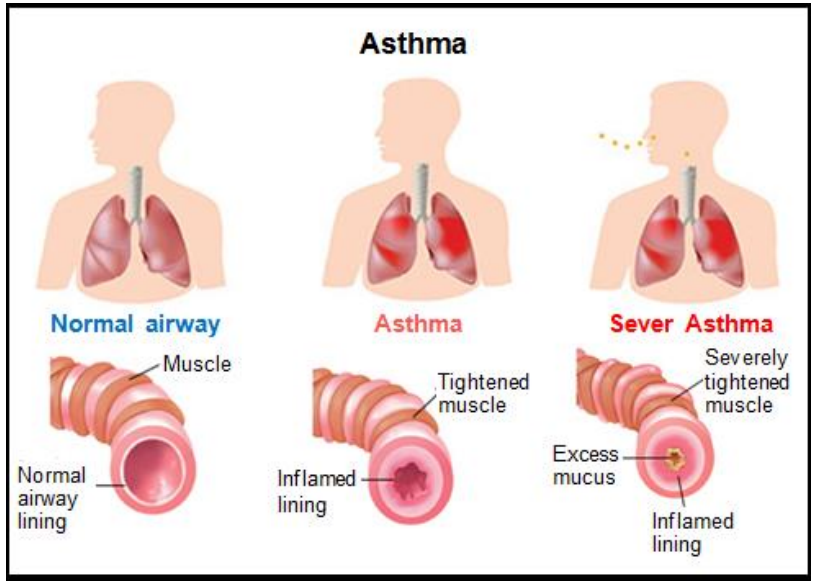
Overview & definition

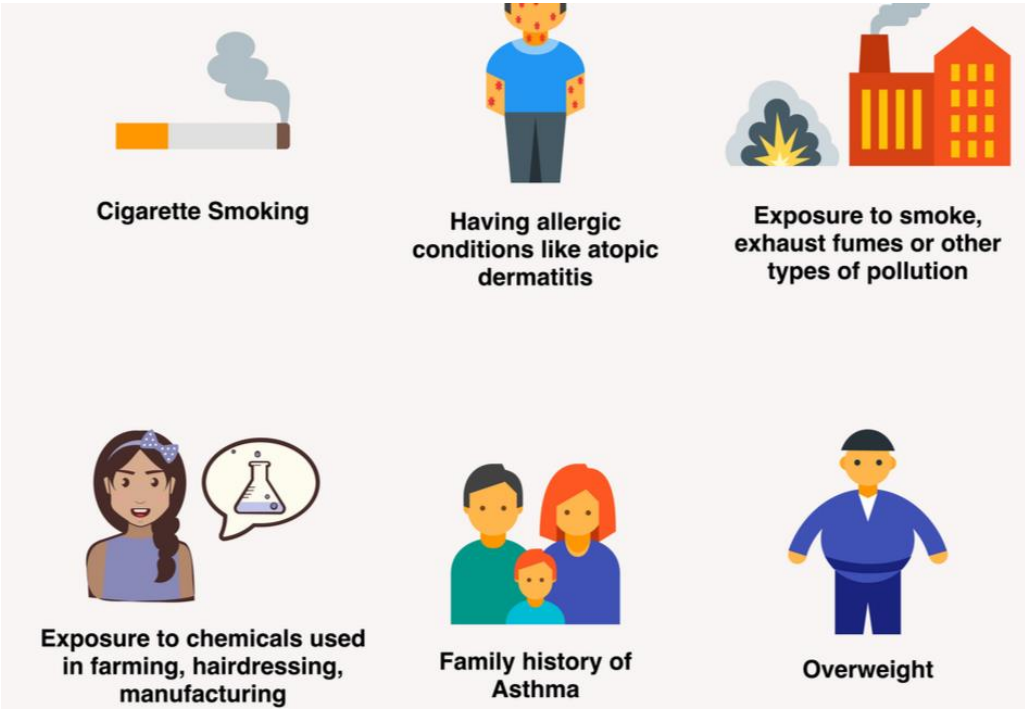
- A chronic inflammatory disease characterized by variable and **reversible airflow obstruction**, and **easily triggered bronchospasms** by hyperresponsive airways inhaled stimuli.

- **<u>Incurable</u>**, but most people can control their symptoms.

- **Majority** of kids with asthma eventually grow out of it.



Risk factors & triggers



Pathophysiology

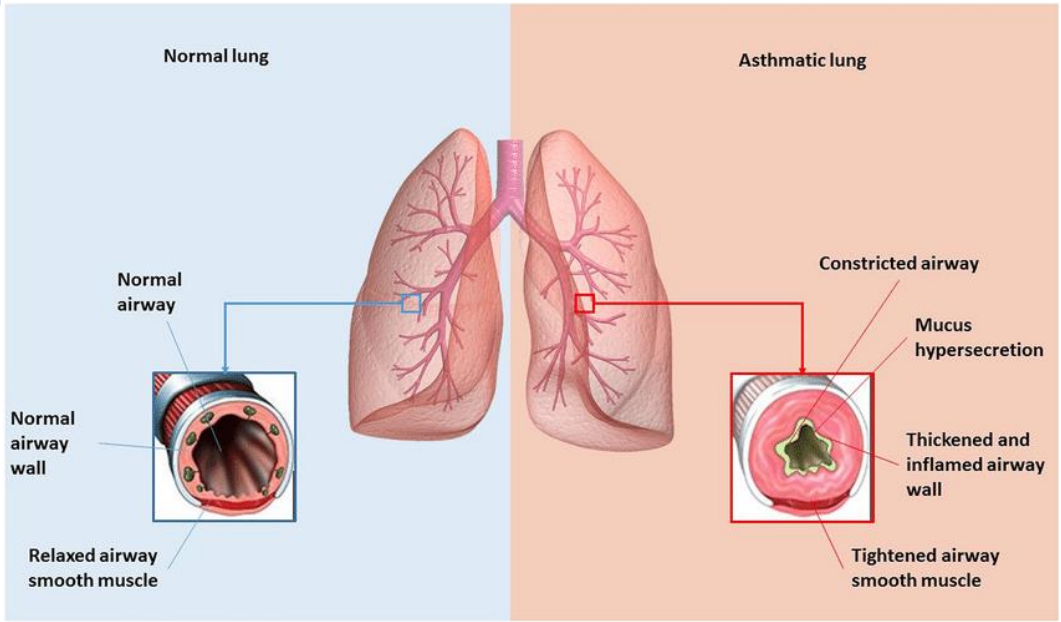
1- Contraction of bronchial smooth muscle

2- bronchial wall inflammation

3- increased secretion of mucus

bronchoconstriction and airflow obstruction.

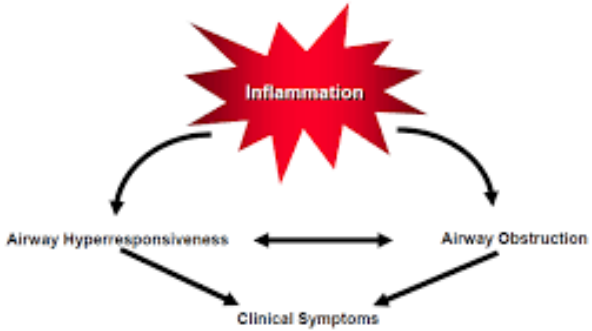
Asthma is usually not a progressive disease. However, if untreated, asthma may cause airway remodeling, resulting in increased severity and incidence of asthma exacerbations and/or death.



Pathophysiology & pathogenesis

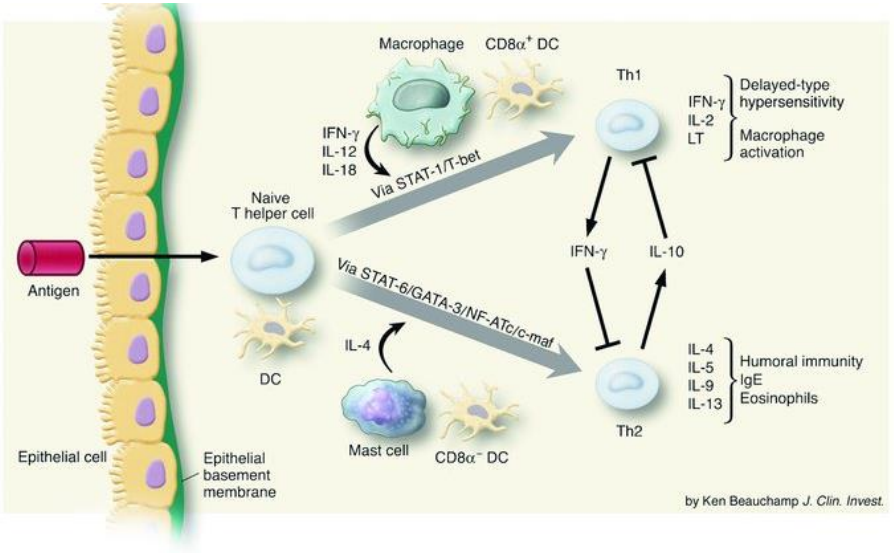
- Asthma pathophysiology components:

1. Airway inflammation
2. Intermittent airflow obstruction
3. hyperplasia of the cells of all structural elements of the airway wall.



- Several immune cells are implicated:

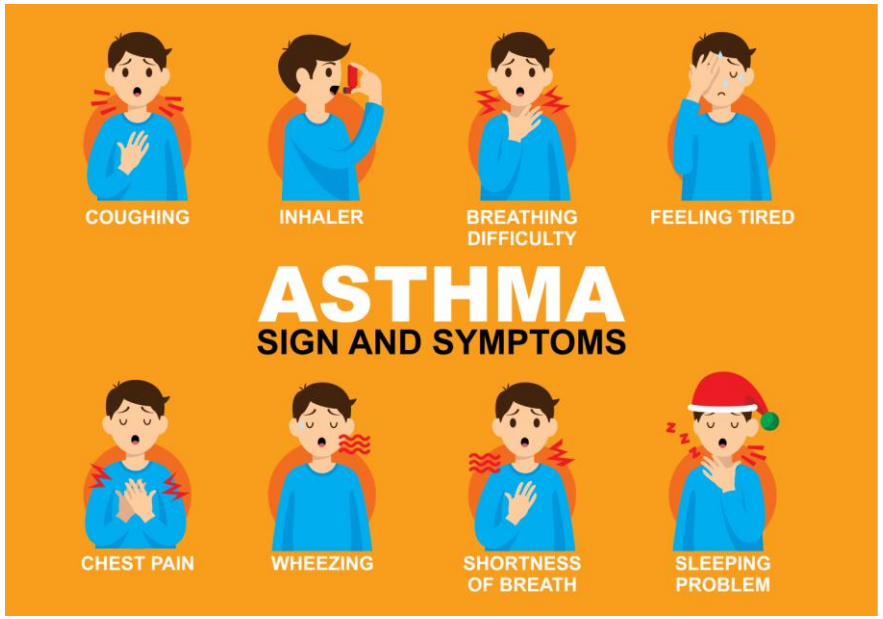
1. Eosinophils and CD4+
2. Mast cells
3. Th2 lymphocytes
4. Basophils



- Foreign materials (allergens)>> ↑ **IgE** (genetically determined)>> IgE antibodies bind to mast cells in the airway mucosa

Signs & symptoms

- Wheezing (could be absent during most severe episode)
- Shortness of breath
- Chest tightness
- Coughing



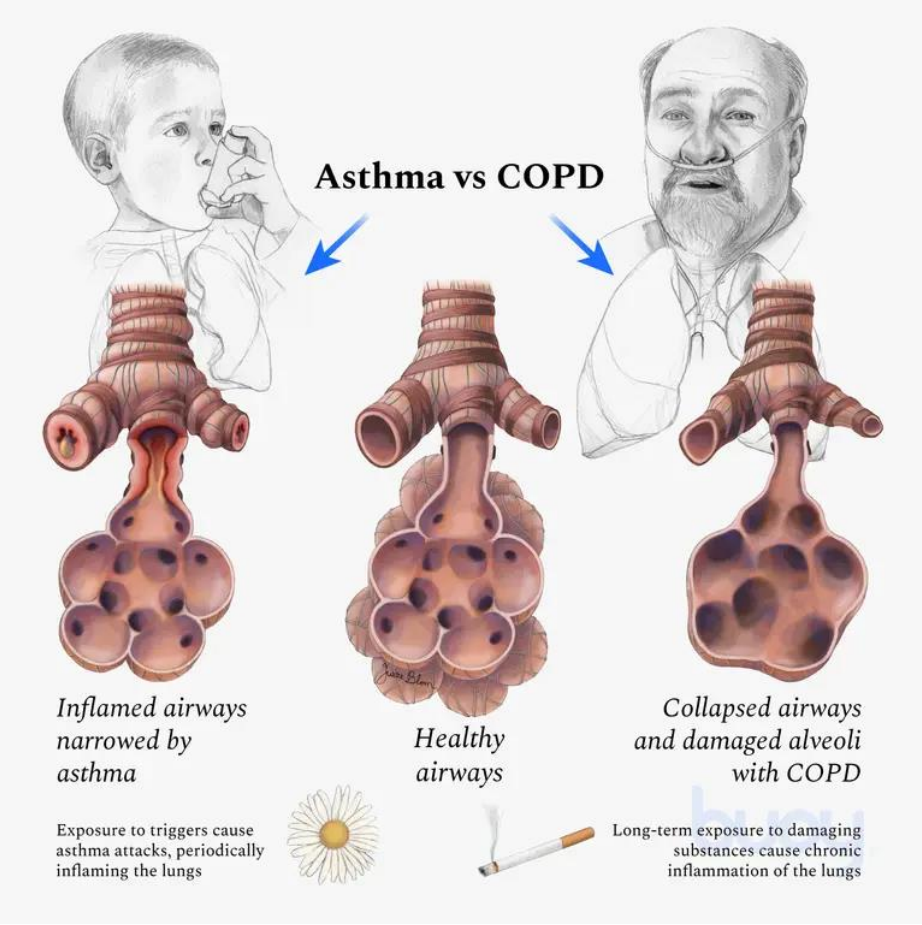
- Symptoms are usually worse at night and in the early morning or in response to exercise or cold air.

Asthma vs COPD

- Asthma is not considered as a part of COPD because:

1. Airway obstruction in asthma is usually **reversible** (if left untreated, it can become irreversible
2. Asthma affects the **bronchi** (emphysema effect the alveoli)

- Asthma + component of irreversible airways obstruction = the asthma-chronic obstructive disease (COPD) overlap syndrome (ACOS).
- people with ACOS exhibit increased morbidity, mortality and possibly more comorbidities



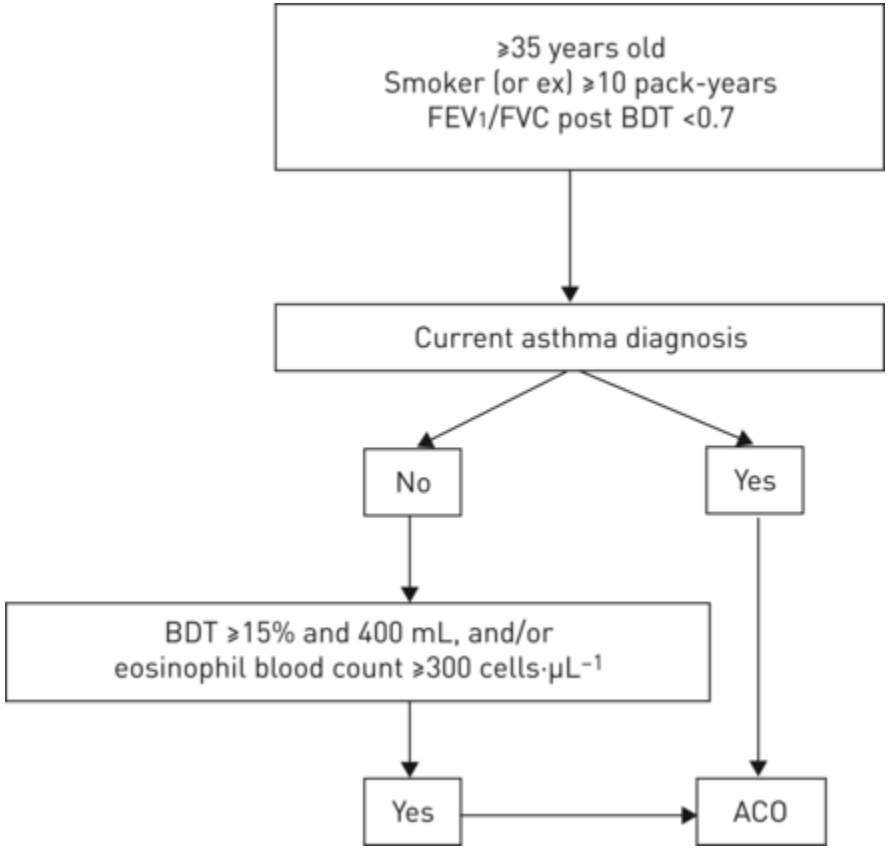
Asthma vs COPD

- Compared to asthma, COPD occurs in **older** patients, **poorly responsive** even to high-dose inhaled corticosteroid therapy, and is associated with **progressive, inexorable loss of** pulmonary function over time, especially with continued cigarette smoking.

	Asthma	COPD
Age of onset	Usually < 40 years	Usually > 40 years
Smoking history	Not causal	Usually > 10 pack-years
Sputum production	Infrequent	Often
Allergies	Often	Infrequent
Disease course	Stable (with exacerbations)	Progressive worsening (with exacerbations)
Spirometry	Often normalizes	Never normalizes
Clinical symptoms	Intermittent and variable	Persistent

Asthma-COPD overlap syndrome (ACOS)

1. age >40 years
2. persistent airflow obstruction
3. history of asthma or evidence of partial bronchodilator reversibility
4. ≥10 pack-years tobacco smoking



Asthma management

- Identifying triggers and eliminating exposure to them is considered the most effective treatment
- Aims of asthma therapy:

1. Decrease the intensity and frequency of asthma symptoms
2. Prevent future exacerbations
3. Minimize limitations in activity related to asthma symptoms

- Medications for asthma are broadly classified into fast-short-acting and long-acting categories

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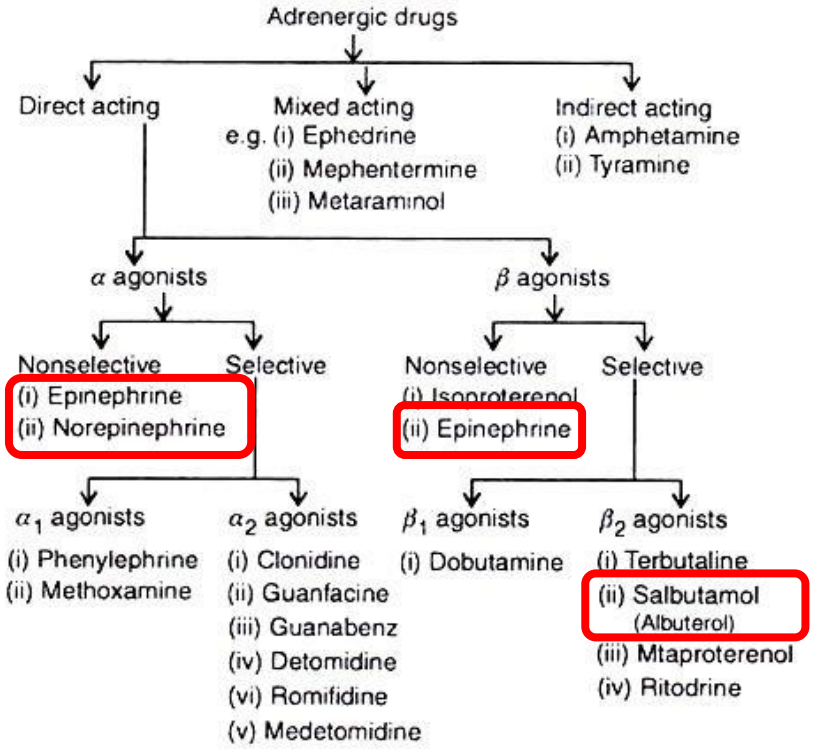
Agents used for Asthma:
Adrenergic agonists

❖ pharmacological asthma related actions:

1. Relax airway smooth muscle
2. Inhibit release of broncho-constricting mediators from mast cells
3. Inhibit microvascular leakage

❖**Epinephrine, albuterol, levalbuterol**



Why is epinephrine preferred over norepinephrine for asthma? it has a stronger effect on β2-adrenergic receptors

Agents used for Asthma:
Adrenergic agonists (Epinephrine)

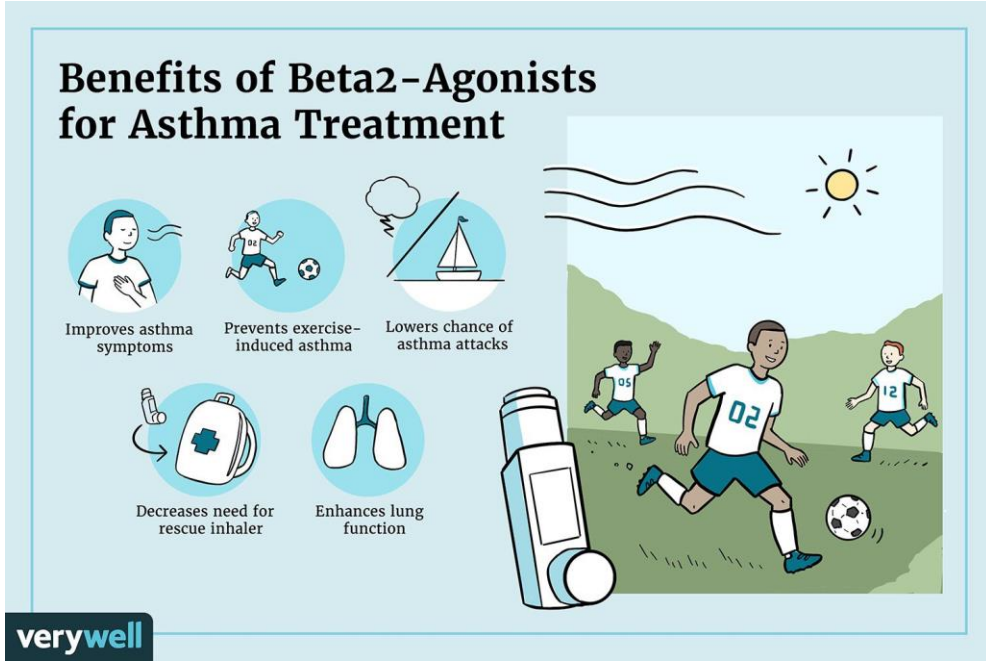
- Best delivered by inhalation (greatest effect on airway + least systemic toxicity)
- Effective, rapidly acting bronchodilator when injected SC or inhaled as from a pressurized canister.
- International asthma guidelines recommend **against** epinephrine (adrenaline) administration in acute asthma unless associated with anaphylaxis or angio-oedema

Agents used for Asthma:
Adrenergic agonists (Epinephrine)

- Maximal bronchodilation is achieved 15 minutes after inhalation and lasts 60–90 minutes.
- tachycardia, arrhythmias, and worsening of angina pectoris are troublesome adverse effects.
- its use in asthma has been displaced by other, more β2 -selective agents.

Agents used for Asthma:
β2-adrenergic agonists

- Used for quick relief of asthma symptoms, and as adjunctive therapy for long-term control of the disease
- SABAs have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours.
- Used for symptomatic treatment of bronchospasm
- Can be used as monotherapy for patients with persistent asthma??



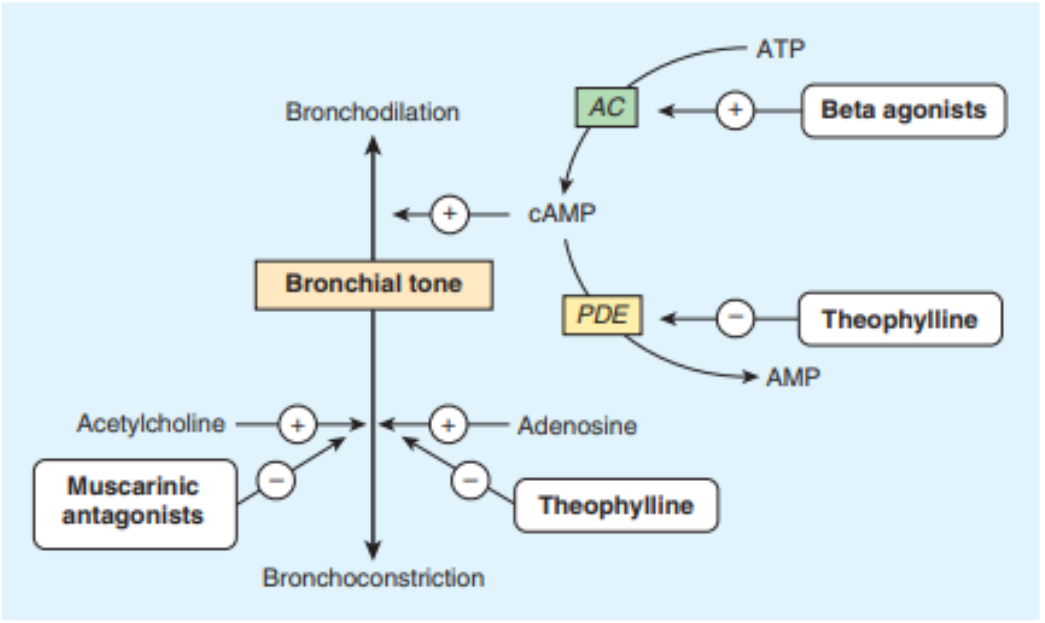
SABAs monotherapy may be appropriate for patients with mild, intermittent asthma or exercise-induced bronchospasm.

Agents used for Asthma:
β2-adrenergic agonists

- **MOA:** COPD lecture

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

- Adverse effects: tachycardia, **hyper**glycemia, **hypo**kalemia, **hypo**magnesemia, and skeletal muscle tremors



Agents used for Asthma:
β2-adrenergic agonists

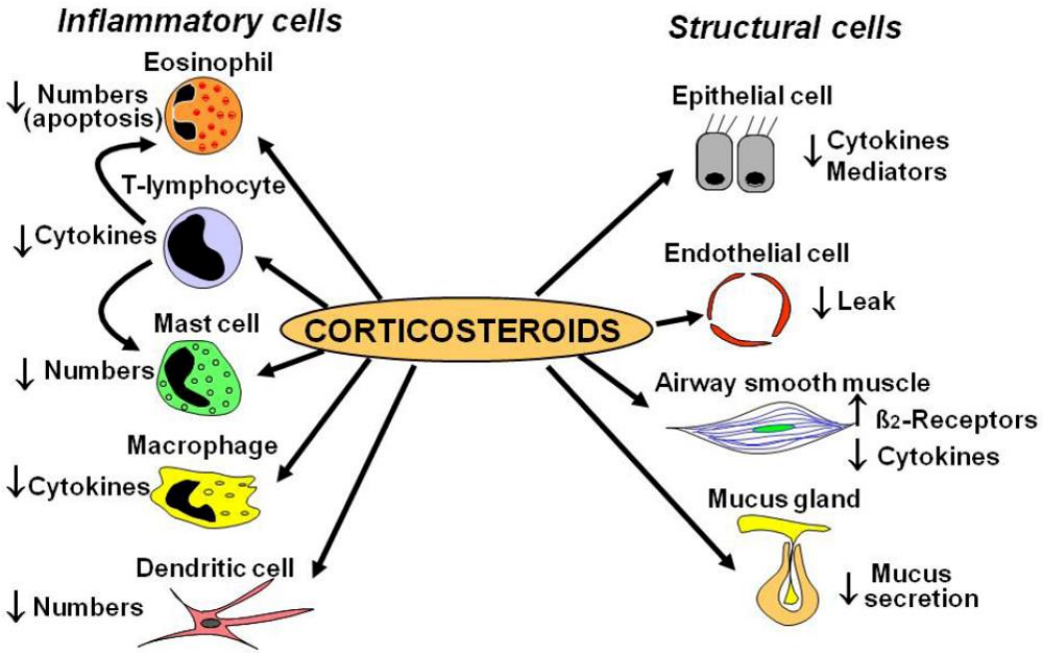
- LABAs used in Asthma: salmeterol and formoterol (both are chemical analogs of albuterol).
- longer duration of action, providing bronchodilation for at least 12 hours (because of their high lipid solubility).
- Use of LABA monotherapy is **contraindicated**, and LABAs should be used **only in combination with an asthma controller medication**, such as an inhaled corticosteroid (ICS).

Salmeterol Multicenter Asthma Research Trial (SMART) randomized trial comparing salmeterol (MDI) VS placebo. An interim analysis in 26,355 patients found an increase in **respiratory-related deaths and asthma-related deaths**

Agents used for Asthma:
Inhaled corticosteroids (ICS)

- These drugs directly targets underlying airway inflammation:

1. Decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes)
2. Reversing mucosal edema
3. Decreasing the permeability of capillaries
4. Inhibiting the release of leukotrienes.

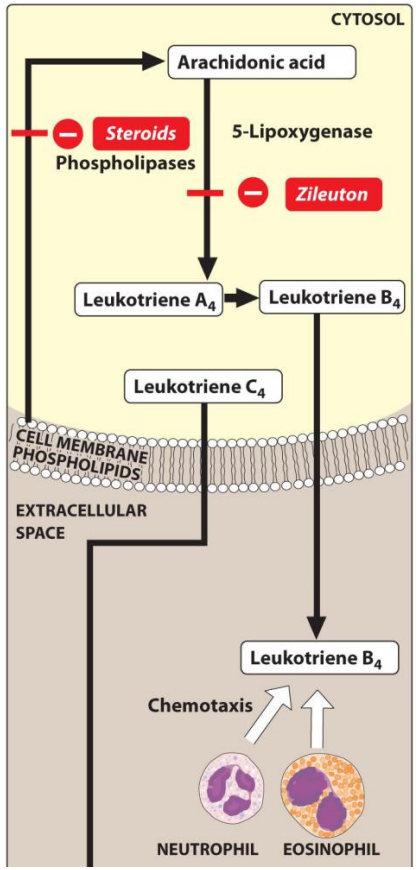


Agents used for Asthma:

Inhaled corticosteroids (ICS)

- Do NOT relax airway smooth muscle directly but **reduce bronchial reactivity** and reduce the frequency of asthma exacerbations if taken regularly

- They inhibit the release of arachidonic acid through inhibition of phospholipase A2, thereby producing **direct anti-inflammatory** properties in the airways



Agents used for Asthma:
Inhaled corticosteroids (ICS)

1- reduce inflammation in the airways
2- decrease the frequency and severity of asthma symptoms
3- improve overall lung function

- ICS are the **drugs of choice for long-term control in patients with persistent asthma**

- **Potentiation** of the effects of β-receptor agonists

- Treatment of severe persistent asthma may require the addition of a short course of oral or intravenous corticosteroids.

Keep in mind that ICS are highly effective for long-term management, but they are not used to treat acute asthma exacerbations.

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Agents used for Asthma:
Inhaled corticosteroids (ICS)

Routes of administration

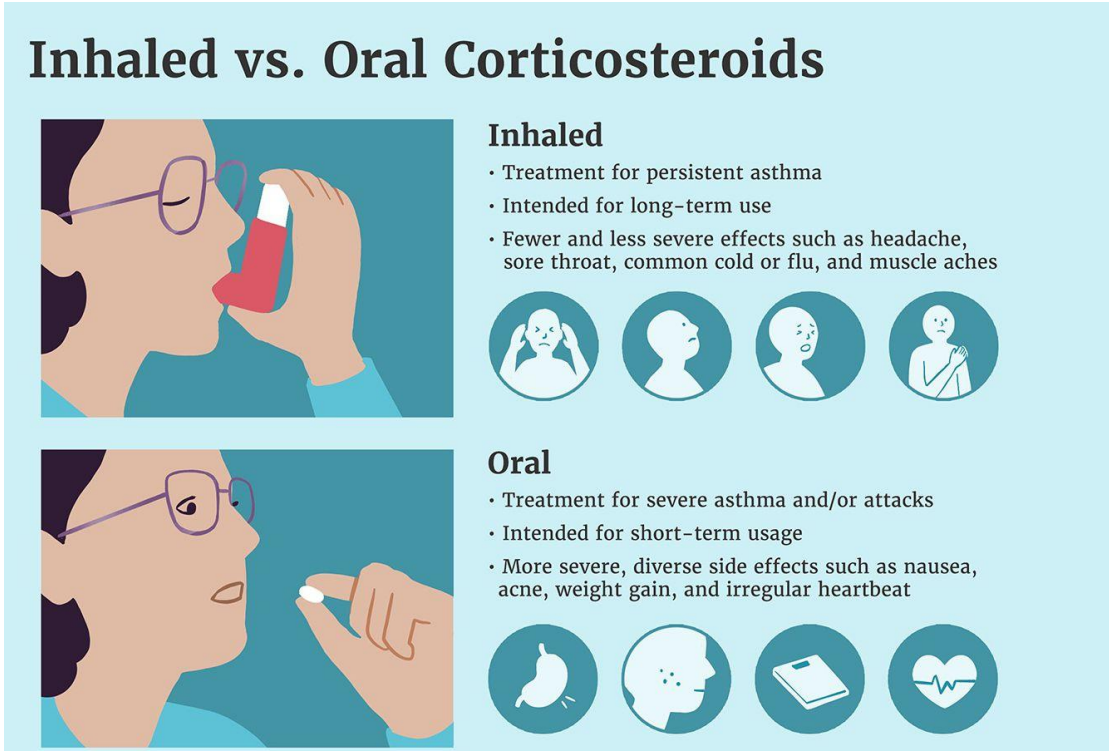
I. Inhalation

This formula has markedly reduced the need for systemic corticosteroid (less side effects) but appropriate inhalation technique is critical to the success of therapy

II. Oral/systemic

Patients with a severe exacerbation of asthma may require IV methylprednisolone or oral prednisone to reduce airway inflammation.

In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis does not occur during the oral prednisone “burst” (short course) typically prescribed for an asthma exacerbation. Thus, a dose taper is unnecessary prior to discontinuation.



Agents used for Asthma:
Inhaled corticosteroids (ICS)

Adverse effects

- ICS, particularly if used with a spacer, have few systemic effects.
- Deposition on the oral and laryngeal mucosa can cause **oropharyngeal candidiasis** (due to local immune suppression) and **hoarseness.**
- Patients should be instructed to rinse the mouth in a "**swish-and-spit**" method with water following use of the inhaler to decrease the chance of these adverse events.
- Chronic maintenance with oral corticosteroids should be reserved for patients who are not controlled on an ICS.

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Agents used for Asthma: Alternative drugs

- Useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment.
- Should be used in conjunction with ICS therapy for most patients.

A. Leukotriene ((LT) modifiers (Zileuton, Zafirlukast, montelukast

B. Cromolyn

C. Cholinergic antagonists (ipratropium and Tiotropium)

D. Theophylline

E. Monoclonal antibodies (Omalizumab, mepolizumab, benralizumab and reslizumab)

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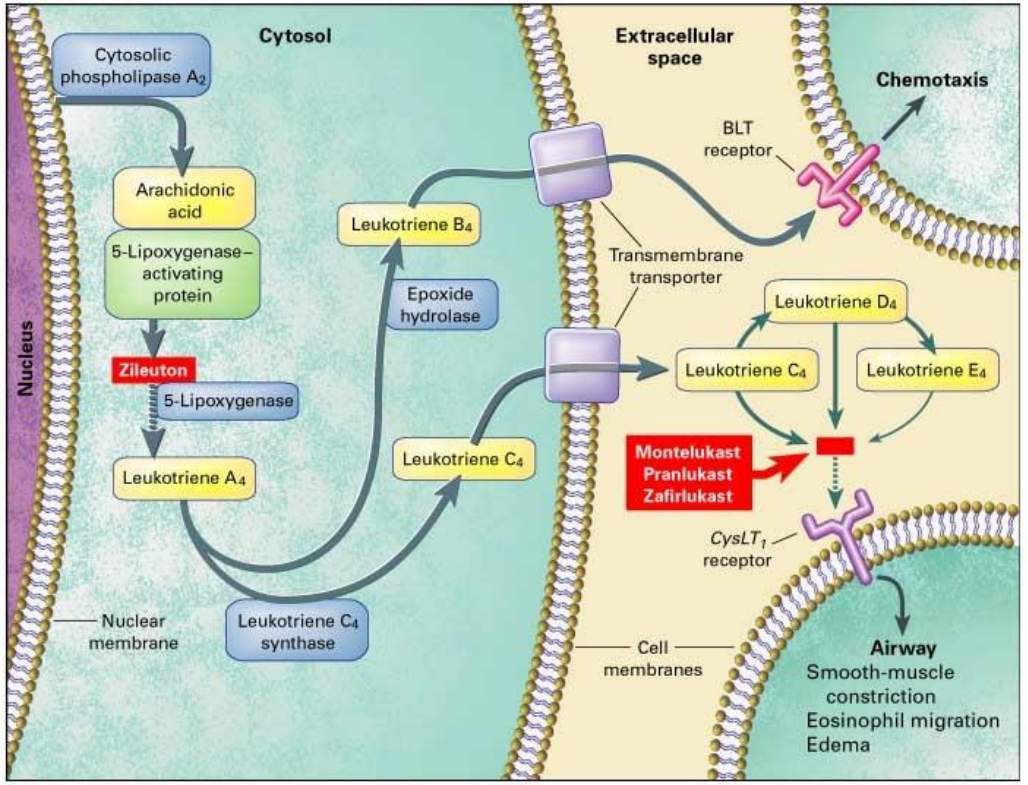
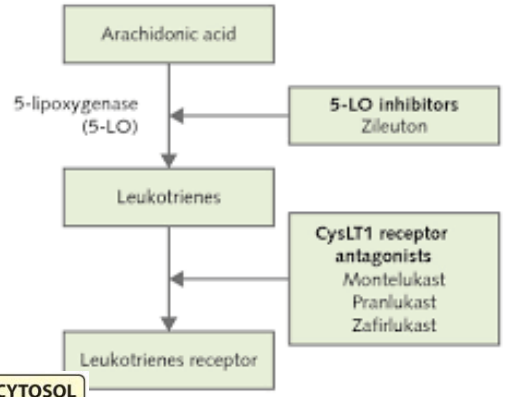
Agents used for Asthma: Leukotriene modifiers

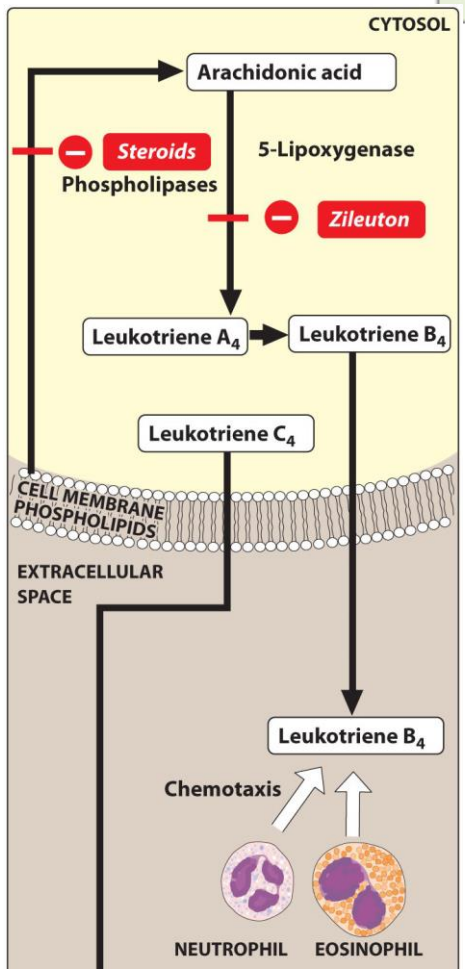
- LTB4 and the cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are **products of the 5-lipoxygenase pathway** of arachidonic acid metabolism and part of the inflammatory cascade.
- 5-Lipoxygenase is found in cells of **myeloid** origin, such as mast cells, basophils, eosinophils, and neutrophils.
- **LTB4** is a potent chemoattractant for **neutrophils** and **monocytes,** stimulates production of proinflammatory cytokines.
- **cysteinyl leukotrienes constrict** bronchiolar smooth muscle, **increase** endothelial permeability, **promote** mucus secretion, eosinophil recruitment and airway remodeling in chronic asthma

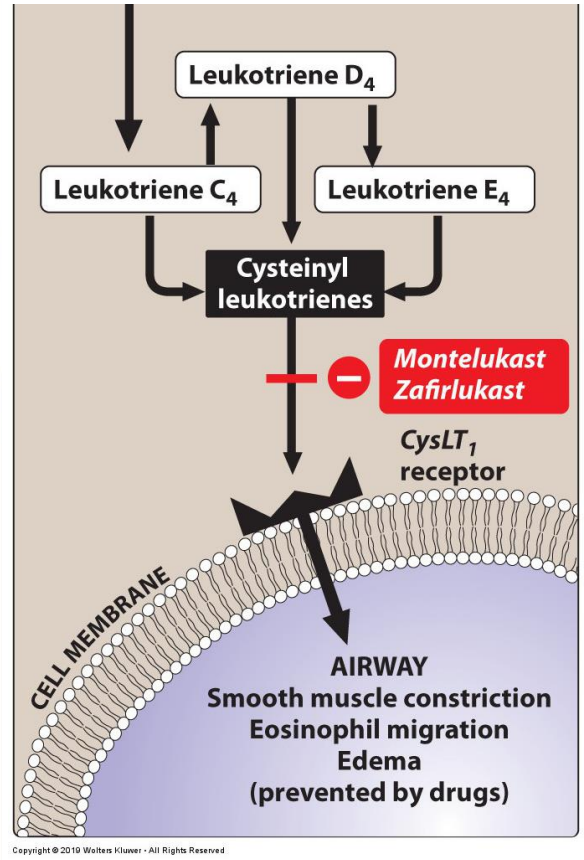


Agents used for Asthma: Leukotriene modifiers

- ✓Zileuton is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of **both** LTB4 and the cysteinyl leukotrienes.
- ✓Zafirlukast and montelukast are selective antagonists of the cysteinyl leukotriene-1 receptor (CysLT1), and they block the effects of cysteinyl leukotrienes. (Approved for the prevention of asthma symptoms).
- ✓Should not be used in situations where immediate bronchodilation is required.
- ✓Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise-induced bronchospasm.







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Agents used for Asthma: Leukotriene modifiers

Pharmacokinetics

- These agents are orally active
- Undergo extensive **hepatic** metabolism (zileuton and zafirlukast reported with liver toxicity).
- Montelukast is the most prescribed (taken without regard to meals+ once-daily treatment).

Adverse effects

- Elevations in serum hepatic enzymes>> requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal.
- Headache and dyspepsia.

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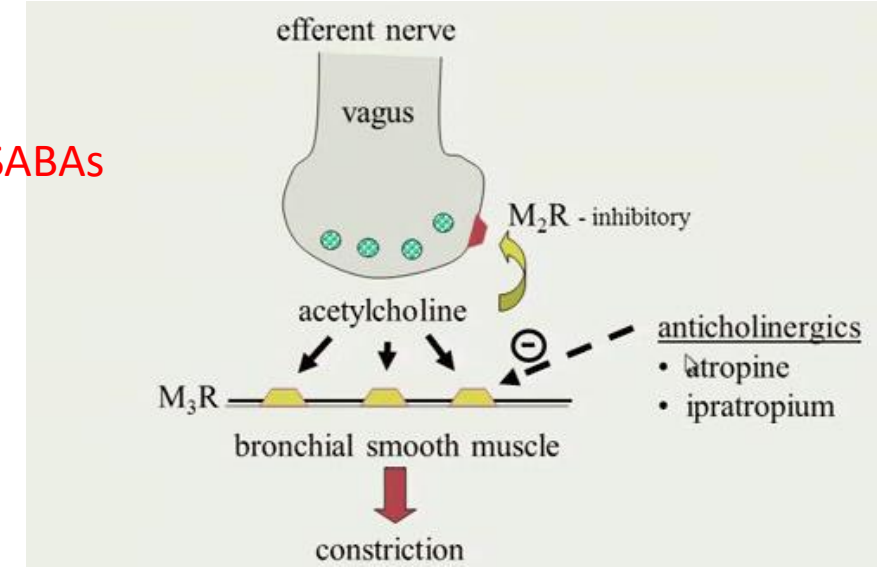
Agents used for Asthma: Cromolyn

- ✓a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine.
- ✓An alternative (prophylaxis) therapy for mild persistent asthma and is available as a nebulized solution.
- ✓NOT a bronchodilator>> NOT useful in managing an acute asthma attack.
- ✓Short duration of action>>dosing three or four times daily
- ✓Adverse effects are minor and include cough, irritation, diarrhea, and unpleasant taste.

Agents used for Asthma: muscarinic antagonist

- Inhaled ipratropium is **NOT** recommended for the **routine** treatment of **acute** bronchospasm in asthma, why? its onset is much slower than that of inhaled SABAs
- Tiotropium (only FDA approved) can be used **as an add-on** treatment in adult patients with severe asthma and a history of exacerbations.
- Adverse effects:

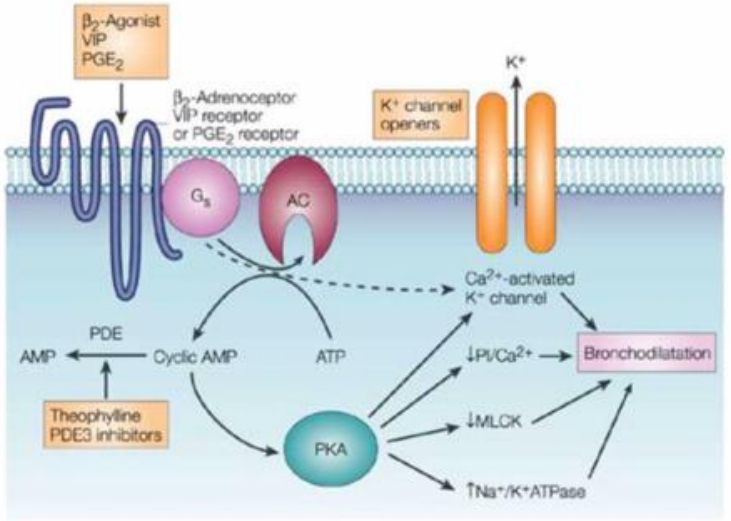
xerostomia and bitter taste are related to local anticholinergic effects.



Agents used for Asthma: Theophylline

- bronchodilator that relieves airflow obstruction ir chronic asthma and decreases asthma symptoms.
- It may also possess anti-inflammatory activity, although the mechanism of action is unclear.
- Overdose may cause seizures or potentially fatal arrhythmias.
- Theophylline is metabolized in the liver and is a CYP1A2 and 3A4 substrate.

Theophylline



PDE=Phosphodiesterase
PKA=Protein Kinase A

Agents used for Asthma: Monoclonal antibodies

- Omalizumab

- Mepolizumab
- Benralizumab
- Reslizumab)

- **Omalizumab**: selectively binds to human **immunoglobulin E (IgE)**>> **decreased** binding of IgE to its receptor on the surface of mast cells and basophils>>**limits the release of mediators** of the allergic response.
- Mepolizumab, benralizumab and reslizumab: interleukin-5 **(IL-5) (antagonists).**
- IL-5 is the major cytokine involved in recruitment, activation, and survival of eosinophils in eosinophilic asthma.
- These agents are indicated for the treatment of **severe persistent asthma in patients who are poorly** controlled with conventional therapy.
- Their use is limited by the high cost, route of administration (IV for reslizumab and subcutaneous for others), and adverse effect profile.
- Adverse effects include serious anaphylactic reactions (rare), arthralgias, fever, rash, and increased risk of infections.
- New malignancies have been reported.

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Asthma classification

Asthma symptoms/lung function	Therapy*
Step 1	
All of the following: ▪ Daytime symptoms ≤2 days/week ▪ Nocturnal awakenings ≤2/month ▪ Normal FEV_1 ▪ Exacerbations ≤1/year	▪ SABA, as needed **or** ▪ Low-dose ICS-formoterol as needed (preferred)$^{\Delta}$
Step 2	
Any of the following: ▪ Daytime symptoms >2 but <7 days/week ▪ Nocturnal awakenings up to 3 to 4 nights/month ▪ Minor interference with activities ▪ Exacerbations ≥2/year	▪ Low-dose ICS daily **and** SABA as needed **or** ▪ Low-dose ICS-formoterol as needed (preferred) **Alternative option(s)** ▪ Daily LTRA **and** SABA as needed
Step 3	
Any of the following: ▪ Daily symptoms ▪ Nocturnal awakenings >1/week ▪ Daily need for reliever ▪ Some activity limitation ▪ FEV_1 60 to 80% predicted ▪ Exacerbations ≥2/year	▪ Low-dose ICS-formoterol as maintenance and reliever therapy$^{\diamond}$ (preferred) **or** ▪ Low-dose ICS-LABA combination daily **and** SABA as needed **Alternative option(s)** ▪ Medium-dose ICS daily **and** SABA as needed
Step 4	
Any of the following: ▪ Symptoms all day ▪ Nocturnal awakenings nightly ▪ Need for SABA several times/day ▪ Extreme limitation in activity ▪ FEV_1 <60% predicted ▪ Exacerbations ≥2/year ▪ An acute exacerbation	▪ Medium-dose ICS-formoterol as maintenance and reliever therapy$^{\diamond}$ (preferred) **or** ▪ Medium dose ICS-LABA daily **and** SABA **Alternative option(s)** Medium-dose ICS daily **plus** anti-leukotriene **and** SABA as needed*

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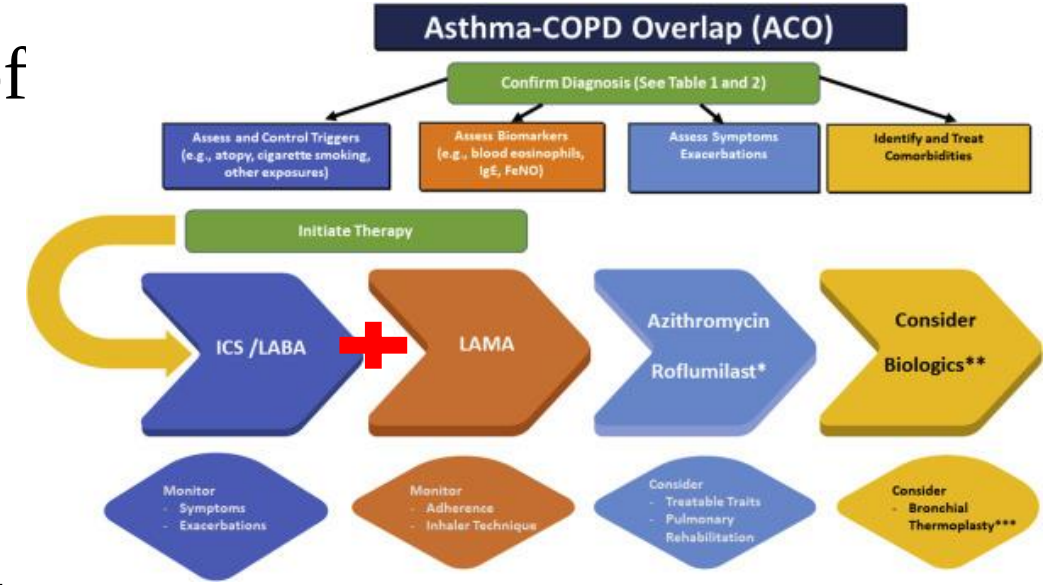
Asthma-COPD overlap syndrome (ACOS)

- Approach similar asthma: ICS
- Inhaled bronchodilator with rapid onset of action (SABA, SAMA combination) for as-needed symptom relief.
- Regular therapy ICS (low to moderate doses) + LABA and/or LAMA may be necessary to control symptoms.
- **LABA monotherapy should be avoided, as in asthma.**



Diego Jose Maselli, Nicola Alexander Hanania, Management of asthma COPD overlap, Annals of Allergy, Asthma & Immunology, Volume 123, Issue 4, 2019, Pages 335-344, ISSN 1081-1206, https://doi.org/10.1016/j.anai.2019.07.021.

Agents under investigation

- Astegolimab: human IgG2 mAb, selectively inhibits the IL-33 receptor, ST2.

https://pubmed.ncbi.nlm.nih.gov/33872652/.

- Tozorakimab: mAb with a dual pharmacological profile that can inhibit IL-33 activities through the ST2 and RAGE/EGFR signalling pathways. To reduce excess inflammation and epithelial remodelling in IL-33-driven disease.
- https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A2397

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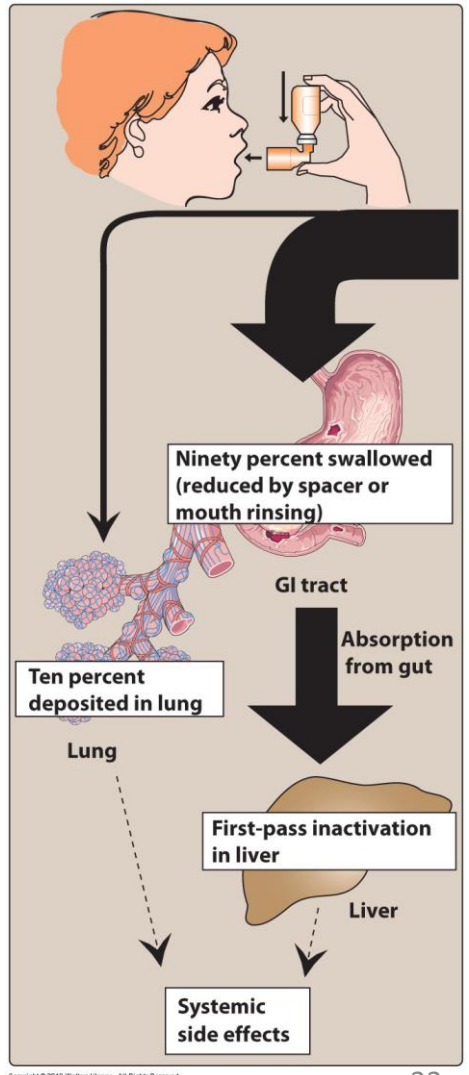
Inhaler Techniques:
Metered-dose inhalers (MDIs) & dry powder inhalers (DPIs)

Exhale before using the inhaler, and then begin to inhale slowly as they press the canister and continue inhaling slowly and deeply throughout actuation.

A large fraction (typically 80% to 90%) of inhaled medication (for example, corticosteroids) is either deposited in the mouth and pharynx or swallowed. The remaining 10% to 20% of a dose of inhaled glucocorticoids that is not swallowed reaches the site of action in the airway.

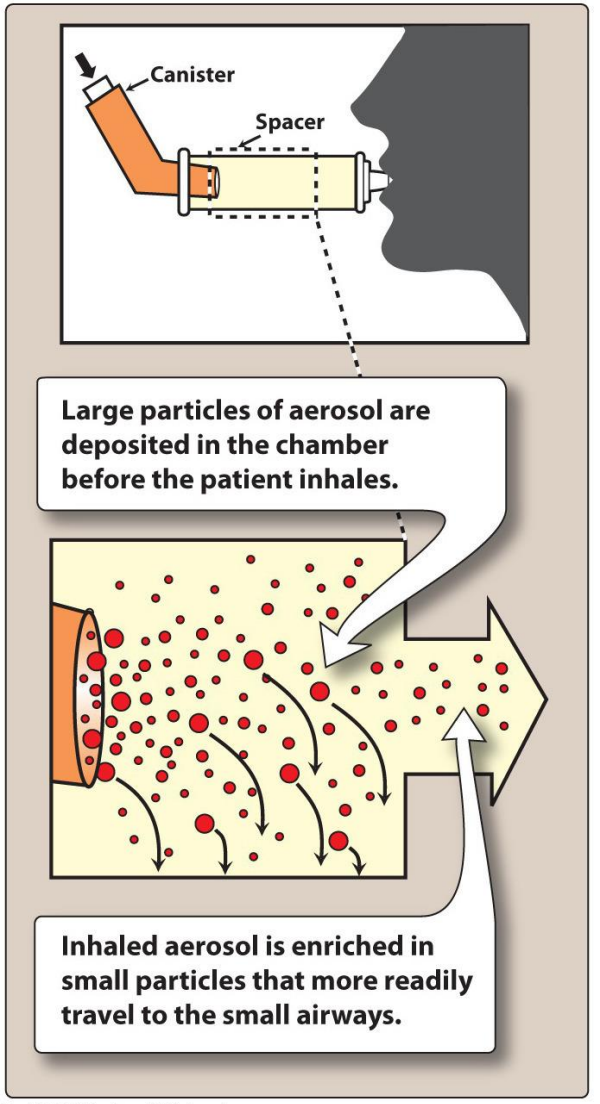
DPIs require a different inhaler technique. Patients should be instructed to inhale quickly and deeply to optimize drug delivery to the lungs. Patients using any type of inhaled corticosteroid device should be instructed to rinse the mouth after use to prevent the development of oral candidiasis.



Inhaler Techniques: Spacers

A spacer is a large-volume chamber attached to an MDI. The chamber reduces the velocity of the aerosol before entering the mouth, allowing large drug particles to be deposited in the device. The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue.

Patients should be advised to wash and/or rinse spacers to reduce the risk of bacterial or fungal growth that may induce an asthma attack.



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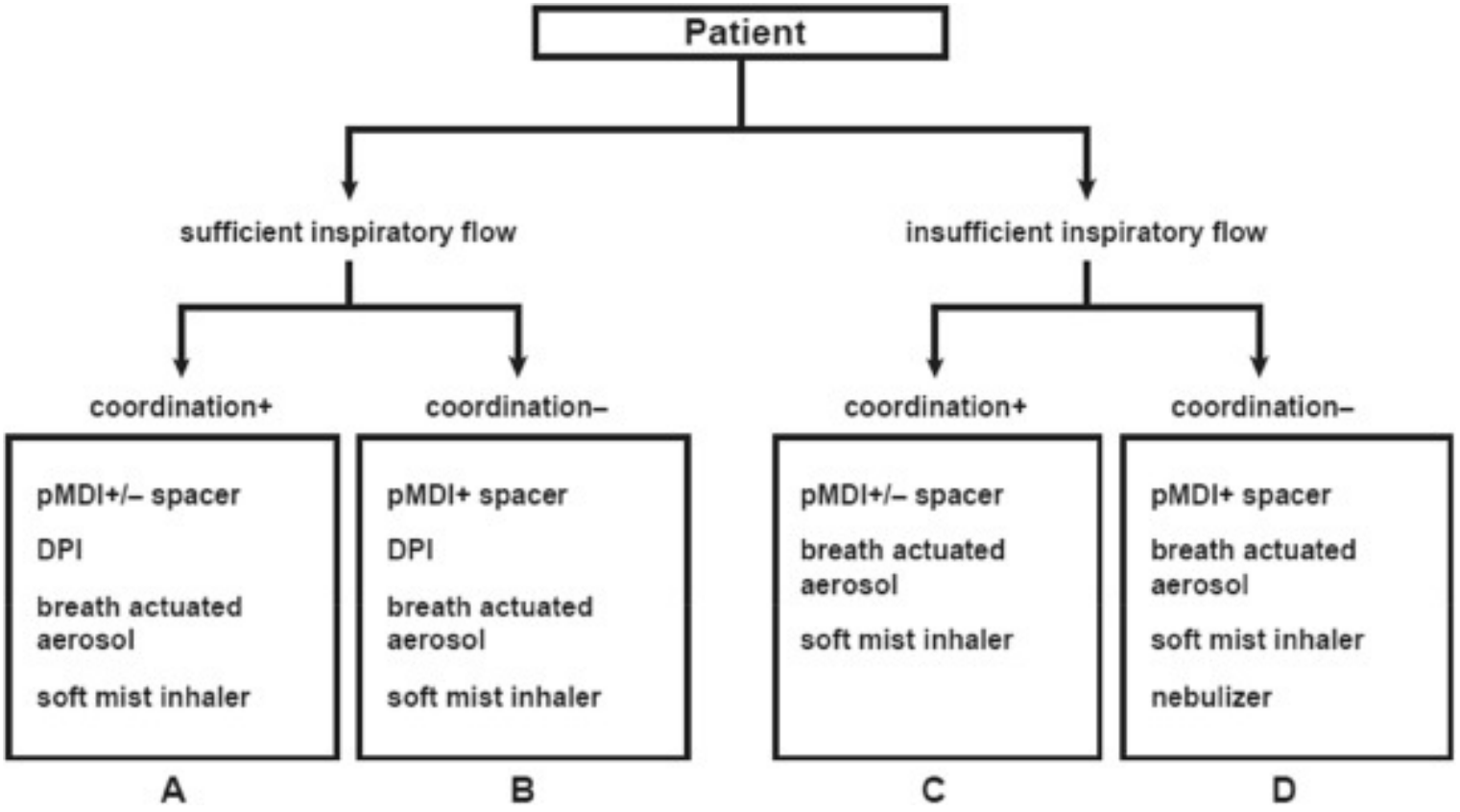
Inhaler Techniques:
Metered-dose inhalers (MDIs) & dry powder inhalers (DPIs)



- https://www.stlouischildrens.org/health-resources/pulse/medical-animation-inhalers

- https://www.youtube.com/watch?v=jSkwBoed6Tw