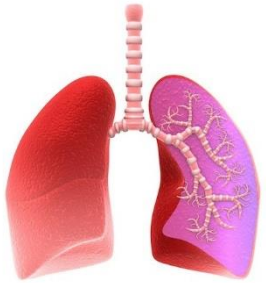
Mustansiriyah University
College of Pharmacy
Depart. of Pharmacology and Toxicology

Drugs for Disorders of the Respiratory System

Pharmacology II/ 4th stage

2024-2025



Asst. Lec. Zakariya Al-Mashhadani

Disorders of the Respiratory System

- Asthma
- Chronic obstructive pulmonary disease (COPD)
- Allergic rhinitis

Each of these conditions may be associated with a troublesome cough, which may be the only presenting complaint.

Medications used to treat common respiratory disorders.

MEDICATION	INDICATION
SHORT-ACTING β_2 ADRENERGIC AGONISTS (SABAs)	
Albuterol	Asthma, COPD
Levalbuterol	Asthma, COPD
LONG-ACTING β_2 ADRENERGIC AGONISTS (LABAs)	
Arformoterol	COPD
Formoterol	Asthma, COPD
Indacaterol	COPD
Olodaterol	COPD
Salmeterol	Asthma, COPD
INHALED CORTICOSTEROIDS	
Beclomethasone	Allergic rhinitis, Asthma, COPD
Budesonide	Allergic rhinitis, Asthma, COPD
Ciclesonide	Allergic rhinitis, Asthma
Fluticasone	Allergic rhinitis, Asthma, COPD
Mometasone	Allergic rhinitis, Asthma
Triamcinolone	Allergic rhinitis, Asthma
LONG-ACTING β_2 ADRENERGIC AGONIST/CORTICOSTEROID COMBINATION	
Formoterol/budesonide	Asthma, COPD
Formoterol/mometasone	Asthma, COPD
Salmeterol/fluticasone	Asthma, COPD
Vilanterol/fluticasone	COPD
SHORT-ACTING ANTICHOLINERGIC	
Ipratropium	Allergic rhinitis, COPD
SHORT-ACTING β_2 AGONIST/SHORT-ACTING ANTICHOLINERGIC COMBINATION	
Albuterol/ipratropium	COPD
LONG-ACTING ANTICHOLINERGIC (LAMA)	
Aclidinium bromide	COPD
Glycopyrrolate	COPD
Tiotropium	Asthma, COPD
Umeclidinium	COPD

Medications used to treat common respiratory disorders

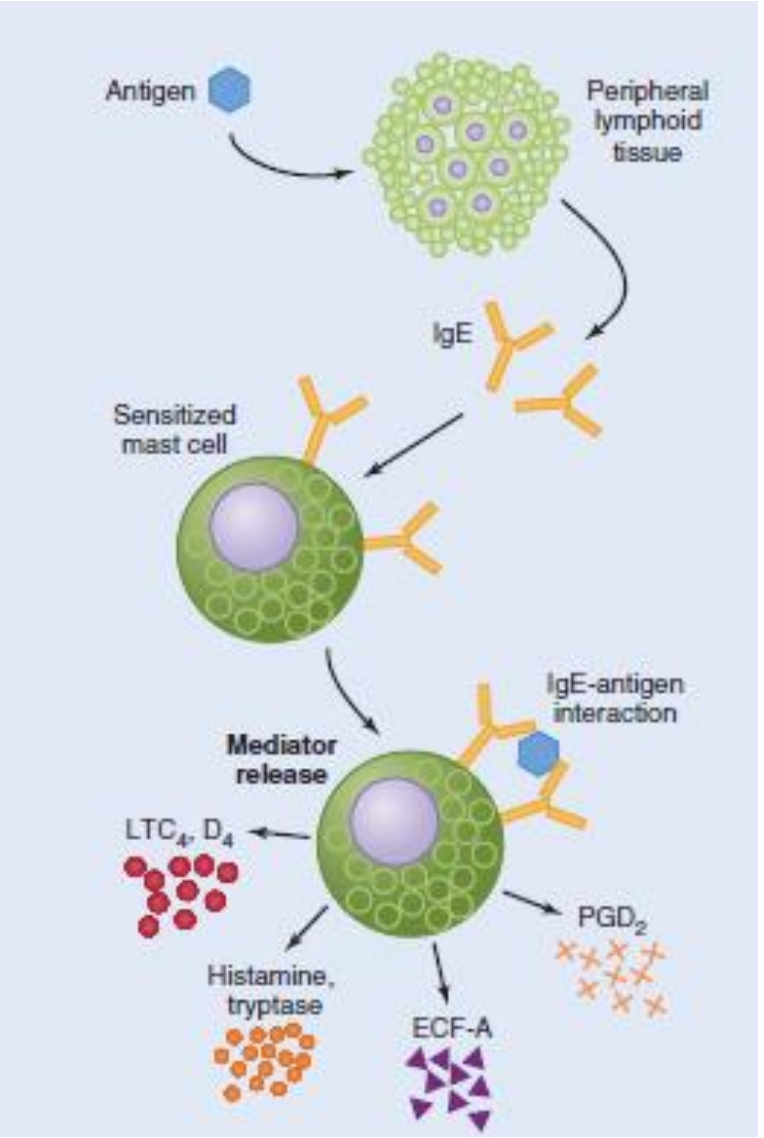
MEDICATION	INDICATION
LABA/LAMA COMBINATION	
Formoterol/glycopyrrolate	COPD
Indacaterol/glycopyrrolate	COPD
Vilanterol/umeclidinium	COPD
Olodaterol/tiotropium	COPD
LEUKOTRIENE MODIFIERS	
Montelukast	Asthma, Allergic rhinitis
Zafirlukast	Asthma
Zileuton	Asthma
ANTIHISTAMINES (H_1-RECEPTOR ANTAGONISTS)	
Azelastine	Allergic rhinitis
Cetirizine	Allergic rhinitis
Desloratadine	Allergic rhinitis
Fexofenadine	Allergic rhinitis
Loratadine	Allergic rhinitis
α-ADRENERGIC AGONISTS	
Oxymetazoline	Allergic rhinitis
Phenylephrine	Allergic rhinitis
Pseudoephedrine	Allergic rhinitis
AGENTS FOR COUGH	
Benzonatate	Cough suppressant
Codeine (with guaifenesin)	Cough suppressant/expectorant
Dextromethorphan	Cough suppressant
Dextromethorphan (with guaifenesin)	Cough suppressant/expectorant
Guaifenesin	Expectorant
OTHER AGENTS	
Benralizumab	Asthma
Cromolyn[1]	Asthma, Allergic rhinitis
Mepolizumab	Asthma
Omalizumab	Asthma
Reslizumab	Asthma
Roflumilast	COPD
Theophylline	Asthma, COPD

Asthma

- Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute bronchoconstriction which cause shortness of breath, cough, chest tightness, wheezing, and rapid respiration.
- Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus .
- Asthma attacks may be triggered by exposure to allergens, exercise, stress, and respiratory infections.
- Asthma can be episodic (seasonal) or chronic in nature (perennial, status asthmatic).

Pathophysiology of asthma

1. Exposure to antigen causes synthesis of IgE, which binds to and sensitizes mast cells and other inflammatory cells.
2. variety of mediators are released .These mediators include the leukotrienes LTC4 and LTD4, tryptase, histamine, and prostaglandin D2. These substances bring about the "**early response**" consisting of bronchoconstriction and increased secretions.
3. In addition, chemotactic mediators such as LTB4 attract inflammatory cells to the airways and several cytokines, and some enzymes are released, resulting in the "**late response**" leading to inflammation.
4. Chronic inflammation leads to marked **bronchial hyperreactivity** to various inhaled substances, including antigens, histamine, muscarinic agonists, and irritants such as sulfur dioxide (SO2) and cold air. This reactivity is partially mediated by vagal reflexes.



early response

Pathophysiology of asthma

- **In the late response** : The airway inflammatory phase leads to brochoconstriction, edema, mucus secretion, vasodilation, and activation of sensory nerves. These changes reduce the size of the airway lumen and increase resistance to airflow, which leads to wheezing and shortness of breath.
- A chronic inflammatory condition can lead to structural modifications in the airway epithelium, causing subepithelial fibrosis, smooth muscle hypertrophy, hyperplasia, angiogenesis, and hyperplasia of mucus-secreting cells.

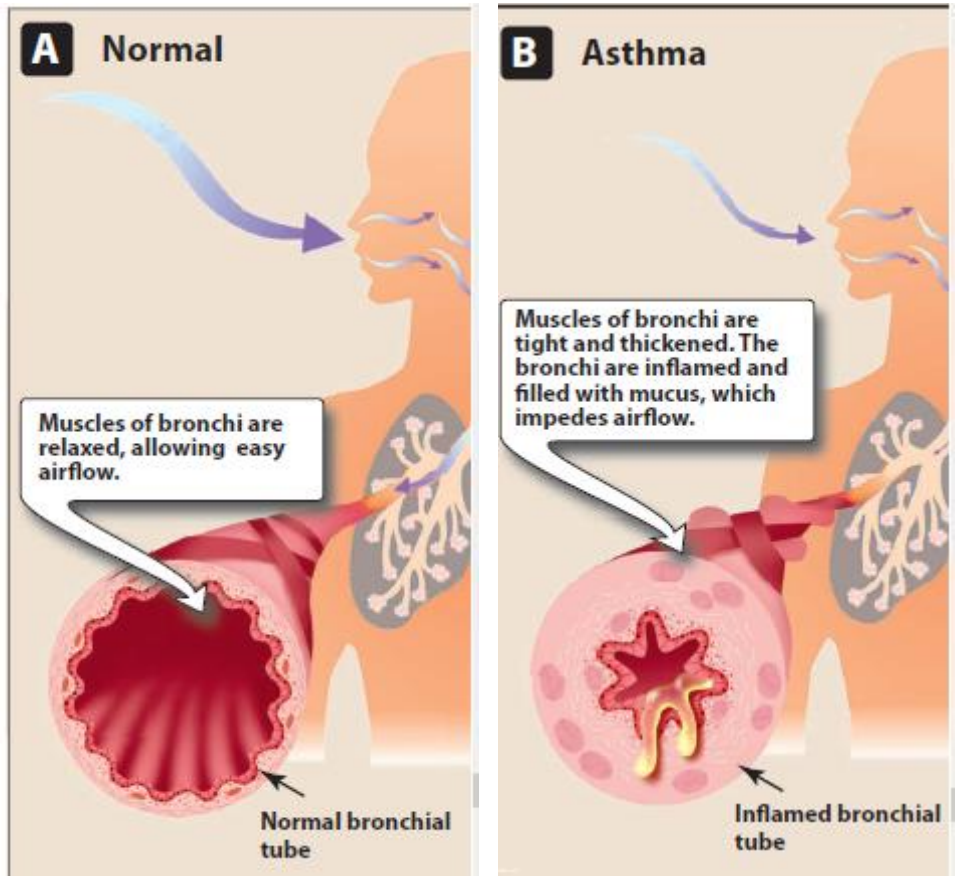
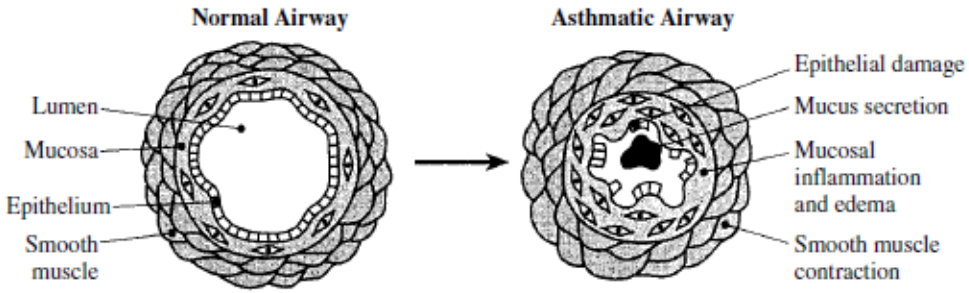
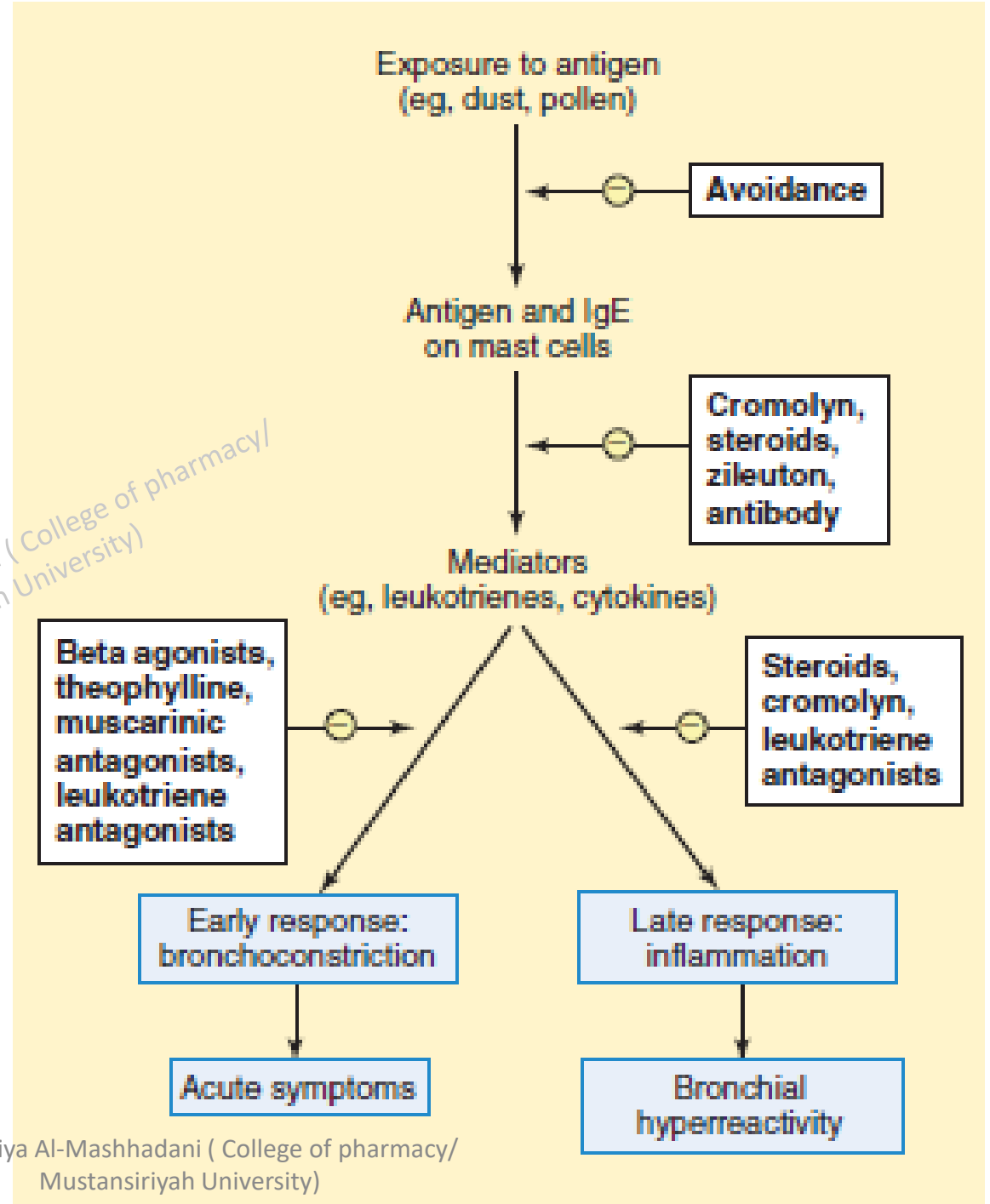


Figure 41.2



late response

Summary of pathophysiology and treatment strategies in asthma.



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Preferred drugs used to treat asthma

- The trigger factor(s) should be identified and avoided
- Regular breathing exercises (such as “Pranayama”) should be started.
- Physical activity and weight loss.
- Bronchodilators and anti-inflammatory agents.

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	NIGHT TIME SYMPTOMS	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Grade 1 Mild Intermittent	Asymptomatic and normal between attacks	Less than 2 times a month	Near normal (80% of normal)	No daily medication	Short-acting β_2 agonist
Grade 2 Mild persistent	More than one time a week but less than one time a day	More than 2 times a month	Near normal (>60% to 80% of normal)	Low-dose ICS	Short-acting β_2 agonist
Grade 3 Moderate persistent	More than once daily	Once a week	60% to 80% of normal	Low-dose ICS + LABA OR Medium-dose ICS	Short-acting β_2 agonist ICS/formoterol is an alternative
Grade 4 Severe persistent	Continual; limited physical activity	Frequent	Less than 60% of normal	Medium-dose ICS + LABA OR High-dose ICS + LABA	Short-acting β_2 agonist ICS/formoterol is an alternative

ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist.

Figure 41.4

Guidelines for the treatment of asthma. In all asthmatic patients, quick relief is provided by a SABA as needed for symptoms.

Preferred drugs used to treat asthma

A. Short-acting β2 agonists (SABAs) have a rapid onset of action (5 to 30 minutes) Quick relief and provide relief for 4 to 6 hours.

- Inhaled β2-adrenergic agonists directly relax airway smooth muscle by activating cAC- cAMP-relaxation.
- All patients with asthma should receive a SABA inhaler for use as needed.
- β2 agonists have no anti-inflammatory effects, and they should not be used as monotherapy for patients with persistent asthma.
- Direct acting β2-selective agonists include albuterol (salbutamol) and levalbuterol. These agents provide significant bronchodilation with little of the undesired effect of α or β1 stimulation.
- A.E: tachycardia, hyperglycemia, hypokalemia, hypomagnesemia, and β2-mediated skeletal muscle tremors are minimized with inhaled delivery versus systemic administration.

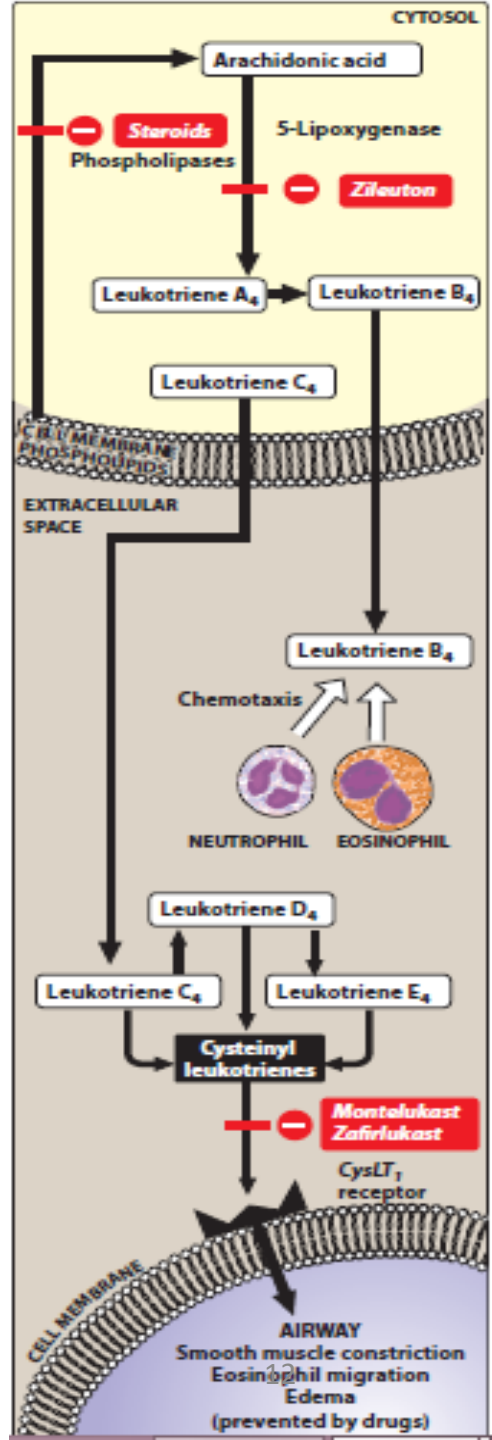
Preferred drugs used to treat asthma

B. long-acting β2 agonists (LABAs) such as : **Salmeterol** and **formoterol** have a long duration of action, providing bronchodilation for at least 12 hours (Long-term control).

- 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).
- ICS remains the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining control in moderate-to-severe asthma.
- Adverse effects of LABAs are similar to quick-acting β2 agonists. ***Bambuterol*** is a prodrug of *terbutaline*. Upon administration, it is slowly released over a period of 24 hours by pseudocholinesterase.

C. Corticosteroids

- inhaled corticosteroid (ICS) are the drugs of choice for long-term control (preventer) in patients with persistent asthma.
- MOA: ICS inhibit the release of arachidonic acid through inhibition of phospholipase A2, thereby producing direct anti-inflammatory properties in the airways.
- Treatment of exacerbations or severe persistent asthma may require the addition of a short course of oral or intravenous corticosteroids.
- PK: Route? ICS? Gland suppreesion? Dose tappring?
- A.E: ICS deposition on the oral and laryngeal mucosa can cause oropharyngeal candidiasis and hoarseness. Patients should be instructed to rinse the mouth in a “swish-and-spit” method with water.



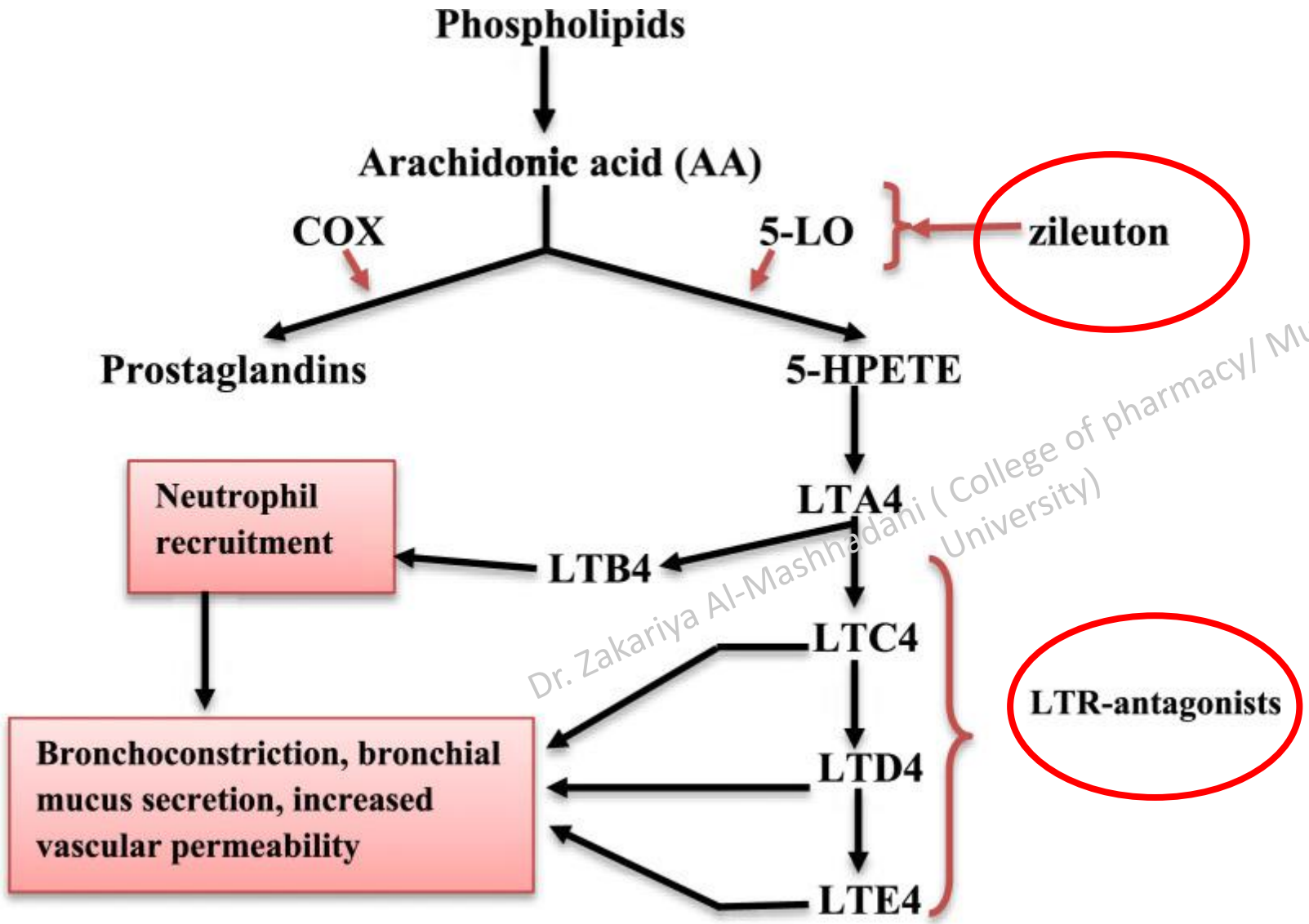
ALTERNATIVE DRUGS USED TO TREAT ASTHMA

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

A. Leukotriene modifiers (leukotriene receptor antagonists and lipoxygenase inhibitors)
B. Mast cell stabilizers
C. Cholinergic antagonists
D. Methylxanthines
E. Monoclonal antibodies

A- Leukotriene modifiers (leukotriene receptor antagonists and lipoxygenase inhibitors)

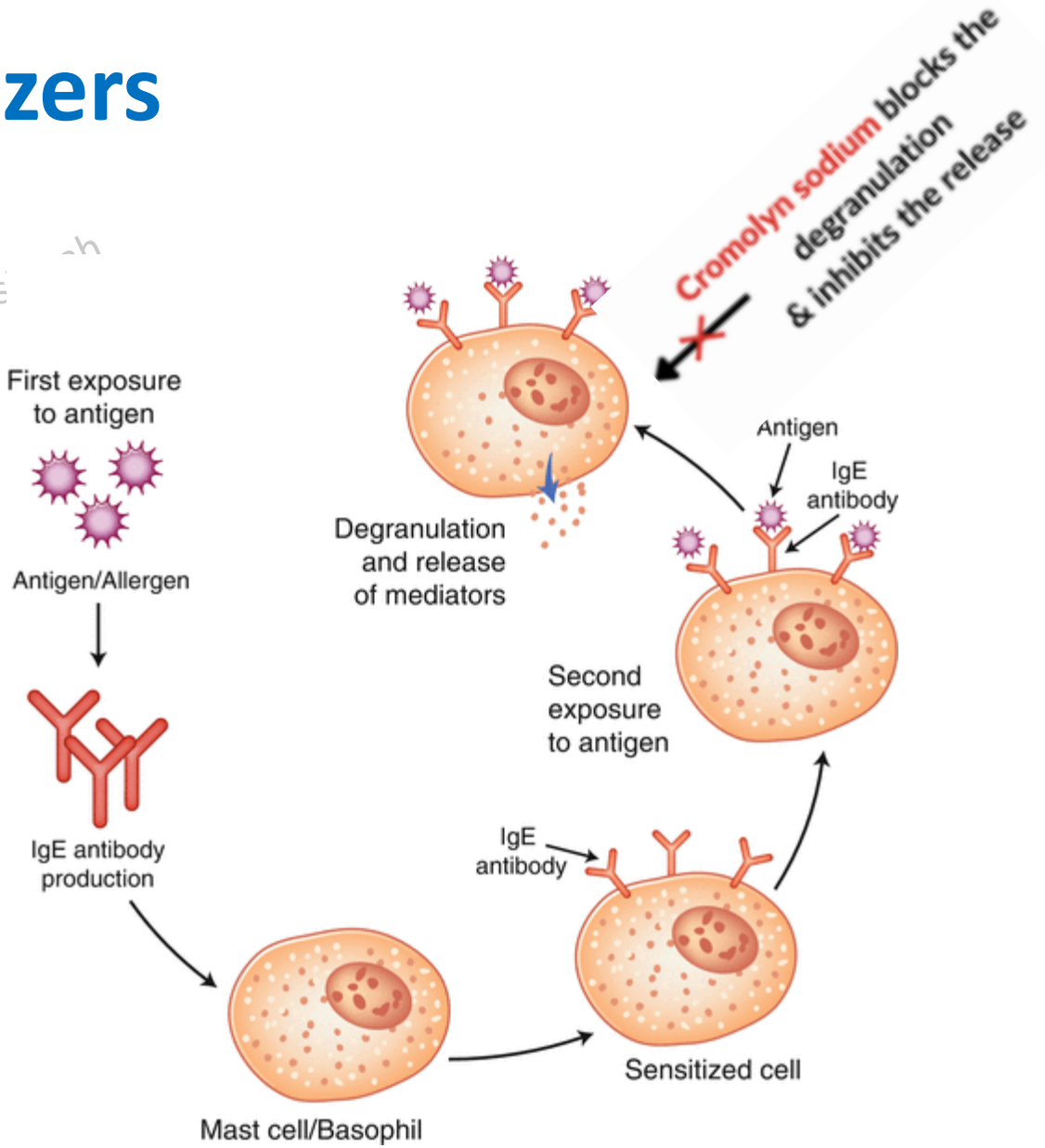
- Leukotrienes (LT) B4 and the cysteinyl leukotrienes, LTC4, LTD4, and LTE4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade. 5-Lipoxygenase is found in mast cells, basophils, eosinophils, and neutrophils.
- LTB4 is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion.
- *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, and they block the effects of cysteinyl leukotrienes.



B- Mast cell stabilizers

- ***Cromolyn*** is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine. It is an alternative therapy for mild persistent asthma. C*romolyn* is not useful in managing an acute asthma attack.

- ***Ketotifen*** is an antihistaminic reported to have mast cell stabilization activity. It shows moderate antiasthmatic activity on prolonged use. It is useful in patients with allergy such as rhinitis, conjunctivitis, and dermatitis.

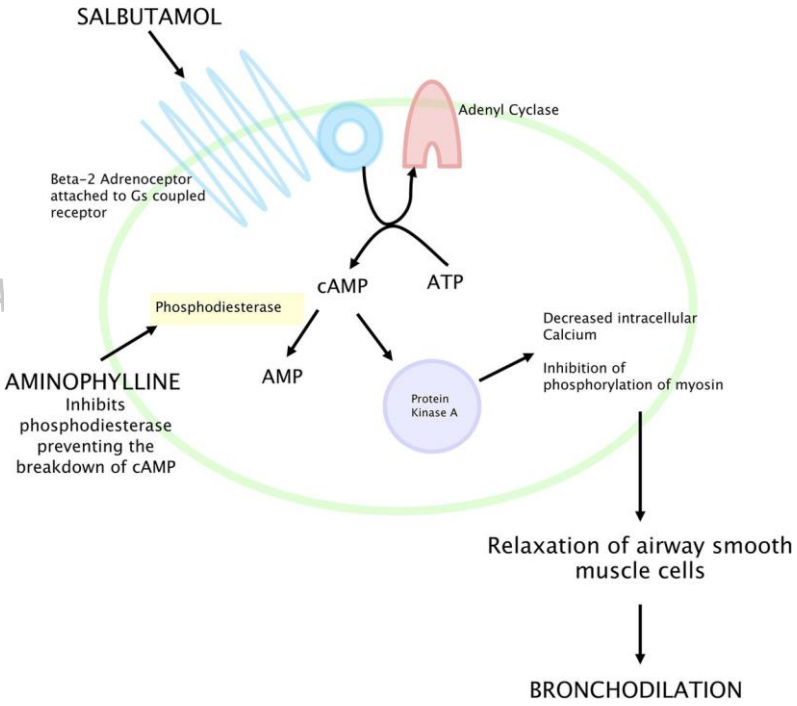


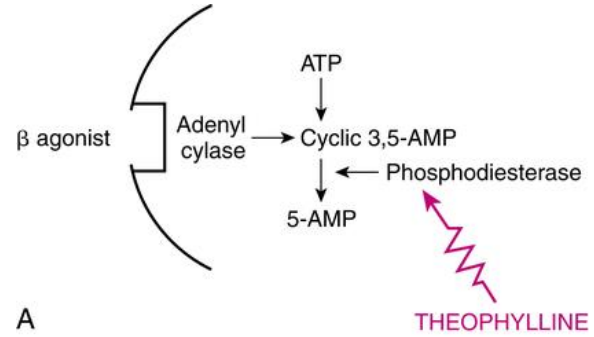
C- Cholinergic antagonists

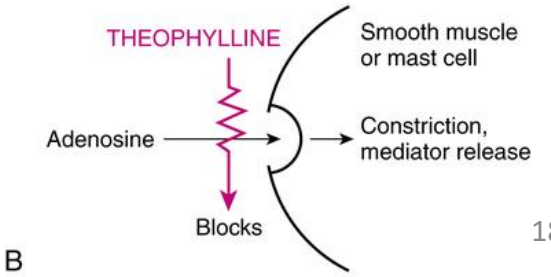
- The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion.
- Inhaled ***ipratropium***, a short-acting quaternary derivative of *atropine*, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with asthma-COPD overlap syndrome.
- ***Tiotropium,*** a long-acting anticholinergic agent, can be used as an add-on treatment in adult patients with severe asthma and a history of exacerbations.
- Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.

D- Methylxanthines

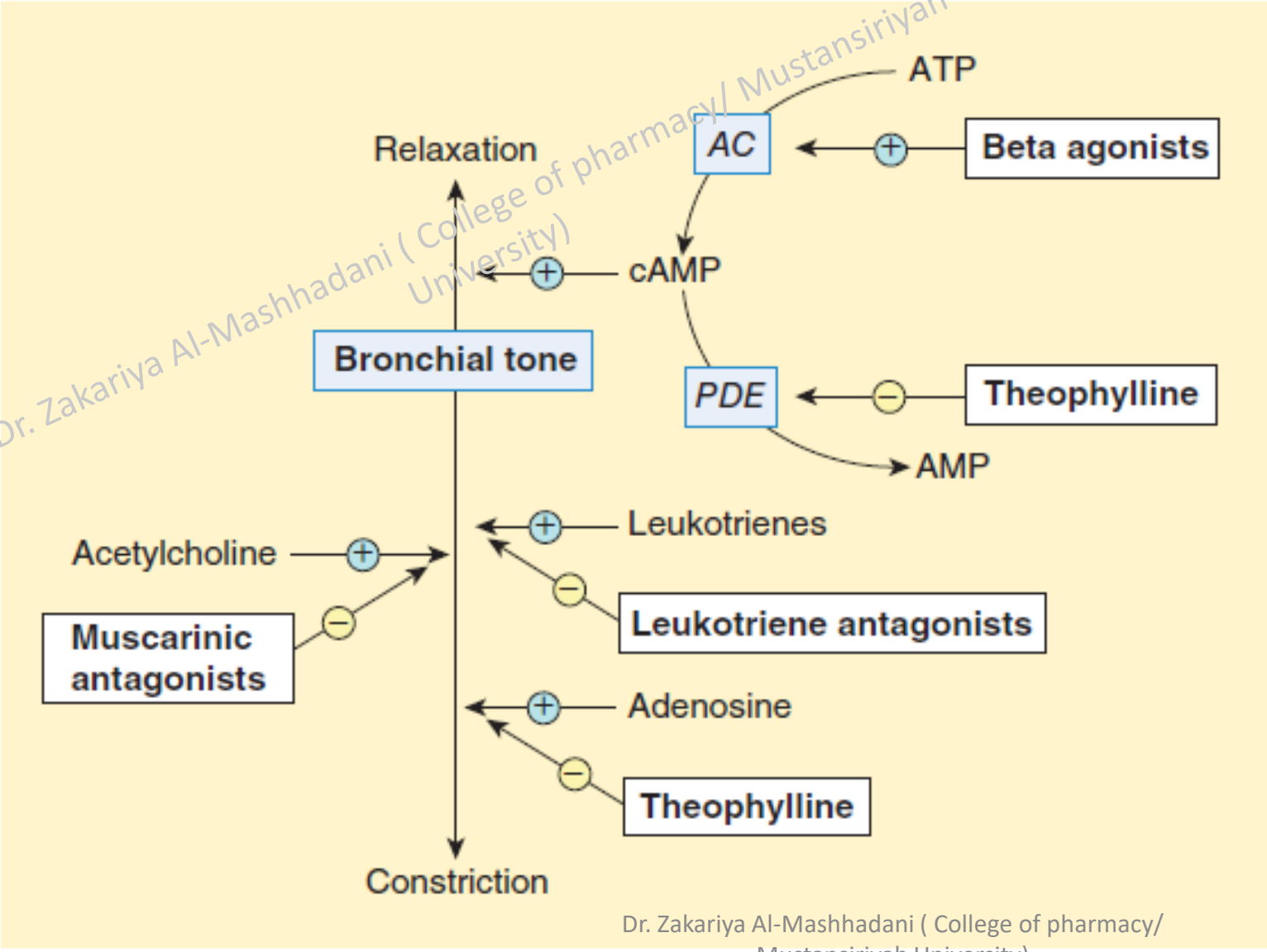
- ***Theophylline*** is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. It may also possess anti-inflammatory activity. Although it is precise, the mechanism of action is unclear. It is a nonselective phosphodiesterase inhibitor(PDE) known to increase cellular cAMP and cGMP levels, which are accounted for the bronchodilation achieved. It is also responsible for its cardiac side effects.
- Additionally, *theophylline* is reported to play a beneficial role in asthma due to its ability to antagonize adenosine receptors resulting in bronchodilation,
- In asthma therapy, *theophylline* has been largely replaced with β2 agonists and corticosteroids !!





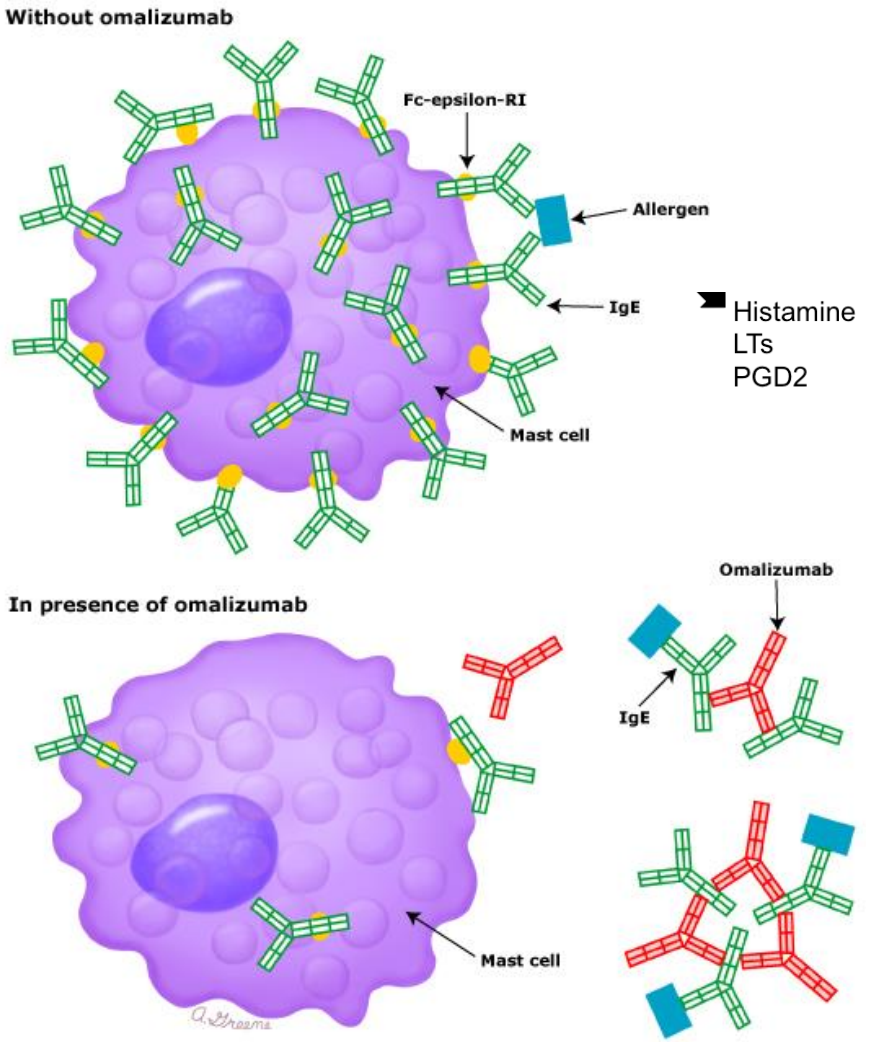


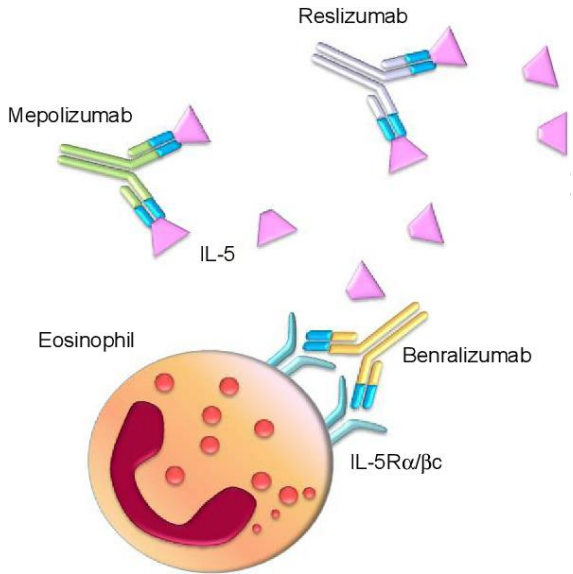
Possible mechanisms of β agonists, muscarinic antagonists, theophylline, and leukotriene antagonists in altering bronchial tone in asthma.



E- Monoclonal antibodies

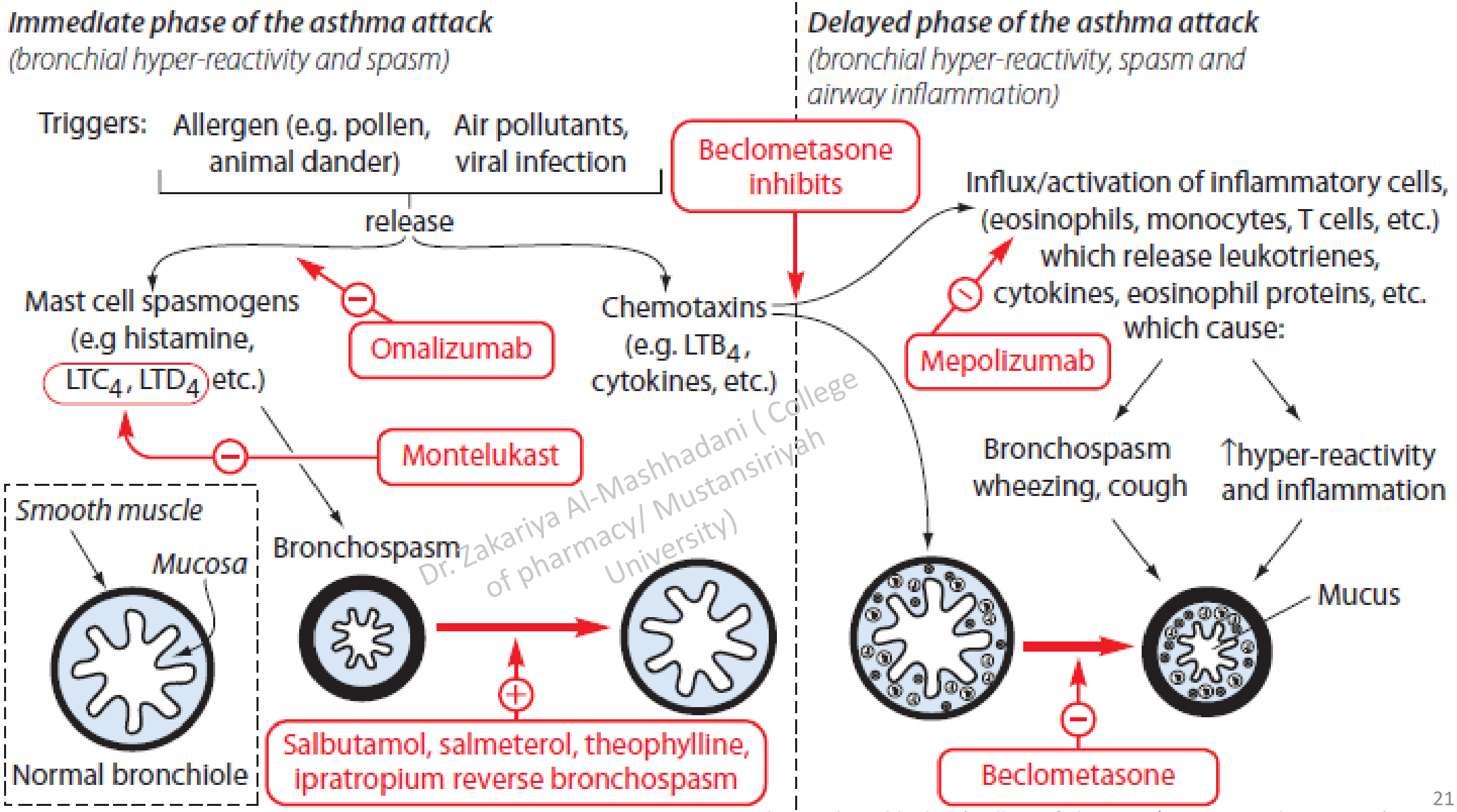
1. ***Omalizumab*** is a monoclonal antibody that selectively binds to human immunoglobulin E (IgE). This leads to decreased binding of IgE to its receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the release of mediators of the allergic response.
2. The monoclonal antibodies ***mepolizumab***, ***benralizumab*** and ***reslizumab*** are 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 only for the treatment of severe persistent asthma in patients who are poorly controlled with conventional therapy

Pathobiology of asthma: bronchial hyper-reactivity, bronchial spasm and inflammation of the airways



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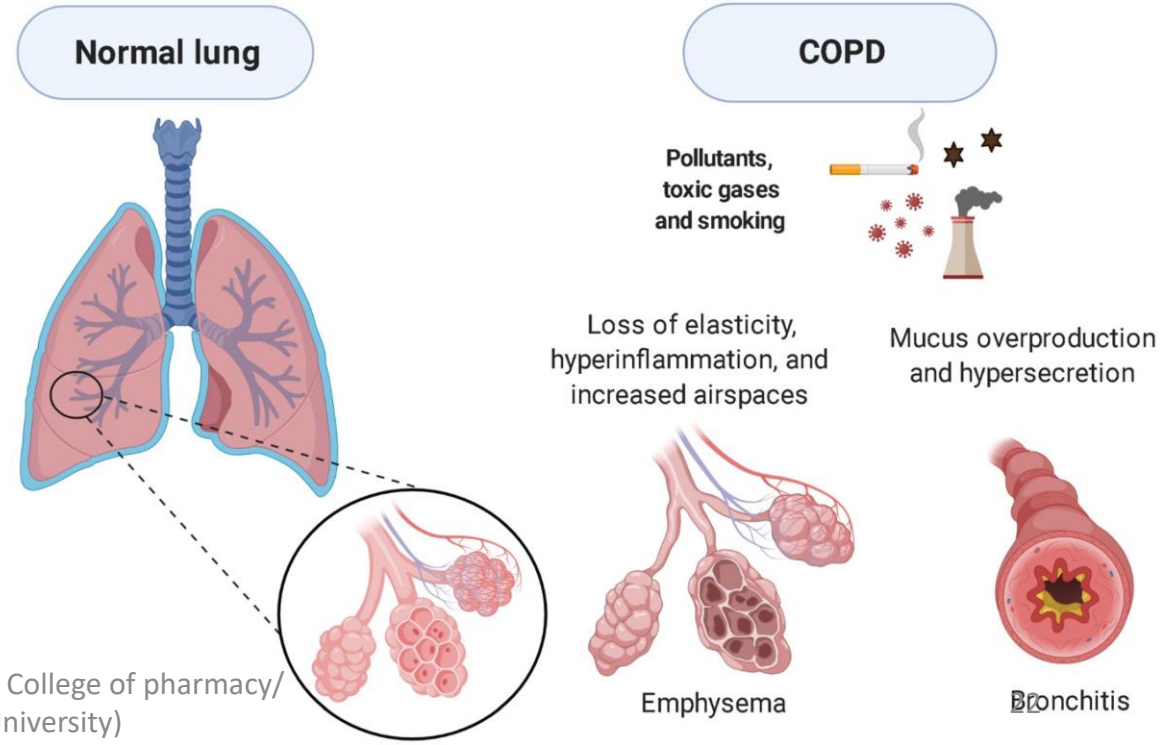
Drugs Used To Treat Chronic Obstructive Pulmonary Disease (COPD)

- COPD is a chronic, irreversible obstruction of airflow that is usually progressive and characterized by persistent symptoms. These may include cough, excess mucus production, chest tightness, breathlessness, difficulty sleeping, and fatigue.
- Although symptoms are similar to asthma, the characteristic **irreversible airflow obstruction** of COPD is one of the most significant differences between the diseases.

- Smoking is the greatest risk factor for COPD
- Drug therapy for COPD is aimed at relief of symptoms and prevention of disease progression.



DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

1. Bronchodilators

- LABAs and LAMAs are preferred as first-line treatment of COPD for all patients .
- LABAs include *vilanterol*, *formoterol*, and *salmeterol*.
- LAMAs *are :Aclidinium* , *tiotropium*, *glycopyrrolate*, and *umeclidinium*

2. Corticosteroids

The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function, and quality of life in COPD patients with FEV1 of less than 60% predicted or patients with symptoms of both asthma and COPD. However, ICS treatment in COPD should be restricted to these patients.

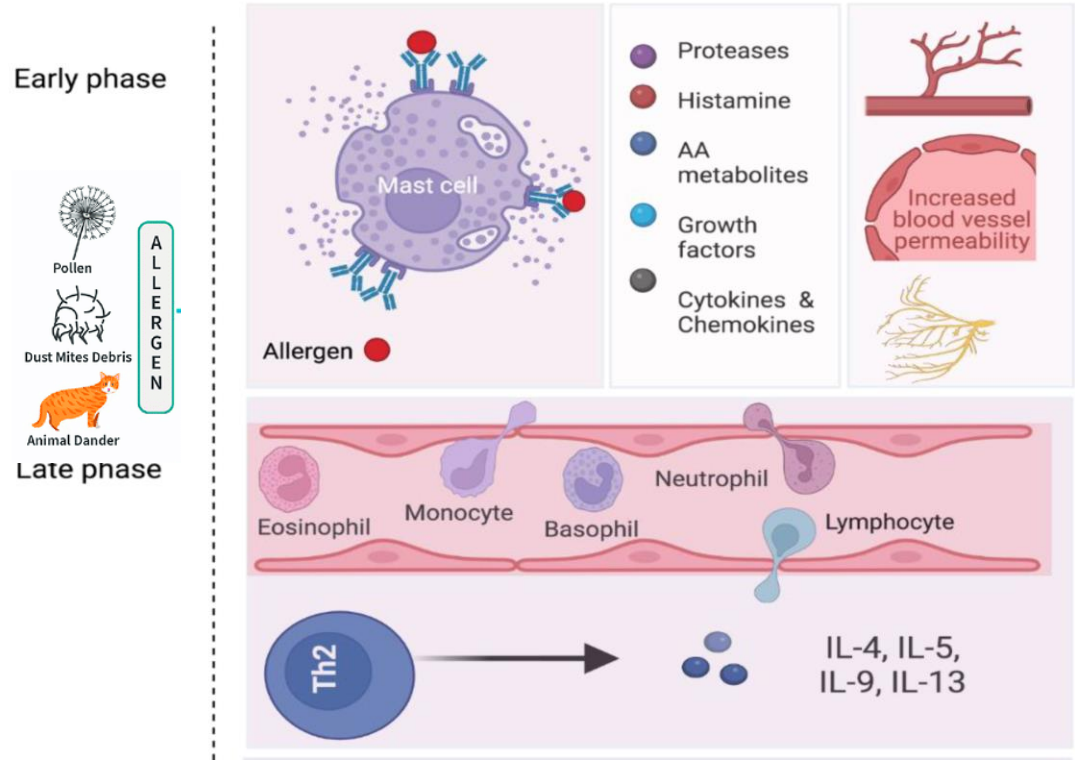
3. Roflumilast

It is an oral phosphodiesterase-4 inhibitor used to reduce exacerbations in patients with severe chronic bronchitis. Although its activity is not well defined in COPD, it is theorized to reduce inflammation by increasing levels of intracellular cAMP in lung cells.

Allergic Rhinitis

Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, nasal congestion, and sometimes a nonproductive cough.

- An attack may be precipitated by inhalation of an allergen (such as dust, pollen, or animal dander). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure. The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration.
- Antihistamines and/or intranasal corticosteroids are preferred therapies for allergic rhinitis.



Drugs Used To Treat Allergic Rhinitis

1. **Oral antihistamines** (H1 receptor antagonists) have a fast-onset of action and are useful for the management of symptoms of allergic rhinitis caused by histamine release, such as sneezing, watery rhinorrhea, and itchy eyes/nose.
2. **Intranasal corticosteroids**, such as *beclomethasone*, *budesonide*, *fluticasone*, *ciclesonide*, *mometasone*, and *triamcinolone*, are the most effective medications for treatment of allergic rhinitis. With an onset of action that ranges from 3 to 36 hours after the first dose, intranasal corticosteroids improve sneezing, itching, rhinorrhea, and nasal congestion.
3. **Short-acting α-adrenergic agonists** ("nasal decongestants"), such as *phenylephrine*, constrict dilated arterioles in the nasal mucosa and reduce airway resistance. Long-acting *oxymetazoline* is also available
4. **Intranasal *cromolyn*** may be useful in allergic rhinitis, particularly when administered before contact with an allergen.

COUGH

- Coughing is an important defense mechanism of the respiratory system in response to irritants
- A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease.
- In some cases, cough may be an effective defense reflex against an underlying bacterial infection and should not be suppressed.
- Before treating cough, identification of its cause is important to ensure that antitussive treatment is appropriate. The priority should always be to treat the underlying cause of cough when possible.

Drugs Used To Treat Cough/Antitussive Agents

A- Opioids cough suppressants

1. ***Codeine***, an opioid, decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion. These therapeutic effects occur at doses lower than those required for analgesia.
2. ***Dextromethorphan*** is a synthetic derivative of *morphine* that has no analgesic effects in antitussive doses. It is a centrally active excitatory amino acid NMDA receptor antagonist and is also reported to antagonize opioid receptors. It has a better adverse effect profile than *codeine* and is equally effective for cough suppression.

B- Nonopioid cough suppressants/expectorants

1. Benzonatate: Unlike the opioids, *benzonatate* suppresses the cough reflex through peripheral action. It anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura.

Drugs Used To Treat Cough/Expectorants

1. **Guaifenesin**: an expectorant that reduces mucus viscosity and loosens mucus in the airways, thereby enhancing the mucociliary clearance of sputum (productive cough).
2. **Acetylcysteine**: reduces sputum viscosity by splitting the disulfidebonds of viscous mucoproteins. It is administered orally for COPD. An intravenous formulation is also used as an antidote in acetaminophen poisoning.
3. **Dornase alfa**: purified recombinant human deoxyribonuclease, an enzyme that hydrolyzes deoxyribonucleic acid (DNA). Patients with cystic fibrosis (CF) have viscous purulent secretions in the airways, resulting in sputum that is difficult to clear. The viscosity of secretions is due, in part, to DNA released from leukocytes that accumulate in response to pulmonary infections in CF. Dornase alfa cleaves extracellular DNA present in purulent pulmonary secretions, thereby reducing sputum viscosity in patients with CF.
4. **Bromhexine** is a potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion and, helps in dissolving hard phlegm/mucus plugs