# Pulmonary pharmacology


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Pharmacology and therapeutics

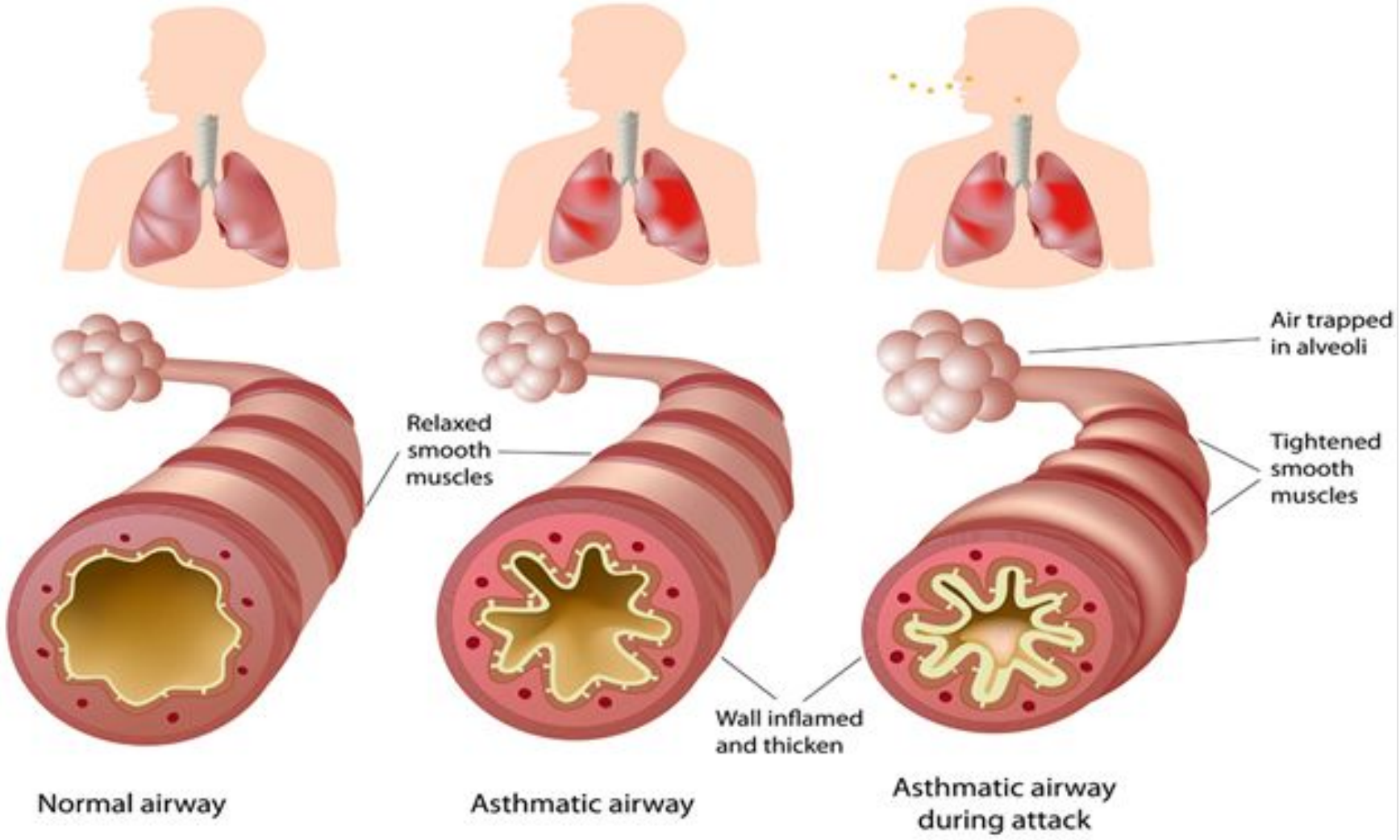
- **Drug therapy of asthma**

- Asthma is **chronic inflammatory disease** characterized clinically by **recurrent attacks** of coughing, shortness of breath, chest tightness, and wheezing.

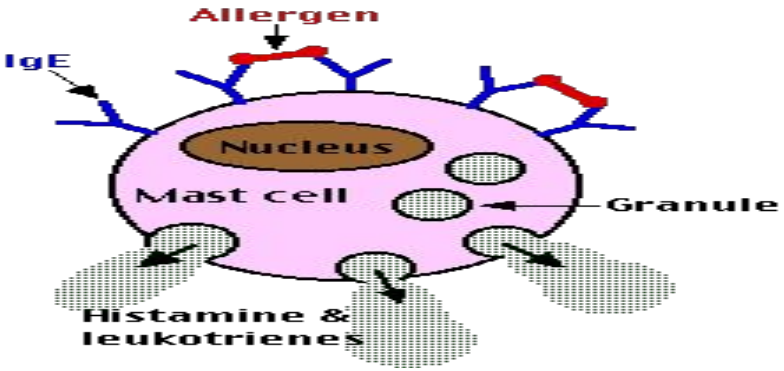
- **Pathology:** (**air flow obstruction**)

- Smooth muscle constriction around airways
- Airways wall edema
- Intraluminal mucus accumulation
- Inflammatory cell infiltration of the submucosa

# Pathology of Asthma



- In **acute exacerbations** of asthma, bronchial smooth muscle contraction (**bronchospasm**) occurs quickly to narrow the airways in response to exposure to a **variety of stimuli** (including **allergens, exercise, cold air, irritants and viral infections**).
- **Bronchoconstriction** results from an IgE-dependent **release of mediators from mast cells** that includes **histamine**, **cysteinyl leukotrienes** (LTC4, LTD4, and LTE4) and **prostaglandins** that directly contract airway smooth muscle.
- **Aspirin** and other nonsteroidal anti-inflammatory drugs can also cause acute airflow obstruction in some patients.

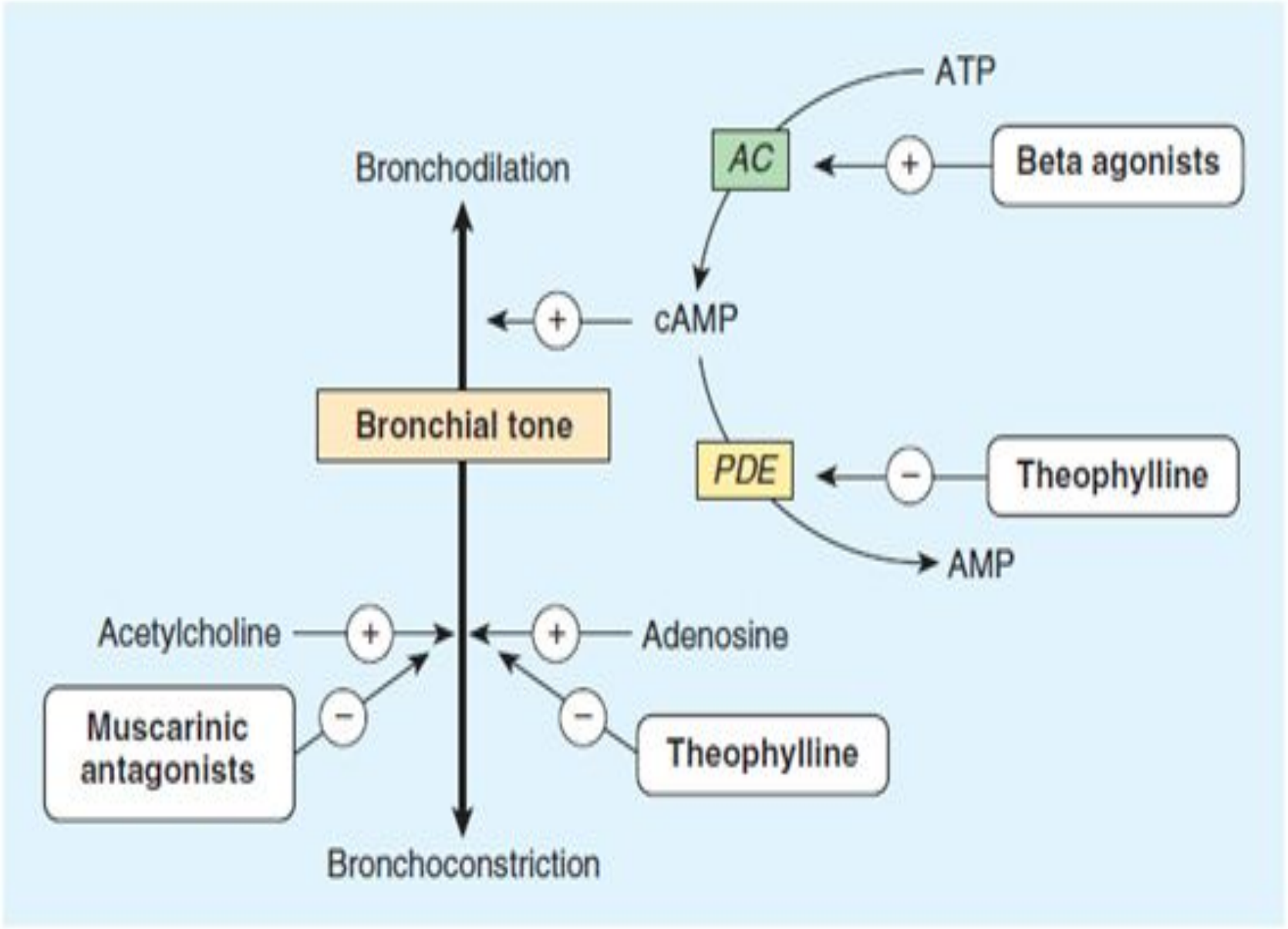


- **Classification of drugs used for treatment of asthma**

## A. According to the mechanism of action:

### 1. Bronchodilators:

- **Selective $\beta_2$ Agonists (SABA & LABA)**
- **Theophylline**
- **Muscarinic Antagonists**


ATP
AC
Beta agonists
Bronchodilation
cAMP
Bronchial tone
PDE
Theophylline
AMP
Acetylcholine
Adenosine
Muscarinic antagonists
Theophylline
Bronchoconstriction

## 2- Anti-inflammatory:

- Corticosteroids
- Leukotriene modifiers (LTRA & 5-LOX inhibitors)
- Anti-IgE drugs (omalizumab)

## 3- Mast cells stabilizers:

- Cromolyn and Nedocromil
- Ketotifen

## According to clinical use:

- **Drugs used** in the treatment of asthma are categorized into two general classes: long-term control medications (**controllers**) **used to achieve and maintain control of asthma** and quick-relief medications (**relievers**) used to **treat acute symptoms and exacerbations.**

- **Relievers Drugs:**

- They **reverse bronchoconstriction** and **relieve symptoms of airflow obstruction** during acute attacks of asthma.

- **Short-Acting $\beta_2$-Agonists (SABAs)**
- Selective $\beta_2$-agonists relax airway smooth muscles by selectively stimulating $\beta_2$-receptors, which **increases cyclic AMP** that inactivate myosin light-chain kinase required for smooth muscle contraction. In addition to bronchodilatation, $\beta_2$-agonists also **stabilize mast cells** (decrease mediators release)
- ***SABAs*** are the ***most effective bronchodilators available***. Due to their **rapid onset of action** (3-5 minutes), effectiveness, and a **duration of action of 4-6 hours**, SABAs are the **drugs of choice for acute asthma symptoms and for preventing EIB (exercise-induced bronchoconstriction).**
- **Salbutamol** (albuterol) is the **most widely used agent**, other drugs include **terbutaline**, **pirbuterol** and **levosalbutamol**

- The **inhaled route** results in **more rapid bronchodilation** at a **lower dose and with fewer side effects** than oral or intravenous administration.
- **Oral therapy** is rarely needed and reserved mainly for **young children who cannot use inhaled therapy**, while **intravenous route is reserved for very sever asthmatic attacks.**
- **Side effects** of SABAs **(tremor, tachycardia, palpitations and arrhythmias, hypokalemia)** are more common after **systemic administration or higher inhaled doses.**
- During exacerbations, frequent or continuous doses also can cause **hypokalemia and hypoxemia**. **Levosalbutamol is associated with less tachycardia and tremor than salbutamol.**

- **Anticholinergic Drugs**
- **Ipratropium** is the **anticholinergic of choice** because it has **few side effects** and available in both **MDI** and **nebulizer** formulations.
- It relaxes airways smooth muscles by **blocking muscarinic ($M_3$) cholinergic receptors.**
- **Reduces intrinsic vagal tone of the airways**
- **minimizes mucous production**
- **Blocks reflex bronchoconstriction secondary to irritants.**

- **Inhaled ipratropium** is used primarily in the **treatment of acute severe asthma**. In addition it may be used as an **alternative bronchodilator for patients who do not tolerate SABAs**. When used in **combination with salbutamol**, ipratropium can **improve lung function and reduce the rate of hospitalization.**

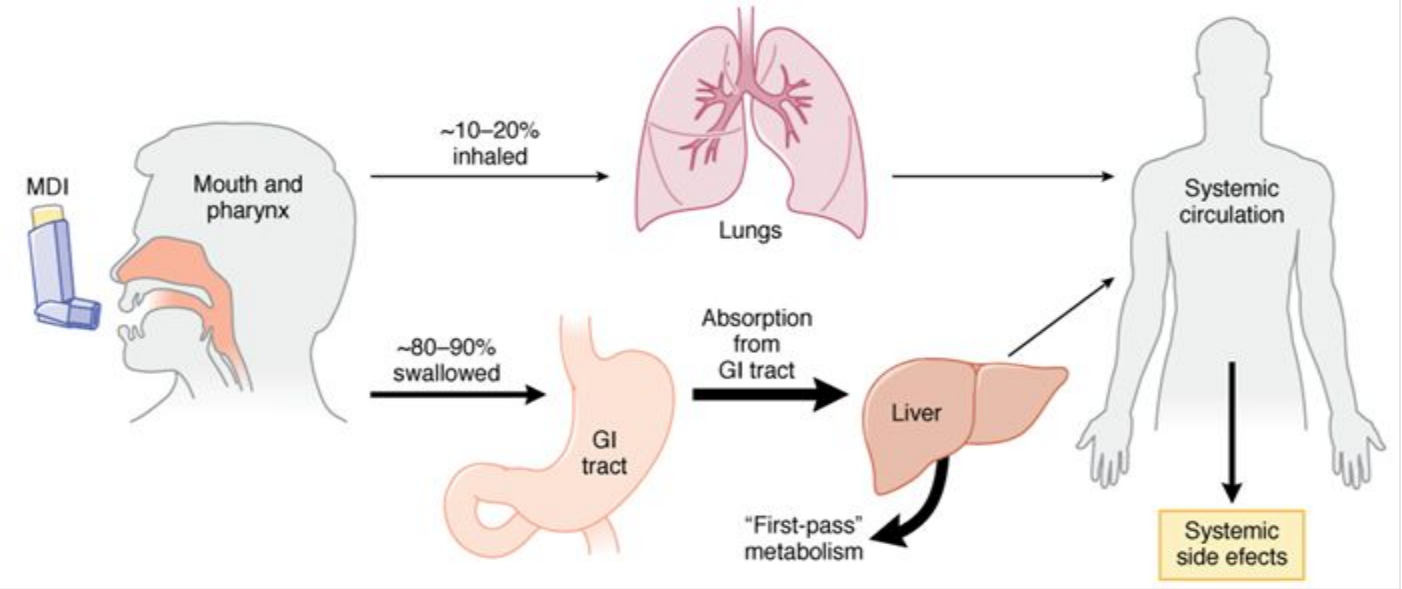
- **Side effects** include **dryness of mouth** and **blurred vision** if sprayed in eyes. During exacerbations, **ipratropium produces less cardiac stimulation** than SABAs.

- **Systemic Corticosteroids (SCS)**
- Systemic corticosteroids are used for **moderate and severe exacerbations** as **adjunct to SABAs** to **prevent progression of exacerbation**, **reverse inflammation**, **speed recovery** and **reduce rate of relapse**.
- **Prednisolone, methylprednisolone or prednisone** are usually used (**orally for mild-moderate attacks** and **parenterally for severe attacks**).
- **Short-term therapy** should continue until patient's symptoms resolve. This usually requires **3-10 days** but may require longer.
- Potential **side effects** associated with ***short-term SCS*** use include **reversible abnormalities in glucose metabolism**, **increased appetite**, **fluid retention**, **weight gain**, **facial flushing**, **mood alteration** and **hypertension**.

- **Aminophylline**
- Aminophylline is a **soluble ethylenediamine salt of theophylline used intravenously** in **severe acute asthmatic attacks**, particularly in patients who had **not responded to conventional therapy.**
- **Controller Drugs:**
- **Inhaled Corticosteroid (ICS)**
- **Inhaled corticosteroids** are the **most effective controller therapy for asthma in all ages**.
- **Corticosteroid** are the **most potent anti-inflammatory drugs currently available for the treatment of asthma.**

- **The anti-inflammatory effects** are mediated through **binding to steroid receptors** that modulate **inflammatory gene expression**. Corticosteroids **block late-phase reaction to allergen**, **suppress the generation of cytokines and release of inflammatory mediators** and **inhibit inflammatory cell migration and activation**.
- **The clinical effects** of ICS therapy include **reduction in severity of symptoms**, **improvement in asthma control and quality of life**, **improvement in lung functions**, **prevention of exacerbations**, **reduction in systemic corticosteroid use**, **emergency care, hospitalizations, and deaths due to asthma.**

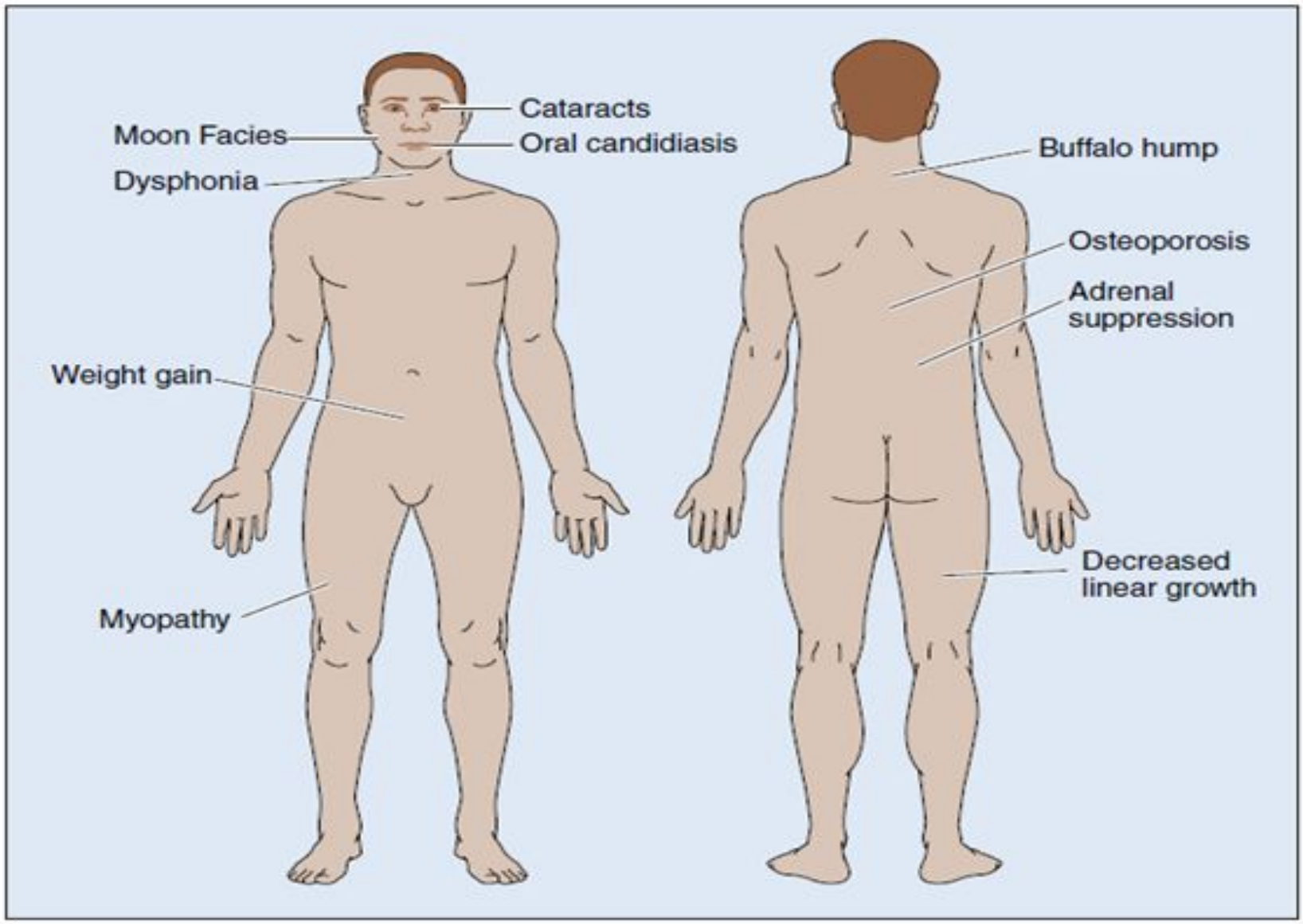
- Approximately **10-20% of the dose from the MDI is delivered to the lungs** (the use of MDIs with spacer devices increases delivery). The **other fraction of the dose is usually swallowed**. The bioavailability of an ICS is dependent mostly on the oral **bioavailability of the swallowed portion** of the dose received and to less extent on the absorption of the dose delivered to the lungs.



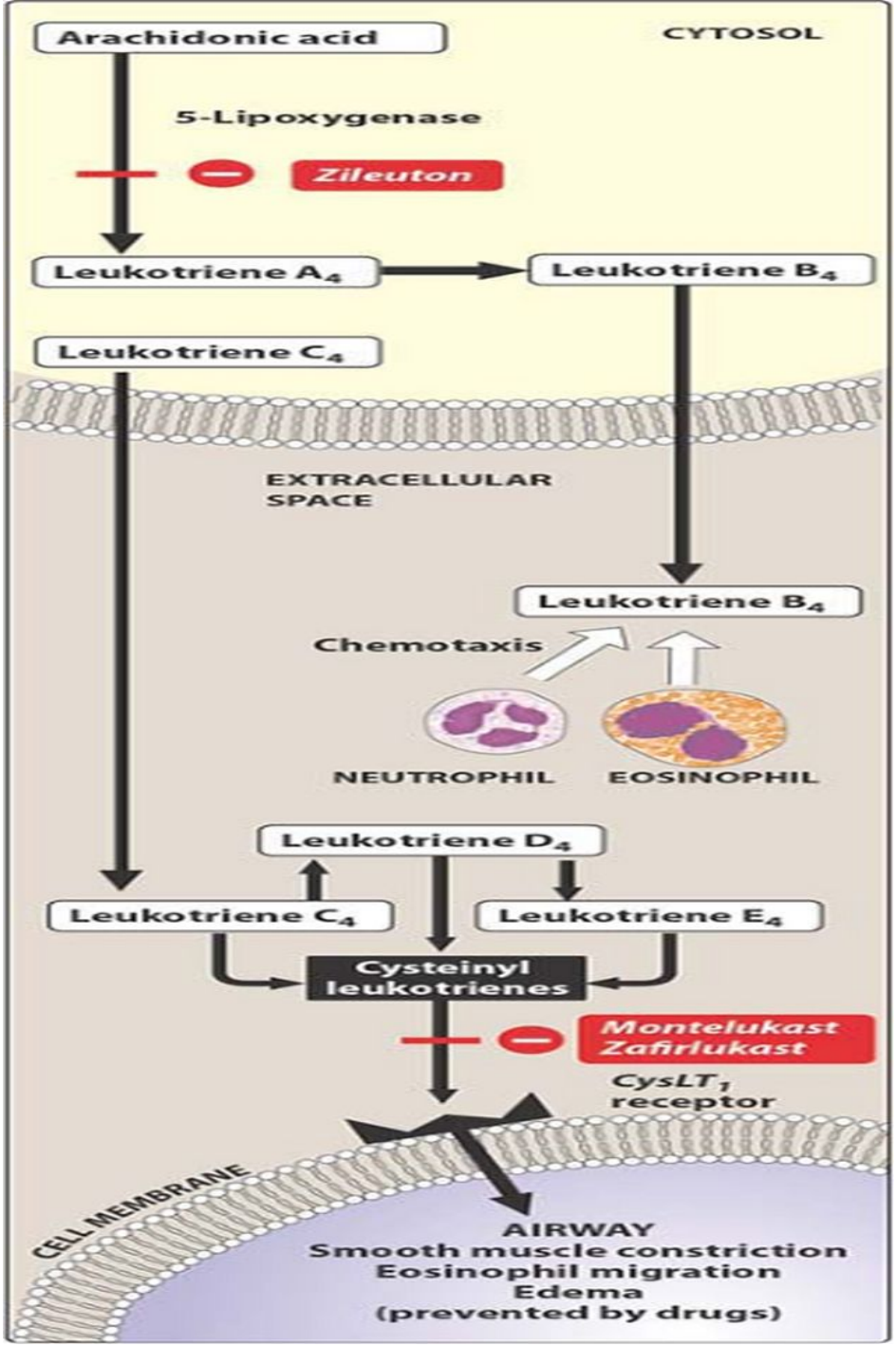
- Generally, **ICSs have lower bioavailability** than **oral systemic corticosteroids**; hence, the risk of potential side effects is substantially reduced with ICS therapy. The oral bioavailability of the swallowed portion of major ICSs are:

- **Beclomethasone: 15%**
- **Budesonide: 11%**
- **Ciclesonide: <1%**
- **Flunisolide: 7%**
- **Fluticasone: <1%**
- **Mometasone: <1%**
- **Triamcinolone: 23%**

# Adverse effects of ICSs



- **Leukotriene Modifiers**
- Leukotriene modifiers include **leukotriene receptor antagonists** (***LTRA***) and a **5-lipoxygenase inhibitor** that are available as **oral controller** drugs for the treatment of asthma. Two **cysteinyl-leukotriene 1 receptor antagonists** are available, **montelukast** (for patients **≥1 year** of age) and **zafirlukast** (for patients **≥7 years** of age). The **5-lipoxygenase inhibitor, zileuton** is available for patients **≥12 years** of age.


Arachidonic acid
CYTOSOL
5-Lipoxygenase
Zileuton
Leukotriene $A_4$
Leukotriene $B_4$
Leukotriene $C_4$
EXTRACELLULAR SPACE
Leukotriene $B_4$
Chemotaxis
NEUTROPHIL
EOSINOPHIL
Leukotriene $D_4$
Leukotriene $C_4$
Leukotriene $E_4$
Cysteinyl leukotrienes
Montelukast
Zafirlukast
$CysLT_1$ receptor
CELL MEMBRANE
AIRWAY
Smooth muscle constriction
Eosinophil migration
Edema
(prevented by drugs)

- Leukotriene modifiers have **anti-inflammatory bronchodilator effects**, they **reduce symptoms** (including cough), **improve lung function**, and **reduce airway inflammation and asthma exacerbations**. They also provides **protection against EIB** and are **very effective in aspirin-induced asthma**.
- **Montelukast is highly safe** drug and demonstrated a **safety profile more than that of ICSs**. **Hepatic dysfunction** have occurred with **zafirlukast and zileuton** treatment. **Both zafirlukast and zileuton inhibit the metabolism of theophylline, resulting in increased serum theophylline levels**.

: **Two approaches to interrupting the leukotriene pathway**

Inhibition of 5-lipoxygenase, thereby preventing leukotriene .synthesis

Inhibition of the binding of $LTD_4$ to its receptor on target tissues, thereby preventing its action including bronchoconstriction, increased bronchial reactivity, mucosal .edema, and mucus hypersecretion

**:Advese effect**

.Elevations in serum hepatic enzymes -1

.eosinophilic vasculitis -2

.headache and dyspepsia -3

Both Zileuton , Zafirlukast are inhibitors of cytochrome -4 .P450

- **Cromolyn Sodium and Nedocromil**

- Cromolyn and nedocromil are **mast cells stabilizers** with similar anti-inflammatory actions. They **block chloride channels** and modulate mast cell mediator release.

thus may inhibit the:

exaggerated neuronal reflexes triggered by stimulation of irritant receptors on sensory nerve endings (e.g. exercise-induced asthma)

- release of preformed cytokines from several type of inflammatory cells (T cells, eosinophils) in allergen-induced asthma

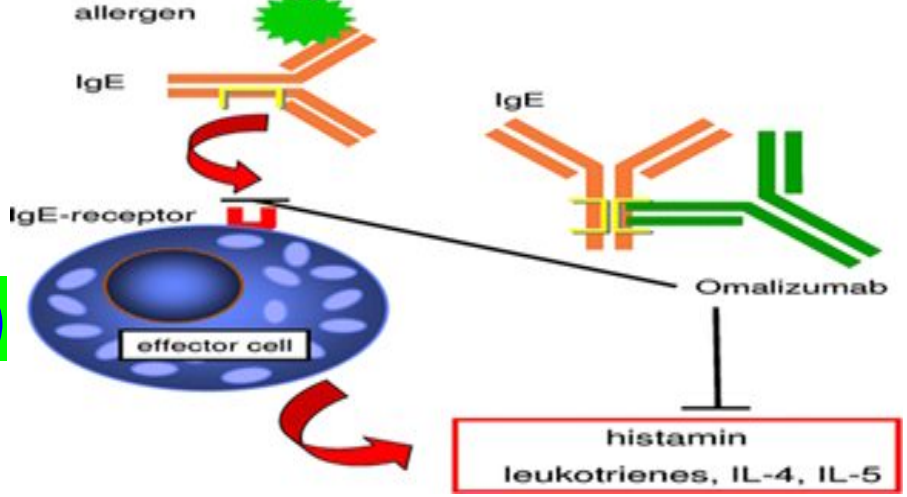
- Although largely devoid of adverse effects, these medications must be administered **frequently (2-4 times daily by inhalation)** and are **less effective** daily controller medications than **ICSs and leukotriene modifying agents.**

- Both drugs have **excellent safety profile** on long term use. **Local side effects include cough and irritation**. Nedocromil also has **unpleasant taste.**

Cromolyn and nedocromil solutions are also useful in reducing symptoms of **allergic .rhinoconjunctivitis**

Applying the solution by **nasal spray or eye drops** several times a day is effective in about 75% of .patients, even during the peak pollen season

- **Anti-IgE (Omalizumab)**




- Omalizumab is a **recombinant DNA-derived humanized** monoclonal antibody that **binds free IgE at the Fc portion**, thereby **preventing its binding to IgE receptors on mast cells and basophils** leads to:
- **decrease in the release of mediators** in response to allergen exposure
- Omalizumab is recommended as an **add-on therapy** for patients **≥12 years** old with **moderate to severe allergic asthma**, **not controlled with inhaled and/or oral corticosteroids.**
- It **reduces exacerbations**, **symptoms** It is given **every 2-4 wk subcutaneously**, the **dosage** based on **body weight and serum IgE levels**.

- Omalizumab is generally well tolerated, although **local injection site reactions** can occur. **Hypersensitivity reactions** (including anaphylaxis) have been very rarely associated with omalizumab use.

It also lessens asthma severity and improves coincident nasal .and conjunctival symptoms of allergic rhinitis

There is also evidence of effectiveness of omalizumab .treatment for chronic urticaria and peanut allergy

# Status asthmaticus

**:types of status asthmaticus 2**

**The first** and the more common type is **slow-onset** attack (this may take a long time because of .inadequate treatment)

**The second** type of severe attack is a **sudden onset** attack (this type of asthma is often brought on by a large exposure to trigger substances such as .pollen,dust or food allergens

# How we diagnosis status asthmaticus

Breathlessness at rest

Inability to speak in sentences or not being .able to speak at all

High respiratory rate (greater than 30 breaths .per min.)

Elevated pulse (more than 120 beats per min.)

Agitation

.Low levels of oxygen in the blood

# How to treat status asthmaticus

**:Standard treatment of SA in the emergency room includes**

oxygen by mask (in high centration, usually ≥60%) -1

inhalation of nebulised salbutamol -2

.intravenous hydrocortisone followed by a course of oral prednisolone -3

Additional measures occasionally used include nebulised ipratropium, -4 intravenous ,salbutamol or aminophylline, and antibiotics (if bacterial .infection is present)

mechanical ventilation is the treatment of the last choice because of the -5 . risk of trauma to the lung

- **Drugs Used to Treat COPD:**

COPD is characterized by airflow limitation that is usually progressive and is believed to reflect an abnormal inflammatory .response of the lung to noxious particles or gases

The condition is most often a consequence of prolonged habitual ,cigarette smoking

.but approximately 15% of cases occur in nonsmokers

***Compared to asthma***, COPD occurs in older patients, is associated ,with neutrophilic rather than eosinophilic inflammation

is poorly responsive even to high-dose inhaled corticosteroid therapy, and is associated with progressive, loss of pulmonary function over .time, especially with continued cigarette smoking

- **Drugs Used to Treat COPD:**

***For relief of acute symptoms***, inhalation of a short-acting β agonist (eg, albuterol), or an anticholinergic drug (eg, ipratropium bromide), .or of the two in combination is usually effective

**For patients with persistent symptoms** of exertional dyspnea and limitation of activities, regular use of a long-acting bronchodilator, whether a long-acting β agonist such as salmeterol or a long-acting .anticholinergic (eg, tiotropium) is indicated

**Theophylline** may have a particular place in the treatment of COPD, as it may improve contractile function of the diaphragm, thus .improving ventilatory capacity

The use of **antibiotics** in COPD is routine, because such exacerbations involve bacterial infection of the lower airways far .more often in COPD than in asthma

# Drugs Used to Treat Allergic Rhinitis

Rhinitis is an inflammation of the mucous , by sneezing, itchy nose/eyes, watery :rhinorrhea, and nasal congestion

A- antihistamines(H1-receptor blockers)

B- alfa-adrenergic agonists

C- coticosteroids

D- cromolyn

- **Drugs Used to Treat Cough:**

- ***Antitussive Agents:***
- 
- **Codeine** and pholcodeine

* decreases the sensitivity of **cough centers** in the central nervous system to peripheral stimuli.
* The therapeutic effects occur at **doses lower than those required for analgesia** but still has common sides effects like **constipation, dysphoria**, and **fatigue**, in addition to its **addictive potential.**

- 
- **Dextromethorphan**

* It is a **synthetic derivative of codeine** that **suppresses the response of the cough center.**
* It has **no analgesic effects**, has a **low addictive profile**, but may cause **dysphoria** at high doses

- 
- ***Mucolytic Agents:***
- Reduce the viscosity of sputum e.g. **Bromhexine and Carbocisteine**

- 
- ***Expectorant Agents:***
- Promote expulsion of bronchial secretions e.g. **Ammonium chloride**

*Thank you*