

RES-209 Topics

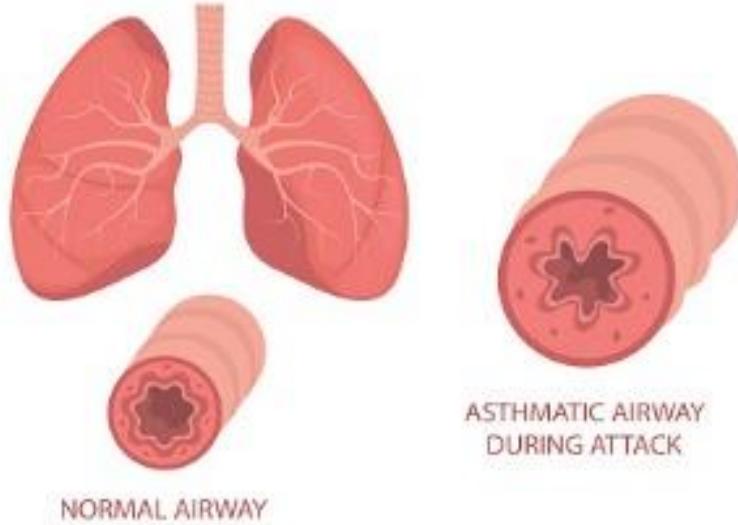
Bronchial Asthma

Pulmonary TB

Pneumonia

**Antitussive &
mucoactive drugs**

Bronchial Asthma



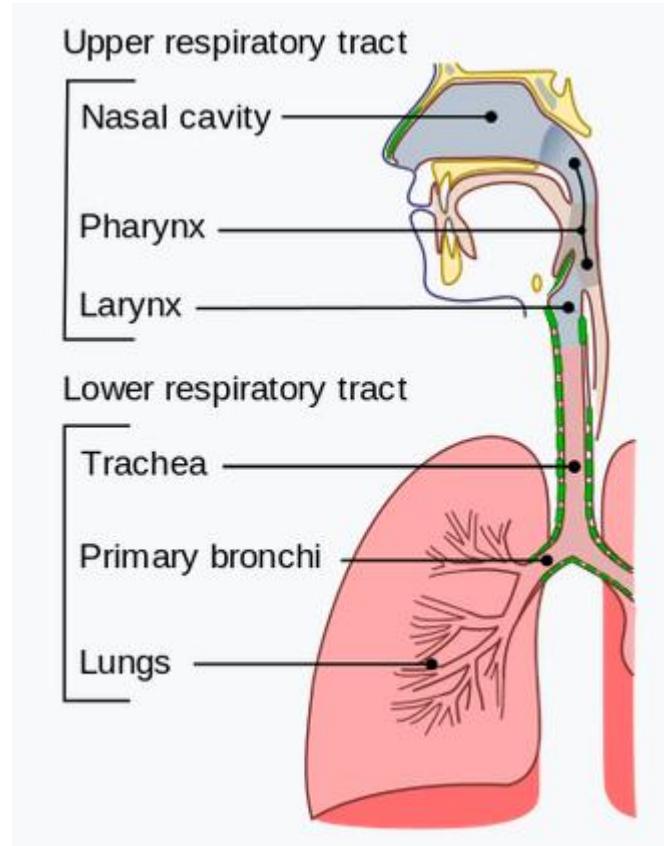
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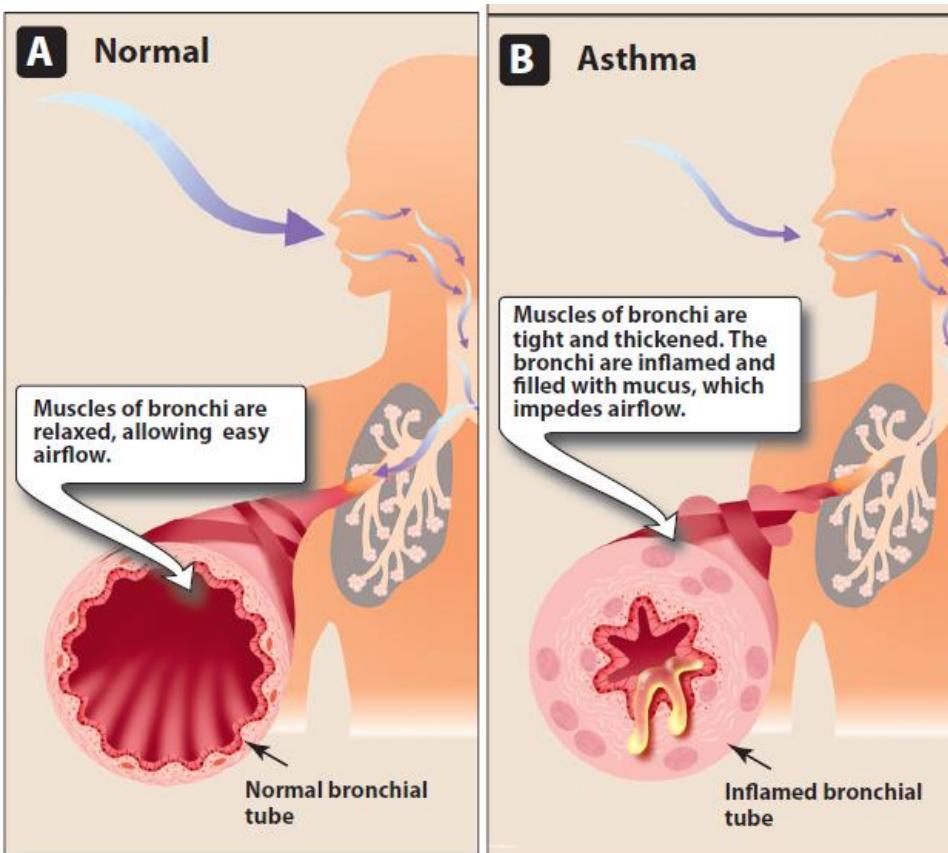
ILOS

- The Pharmacology of drug groups used in management of bronchial asthma.
- Management of status asthmaticus.
- Stepwise approach in management of bronchial asthma.

Respiratory System



Bronchial Asthma



- Bronchial asthma is **chronic inflammatory disorder** with **bronchial hyper-responsiveness** and **bronchospasm** in response to both **chemical** and **physical** stimuli.
- It is manifested by episodes of **coughing, shortness of breath, chest tightness** and **wheezing** particularly at night or in the early morning
- These **episodes** are usually **associated with widespread but variable airflow obstruction** that is **reversible** either spontaneously or following treatment.

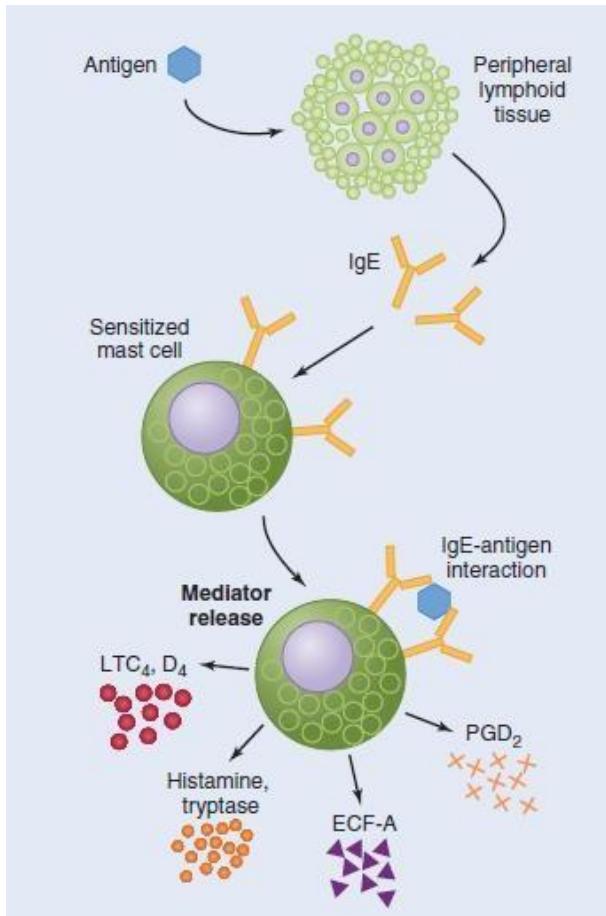
Lippincott's Pharmacology 6th edition

Asthma Triggers



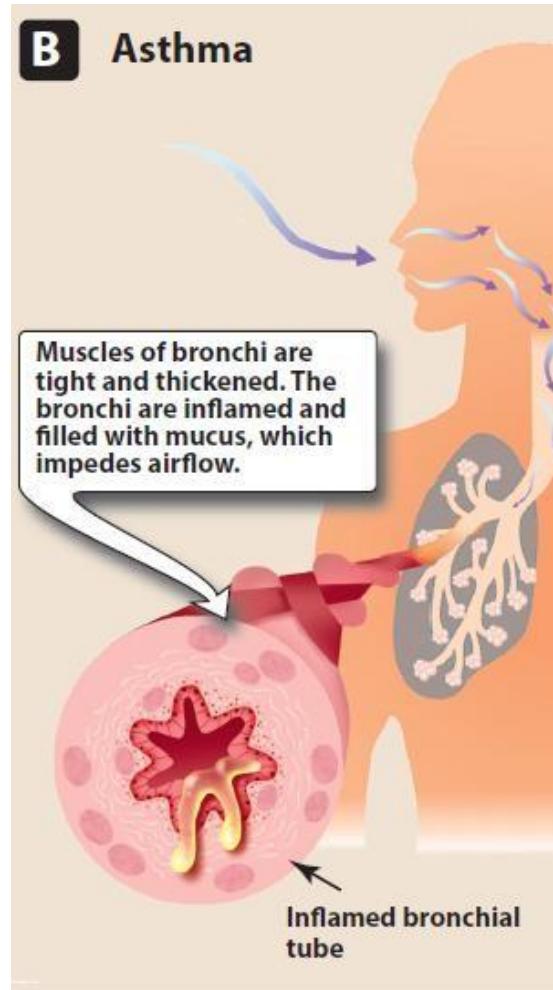
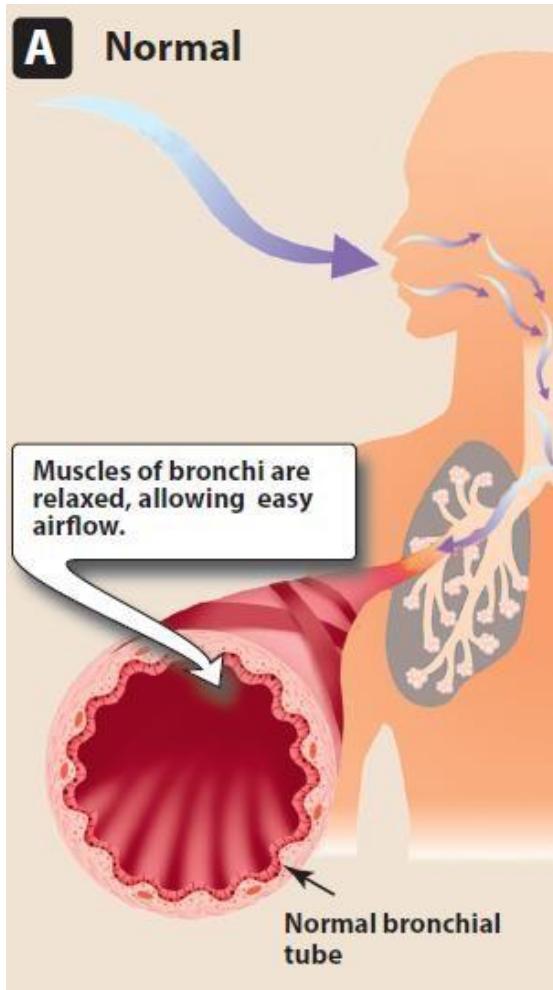
- **Pollen grains.**
- **Pet** (fur or feathers, urine, saliva and dander).
- **Exercise.**
- **Chronic sinusitis or rhinitis**
- **House-dust mites.**
- **Cockroach waste & decomposing carcass.**
- **Mold and mildew spores.**
- **Tobacco smoke.**
- **Perfumes, scented hairsprays.**
- **Cleaning solutions.**
- **Pesticides & paint fumes.**
- **Stress & emotions.**
- **Drugs (β -blockers & NSAIDs)**

Pathogenesis



- Exposure to one of asthma triggers (**antigen**) causes **synthesis of IGE** which **binds to and sensitizes mast cells and other inflammatory cells**.
- When **sensitized cells are challenged with the antigen**, degranulation of mast cell with **release of numerous inflammatory mediators** (manifestations of asthma).

Inflammatory Mediators



Early
↓

Bronchoconstriction
(contraction of bronchial smooth muscle)

Late
↓

Inflammation of the bronchial wall leading to **oedema, increased secretion of mucus & increase parasympathetic tone (more bronchoconstriction)**



Coughing



Wheezing



SHORTNESS OF BREATH



Chest tightness

Signs & symptoms

- Wheezing
- Coughing
- Shortness of breath
- Chest tightness

3-Estimation of severity

Clinical assessment

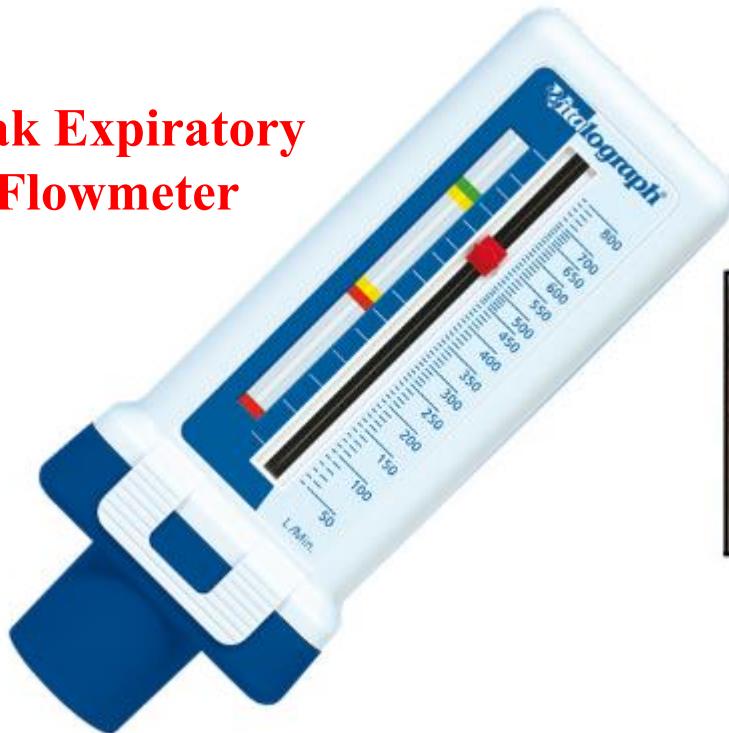
Measurement of peak expiratory flow rate

Pulse Oximetry

Other markers of severity are:

- Inability to speak in sentences or phrases (i.e. only one word at a time).
- Altered level of consciousness.
- Cyanosis indicates life-threatening asthma.

Peak Expiratory Flowmeter



Take a
Deep Breath

Blow out hard
and fast

Record the
reading on the
meter



Pulse Oximetry

4-Management

Prevention of attacks

Bronchodilators
(Reliever Drugs)

- β_2 -agonist
- Muscarinic antagonists
- Theophylline

Anti-inflammatory
(Controller drugs)

- Corticosteroids
- Anti-IGE antibodies
- Leukotriene antagonists
- Mast cell stabilizers

Goals of therapy

- Decrease the intensity and frequency of asthma symptoms.
- Decrease the degree to which the patient is limited by these symptoms.

A) Prevention of attack

- Avoidance of trigger factors
- Appropriate management of acute exacerbations
- Appropriate management of chest infections
- Appropriate long-term medication use by inhalational corticosteroids
- Avoidance of bronchoconstrictor drugs

B) Drug Treatment



Bronchodilators

**β_2 - adrenergic
agonist**

Methylxanthines

**Anti-cholinergic
drugs**

**Anti-inflammatory
drugs**

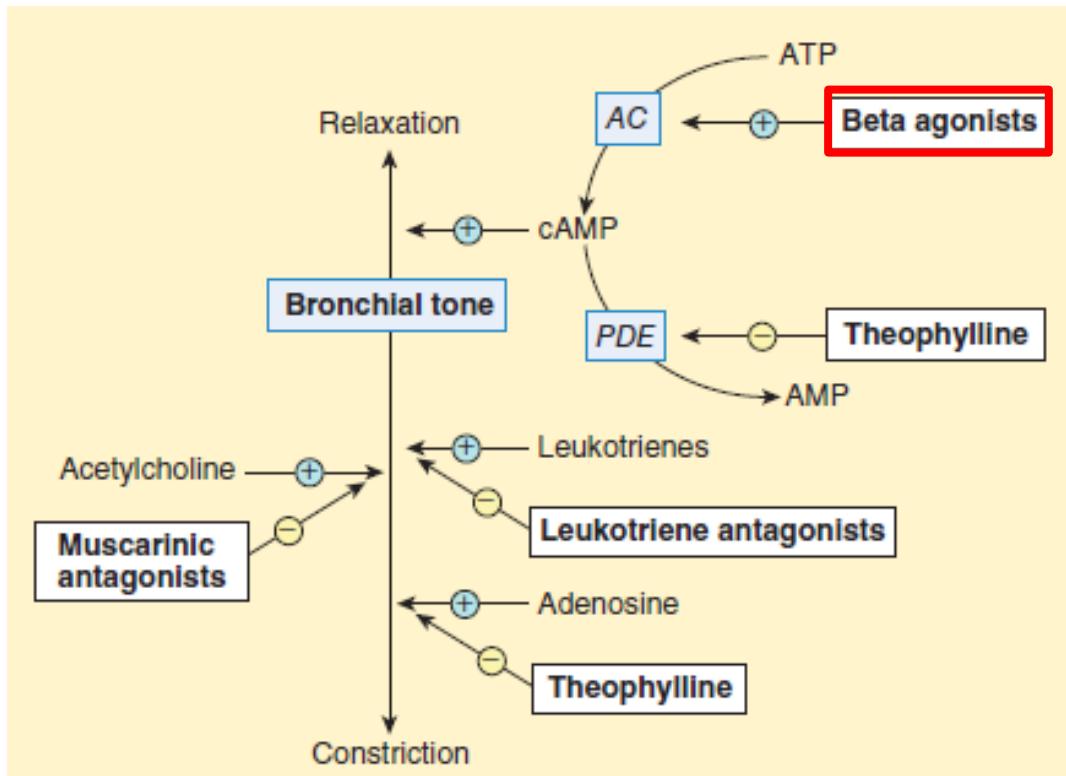
Corticosteroids

**Anti-IgE antibodies
(Omalizumab)**

**Leukotrienes
antagonists**

**Mast cell membrane
stabilizers**

I-B₂- adrenergic agonists



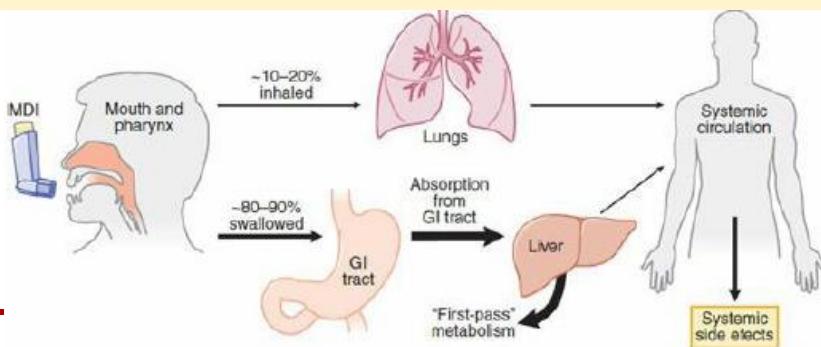
Examples

Mechanism of action

Routes of administration

Side effects

Clinical Uses



Examples

- 
- **Short acting** (4-6 hours).....Albuterol (salbutamol), terbutaline, metaproterenol.
 - **Long acting** (6-12 hours) Salmeterol, formoterol.
 - **Ultra-long-acting**.....Indacaterol & olodaterol

Short acting	Long acting	Ultra-long-acting
Salbutamol (albuterol), terbutaline & metaproterenol	Salmeterol & formoterol	Indacaterol & olodaterol
<p># They have rapid onset and short duration of action (4-6 hours)</p> <p># Used in acute attacks</p> <p># Available as metered-dose inhalers and Nebulized therapy</p>	<p># Slow onset and longer duration of action (up to 12 hours) as a result of high lipid solubility.</p> <p># These drugs appear to interact with inhaled corticosteroids to improve asthma control.</p> <p># Because they have no anti-inflammatory action, they should not be used as monotherapy for asthma.</p> <p># Used as a prophylactic treatment.</p>	<p># Taken only once a day but are currently FDA-approved only for the treatment of chronic obstructive pulmonary disease (COPD).</p>

Mechanism of action



Binding to β_2 receptors on airway smooth muscle cells **stimulates adenylyl cyclase** and increases the formation of intracellular cAMP, thereby:

- **relaxing airway smooth muscle and**
- **inhibiting release of mediators inducing bronchoconstriction from mast cells.**

Routes of administration



- **Inhalation** management of acute attack.
- **Oral** maintenance treatment.

- **Advantages of inhalational route:**

1. Rapid onset of action.
2. It permits direct delivery of the drug to the site of action.
3. It reduces the possibility of general systemic side effect.
4. The total dose administered is very small and this further limits the adverse effects.
5. It provides large surface area for absorption.

- Can be given in **nebulizer** or **metered dose inhaler (MDI)**.

I-Nebulizer

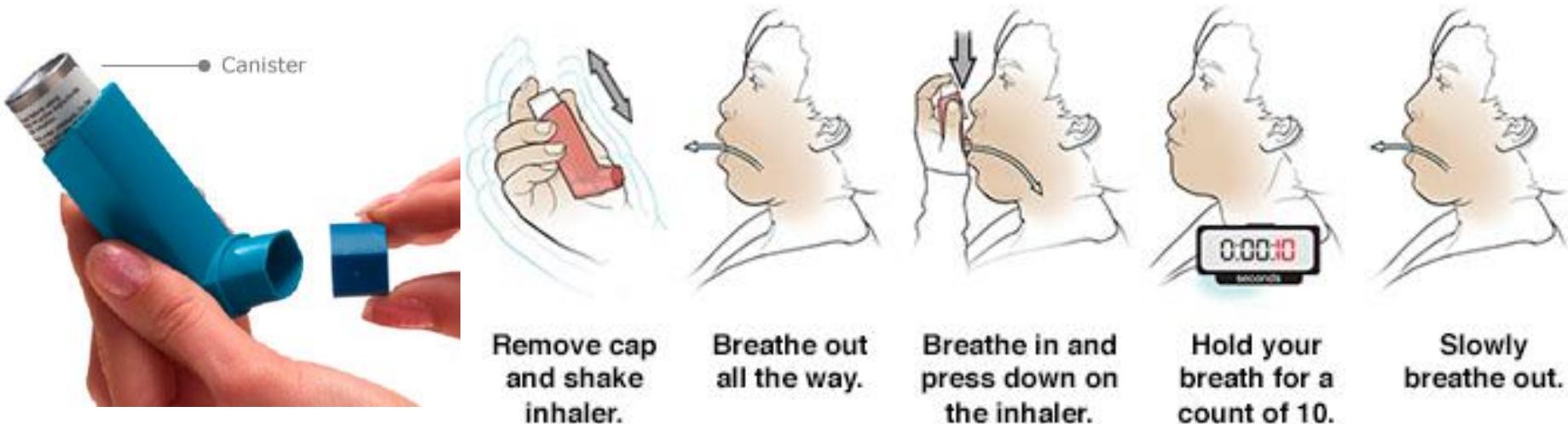


- **Nebulizers** are electric- or battery-powered machines that turn liquid asthma medicine into a fine mist that's inhaled into the lungs.
- The user breathes in the mist through a mouthpiece or facemask.
- It usually takes about 5 or 10 minutes to give medication by **nebulizer**, and sometimes longer.

II- Inhaler

- **Metered dose inhaler.**
- **Dry powder inhaler.**
- **Spinhaler**

A- Metered dose inhaler



- These devices **push out a pre-measured spray of medicine**. When the person squeezes the inhaler, a measured "puff" of medicine is released.
- Some MDIs **have counters that indicate how many doses remain**.
- Kids who use a metered dose inhaler also might use a spacer.



© Healthwise, Incorporated

B- Dry powder inhaler



Dry powder inhalers deliver medicine in powder form, but they don't spray out. The user must do more of the work, inhaling the powdered medicine quickly and quite forcefully. At around 5 or 6 years of age, most kids are able to do this.

Symbicort



**Budesonide & Formoterol
(Dry powder inhaler)**

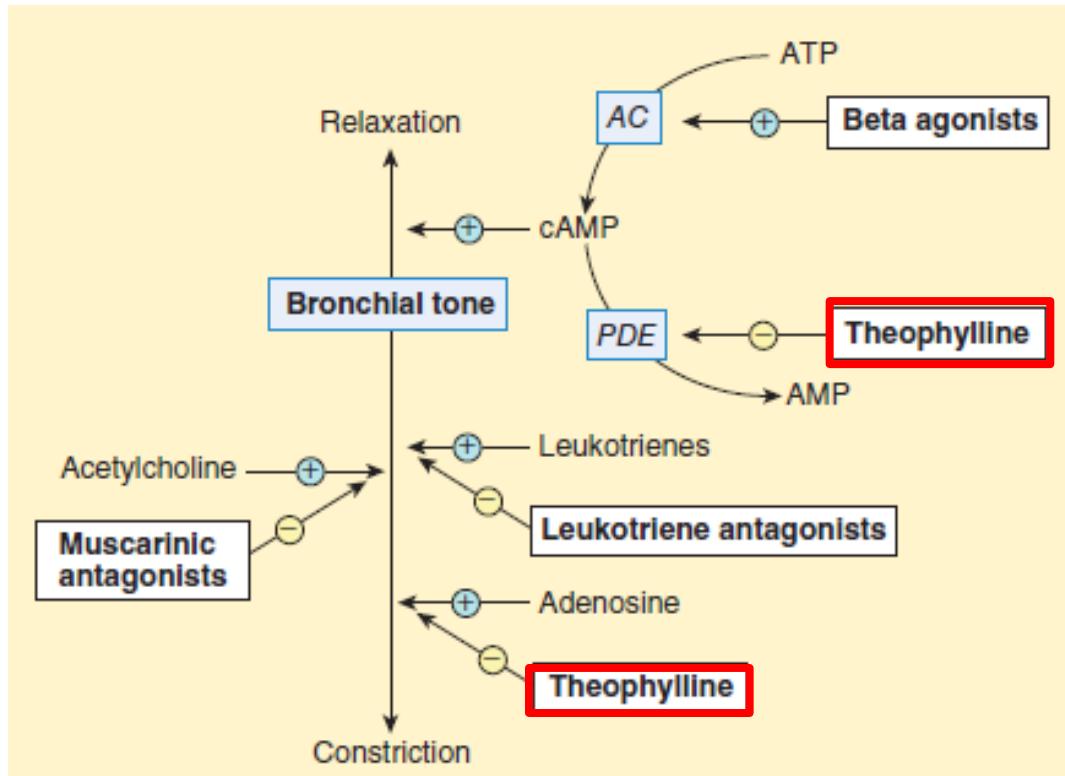
Side effects

- 
1. **Tremors** due to Stimulation of β_2 receptors on skeletal muscles.
 2. Other does-dependent effects (these are rare and **occur with high dose**) resulting from **weak activation of β_1 or β_2 - receptor** as **tachycardia**.
 3. **Tolerance** and rarely hyper-reactivity of bronchi and exacerbation of asthma.

Clinical Uses

- 
1. **Asthma:** (long-term treatment and prophylactic), or maintenance therapy (aerosol or oral tablets) or in acute attacks by nebulizers.
 2. **Chronic obstructive pulmonary disease (COPD).**

II-Theophylline & other Xanthine derivatives



Mechanism of action

Pharmacokinetics

Side effects

Clinical Uses
(Theophylline,
aminophylline)

TDM

Mechanism of action



- By **inhibition of phosphodiesterase 3 (PDE3)** and thus increasing cAMP conc. Increased cAMP reduce the tone in bronchial smooth m. and stabilizes mast cell membrane.
- **Inhibits adenosine receptors** (adenosine in asthmatics can cause bronchoconstriction).
- Anti-inflammatory effect.

Pharmacokinetics



- Theophylline is **well absorbed from the gut** and it is extensively metabolized in the liver, difference in the hepatic metabolism are the principle reason for the wide variation in kinetics both between individuals and within the same individual during the course of illness.
- **Average t_{1/2} in adult is about 8-12hr so it is given 2-3 times daily.**

Side effects



- **Tachycardia, arrhythmia and palpitation** at therapeutic doses.
- **Nausea, vomiting and diarrhea** at high therapeutic doses and **convulsions** are associated with plasma level above 30 μ g/l.

Clinical Uses

■ Theophylline

- Oral theophylline preparations are useful in **long-term treatment of asthma & reversible COPD**.
- A useful bronchodilator response can be often achieved with in the therapeutic range & the side effects can be minimized with the aid of plasma level measurements (TDM).

■ Aminophylline:

It consists of **theophylline and ethylene-diamine** in ratio of 2:1 it is used in:

1. Severe acute attacks of asthma & status asthmatics (slow i.v injection).
2. Exacerbation of **COPD**.
3. Acute left ventricular failure with pulmonary edema.

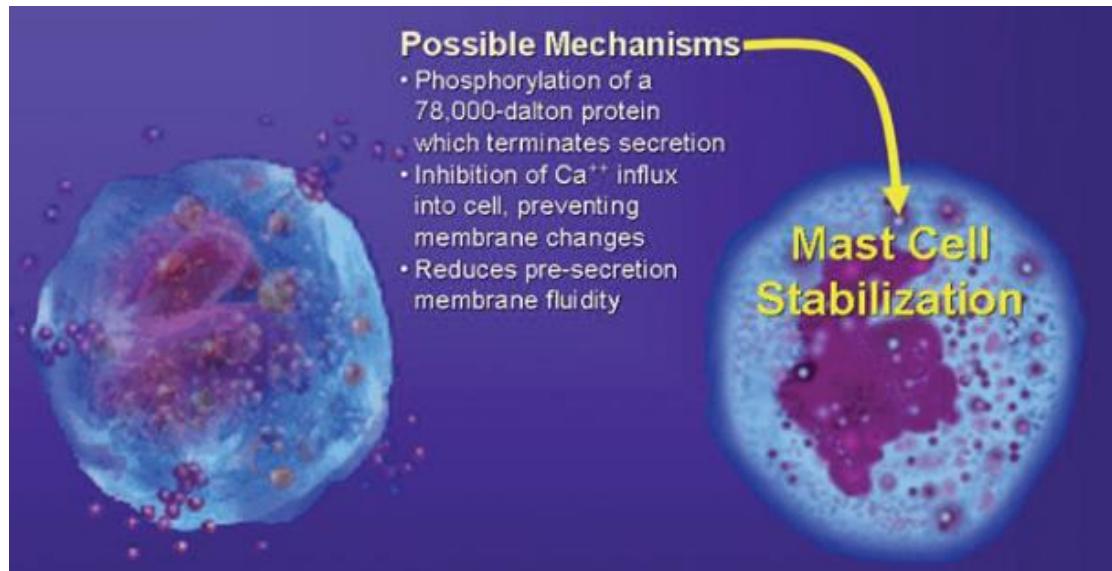
■ Roflumilast:

- Selective inhibitors of **PDE4**, has been approved by the FDA as a treatment for COPD.
- It is also acts as **adenosine receptors antagonist** (stimulation of adenosine receptors provokes contraction of isolated airway smooth muscle and histamine release from airway mast cells).

III-Anti-cholinergic drugs

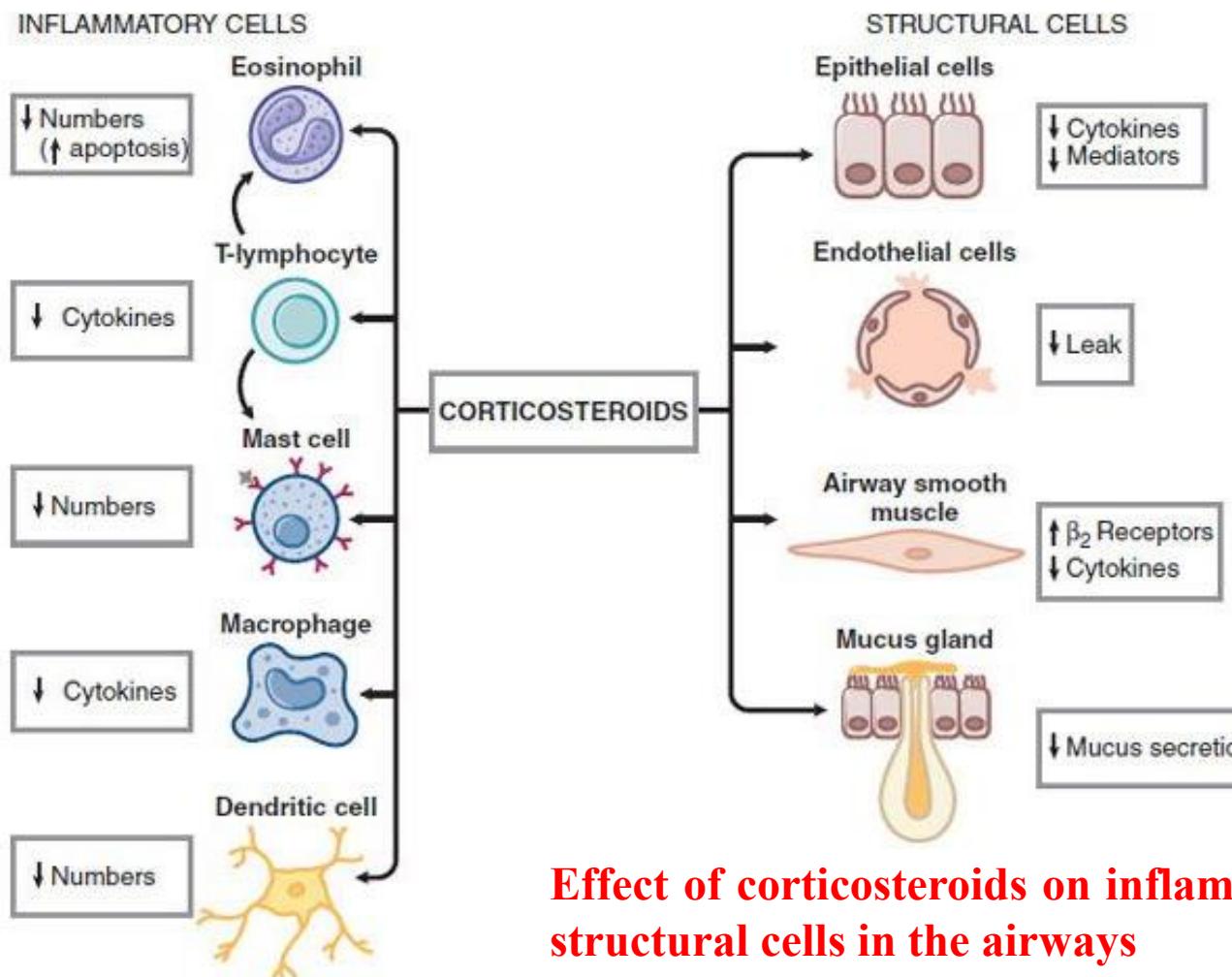
- **Ipratropium** is an analogue to atropine that **inhibits acetylcholine mediated bronchospasm**.
- The effect of ipratropium lasts for **4-6 hours**.
- The drug is given by **inhalation**, thus its action is confined to the mouth and airway; side effects are minimal.
- **Tiotropium** is another bronchoselective compound like Ipratropium, given by **inhalation, has longer duration of action (24 hours) so it is amenable to once- daily dosing**.
- **Ipratropium** is effective in **patients with COPD**. Longer acting antimuscarinic agent, **tiotropium** is approved for **maintenance therapy of COPD**.

IV- Mast cell membrane stabilizers

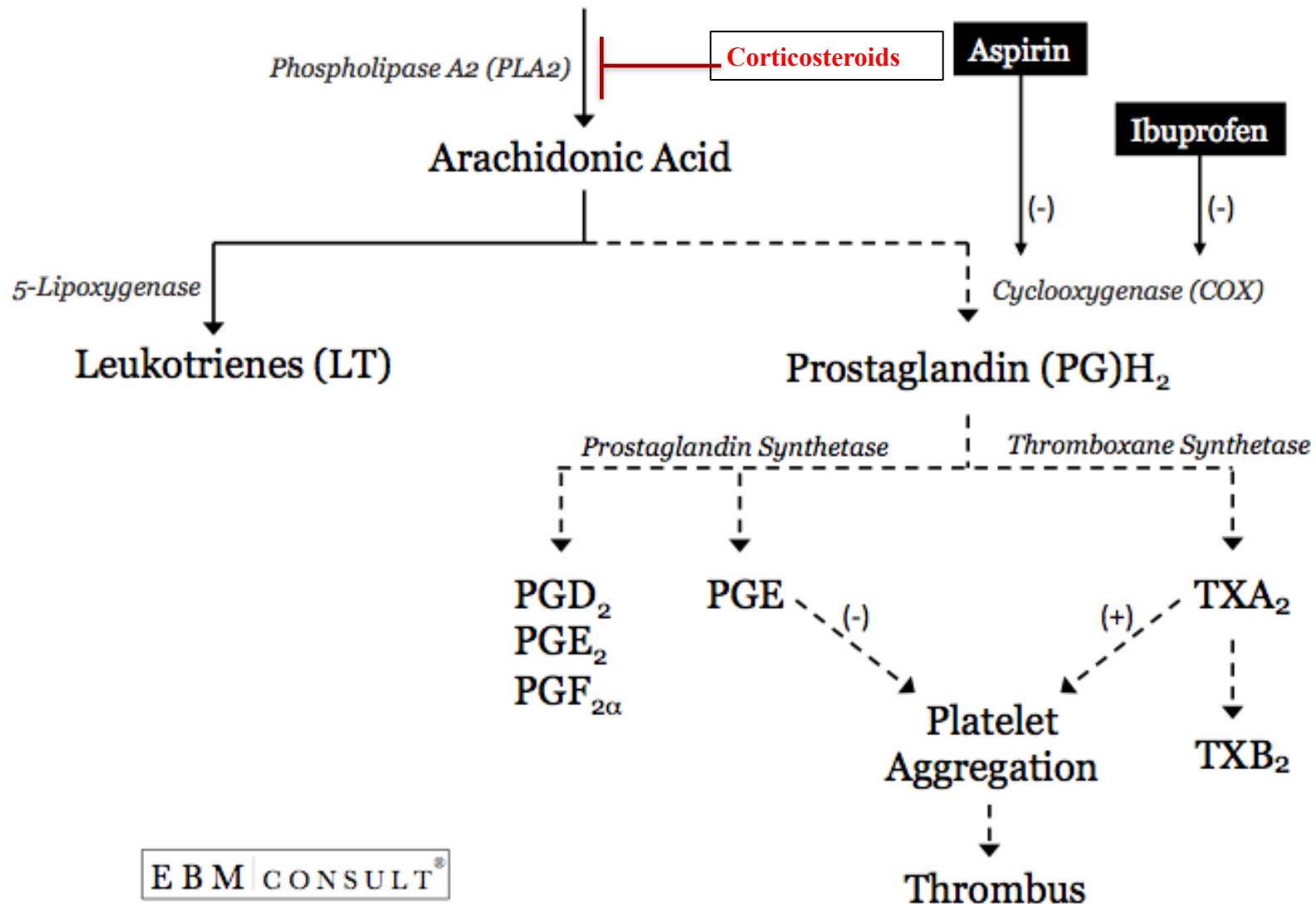


- They stabilize sensitized mast cell and inhibit the release if bronchoconstrictor agents like: histamine, serotonin & SRS-A (slow reacting substances for anaphylaxis) and leukotrienes.
- They are **not useful in managing an acute asthma attack** but only as a **prophylactic treatment**.
- Mast cell stabilizers are useful in extrinsic (Allergic) asthma particularly in **children & young adults & can prevent exercise induced asthma.**
- Na Cromoglycate is administered locally to the lung by **inhalation**.

V- Corticosteroids



Cell Membrane Phospholipid



Mechanism of action



- The actions on the bronchi is not fully understood, their effect are the result of the following action:

- A. **Anti-inflammatory:** they inhibit phospholipase A2 inhibiting the formation of arachidonic acid from mast cell membrane phospholipids with subsequent inhibition of inflammatory mediators.
- B. **Reduction of mucosal edema** and increase airflow.
- C. **Modification of immune response & stabilization of mast cells.**
- D. **Increase β_2 - receptor responsiveness** to agonist.

In the management of airway obstruction they are given by **inhalation, orally and IV** according to the condition.

Inhalational



- **Beclomethasone & fluticasone.**
 - Represents a cornerstone in the management of bronchial asthma because of the adverse effect associated with systemic steroid are minimized (systemic steroids are relatively toxic drugs).
 - Inhaled corticosteroid should replace long term oral corticosteroid therapy wherever possible (adverse effects are usually very much less than those of systemic agents but infection of pharynx & larynx with candidiasis may occur).
- **Ciclesonide:**
 - the most recently approved ICS, is a prodrug activated by bronchial esterases, and has been associated with less frequent candidiasis.

I.V corticosteroids



- **Hydrocortisone (cortisol).**

- **I.V corticosteroids:** When there is severe unresponsive asthma, especially when there is respiratory failure.
- Hydrocortisone (cortisol) is given I.V.
- There is a delay in the onset of any steroid & this occurs because the receptors of steroid are found inside cytoplasm and thus they need more time to exert their effect for this reason.

Oral corticosteroid



- **Prednisolone.**

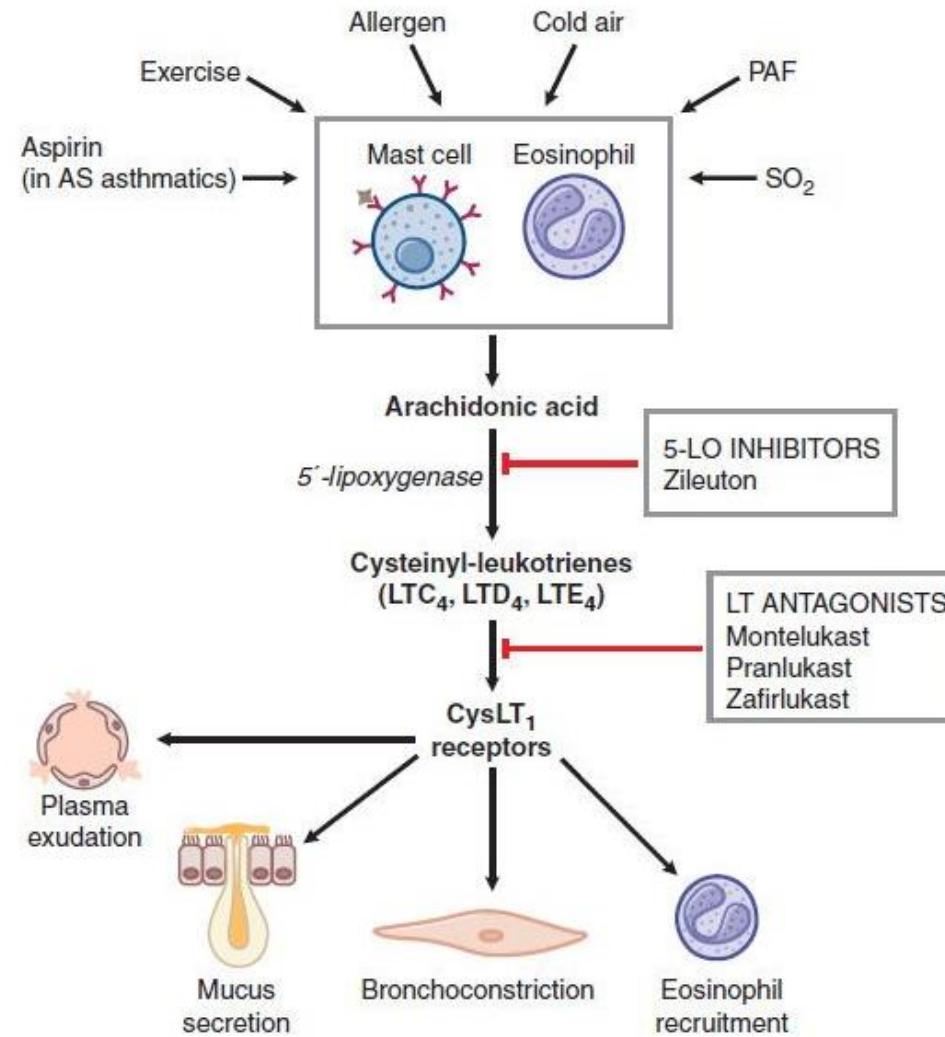
- Patients with severe exacerbation of asthma require high doses of prednisolone by mouth after I.V hydrocortisone.

Side effects



- **Oropharyngeal candidiasis**, this is easily treated with topical cotrimazole.
- **Systemic side effects**: osteoporosis, gastritis, edema, hyperglycemia, hypertension.

VI- Cysteinyl leukotriene receptor antagonist



Zafirlukast



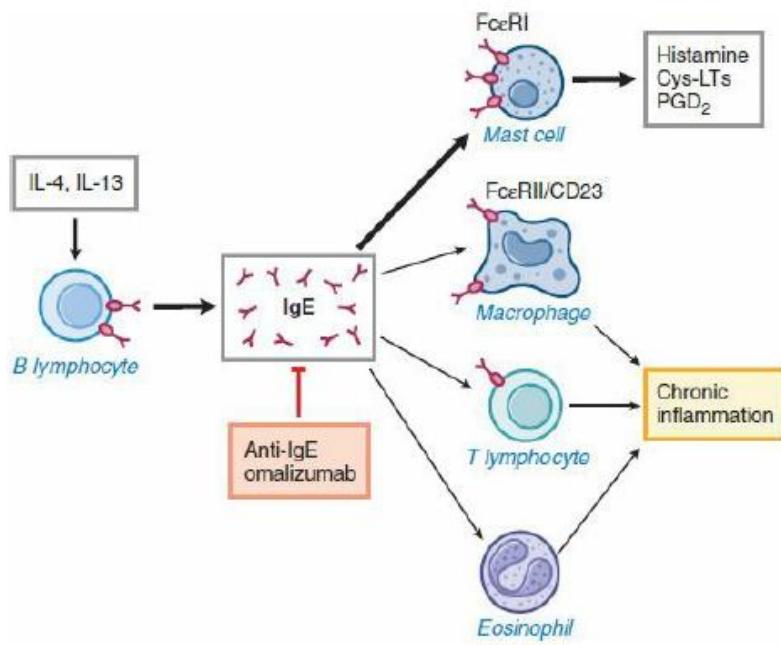
- A potent competitive **antagonist at LTD4 receptor.**
- It prevents aspirin induced asthma, antigen induced and exercise induced bronchospasm.
- It is better to be combined with β_2 receptor agonist (additive effect).

Zileuton



- **5-Lipoxygenase inhibitor** act by preventing the production of leukotrienes.
- Its hepatotoxic potential limits its use.

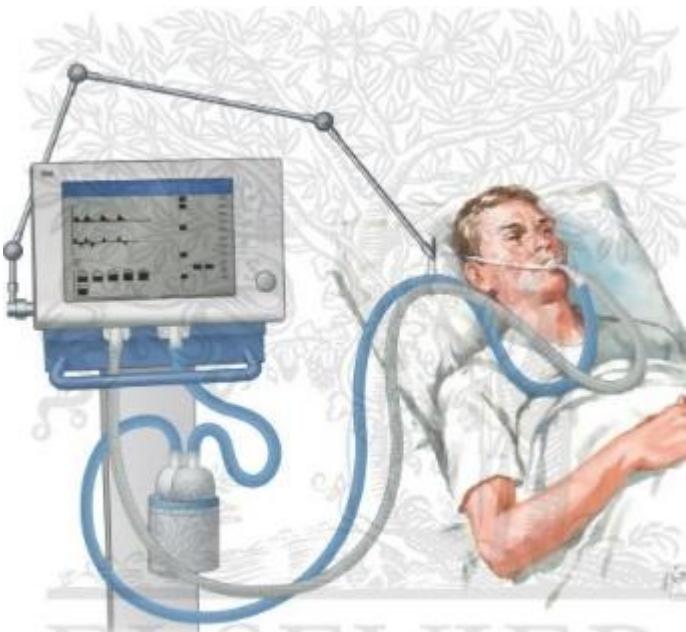
VII- (Anti-IgE Monoclonal Antibodies) (Omalizumab)



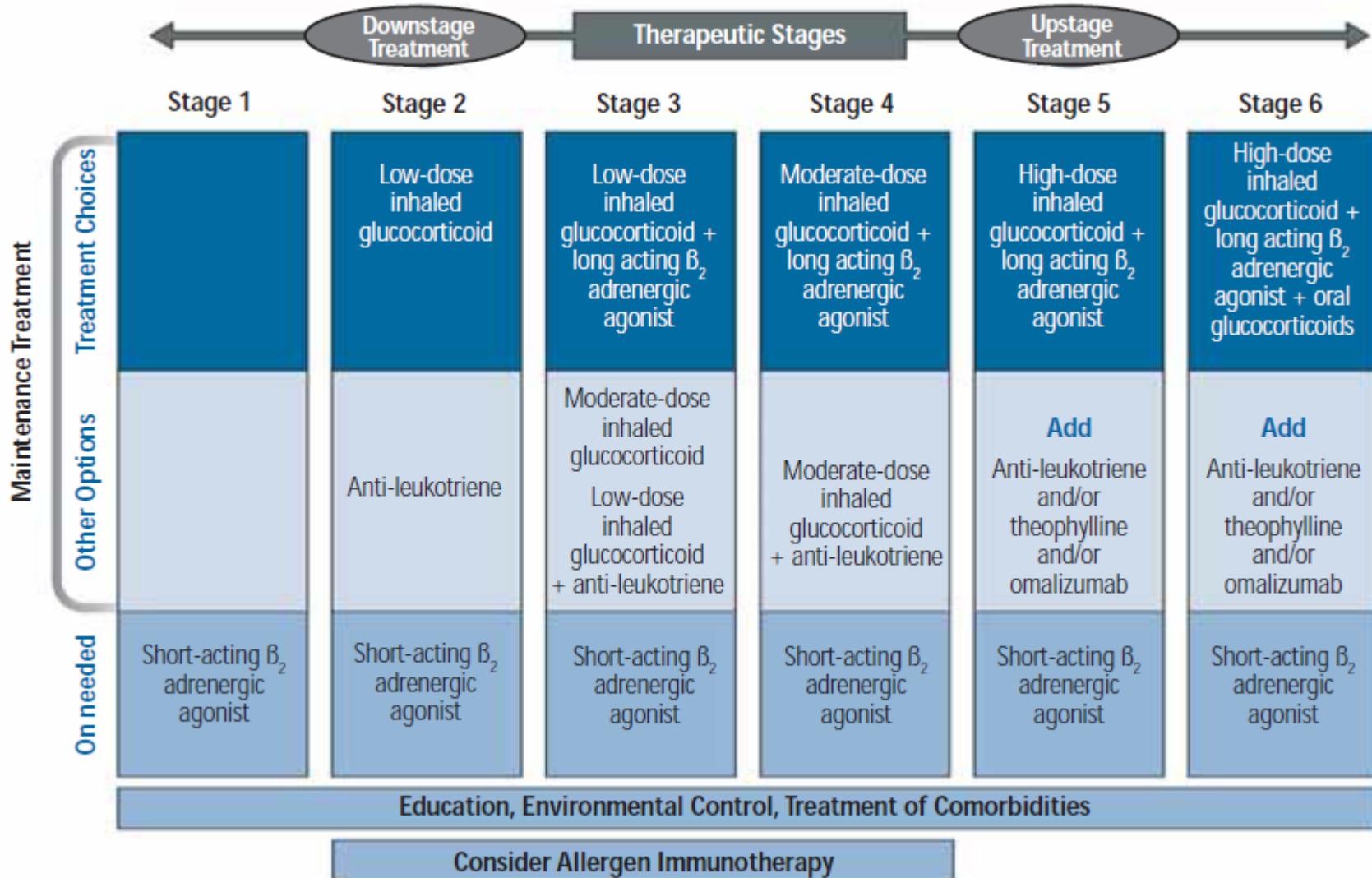
- **Omalizumab** is a recombinant humanized monoclonal antibodies that selectively **binds to the free circulating IGE** to form a complex that inhibits the binding of IGE to its receptors on mast cells and basophils. This action **prevents the release of mediators of allergic response that cause bronchospasm**.
- Omalizumab is used for treatment of patients with **moderate to severe persistent allergic asthma** in patients 12 years or older who show failure to other conventional medications.
- The drug is given **SC every 2-4 weeks** based on the patient weight and serum level of IgE as measured before treatment.

Goodman manual (2014)

Status Asthmaticus



- This is a severe prolonged asthmatic attack that is refractory to the conventional modes of therapy .
- It is a medical emergency requiring immediate management in a hospital in the respiratory care unit.
- The therapeutic regimen for such case consists of:
 - 1- Controlled flow oxygen therapy.
 - 2- IV corticosteroids.
 - 3- Inhaled or parenteral sympathomimetic.
 - 4- Antibiotics for presumed or existing airway infection.
- IV aminophylline may be added.
- If no improvements and signs of respiratory failure supervene, tracheal intubation and mechanical ventilation are necessary.



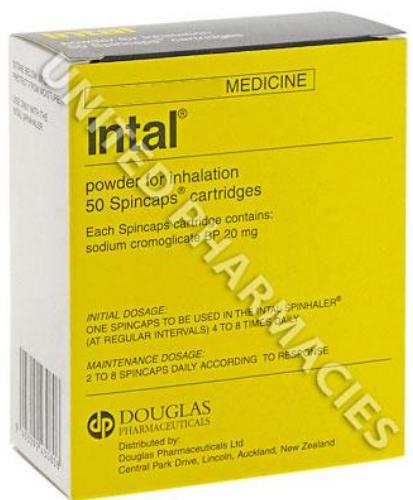
Commercially Available Drugs



B₂-adrenergic agonists



Theophylline & their derivatives



Anticholinergic Drugs

Na Cromoglycate



Cortecosteroids



Omalizumab

Leukotrienes antagonists

