



RESPIRATORY PHARMACOLOGY





- **Learning objectives**

❑ *At the end of the chapter the students will be able to learn*:

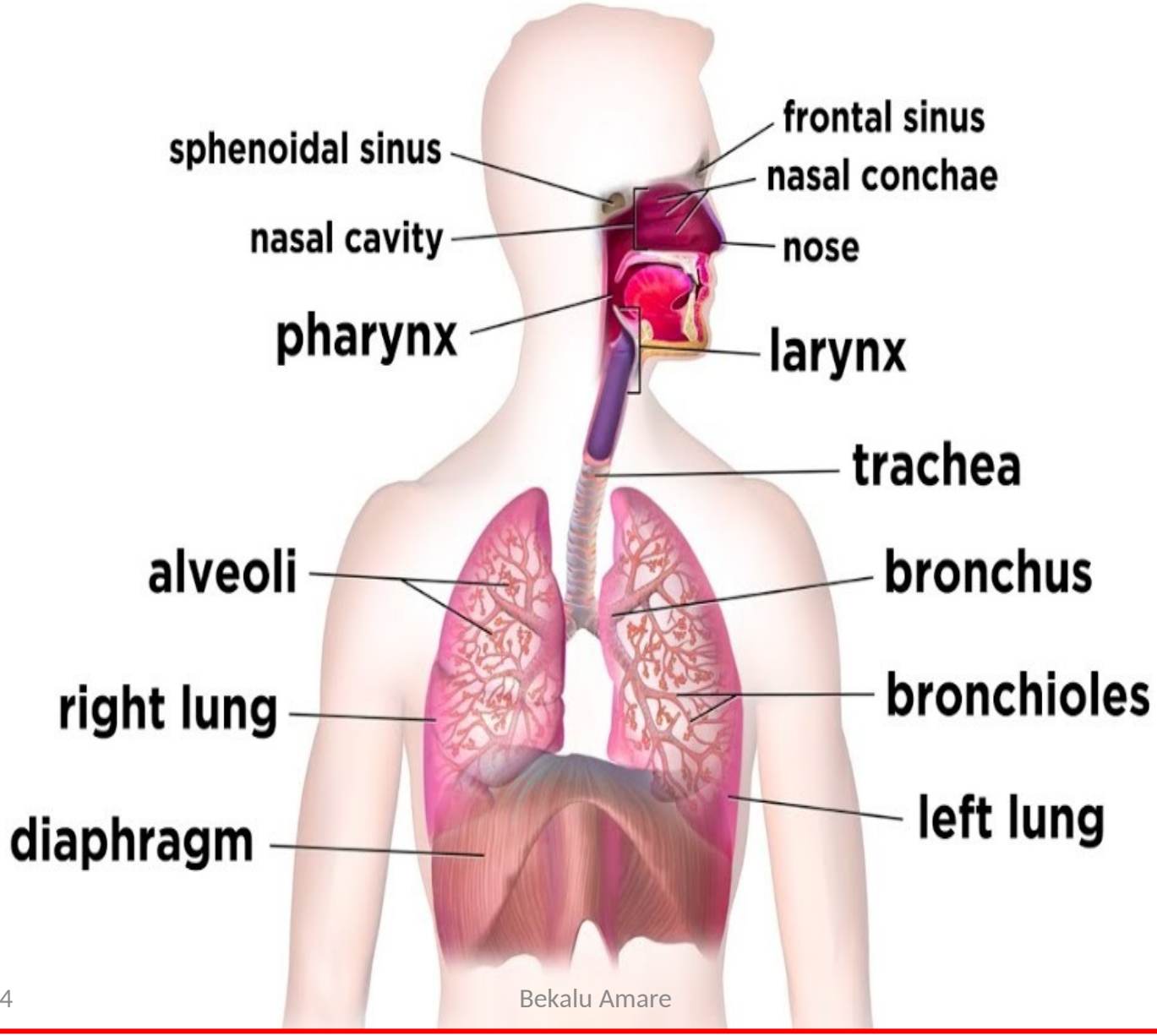
- Detail description of drug used to treat bronchial asthma, cough, nasal congestion as a result of some disorders and allergic condition.
- Broad classification of drugs used to treat bronchial asthma.
- The pharmacokinetics, mechanism of action, side effects of each group of drugs used to treat bronchial asthma, COPD.

Commonly encountered respiratory diseases

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

- Adequately controlled through a combined approach of appropriate **lifestyle changes and medication mgt**

The Respiratory System

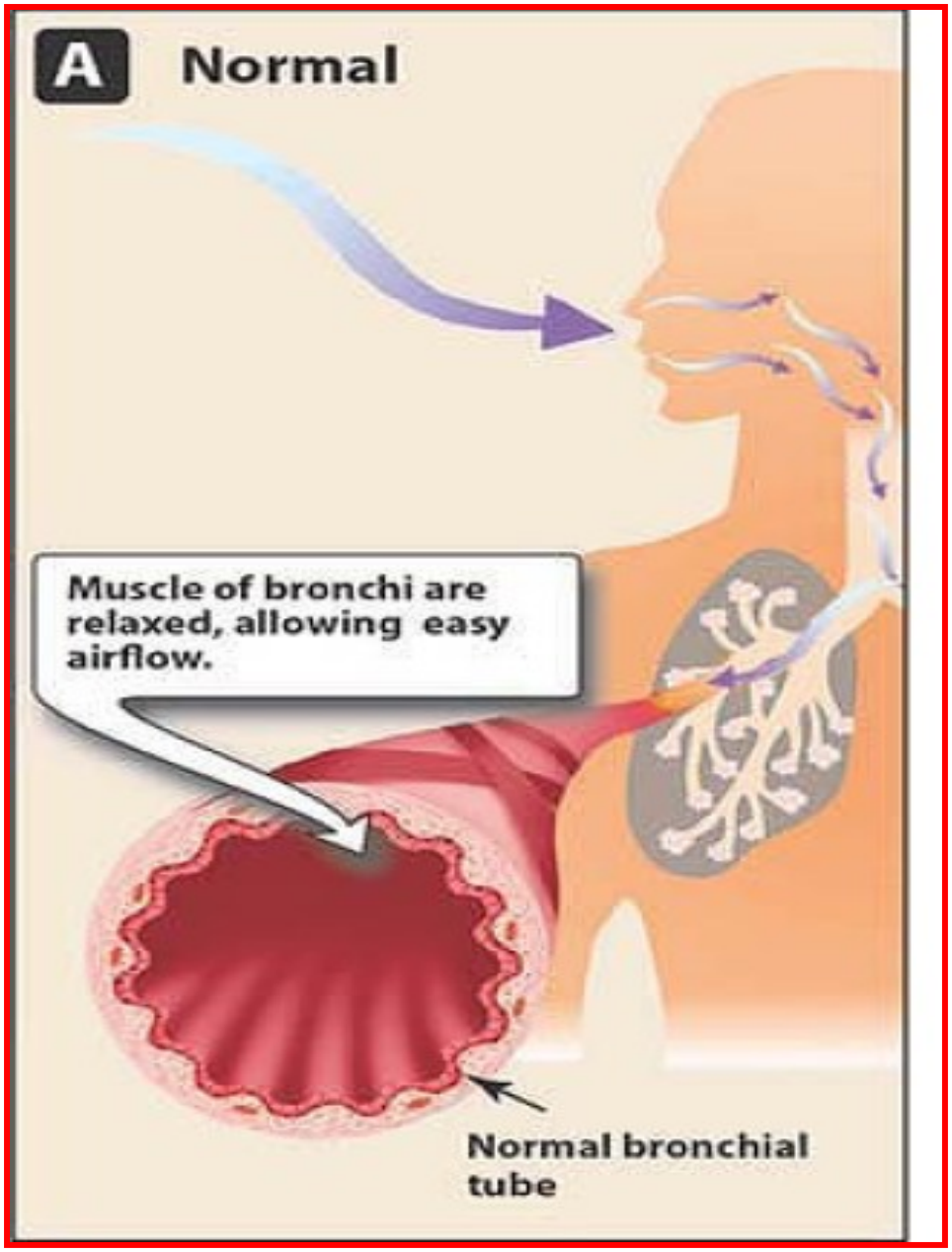


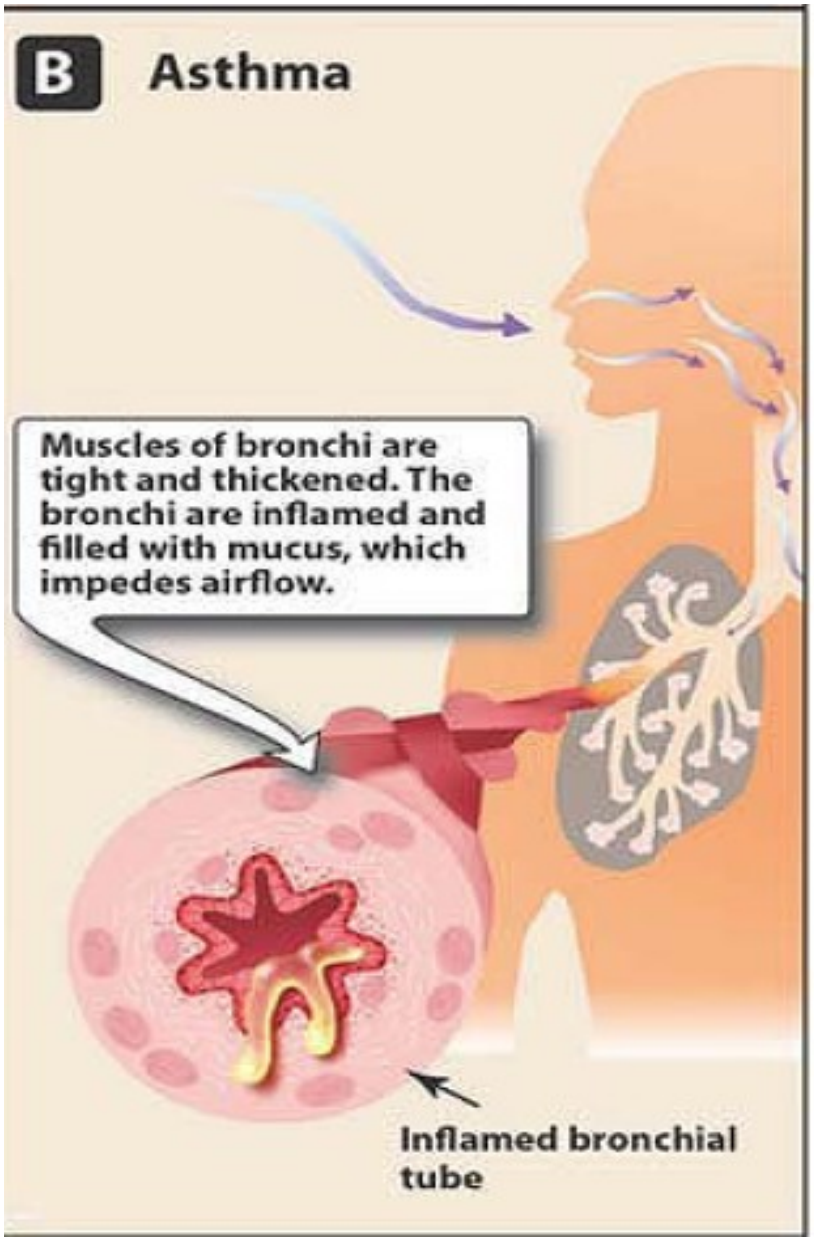
Asthma

Clinical features of asthma

- Asthma is defined as recurrent **reversible** airway obstruction, with attacks of wheeze, shortness of breath and often nocturnal cough. Severe attacks cause hypoxemia and are life-threatening.
- Essential features include:
  - airways inflammation, which causes
  - bronchial hyper-responsiveness, which in

- Narrowing of the airway in acute asthmatic attacks results from
  - Contraction of the airway smooth muscle
  - Thickening of the bronchial mucosa
    - » Edema
    - » Lymphocyte and eosinophils infiltration
    - » Hyperplasia of secretory, vascular, and smooth muscle cells
    - ❖ Most often indicates a parasitic infection, an allergic reaction or cancer


A
Normal
Muscle of bronchi are relaxed, allowing easy airflow.
Normal bronchial tube

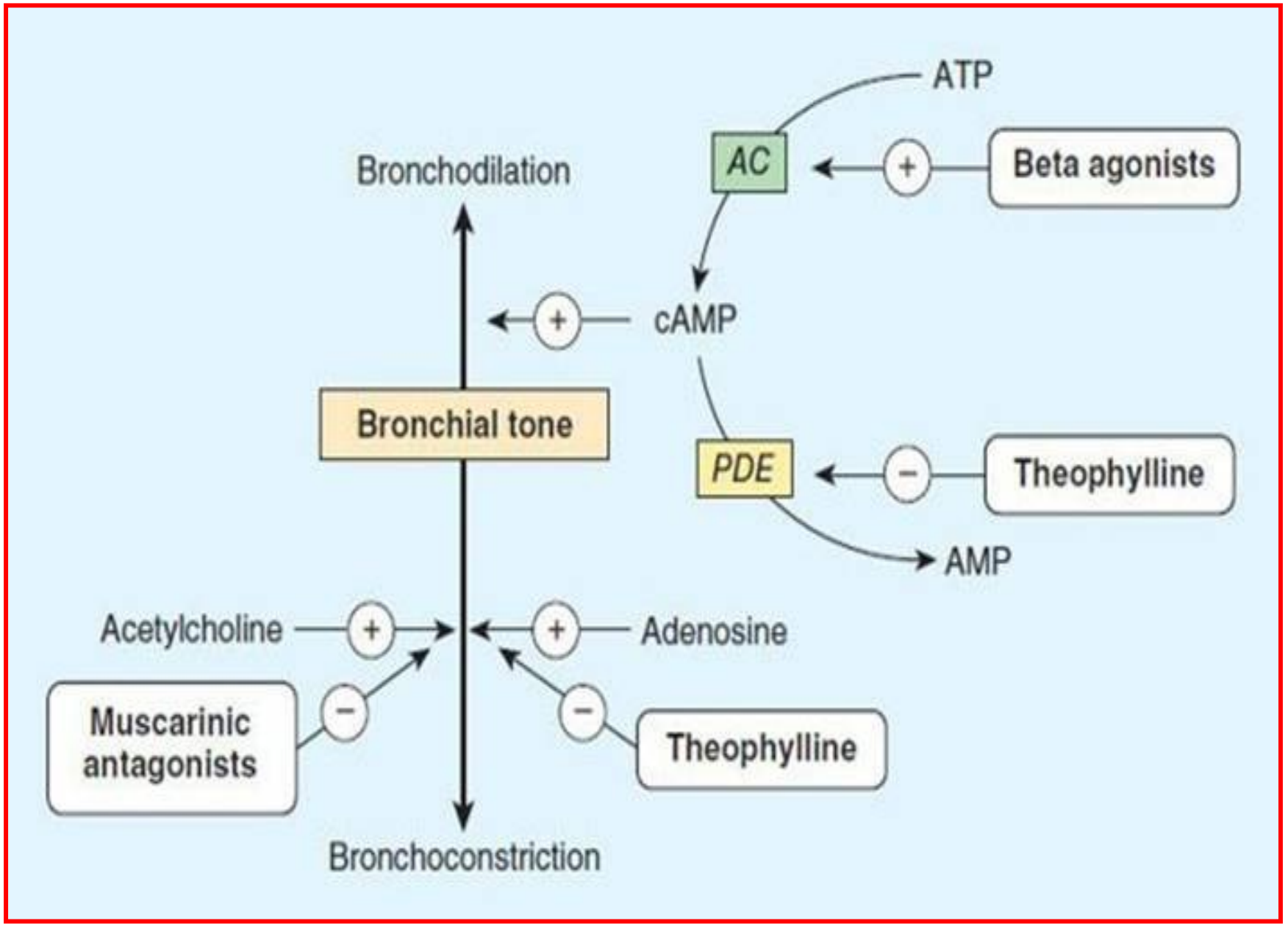

B
Asthma
Muscles of bronchi are tight and thickened. The bronchi are inflamed and filled with mucus, which impedes airflow.
Inflamed bronchial tube

Risk Factors

- Genetic
- Exercise
- Cold air
- Sulfur dioxide
- Drug induced asthma or
- allergen (proteins from house dust mites, cockroach, cat dander, molds, and pollen)

Control of bronchial smooth muscle contraction

- Bronchodilation is promoted by cAMP. Intracellular levels of cAMP can be increased by:
  - **Adrenoceptor agonists**, which increase the rate of its synthesis by adenylyl cyclase (AC);
  - **Phosphodiesterase (PDE) inhibitors** such as theophylline, which slow the rate of its degradation.
- **Muscarinic antagonists**
- **Adenosine antagonists**


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

Route of Administration

- Drugs can be delivered
  - Topically to the nasal mucosa
  - Inhaled into the lungs, or
  - Given orally or parenterally for systemic absorption

Treatment of Asthma

- Antiasthmatic drugs include:
  - ❖bronchodilators and anti-inflammatory agents

1. Bronchodilators

α) $_{L}\pi_{2}$-adrenoceptor agonists

b) Methylxanthines

c) Muscarinic antagonists

2. Corticosteroids

3. Mast cell stabilizers

4. Leukotriene modifiers

- Zileuton
- Zafirlukast, Montelukast

Bronchodilators

Beta$_2$ adrenoreceptor agonists

- ***MOA***
  - Activation of B_2 – Receptors ≡ ↑ cAMP ≡ bronchial smooth muscle relaxation
  - Inhibits the function of numerous **inflammatory cells**
    - »Mast cells, basophils, eosinophils, neutrophils, and lymphocytes

1.Short acting B_2 agonists

- **Salbutamol, Terbutaline, Pirbuterol. Metaproterenol**



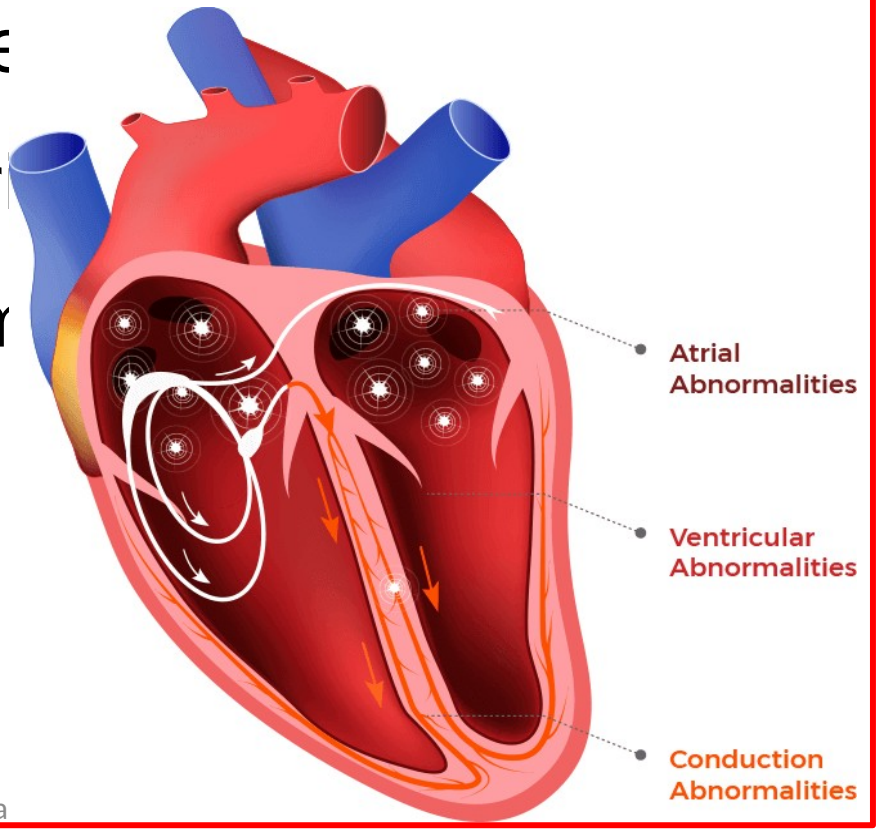
- Onset of action within 5 minutes a
  inhalation
- Duration of action spans 2-6 hrs
- Available in Metered-dose inhalers and nebulized aerosols
- **Rapid symptomatic relief** of dyspnea associated with asthmatic attack

2. Long- acting B_2- agonists

- **Salmeterol & Formoterol**
- Long duration of action (> 12 hours)
- Used for maintenance Rx of asthma
  - » Taken Regularly
- **Agent of choice for nocturnal asthma**
- To significantly inhibit the inflammation a **combination** with steroids is recommended
  - **Salmeterol and fluticasone**
  - **Formoterol and budesonide**

Adverse Effects of B_2- agonists

- Inhalational use → adverse effects are uncommon
- Oral & parentral use
  - –if dosage is exce
    - » angina pector
    - » tachyarrhythm
    - » Tremor





Non B_2 specific bronchodilators

- **Epinephrine (Adrenaline)**
  - **Effective and rapidly acting bronchodilator (sc or inhalation)**
  - Peak bronchodilation is achieved 15 minutes after inhalation and lasts 60-90 minutes
  - Its use in asthma has been displaced by selective agents
    - **Reserved to treat acute vasodilation, shock and bronchospasm of anaphylaxis**

Non B_2 specific bronchodilators…

- **Ephedrine**
  - Mixed-acting sympathomimetic drug
  - Ephedrine is now used infrequently to treat asthma
  - **As compared to epinephrine**
    - ✓ **Ephedrine** has a longer duration, oral activity, more pronounced central effect, much lower potency
- **Isoproterenol**
  - Very potent bronchodilator; when inhaled, maximal effect with in 5 minutes, has 60-90 minute duration of action
  - It is now rarely used

Methylxanthines

Used only when other drugs such as beta 2 specific agents are ineffective.

- **Theophylline, Caffeine,Theobromine**
- **Theophylline**
  - *MOA*
    - a) By inhibiting PDE ⟹ ↑cAMP ⟹ bronchodilation
      - ↓ **Release of inflammatory diators**



ition of cell surface receptors for sine

Treatment of asthma

- **Pharmacological Effects**
  - Prominent actions are:
    - Bronchodilator
    - CNS stimulation
    - Other actions include
      - Cardiac stimulation (↑ catecholamine release)
      - Vasodilation (except cerebral blood vessels)
      - GIT - ᨒ gastric acid & digestive enzymes
      - Diuresis

- **Therapeutic uses**
  - Relieve airway obstruction in **acute asthmatic attack**
  - Add-on therapy
  - **noctural asthma** (b/c of prolonged effects)
  - IV theophylline (**Aminophylline**) is employed in emergencies.
- **Toxicity**
- **has a narrow therapeutic window**:
  - Most likely at plasma levels > 40mg/L
    - » **Ventricular arrhythmia**

Drug Interactions

- ✓ Drugs that ↓ theophylline levels
  - Phenobarbitone, Phenytoin, carbamazepine,rifampicin
- ✓ Drugs that ↑ theophylline levels
  - Cimetidine , erythromycin, ketoconazole

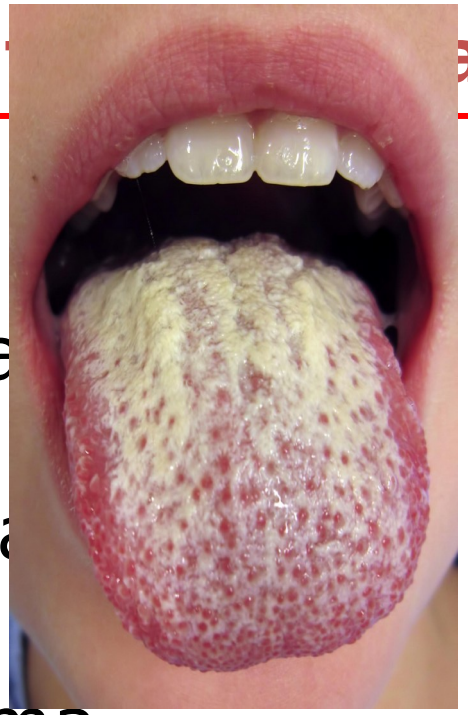
Anticholinergic Agents

- **Ipratropium bromide, tiotropium**
- Available for inhalational administration
- **M_3 receptor antagonism** is responsible for the bronchodilation
- Slow and low intensity bronchodilation
- **Combined use with β_2-agonist provides better outcomes**
- Tiotropium has long duration of action (24 hrs duration)
  - ✓Improve functional capacity of pts with COPD
  - =/Most common side effect is dry mouth

Corticosteroids

- The most effective drugs available for **long term control**
- ***MoA:*** Act primarily by suppressing:-
  - » Synthesis & release and activation of inflammatory mediators
  - » Edema of the air way mucosa (2° to ↓vascular permeability)
  - » Reduces bronchial hyperreactivity
  - ➢ ↑number of B_2 adrenoceptors ↓↑ responsiveness to agonist

Treatmen a



Rout of therapy:

1) **Inhalational therapy**
   - Considered 1st line thera
   - Low risk
   - Should be used with B_2- a
2) **Oral therapy**
   - For pts with severe asthma
   - Duration should **be as short as possible** (toxicity)
3) **Injectable**

Adverse Effects:

a) Inhalational

- ✓ Oropharyngeal candidiasis
- ✓ Dysphonia

Treatment of asthma

b) **Oral**

- Used for > 15 days can be hazardous =systemic toxicity
  - Osteoporosis
  - Hyperglycemia
  - PUD
  - Adrenal suppression
  - Suppression of growth in children

C) **Parenteral**

- **Systemic toxicity**

Severe acute asthma (status Asthmaticus)



- Medical emergency
- Hospitalization
- Treatment includes **oxygen**
- Inhalation of **salbutamol** given by nebulizer
- Intravenous Hydrocortisone/**salbutamol** or **aminophylline**, and
- **Antibiotics** (if bacterial infection is present)

Mast cell stabilizers

- **Cromolyn Sodium, nedocromil**
  - **Very safe & effective for prophylaxis of asthma**
  - Administered by inhalation
  - **MoA**
    - ✓ Acts by stabilizing the cytoplasmic membrane ⟹ ↓ release of mediators
    - ✓ Inhibits activation of other inflammatory cells
    - ✓ Chronic administration ⟹ ↓ Inflammation & bronchial hyperreactivity

- **Therapeutic uses:**
  - » Asthma (long term controller)
  - » Exercise, unavoidable allergen exposure induced asthma (prophylaxis)
  - » Allergic rhinitis
- **Adverse effects**
  - ✓Throat irritation, cough and mouth dryness, and rarely chest tightness and wheezing

Leukotriene Antagonists

- Leukotrienes are mediators released from mast cells upon contact with allergens.
- Contribute powerfully to both inflammation and bronchoconstriction
- Can either block the synthesis of leukotrienes or block their receptors.
- **Zileuton** is the prototype of those that block the **synthesis** of leukotrienes
- **Zafirlukast** is the prototype of those that block their **receptors**

ONIC OBSTRUCTIVE PULMONARY DISEASE (CO

Cigarette smoking is the main cause

- **Clinical features.** morning cough during the winter, often initiated by a cold. There is progressive breathlessness, airflow obstruction
- **Pathogenesis.** There is small airways fibrosis, resulting in **Irreversible obstruction**, and/or destruction of alveoli and of elastin fibers in the lung parenchyma.

- **Principles of treatment.**
- **Stopping smoking**,
  - Short- and long-acting inhaled bronchodilators (**ipratropium, salbutamol**)
  - Long-term **oxygen** therapy
  - Broad-spectrum antibiotics (e.g. **cefuroxime**)
  - glucocorticoid (intravenous

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

Management

- ✓ Oral antihistamines (loratadine, cetirizine)
- ✓ Decongestants (Xylometazoline, 2 - 3 drops).
- ✓ Corticosteroids (Beclomethasone) and
- ✓ Cromolyn can also be used

Cough: - is protective reflex mechanism that removes foreign material and secretions from the bronchi and bronchioles

- It can be inappropriately stimulated by inflammation in the respiratory system

Drugs to treat Cough

1. Expectorants

- Thin the mucus that blocks the air tubes, lubricate the irritated respiratory tract, intended to increase the **productivity of cough**

- Reduce mucus viscosity facilitating its removal by coughing

E.g Guaifenesin

2. Mucolytics*:* make mucus more watery and easier to cough up

E.g Acetylcysteine

3. Antitussives

- Act in the brain stem, depressing cough center
- Used only for **dry** (**unproductive**) cough
- Can cause harmful sputum thickening and retention
- Should not be used for the cough associated with asthma

Drugs

- **Dextromethorphan,**
- **Codeine,**
- **hydrocodone,**
- **hydromorphone**