

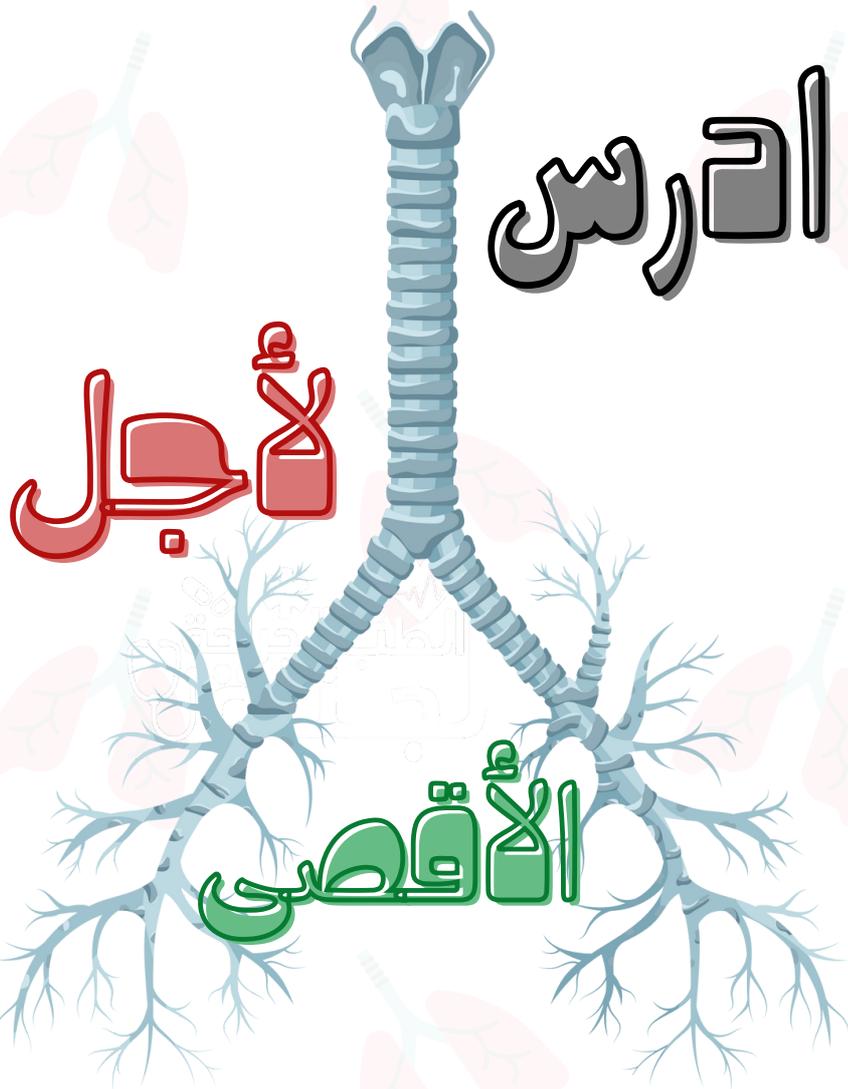
# PHARMACOLOGY SHEETS

## RS MODULE

Doctors 2021 - رّوح - Medicine - Mu

### DRUG THERAPY FOR BRONCHIAL ASTHMA

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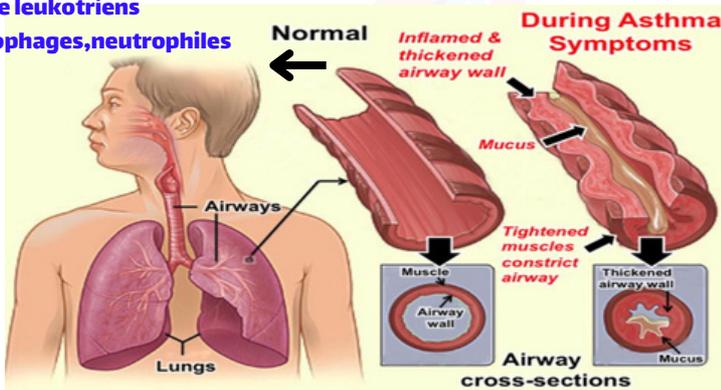
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# Bronchial Asthma

- **Inflammatory disease** characterized by **reversible** (irreversible bronchial construction --> chronic obstructive lung disease as acute bronchial emphysema) **airway obstruction** due to **bronchoconstriction, mucosal edema, cellular infiltration, and viscid secretions**
- Manifested clinically by **paroxysms** of dyspnea, cough and wheezes

Secrete leukotriens  
,macrophages,neutrophiles

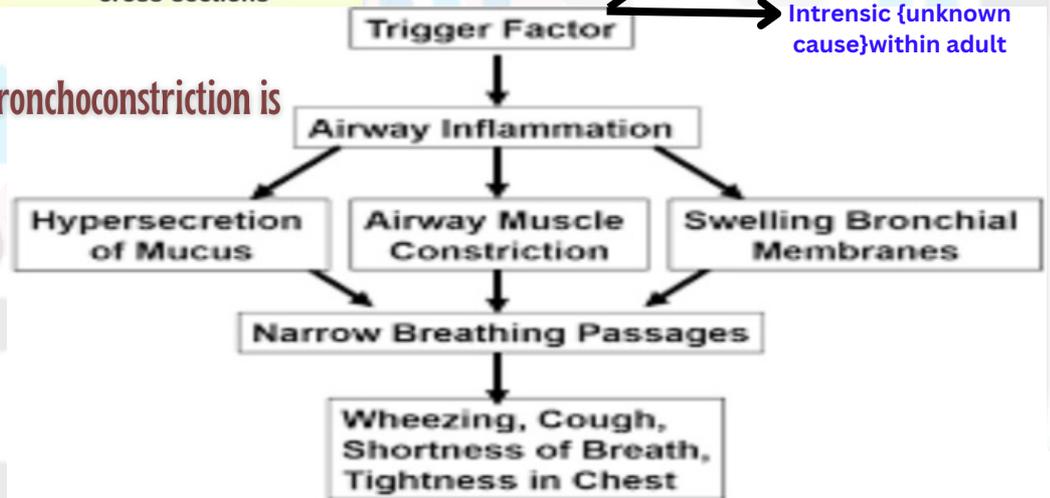


Extinsic ;common within children like allergy and its easier than intrinsic

Intrinsic {unknown cause}within adult

main mediator that cause bronchoconstriction is

LTs



## Drug therapy for bronchial asthma

### 1- Bronchodilators

- B2 agonist (بتشتغل مباشرة على Rec)
- Anticholinergics
- Methylxanthines.

### 2- Anti-inflammatory drugs (mostly as prophylaxis)

- Corticosteroids (the mostly powerful)
- Mast cell stabilizers
- Omalizumab
- Leukotriene antagonists

### 3- Supportive treatment

- Mucolytics & expectorants inhalation
- Antimicrobials
- Oxygen

# Bronchodilators

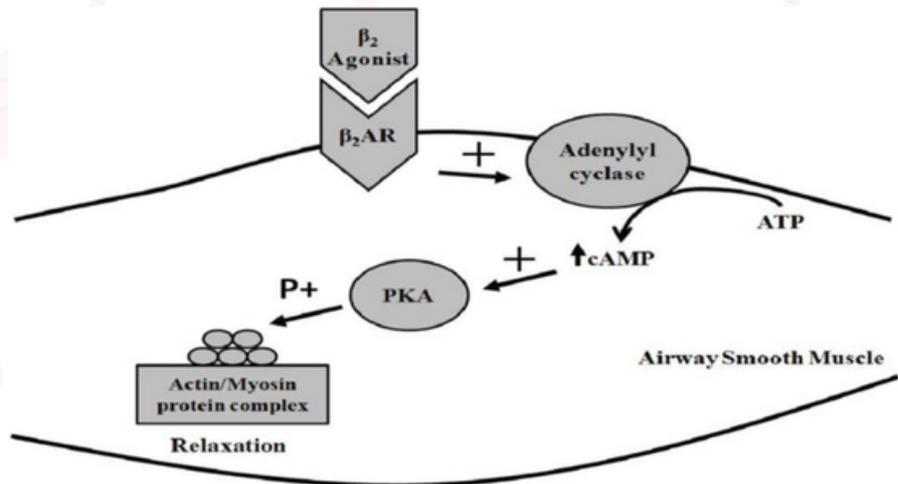
## 1- $\beta_2$ agonists (used as a V.D) bind with G-coupled Rec

A. Non-selective  $\beta$ -agonists ( $\beta_1, \beta_2$ ): Adrenaline ( used only in bronchial asthma due to anaphylactic shock but it can cause a tachycardia and arrhythmia)

Selective  $\beta_2$  agonists:

- **Short-acting:** salbutamol, terbutaline (4-6 H) so we give it in acute attack (need 5 to 15 minutes to work)
- **Long acting:** salmeterol and formoterol (12 H) as a prophylaxis between the attacks

Activation of PKA by cyclic AMP depletes intracellular calcium stores and reduces calcium availability for vasoconstriction.



• Selective  $\beta_2$  agonists replaced non-selective  $\beta$  agonists as they lack their side effects e.g. palpitation, tachycardia and arrhythmias

1) Salbutamol: Short acting beta2 agonist (SABA) Farcolin acts as salbutamol

we use it instead of adrenaline to avoid the side effects of adrenaline

▪ Selective stimulant of  $\beta_2$  adrenergic receptors ▪ Selective action on the bronchi

▪ Given orally & by inhalation (saline we add 5 drops in a nebulizer)

2) Terbutaline: Short acting beta2 agonist (SABA)

▪ Like salbutamol but has a delayed onset of action

3) Salmeterol & Formoterol: long acting beta2 agonist (LABA)

▪ Selective long-acting  $\beta_2$  agonists

▪ Given by inhalation for long-term prevention of bronchial asthma

▪ Should be combined with inhaled corticosteroids to avoid tolerance



## Adverse effects:

- Tremors
- Tachycardia: Arrhythmia may occur in patients with underlying cardiac diseases eg, ischemic heart disease
- Tolerance (that's why i give cortisone , making the receptor more sensitive )
- Hypokalemia (should take K<sup>+</sup> in food)

**Note:** Adverse effects occur more frequently with oral preparations than with inhalation

**Note:** Nebulizers (by deep inspiration) provide more quantity of the drug than MDIs, so nebulized  $\beta_2$  agonists can cause more adverse effects

## 2- Methylxanthines (Aminophylline & Theophylline)

### Mechanism of action:

- PDE inhibitors → cAMP which causes redistribution of intracellular Ca<sup>2+</sup> → bronchodilatation
- Block adenosine receptors (like caffeine) → bronchodilatation
- Improve diaphragmatic contraction & ventilatory response to hypoxia
- mediators release from mast cell.



### Pharmacokinetics:

- Theophylline is absorbed by all routes
- Distributed all over the body & passes BBB and placental barrier
- Metabolized in liver (by xanthine oxidase) into soluble methyluric acid (not precipitated in the joints → not contraindicated in gout)
- Narrow therapeutic window with low safety

## Pharmacological actions:

- **Relaxation of the smooth muscle** (bronchial, intestinal, biliary, ureteric and vascular smooth muscles "except cerebral blood vessels" → vasodilatation and hypotension)

- **CVS: Direct: positive inotropic & chronotropic effects - VD (hypotension)**

**Central: stimulation of CIC (bradycardia) & VMC (hypertension)**

- **Large & rapid IV injection → hypotension & arrhythmia.**

## Precautions:

- **Monitoring of plasma level (to avoid toxicity)**

- **Slow IV administration to avoid hypotension & arrhythmia.**

## Note: Roflumilast:

- **Selective PDE-4 inhibitor** → selective action on airways & inflammatory cells → fewer adverse effects than methylxanthines

- **Approved for treatment of COPD (chronic obstructive disease)**

## 3- Muscarinic (M) Antagonists

**Not use alone ,we should use it with B2 agonist**

**\*Active as passive bronchodilators**

- **Atropine (tertiary amine) blocks bronchial M receptors, but it is not effective in bronchial asthma because:**

**1. Cholinergic pathways play a minor role in pathogenesis of bronchial asthma**

**2. Non-selective effects:**

- **Dryness of bronchial secretions** ▪ **↓ Muco-ciliary function**

- **Ipratropium bromide:**

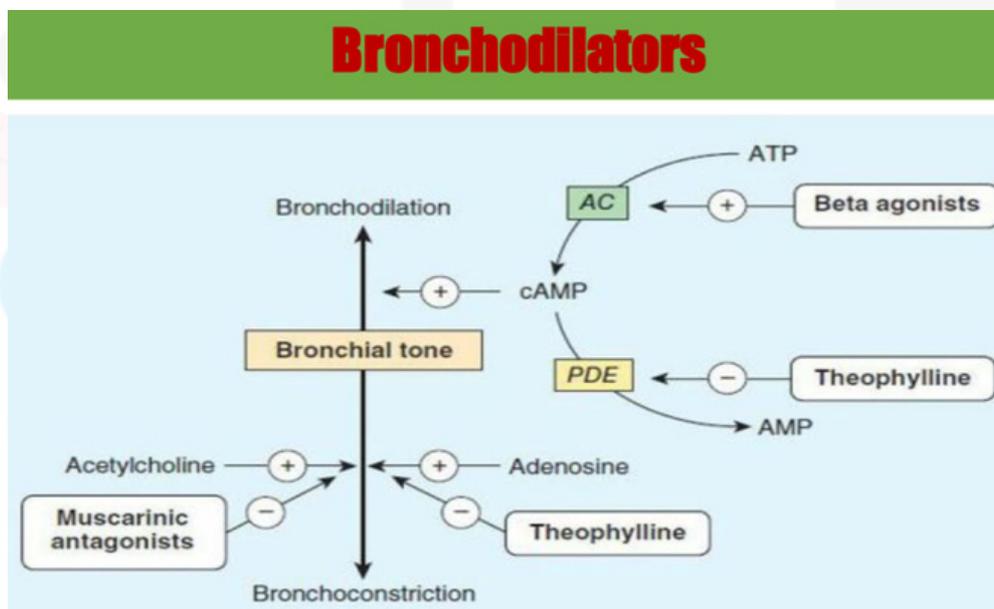
✓ **Quaternary ammonium derivative of atropine**

✓ **Minimal amounts are absorbed → no systemic adverse effects**

✓ **More selective (causes bronchodilation without effects on sputum viscosity or ciliary function)**



- ✓ **No central effects**
- ✓ **Given by inhalation & can be combined with  $\beta_2$  agonists**
- ✓ **Short-acting** → used 3-4 times daily
  - **Tiotropium**: differs from ipratropium in the following:
    - ✓ **Long-acting** (given once/day)
    - ✓ **Given by inhalation**
    - ✓ **Approved for treatment of COPD with no cardiac adverse effects.**



## Anti-Inflammatory Drugs

### 1- Corticosteroids

- ✓ **↑ Synthesis of lipocortin** → **↓ PLA2 activity** → **↓ arachidonic acid, PGs and LTs synthesis**
- ✓ **Immunosuppressive action** (↓ antibody synthesis) & **inhibition of Ag/Ab reaction & mast cell stabilization**
- ✓ **↓ Capillary permeability & reduce mucosal edema**
- ✓ **↑ Catecholamines effect through:**
  - **Block neuronal reuptake**
  - **↑ Methylation of noradrenaline to adrenaline**



## Uses in bronchial asthma:

✓ **Prophylaxis (in between attacks)** ✓ **Repeated nocturnal (at night) asthma**

✓ **Acute severe asthma**

## Preparations:

**A. Inhalation:** beclomethasone, **budesonide**, fluticasone (long-acting)

**B. Parenteral:** **methyl prednisolone (IV)**, **hydrocortisone**, **dexamethsone**, ACTH

**C. Oral:** prednisolone

## Adverse effects:

**\*\*corticosteroids contraindicated in children because it inhibits growth**

### A. Inhalation:

✓ **Oral moniliasis (treated by nystatin) by candida**

✓ **Dysphonia due to weakness (myopathy) of adductor muscle of the cord**

**B. Suppressive effects:** adrenocortical suppression

**C. Cushing's syndrome (with the use of large doses of corticosteroids)**

**D. Metabolic:** hypokalemia, hyperglycemia, salt & water retention, weight gain and hypertension

### E. Cataract

## 2- Leukotriene Antagonists **Good choice for children instead of corticosteroid**

▪ **They include:**

**1. LT receptor antagonists (Montelukast & zafirlukast)**

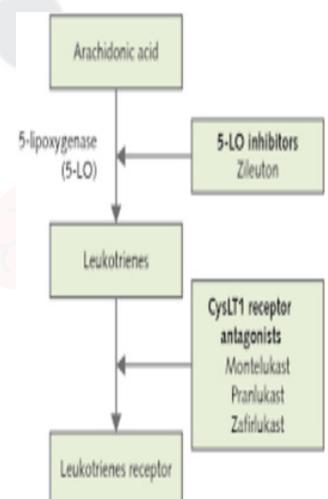
**2. 5-LOX inhibitors (zileuton):** ↓LTs synthesis

▪ **Pharmacokinetics:**

✓ **All members are given orally**

✓ **Zafirlukast absorption is affected by food so taken before meals**

✓ **They are metabolized by liver**



## ▪ Uses:

✓ prophylaxis of bronchial asthma especially aspirin-induced asthma because COX is inhibited therefore the entire pathway is toward LTs.

## ▪ Adverse effects:

### ✓ Liver toxicity:

❖ Regular monitoring of liver transaminases is required if their levels exceeded 3-5 times the normal level, these drugs should be discontinued

❖ More reported with zileuton

✓ Systemic vasculitis (Churg-Strauss syndrome): rare



## 3- Mast cell stabilizers

### Members:

1. Disodium cromoglycate (Cromolyn sodium)

2. Ketotifen

✓ They are not bronchodilators

✓ So, they cannot relieve acute attacks of asthma

✓ They can be effective only if given before the exposure the antigen

✓ Mechanism: stabilization of mast cell membrane (possibly by blocking calcium influx) →. release of allergic mediators eg, histamine & LTs.

✓ They are useful chiefly for asthma prophylaxis, particularly children & young adults

✓ Ketotifen has additional antihistamine effect

### ✓ Route:

▪ Disodium cromoglycate: inhalation

❖ It is also available as nasal spray for allergic rhinitis & as eye drops for allergic conjunctivitis

▪ Ketotifen: oral administration

### ✓ Adverse effects:

▪ Disodium cromoglycate:

❖ Local irritation: bronchospasm & cough

▪ Ketotifen:

❖ Drowsiness



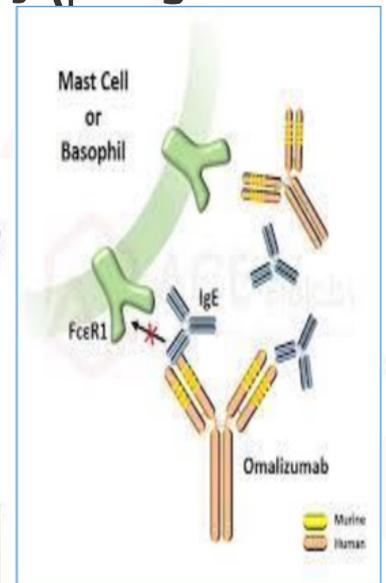
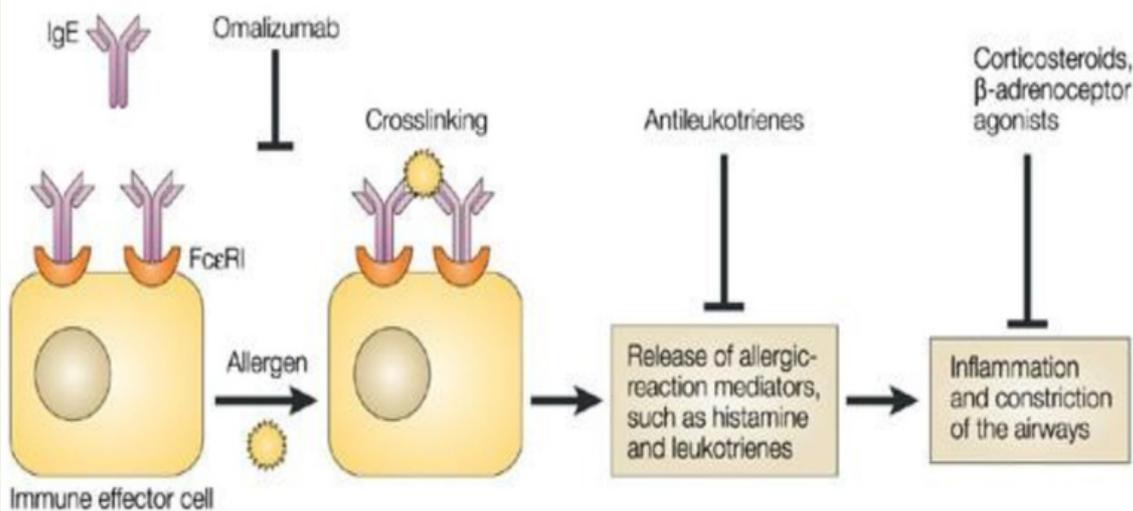
## 4-Omalizumab (very expensive drug)

✓ Selectively binds to human IGE → inhibits IGE binding to its receptor on mast cells & basophils surface →. ↓ release of inflammatory mediators. **Therefore, it is appropriate only for extrinsic asthma.**

✓ It decreases severity and frequency of asthma exacerbations

✓ Used in patients resistant to conventional therapy ( $\beta$ 2 agonists & inhaled corticosteroids)

✓ Its use is limited by its high cost



Nature Reviews | Drug Discovery

## Bronchial Asthma Prophylaxis

✓ Control of predisposing factors

✓ Desensitization of the triggering substance for asthma

✓ Drugs that prevent or diminish the frequency of the attacks:

1. Bronchodilators (long duration)
2. Corticosteroids (oral or inhalation)
3. LT antagonists
4. Mast cell stabilizers

**Not bronchodilator so we can't use it with acute attacks asthma  
-it given before exposure to the antigen**

5. Omalizumab

**Most pediatrics who suffer from asthma will be relieved completely at the age of 5-6 years**



# Acute attack

Inhaled short-acting  $\beta_2$  agonist e.g. salbutamol or terbutaline

## Long-term prophylaxis (Between attacks):

Severity	Long-term control	Quick relief of acute symptoms
<b>Intermittent</b> Less than 2/ week	No daily medication.	Short-acting $\beta_2$ agonist
<b>Mild persistent</b> more than 2/ week	Low-dose inhaled corticosteroids (ICS).	Short-acting $\beta_2$ agonist
<b>Moderate persistent</b> daily	Low- to medium-dose ICS + long-acting $\beta_2$ agonist (LABA).	Short-acting $\beta_2$ agonist
<b>Severe persistent</b> continual	High-dose ICS + LABA	Short-acting $\beta_2$ agonist

## Acute severe asthma (Status asthmaticus)

### ✓ Treatment:

1. Hospitalization & O<sub>2</sub> therapy

2. **Inhaled short-acting  $\beta_2$  agonist** (frequent or continuous administration) is the **1st line of choice**. **Ipratropium bromide** should be added.

3. **Systemic corticosteroids:**

- Oral prednisolone (or)
- IV hydrocortisone or methylprednisolone (if the patient has vomiting or unable to swallow)

4. **IV fluids** (some patients are dehydrated). **K<sup>+</sup> supplements** are considered (repeated administration of  $\beta_2$  agonists  $\rightarrow$  hypokalemia)

5. If failed to improve, **aminophylline slow IV infusion** can be administered

6. **Mechanical ventilation** is considered if the patient still deteriorating

7. On discharge, oral prednisolone should be continued for short courses

اللهم عليك باليهود ومن يعاونهم،

يا حي يا قيوم زلزل الأرض من تحت أقدامهم ، اللهم ارسل عليهم طيراً ابابيل ترميهم بحجارة من سجيل ، اللهم وأجعلهم الثقلين عبرة وآية ، اللهم عليك بهم فإنهم لا يعجزونك حسبنا الله ونعم الوكيل .