S. B. K. S. Medical Institute & Research Center

Subject: Pharmacology

Topic:

Respiratory System: Drugs used in Bronchial Asthma - PART ONE

II MBBS Batch

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COMPETENCY BASED UNDERGRADUATE CURRICULUM FOR

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CODE: PH 1.33

COMPETENCY:

Describe the mechanism of action, types, side effects, indication and contraindication of the drugs used in Bronchial Asthma.

Respiratory System

Integration Teaching:

Respiratory Medicine

Disorders of Respiratory Function

1. Bronchial asthma

2. Cough

3. Allergic rhinitis

4. Chronic obstructive pulmonary disease

(COPD, also called emphysema)

Introduction: Bronchial Asthma

- **Inflammatory response to allergen**
- **Antibody binds with & ruptures mast cells**
  - **Releases histamine, prostaglandins, leukotrienes**
- **Two primary issues**
  - **Bronchoconstriction**
  - **Inflammation (mucous production)**

Clinical manifestations

Classic signs and symptoms of asthma:

- attacks of expiratory dyspnea
- shortness of breath
- cough
- chest tightness
- wheezing (high-pitched whistling sounds when breathing out)
- sibilant rales (hissing sound)

Clinical Hallmarks

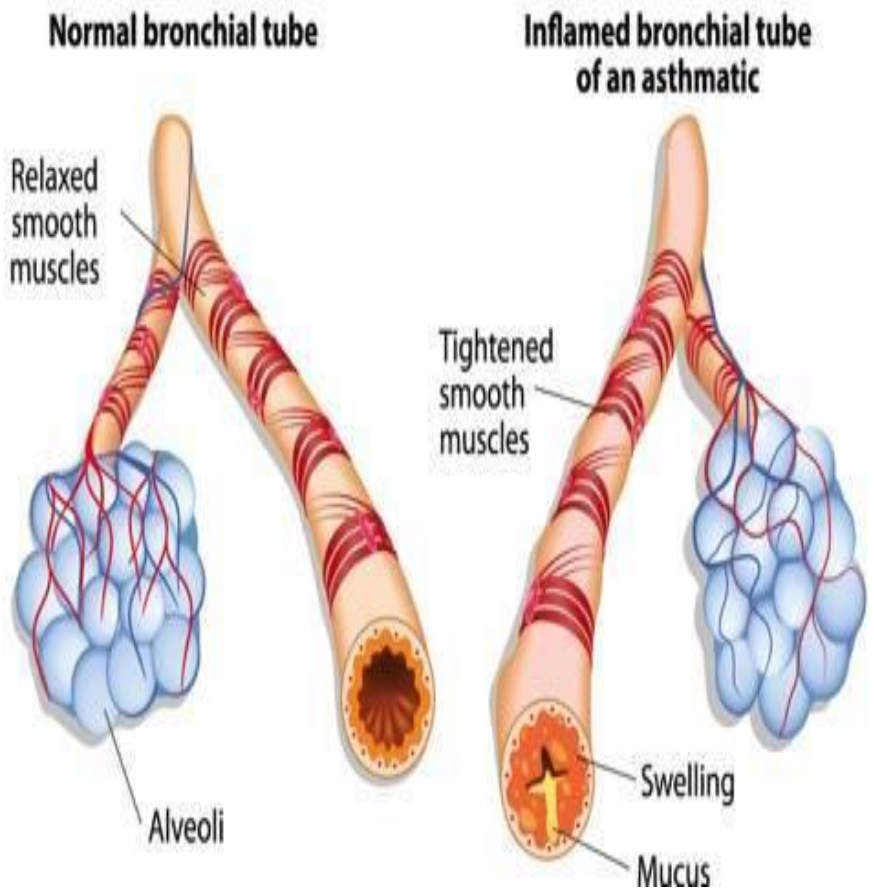
- **Recurrent, episodic bouts of coughing, shortness of breath, chest tightness, and wheezing.**
- **In mild asthma, symptoms occur only occasionally**
- **But in more severe forms of asthma frequent attacks of wheezing dyspnea occur, especially at night, and chronic activity limitation is common.**

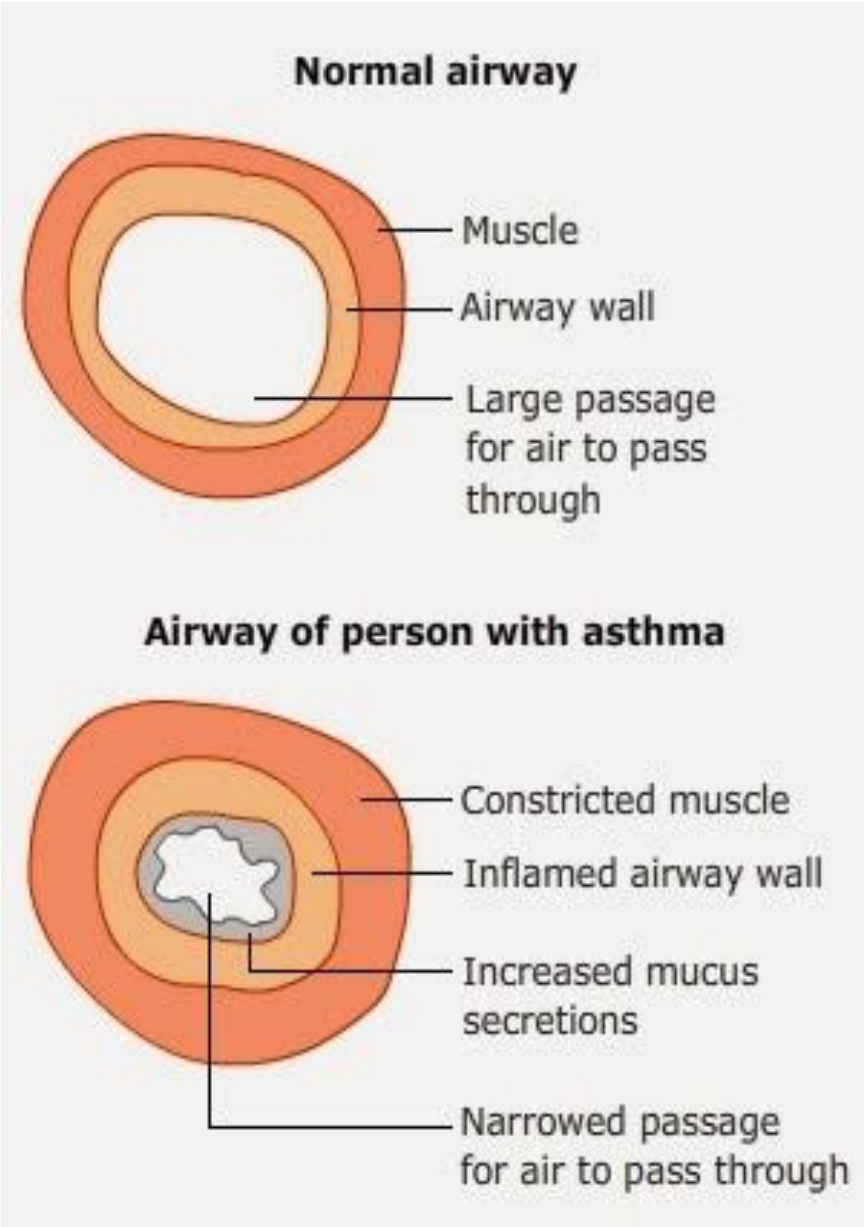
- **A clinical syndrome characterised by recurrent cough/paroxysmal dyspnoea, chest tightness and wheeze due to increased resistance to air flow through the narrowed bronchi.**

- **Characterize by dyspnea and wheeze due to increased resistance to the flow of air through the bronchi.**

- **The tracheobronchial smooth muscle is hyper responsive to various stimuli like dust, allergens, cold air, infection and drugs.**

BRONCHOCONSTRICTION (ASTHMA)





Narrowing is brought about by:

- **Bronchial hyper-reactivity and bronchospasm.**
- **Cellular infiltration and oedema of the bronchial mucosa.**
- **Blockage of the bronchial lumen by inspissated (viscous/thick) mucus.**

Etiology & Pathophysiology

- **The <u>etiology</u> of bronchial asthma is multifactorial:**

genetic, developmental, environmental, inflammatory & immunological.

- **<u>Pathogenesis</u>:**

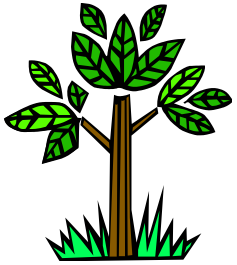
(a) Inflammation due to infiltration of eosinophils, mast cells, CD4 lymphocytes.

(b) Mucus cell hyperplasia.

(c) Re-modelling of the airways with fibrosis.

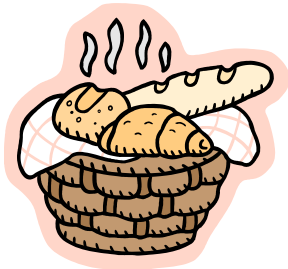
Some allergens which may cause asthma

House-dust mites which live in carpets, mattresses and upholstered furniture

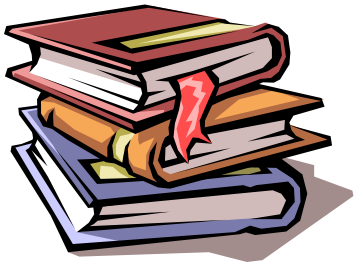


Plant pollen

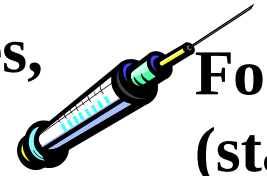
Spittle, excrements, hair and fur of domestic animals



Dust of book depo-sitories



Pharmacological agents (enzymes, antibiotics, vaccines, serums)



Food components (stabilizers, genetically modified products)

Two types:

- **Extrinsic asthma: It is mostly episodic, less prone to status asthmaticus.**

- **Intrinsic asthma: It tends to be perennial (recurring), status asthmaticus is more common.**

Pathophysiology of Asthma

Immediate phase of the asthma attack (bronchial hyper-reactivity and spasm)

Triggers: Allergen (e.g. pollen, Air pollutants, animal dander)

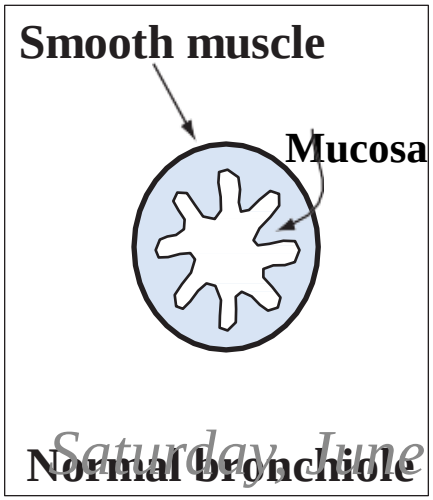
viral infection

release

Mast cell spasmogens (e.g. histamine, LTC_4, LTD_4 etc.)

Chemotaxins (e.g. LTB_4, cytokines etc.)

Bronchospasm



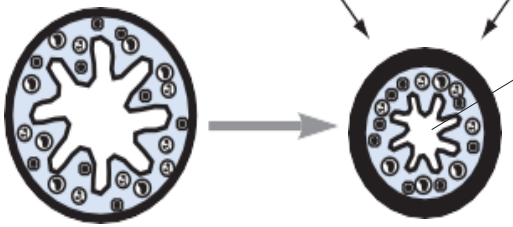
Delayed phase of the asthma attack (bronchial hyper-reactivity, spasm and airway infammation)

Influx /activation of inflammatory cells, (eosinophils, monocytes, T cells etc.) which release leukotrienes, cytokines, eosinophil proteins etc. which cause:

Bronchospasm wheezing, cough

hyper-reactivity & inflammation

Mucus



Mast cells (present in lungs) and inflammatory cells produce a multitude of mediators:

- **Release of mediators stored in granules *(immediate):* histamine, protease enzymes, TNF alpha.**
- **Release of phospholipids from cell membrane followed by mediator synthesis (within minutes): PGs, LTs, PAF.**
- **Activation of genes followed by protein synthesis (over hours): Interleukins, TNF alpha.**

- **These mediators together constrict bronchial smooth muscle, cause mucosal edema, hyperaemia and produce viscid secretions, all resulting in reversible airway obstruction.**

- **Bronchial smooth muscle hypertrophy occurs over time and damage to bronchial epithelium accentuates the hyperreactivity.**

Asthma

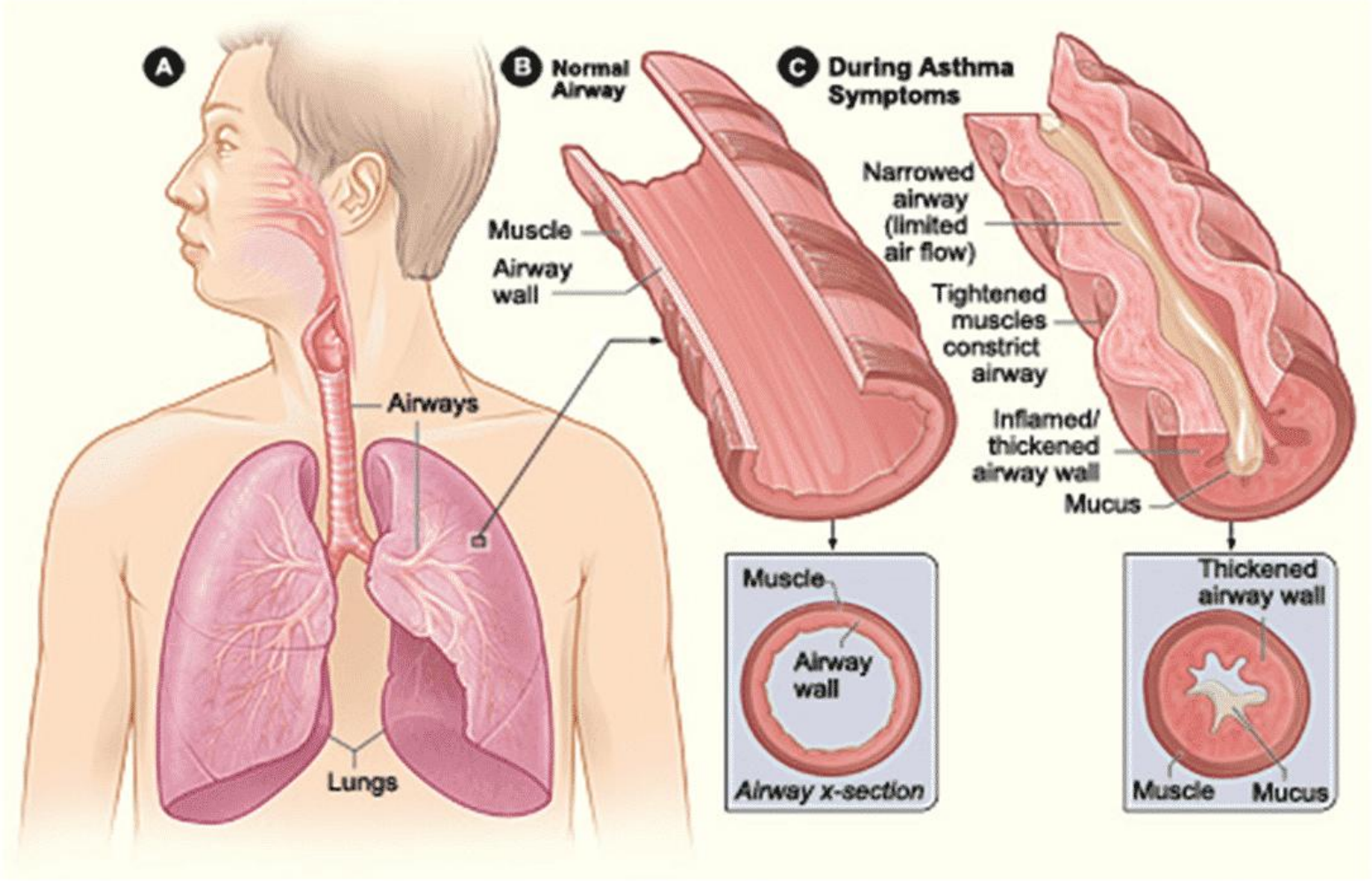


Image via: nhlbi.nih.gov

Clinical Classification of Bronchial Asthma

I. Mild Intermittent Asthma:

- **The patient gets discrete, infrequent, acute attacks, which are relieved by bronchodilators, with no disability between the attacks.**

- **There is often a recognisable precipitating factor such as allergy, an upper respiratory tract infection or psychological trauma.**

II. Chronic Persistent Asthma:

- **Generally due to the presence of chronic inflammation & thickening of mucosa of the bronchioles with resultant excessive secretion of mucus.**

- **Decreased elastic recoil of the lung tissue & finally hyperreactivity of the bronchi with bronchospasm.**

- **Symptoms are persistent & relief of bronchospasm with medicines is incomplete.**

CHRONIC FORM SUBDIVIDED:
Mild, Moderate & Severe grades:

- **Depending on the interference with daily activities & with sleep, & the degree of incapacity.**
- **Clinically, there is more or less persistent dyspnoea and wheeze, with superadded acute attacks.**
- **In some patients, chronic asthma co-exists with COPD.**

III. Severe Acute Asthma (Status Asthmaticus):

- **Where an acute attack is severe, persistent and does not respond to standard treatment.**
- **It is accompanied by evidence of respiratory insufficiency or failure.**

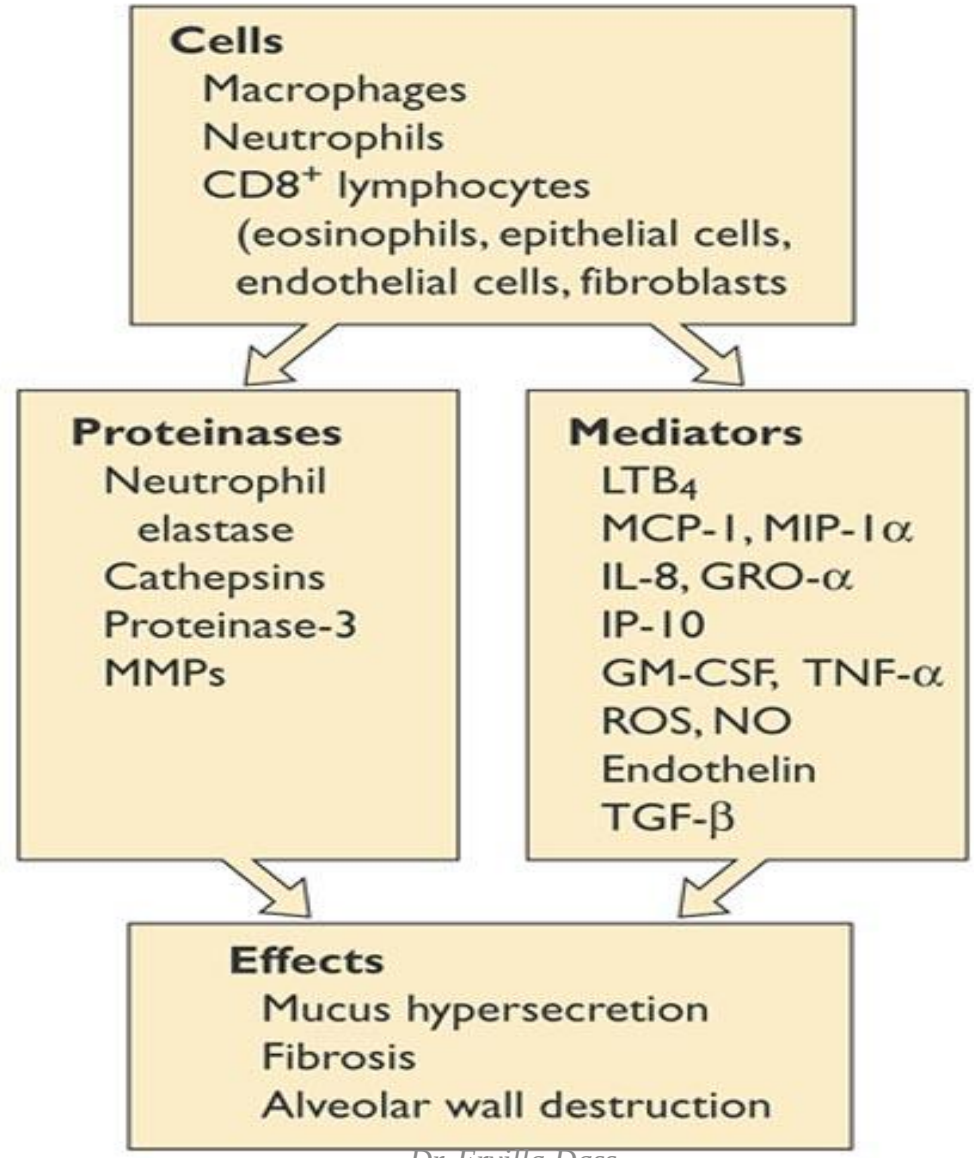
IV. Exercise-induced Bronchospasm:

- **The attack is precipitated by exercise or by inhalation of cold air.**

Chronic Obstructive Pulmonary Disease

- **COPD is characterized by airflow limitation caused by chronic bronchitis or emphysema <u>often associated with long term tobacco smoking</u>. This is usually a slowly progressive and largely irreversible process, which consists of increased resistance to airflow, loss of elastic recoil, decreased expiratory flow rate, and overinflation of the lung.**
- **COPD is clinically defined by a low FEV1 value that fails to respond acutely to bronchodilators, a characteristic that differentiates it from asthma.**

Cellular mediators and cytokines in COPD



Principles of Therapy

Control of asthma involves:

(1) Environmental control

(2) Pharmacological therapy

(3) Treatment of co-morbidities

(1) ENVIRONMENTAL CONTROL:

Avoid triggers:

Respiratory irritants like infection & smoking & environmental/occupational pollutants & allergens (dust, mite, pollen, etc.), if known.

(2) PHARMACOLOGICAL THERAPY

Aims:
(1) Relieving bronchospasm
(2) Reducing bronchial inflammation
(3)Prevention of repeated attacks

Bronchodilators and anti-inflammatory drugs are the mainstay of the therapy.

(3) TREATMENT OF CO-MORBIDITIES

Include treatment of infection, correction of dehydration & acidosis in severe acute attack, controlled administration of oxygen, when needed.

- **A programme of graded exercise training is advised.**
- **As physical exercise tends to precipitate acute attacks in some patients, an exercise which does not precipitate such attacks (e.g., swimming) is preferred in these patients.**
- **Psychological treatment.**

Approaches To Treatment

1. **Prevention of AG:AB reaction:** Avoidance of antigen, hyposensitization - possible in extrinsic asthma and if antigen can be identified.
2. **Neutralization of IgE (reaginic antibody):** Omalizumab.
3. **Suppression of inflammation and bronchial hyperreactivity:** Corticosteroids.
4. **Prevention of release of mediators:**

   Mast cell stabilizers.

5. **Antagonism of released mediators:** Leukotriene antagonists, antihistamines, PAF antagonists.
6. **Blockade of constrictor neurotransmitter:** Anticholinergics.
7. **Mimicking dilator neurotransmitter:** Sympathomimetics.
8. **Directly acting bronchodilators:** Methylxanthines.

CLASSIFICATION:

I. BRONCHODILATORS:

A. BETA SYMPATHOMIMETICS:

- **Selective beta-2 adrenergic receptor agonists:**

(a) Short acting: Salbutamol, Isoetharine, Bitolterol, (a prodrug), Fenoterol, Rimeterol.

(b) Long acting: Salmeterol, Formoterol, Arformoterol, Indacaterol.

- **Non-selective beta adrenergic agonists:**

Orciprenaline, Adrenaline and Ephedrine.

B. Phosphodiesterase inhibitors:
Theophylline (anhydrous), Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Theophylline ethanolate of piperazine, Doxophylline.

C. Anticholinergics: Ipratropium bromide, Tiotropium, Aclidinium.

II. ANTI-INFLAMMATORY DRUGS:

a) Corticosteroids:

Systemic: Hydrocortisone, Prednisolone and others.

Inhalational: Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide.

b) Leukotriene (LT) modifiers:

1. **LT receptor antagonists:**
   Montelukast; Zafirlukast.

2. **LT synthesis inhibitors:**
   Zileuton.

c) Mast cell stabilisers:
Sodium cromoglycate; Nedocromil.

d) PAF antagonists: Ketotifen.

III. ANTI-IGE ANTIBODY:

Omalizumab.

Drugs Used In The Prevention Of Acute Attacks (Maintenance Therapy)

(1) Inhaled long acting β-agonists (LABA) e.g. salmeterol, formoterol.

(2) Inhaled glucocorticoids

(3) Oral theophylline and

(4) Oral leukotriene modifiers

Drug therapy
Two drug categories are used:

Anti-inflammatory drugs (basic)

Are divided into:

- **hormone-containing (Corticosteroids)**
- **Non-hormone-containing (Cromones, Leukotriene receptor antagonists)**

Bronchodilators

Three groups:

- **Beta 2-agonists**
- **Anticholinergic Drugs**
- **Methylxanthines**

Bronchodilators

Beta 2-agonists

Stimulates Beta 2-adrenergic receptors of bronchi

Anticholinergic drugs

reduce tonus of vagus

SMOOTH MUSCLE RELAXATION

Methylxanthines

inhibit phosphodiesterase

Drug Therapy During an Acute Attack

Selective short acting β2 adrenergic receptor agonists (SABA)

- Relax the smooth muscle of all airways.
- Enhance mucociliary clearance from the respiratory tract.
- Suppress microvascular leakage in the airway.
- Inhibit mediator release from the mast cells and the basophils, and cytokine release from the inflammatory cells in the airway.
- May inhibit release of acetylcholine.

EXAMPLES OF SABA :

- Salbutamol, Levo-salbutamol
- Terbutaline, fenoterol, bitolterol, pirbuterol, tolubuterol and rimiterol
- FENOTEROL has been associated with greater cardiac toxicity in patients with acute asthma.

USES OF SABA - VERY EFFECTIVE FOR:

(1) Treating acute attacks and

(2) Prevention of exercise-induced asthma.

- **Inhaled Beta 2-agonists are the basic drug group among bronchodilators.**

  - Short-acting (duration of action 5-6 h) b2-agonists - salbutamol, fenoterol - are used for quick relief of asthma symptoms.
  - Long-acting (> 12 h) b2-agonists - salmoterol, farmoterol - for prevention of asthma symptoms occurring.

Adverse effects

- Skeletal muscle tremors, vasodilation, tachycardia, hyperglycemia, hypokalemia, hypomagnesemia.

- These are minimal when the drugs are given by inhalation.

ANTICHOLINERGICS:

Ipratropium bromide, Oxitropium, Tiotropium

- Preferred drug in patients with COPD.
- It is particularly useful in patients with concomitant heart disease and those intolerant to β agonists.
- Used predominantly in night-time asthma and in elderly patients because of the least cardiotoxic effect.

•A combination of ipratropium and a beta adrenergic agonist by inhalation produces additive effects because ipratropium acts on large and medium sized bronchi; whereas β2 agonist act on the smaller bronchi.

•It is also useful in asthmatic attack induced by β–blockers.

Anti-cholinergic drugs

- Uses :
  - COPD
  - Bronchial asthma as an adjuvant to β2 agents
- Oxytropium :
  - Is related to ipratropium and is given twice a day as aerosol.
- Tiotropium :
  - is a longer acting drug with a duration of action of 24 hrs.

XANTHINE DERIVATIVES

- Naturally occuring : methylxanthines
  - Caffeine, theophylline, theobromine.
- Of them, **Theophylline** is the most effective compound in producing relaxation of the bronchial muscle.
- Theophylline & its related compounds :
  - Aminophylline, choline theophyllinate, etophylline.

- Theophylline and its compounds have been extensively used in asthma, but are not considered first line drugs any more. They are used more often in COPD.
- Methylxanthines in comparison with other bronchodilators have the less bronchodilating potential.
- There are long-acting (>12 h) - Doxophylline A long-acting oral methylxanthine & short-acting (aminophylline, theophylline) drugs in this group.

Theophylline

- Mechanism of action (MOA) :
  - It inhibits the enzyme phosphodiesterase (PDE) and thus prevents degradation of cAMP to 5 AMP.
- This increases the intracellular cAMP production resulting in
  - Relaxation of plain muscle
  - Cardiac stimulation
  - Inhibition of activation of inflammatory cells.
  - Inhibits adenosine receptors on the cell surface.

Theophylline

- Therapeutic uses :
  - Acute attack of Bronchial asthma
    - Aminophylline (250-500 mg) slow i.v infusion, it acts rapidly in severe attacks.
  - Prophylaxis of mild to moderate bronchospasm
  - COPD with CCF
  - Apnea of preterm infants.
- Sustained release preparations are available which produce blood levels for 12 hours

AMINOPHYLLINE:

Therapeutic uses:

1) Acute attack of asthma:

- If treatment with inhaled selective SABA in adequate doses fails to relieve an acute attack in about half to one hour, aminophylline is administered by IV infusion in 5% glucose in a dose of 5 mg/kg over 15-30 minutes, followed by 0.5-1 mg/kg per hour for several hours.
- The infusion rate should be lowered in patients with cirrhosis, pneumonia, acute viral infection and congestive heart failure and in patients receiving drugs which interfere with its metabolic degradation.

2) Chronic persistent asthma:

- Slow release oral preparations may be useful in patients with persistent bronchospasm between acute attacks and in preventing nocturnal attacks.
- However, these preparations may also prolong the toxic effects as peak plasma level is reached 12-24 hours after the ingestion.
- **NOTE**: If an acute asthmatic attack is not terminated within 2 hours by the above measures, the patient should be treated as a case of severe acute asthma (status asthmaticus).

Adverse reactions

- Gastric irritation, anorexia, nausea, vomiting, abdominal discomfort, headache, tremor, anxiety, nervousness, tachycardia and insomnia, cardiac arrhythmias and convulsions.

Combined inhaled drugs (corticosteroids with b2-agonists) – with use of delivery devices (nebulisers, spacers, spinhalers) enhance the effectiveness of asthma therapy.

Leukotriene (LT) modifiers:

(a) LT receptor antagonists: Montelukast; Zafirlukast.

(b) LT synthesis inhibitors: Zileuton.

(a) **Montelukast and Zafirlukast -** Both have similar actions and clinical utility. They competitively antagonize cysLT1 receptor mediated bronchoconstriction, increased vascular permeability and recruitment of eosinophils.

Montelukast and zafirlukast

- **Montelukast** and **zafirlukast** are **indicated** for

prophylactic therapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids.

- Are very safe drugs; produce **few side effects** like headache and rashes. Eosinophilia and neuropathy are infrequent. Few cases of Churg-Strauss syndrome (vasculitis with eosinophilia) have been reported.

ZILEUTON:

- It is a 5-LOX inhibitor, blocks LTC4/D4 as well as LTB4 synthesis. It therefore has the potential to prevent all LT induced responses including those exerted by activation of cysLT1 receptor.
- However, clinical efficacy in asthma is similar to montelukast.
- The duration of action of zileuton is short and it has **hepatotoxic potential**. These limitations have **restricted its use**.

MAST CELL STABILIZERS

- **Sodium cromoglycate (Cromolyn sodium)**
- Synthetic chromone derivative which inhibits degranulation of mast cells (as well as other inflammatory cells) by trigger stimuli.
- Release of mediators of asthma like histamine, LTs, PAF, interleukins, etc. is restricted.
- It is also not a bronchodilator and does not antagonize constrictor action of histamine, ACh, LTs, etc.
- Therefore, it is **ineffective** if given during an asthmatic attack.

USES

1. **Bronchial asthma**: Sod. cromoglycate is used as a long-term prophylactic in mild-to-moderate asthma.
2. **Allergic rhinitis**: Not a nasal decongestant, but regular 4 times daily prophylactic use as a nasal spray produces symptomatic improvement in many patients after 4–6 weeks: need for nasal decongestants is reduced.
3. **Allergic conjunctivitis**: Regular use as eye drops is beneficial in some chronic cases.

Antihistaminics & Mast Cell Stabilisers

KETOTIFEN: PAF antagonists & H1 receptor blocker, is claimed to be useful in asthma. It is believed to inhibit airway inflammation induced by platelet activating factor (PAF) in primates. It can cause drowsiness. Its usefulness in asthma is equivocal.

- Mast cell stabilisers such as **cromolyn sodium** 4%, **ketotifen** 0.025%, **nedocromil** 2% and **epinastin** 0.05% can also be used to treat allergic and vernal conjunctivitis.

ANTI-IgE ANTIBODY

<u>Omalizumab:</u> It is a humanized monoclonal antibody against IgE.

Administered s.c., it neutralizes free IgE in circulation without activating mast cells and other inflammatory cells.

On antigen challenge, little IgE is available bound to the mast cell surface receptors (FcεR1) to trigger mediator release & cause bronchoconstriction.

• In severe extrinsic asthma, omalizumab has been found to reduce exacerbations and steroid requirement.

• No benefit has been noted in nonallergic asthma.

• It is very expensive; use is reserved for resistant asthma patients with positive skin tests or raised IgE levels who require frequent hospitalization.

• It is being tried in other allergic diseases as well.

REFERENCE TEXT BOOKS

- **K. D. Tripathi M.D., Essentials of Medical Pharmacology.**

- **Satoskar & Bhandarkar, Pharmacology and Pharmacotherapeutics.**

- **EVIDENCE**

Satoskar & Bhandarkar, Pharmacology and Pharmacotherapeutics , Revised 24th Edition , 2015, pg . 572 to 588

Source of Information	Chapter	Author	Information	Level of evidence
Pharmacology and Pharmacotherapeutics – R. S. Satoskar, S. D. Bhandarkar, Nirmala N. Rege POPULAR PRAKASHAN, Mumbai.	Chapter 27 Pharmacotherapy of Bronchial Asthma	Satoskar & Bhandarkar	*On completion of this chapter, the student will:* Discuss drugs used in the treatment of bronchial asthma. They will describe the mechanism of action ,types ,side effects, indication and contraindication of the drugs. They will be	Level of evidence - Grade one

Barnes P. J. (2006). Drugs for asthma. British journal of pharmacology, 147 Suppl 1(Suppl 1), S297–S303. https://doi.org/10.1038/sj.bjp.0706437

Source of Information	Chapter	Author	Information	Level of evidence
British journal of pharmacology. 2006	**Drugs for asthma.**	**Barnes P. J.**	**provides an overview of drugs for asthma**	Level of evidence - Grade two