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

Subject: Pharmacology

Topic: Pharmacotherapy of Bronchial Asthma: Session I

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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

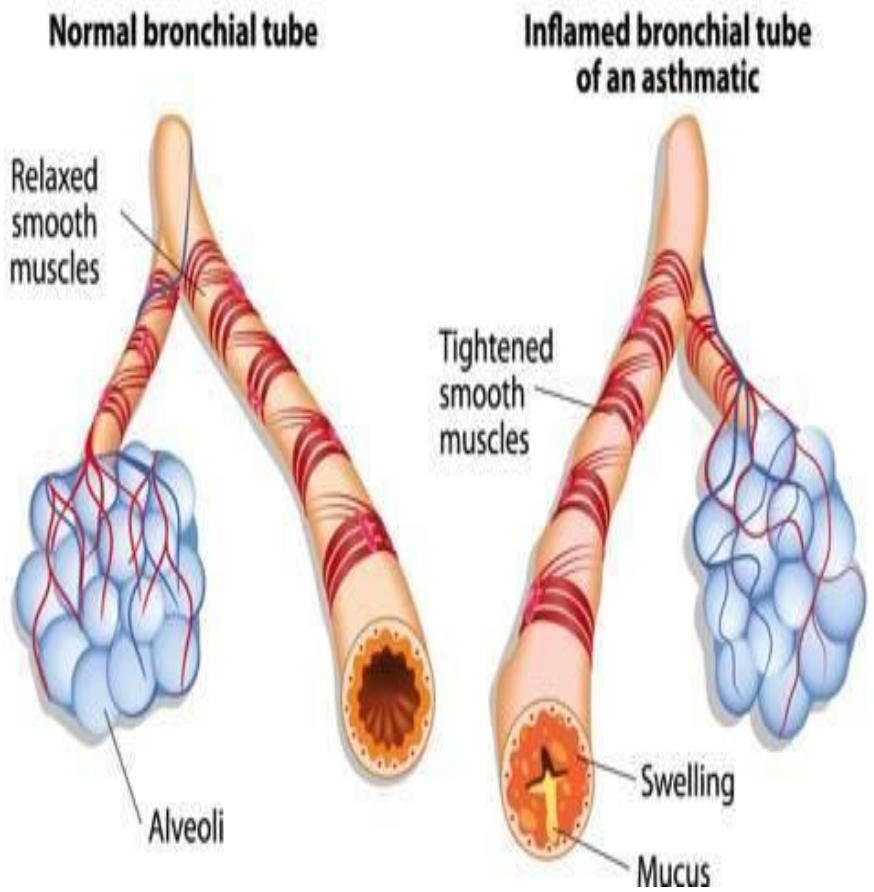
- **Recurrent, episodic bouts of coughing, shortness of breath, chest tightness, and wheezing.**
- **In mild asthma, symptoms occur only occasionally**
- **But in more severe forms of asthma frequent attacks of wheezing dyspnea occur, especially at night, and chronic activity limitation is common.**

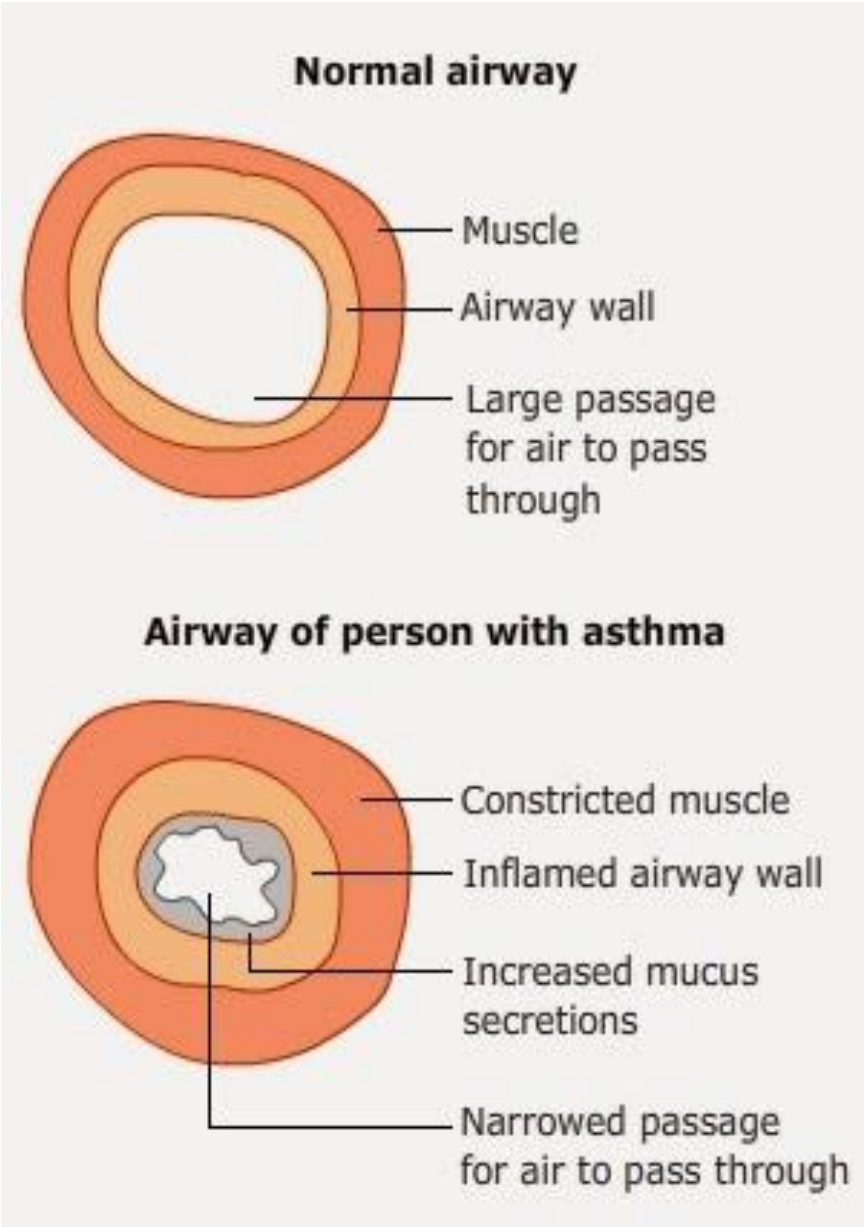
- **A clinical syndrome characterised by recurrent cough/paroxysmal dyspnoea, chest tightness and wheeze due to increased resistance to air flow through the narrowed bronchi.**

- **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:**

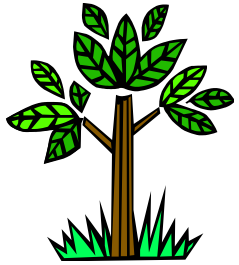
genetic, developmental, environmental, inflammatory & immunological.

- **<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.

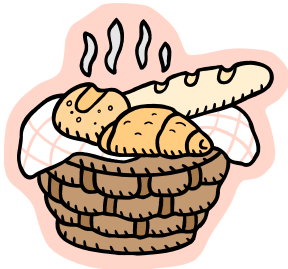
Some allergens which may cause asthma

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



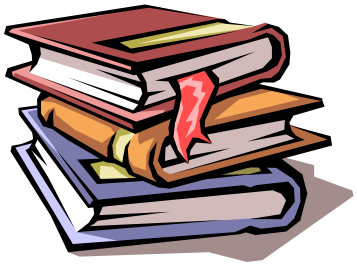
Plant pollen

Spittle, excrements, hair and fur of domestic animals

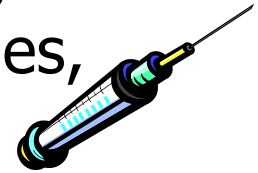


Food components (stabilizers, genetically modified products)

Dust of book depo-sitories



Pharmacological agents (enzymes, antibiotics, vaccines, serums)



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)

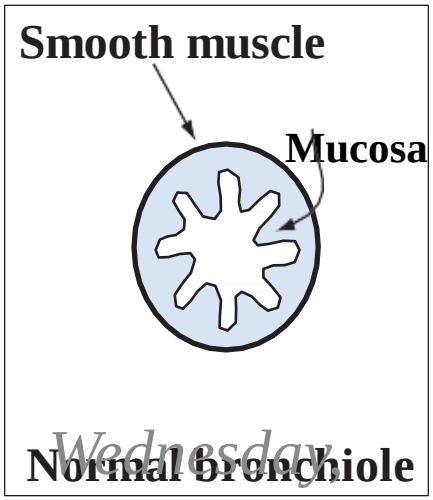
viral infection

release

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

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

Bronchospasm



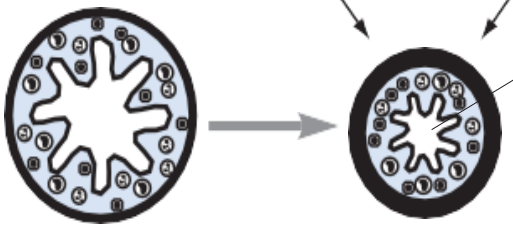
Normal bronchiole

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

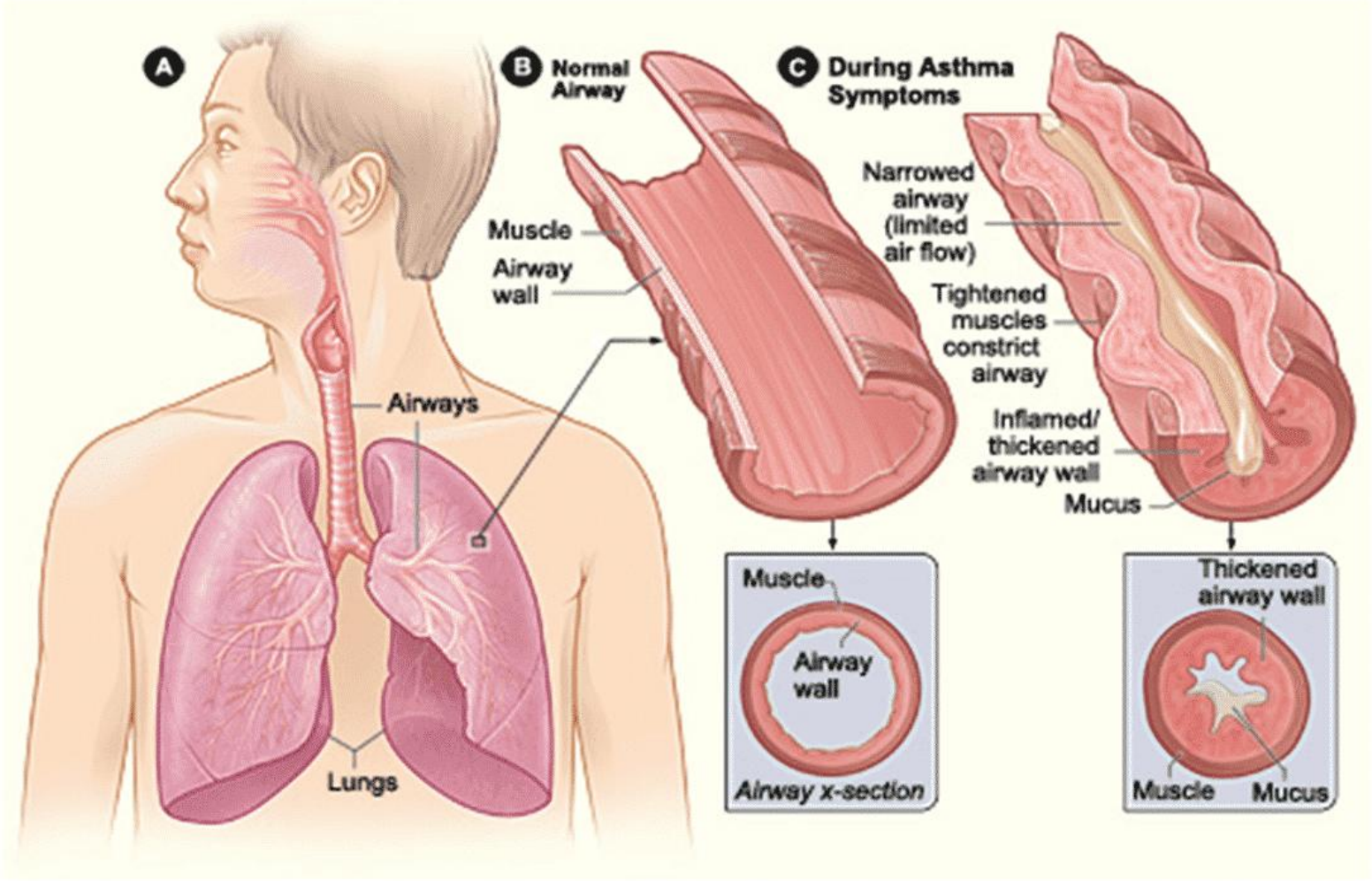


Image via: nhlbi.nih.gov

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.**

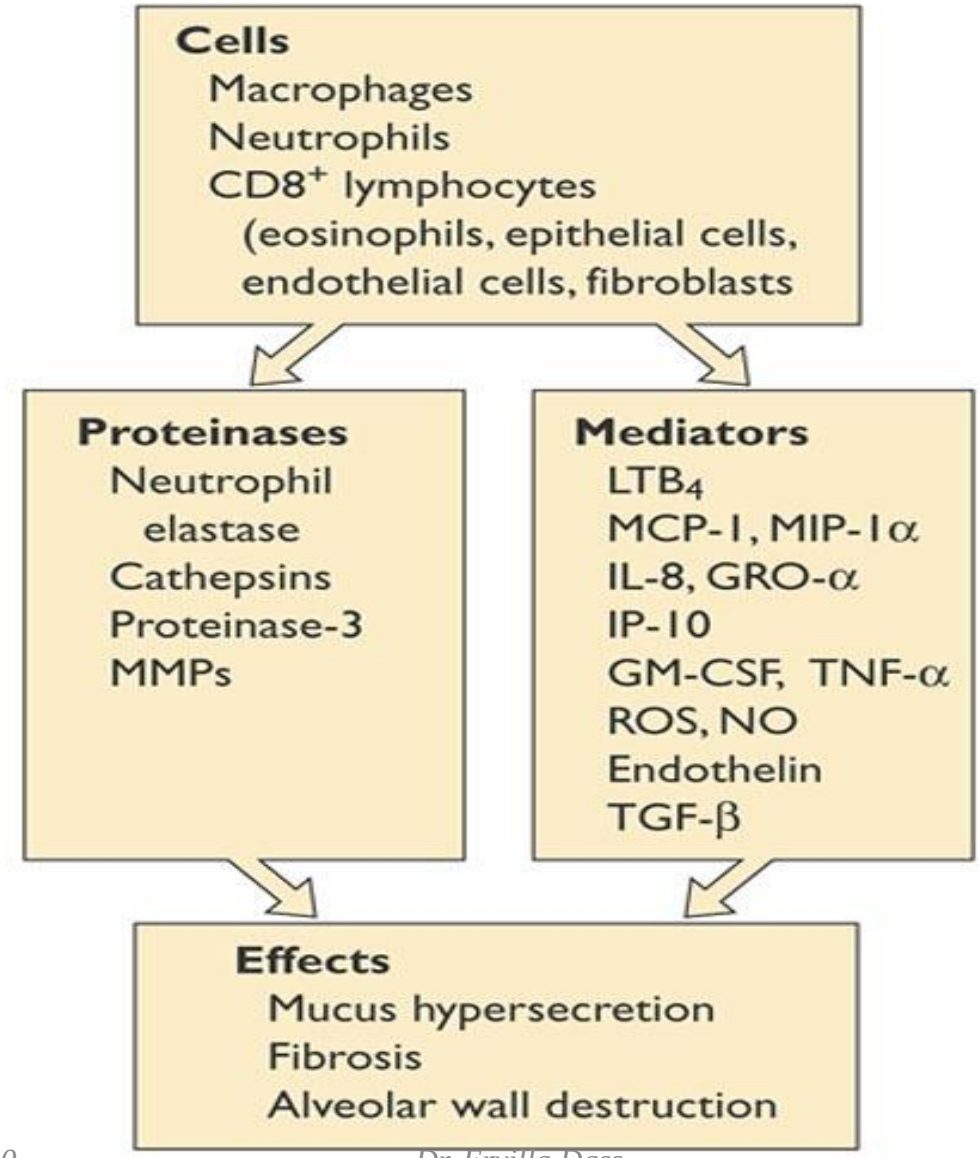
IV. Exercise-induced Bronchospasm:

- **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.

MCQs

- **Read the following MCQs and answer in the comment box with roll no.**

Q. 1. During Inflammatory response to allergen the following gets liberated from ruptured mast cells:

A. Histamine

B. Prostaglandins

C. Leukotrienes

D. All of the above

Q. 2. Which of the below mentioned is/are the clinical hallmark/s of asthma:

A. recurrent, episodic bouts of coughing

B. shortness of breath

C. chest tightness

D. All of the above

Q. 3. In patients with Bronchial Asthma, wheezing is due to which of the following:

A. Increased resistance to the flow of air through the bronchi

B. Decreased resistance to the flow of air through the bronchi

C. Increased resistance to the flow of air through the lungs

D. None of the above

Q. 4. In patients with asthma, tracheobronchial smooth muscle is hyper responsive to which of the following stimuli:

A. Dust

B. Allergens

C. cold air

D. All of the above

Q.5 . Asthma is a chronic inflammatory disease of:

A. Airways

B. Lungs

C. Respiratory Allergic Disease

D. allergic disease

REFERENCE TEXT BOOKS

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

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

Practice questions:

Q. 1. Mention the factors responsible for the cause/etiology of asthma.

Q. 2. Classify drugs used in bronchial asthma based on mechanism of action.

Q. 2. Multitude of mediators are produced mainly by which cells? Name mediators involved in the pathogenesis of asthma.