

Asthma

Asthma (**Panting**) is a chronic inflammatory airway disease characterized by allergen-induced airway hyper-responsiveness, airway inflammation, and remodeling. many cells and cellular elements play a role: (**Mast cells, Eosinophils, Neutrophils, T-lymphocytes, Macrophages, and epithelial cells IL-4,5,13**). In susceptible individuals, the inflammation causes recurrent coughing (particularly at night or early in the morning or in response to exercise or cold air), wheezing, breathlessness, and chest tightness leading to **airflow obstruction** (swelling & narrow) that is often **reversible either spontaneously or with treatment**. Asthma causes Smooth muscle **hyperplasia and excessive mucus Inflammation**.

The inflammation in allergic asthma is characterised by:

- 1- Allergic reaction **through IgE-dependent mechanisms with mast cell**
- 2- Infiltration with eosinophils resembles response to parasitic and worm infections.

Classification: Asthma may classified as atopic (extrinsic) or non-atopic (intrinsic), based on whether symptoms are precipitated by allergens (atopic) or not (non-atopic).

Types of asthma

1-Allergic asthma is the **most common type usually starts in childhood**. People with allergic asthma **often have other allergic diseases** such as eczema, hay fever (allergic rhinitis), or food and drug allergies. Allergic asthma associated with **family history**.

2-Non-allergic asthma this condition is **triggered by factors** such as exercise, stress, anxiety, cold or dry air and hyperventilation. It usually occurs after midlife.

3- Allergic bronchopulmonary mycosis (ABPM) is a clinical syndrome associated with immune sensitivity to various fungi (*Aspergillus* spp).

4- Aspirin-induced asthma: people with this type, **taking aspirin or other NSAIDs** (non-steroidal anti-inflammatory drugs [naproxen, ibuprofen]) triggers an asthma attack. **Aspirin-induced asthma is more common in adults than children. This type of asthma is usually severe.** It is also called **aspirin-exacerbated respiratory disease**.

5- Adult-onset Asthma This type of asthma is **more severe than childhood-onset asthma**. People with this type their **lung function declines more quickly** they usually have **high levels of eosinophils and not have other allergic diseases**. It is more likely in

Women than men and in people who are very overweight. Adult-onset asthma **does not run in families. Certain types of work, Cigarette smoking, Stressful life events**

6- Asthma with fixed airflow obstruction: it is associated with more frequent exacerbations lead to mortality. **Remodeling of airway wall(increased airway smooth muscle mass and airway wall fibrosis) may be the cause.**

7- Exercise-induced asthma: happens when the **airways narrow during or after exercise**. During exercise in **cold, dry air, the lungs lose water, heat, or both** these losses cause the **airways to narrow**.

8- Cough-variant Asthma: occur in Children than adults. The cough is typically dry and unproductive, and it may be worse at night. Described as a milder form of asthma.

9- Occupational Asthma:It start or get worse because of exposure to allergens at work.

10- Nighttime (Nocturnal) Asthma: The cause **is not clear**. Some studies showed that **inflammation at night**. They also have harder for air to get in and out of the lungs.

11- Asthma with obesity: Sleep apnea, a condition that leads to difficulty breathing .

Pathophysiology and the Immunological reaction of Asthma:

Effect of Allergen (Dust, pollen, mite debris, animal dander)

Cell and mediators that involved:

Plasma Cells that produce antibodies (**immunoglobulin**) **IgE** Antibody in allergic disease

Mast Cell: Degranulation to produce **Histamines, Prostaglandins and Leukotrienes**.

Many different inflammatory cells are involved in asthma:

1-Mast cells

Mast cells are important in initiating the acute bronchoconstrictor responses to allergen or indirect stimuli, such as exercise. In asthmatic Patients there is **increase** in mast cell in airway smooth muscle . Treatment with **prednisone** results in a decrease in the number of positive mast cells it play a role in **airway remodelling** by stimulation of human lung fibroblast proliferation.

2-Macrophages

Macrophages produce many different cytokines that may orchestrate the inflammatory response. Alveolar macrophages **normally have a suppressive effect on lymphocyte function** by (**IL-10**) and its secretion is reduced in alveolar macrophages with asthma.

3-Dendritic cells (D.C)

Dendritic cells play a critical role in the development of asthma. DC in the respiratory tract **act as very effective APC**. Dendritic cells take up allergens, process them to peptides **and migrate** to local lymph nodes **where they present the allergenic peptides to T-lymphocytes**.

4-Eosinophils

Allergen inhalation results in a marked increase in Eosinophils and linked to the development of **airway hyperresponsiveness (AHR)** through the release of basic proteins and oxygen-derived free radicals, activated eosinophils induce airway epithelial air way damage.

5-T-Lymphocytes (Th.2)

T-lymphocytes play important role in **coordinating** the inflammatory response in asthma through the release of specific cytokines, resulting in the recruitment and survival of eosinophils and in the maintenance of mast cells in the airways. **Regulatory Tcell (Treg cells)** suppress the immune response through the secretion of inhibitory cytokines, **such as IL-10 and transforming growth factor (TGF) beta.**

6-B-Lymphocytes :In allergic diseases B-lymphocytes secrete IgE. **CD40 on T-cells** is an important accessory molecule that signals through interaction with CD40-L (ligand) on B-cells.

7-Basophils :There is also an increase in the numbers of basophils, as well as mast cells, in induced sputum after allergen challeng.

8-Structural cells

Structural cells of the airways, including **epithelial cells, endothelial cells, fibroblasts and airway smooth muscle cells** may also be an important source of inflammatory mediators.

Inflammatory mediators

Many mediators have been implicated in asthma plays pathological features of allergic diseases.

1-Lipid mediators

The cysteinyl-leukotrienes, are potent constrictors of human airways.

2- Cytokines

Many inflammatory cells (macrophages, mast cells, eosinophils and lymphocytes) are capable to produce cytokines. The cytokines are importante in asthma include the **lymphokines** secreted by T-lymphocytes: **IL-3**, which is important for the survival of mast cells in tissues, **IL-4** which is critical in switching B-lymphocytes to produce IgE. Other cytokines, such as IL-10, IL-12 and IL-18, have role and inhibit the allergic inflammatory process.

3- Chemokines

Chemokines appear to act in sequence in determining the final inflammatory response. Several chemokines, including **eotaxin, eotaxin-2, eotaxin-3, RANTES.**

4-Oxidative stress

there is increased oxidative stress in allergic inflammation, macrophages and eosinophils, **produce reactive oxygen species.**

5- Endothelins

Endothelins are potent peptide mediators that are vasoconstrictors and bronchoconstrictors. **Endothelin-1** levels are increased in the sputum of patients with asthma.

6- Nitric oxide

NO is produced by several cells in the airway by NO synthases. The combination of increased oxidative stress and NO and By substrate competition, nitric oxide can control the arginase pathway and induces airway remodeling, smooth muscle contraction and mucus production..

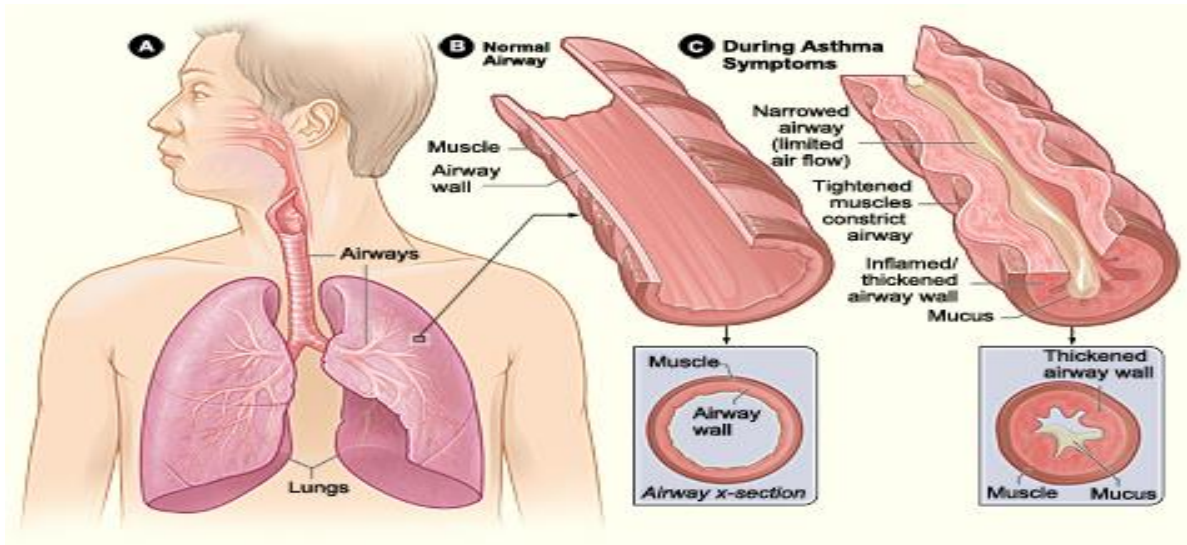


Figure C shows a cross-section of an airway during asthma symptoms.

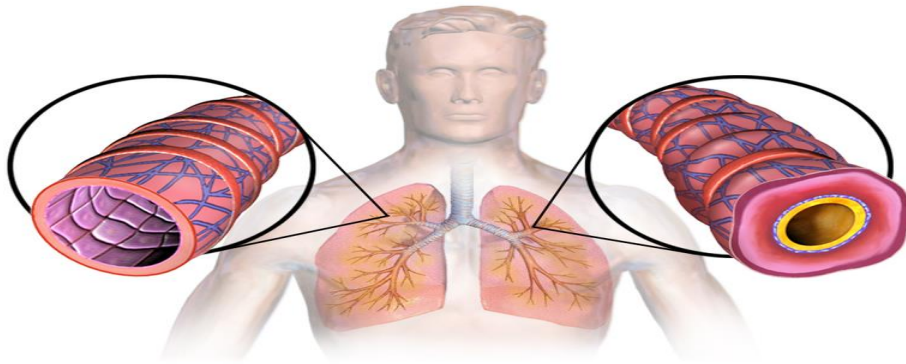
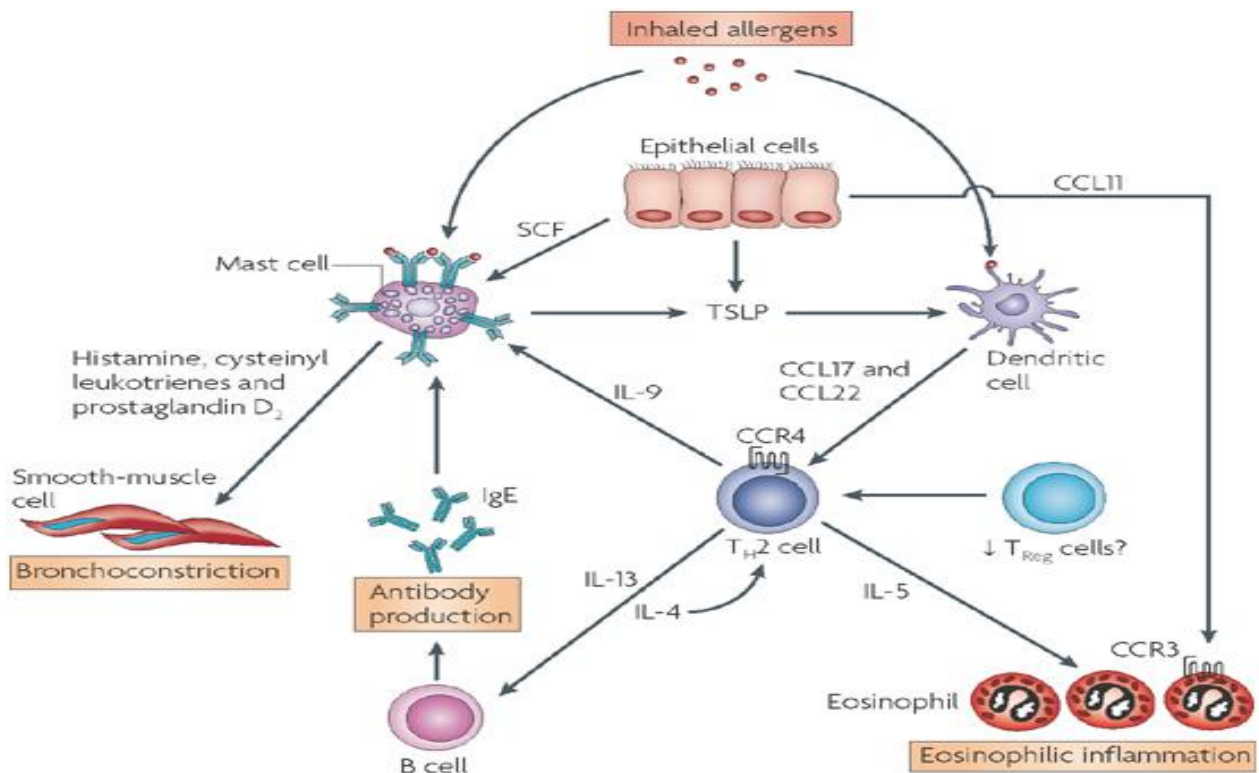


Diagram of asthma

Immunology of asthma :-

Asthma associated with a **T helper (Th)2 response**. **Dendritic cells (DCs)** are pivotal during sensitization to allergens but clearly require epithelium-derived signals to become activated. Epithelial cells also contribute to the activation and the survival of mast cells (MCs), basophils, and eosinophils. In turn, these innate cells can activate DCs to sustain Th2 immunity.



Inhaled allergens activate sensitized mast cells by crosslinking surface-bound IgE molecules to release several bronchoconstrictor mediators, including **cysteinyl leukotrienes and prostaglandin D₂**. Epithelial cells release stem-cell factor (SCF), which is important for maintaining mucosal mast cells at the airway surface. Allergens are processed by dendritic cells, to release the chemokines to attract T helper 2 (T_{H2}) cells. T_{H2} cells have a central role in orchestrating the inflammatory response in allergy through the release of **interleukin-4 (IL-4)** and **IL-13 (which stimulate B cells to synthesize IgE)**, IL-5 (which is necessary for eosinophilic inflammation) and **IL-9** (which stimulates mast-cell proliferation). **Patients with asthma may have a defect in regulatory T (T_{Reg}) cells.**

Asthma risk factors : Risk factors for asthma include **a family history of allergic disease**, the presence of allergen-specific immunoglobulin E (IgE), viral respiratory illnesses, exposure to aeroallergens, cigarette smoke, obesity, .

Genetic factors may control individual predispositions to asthma. Also **Sex :** Boys have been shown to be at greater risk for asthma than girls. **age**, women aged 40 years have a greater prevalence of asthma than do men.

Age predilection Disease onset can occur in people of any age, but children often present when younger than 6 years. It is one of the most common chronic diseases of childhood.

Laboratory Tests

- 1- **Skin tests** :Skin testing is one of the most useful ways of determining specific allergen sensitivity, such tests for allergen-specific IgE . **Skin testing** is recommended for antigens exposed.
- 2- **Blood tests** "Blood tests (in vitro) for allergen-specific IgE, such as the radioallergosorbent test (RAST), However, skin testing is more specific, more sensitive, and usually less expensive than in vitro testing. The serum IgE level is elevated only approximately half the time in patients with allergic disease. **High IgE level** is also seen in allergic bronchopulmonary aspergillosis. atopic dermatitis.
- 3- **Lung function tests :Spirometry** :- is the most common of the pulmonary function tests (PFTs). It measures **lung function**, specifically the **amount (volume) and/or speed (flow) of air that can be inhaled and exhaled**.
- 4- **Peak airflow:-** is a person's **maximum speed of expiration**, it isa small, hand-held device used to monitor the **degree of obstruction in the airways**.
- 5- **FeNO tests (exhaled nitric oxide):-** The fraction of exhaled NO (FE_{NO}) is a promising biomarker for the diagnosis, follow-up and as a guide to therapy in adults and children with asthma.
- 6- **Provocation tests:-** s the test may also be called a **methacholine challenge test** or **histamine challenge test** respectively. Both drugs provoke **bronchoconstriction, or narrowing of the airways**.