PATHOLOGY TEAM 436

MEDICINE
KING SAUD UNIVERSITY

اللهم لاسهلًا إلا ماجعلته سهلًا وأنت تجعل الحزن إن شئت سهلاً

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Bronchial Asthma

Editing file

Objectives

- **1- Understand asthma as an episodic, reversible bronchoconstriction caused by increased responsiveness of the tracheobronchial tree to various stimuli.**
- **2- Know that asthma is divided into two basic types: extrinsic or atopic allergic and intrinsic asthma. .**
- **3- Understanding the morphological changes (gross and microscopic) seen in the lungs in cases of severe asthma.**

Doctor notes: green
Important : red
Extra explanation grey

Introduction to the respiratory tract :

Conductive zone :

Primary (main) bronchi , secondary (labor)bronchi , tertiary (segmental bronchi) , smaller bronchi , bronchioles , terminal bronchioles

Respiratory zone :

Respiratory bronchioles , alveolar ducts , alveolar sacs , alveoli .

-For more details go back to the anatomy and histology of the lung- [1]

Gas Exchange depends on different factors :

1-compliance (stretchability) of lung

2- can only occur in alveoli that are both ventilated and perfused

ALREKABI : RESPIRATORY SYSTEM STARTS AT THE PHARYNX NOT LARYNX

Spirometer:

Is an equipment Used for measuring the volume of air inspired and expired by the lungs (Pulmonary function test).

In Order to be able to read the spirometery some definitions that you have to be aware of in results:

Forced Expiratory Volume(FEV1) : Volume of air blown out forcibly in the first second . it depends on Body size . what do you think would happen with this number with asthma ?

well, since it is an obstructive disease, there must be problems with air coming out of the .lung , this will make the patient able to expire less air. Thus, FEV1 will be decreased

Forced Vital capacity (FVC): total volume of expired air. FVC=TLC -RV

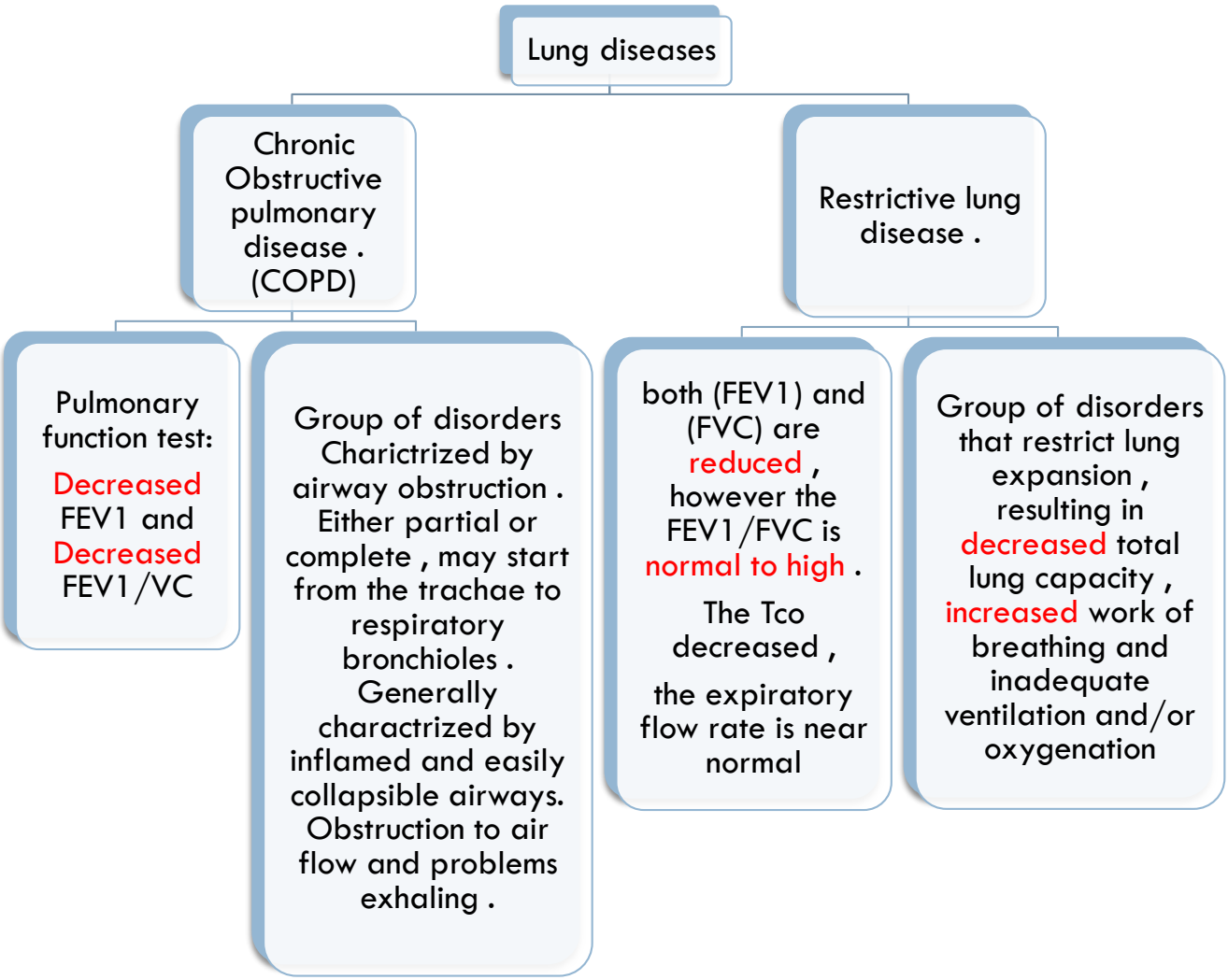
obstructive lung disease, there is no problem with the amount of air in the lungs. In fact, there may be an increase in the amount of air in the lung because when the patient can't exhale the air, it will stay inside the lung causing hyperinflation. FVC will be **normal or slightly increased** .

PEF: Peak Expiratory Flow: This is the ratio between FEV1/FVC. Since FEV1 is decreased, and FVC is normal or increased, the ratio between them would be lower than normal .

[1] مهم معرفة الاناتومي والهستولوجي للرئة

Diffusing capacity (DLCO or TLCO): absorption of monoxide in one breath (gas exchange) . it depends on the concentration of blood hemoglobin, which has strong affinity for CO , and it assess the ability of the lung to exchange gas efficiently

Conclusion: In COPD and asthma patients, FEV1 is less, FVC is normal or increased, and PEF is lower than normal



Types of obstructive lung disease : (Diffuse lung disease)

1-bronchial asthma
2- chronic obstructive pulmonary disease (COPD)
A.chronic bronchitis
B.Emphysema
3-bronchiectasis

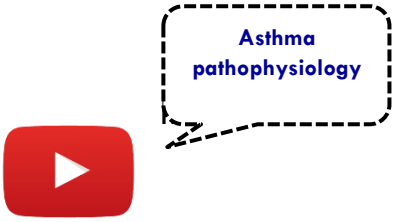
Bronchial Asthma : (BA)

It is a **chronic** relapsing inflammatory obstructive lung disease characterized by hyper-reactive airways.

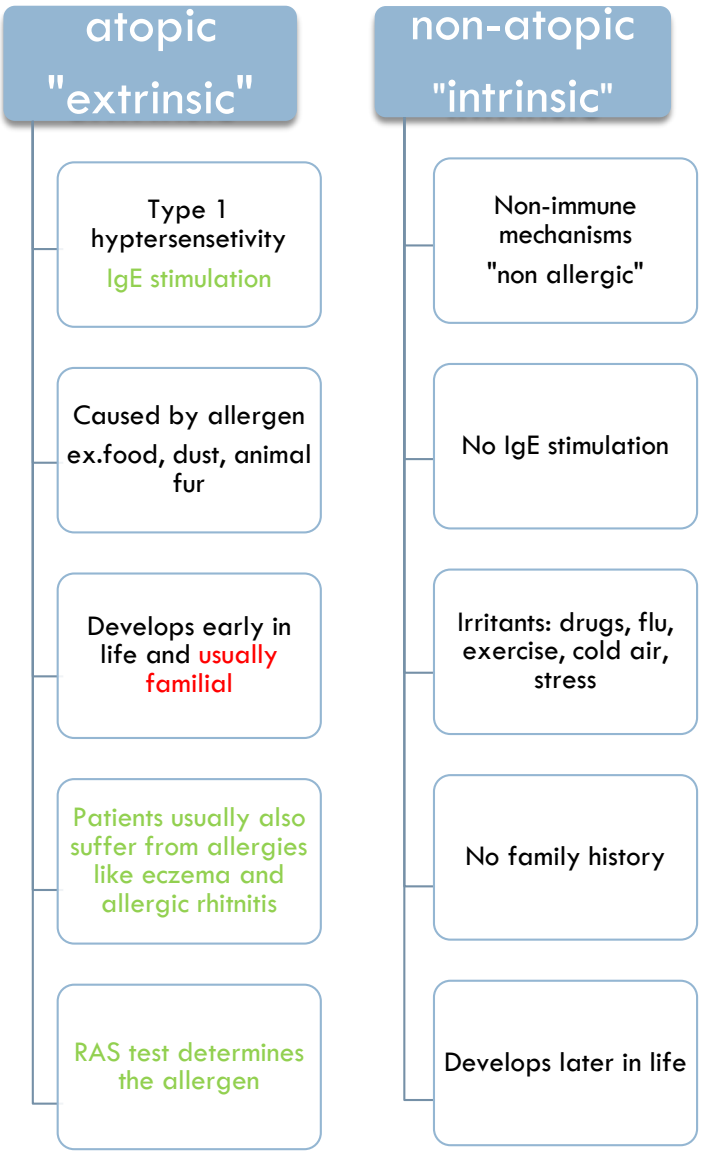
It is **reversible** bronchoconstriction/spasm characterized by hyper-irritability of the airways due to increased responsiveness of the tracheobronchial tree to various stimuli.
Eosinophils will be high
Bronchial Smooth muscle cell hypertrophy and hyper-reactivity

BA targets which part of the respiratory system?

Primarly targets Bronchi and terminal bronchioles
the most common respiratory disease in **children**



Types of Asthma :



Other types mentioned in Robbins:

Drug-induced: pharmacological agents provoke asthma, such as Aspirin

Occupational: stimulated by fumes, organic, and chemical dusts such as plastic, wood, and platinum. Can be considered a type of atopic asthma

Pathogenesis of Asthma:

The major etiologic factors of asthma are genetic predisposition to type 1 hypersensitivity (atopy) ,acute and chronic airway inflammation with edema ,and bronchial hyper-responsiveness[2] to a variety of stimuli.

Note: Airflow obstruction can be caused by a variety of changes, including acute

Bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling.

The degree of airway hyper-responsiveness generally correlates with the clinical severity of asthma.

In atopic and occupational asthma, the disease process is a type I hypersensitivity reaction involves many cell types.

and numerous inflammatory mediators, but the role of type 2 helper T (TH2) cells[3] may be critical to the pathogenesis of asthma.

The classic atopic form of asthma is associated with an excessive TH2 reaction against environmental antigens

Steps of the pathogenesis:

T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines, and the pathogenetic mechanisms have been best studied in atopic asthma.

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[2] Bronchial hyper-responsiveness: causes exaggerated bronchoconstriction.

[3] What is the difference between TH1 & TH2?
TH1 in protective immunity.
TH2 in allergic disease.

First there is initial sensitization:

First time exposure to an inhaled allergen (antigen) will stimulate the the TH2 cells (CD4 TH2) to produce cytokines TH2 cell is an activated cells in asthmatic patients.

interleukin IL- 4, IL-5 and IL-13, IL10

IL-4 > activates the (TH2) cells and stimulates IgE production

IL-5 > activates eosinophils. Eosinophils play a major role in allergic reaction and it contains granules that contain a protein called "Major basic protein", so in asthmatic patients there will be an increase in the number of Eosinophil.

IL-13 > stimulate mucus production and promotes IgE production by B cells.

IL-10 > activated the TH2 cells. TH2 cells activated by allergen.

IL-10 يعتمد علىactivation واستمرارية هذا ال

IgE coats submucosal mast cells, which on re-exposure to allergen release granule content Histamine and serotonin (5 hydroxytryptamine) and it will be lead to bronchoconstriction, edema

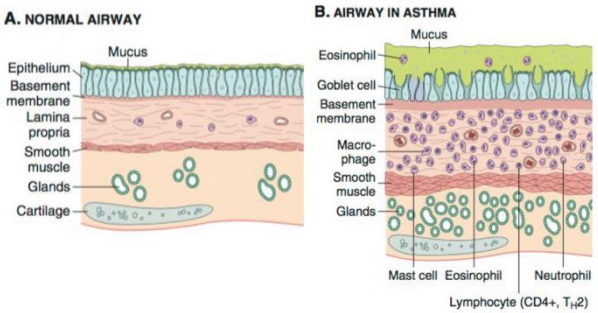
mast على يكون موجود اليantibody receptor (IgE) ويرتبط مع الallergen or antigen يعني يجي ال cells ويطلعلي الgranules

this induces two waves of reaction: an early (immediate) phase and a late phase.

What do we mean by re-exposure?

First time, our bodies only make IgE, as there are no symptoms. However the second time symptoms start to appear because our bodies have already made IgE before.

The early reaction is dominated by bronchoconstriction, increased mucus production (mucus blockade) and variable vasodilation.



A and B, Comparison of a normal bronchus with that in a patient with asthma.

Note the accumulation of mucus in the bronchial lumen resulting from an increase in the number of mucus-secreting goblet cells in the mucosa and hypertrophy of submucosal glands. In addition, there is intense chronic inflammation due to recruitment of eosinophils, macrophages, and other inflammatory cells. Basement membrane underlying the mucosal epithelium is thickened, and smooth muscle cells exhibit hypertrophy and hyperplasia.

C. Inhaled allergens (antigens) elicit a TH2-dominated response favoring IgE production and eosinophils recruitment (priming or sensitization) .

D. On re-exposure to antigen (Ag), the immediate reaction is triggered by antigen-induced cross-linking of IgE bond to IgE receptors on mast cells in airway.

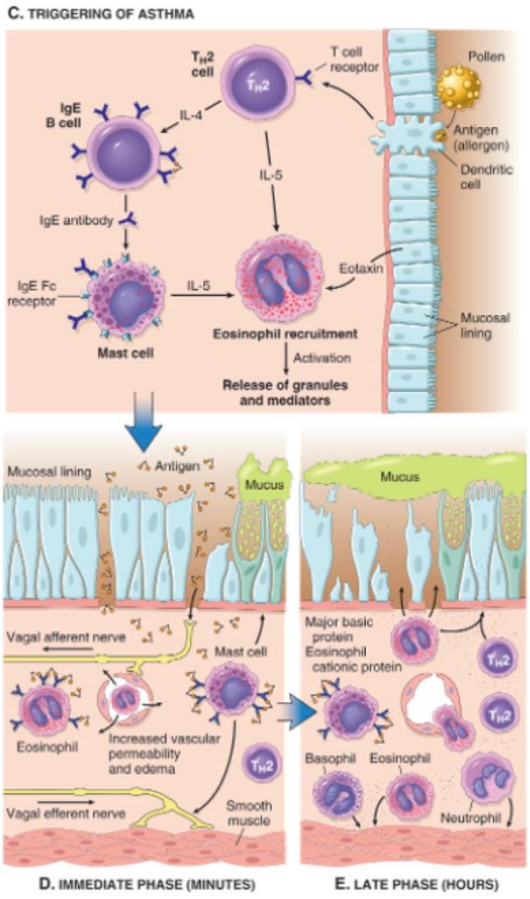
These cells release preformed mediators.

Collectively, either directly or through neural reflexes. The mediators induce bronchospasm, increase vascular permeability and mucus production, and recruit additional mediator-releasing cells from blood.

E. the arrival of recruit leukocytes (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) signals the initiation of the late phase of Asthma and a fresh round of mediator release from leukocyte, endothelium, and epithelial cells.

Factors, particularly from eosinophils (e.g., major basic protein, eosinophil cationic protein), also cause damage to the epithelium.

IgE, immunoglobulin E.



Phase 1: Acute-phase response (the early stage):

Begin 30 to 60 **minutes** after inhalation of antigen/aeroallergens (e.g. allergens, drugs, cold, exercise).

The exposure results in the stimulation and degranulation of **mast cells, eosinophils,** and **basophils** with the release of inflammatory mediators from these cells and also from activated **macrophages**. The released mediators induces bronchoconstriction/spasm (triggered by direct stimulation of subepithelial vagal receptors), increased vascular permeability, inflammation and injury of the bronchial walls and bronchial epithelium and excess mucous secretion.

Phase 2: Late phase reaction/ late asthmatic response:

Responsible for the morphologic changes that occur in asthma

It is the airway edema which occurs 6-24 **hours** following allergen exposure.

Inflammation, with activation of eosinophils (releases major basic protein & cationic protein into the bronchial lumen which are toxic to epithelial cells and cause epithelial cell damage which further impairs mucociliary function) neutrophils, and T cells. These cells Activated by chemotactic factors released during the early stage of asthma.

Epithelial cells produce chemokines that attract more Th2 cells and eosinophils (including eotaxin, a potent chemoattractant and activator of eosinophils). Thus amplifying the inflammatory reaction, without any additional antigen (allergen).

Repeated bouts of inflammation leads to structural changes in the bronchial wall, collectively referred to **AIRWAY REMODELING.**

These changes include hypertrophy of bronchial smooth muscles and mucus glands, and increased vascularity and deposition of subepithelial collagen , which may occur as early as several years before initiation of symptoms.

Asthma is a complex genetic disorder in which multiple susceptibility interact with environmental factors to initiate the pathologic reaction.

A susceptibility locus for atopic asthma:

A. On the long arm of chromosome 5 (5q):

At this loci there are several genes involved in regulation of IgE synthesis and mast cell and eosinophil growth and differentiation map. These genes are responsible of the production of IgE in many ways.

These genes include:

-
IL13 (genetic polymorphisms linked with susceptibility to the development of atopic asthma)

- CD14 (single-nucleotide polymorphisms associated with occupational asthma)

- Class II HLA alleles (tendency to produce IgE antibodies)

- IL-4 receptor gene (atopy, total serum IgE level, and asthma).

- β2- adrenergic receptor gene.

B. On the long arm of chromosome 20 (20q):

Another important locus is on 20q where ADAM-33 regulate proliferation of bronchial smooth muscles and fibroblasts is located (this controls airway remodeling).

Level of YKL-40[4] is a marker of asthma:

Chitinases and chitinase-like proteins play a role in Th2-type inflammation. Thus, they may be useful in diagnosing and monitoring of asthma.
Chitinase family member with no enzymatic activity.

Inflammatory Mediators of Bronchial Asthma using Atopic Asthma as a model:

Inflammatory mediator produced are :

- Leukotrienes mediate allergic reactions synthesized by inflammatory cells found in the airway (eosinophils, macrophages, mast cells).

C4, D4 & E4 (induce bronchospasm, vascular permeability & mucous production increase bronchial hyper-reactivity, mucosal edema).

لاحظ ان الحروف متسلسله .

it's the chemical mediators that we should know in asthma.

- Prostaglandins D2, E2, F2 (induce bronchospasm and vasodilatation)

- Histamine from the mast cells (induce bronchospasm and increased vascular permeability)

- Platelet-activating factor (cause aggregation of platelets and release of histamine)

- Mast cell tryptase (inactivate normal bronchodilator).

- Tumor necrosis factor (amplify the inflammatory response)

The inflammatory mediators lead to:

1- smooth muscle contraction, bronchospasm.

2- mucous secretion.

3- increased vascular permeability and edema.

So as a summary:

As a result of the action of these four interleukin IL-4,IL-5,IL-13,IL-10 + the action of the Eosinophil >> mucus blockade – hyperplasia of smooth muscles cells – accumulation of the eosinophil and inflammatory cells – fibrosis of bronchial wall – thickness in the basement membrane.

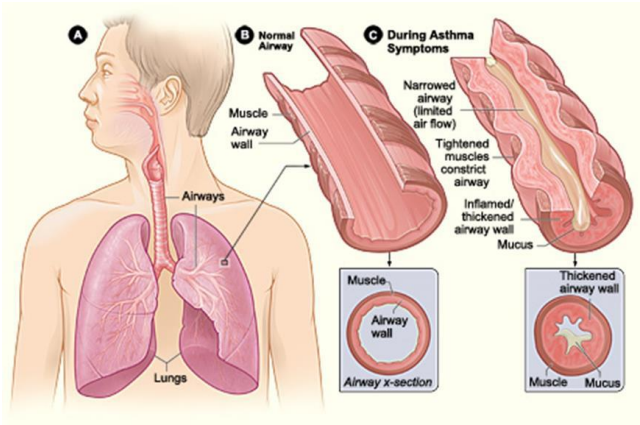
The Morphologic Changes

The morphologic changes in asthma have been described in persons who die of prolonged severe attacks (**status asthmaticus**) and in mucosal biopsy specimens of persons challenged with **allergens.**

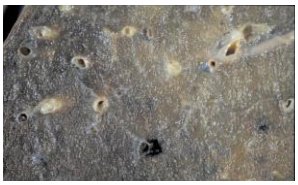
Gross:

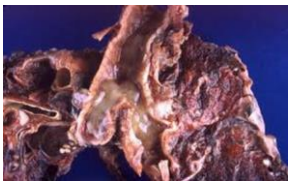
- lungs are overdistended because of (*overinflation), and there may be small areas of [4]**atelectasis.**
- occlusion of bronchi and bronchioles by thick, tenacious **mucous plugs**

*Why is there a hyperinflated lung? (435
The victim labors to get air into the lungs and then cannot get it out, so that there is progressive hyperinflation of the lungs with air trapped distal to the bronchi, which are constricted and filled with mucus and debris.



mucous plugs :

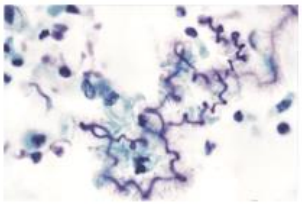




Microscopic(histologic):

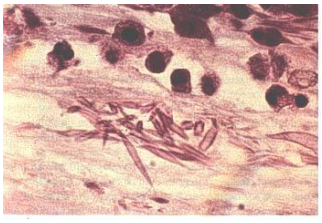
-the mucous plug contains:

1- **Curschmann spirals:** whorls of shed epithelium, Coiled , basophilic plugs of mucus formed in the lower airways and found in sputum and tracheal washings.



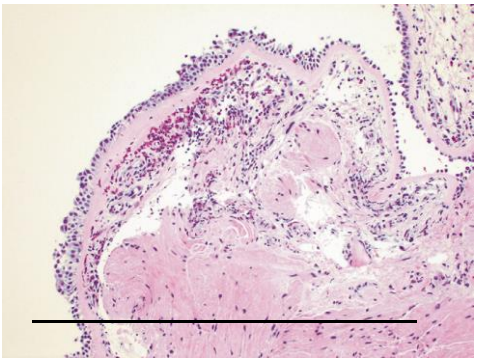
2- **Eosinophilic infiltrate and proliferation**

3- **Charcot-Leyden crystals:** Eosinophilic needle-shaped crystalline structures. (collections of crystalloids made up of eosinophil proteins, can be obtained from biopsy or in sputum , and in tissues containing heavy amounts of eosinophils)



-Airway remodeling:

- Thickening of airway wall
- Hypertrophy of bronchial smooth muscle.
- Increased vascularity in submucosa and deposition of subepithelial collagen.
- Subbasement membrane fibrosis.
- Thickening and hyalinization of basement membranes
- Hyperplasia (increase in size) of submucosal glands and goblet cells.
- Metaplasia of the airway epithelium



Partial or complete collapse of the lung[4]

CLINICAL COURSE of BA

- The clinical manifestations vary from occasional **wheezing** to **paroxysms** of **dyspnea** and **respiratory distress.**
- In a classic asthmatic attack there is **dyspnea, cough, difficult expiration, progressive hyperinflation of lung and mucous plug in bronchi**. This may resolve spontaneously or with treatment.
- Nocturnal cough
- Increased anteroposterior diameter, due to air trapping and increase in residual volume
- Status asthmaticus – severe cyanosis and persistent dyspnea, may be fatal

STATUS ASTHMATICUS

- It is the most **severe** form of asthma. It refers to severe bronchoconstriction that does not respond to the drugs that usually abort the acute attack. There is severe acute paroxysm of respiratory distress.
- This situation is potentially serious and requires hospitalization. Patients in status asthmaticus have **hypoxemia** and often **hypercapnia**.
- In particularly severe episodes the ventilatory functions may be so impaired so as to cause severe cyanosis and even death.
- They require oxygen and other pharmacologic interventions.
- It may persists for days and even weeks.

COMPLICATIONS OF ASTHMA

- **Airway remodeling**: some persons with long standing asthma develop permanent structural changes in the airway with hypertrophy of muscle, thickened BM and increased glands. These result in progressive loss of lung function with increase airflow obstruction and airway responsiveness.
- **Superimposed infection** i.e. pneumonia
- **Chronic bronchitis** (i.e. Asthmatic bronchitis: chronic bronchitis with superimposed asthma)
- **Emphysema, pneumothorax and pneumomediastinum**
- **Bronchiectasis**
- **Respiratory failure** requiring intubation in severe exacerbations i.e. status asthmaticus
- In some cases **cor pulmonale** and heart failure develop.

Prognosis

- Approximately half the children diagnosed with asthma in childhood outgrow their disease by late adolescence or early adulthood and require no further treatment.
- Patients with poorly controlled asthma develop long-term changes over time (i.e. with airway remodeling). This can lead to chronic symptoms and a significant irreversible component to their disease.
- Many patients who develop asthma at an older age also tend to have chronic symptoms.
    - Remission—approximately 50% of cases of childhood asthma resolve spontaneously but may recur later in life; remission in adult-onset asthma is less likely.
    - Mortality—death occurs in approximately 0.2% of asthmatics. Mortality is usually (but not always) preceded by an acute attack and about 50% are more than 65 years old.

Prevention

- Control of factors contributing to asthma severity. Exposure to irritants or allergens has been shown to increase asthma symptoms and cause exacerbations.
- Clinicians should evaluate patients with persistent asthma for allergen exposures and sensitivity to seasonal allergens. Skin testing results should be used to assess sensitivity to common indoor allergens.
- All patients with asthma should be advised to avoid exposure to allergens to which they are sensitive.

SUMMARY

Asthma

- Asthma is characterized by reversible bronchoconstriction caused by airway hyperresponsiveness to a variety of stimuli.
- Atopic asthma is caused by a T_H2 and IgE-mediated immunologic reaction to environmental allergens and is characterized by acute-phase (immediate) and late-phase reactions. The T_H2 cytokines IL-4, IL-5, and IL-13 are important mediators.
- Triggers for nonatopic asthma are less clear but include viral infections and inhaled air pollutants, which can also trigger atopic asthma.
- *Eosinophils* are key inflammatory cells found in almost all subtypes of asthma; eosinophil products such as major basic protein are responsible for airway damage.
- Airway remodeling (sub-basement membrane thickening and hypertrophy of bronchial glands and smooth muscle) adds an irreversible component to the obstructive disease.

Thank you

اللهم إني استودعتك ما قرأت وما حفظت فرده إلي وقت حاجتي

Girls

Leader:

Munirah aldofyan

Members :

1- **haneen alsubki**
2- **samar alqahtani**
3- **najd altheeb**
4- **lama alfawzan**

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Leader: **faisal algharbi**

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