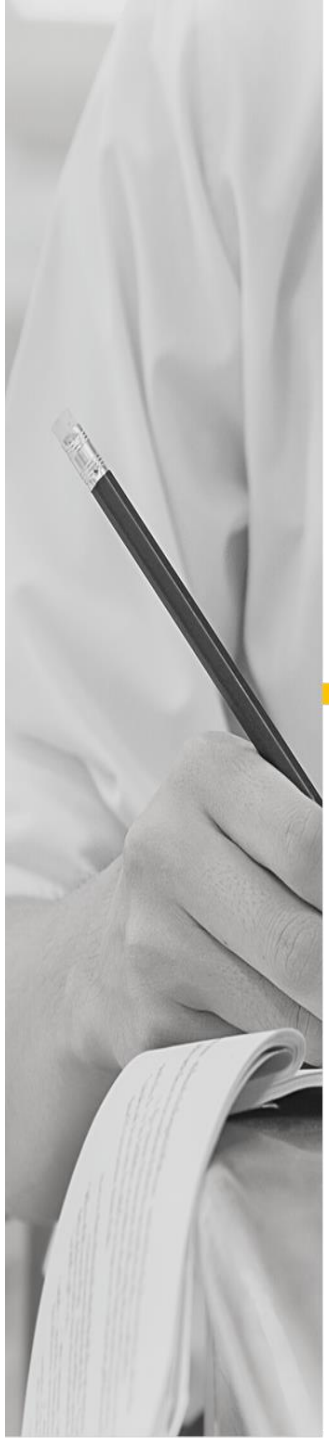

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Subject name:Advanced Pharma

Subject year: MSc - PHARMA

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TIKRIT UNIVERSITY

COLLEGE OF VET. MEDICINE

FIRST TERM – M.Sc PHARMACOLOGY

ADVANCED PHARMACOLOGY

RESPIRATORY PHARMACOLOGY

DRUGS USED IN MANAGEMENT OF ASTHMA

PROF DR HUSAMULDEEN ALNAJAR

Physiology of Respiration:

- **Respiration is controlled by spontaneous rhythmic discharges from the respiratory centre in the medulla, modulated by input from higher central nervous system (CNS) centers and vagal afferents from the lungs (partial pressure of carbon dioxide in arterial blood (*PACO2)* and of oxygen (*PAO2))*.**

- Some voluntary control can be superimposed on the automatic regulation of breathing, implying connections between the cortex and the motor neurons innervating the muscles of respiration.
- Irritant receptors and C fibers respond to chemical irritants and cold air, and also to inflammatory mediators.

Efferent pathways controlling the airways

- **Autonomic innervation**
- ***Parasympathetic innervation*. Parasympathetic innervation of bronchial smooth muscle predominates. M3 receptors are pharmacologically the most important. They are found on bronchial smooth muscle and glands, and mediate bronchoconstriction and mucus secretion.**
- **A distinct population of NANC nerves also regulates the airways. Bronchodilators released by these nerves include *vasoactive intestinal polypeptide* and *nitric oxide*.**

- ***Sympathetic innervation.***
- β2- adrenoceptors are abundantly expressed on human airway smooth muscle (as well as mast cells, epithelium, glands and alveoli) and β agonists relax bronchial smooth muscle, inhibit mediator release from mast cells and increase mucociliary clearance.
- Non-myelinated sensory fibres linked to irritant receptors in the lungs release tachykinins such as *substance P, neurokinin A* and *B* which act on smooth muscle, secretory and inflammatory cells, producing inflammation.

Pulmonary diseases

- Common symptoms of pulmonary disease include shortness of breath, wheeze, chest pain and cough with or without sputum production or haemoptysis—blood in the sputum.
- Ideally, treatment is of the underlying disease, but sometimes symptomatic treatment, for example of cough, is all that is possible.

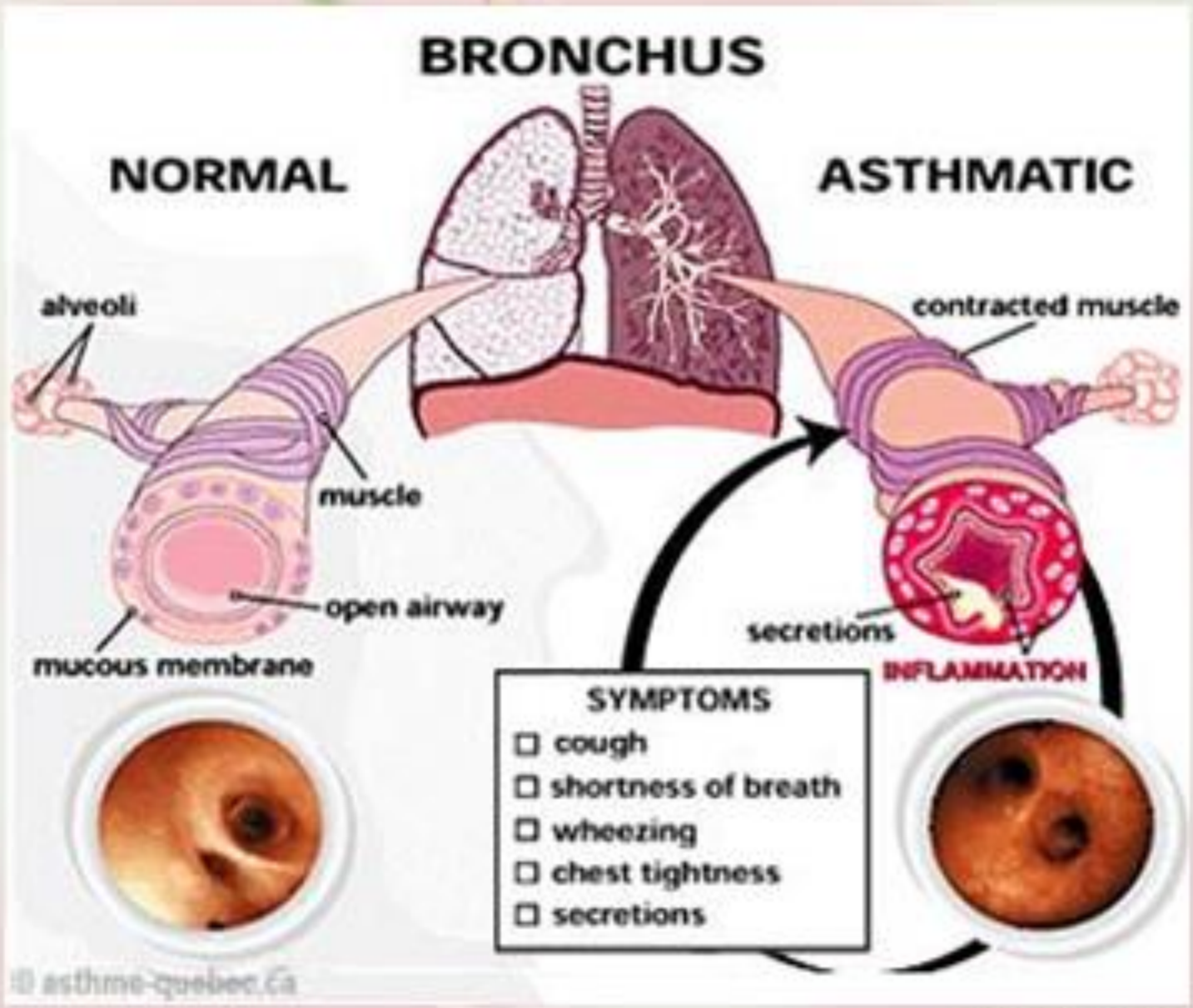
Asthma

- IN 2023 MORE THAN 300 MILLION ASTHMATIC PATIENTS GLOBALLY.
- MORE THAN 100 MILLION AT RISK OF DEVELOPING ASTHMA.
- 1 DEATH BY ASTHMA IN EVERY 250 DEATH




Definition

- Asthma is an inflammatory condition in which there is recurrent reversible airways obstruction in response to irritant stimuli that are too weak to affect non-asthmatic subjects.
- Asthmatic patients experience intermittent attacks of wheezing, shortness of breath with difficulty especially in breathing out and sometimes cough.
- Acute attacks are reversible, but the underlying pathological disorder can progress in older patients to a chronic state.

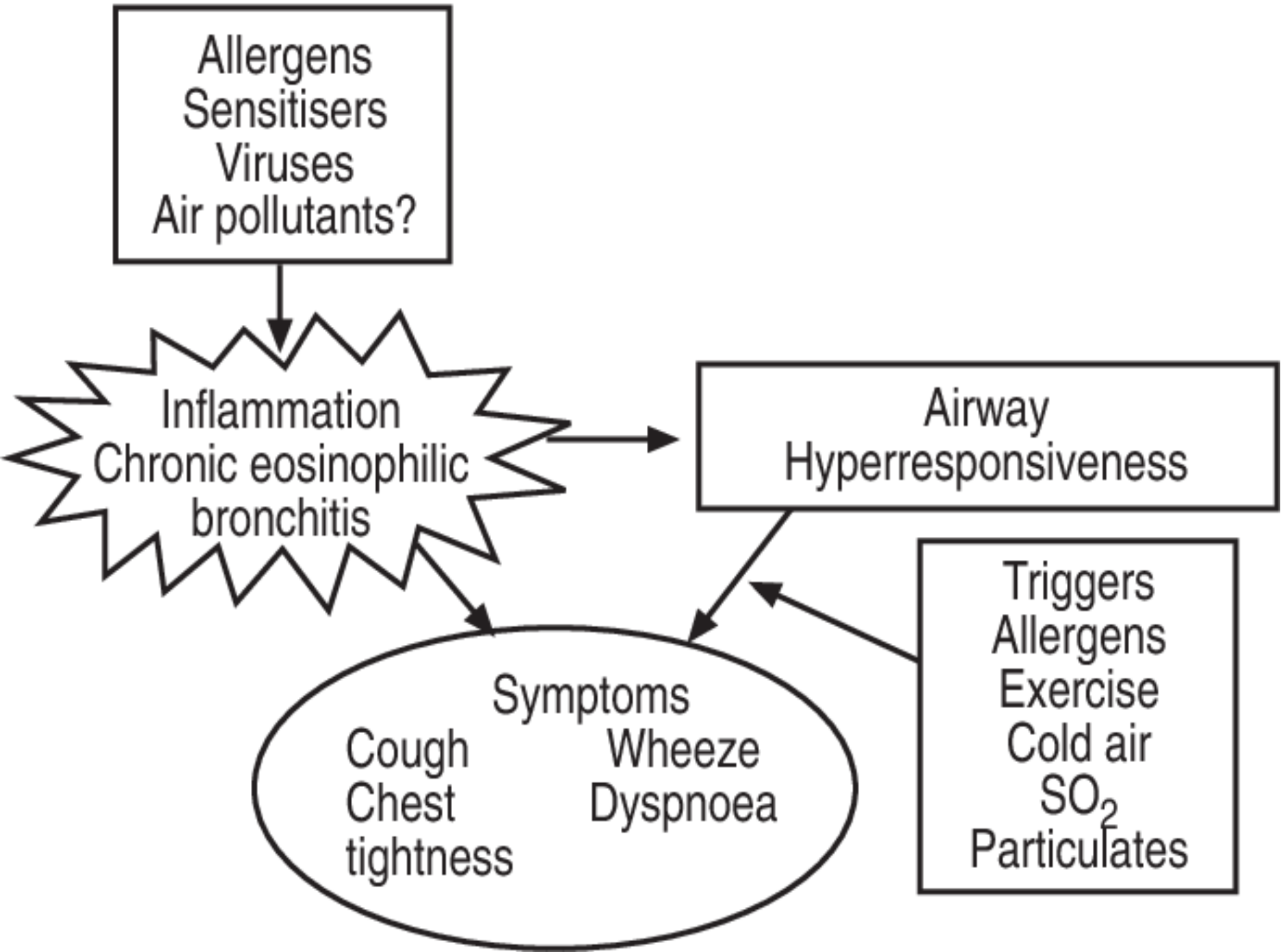

BRONCHUS
NORMAL
ASTHMATIC
alveoli
muscle
open airway
mucous membrane
contracted muscle
secretions
INFLAMMATION
SYMPTOMS
cough
shortness of breath
wheezing
chest tightness
secretions
© asthme-quebec.ca

Many cells and cellular elements play a role in asthma, in particular:

- *Mast cells*
- *Eosinophils*
- *Neutrophils*
- *T lymphocytes*
- *Macrophages*
- *Epithelial cells*

Symptoms

- *Coughing (particularly at night or early in the morning)*
- *Wheezing*
- *Breathlessness*
- *Chest tightness*
- *Reversible airflow obstruction*
- There is a wide spectrum of disease severity, ranging from patients with occasional, mild bouts of breathlessness to patients who wheeze daily despite continuous high dosages of medication.


Allergens
Sensitisers
Viruses
Air pollutants?
Inflammation
Chronic eosinophilic
bronchitis
Airway
Hyperresponsiveness
Triggers
Allergens
Exercise
Cold air
SO_2
Particulates
Symptoms
Cough
Chest
tightness
Wheeze
Dyspnoea

Etiology

1. **Childhood-onset asthma(atopic) :**

- Positive family history of asthma and allergy to tree and grass pollen, house dust mites, household pets, and molds due to the genetic predisposition for the development of immunoglobulinE (IgE)–mediated response to common aeroallergens (atopy).

2. Adult-onset asthma:

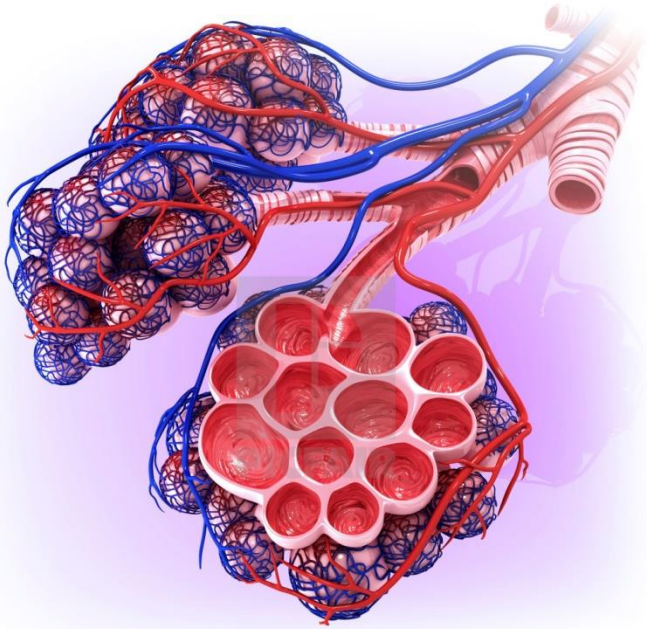
- a negative family history and negative skin tests to common aeroallergens.
- Some of these patients may have nasal polyps, aspirin sensitivity, and sinusitis.
- Exposure to factors (e.g., wood dust, chemicals) at the workplace that may cause airway inflammation is also important in many adults.

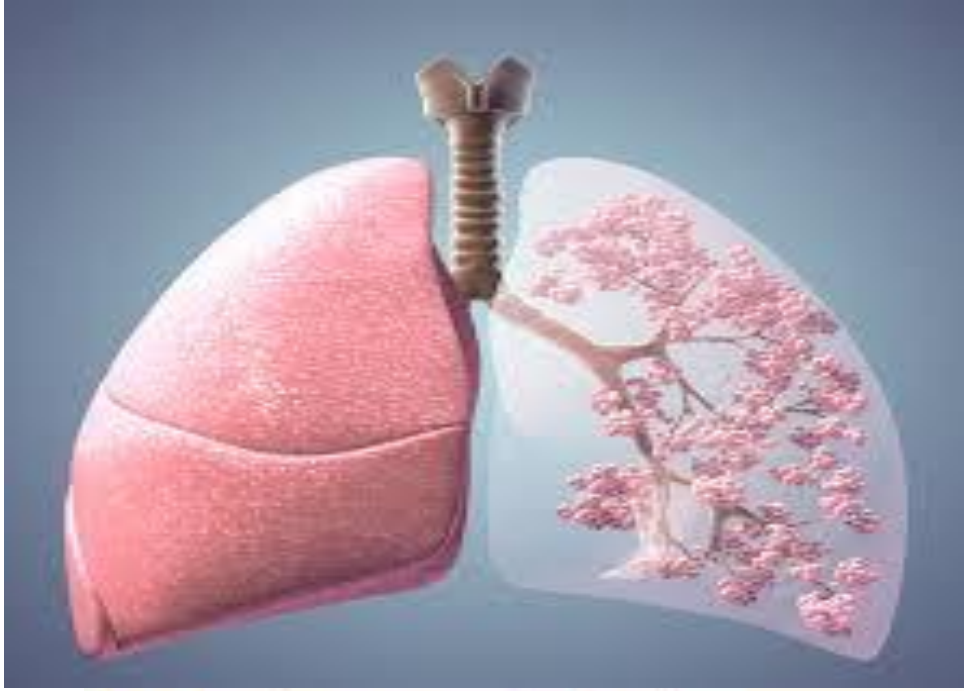
Other types of asthma

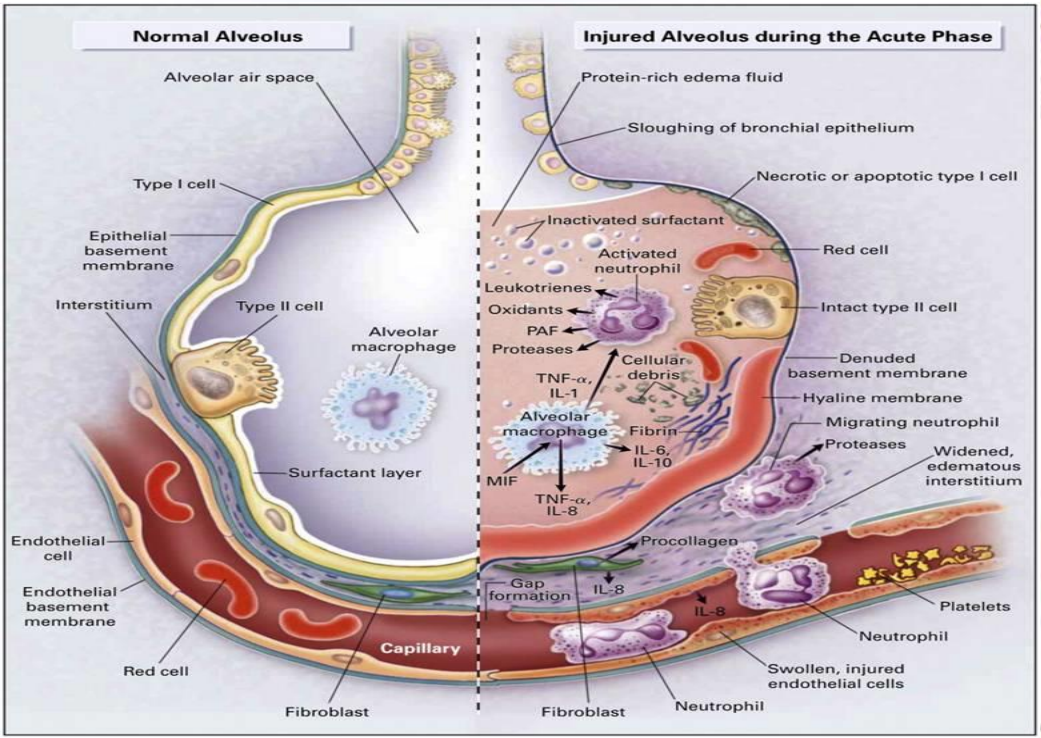
- Environmental asthma.
- Exercise-induced asthma.
- Occupational asthma
- Aspirin-induced asthma

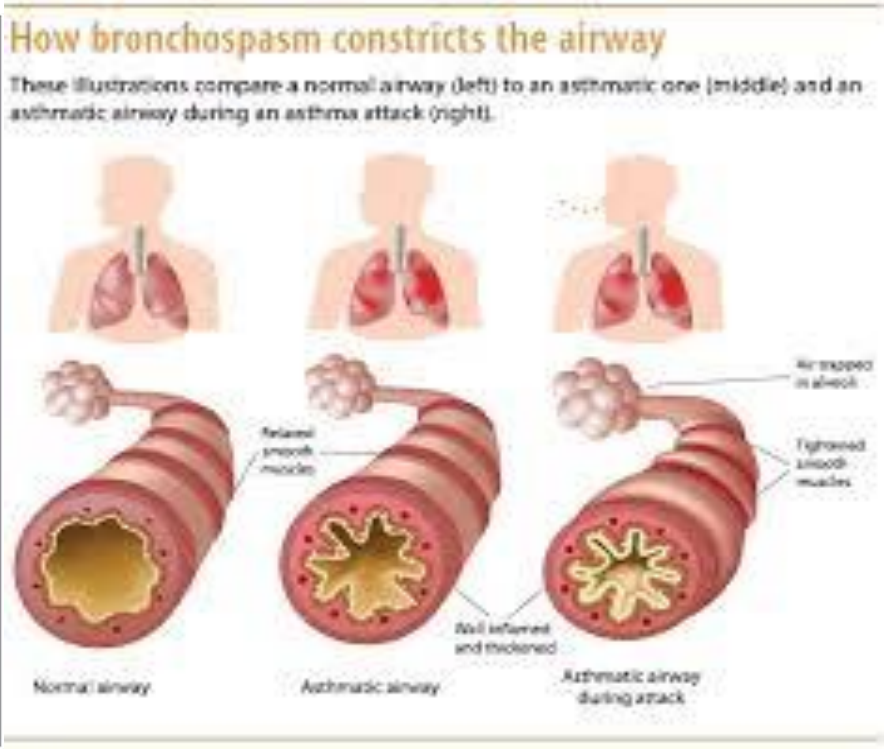
PATHOGENESIS OF ASTHMA

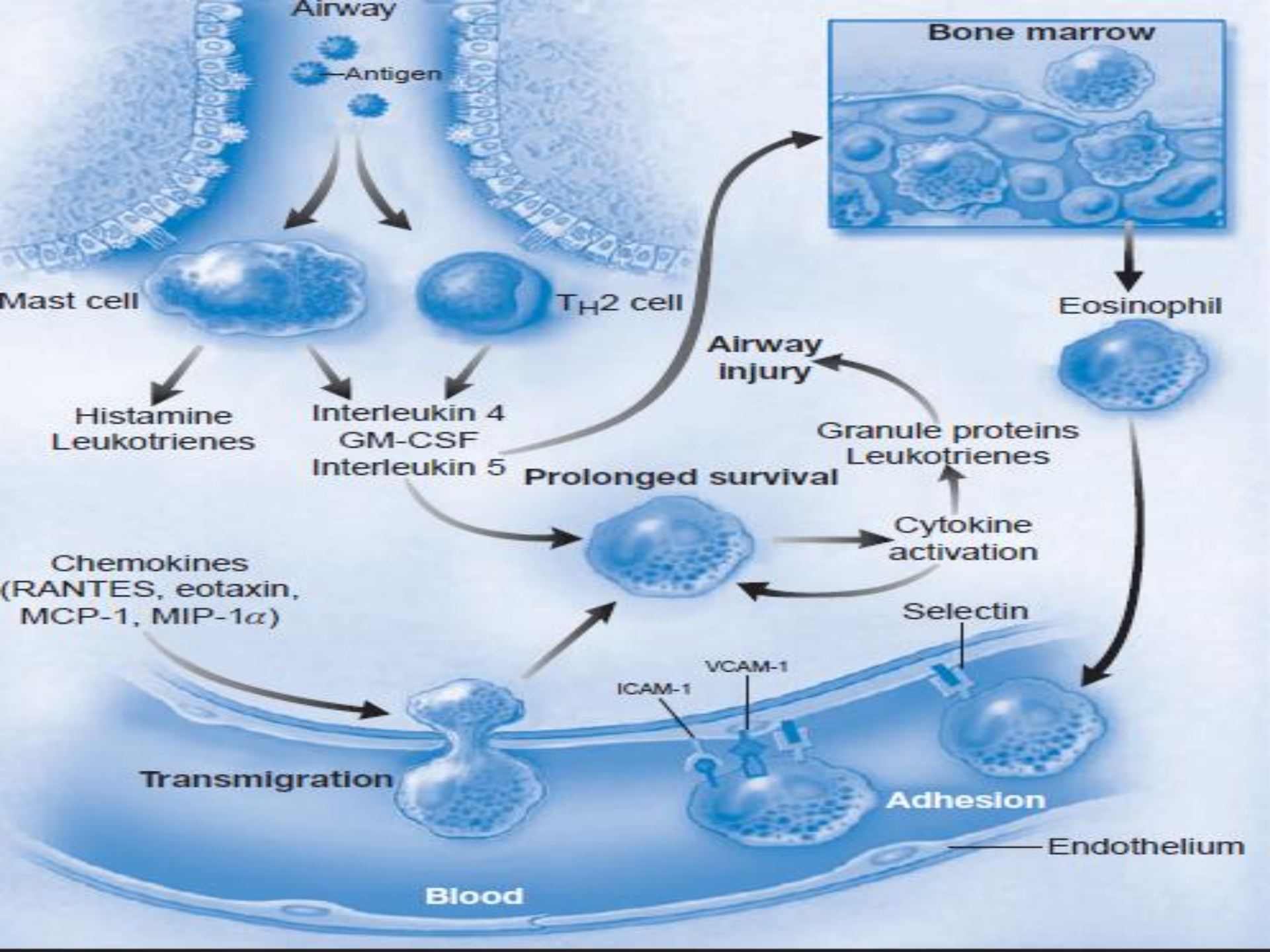
- The classic immunologic model of asthma presents it as a disease mediated by reaginic immune globulin (IgE).
- After exposure to an asthma-precipitating factor (e.g., aeroallergen), IgE is produced and bind to mast cells in the airway mucosa.

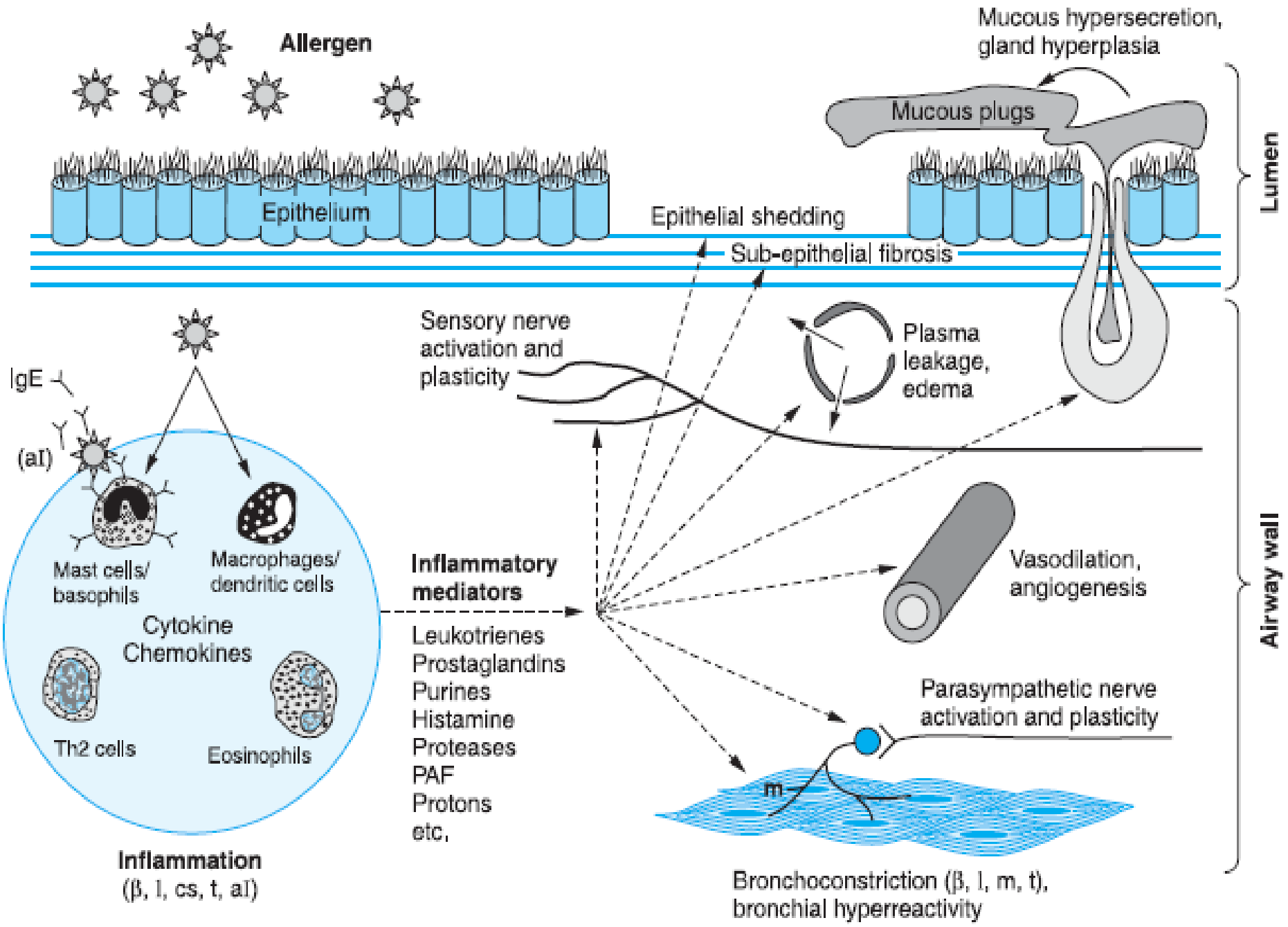





Normal Alveolus
Injured Alveolus during the Acute Phase
Alveolar air space
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Capillary
Red cell
Fibroblast
Protein-rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Activated neutrophil
Red cell
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
Cellular debris
TNF-α, IL-1
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
Migrating neutrophil
IL-6, IL-10
Proteases
MIF
TNF-α, IL-8
Widened, edematous interstitium
Procollagen
Gap formation
IL-8
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

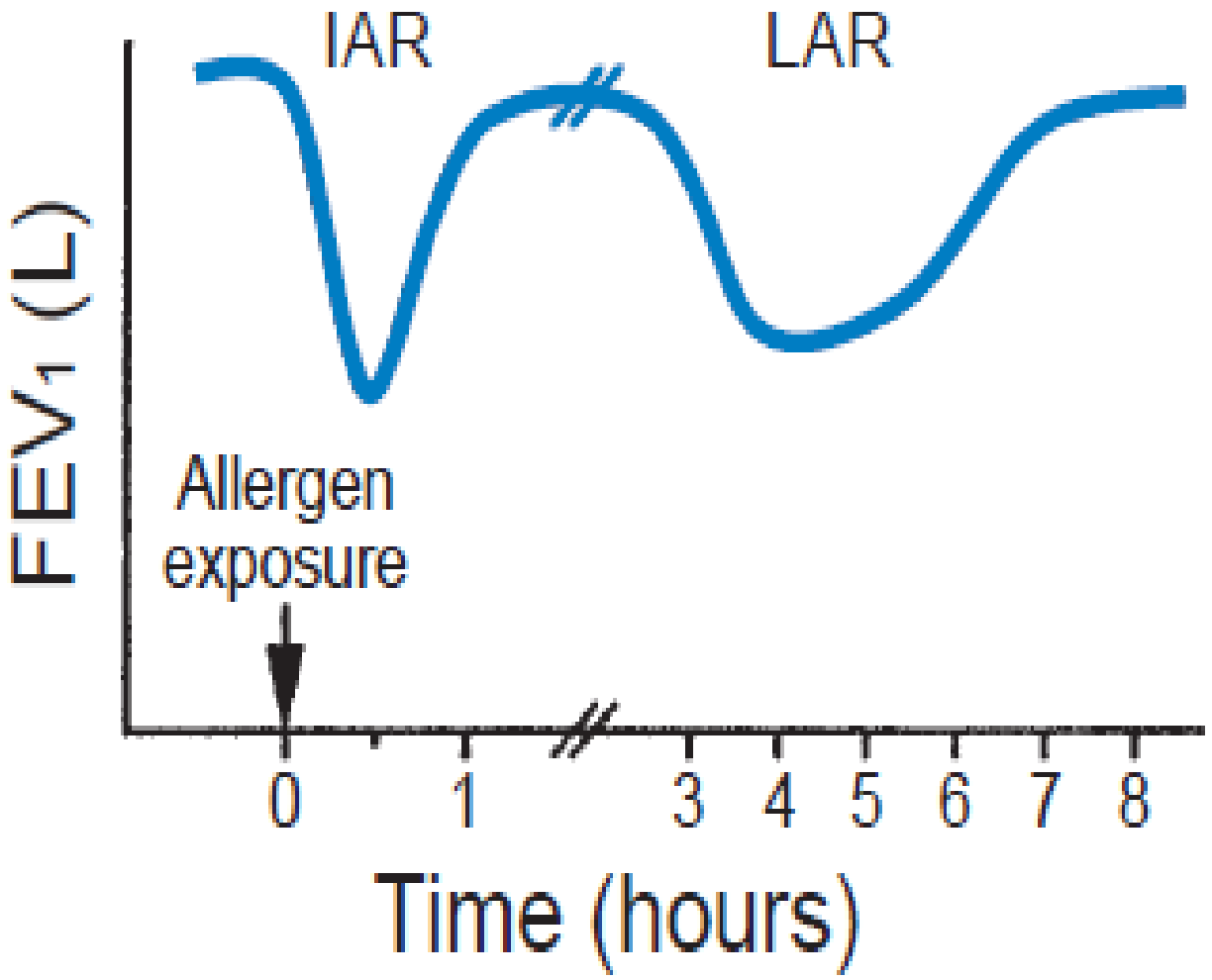

How bronchospasm constricts the airway
These illustrations compare a normal airway (left) to an asthmatic one (middle) and an asthmatic airway during an asthma attack (right).
Normal airway
Asthmatic airway
Asthmatic airway during attack


Airway
Antigen
Bone marrow
Mast cell
T_H2 cell
Eosinophil
Airway injury
Histamine
Leukotrienes
Interleukin 4
GM-CSF
Interleukin 5
Granule proteins
Leukotrienes
Prolonged survival
Cytokine activation
Chemokines
(RANTES, eotaxin,
MCP-1, MIP-1α)
Selectin
VCAM-1
ICAM-1
Transmigration
Adhesion
Endothelium
Blood

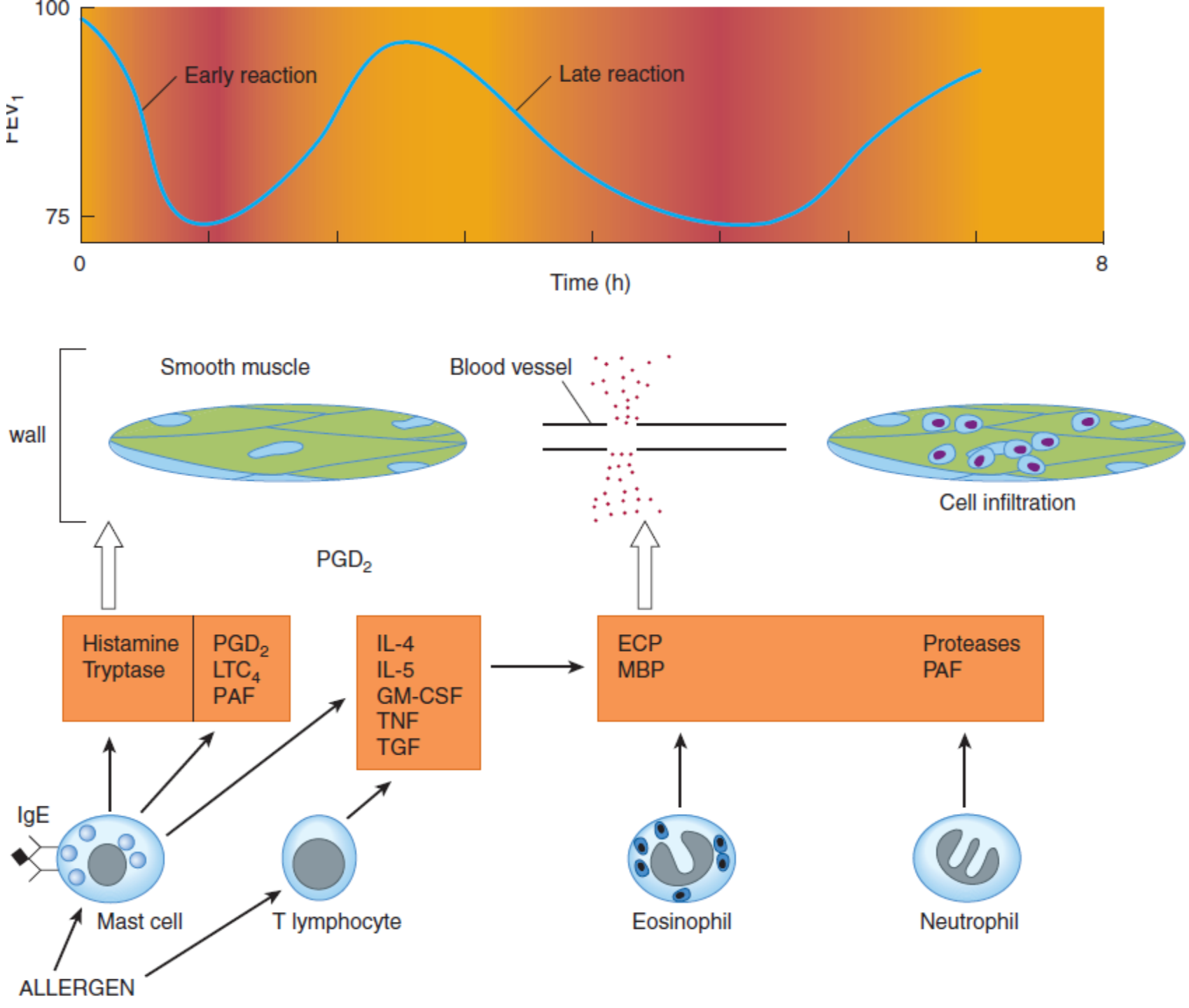

Allergen
Mucous hypersecretion, gland hyperplasia
Mucous plugs
Epithelium
Epithelial shedding
Sub-epithelial fibrosis
Lumen
Airway wall
Sensory nerve activation and plasticity
Plasma leakage, edema
IgE
(aI)
Mast cells/ basophils
Macrophages/ dendritic cells
Cytokine Chemokines
Th2 cells
Eosinophils
Inflammation (β, l, cs, t, aI)
Inflammatory mediators
Leukotrienes
Prostaglandins
Purines
Histamine
Proteases
PAF
Protons
etc,
Vasodilation, angiogenesis
Parasympathetic nerve activation and plasticity
m
Bronchoconstriction (β, l, m, t), bronchial hyperreactivity

- On re-exposure to a specific allergen, antigen-antibody interaction on the surface of the mast cells triggers both the release of mediators stored in the cells' granules and the synthesis and release of other mediators.
- Histamine, tryptase, leukotrienes C 4 and D 4 , and prostaglandin D 2 that are released diffuse through the airway mucosa, triggering the muscle contraction and vascular leakage responsible for the acute bronchoconstriction of the "early asthmatic response."

- Early- phase: bronchoconstriction developed immediately after inhalation of allergen and improved after one hour.
- This response is often followed in 3–6 hours by a second, more sustained phase of bronchoconstriction, the “late asthmatic response,” which is associated with an influx of inflammatory cells into the bronchial mucosa and with an increase in bronchial reactivity that may last for several weeks after a single inhalation of allergen.


IAR
LAR
FEV1 (L)
Allergen exposure
0
1
3
4
5
6
7
8
Time (hours)

- Inflammatory mediators are released from bronchial mast cells, T lymphocytes, and epithelial cells.
- These mediators direct the migration and activation of other inflammatory cells, most notably eosinophils, to the airways.
- Eosinophils release biochemicals (e.g., major basic protein (ECP) and eosinophil cationic protein (ECP)) that cause airway injury, including epithelial damage, mucus hypersecretion, and increased reactivity of smooth muscle


100
75
FEV1
Early reaction
Late reaction
0
8
Time (h)
wall
Smooth muscle
Blood vessel
Cell infiltration
PGD2
Histamine
Tryptase
PGD2
LTC4
PAF
IL-4
IL-5
GM-CSF
TNF
TGF
ECP
MBP
Proteases
PAF
IgE
Mast cell
T lymphocyte
Eosinophil
Neutrophil
ALLERGEN

Cell type	Mediator category	Mediator	Function/pathologic effects
Mast cells and basophils			
	Stored preformed in cytoplasmic granules	Histamine	Increases vascular permeability; stimulates smooth muscle cell contraction
		Enzymes: neutral proteases (tryptase and/or chymase), acid hydrolases, cathepsin G, carboxypeptidase	Degrade microbial structures; tissue damage/remodeling
	Major lipid mediators produced on activation	Prostaglandin D_2	Vasodilation, bronchoconstriction, neutrophil chemotaxis
		Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction, mucus secretion, increased vascular permeability
		Platelet-activating factor	Chemotaxis and activation of leukocytes, bronchoconstriction, increased vascular permeability
	Cytokines produced on activation	IL-3	Mast cell proliferation
		TNF, MIP-1α	Inflammation/late phase reaction
		IL-4, IL-13	IgE production, mucus secretion
		IL-5	Eosinophil production and activation
Eosinophils			
	Stored performed in cytoplasmic granules	Major basic protein, eosinophil cationic protein	Toxic to helminths, bacteria, host cells
		Eosinophil peroxidase, lysosomal hydrolases, lysophospholipase	Degrades helminthic and protozoan cell walls; tissue damage/remodeling
	Major lipid mediators produced on activation	Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction; mucus secretion, increased vascular permeability
	Cytokines produced on activation	IL-3, IL-5, GM-CSF	Eosinophil production and activation
		IL-8, IL-10, RANTES, MIP-1α, eotaxin	Chemotaxis of leukocytes

Abbreviations: GM-CSF, granulocyte-monocyte colony-stimulating factor; IL-3, interleukin-3, MIP-1α, monocyte inflammatory protein-1α; RANTES, regulated by activation, normal T cell expressed and secreted; TNF, tumor necrosis factor.

- Bronchoconstriction itself seems to result not simply from the direct effect of the released mediators but also from their activation of neural or humoral pathways.
- Remodeling of airways may occur. Reversibility of airflow limitation may be incomplete in some patients. Persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis.

Diagnosis and Monitoring

1. HISTORY:

- **Symptoms:** wheezing, chest tightness, shortness of breath, coughing, mucus production.
- **Pattern of symptoms:** Perennial, seasonal, or both
- Continual, episodic, or both
- Onset, duration, frequency (number of days or nights, per week or month)
- Diurnal variations, especially nocturnal and on awakening in early morning

- **REMMEBER ALWAYS : Precipitating and/or aggravating factors &**

Family history

2.PULMONARY FUNCTION TESTS

- **SPIROMETRY:** is used to evaluate the performance of the patient's lungs, thorax, and respiratory muscles in moving air into and out of the lungs.
- The forced expiratory volume (FEV): measures how much air a person can exhale during a forced breath.
- The FEV is measured by having the patient exhale into the spirometer as forcefully and completely as possible after maximal inspiration.
- The resulting volume curve is plotted against time.

- The FEV1 usually is expressed as a percentage of the total volume of air exhaled and is reported as the FEV1 to force vital capacity (FVC) ratio.
- FVC, the maximal volume of air exhaled with maximally forced effort from a position of maximal inspiration.
- Healthy persons generally can exhale at least 75% to 80% of their VC in 1 second and almost all of it in 3 seconds.

PEAK EXPIRATORY FLOW (PEF)

- The PEF is the maximal flow that can be produced during the forced expiration.
- A healthy average-sized young adult man typically has a PEF of 550 to700 L/minute.

Goals of Therapy

1\ To ***Reduce Impairment.***

2\To ***Reduce Risk***

- Asthmatic bronchospasm results from a combination of release of mediators and an exaggeration of responsiveness to their effects predicts that asthma may be effectively treated by drugs with different modes of action.

- Drugs that reduce the amount of IgE bound to mast cells (anti-IgE antibody)
- Drugs prevent mast cell degranulation (cromolyn or nedocromil, sympathomimetic agents, calcium channel blockers)
- Drugs block the action of the products released (antihistamines and leukotriene receptor antagonists)
- Drugs inhibit the effect of acetylcholine released from vagal motor nerves (muscarinic antagonists)
- Drugs directly relax airway smooth muscle (sympathomimetic agents, theophylline).

SYMPATHOMIMETIC AGENTS

- They relax airway smooth muscle.
- They inhibit release of bronchoconstricting mediators from mast cells.
- They may also inhibit microvascular leakage and increase mucociliary transport by increasing ciliary activity.

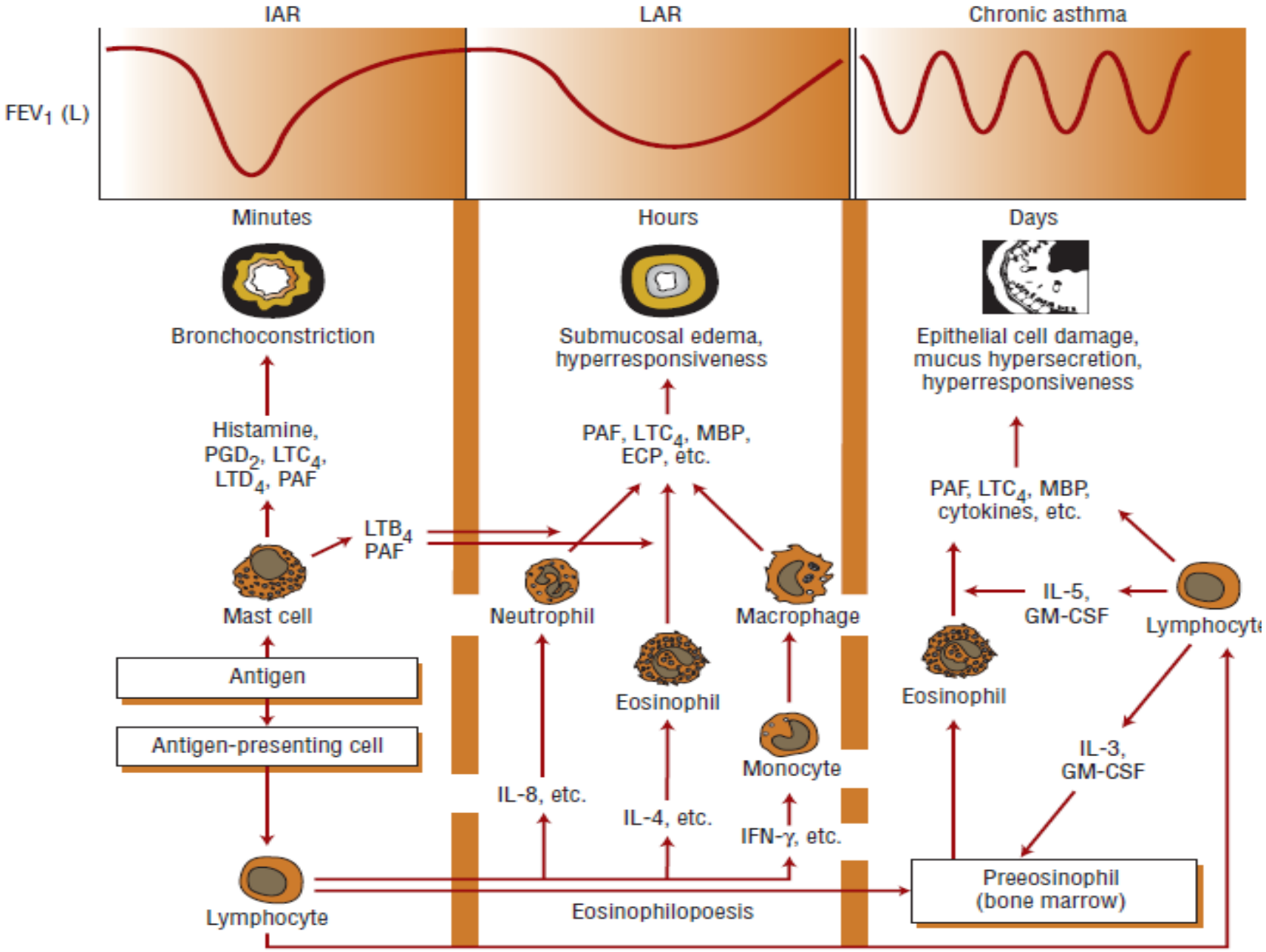
- As in other tissues, the β agonists stimulate adenylyl cyclase and increase the formation of intracellular cAMP.
- They causes tachycardia and skeletal muscle tremor as side effects.
- Adrenoceptor agonists are best delivered by inhalation because this results in the greatest local effect on airway smooth muscle with the least systemic toxicity

- **Non-selective β agonists:**
- Epinephrine
- Ephedrine
- Isoproterenol

- **Selective β 2 agonists:**
- Salbutamol
- Terbutaline
- Metaproterenol
- Salmoterol
- Formoterol

- They are effective after inhaled or oral administration.
- All can be diluted in saline for administration from a hand-held nebulizer.
- Oral dosage forms are associated with systemic side effects like tremors and nervousness.

- Terbutaline is available as subcutaneous injection which is indicated for severe asthma requiring emergency treatment when aerosolized therapy is ineffective.
- Salmoterol and formoterol are long acting agents (12 hours or more) as a result of high lipid solubility. This permits them to dissolve in the smooth muscle cell membrane in high concentrations.
- Because they have no anti-inflammatory action, they are not recommended as monotherapy for asthma.


IAR
LAR
Chronic asthma
FEV1 (L)
Minutes
Hours
Days
Bronchoconstriction
Submucosal edema, hyperresponsiveness
Epithelial cell damage, mucus hypersecretion, hyperresponsiveness
Histamine, PGD2, LTC4, LTD4, PAF
PAF, LTC4, MBP, ECP, etc.
PAF, LTC4, MBP, cytokines, etc.
LTB4
PAF
Mast cell
Neutrophil
Macrophage
IL-5, GM-CSF
Lymphocyte
Antigen
Eosinophil
Eosinophil
Antigen-presenting cell
Monocyte
IL-3, GM-CSF
IL-8, etc.
IL-4, etc.
IFN-γ, etc.
Lymphocyte
Eosinophilopoesis
Preeosinophil (bone marrow)

METHYLXANTHINE DRUGS

- The three important methylxanthines are **theophylline, theobromine,** and **caffeine.**
- Their major source is beverages (tea, cocoa, and coffee, respectively).
- A theophylline preparation commonly used for therapeutic purposes is **aminophylline**

Mechanism of Action

- Several mechanisms have been proposed for the actions of methylxanthines, but none has been firmly established.
- At high concentrations, they can be shown in vitro to inhibit several members of the phosphodiesterase (PDE) enzyme family.

- PDE enzyme hydrolyzes cAMP and cGMP both induce smooth muscle relaxation. Though, inhibition of PDE enzyme results in cAMP and cGMP accumulation and as a result smooth muscle relaxation.
- Cyclic AMP is responsible for stimulation of cardiac function, relaxation of smooth muscle, and reduction in the immune and inflammatory activity of specific cells.
- PDE4 appears to be the most directly involved in actions of methylxanthines on airway smooth muscle and on inflammatory cells.

Pharmacodynamics

- The methylxanthines have effects on the central nervous system, kidney, and cardiac and skeletal muscle as well as smooth muscle. Of the three agents, theophylline is the most selective in its smooth muscle effects, whereas caffeine has the most marked central nervous system effects.

Clinical Uses

- Theophylline is the most effective bronchodilator, and it has been shown repeatedly both to relieve airflow obstruction in acute asthma, to reduce the severity of symptoms in patients with chronic asthma.
- Theophylline should be used only where methods to measure theophylline blood levels are available because it has a narrow therapeutic window.
- Its' therapeutic and toxic effects are related to its blood level.

- Improvement in pulmonary function is correlated with plasma concentration in the range of 5–20 mg/L.
- Anorexia, nausea, vomiting, abdominal discomfort, headache, and anxiety occur at concentrations of 15 mg/L in some patients and become common at concentrations greater than 20 mg/L.
- Higher levels (> 40 mg/L) may cause seizures or arrhythmias.

- Theophylline is metabolized by the liver, so usual doses may lead to toxic concentrations of the drug in patients with liver disease.
- Clearance may be increased through the induction of hepatic enzymes by cigarette smoking or by changes in diet.
- Neonates and young infants have the slowest clearance.

- Theophylline improves long-term control of asthma when taken as the sole maintenance treatment or when added to inhaled corticosteroids.
- Its use requires occasional measurement of plasma levels; it often causes unpleasant minor side effects (especially insomnia); and accidental or intentional overdose can result in severe toxicity or death.

- For oral therapy with the prompt-release formulation, the usual dose is 3–4 mg/kg of theophylline every 6 hours.
- Changes in dosage result in a new steady-state concentration of theophylline in 1–2 days, so the dosage may be increased at intervals of 2–3 days until therapeutic plasma concentrations are achieved (10–20 mg/L) or until adverse effects develop.

ANTIMUSCARINIC AGENTS

- Observation of the use of leaves from *Datura stramonium* for asthma treatment in India led to the discovery of atropine, a potent competitive inhibitor of acetylcholine at postganglionic muscarinic receptors, as a bronchodilator.

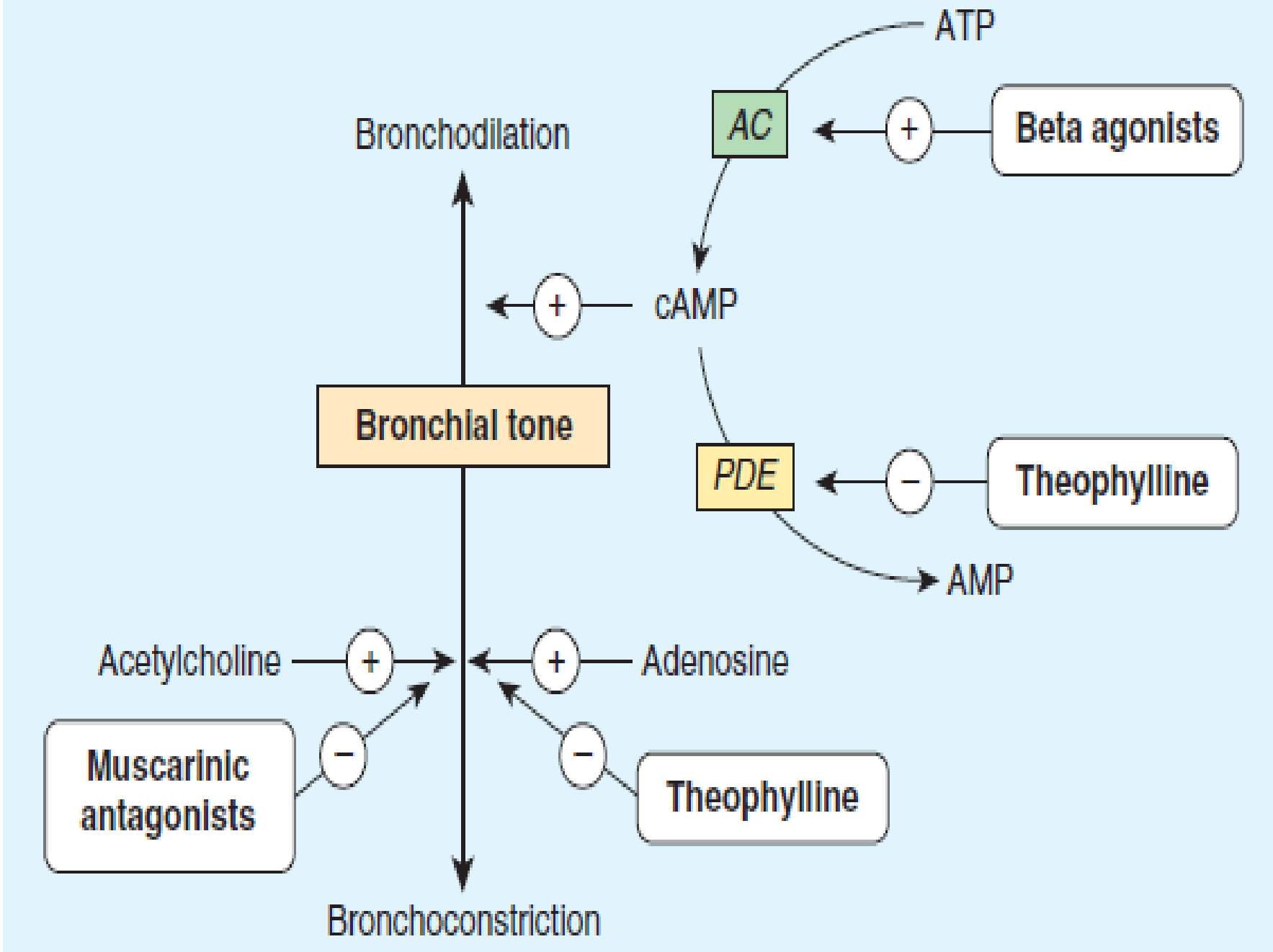
Mechanism of Action

- Muscarinic antagonists competitively inhibit the effect of acetylcholine at muscarinic receptors. So, they block smooth muscle contraction induced through muscrinic receptors, in addition, they reduce mucus secretion.

Clinical Uses

- **Atropine:** it causes bronchodilation in a small dose. But, its' systemic absorption limited its' use (systemic side effects).
- **Ipratropium bromide:** when inhaled, it is poorly absorbed into the circulation and does not readily enter the central nervous system.

- Antimuscarinic agents are valuable for patients intolerant of inhaled β-agonist agents.
- The addition of ipratropium enhances the bronchodilation produced by nebulized salbutamol in acute severe asthma.


ATP
AC
Beta agonists
Bronchodilation
cAMP
Bronchial tone
PDE
Theophylline
AMP
Acetylcholine
Adenosine
Muscarinic antagonists
Theophylline
Bronchoconstriction

CORTICOSTEROIDS

- Corticosteroids have been used to treat asthma since 1950 and are presumed to act by their broad anti-inflammatory efficacy, mediated in part by inhibition of production of inflammatory cytokines.
- They do not relax airway smooth muscle directly but reduce bronchial reactivity and reduce the frequency of asthma exacerbations if taken regularly.

- The most important action is inhibition of the infiltration of asthmatic airways by lymphocytes, eosinophils, and mast cell.

- Glucocorticoids decrease formation of cytokines, in particular the Th2 cytokines that recruit and activate eosinophils and are responsible for promoting the production of IgE and the expression of IgE receptors.
- Glucocorticoids also inhibit COX-2.
- They could inhibit production of leukotrienes and platelet-activating factor.
- Corticosteroids inhibit the allergen-induced influx of eosinophils into the lung.
- Glucocorticoids up regulate β2-adrenoceptors, decrease microvascular permeability and indirectly reduce mediator release from eosinophils by inhibiting the production of cytokines (e.g. IL-5 and granulocyte-macrophage colony stimulating factor) that activate eosinophils.
- Reduced synthesis of IL-3 (the cytokine that regulates mast cell production) may explain why long-term steroid treatment eventually reduces the number of mast cells in the respiratory mucosa, and hence suppresses the early-phase response to allergens and exercise.

Clinical Uses

- Clinical studies of corticosteroids consistently show them to be effective in improving all indices of asthma control—severity of symptoms, bronchial reactivity, frequency of exacerbations, and quality of life.

- Because of severe adverse effects when given chronically, oral and parenteral corticosteroids are reserved for patients who require urgent treatment, ie, those who have not improved adequately with bronchodilators or who experience worsening symptoms despite maintenance therapy.

- Urgent treatment is often begun with an oral dose of 30–60 mg prednisone per day or an intravenous dose of 1 mg/kg methylprednisolone every 6–12 hours; the daily dose is decreased after airway obstruction has improved.
- Systemic corticosteroid therapy can be discontinued in 7–10 days.
- Corticosteroids should be administered at the early morning, however for prevention of nocturnal episodes, it better to be administered at the evening.

- The introduction of corticosteroids such as **beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, and triamcinolone** has made it possible to deliver corticosteroids to the airways with minimal systemic absorption.
- An average daily dose of four puffs twice daily of beclomethasone (400 mcg/d) is equivalent to about 10–15 mg/d of oral prednisone for the control of asthma, with far fewer systemic effects.

Side-effects

- Oropharyngeal candidiasis.
- Hoarseness. (spacer)
- Osteoporosis
- Cataracts

- In children, inhaled corticosteroid therapy has been shown to slow the rate of growth by about 1 cm over the first year of treatment.
- Regular high doses can produce some adrenal suppression, particularly in children.

oral thrush.

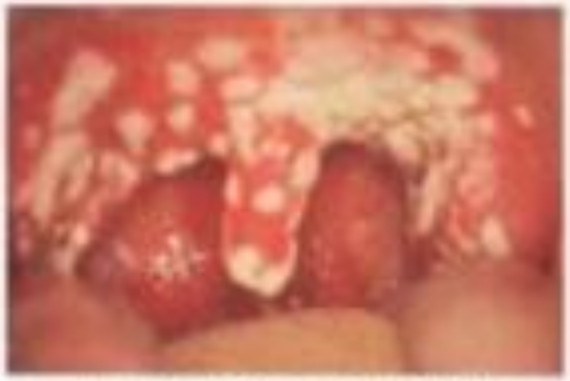
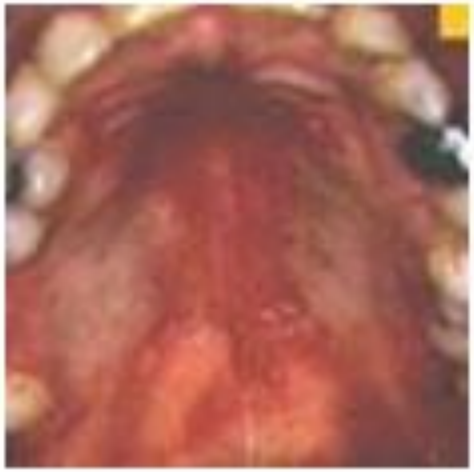
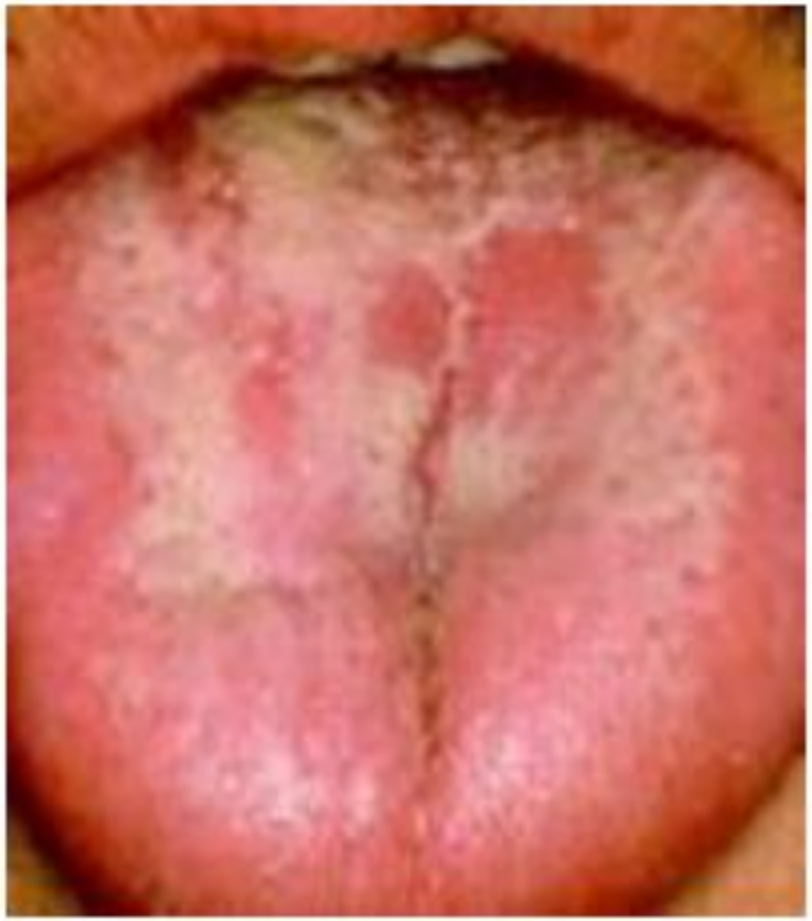


Fig. 3 Candidiasis of the palate





Hypothalamic-pituitary-adrenal-axis suppression

Ophthalmic effects

Diabetes

Osteoporosis

Reduced growth velocity

Respiratory infections

Adverse effects

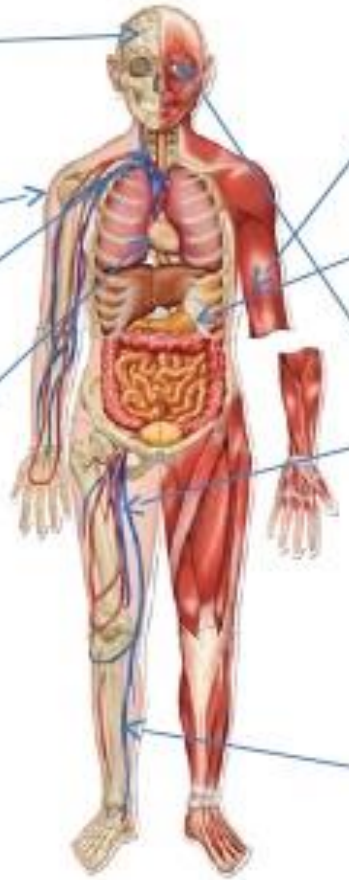
- Occur with prolonged use of high doses
- Cushing's disease

Psychiatric
- Sleep disturbance/activation
- Mood disturbance
- Psychosis

Skin/soft tissue
- Cushingoid appearance
- Abdominal striae
- Acne
- Hirsutism
- Oedema

Neurologic
- Neuropathy
- Pseudomotor cerebri

Cardiovascular
- Hypertension



MSK
- Osteoporosis
- Asceptic necrosis of bone
- Myopathy

Endocrine
- Diabetes mellitus
- Adrenal cortex suppression

Immunologic
- Lymphocytopenia
- Immunosuppression
- False-negative skin test

Opthalmic
- Cataract
- Narrow-angle glaucoma

Developmental
- Growth retardation

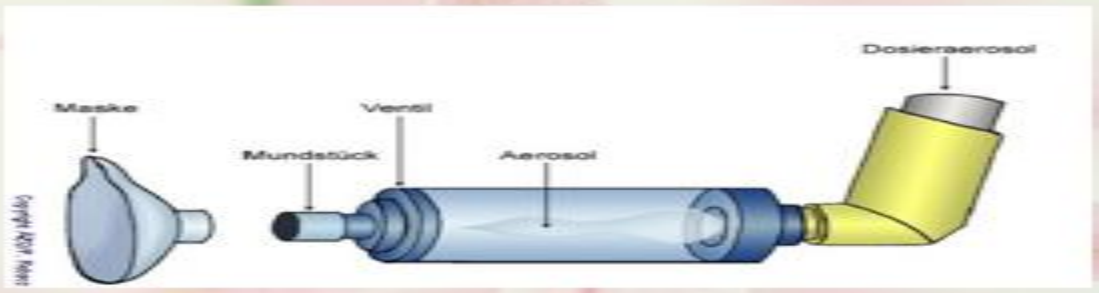
- **Ciclesonide** is a new prodrug which is activated in bronchial epithelial cells. When absorbed into the circulation, the active product is tightly bound to serum proteins, and so has little access to glucocorticoid receptors in skin, eye, and bone, minimizing the side-effects.

- Inhaled corticosteroids are thus properly labeled as “controllers.” They are effective only so long as they are taken.
- Another approach to reducing the risk of long-term, twice daily use of inhaled corticosteroids is to administer them only intermittently, when symptoms of asthma flare. Taking a single inhalation of an inhaled corticosteroid with each inhalation of a short-acting β-agonist reliever.

- A 5–10 day course of twice-daily high-dose budesonide or beclomethasone when asthma symptoms worsen has been found to be as effective as regular daily therapy in adults and children with mild to moderate asthma.

CROMOLYN & NEDOCROMIL

- Cromolyn sodium (disodium cromoglycate) and nedocromil sodium.
- Both have low solubility, are poorly absorbed from the gastrointestinal tract, and must be inhaled as a microfine powder or microfine suspension.



- When taken by inhalation, they effectively inhibit both antigen and exercise-induced asthma, and chronic use (four times daily) slightly reduces the overall level of bronchial reactivity.

- These drugs have no effect on airway smooth muscle tone and are ineffective in reversing asthmatic bronchospasm; they are only of value when taken prophylactically.

Mechanism of Action

- Cromolyn and nedocromil are thought to alter the function of delayed chloride channels in the cell membranes, inhibiting cell activation. This leads to inhibition of cough, inhibition of mast cells degranulation. They also possess an inhibitory effect on esinophils.
- The inhibitory effect is specific to mast cells found in the lungs. Cromoglicate is a ‘mast cell stabiliser’, preventing histamine release from mast cells.

- Because the drugs are so poorly absorbed, adverse effects of cromolyn and nedocromil are minor and are localized to the sites of deposition.
- Throat irritation, cough, and mouth dryness, and, rarely, chest tightness, and wheezing.
- Some of these symptoms can be prevented by inhaling a β 2 -adrenoceptor agonist before cromolyn or nedocromil treatment.

LEUKOTRIENE PATHWAY INHIBITORS

- Leukotriene B 4 (LTB 4) is a potent neutrophil chemoattractant, and LTC 4 and LTD 4 exert many effects known to occur in asthma, including bronchoconstriction, increased bronchial reactivity, mucosal edema, and mucus hypersecretion.

- Two approaches: inhibition of 5-lipoxygenase, thereby preventing leukotriene synthesis; and inhibition of the binding of LTD 4 to its receptor on target tissues, thereby preventing its action.
- **Zileuton**, a 5-lipoxygenase inhibitor, and **zafirlukast and montelukast**, LTD 4 –receptor antagonists.

- Their effects on symptoms, bronchial reactivity, and airway inflammation are less marked than the effects of inhaled corticosteroids, but they are more nearly equal in reducing the frequency of exacerbations.
- They are taken orally; some patients—especially children—comply poorly with inhaled therapies.
- Montelukast is approved for children as young as 6 years of age.

- Zileuton is the least prescribed because of reports of liver toxicity.

Ketotifen

- It is a non-bronchodilator antiasthmatic drug inhibits the effects of inflammatory mediators so it exerts an antiallergic activity. It possesses histamine H1 receptor blocking activity. It also inhibits the acccumulation of eosinophils in the airways, and antagonize the bronchoconstriction induced by leukotrienes.
- It is used as prophylactic therapy.

Anti-IgE Monoclonal Antibodies

- **Omalizumab (an anti-IgE monoclonal antibody)** inhibits the binding of IgE to mast cells but does not activate IgE already bound to these cells and thus does not provoke mast cell degranulation.
- Omalizumab's most important effect is reduction of the frequency and severity of asthma exacerbations, even while enabling a reduction in corticosteroid requirements.

- Omalizumab is administered subcutaneously every 2-4 weeks

- Anaphylactic shock was recorded in few patients taking this drug. That is why self administration is not recommended.

MANAGEMENT OF ACUTE ASTHMA

- The treatment of acute attacks of asthma in patients reporting to the hospital requires close, continuous clinical assessment and repeated objective measurement of lung function.
- For patients with mild attacks, inhalation of a β 2 - receptor agonist is as effective as subcutaneous injection of epinephrine.

- Treatment includes **oxygen** (in high concentration, usually ≥ 60%), inhalation of **nebulised salbutamol**, and **intravenous hydrocortisone** or **methylprednisolone** followed by a course of **oral prednisolone.** Additional measures occasionally used include **nebulised ipratropium, intravenous salbutamol** or **aminophylline,** and **antibiotics** (if bacterial infection is present). Monitoring is by PEFR or FEV1, and by measurement of arterial blood gases and oxygen saturation.
- General anesthesia, intubation, and mechanical ventilation may be lifesaving if respiratory failure supervenes.

THANKS


Courage
Faith
Strength
Motivation
Forgiveness
Believing
in Yourself
All Start
With You
Facebook.com/CirclesOfInspiration
~Anna Pereira