

# Therapy of Bronchial Asthma

# Definition of Bronchial Asthma

The Global Initiative for Asthma (GINA) provides a new practical asthma definition:

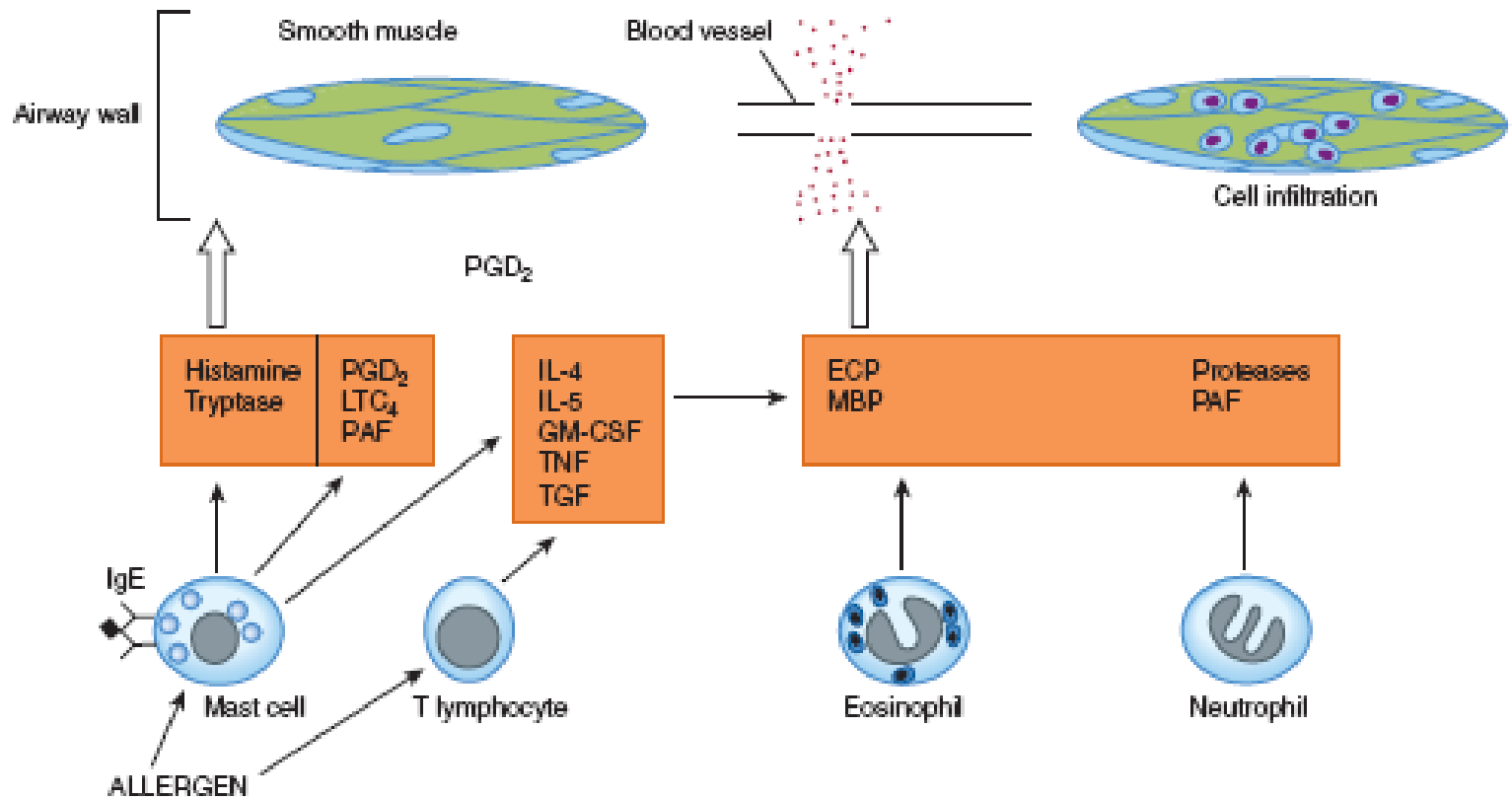
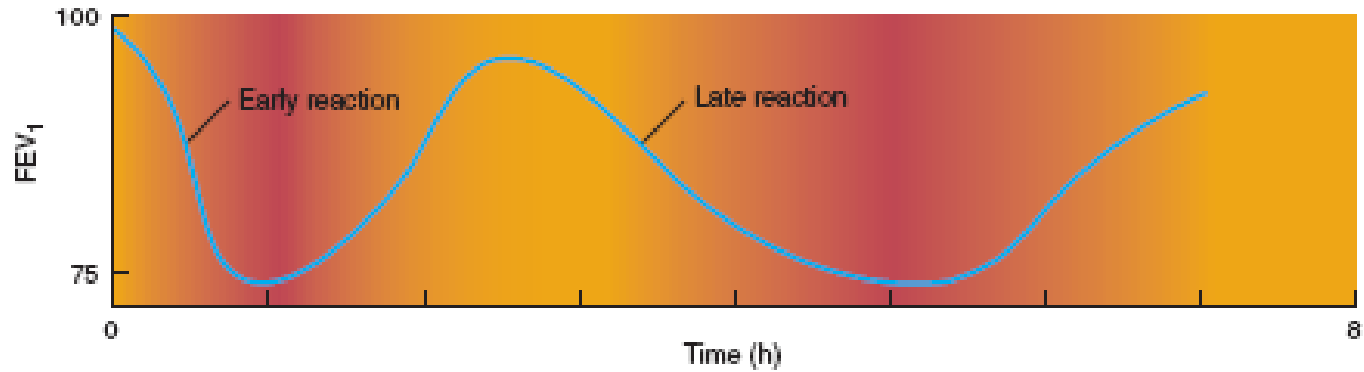
- “Asthma is a heterogeneous disease, usually characterized by **chronic airway inflammation**. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.”

# Definition of Bronchial Asthma

- Airway obstruction in asthma **may become irreversible** and also **worsen over time owing to airway remodeling**.
- **The most common cause of death from asthma is inadequate assessment of the severity of airway obstruction and inadequate therapy.**

# Pathophysiology of Bronchial Asthma

- Major characteristics of asthma include a variable degree of airflow obstruction (related to bronchospasm, edema, and mucous hypersecretion), **bronchial hyper-responsiveness (BHR)**, and airway inflammation.
- Inhaled allergen challenge in allergic patients leads to an early phase reaction that may be followed by a late-phase reaction.

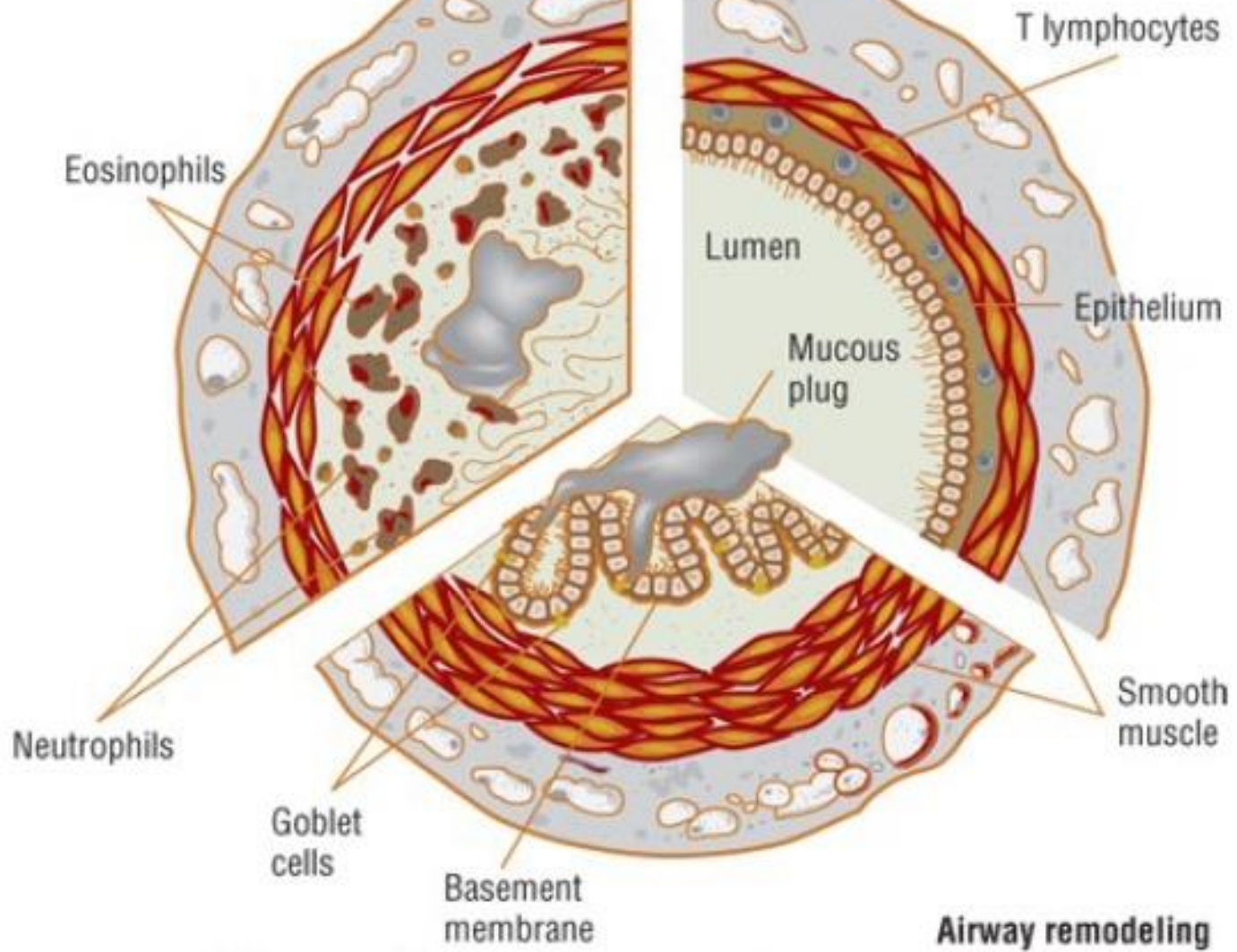


## Figure :

**Conceptual model for the immunopathogenesis of asthma. Exposure to allergen causes synthesis of IgE, which binds to mast cells in the airway mucosa. On reexposure to allergen, antigen-antibody interaction on mast cell surfaces triggers release of mediators of anaphylaxis: histamine, tryptase, prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), leukotriene C<sub>4</sub>, and platelet-activating factor (PAF). These agents provoke contraction of airway smooth muscle, causing the immediate fall in FEV<sub>1</sub>. Reexposure to allergen also causes the synthesis and release of a variety of cytokines: interleukins 4 and 5, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF), and tissue growth factor (TGF) from T cells and mast cells. These cytokines in turn attract and activate eosinophils and neutrophils, whose products include eosinophil cationic protein (ECP), major basic protein (MBP), proteases, and platelet-activating factor. These mediators cause the edema, mucus hypersecretion, smooth muscle contraction, and increase in bronchial reactivity associated with the late asthmatic response, indicated by a second fall in FEV<sub>1</sub> 3-6 hours after the exposure.**

**Inflammation**

**Normal bronchus**



# Pathophysiology of Bronchial Asthma

## Remodeling of the Airways:

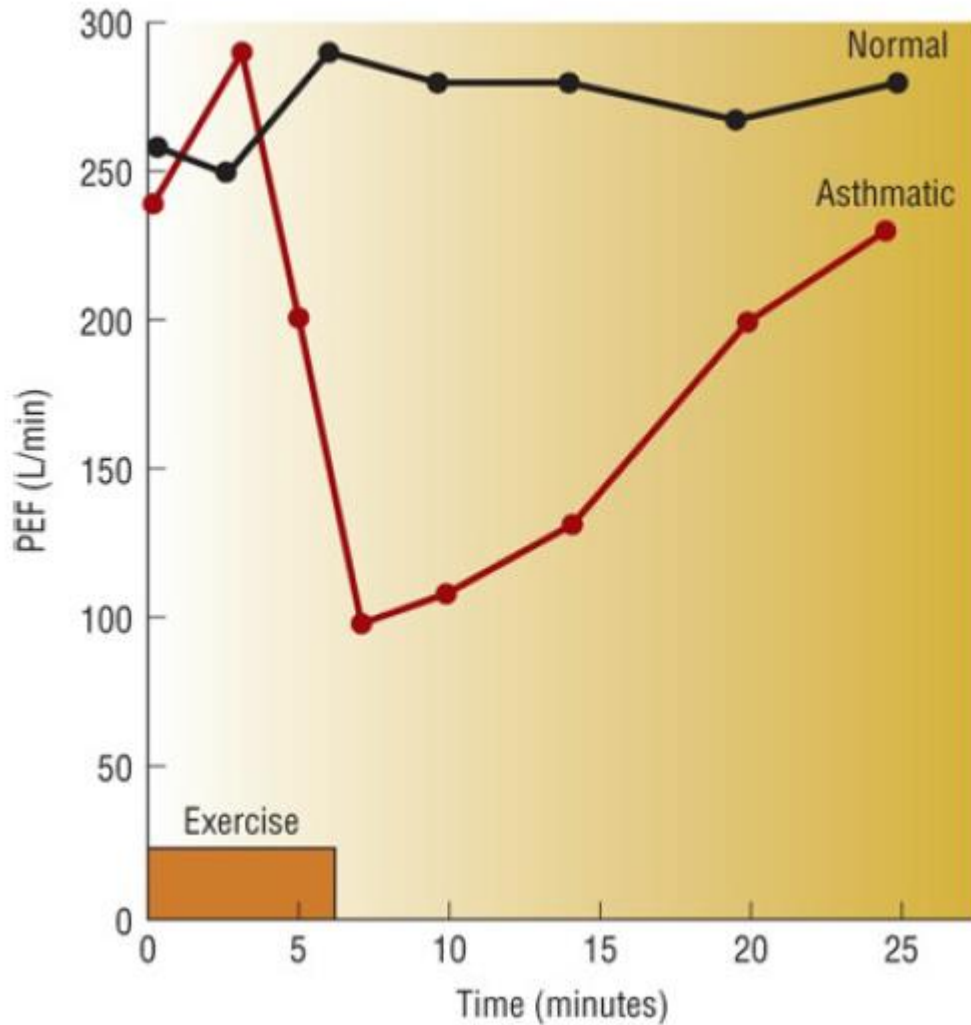
- Remodeling presents as **extracellular matrix fibrosis, an increase in smooth muscle and mucous gland mass, and angiogenesis.**
- **Tryptase** ( a smooth muscle mitogen) plays a role.
- Airway remodeling represents an **irreversible process.**



# Pathophysiology of Bronchial Asthma

## Exercise-Induced Bronchospasm (EIB):

- EIB is defined as a drop in FEV1 of 10% or greater from pre-exercise value.
- EIB is provoked more easily in cold, dry air, and airborne particulate matter.
- Warm, humid air can blunt or block it.
- The exact pathogenesis of EIB is unknown.
- Studies have demonstrated increased plasma histamine, cysteinyl leukotrienes, prostaglandins, and tryptase concentrations during EIB, suggesting a role for mast cell degranulation.



**Typical responses to exercise in a normal subject and an asthmatic subject. Note the initial bronchodilation. (PEF, peak expiratory flow)**

# Pathophysiology of Bronchial Asthma

## Nocturnal Asthma:

- It represents **worsening of asthma during sleep**.
- It may be associated with diurnal patterns of endogenous cortisol secretion and circulating epinephrine.
- Factors that may worsen nocturnal asthma include allergies, **gastroesophageal reflux**, obstructive sleep apnea, and sinusitis, which must be considered when evaluating these patients.
- **Experts consider nocturnal symptoms to be a sign of inadequately treated persistent asthma.**

# Factors Contributing To Asthma Severity

## Respiratory infection:

- Respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza, *Mycoplasma pneumoniae*, *Chlamydia*.

## Allergens:

- Airborne pollens (grass, trees, weeds), house dust mites, animal dander, rodents, cockroaches, fungal spores.

## Exercise:

- Particularly in cold, dry climate.

# **Factors Contributing To Asthma Severity**

## **Environment:**

- **Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke (including 2nd and 3rd hand), wood smoke, energy efficient buildings (increase indoor air pollution), meteorological conditions related to climate change, scented home products, cleaners, and perfumes.**

## **Emotions:**

- **Anxiety, stress, laughter.**

# **Factors Contributing To Asthma Severity**

## **Occupational stimuli:**

- Bakers (flour dust); farmers (hay mold); spice and enzyme workers; occupational cleaners, printers, (arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides).**

# Factors Contributing To Asthma Severity

## Drugs:

- Acetaminophen, Aspirin, NSAIDs (cyclooxygenase inhibitors), sulfites, benzalkonium chloride, nonselective  $\beta$ -blockers.

# Therapy of Bronchial Asthma

## Aerosol Therapy for Asthma:

- Aerosol delivery is a **site-specific topical route**.
  1. Inhalation of short-acting  $\beta_2$ -agonists provides more rapid bronchodilation compared to parenteral or oral administration. It also provides better protection against EIB.
  2. Inhalational corticosteroids (ICSs) have also enhanced local lung actions and reduced systemic effects of corticosteroids.



# Therapy of Bronchial Asthma

- **Some agents (formoterol, salmeterol, and ipratropium bromide) are only effective by inhalation.**
- **Therefore, understanding of aerosol drug delivery is essential to optimal asthma therapy.**
- **You should be aware of this and teach patients how to use inhalers.**

# Therapy of Bronchial Asthma

## Acute Severe Asthma in the Emergency Department:

1. It is important that **therapy NOT be delayed.**
2. **Lung function testing (PEF or FEV1) should be monitored** before treatment, and at 1-hour after start of treatment and then periodically until response is achieved or no further improvement is evident.
3. **Oxygen saturation should be monitored closely, and oxygen therapy implemented when needed.**

# Therapy of Bronchial Asthma

4. Arterial blood gases are reserved for patients who are poorly responsive to initial treatment or deteriorating.
5. The primary therapy of acute exacerbations is pharmacologic, which includes (all):
  - a. short-acting inhaled  $\beta_2$ -agonists
  - b. systemic corticosteroids
  - c. inhaled ipratropium (when response is inadequate)
  - d. and O<sub>2</sub>.
4. Treatments are **typically administered concurrently** to facilitate rapid improvement.

# Therapy of Bronchial Asthma

**Also pay attention to the following:**

1. Correction of dehydration.
2. **Do NOT use sedatives** because anxiety may be a sign of hypoxemia, which could be worsened by central nervous system depressants.
3. **Antibiotics are NOT indicated** because viral respiratory tract infections are the primary cause of asthma exacerbations.
  - Antibiotics should be reserved for patients who have pneumonia.
4. Mycoplasma and Chlamydia are infrequent causes of severe asthma exacerbations but **should be considered in patients with high O<sub>2</sub> requirements.**

# Therapy of Bronchial Asthma

## Short-Acting $\beta_2$ -Agonists:

- The short-acting inhaled  $\beta_2$ -agonists are the most effective bronchodilators and the treatment of first choice for the management of acute severe asthma.
- In more severely obstructed patients, **continuous nebulization** decreases the hospital admission rate, provides greater improvement in the FEV1 and PEF, and reduces duration of hospitalization **when compared with intermittent** (hourly) nebulized albuterol (salbutamol) **in the same total dose.**

# Therapy of Bronchial Asthma

- **Intravenous  $\beta_2$ -agonists have NO role** in the management of patients with severe exacerbations.
- **Aerosolized  $\beta_2$ -agonists** can also be delivered successfully through mechanical ventilator circuits to infants, children, and adults in respiratory failure secondary to severe airway obstruction.

# Therapy of Bronchial Asthma

- The  $\beta_2$ -agonists relax airway smooth muscle regardless of the mechanism of constriction.
- **Regular treatment** (four times daily) does **NOT** improve symptom control over as-needed use and **is NOT indicated**.
- Long-term administration of  $\beta_2$ -agonists **does** **NOT** reduce bronchial hyperresponsiveness (BHR).

# Therapy of Bronchial Asthma

- **Short-acting inhaled selective  $\beta_2$ -agonists are also the first treatment of choice for EIB.**
- **They inhibit EIB in a dose-dependent fashion and provide complete protection for ~ 2-hour period following inhalation.**
- **Two inhalations prior to exercise prevent EIB completely.**



# Therapy of Bronchial Asthma

## Adverse Reactions:

1. **Initially**, inhaled  $\beta_2$ -agonists produce vasodilation, worsening ventilation–perfusion mismatch, slightly lowering  $O_2$  saturation or  $PaO_2$ .
2.  $\beta_2$ -Adrenergic stimulation, especially at high doses, activates  $Na^+$ - $K^+$ -ATPase, gluconeogenesis, and insulin secretion,  $\rightarrow$  a mild-to-moderate decrease in serum potassium, magnesium, and phosphate concentration (drives potassium into the cell).

# Therapy of Bronchial Asthma

3. Tachycardia mediated in part by baroreceptor reflex mechanisms (as a result of the drop in blood pressure from vasodilation), as well as by direct stimulation of cardiac  $\beta_2$ -receptors and some  $\beta_1$  stimulation at high concentrations.
  - An elevated heart rate is NOT an indication to use lower doses or to avoid using inhaled  $\beta_2$ -agonists.

# Therapy of Bronchial Asthma

4. Chronic administration leads to down regulation of  $\beta_2$ -receptors and a decreased binding affinity (desensitization) → tolerance.
  - Tolerance reduces duration of action.
  - It occurs within a week of regular administration and does NOT worsen with continued use.
  - Systemic corticosteroid therapy can both prevent and partially reverse this effect.
  - The use of ICSs have minimal ability to prevent tolerance to  $\beta_2$ -agonists.

# Therapy of Bronchial Asthma

## Long-Acting Inhaled $\beta_2$ -Agonists (LABAs):

- Formoterol and salmeterol, provide long-lasting bronchodilation ( $\geq 12$  hours).
- Unlike the more water-soluble short-acting  $\beta_2$ -agonists, the long-acting agents are lipid soluble.
- ULTRA-LABA (indacaterol, vilanterol, and olodaterol), have a 24-hour duration of effect.
- Increased respiratory deaths in salmeterol users have been reported.

# Therapy of Bronchial Asthma

## Corticosteroids:

- **Systemic corticosteroids** are indicated in all patients with acute severe asthma exacerbations, and should be administered within one hour of presentation.
- Clinical improvement is noted after ~ 4 hours.
- **IV therapy offers NO therapeutic advantage** over oral administration, except in patients who are too-dyspneic to swallow, who are vomiting, or who are intubated.

# Therapy of Bronchial Asthma

- Adults are treated for 5 - 7 day, but children typically require only 3 - 5 days.
- Dexamethasone (1-2) doses vs a 5-day course of prednisolone may be an option for children and has the benefit of improving vomiting.
- Tapering the systemic corticosteroid dose following discharge from the hospital is unnecessary, in patients prescribed inhalational corticosteroids (ICSs) for outpatient therapy.

# Therapy of Bronchial Asthma

## Systemic Corticosteroids:

Corticosteroids are the **most effective anti-inflammatory agents** to treat asthma.

Actions relevant to bronchial asthma include:

1. Increase the number and responsiveness of  $\beta_2$ -adrenergic receptors .
2. Reduce mucus production and hypersecretion.
3. **Reduce bronchial hyper-responsiveness (BHR).**
4. Reduce airway edema and exudation.

# Therapy of Bronchial Asthma

- 5. Increase production of anti-inflammatory mediators.**
- 6. Suppress several pro-inflammatory cytokines such as IL-1, GM-CSF, IL-4, IL-5, IL-6, and IL-8, thus, reducing inflammatory cell activation, recruitment, and infiltration.**
- 7. Decrease vascular permeability.**



# Therapy of Bronchial Asthma

- The time required to see a particular effect is variable, depending on the time required for: new protein synthesis, decreased formation of the particular mediator, and resolution of the inflammatory response.
- Cellular and biochemical effects are immediate, but the time required to produce a clinical response is variable.
- $\beta_2$ -Receptor density increases within 4 hours of corticosteroid administration, while improved responsiveness to  $\beta_2$ -agonists occurs within 2 hours.

# Therapy of Bronchial Asthma

- In acute severe asthma, 4-12 hours are required before clinical response is noted.
- Reversal of increased BHR requires at least 1 week of therapy.
- Drugs used include prednisone, methylprednisolone and dexamethasone.

# Some Adverse effects of systemic corticosteroids

1. Suppression of the hypothalamic-pituitary-adrenal axis.
2. Growth retardation.
3. Skeletal muscle myopathy.
4. Osteoporosis and fractures.
5. Aseptic bone necrosis.
6. Pancreatitis.
7. Pseudotumor cerebri.
8. Psychiatric disturbances.
9. Sodium and water retention.
10. Hypokalemia
11. Hyperglycemia
12. Hypertension
13. Impaired wound healing
14. Immunosuppression
15. Glaucoma
16. Posterior subcapsular cataract
17. Central redistribution of fat
18. Moon face
19. etc

# Therapy of Bronchial Asthma

- Because short-term (1-2 weeks) high-dose corticosteroids (1-2 mg/kg/day of prednisone) do NOT produce serious toxicities, the ideal use is to administer the systemic corticosteroids in a short “burst” and then to maintain the patient on long-term control therapy with ICSs.

# Therapy of Bronchial Asthma

- **Adult patients receiving at least 8 bursts ( $\leq 10$  days each) have a similar decrease in trabecular bone density as patients on daily or alternate-day corticosteroids over 1 year.**
- **Shorter-acting corticosteroids such as prednisone produce less adrenal suppression than the longer-acting dexamethasone.**

# Therapy of Bronchial Asthma

## Inhaled Corticosteroids:

- The ICSs have high anti-inflammatory potency, approximately 1,000-fold greater than endogenous cortisol.
- Aerosol delivery of the preparations is remarkably variable, ranging from 10-60%.
- Different devices for the same chemical entity may result in two-fold differences in delivery, so you should be careful when changing devices.

# Therapy of Bronchial Asthma

- The ICSs that are currently available for use are: **beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, fluticasone furoate, and mometasone furoate.**
- Because they are lipophylic, systemic clearance of the available ICSs is very rapid (~ the rate of liver blood flow), with the exception of ciclesonide, which is inactivated also by blood esterases.

# Therapy of Bronchial Asthma

- The ICSs produce dose-dependent systemic effects, contributed by the orally absorbed fraction and the fraction absorbed from the lung.
- Mouth rinsing and spitting will reduce their oral bioavailability.



# Therapy of Bronchial Asthma

- The ICSs are considered the preferred long-term control therapy for persistent asthma in all patients.
- Low- to medium-dose ICSs reduce BHR, improve lung function, and reduce severe exacerbations leading to reduced ED visits and hospitalizations.
- They do NOT reduce airway remodeling and loss of lung function seen in patients with persistent asthma.

# Therapy of Bronchial Asthma

- For patients inadequately controlled on low-dose ICSs, the dose may be increased.
- **Alternatives: addition of LTRAs or theophylline to ICSs.**
- Doses of ICSs in the high range significantly enhance the risk of toxicity.
- **High doses of ICSs plus LABA are reserved for patients with severe persistent asthma.**

# Therapy of Bronchial Asthma

**Beneficial effects of inhaled corticosteroids:**

- 1. Decreased eosinophil and mast cell number.**
- 2. Decrease T-lymphocyte cytokine production.**
- 3. Inhibit transcription of inflammatory genes.**
- 4. Reduce endothelial cell leak.**
- 5. May up-regulate  $\beta_2$ -receptors.**
- 6. Reduce airway epithelial sub-basement membrane thickening.**

# **Some Potential Adverse Effects of inhaled corticosteroids**

- 1. Hoarseness, dysphonia (myopathy of vocal cords), thrush.**
- 2. Growth retardation**
- 3. Myopathy.**
- 4. Osteoporosis, fractures and aseptic necrosis of the hip.**
- 5. Posterior sub-capsular cataract and glaucoma.**
- 6. Adrenal axis suppression.**
- 7. Immuno-suppression and impaired wound healing.**
- 8. Easy bruising and skin striae.**
- 9. Hyperglycemia and hypokalemia.**
- 10. Hypertension.**
- 11. Psychiatric disturbances.**

# Therapy of Bronchial Asthma

## The response to ICSs is delayed:

- Most symptoms will improve in the first 1-2 weeks of therapy and maximum improvement will be reached in 4-8 weeks.
- Improvement in baseline FEV1 and PEF may require 3 to 6 weeks for maximum improvement.
- Improvement in BHR requires 2-3 weeks and approaches maximum in 1-3 months but may continue to improve over 1 year.
- Sensitivity to exercise challenge decreases after 4 weeks of therapy.

# Anticholinergics

- Unlike  $\beta_2$ -agonists, they are **NOT functional antagonists**; they only reverse cholinergic-mediated bronchoconstriction (bronchial tone is maintained by parasympathetic nerves).
- **A number of the triggers and mediators of asthma produce bronchoconstriction in part through vagal reflex mechanisms** (histamine, prostaglandins, sulfur dioxide, exercise, and allergens).

# Anticholinergics

- Anticholinergics have NO effect on BHR.
- Anticholinergics attenuate but do NOT block EIB.
- Ipratropium bromide is a nonselective antagonist of muscarinic receptors → bronchodilation ( $M_3$ -receptors).
- Blockade of presynaptic  $M_2$ -receptors allows the release of acetylcholine → paradoxical bronchoconstriction.

# Anticholinergics

- The quaternary ammonium derivatives (ipratropium bromide and tiotropium) have little absorption across respiratory mucosa and do NOT penetrate the blood–brain barrier, thus **they have negligible systemic effects with a prolonged local effect.**
- They also do NOT significantly affect mucociliary clearance or respiratory secretions.



# Anticholinergics

- Duration of action of Ipratropium bromide is 4-8 hours, while that of Tiotropium bromide is 24 hours.
- Ipratropium bromide is only indicated as adjunctive therapy in acute severe asthma NOT completely responsive to  $\beta_2$ -agonists alone, which may produce further improvement in lung function.

# Anticholinergics

- There is NO benefit to continuing combined anticholinergic and  $\beta_2$ -agonist therapy during hospitalization on duration of stay or clinical outcomes.
- When used via nebulizer, and if a tight mask or mouthpiece is NOT used, **ipratropium bromide that deposits in the eyes may produce dilation of pupil and difficulty in accommodation.**

# Methylxanthines

- Methylxanthines have been used for asthma therapy for more than 50 years, but their use has much declined because of the high risk of **severe life-threatening toxicity and numerous drug interactions.**
- Theophylline is a moderately potent bronchodilator with mild anti-inflammatory properties.

# Methylxanthines

- Like  $\beta_2$ -agonists, theophylline is a functional bronchodilator.
- Preferably used as sustained-release product orally, or by short IV infusion as aminophylline (theophylline ethylenediamine).
- It stimulates endogenous catecholamine release.
- Theophylline therapeutic concentration is 5 -15  $\mu\text{g}/\text{mL}$ .
- It has a low therapeutic index.

# Methylxanthines

- **Sustained-release theophylline is less effective than ICSs and NOT more effective than oral sustained-release  $\beta_2$ -agonists or LT antagonists.**
- **The addition of theophylline to ICSs is similar to doubling the dose of the ICS, and is less effective than LABAs as adjunctive therapy.**
- **The addition of theophylline to patients with poorly controlled asthma receiving ICS/LABA combination does NOT improve outcomes.**

# Methylxanthines

- Toxicities include caffeine-like effects of nausea, vomiting, tachycardia, jitteriness, and difficulty sleeping to **more severe toxicities such as cardiac tachyarrhythmias and seizures.**
- Theophylline is eliminated primarily by metabolism via cytochrome P450s (mainly CYP1A2 and CYP3A3).

# Methylxanthines

## Theophylline clearance varies widely:

1. In normal adults, the mean plasma clearance is 0.69 mL/kg/min.
2. Children clear theophylline faster than adults (1–1.5 mL/kg/min).
3. Neonates and young infants have the slowest clearance.
4. Even within the same age groups, theophylline clearance can vary 2-3 folds.
5. Even when maintenance doses are modified to correct for the above factors, plasma concentrations vary widely.

# Methylxanthines

## Drug Interactions:

### Drugs that reduce theophylline clearance:

- **Cimetidine, erythromycin, clarithromycin, allopurinol, propranolol, interferone, thiabendazole, ticlopidine, zileuton, quinolones.**

### Drugs that increase theophylline clearance:

- **Rifampin, phenobarbital, carbamazepine, phenytoin, charcoal-broiled meat, high-protein diet, smoking, sulfinpyrazone, moricizine.**



# Leukotriene Modifiers

- **Two cysteinyl-LT receptor antagonists (zafirlukast and montelukast) and one 5-lipoxygenase inhibitor (zileuton) are available.**
- **They reduce allergen-, exercise-, cold air, hyperventilation-, irritant-, and aspirin-induced asthma.**
- **Zileuton use is limited due to hepatic toxicity and inhibition of CYP3A4 isoenzymes (drug interactions).**

# Leukotriene Modifiers

- **These drugs improve pulmonary function tests (FEV1 and PEF), decrease nocturnal awakenings, decrease  $\beta_2$ -agonist use, and improve asthma symptoms.**
- **They are effective orally, and can be used once or twice a day.**
- **They may be useful in patients with aspirin-sensitive asthma.**

# Leukotriene Modifiers

- **Montelukast may be used for EIB in adults, but it is less effective than short-acting inhaled  $\beta_2$ -agonists.**
- **NOT that effective in adults with severe uncontrolled asthma.**
- **They are NOT as effective as LABAs when added to ICSs for moderate persistent asthma.**
- **They are less effective in asthma than low doses of ICSs.**

# Leukotriene Modifiers

## **Adverse effects:**

- **A rare idiosyncratic syndrome similar to the Churg-Strauss syndrome (eosinophilia, heart failure, and eosinophilic vasculitis) has been reported with zafirlukast and montelukast.**
- **Neuropsychiatric events (suicidal thoughts).**
- **Fatal hepatic failure (zafirlukast).**

# Anti-IgE (Omalizumab)

- It is a recombinant anti-IgE antibody that can be used for the **treatment of allergic asthma** NOT well controlled on oral corticosteroids or ICSs.
- It binds to the Fc portion of the IgE antibody preventing the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils.
- This action leads to a decrease in the release of mediators in response to allergen exposure.

# Anti-IgE (Omalizumab)

- It decreases FcεRI expression on basophils and airway submucosal mast cells over 8 to 12 weeks.
- It is administered subcutaneously (peak serum concentration is achieved in 3-14 days).
- It is eliminated primarily through the reticuloendothelial system and has an elimination half-life of ~ 20 days.
- It should be administered under strict medical observation with drugs for treating anaphylaxis available.

# Anti-IgE (Omalizumab)

- It can be used in patients greater than 6 years of age with allergic asthma.
- It is very expensive.
- Therapy is associated with a 0.2% rate of anaphylaxis.
- **Anaphylaxis may occur up to 24 hours following injection.**