Bronchial Asthma

I. What is Bronchial Asthma?

Bronchial asthma is a condition characterized by:

- **High responsiveness of the airway** to a variety of stimuli
- Resulting in **widespread narrowing of the airways**
- Severity **varies spontaneously or with treatment**
- Airflow obstruction is **reversible**

II. Structural & Pathological Basis of Asthma

Airway narrowing in asthma results from **multiple simultaneous pathological processes**:

1. Dynamic (Functional) Changes

- **Bronchospasm** → smooth muscle contraction → airway narrowing
- **Mucosal edema** → mucosal thickening → further narrowing

2. Obstructive Changes

- **Mucus hypersecretion** → mechanical airway occlusion

3. Chronic Remodeling Changes

- **Subepithelial collagen deposition**
- **Hyperplasia** of: Smooth muscle, Blood vessels, Secretory glands and Goblet cells

(These explain **persistent hyperreactivity and airflow limitation, even between episodes**)

III. Clinical Manifestations

Asthma typically presents with **episodic attacks** of:

- Coughing
- Shortness of breath (dyspnea)
- Chest tightness
- Wheezing

Asthma in a nutshell: A **chronic inflammatory disease of the airways** characterized by **persistent inflammation** with **episodic exacerbations**.

⇒ **Allergen exposure initiates** and maintains the underlying IgE-mediated inflammation in asthma, **but most acute asthma exacerbations are triggered by viral respiratory infections** rather than direct allergen exposure.

IV. Mediators Responsible for Bronchoconstriction & Inflammation in Asthma

A. Bronchoconstrictor Substances, agents capable of inducing airway narrowing include: **Acetylcholine, β-blockers**, Adenosine, α-adrenergic agonists, **Prostaglandins ($PGF_2\alpha$, PGD_2)**, Serotonin, Bradykinin, **Histamine, Leukotrienes (LTC_4, LTD_4)**, Platelet-activating factor

(Blocking any of these mediators would relief bronchoconstriction)

B. Inflammatory Triggers

- **IgE-mediated allergic reactions**
- **Viral respiratory infections**

(Preventing the inflammation also would relief the hypersensitivity and chronic remodeling changes caused by the persistent inflammation in asthmatic patients)

V. Pathogenesis of Bronchial Asthma:

⇒ **IgE-Mediated (Immunologic) Model:**

1. IgE antibodies bind to **airway mast cells**
2. Upon **re-exposure to antigen**, antigen–IgE interaction occurs on **mast cell** surface causing mast cells to granulate and release:
   - Histamine
   - Leukotrienes C_4 & D_4
   - PGD_2
   - Eosinophil & neutrophil chemotactic factors

<u>These mediators cause both Bronchoconstrictive and Inflammatory actions:</u>

A. Early Asthmatic Response: within the **first 10–20 minutes** after exposure:

- **Acute Bronchoconstriction**
  (Due to the **Bronchoconstrictive effects** of the Mast cells' Mediators)

B. Late Asthmatic Response: within **3–6 hours** after exposure:

- **Airway inflammation**
- **Cellular infiltration**
- **Mucus hypersecretion**
- **Sustained bronchoconstriction**
  (Due to the **Inflammatory effects** of the Mast cells' Mediators)

⇒ **Role of Eosinophils in Asthma** (recruited by the eosinophil chemotactic factors released by mast cells)**:**

Eosinophils contribute through:

- Release of **major basic protein**
- Release of **eosinophil cationic protein**

Effects of these proteins:

- Epithelial sloughing
- Increased airway smooth muscle contractility

(Both contributing more for the inflammation and bronchoconstriction in Asthma)

⇒ **Role of TH2 Cytokines** (recruited by other cytokines released by the mast cells)**:**

Produced mainly by **TH2 lymphocytes**:

- IL-4, IL-5, IL-9, IL-13
- GM-CSF, TNF, TGF

Actions:

- **Recruit and activate eosinophils & neutrophils**
- **Stimulate IgE synthesis by B lymphocytes**
- **Increase mucus production by bronchial epithelium**

(Further contributing for the inflammation and bronchoconstriction in Asthma)

VI. Limitations of the Allergic Model:

- IgE-mediated asthma applies only to **a subset of patients (There are multiple other types of asthma)**
- Allergen challenge does **not explain all asthma features (Not all manifestations that arise in allergic asthma can be explained by the IgE-Mediated (Immunologic) Model)**

VII. Epidemiology of Allergic asthma:

- Common in **childhood**
- Less common in **adult-onset asthma**

VIII. Clinical Asthma Phenotypes:

Asthma may be described as:

- Extrinsic vs intrinsic (Ex: Allergic asthma is considered an **Extrinsic asthma**)
- Aspirin-sensitive
- Adult-onset
- Post-viral
- Obesity-related

Drugs for Asthma

⇒ **CORE PRINCIPLE:**
Asthma treatment targets **two problems**:

1. **Bronchoconstrictive Episodes** → bronchodilators (*Symptom relief)*
2. **Persistent Airway inflammation** → anti-inflammatory drugs (*disease control)*

(So Asthma treatment needs a **Combined Therapy**)

Bronchodilators

(Symptom relief – NOT disease control)

1. β_2-Adrenergic Agonists Inhalers (Main Bronchodilators):

⇒ **Mechanism:**
β_2 stimulation → ↑ **cAMP in airway smooth muscle** → muscle relaxation → Bronchodilation

Classification & Use:

Short-acting (SABA)
- ***Albuterol, Terbutaline***
- **Maximal Bronchodilation within: 15 min**, **duration of action: 3–4 h**
- **Rescue drug for acute attacks**

Long-acting (LABA)
- ***Salmeterol, Formoterol*** **(duration of action: 12 h**)
- **Highly Lipid Soluble**

Ultra-long acting
- ***Indacaterol, Vilanterol*** **(once daily)**
- May be used as a **monotherapy in COPD**

Additional Effects
- ↓ mast-cell mediators release
- ↓ microvascular leak
- ↑ mucociliary clearance (↑ Ciliary activity)

Adverse Effects

- **Lactic acidosis**: β_2-adrenergic agonists increase cellular metabolism, leading to increased lactate production; this metabolic lactic acidosis **may contribute to dyspnea** despite bronchodilation.
- **Hypokalemia**: β_2-adrenergic agonists **increase the activity of the Na^+/K^+-ATPase pump in skeletal muscle**, driving potassium into cells and causing hypokalemia, which may lead to **muscle tremors** and **occasional weakness.**
- **Tachyphylaxis (tolerance)**: regular use of β_2-adrenergic agonists leads to a reduction in response after several days, reflecting the development of tolerance.

2. Antimuscarinic Agents Inhalers (Atropine Derivatives):

Drugs:

- **Short-acting** (DOA~ 4hours): **Ipratropium**
- **Long-acting** (DOA~ 24hours or more): **Tiotropium**

Mechanism:
Block M_3 receptors → ↓ bronchoconstriction & mucus secretion

(The magnitude of action is proportional to the contribution of parasympathetic stimulation to airway smooth muscle tone in asthmatic patients)

Use:

- Mainly **COPD**
- Could be used as a vasodilator in asthma (but **β_2-Adrenergic Agonists are first line)**

Adverse Effects:

- **Dry mouth**, which can be managed using a **spacer** to reduce oropharyngeal deposition, or by **dose reduction**.
- May be associated with **increased risk of dementia with advancing age**.

(Unlike atropine, these drugs do not inhibit mucociliary clearance, which prevents accumulation of secretions, further contributing to opening the airways)

3. Methylxanthines (Theophylline, caffeine and theobromine)

- **Theophylline** was once a mainstay in **asthma treatment**, but its use has markedly declined due to:
  - **Greater efficacy** of **inhaled β_2-agonists**
  - **Significant toxicities**: nausea, vomiting, tremor, seizures, and arrhythmias
  - **Narrow therapeutic index**, requiring **serum level monitoring**
  - **Multiple drug–drug interactions**

- Despite this, **theophylline may still be used:**
  - To treat **apnea of prematurity**
  - In **selected patients with bronchial asthma** when other therapies are inadequate

Anti-Inflammatory Drugs

(Disease-modifying – MOST IMPORTANT)

1. Corticosteroid Inhalers (Cornerstone of Asthma Therapy)

Forms:

- **Inhaled (first-line):** Beclomethasone, Budesonide, Triamcinolone and Fluticasone, etc.

- **Systemic (For severe attacks only):** Prednisone (PO), Methylprednisolone (IV)

Mechanism of Action:

- Most important action is **inhibition of infiltration of asthmatic airways by leukocytes (eosinophils, mast cells, lymphocytes)**
- ↓ cytokine production
- Inhibit phospholipase A_2 → ↓ PGs & leukotrienes
- ↓ airway hyperreactivity (chronic use)

Clinical Effects:

- **Reduce bronchial hyperreactivity and thus decrease asthma exacerbations**
- **Improve overall asthma control**, including: symptom severity and frequency of attacks
- **Restore β_2-agonist responsiveness**
- **Vasoconstriction of engorged bronchial mucosal vessels**, reducing mucosal edema.

(Corticosteroids do not directly relax airway smooth muscle and therefore do not relieve acute asthma attacks. -that's the action of bronchodilators-)

Adverse Effects:

- **Oropharyngeal candidiasis** (due to local immunosuppression during administration, mouth wash after administration could be helpful)
- **Dysphonia (hoarseness of voice)** — due to a **local effect on the vocal cords**
- **Suppression of the hypothalamic–pituitary–adrenal (HPA) axis** (At very high doses only)

2. Mast Cell Stabilizers (Cromolyn, Nedocromil):

- **Prevent mast-cell degranulation**, was previously widely used, however these days inhaled **corticosteroids show higher efficacy**.
- Can be used in **Exercise-induced asthma.**
- **Cromolyn** is available for **allergic rhinoconjunctivitis and other mast-cell–mediated disorders** as a **nasal spray (over-the-counter)** and as an **oral solution.**
- **Both cromolyn and nedocromil** can also be prescribed as **ophthalmic solutions**.

3. Leukotriene Pathway Inhibitors:

Drugs:

- **Zileuton** (5-lipoxygenase inhibitor)
- **Montelukast, Zafirlukast** (LT receptor antagonists)

Role, Useful in:

- **Aspirin-exacerbated Asthma**
- **Exercise-induced asthma**

Advantage: Administrated orally (=Can be given to patients who can't use inhalers)

Adverse Effects:

- **Hepatotoxicity and liver failure**
- **Dyspepsia**
- **Neuropsychiatric effects**: increased suicidality, nightmares and behavioral changes in Children (esp. montelukast)

Drug interactions:

- **Leukotriene pathway inhibitors cause CYP-mediated drug interactions: zileuton** inhibits multiple CYP enzymes (including **CYP3A4**), **reducing metabolism** of **theophylline, warfarin, propranolol, and terfenadine**, while **zafirlukast** inhibits **CYP2C9** also causing an **increase in warfarin** levels.
- **Erythromycin reduces leukotriene receptor antagonist bioavailability**.

Targeted (Biologic) Therapy

*(**For Severe, Irresponsive asthma**)*

1. Anti-IgE: Omalizumab

- **Blocks IgE–Fcε receptor binding**
- Given to patients with **severe irresponsive asthma**

2. Anti-IL-5 Mepolizumab, Reslizumab /Anti-IL-5R: Benralizumab:

- Given for severe **eosinophilic asthma** (Patients with airway and peripheral eosinophilia)

3. Anti-IL-4 / IL-13: **Dupilumab**

- Dupilumab is used in **moderate-to-severe eosinophilic asthma**
- Initiation should be **avoided in patients with very high baseline eosinophil counts (>1500 eosinophils/μL**), as it **may cause a transient increase in peripheral eosinophilia**.

4. Anti-TSLP: **Tezepelumab**

- Blocks upstream **epithelial cytokine that mediates inflammation** (Thymic Stromal Lymphopoietin)
- Given to patients with **severe asthma**

Adverse Effects of Monoclonal Ab drugs:

- **Hypersensitivity / anaphylaxis**: all monoclonal antibody drugs carry a **risk of hypersensitivity reactions or anaphylaxis**, as the immune system may develop response against these humanized anti-bodies.
- **Reactivation of dormant chronic infections**: most monoclonal antibody therapies may lead to reactivation of dormant chronic infections, **particularly herpes zoster**, due to modulation or suppression of immune responses.

Don't forget: **Asthma treatment relies on combined therapy,** using a **bronchodilator** together with an **anti-inflammatory agent**; for most patients, the **first-line regimen** is **inhaled β_2-adrenergic agonists combined with inhaled corticosteroids**.

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