DRUGS USED IN OBSTUCTIVE AIRWAY DISESASE

Asthma: Is a chronic inflammatory disorder of the airways where many cells and cellular elements associated in causing airway hyperresponsiveness leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are associated with widespread but variable airflow obstruction often reversible, either spontaneously or with treatment.

COPD: Is a disease state characterized by airflow limitation (*chronic bronchitis, emphysema, or both)* that is not fully reversible. Such airflow limitation is usually progressive and associated with an abnormal response of the lungs to noxious particles or gases.

Similarities Between COPD and Asthma:

- Both result from gene-environment (multifactorial) interactions. Both are chronic inflammatory diseases which involve airway limitation. Both are usually characterized by mucus hypersecretion and bronchial hyperreactivity.

Differences:

Asthma	COPD
In young patients	Later in life
Non smokers	Tobacco related
History of allergy	No history
Intermediate & small airways No parenchymal involvement	Small airways + parenchymal involvement
Inflammatory reaction involves Eosinophils/ Mast cells CD4+ T lymphocytes	Inflammatory reaction involves Neutrophils / Macrophages CD8+ T lymphocytes
Normal lung volume & elastic recoil If chronic → Remodeling → Plasma Membrane thickening / Smooth muscle Hypertrophy	Hyperinflation / Loss of elastic recoil Alveoli emphysematous & destroyed Gradually on going progression
Completely or partially reversibly airflow limitation	Completely irreversible
Symptoms come and go, more at night	Symptoms are chronic, persist in the morning

Asthma

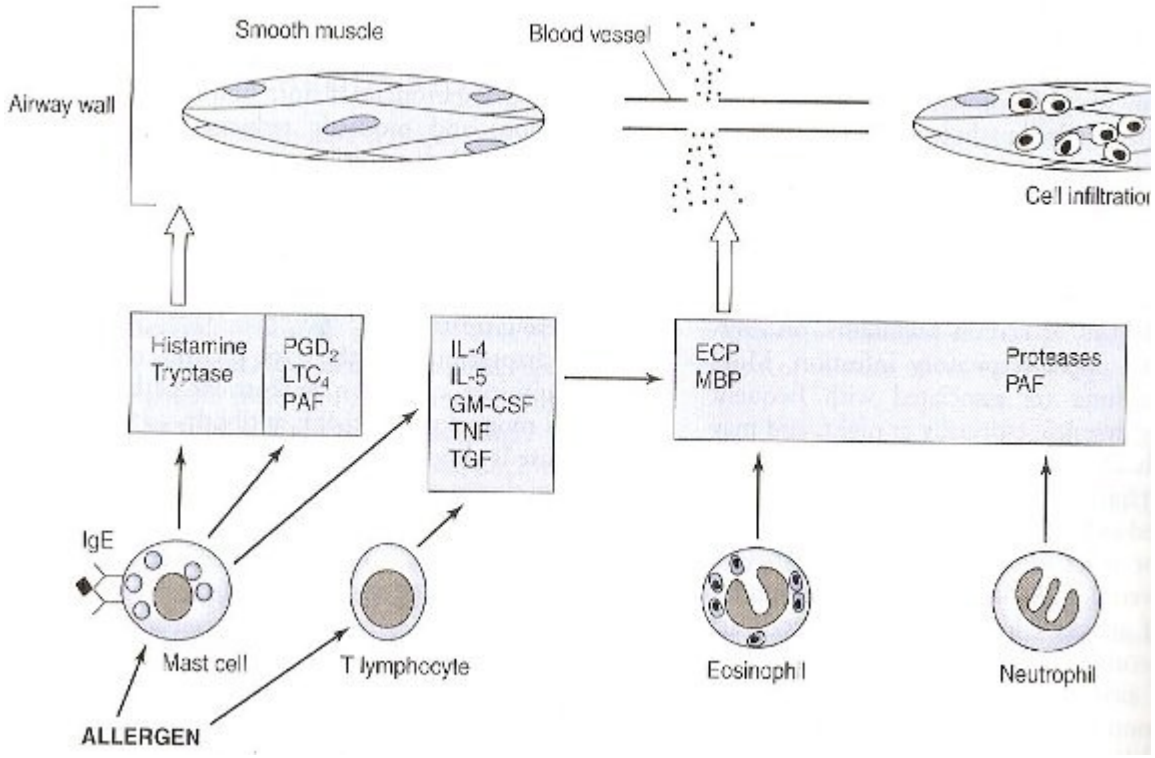
Types:

1. **Extrinsic (atopic):**

- Triggered always by allergens: food, pollens, spores, animal dander, etc
- Provoked whenever there is an exposure to previous trigger
- More common than intrinsic triggers, and the etiology follows type I hypersensitivity immune reaction

2. **Intrinsic (non-atopic):**

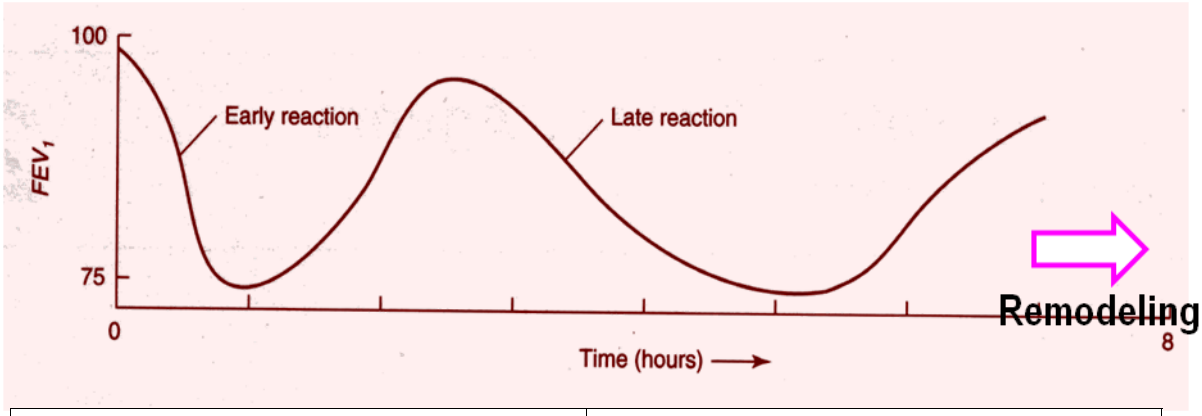
- Triggered initially by infections, drugs (NSAIDs), dust, pollutants, chemicals, irritants…
- Can occur without any apparent provocation
- Less common and the etiology remains unknown



Pathogenesis:

1. Allergens provoke IgE production.
2. IgE antibodies bind to mast cells in the airway mucosa.
3. On reexposure mast cells will release mediators stored in their granules.
4. Histamine, leukotrienes, and prostaglandin D, are released leading to triggering the muscle contraction and vascular leakage.
5. This constitutes the early asthmatic phase.
6. Late asthmatic phase is caused by influx of inflammatory cells.
7. Mediators responsible for late phase are interleukins.

Bronchospasm can be provoked by nonallergenic stimuli. This is a characteristic of asthma, and is called "nonspecific bronchial hyperreactivity"

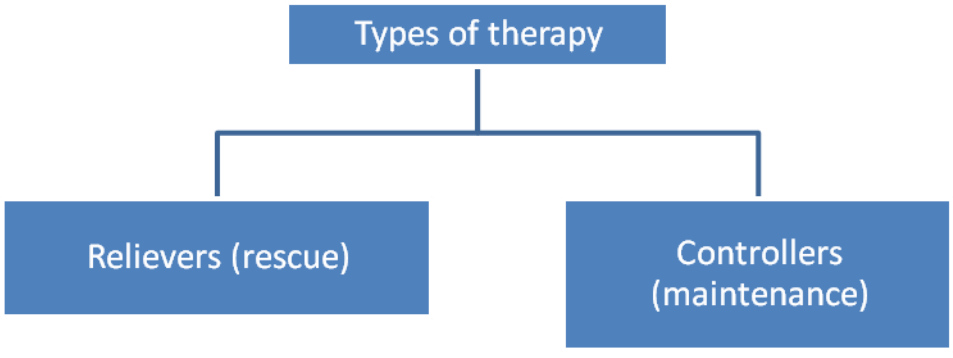


Early phase	Late phase
Mediated by: histamine & leukotrienes	Leukotrienes, cytokines, chemokines
Bronchial constriction & mucosal thickening	Eosinophil infiltration & inflammation
Viscid plugs of mucus secretions	Airflow obstruction & airway hyperresponsivness

Airway remodeling: Occurs due to repeated attacks mediated by tissue proteases, ROS, matrix metaloproteinases, growth factors epithelial damage, subepithelial fibrosis, and bronchial smooth muscle cell hyperplasia with residual inflammatory reaction. At this stage asthma becomes irreversible.

Goals of Therapy:
Is to REDUCE INFLAMMATION as it is the major initiator of remodeling.
Thus, it is easy to infer that the first line of treatment is inhaled corticosteroids.
Furthermore, relieving airflow obstruction symptoms by bronchodilators is an important concept in treating asthma.

Outcomes of Therapy, patients would be able to:
1. Participate in activities without asthma symptoms
2. Sleep through the night without asthma symptoms
3. Have normal lung function
4. Have few emergency room visits and hospitalization
5. Have few side effects from the medication



Relievers
Induce bronchodilation to relieve acute asthma symptoms

- Selective β_2 agonists (short duration)
- Non-selective β_2 agonists
- Anti-cholinergics
- Phosphodiesterase inhibitors

Controllers
Decrease airway inflammation to reduce tissue remodeling

- Corticosteroids
- Antileukotrienes
- Cromones
- Anti IgE monoclonal antibodies

Prevent recur of acute symptoms:

- Selective long acting β agonists
- Longer acting anticholinergics

Methods of Administration:
In general, inhalation therapy is the standard method of administration unless:

- The bronchial airway is almost obstructed in severe asthmatic state, status asthmaticus(a life-threatening with severe prolonged exacerbation of asthma that does not respond to standard treatments).
- In children who cannot use inhalational devices
- In those who develop worsening of cough and bronchospasm by the aerosols

Advantages of inhalation therapy:

- Targeted delivery to site of action
- Rapid onset; optimal in acute attacks
- Minimal dosage needed
- Less systemic side effects
- Well tolerated

Inhalation devices:

- **Metered-dose inhaler:** contain a pressurized inactive gas that propels the drug through a metering valve that dispenses a constant volume of drug in the propellant to be inhaled directly in each puff into the lung. Inhalation technique is critical for optimal drug delivery.

- **Dry powder inhaler**: Drug is formulated in a filler and contained in a capsule in the device that is punctured to release the powder. It is breath-activated and does not need patient coordination

N.B. INHALERS only need a slow deep breath and holding it for 5 to 10 seconds. Proper rinsing of the mouth with water is a is advisable to avoid oral infection eg, candidiasis.

- **Inhaler with spacer**: Usually consist of metered-dose inhalers connected to a spacer. Spacer (a holding chamber), ensures the following:

1. Catch all mist particles coming out from the inhaler to be kept within it, till every single particle is inhaled.
2. Prevents drug particles from being deposited in the mouth

A facemask can be fit sometimes, instead of a mouthpiece

- **Nebulizers**: Are electronic devices that transform liquid into very fine mist to be inhaled deeply into the lungs through a face mask or mouth piece. Useful in patients who are very breathless, mainly in hospitals for severe attacks

Requires measuring the amount of medication carefully that is poured into the cup attached to the nebulizer tubing.

1-Relievers

- Used during acute attacks
- Action lasts for 4-6 hours

Selective β_2 agonists (salbutamol, salmeterol, formoterol, terbutaline)

Adrenergic receptor (AR): G_s protein coupled.

Mechanism of action:

1. **On bronchial smooth muscle:** stimulation of AR —> muscle relaxation
2. **On presynaptic parasympathetic fibers:** stimulation of AR —> ↓ ACH release —> muscle relaxation.
3. **On bronchial epithelium:** stimulation of AR —> release of nitric oxide NO —> muscle relaxation.
4. **On mucociliary function and microvascular leak:** stimulation of AR lead to:

- ↓ microvascular leak —> ↓edema
- ↑ mucos secretion + ↑ ciliary beating —> ↑ mucociliary clearance

5. **On mast cells, eosinophills, T-lymphocytes:** stimulation of AR —> ↓ mediator & cytokines release —> ↓ inflammation. (used as controller action not reliever)

Note: There is no or little desensitization of AR to bronchodilation action of short acting β agonists.

Benefits of Relievers:

- In rescue therapy: Selective bronchodilation without cardiac or systemic toxicity
- Maximum effects occur in 30 minutes
- In prophylaxis Effective in protecting against various challenges: exercise, cold air, and allergen prior to known exposure to triggers.

Administration frequency:

For a 4-hour dosing: 4 puffs. The frequency can be increased to a 2-hour dosing regimen: with 8 puffs per two hours

Other forms of Drugs:

- Albuterol and terbutaline are available in tablet form, but this route of administration presents no advantage over inhaled treatment
- Terbutaline is available for subcutaneous injection. Indicated for severe asthma.

Adverse effects: Exceeding the recommended dosage frequency or not following instructions (i.e mouth rinsing) will exaggerate systemic side-effects in the form of increased heart rate, cardiac arrhythmias, tremors, muscle cramps, and metabolic disturbances.

Anticholinergics

Tiotropium inhibits muscarinic receptors one and three. While **ipratropium** inhibits M_2 receptor in addition.

Mechanism of action:

- Inhibition of M3 receptors —> bronchodilation
- Inhibits mucus secretion

Pharmacokinetics:

- Given regularly only by inhalation to decrease the rate of developing tolerance
- Have slow onset of action with 30-60 minutes till the appearance of action
- Ipratropium: short acting (6-8h), weaker (used as reliever)
- Tiotropium: long acting (>24h), superior (used as controller & in COPD)

Benefits of using anticholinergics:

- Give the best results in COPD
- Given as a second line treatment in β_2 agonist refractoriness

Adverse effects: dry mouth, constipation, headache, and urinary retention

Phosphodiesterase Enzyme Inhibitors

Non-selective:
Caffeine, theobromine, theophylline (PO), amino-phylline (PO or parenteral route)

PDE_4 selective:
Cilomilast (PO) used in COPD

Mechanism of Action:

Non-selective inhibition of PDE —> no inactivation of cAMP which leads to:

1. Bronchodilation
2. ↓Microvascular leak
3. ↑ Ciliary beating
4. Antiinflammatory effect:

- Negative mast cell degranulation, leukotriene synthesis
- Negative T-cell response (particularly CD 8)
- ↑ Response to corticosteroids

Another proposed mechanism is blocking adenosine's effect on cell surface receptors. (tolerance does not develop)

Other pharmacological effects:

- On CNS: stimulation of higher cortex (eg, wakefulness, delayed fatigue) and medullary centers, cerebral vasoconstriction.
- On CVS: positive inotropic and chronotropic effects, vasodilation, ↓BP , and coronary artery dilation
- GIT: ↑ Gastric acid secretions
- Kidney : ↑ Renal blood flow—> diuresis
- Skeletal muscles: improve contractility and reverse fatigue of the diaphragm in patients with COPD

Pharmacokinetics:

- Absorbed orally (better if given after meals)
- Metabolized in the liver by CYP 450
- $T_{1/2}$= 8h

Benefits of Using PDE inhibitors:

ØAs RESCUE THERAPY in HOSPITAL for severe asthma (if β_2 inhalation fails) or if there is status asthmaticus by slow IV infusion

ØAs CONTROLLER 2nd line therapy for bronchodilatory and antiinflammatory potentials. Given as sustained-release oral preparation.

Adverse Effects: has a narrow therapeutic index—> must be monitored.

- Nausea, vomiting, anorexia, diarrhea
- Tachypnea
- Headache, restlessness, insomnia, anxiety
- Cardiac arrhythmias (ventricular may be fatal), hypotension when levels > 30 mg/L
- Seizures when levels > 40 mg/L Uncontrolled seizures may lead to hyperthermia and rhabdomyolysis

Drug interactions:

- Its therapeutic level and $t_{1/2}$ decreases with concomitant administration of enzyme inducers (phenobarbitone, rifampin)
- Its therapeutic level and $t_{1/2}$ increase with concomitant administration of enzyme inhibitors (cimetidine, erythromycin)

Theophylline is the cheapest, most selective and effective PDE inhibitor.

Caffeine has the most marked CNS effects

Non selective β_2 agonists

Adrenaline (acts on all AR): Potent, rapidly acting (5 min), maximum effects (15 min), lasts for 60-90 minutes. Was formerly a mainstay of therapy given S.C. in home settings. Now reserved mainly to status asthmaticus given by slow drip infusion in hospital settings. Systemic ADR and contraindications of non-selective α & β AR agonists has to be considered.

Isoprenaline (non-selective β agonist): Potent, rapidly acting (5 min), maximum effects (15 min), lasts (60-90 min). Was formerly a mainstay of therapy to be given S.C. in home settings Now reserved mainly to status asthmaticus, to be given by slow drip infusion in a hospital settings Systemic ADRs & contraindications of non-selective a & β AR activation has to be considered

Ephedrine: compared with adrenaline, ephedrine has a longer duration, oral activity, more pronounced central effects, and much lower potency. It is now used infrequently for treating asthma.