Disorders of Respiratory Function

Classification

Main disorders of the respiratory system are:

1. Bronchial asthma.
2. Cough
3. Coronary obstructive pulmonary disease (COPD).
Asthma

- Recurrent attack of airway obstruction in response to external stimuli
- Chronic inflammatory disorder of airways.
- Airway hyper-reactivity abnormal sensitivity to wide range of external stimuli.
Exacerbations?

Exercise → Mediator cell → LTC₄, LTD₄, LTE₄ → Airway obstruction / inflammation / remodelling?

Allergen

Cold air

Aspirin (sensitivity)
Symptoms

- Immediate phase (bronchospasm).
- Late Phase (inflammation, bronchospasm, vasodilatation, Mucus secretions).
- Cough
- Dysnea
- Wheezing
Causes

- **Extrinsic asthma** *(Allergic asthma).*
- **Intrinsic asthma**
  - Infection
  - Stress
  - Cold air *(Exercise asthma).*
  - Drugs as aspirin *(iatrogenic asthma).*
Airways Innervation

Efferent

No sympathetic supply.

- B2 in
  - smooth muscles
  - Glands
  - Mast cells
  - Increased mucociliary clearance.

Parasympathetic supply

- M3 receptors in smooth muscles and glands.
**Afferents**

1. **Irritant receptors (vagal fibres).**
   - Upper airways

2. **C-fiber receptors (sensory fibers).**
   - Lower airways.
Asthma

Drugs:

I. Bronchodilators (are relievers).

They reverse the bronchospasm of immediate phase.

a. β2 - adrenoreceptor agonists.

b. Antimuscarinics.

c. Xanthine preparations.
II-Anti - inflammatory Agents (are controllers):

These inhibitors prevent the inflammatory components of both phases (are not relievers).

1- Glucocorticoids.
2- Mast cell stabilizers.
3- Leukotrienes pathway inhibitors 
   a. 5-Lipoxygenase inhibitors.
   b. Leukotriene-receptor antagonists.
4- Anti-IgE monoclonal antibody 
   Omalizumab
Sympathomimetics

Mechanism of Action

1- Relax airway smooth muscles (direct B2 - stimulation).

2- Increase adenyl cyclase enzyme $\rightarrow$ cAMP $\rightarrow$ Bronchodilation

3. Inhibit mediators release from mast cells.

4. Increase mucus clearance by (increasing ciliary activity - affecting composition of mucous secretions).
Classification

1-Non selective B-agonists.

Epinephrine - Isoprenaline
Orciprenaline - Ephedrine.

2-Selective B2-agonists.

Salbutamol
Terbutaline – Salmeterol
Albuterol - metaproterenol.
**Epinephrine**

Very effective

rapid action bronchodilator

S.C. or by inhalation by nebulizer or aerosol.

Maximum effect is achieved after 15 min

Duration of action is 60-90 min.

**Disadvantages**

1- Not effective orally (*first pass*).

2- Hyperglycemia # in Diabetes.

3- CVS side effects: Tachycardia, arrhythmia, hypertension # angina.

4- skeletal muscle tremor.
Isoprenaline (isoproterenol)

- Potent bronchodilator
- Given by sc or inhalation as nebulizer or aerosol
- Rapid action (within 5 min).
- Duration of action is 60-90 min.

Disadvantages

As epinephrine
Orciprenaline

1- Delayed onset of action.
2- Effective orally (20 mg every 6h).
3- Longer duration of action.
4- Effective by inhalation with rapid onset.

Disadvantages: As epinephrine.
Ephedrine

**Advantages**
1- orally active (25 mg / 6h), or injection.
2- Longer duration of action.
3- Delayed action and lower potency

**Disadvantages**
1- Insomnia, nervousness, tremors.
2- **CVS side effects**: Used only prophylactic between attacks.
3- Tachyphylaxis (depletion of mediator + down-regulation)
Selective B2 –agonists

1- Drugs of choice for asthma
2- Longer duration of action (3 – 4 hr) or salmeterol & formoterol (12 h).
3- can be given orally, parenterally or by inhalation.
4- Maximal action reaches (15-30 min).
5- Minimal CVS side effects.
6- Suitable for asthmatic patients with hypertension or heart failure.
8- inhalation:

- Metered-dose inhaler
- Nebulizer
Examples

Short acting
Salbutamol (Albuterol) (orally, inhalation, iv)
Terbutaline (S.C, orally, inhalation)
Metaproterenol (inhalation).
Salbutamol is used for premature labor

Long acting
Salmeterol & formoterol (*high lipid solubility*).
*Used in combination with corticosteroids*
Disadvantages

1- Skeletal muscle tremors.
2- Tolerance (B-receptors down regulation).
3- Tachycardia (B1 - stimulation).
Muscarinic antagonists

Ipratropium – Tiotropium
Quaternary derivatives of atropine.
Blocks all subtypes of muscarinic receptors.

Kinetics
Not absorbed orally
Given by aerosol inhalation
Slow onset of action (30 min.)
Duration of action 3-5 hr.
Pharmacodynamics

Bronchodilators

No effect on late inflammatory phase

Less effective than B2-agonists.

Does not enter CNS

No systemic side effects.
Uses
1. Chronic obstructive pulmonary diseases
2. Patients intolerant to B2 agonists
3. Adjuncts to b2 agonists & steroids for acute asthma

Tiotropium
Longer acting (24 h).
Used for COPD
Methylxanthines

Theophylline - Theobromine - Caffeine.
Aminophylline (theophylline + ethylene diamine).

Mechanism of Action

1- are phosphodiesterase inhibitors

↑ cAMP → bronchodilation

2- Adenosine receptors antagonists (A1).

3- Anti inflammatory action (Stabilization of mast cell membrane).

4- reduce release of cytokines and chemokines

5- Increase diaphragmatic contraction.
Pharmacological Effects:

1- Anti asthmatic action.

2- CNS stimulation.
   * Decrease of fatigue & elevation of mood.
   * Tremors, nervousness, Insomnia.
   * Respiratory Stimulant.
   * Toxic dose → convulsion.

3- Relaxation of smooth muscles bronchial, intestinal, uterine and blood vessels.
4- GIT : Increase gastric acid and digestive enzymes secretions.

5- CVS:
Heart : + ve Inotropic + ve chronotropic.
BP: Direct vasodilatation except cerebral b.v.
BP: Normal dose, insignificant increase.
Large dose : Severe hypotension and arrhythmia.
Blood: reduce blood viscosity & improve blood flow.
6- Kidney:
* weak diuretic action.
* $\uparrow$ GFR $\rightarrow$ due to afferent glomerular dilatation.

7- SK. muscle: $\uparrow$ diaphragmatic contraction $\rightarrow$ improve ventilation.
Pharmacokinetics
1- Well absorbed orally (must be given after meals)

*Theophylline (orally)*
*Aminophylline (orally, rectal, parenteral).*

2- Metabolized in the liver (\( t_{\frac{1}{2}} = 8 \text{ h} \)).
3- Low therapeutic index.

\( T_{\frac{1}{2}} \text{ is decreased by} : \)
1- Smoking & drinking.
2- Children.
3. Enzyme inducers (rifampicin, phenobarbitone - phenylbutazone).

$T_{1/2}$ is increased by

1- Liver dysfunction.
2- Hepatic blood flow (CHF, B-blockers).
3- Renal disease (10% is eliminated).
4- Enzyme inhibitor (Cimetidine, erythromycin, ketoconazole, O.C. pills).
Uses

1. Second line drug in asthma (orally as sustained-release preparation, 12 h, nocturnal bronchospasm).
2. For status asthmaticus (slow infusion) aminophylline (theophylline + ethylene diamine).
3. Intermittent claudication (pentoxifylline).
Side Effects

1- CNS side effects: Insomnia, nervousness.

2- GIT disturbance: nausea, vomiting, anorexia.

3- Low or narrow safety margin
   Monitoring of theophylline level is necessary (5 - 20 mg / L).

4- CVS effects: Hypotension, arrhythmia, Cardiac arrest.
II - Anti - inflammatory Agents

1- Mast cell stabilizers.
2- Glucocorticoids.
3- Leukotrienes antagonists.
   a. 5-Lipoxygenase inhibitors.
   b. Leukotriene–receptor antagonists.
4- Anti-IgE monoclonal antibody
   Omalizumab
II- Anti-inflammatory Agents

- Are not bronchodilators
- These inhibitors prevent the inflammatory components of both phases.
- Have No direct effect on bronchial smooth muscles
- Not effective in terminating acute attack of asthma.
- Used as prophylactic medications
- Effect usually attained after 2-4 weeks (Late).
- Maximum action at 9-12 months.
Glucocorticoids

Mechanism of action

1. Inhibition of phospholipase A2.
2. Inhibition of antigen-antibody reaction.
3. Mast cell stabilizers.
4. Inhibition of inflammatory cytokines
5. Decrease capillary permeability and mucosal oedema
Pharmacodynamics

- Not bronchodilators
  (Not effective in immediate phase)
- Reduce bronchial hyper-reactivity.
- Effective in exercise and allergic-induced asthma.
Pharmacokinetics

Routes of administration

Orally
prednisone, prednisolone, dexamethasone.

Inhalation
Ciclesonide, Fluticasone, Beclomethasone
Budesonide, Triamcinolone

Injection
Hydrocortisone, dexamethasone
Methyl-prednisolone.
Uses

1. First line of therapy in moderate to severe asthma (inhalation).
2. Status asthmaticus (i.v.).
3. Their effects are potentiated by B2 agonists.
Side Effects

Oral corticosteroids produce systemic effects.

- Osteoporosis
- Cataract
- Thinning
- Adrenal suppression
- Growth retardation
2. Inhalation has less side effects.

- Oropharyngeal candidiasis (thrush).
- Dysphonia (voice hoarseness).
- **Ciclesonide**
  - given by inhalation
  - prodrug cleaved by esterases in bronchial epithelial cells
  - active drug is tightly bound to serum protein
  - Little access to corticoids receptors in other tissues
Mast cell stabilizers

Cromolyn sodium (disodium cromoglycate)
Nedocromil

Pharmacokinetics
- are insoluble
- Inhalation
  **Cromolyn** (aerosol, microfine powder, nebulizer)
  **Nedocromil** (aerosol)
  low bioavailability (10% is absorbed)
  - T1/2 is 90 minutes.
  - Excreted unchanged in urine 50 % and bile 50 %.
Mechanism

Inhibit mast cell degranulation by stabilization of mast cell membrane

Pharmacodynamics

▪ not bronchodilators
▪ reduce bronchial hyper-reactivity
▪ effective in exercise, antigen and irritant -induced asthma
▪ children respond better than adults
▪ Less effective than corticosteroids
Side Effects

1. Minor upper respiratory tract irritation <t>throat irritation, cough, burning sensation, mouth dryness relieved by B2-agonist before cromolyn or nedocromil.</t>

2. Hypersensitivity reactions (dermatitis, anaphylaxis).
**Uses**
Prophylaxis in asthma especially in children.
Allergic rhinitis.
Conjunctivitis

**Contraindications**
Acute attacks (reflex airway obstruction).
Leukotrienes pathway inhibitors

Cysteinyl leukotrienes (C4, D4, and E4)

- bronchoconstriction
- bronchial reactivity
- mucosal edema & mucus hypersecretion
- cellular infiltration

Important mediators of the inflammatory response. Produced by cells as macrophages, mast, eosinophils & basophils.
LTB4
potent neutrophil chemoattractant.

Leukotriene receptors
Two subtypes of the cysteinyl leukotriene receptors; CysLT1 and CysLT2.
Only CysLT1 is present in human airways.

Leukotrienes pathway inhibitors
5-Lipoxygenase inhibitors.
Leukotriene–receptor antagonists.
5-Lipoxygenase inhibitors

Zileuton

Block the production of

- spasmogenic leukotrienes (LTC4 & LTD4).
- Chemotaxin (LTB4).
- Given orally
- Short duration of action.
- Short half life (3-4 times/ day).
- Reduces late phase of inflammation.
- Mild to moderate asthma
- Potentiate corticosteroid actions (Low dose).
Leukotriene–receptor antagonists

Zafirlukast, Montelukast, Pranlukast, Cinalukast

- a potent, competitive antagonist of CysLT1 receptor to LTD4.
- LTD4 –receptor antagonist
- Taken orally.
Uses

- Bronchodilators (1/3 of salbutamol).
  1. Mild asthma
  2. Aspirin-induced asthma
  4. Montelukast is approved for children (6 years old).

Dose

Zafirlukast (20 mg twice daily)
Montelukast (10 mg once daily in adult & 4 mg in children)
Side effects of LT pathway inhibitors

- Less effective than corticosteroids.
- Elevation of liver enzymes.
- Headache
- Dyspepsia.
- Churg-Strauss syndrome.
Anti-IgE monoclonal antibody

- Omalizumab, s.c. twice weekly.
- inhibits binding of IgE to mast cells.
- inhibits IgE synthesis by B-lymphocytes
- Reduce eosinophilic bronchial inflammation.
- reduces early & late response to antigen
- reduces corticosteroid requirement
- reduces frequency & severity of exacerbation.
- reserved for patients with chronic severe asthma frequent exacerbations
- High cost
Cough

Physiological Cough (Productive Cough)
Is a protective reflex mechanism that removes foreign material and secretions from the bronchi and bronchioles.

Unproductive Cough
occurs due to exposure to irritant vapors or gases or due to pathological conditions as chronic bronchitis.
Antitussives

Are drugs used to suppress dry cough

1. **Peripheral antitussives** :
   1. Benzonatate
   2. Local anesthetics
   3. Humidifying aerosol & steam inhalation
   4. Demulcent
Peripheral antitussives

1. **Benzonatate**
   - Inhibition of pulmonary stretch receptor

2. **Local anesthetics (lidocaine, tetracaine)**
   - Inhibit cough reflex
   - Used before bronchoscopy & bronchography.

3. **Demulcent**
   - Cough originating above larynx
   - Form a protective coat over irritated pharyngeal mucosa
   - Syrup or lozenges (glycerin, acacia).
4. Humidifying aerosol & steam inhalation

- Act as demulcent
- Decrease viscosity of bronchial secretion
- Water inhalation as aerosol or steam with or without medication
- Benzoin tincture & Eucalyptus
Central antitussives.

a. Narcotic analgesics
   morphine, codeine, methadone

b. Synthetic narcotic analgesics
   Dextromethorphan-levopropoxyphene

c. Antihistaminics (H1-Blockers)
   diphenhydramine - triprolidine
Narcotic analgesics

Are drugs used to suppress dry cough

**Codeine**

1. opiate with less addiction liability.
2. Potent antitussive
3. Weak analgesic.
Side Effects

1- Constipation.
2- Inhibition of mucociliory clearance (thick sputum).
3- Decrease secretions in the bronchioles.
4- Drowsiness & mild respiratory depression.
5- Dependence.
6- Dry mouth.
Synthetic narcotic analgesics

dextromethorphan - levopropoxyphene.

Dextromethorphan

1. As potent as codeine.
2. No drowsiness.
3. Less constipating effect.
4. No respiratory depression.
5. No inhibition of mucociliary clearance.
6. No addiction.
Antihistaminics (H1-Blockers)

Diphenhydramine
Triprolidine.

Side Effects
- Anticholinergic actions
- Sedation
- Drowsiness.
NOTES

- Antitussives are used for dry cough.
- Contraindicated in
  - chronic bronchitis
  - cough associated with asthma
    (harmful sputum thickening and retention).
Expectorants

Are drugs used to facilitate expulsion of secretions and exudates from the respiratory passages by cough.

Classification

1. Sedative Expectorants

They increase the fluidity of sputum and its expulsion by cough.
- Potassium citrate
- Potassium acetate
- Ammonium chloride
- Ipecaquana
- Na and K iodide.

They can be used for inflammatory condition of respiratory mucosa due to their soothing effect.
2- **Stimulant expectorants**

These drugs are used in chronic inflammation of respiratory mucosa (chronic bronchitis).

e.g. trepene → hydrate - guaiacol.

They promote healing and repair of mucosal tissues.
Mucolytics

acts by reducing the viscosity of sputum.

1. Acetyl cysteine (interfering with disulphide bonds in mucus).
2. Bromophexine (destroy mucopolysaccharide structure of mucus).
3. Steam inhalation

Uses

1. Acute and chronic bronchitis
2. Asthma
Exacerbation
Assess pulmonary function by spirometry
Fall in forced expiratory volume in 1 sec (FEV1)
Nitric oxide in exhaled air
High No. of eosinophils in sputum.
Nocturnal symptoms (2-3 times a month).