Treatment of Bronchial Asthma

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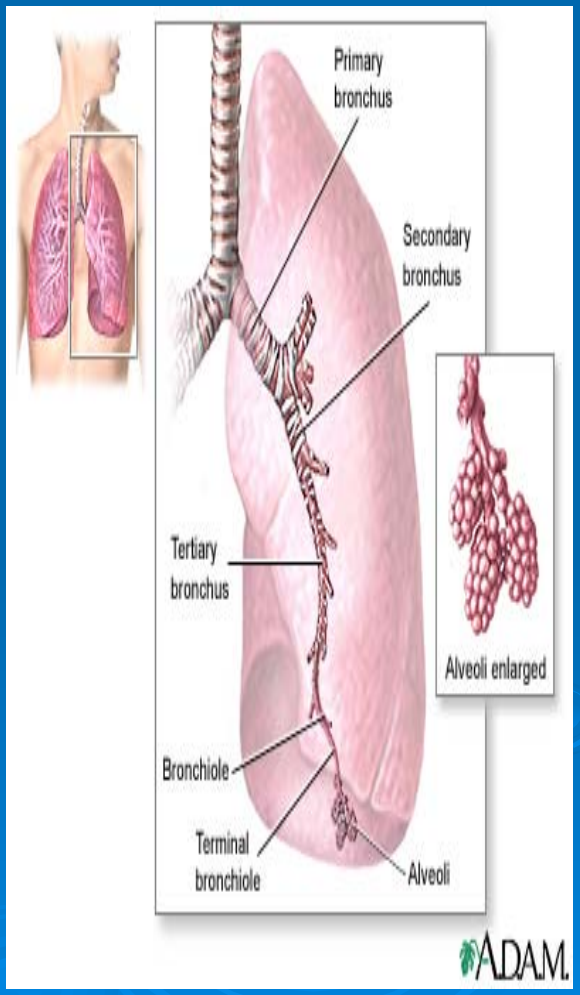
Bronchial Asthma

- Is a chronic disease that affects 10 million patients (4-5% of U.S population)
  - 2 million E.R visits annually
  - 500,000 hospitalizations
  - 5000 deaths



Bronchial Asthma

- B.A is characterized by attacks of shortness of breath associated with cough, chest tightness & wheezing & rapid respiration
- Disease may present as acute recurrent episodes of shortness of breath or may be a chronic disorder
- Attacks may be precipitated by exposure to allergens, dust, cold air, after exercise & respiratory infections

Types of Bronchial Asthma

1. Extrinsic Asthma

- is **commonest** & occurs in **young patients** who develop **allergy** to inhaled antigenic substances (house-dust mite, pollens, grass & animals)

- Allergen avoidance is particularly relevant to managing this type of asthma

2. Intrinsic Asthma

- Occurs in **older patients** the absence of an obvious allergen or atopy

- Bronchospasm is induced exercise, cold air & inhalation of chemicals

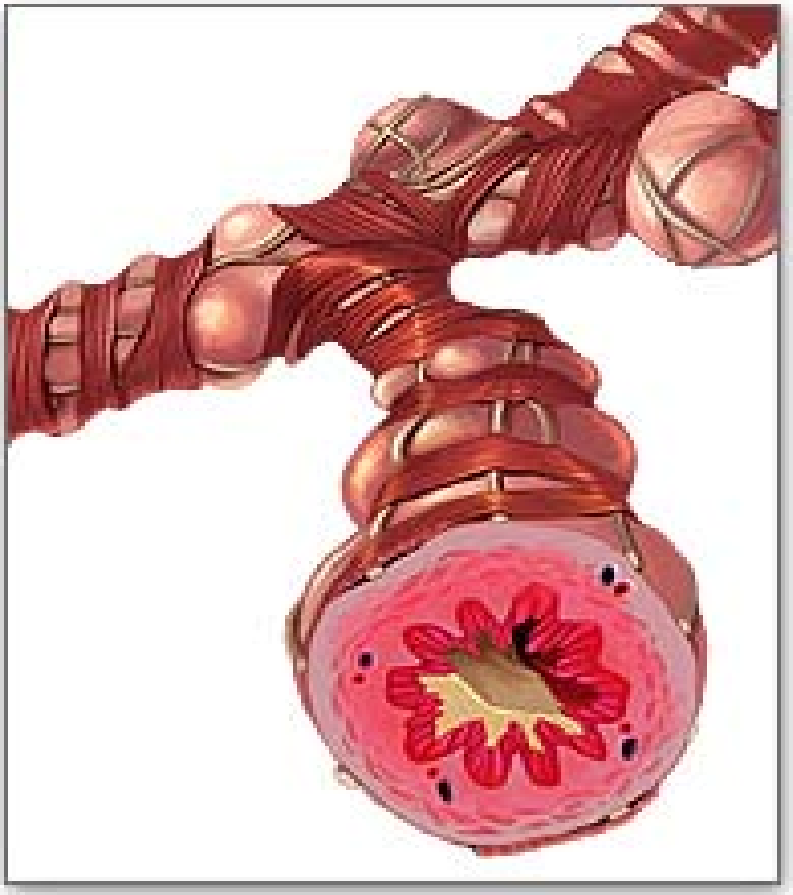
Common Asthma Triggers

Pathogenesis of B.A

- BA is characterized by **airway obstruction** is due to **bronchoconstriction** that result from:
  - Contraction of bronchial smooth muscle
  - Inflammation of bronchial wall
  - Increased mucous secretion

Normal bronchiole

Asthmatic bronchiole



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Pathogenesis of B.A

- Inflammatory mediators are liberated from mast cells, eosinophils, neutrophils, monocytes & macrophages

Aims of Asthma Therapy

- Short-term relief is most effectively obtained by reversal of airway constriction using bronchodilators including β2-agonists, theophylline & some antimuscarinics
- Long-term control is often achieved with an anti-inflammatory agent like inhaled corticosteroid, leukotriene antagonists or with inhibitor of mast cell degranulation like cromoglicate

Approach to management of asthma

1. Prevention of exposure to allergens (appropriate for extrinsic asthma)
2. Reduction of bronchial inflammation & hyperactivity
3. Dilatation of narrowed bronchi (bronchodilators)

Reduction of bronchial inflammation &. 2 hyperactivity

- Glucocorticoids:

(Prednisolone, beclomethasone, fluticasone, budesonide)

- Cromoglicate
- Leukotriene receptor antagonists:

(Montelukast & zafirlukast)

- Omalizumab (Xolair)

Reduction of bronchial inflammation &. 2 hyperactivity

A. Glucocorticoids have useful anti-inflammatory efficacy & produce gradual reduction in bronchial hyperactivity

Mechanisms of action of CS in asthma include:

- Inhibition of influx of inflammatory cells into lungs after allergen exposure as macrophages, eosinophils & lymphocytes
- Inhibition of release of mediators from macrophages & eosinophils
- Reduction of mucous oedema
- Reduction of leukotriene release

Glucocorticoids

- Include **oral prednisolone** & **inhalational beclomethasone, fluticasone & budesonide**
- **They are not direct bronchodilators** & produce their effects after delay period (not immediate)
- **Chronic use of inhaled CS** effectively reduces symptoms & improves pulmonary function
- They are indicated in patients with **moderate to severe asthma** that need frequent daily administrations of β2-gonists

Glucocorticoids

-Topical adverse effects:
oral candidiasis (thrush)
& hoarseness of voice
can be reduced by using
a spacer device & rinsing mouth

- Patients are maintained on minimum doses of inhaled CS to avoid adverse effects

Pharmacokinetics

- Inhaled CS drugs have reduced use of systemic CS. Proper administration is essential as large portion of inhaled drug may precipitate in mouth, pharynx & swallowed
- Systemic corticosteroids may be administered in **severe attacks** either as oral prednisolone or IV methylprednisolone

B. Cromoglicate (Cromolyn)

- This is effective anti-inflammatory agent used prophylactically in asthma but **not in acute asthmatic attacks** as it does not reverse bronchospasm
- It is given as fine powder by inhalation or as aerosol solution for period of 6-8 weeks to reduce bronchial reactivity

C. Leukotriene receptor antagonists

- Montelukast & zafirlukast that block LTD4-receptors & prevent bronchoconstrictor effects of leukotrienes C4, D4 & E4
- Montelukast is used **orally** once daily, zafirlukast is used **orally** twice daily
- **Used as prophylaxis**
- They are well-tolerated & used to reduce frequency of exacerbations
- some patients respond well to these agents particularly where leukotrienes are important & involved as in aspirin-induced asthma (also with other NSAIDs)

D- Omalizumab (Xolair)

- A recombinant-derived **monoclonal antibody**
- Useful in **prophylaxis of asthma** in patients with **moderate to severe cases**, who are poorly controlled by conventional therapy
- It binds to immunoglobulin IgE, decrease binding of IgE to receptor on mast cells, limits release of mediators of allergic response
- Due to high cost, not used as first-line

Bronchodilatation. 3

- Selective β2-agonists:
  (sulbutamol, salmeterol)
- Theophylline
- Antimuscarinic:
  (ipratropium & oxitropium)

Bronchodilatation. 3

A. Selective β2-agonists

-The predominant adrenoceptors in bronchi are of β2 & their stimulation leads to bronchodilatation & stabilization of mast cells & inhibition of release of mediators

They are divided into:

1. Short-acting agents like salbutamol & terbutaline
2. Long-acting agents as salmeterol

Salbutamol (Ventolin; Albuterol)

- It is useful in treatment of **acute attacks** can be given by inhalation, orally or by injection in severe cases
- Inhaled salbutamol produces **rapid effects** but up to 20% may be absorbed & may produce systemic effects
- Its t ½ is about 4 hours

Salbutamol

- Salbutamol acts within few minutes & reaches maximum in 30 minutes & action lasts 4-6 hours
- It is given as 1-2 puffs 4-time daily
- **Adverse effects:** tremor, tachycardia & hypokalemia due to shift of potassium into cells

Salmeterol

- is **long-acting β2-agonist,** has slower onset of action & longer duration (12 hr)
- It should not be used for treatment of acute attacks because of its slow onset of action (15-30 min) but **used for as prophylaxis in chronic asthma**

B. Theophylline

- It is a bronchodilator useful in acute asthma attacks & in chronic asthma most commonly in its soluble form **aminophylline**
- Has been replaced by B2 agonists and CS due to narrow therapeutic window, side effects and drug interactions

Pharmacokinetic of Theophylline

- Given orally or by **IV infusion** (in the form of **aminophylline**)
- Absorption is good
- The t ½ is about 8 hours
- To enhance theophylline solubility, it is usually mixed with EDTA forming **aminophylline**
- **Aminophylline** can be administered IV (slowly) (status asthmaticus)

Theophylline

- **Adverse effects:** nausea, vomiting, insomnia & hypotension
- Has a narrow therapeutic index
- Arrhythmias & convulsions may develop with high doses

C. Antimuscarinic

- These antagonists include inhaled ipratropium & oxitropium, which are synthetic derivatives of atropine
- They are bronchodilators less effective than adrenergic agonists
- They block vagus-mediated effects on bronchi (M3-induced bronchospasm & increase mucous secretion)

C. Antimuscarinic Bronchodilators

- They are useful as bronchodilators in acute severe asthma combined with β2-agonists to potentiate bronchodilatation

Drug treatment of asthma

- Patients with mild asthma & occasional attacks require inhaled B2 agonists
- If patients require frequent inhalations with nocturnal symptoms, inhaled CS or cromoglicate or oral LRA may be added
- Theophylline is reserved for patients with poor control

The Five-step Approach to treatment of chronic asthma

Step 1 short acting β2-agonist (occasional) e.g. salbutamol 1-2 puffs

Step 2 regular low dose inhaled CS or inhaled cromoglicate

Step 3 regular inhaled CS + regular long acting β2-agonist

Step 4 high-dose inhaled CS + regular long acting β2-agonist or Theophylline or leukotriene antagonist

Step 5 step 4 + long term oral prednisolone

Treatment of acute severe asthma
)Status Asthmaticus(

1. Oxygen administration
2. Salbutamol nebulizer
3. Prednisolone orally or hydrocortisone IV

If the patient is still not improving:

4. Give ipratropium inhalation
5. Give salbutamol or aminophylline by slow IV infusion