BRONCHIAL ASTHMA

OBJECTIVES:

At the end of this lecture the student is supposed to be able to:

- Define bronchial asthma.
- Understand its epidemiology and classification.
- Describe its etiology, pathology, and pathogenesis.
- Differentiate between atopic and non-atopic asthma.
- Enumerate the precipitating factors, and the mechanism by which they induce bronchial asthma.
- State the clinical features of b. asthma.
- List the features that indicate severe, and life threatening b. asthma.
- Define acute severe asthma and describe its clinical features.
- Outline the diagnosis of b. asthma.
- Mention the role of chest X-ray in b. asthma.
- Outline the therapy of b. asthma.
- Recall the specific drugs that are used in b. asthma.
- Talk about the step-wise management of chronic b. asthma.
- Outline treatment of acute severe asthma.
- Define the role of monitoring in the management of b. asthma.
- Outline the treatment of life-threatening b. asthma.

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BRONCHIAL ASTHMA

TERMINOLOGY

Asthma fr. G.= panting

ربا: ارتفع، زاد، كثر
ومنه الربوة أوالرابية والتربية
الرَبْـو(وجمعه أرباء)= زيادة في النَفَس = النَـفـَس العالي
ربا الفرس ربواً= انتفخ
الربوة= انتفاخ الجوف

DEFINITION

- Pathological definition:
  - A respiratory disorder characterized by chronic air way inflammation and increased air way responsiveness.
- Physiological definition:
  - Air flow limitation that is variable over a short time or is reversible with treatment.
  - In chronic asthma, airflow limitation may be irreversible.
- Clinical definition:
  - Wheeze, cough, chest tightness and dyspnea that usually come in attacks.
  - It may be chronic (i.e. the patient is never free from symptoms)
  - It is not one disease but a syndrome of many etiologies.

EPIDEMIOLOGY

There is geographical variation over the world
Its prevalence is increasing.
It occurs at any age
In the 2nd decade 10-15% of populations are affected.

CLASSIFICATION

1. Extrinsic asthma- there is a definite external cause
2. Intrinsic (cryptogenic) asthma- no identified causative agent.

OR:

1. Atopic asthma - due to atopy
2. Non-atopic asthma -due to non-atopic factors

PATHOLOGY

The primary abnormality is narrowing of the air ways due to:

1. Smooth muscle contraction (due to hyper responsiveness)
2. Thickening of the airway (due to cellular infiltration and inflammation)
3. Secretions within the airway lumen.

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PATHOGENESIS

The pathogenesis is complex; not well understood
Exposure to antigen is followed by:

- Presentation of the antigen by macrophages [dendritic cell] to T-lymphocytes, T cells activation, and secretion of cytokines (interleukins).
- The cytokines (IL9, IL4) attract and stimulate Mast cell leading to release of mediators [leukotrine C4, prostaglandin D2, and histamine] that lead to:
    - Contraction of smooth muscles
    - Mucus secretion
    - Dilatation of blood vessel and edema
- The cytokines (IL3, IL5)→ attract and stimulate Eosinophils leading to release of mediators [LT C4, Major basic protein, Eosinophilic cationic protein, Perioxidase] that induce local Inflammation in the bronchial walls.
- The cytokines (IL4, IL13) maintain the allergic reaction and produce the late phase reaction.
- Chronic inflammation of the air ways leads to remodeling of air ways (i.e. Thickening of the bronchial walls) due to:
    1. Smooth muscles hypertrophy and hyperplasia.
    2. Deposition of collagen and matrix below the basement membrane of the air ways.
    3. Damage of epithelium and loss of cilia and epithelial metaplasia.
    4. Increase in the number of mucus secreting goblet cells.

ETIOLOGY

- It is multifactorial i.e. genetic susceptibility and environmental factors
- There are two major factors:

A. Atopy that produces Atopic asthma
B. Bronchial hyper-responsiveness that produces other forms of b. asthma

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Atopy:

- From Greek: A (not) + topy (topos: place) meaning: not in its place.
- Definition of atopy:

  It is the phenomenon of formation of large quantities of Ig E antibodies in response to little amounts of common environmental antigens such as: house-mite dust or grass pollen.
  Atopic patients have a higher prevalence of allergic rhinitis, urticaria or eczema.

Causes of atopy:

1- Inherited genes (Polygenic):

- Disorder of cytokine reaction genes(chromosome 5)
- Disorder of IL-4 cluster gene

2- Sensitization to common allergens and pollutants due to early childhood exposure to:

1. Allergens: e.g.House dust mite in carpets, soft furniture & beds, Pet-derived allergens (dogs & cats), Fungal spores, Cockroach antigens, Pollens (grass, flowers & rapeseed)
2. Pollutants (NO_2 & SO_2 from fuel burning)
3. Ozone (NO_2 + sunlight + O_2)
4. Cigarette smoke (exposure immediately following birth)

3. Smoking during pregnancy- It ↑the risk of developing atopy in infancy
4. Growing up in a relatively clean environment may predispose to atopy, due to poor development of immune system.

Atopy is tested by: Prick test

Bronchial hyperresponsiveness:

- Bronchial hyper-responsiveness is found in most asthmatics
- Bronchial hyper-responsiveness is tested by bronchial provocation tests [with histamine or methacholine inhalation]

PRECIPITATING FACTORS

1. Allergens

- Fecal particles of the house-mite dust in carpets, soft furniture & beds (the major allergen all over the world)
- Pet-derived allergens (dogs & cats)
- Fungal spores
- Cockroach antigens
- Pollens (grass, flowers & rapeseed)
- Other allergens

2. Occupational factors

>200 materials e.g. wood dust, epoxy resins…etc.
→ occupational asthma.
The mechanism is variable:
Ig E releated (Linked to formation of I.g E)

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- e.g. laboratory animals, flour, grain, proteolytic enzymes in biologic washing powders, platinum salts.

I.g E unrelated:

- Undetermined mechanism:
- e.g Isocyanates in varnishes and Spray painting.

Risk of occupational asthma increases in smokers.

3. Drugs

Precipitate asthma through different mechanisms

B-blockers (even if topical): block bronchodilator B2 receptors

NSAID: block cyclo-oxygenase (COX) pathway →prevents synthesis of PG in the air ways.

*Only 10% of asthmatics are sensitive to NSAID.

Sulphiting agents (food preservatives)-mechanism is unknown

4. Atmospheric pollution

- Irritant dusts, vapours and fumes: SO2, NO2, Ozone, tobacco smoke (passive smoking ↑ asthma)

5. Emotional factors

- Increase asthma but no evidence that asthmatic patients are more psychologically disturbed than non-asthmatic peers.

6. Respiratory infections

- Usually viruses e.g. Rhino virus, may be bacteria
- Inflammation of airways → increased response of airways to vagal stimuli.

7. Exercise (and cold air)

- Exercise causes dryness and cooling of the bronchial mucosa

→ induces mast cells.

CLINICAL FEATURES

- Onset: at any age. It is common in children
- The patients are usually atopic (=extrinsic or atopic asthma)
- **Symptoms**
  - Episodic attacks of wheeze, breathlessness, cough, and sense of chest tightness. The patients are usually free of symptoms in between the attacks.
  - The attacks are variable in severity
  - Attacks can be: mild- severe-or- life threatening.
  - Asthma may sometimes be chronic i.e. the patient is never free of wheeze or breathlessness. This sort is more common in older patients, and the patients are usually non-atopic
  - Cough may be the only symptom (cough-variant asthma)
  - Viral infections or exposure to allergens are the usual precipitating factors.

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- Symptoms may specifically be provoked by exercise (exercise-induced)
- Diurnal variation of symptoms is a characteristic feature of b. asthma:
  - PEFR worsen in early morning (morning dip).
  - Symptoms often disturb sleep (nocturnal asthma)

- **Features that indicate severe asthma:**

  Inability to complete a sentence in one breath.
  Respiratory rate ≥ 25 breaths/ min
  Tachycardia > 110 beats/ min.
  Pulsus paradoxus
  PEFR <50% of predicted value

- **Features that indicate life threatening asthma:**
  - Inability to talk
  - Exhaustion and poor respiratory effort
  - Nearly absent sounds of air entry (Silent chest)
  - Central cyanosis
  - Confusion or coma
  - Bradycardia
  - PEFR <30% predicted (may be unrecordable)
  - Pa CO2: normal (5-6 kPa) or hypercapnea > 6 kPa
  - Pa O2: sever hypoxemia (<8 kPa)
  - Low PH (<7.35)

- **Acute severe asthma**
  - Severe and progressive symptoms over hours or days
  - Extreme respiratory distress (use of accessory muscles of respiration)
  - Tachypnea
  - Hyper-inflated chest
  - Tachycardia
  - Pulsus paradoxus
  - Sweating
  - ± central cyanosis (ominous sign)
  - if very severe air flow limitation → (silent chest) + bradycardia [=ominous signs]
  - A life threatening attack of asthma (=A medical emergency)
  - Treatment should start immediately at home with subsequent transfer to hospital
  - Mortality 1500 patients/ year in UK.

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DIAGNOSIS

- There is no single satisfactory diagnostic test.
- Diagnosis is made by:
  - Suggestive history + reversibility with bronchodilators:
    - ≥15% improvement in FEV1 or PEFR after bronchodilator
  - Suggestive history + variability of severity:
    - ≥15% spontaneous change in PEFR during 1 week of home monitoring
  - Provocation tests (done if above are negative):
    - Exercise (or hyperventilation) test
    - Histamine or methacholine test in gradually increasing doses→ ↓ FEV1
    - Occupational exposure test.
- Skin-prick tests (done to identify allergens)

  A wheal develops 15 min. after allergen injection in the epidermis of forearm.

INVESTIGATIONS

The following investigations are to be done:

- WBC counts: eosinophelia especially in aspergillosis.
- Serology for aspergillus antibody titers (if there is eosinophelia or suggestive shadowing)
- Arterial blood gas analysis (especially in acute severe asthma)
- CXR:
  1. Normal in between attacks
  2. Hyper-inflated in acute episode
  3. Hyper inflated chest + pigeon-chest deformity (on lateral films) in chronic asthma.
  4. Lobar or segmental collapse due to thick sputum
  5. Pneumothorax, mediastinal, pericardial or subcutaneous emphysema.
  6. Fleeting shadowing in aspergillus allergy.
  7. Segmental or sub-segmental collapse + proximal bronchiectasis in broncho-pulmonary aspergillosis.
  8. Indication of CXR:
     a. All patient with acute severe asthma
     b. If poor response to therapy
     c. To exclude pneumothorax before assisted ventilation initiated.

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MANAGEMENT

The main outlines of therapy include:

1. Patient and family education
2. Antismoking advice
3. Avoidance of precipitating factors
4. Specific drug treatment
5. Self-management programs:
   - **a)** Monitoring of PEFR & symptoms
   - **b)** Supplying the patients with written action plan showing patients how to act early in exacerbations

Specific drug therapy:

The main drug groups are:

1. B2- adrenoceptor agonists
2. Anticholinergic bronchodilators
3. Corticosteroids
4. Leukotriene receptors antagonists
5. Immunosuppressive drugs
6. Aminophylline

1. B2- adrenoceptor agonists: → relax bronchial smooth muscles

Shortacting: salbutamol, terbutaline

Long acting: salmeterol, formoterol

2. Anticholinergic bronchodilators: → bronchdilatation

Ipratropium bromide

Oxitropium bromide

3. Corticosteroids

→ anti-inflammatory effect

→ The Response to steroid therapy is tested by giving Prednisolone (30 mg/ day for 2 weeks).

→ An improvement in FEV1>15% confirms the reversibility and indicates that inhaled steroids may prove beneficial.

→ Inhaled steroids (beclomethasone, budesonide)

→ Used for maintenance therapy of all cases, except the very mild.

→ Side effects: oral candidiasis, hoarseness & rarely cataract [spacers used to reduce side effects)

→ Oral steroids (prednisolone)

→ Occasionally necessary if inhaled steroids ineffective

→ Side effects (…)

4. **Leukotriene receptors antagonists (montelukast, zaferlukast)-**

→ antileukotriene

Particularly effective if high dose inhaled or oral steroids ineffective, and in patients with asthma by aspirin.

5. Immunosuppressive drugs:

Methotrexate in low doses in severe asthma as steroid sparing drug.

6. Aminophylline (i.v.) :

→bronchodilators & other functions

Sometimes used in acute severe asthma.

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Stepwise management of bronchial asthma

Management approach in adults based on asthma control.

<table>
<tr><th>Asthma suspected</th><th colspan="5">Asthma diagnosed</th></tr>
<tr><td rowspan="4"></td><td rowspan="3"></td><td rowspan="3"></td><td></td><td></td><td rowspan="2">daily steroid tablet in the lowest dose providing adequate control

Maintain high-dose ICS

Consider other treatments to minimize use of steroid tablets

Refer patient for specialist care</td></tr>
<tr><td>stop LABA (if no response to it)
+
High dose of ICS</td><td>• high dose ICS
• May add a fourth drug, eg.
1. LTRA
2. SR-theophylline
3. Beta agonist tablet
4. LAMA

Refer patient for specialist care</td></tr>
<tr><td rowspan="2">Low dose ICS + LABA</td><td>LABA
+
medium dose ICS</td><td rowspan="2">LABA
+
Low dose ICS
+
consider:
1. LTRA
2. SR-theophylline
3. LAMA</td></tr>
<tr><td>Low dose ICS</td></tr>
<tr><td colspan="6">Short-acting β2 agonists as required
• Consider moving up if using three doses a week or more
• Move down to find and maintain lowest controlling therapy
• Move up to improve control as needed</td></tr>
</table>

ICS = inhaled corticosteroids (glucocorticoids);
LABA = long-acting β2-agonist;
LAMA = long-acting muscarinic antagonist;
LTRA = leukotriene receptor antagonist;
SR = sustained-release

From British Thoracic Society and SIGN guideline 153: British guideline on the management of asthma (2016).

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Immediate treatment of patients with acute severe asthma:

<table>
<tr><td colspan="5">MEASURE PEAK EXPIRATORY FLOW
Convert PEFR to % best or % predicted</td></tr>
<tr><td>Life-threatening/acute severe
PEFR 0-50%</td><td colspan="2">Moderate
PEFR 51-75%</td><td colspan="2">Mild
PEFR 76-100%</td></tr>
<tr><td>• Arterial blood gas
• Nebulised salbutamol 5 mg or terbutaline 2.5 mg 6–12 times daily or as required
• Oxygen–high-flow/60%
• Prednisolone 40 mg orally (or hydrocortisone 200 mg IV)</td><td colspan="2">• Arterial blood gas
• Nebulised salbutamol 5 mg or terbutaline 2.5 mg
• Oxygen–high-flow/60%
• Prednisolone 40 mg orally</td><td colspan="2">Did patient receive nebulised therapy before PEF recorded?</td></tr>
<tr><td rowspan="2">• Intravenous access, chest X-ray,
• plasma theophylline level,
• plasma K+</td><td colspan="2" rowspan="3">Wait 30 mins ⇐ Yes

Measure PEF</td><td>Yes</td><td>No</td></tr>
<tr><td></td><td>• Usual inhaled bronchodilator
• Wait 60 mins</td></tr>
<tr><td>Admit</td><td></td><td>Home
• Usual treatment
• If worsen, return immediately
• Appointment with GP within 48 hours</td></tr>
<tr><td>Administer repeat salbutamol 5 mg + ipratropium bromide 500 µg by oxygen-driven nebulizer

• Consider continuous salbutamol nebuliser 5–10 mg/hr

• Consider intravenous magnesium sulphate 1.2–2.0 g over 20 mins, or

• Aminophylline 5 mg/kg loading dose over 20 mins followed by a continuous infusion at 1 mg/kg/hr

• Correct fluid and electrolytes (especially K+)</td><td>PEF < 60% predicted</td><td>PEF > 60% predicted</td><td colspan="2"><u>Home</u>
• Check with senior medical staff
• Prednisolone 40 mg daily for 5 days
• Start or double ICS
• Return immediately if worse
• Appointment with GP within 48 hours</td></tr>
</table>

<u>If no response within 1 hour transfer to ICU for possible intubation and mechanical ventilation.</u>

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