Respiratory Diseases
Lecture: 6

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Asthma

Asthma is a chronic inflammatory disorder of the airways (atopic) in which many cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

It is referred to a disorder of the respiratory system leading to difficulty in breathing.

This inflammation causes symptoms, which are associated with widespread, but variable airflow obstruction that is reversible either spontaneously or with treatment, and causes associated increase in airway responsiveness to a variety of stimuli.

Classification of asthma

Epidemiology

The probability of children having asthma-like symptoms is estimated to be 5-12% with a higher occurrence in boys than girls and in children whose parents have allergic disorder. Between 30-70% of children will become symptom-free by adult-hood.

More common in children

Upon reaching puberty, boys to girls ratio becomes equal
Asthma is considered to be a consequence of western civilization, and related to a number of environmental factors. Air pollution may be interacting with smoking, dietary, and other factors increase the incidence of asthma.

و هنا يجي في دماغك سؤال يقول الاكل اخره يعمل شويه rash و بتاع بس يعمل asthma! أه بس قليل يعني

Etiology

The abnormality causing asthma is hyper-reactivity of the lungs to one or more stimuli.

Normal functions of lung include mucus secretion, ciliary motion, and muscle contractility.

One of the most common trigger factors is the allergen found in the house dust mite feces, which is present in bedding, carpets and soft furnishing. Pollens can cause seasonal asthma. The role of occupation in asthma has become apparent with increased industrialization.

There are many causes of occupational asthma, and bronchial reactivity may persist for years after exposure to the trigger factor.

Food allergy usually results in GIT disturbances and eczema rather than asthma.

Drug-induced asthma can be severe, and the most common causes are:

- B-receptor blockers:
  - The administration of β-blockers even in the form of eye drops can cause B-receptor blockade and bronchoconstriction. Selective B-blockers are thought to pose slightly less risk, but as these lose their selectivity at higher doses it is generally recommended that this group of drugs is avoided in asthma patients
  - That is a relative contraindication
  - Completely contraindicated in uncontrolled or severe pulmonary diseases pneumonia

- Prostaglandin synthesis inhibitors:
  - Aspirin and NSAIDs can cause severe bronchoconstriction in susceptible individuals.
  - Aspirin inhibits prostaglandin synthetase, which normally converts Arachidonic acid to prostaglandins. When this pathway is blocked an alternative reaction predominates, leading to an increase in production of bronchoconstrictor Leukotrienes (LTs)
  - We can shift them to Cox-2 inhibitors but cautious use due to cardiovascular events

- ACEI:
  - Not contraindicated
  - Example if an asthmatic patient is suffering from heart failure we will use the ACEIs
  - Stopped in case of pulmonary function deterioration not cough
Pathophysiology

Asthma is characterized by increase in eosinophil titre (acidic cells)

Airway inflammation & Inhaled allergens cause:

A) Early-phase asthmatic response, with symptoms peaking within 15 minutes and subsiding after 1 hour.

✓ Allergens activate airway mast cells bearing specific IgE antibodies, leading to cell degranulation and releasing inflammatory mediators e.g., histamine and eicosanoids.
✓ The mediators cause mucus hypersecretion and plasma leakage from blood vessels, causing bronchial edema, wall thickening, and blocking of the airway lumen.
✓ Remove the cause and take medications otherwise it will continue to the late phase

B) In late-phase asthmatic response, an influx of eosinophils releases further mediators.

• Late-phase response causes more changes and the smooth muscle around the airways becomes hyper-reactive, contracting readily in response to allergens.
• A long-term consequence of airway inflammation is airway remodeling, involving:
  i) Epithelial and goblet cell – hyperplasia
  ii) Increased mucus secretion
  iii) Fibrosis with collagen deposition in the basement membrane and sub-mucosa
  iv) Increased thickness of smooth muscle

• With bronchial walls thickened and airway remodeling, small contraction of bronchial smooth muscle can lead to dramatic increases in airway resistance.
Bronchial hyper-reactivity

Airway inflammation also leads to bronchial hyper-reactivity, described as excess airway narrowing in response to stimuli.

Airflow obstruction

Bronchospasm, edema, and mucus hypersecretion lead to reversible airflow obstruction. Variable airflow obstruction is demonstrated by measuring forced expiratory volume (FEV1), peak expiratory flow (PEP), or hyper-responsiveness to methacholine challenge.

Exercise-induced

In exercise-induced asthma, vigorous exercise causes pulmonary function to increase during the first few minutes but then decrease after 6 to 8 minutes.

Exercise-induced asthma is considered moderately severe if FEVI drops more than 30% below baseline.

It is more provoked in cold dry air (degranulate mast cells), whereas warm humid air can blunt it.

Mast cell degranulation plays a role, with increased histamine and tryptase concentrations.

Some patients have a late response similar to late-phase asthmatic response and an associated secondary rise in neutrophil chemotactic factor. (Mostly spasm without inflammation)

Prophylactic measures:

- Warm up before exercise
- SABA before exercise
- LT antagonists
- cromoglycate

Aspirin-induced asthma:

Approximately 10-20% of adults with asthma are ASA-sensitive. In doses higher than 100mg

Cyclooxygenase (COX) inhibition plays a central role.

ASA and other NSAIDs inhibit the COX enzyme, preventing metabolism of arachidonic acid to prostaglandins, and, leading to excess leukotriene production which promote histamine release from mast cells, leading to inflammation and bronchospasm. Most ASA-sensitive patients can tolerate COX-2 specific NSAIDs.

You can shift to clopidogrel as anti-platelet
Clinical manifestations:

The symptoms of asthma tend to be variable, intermittent, worse (not more) at night and provoked by triggers. The usual presenting features of asthma are:

- Wheezing caused by airflow limitation, resulting in a high-pitched whistling sound that is usually heard on expiration
- Shortness of breath
- Chest tightness or dyspnea (the sensation that patients often feel is caused by the increased work needed to breathe when the airways are constricted)
- Cough, particularly at night and early in the morning (probably results from the stimulation of sensory nerves in the airways by inflammatory mediators that are released by various cells involved in asthma.

Diagnosis is made by a combination of a full history from the patient together with lung function tests before and after treatment.

The history of asthma patients often includes the presence of atopy and allergic rhinitis in the patient or within the close family.

Acute severe asthma is a dangerous condition that requires hospitalization. It occurs when bronchospasm has progressed to a state where the patient is breathless at rest and has a degree of cardiac stress.

- The breathlessness is so severe that the patient can’t talk or lie down.
- Severe acute asthma can increase the pulse rate to more than 110 beats/min.
- Breathing can be rapid (>30 breaths/min) and shallow leading to low arterial oxygen tension (PaO2) with the patient becoming fatigued, cyanosed, confused and lethargic.
- The arterial carbon dioxide tension (PaCO2) is low in acute asthma. If it is high it should respond quickly to emergency therapy. Hypercapnia (high PaCO2 level) that does not diminish is a more severe problem, and indicates respiratory failure progression.
- At first the patient had hypercapnia due to breathlessness; however, tachypnea can lead to hypocapnia and respiratory alkalosis because CO2 has higher diffusion rate than O2.

Investigations:

A careful medical history, physical examination and lung function tests provide the information needed to diagnose most cases of asthma. However, the process is not always straightforward and it can take time to make an accurate diagnosis. Eczema, hay fever and a family history of asthma or atopic diseases are often associated with asthma but they are not necessarily elements of an asthma diagnosis. There is no single satisfactory diagnostic test for all types of asthma.
The function of the lungs can be measured to diagnose and monitor respiratory diseases. A series of tests has been developed to assess asthma as well as other respiratory diseases.

1. **Forced expiratory volume (FEV1)**
   A measure of the forced expiratory volume in the first second of exhalation.
   This is measured by a lung function assessment apparatus such as spirometer. It is the most useful test for airways function abnormalities.
   The patient inhales as deeply as possible and then exhales as forcefully and completely as possible into a mouthpiece connected to the spirometer.

2. **Forced vital capacity (FVC)**
   This is an assessment of the maximum volume of air exhaled with maximum effort after maximum inspiration.
   FEV1 is expressed as a percentage of the total volume of air exhaled, and is reported as the FEV1/FVC ratio.
   This ratio is a useful and highly reproducible measure.
   Normal individuals can exhale at least 75% of their total capacity in 1 second.
   Any reduction indicates deterioration in lung performance.

3. **Peak expiratory flow rate (PEFR)**
   It's measured by the peak flow meter which is a useful means of self-assessment.
   It gives less reproducible results but has the advantage that the patient can do regular tests at home.
   PEFR is the maximum flow rate that forced during expiration.
   PEFR can be used to assess the improvement/deterioration in the disease as well as the effectiveness of treatment.
   The measurement of FEV1, FVC, or PEFR doesn’t detect early deterioration of lung function such as bronchospasm and mucus plugging in the smaller airways.

4. **Assessing PaO2 and P„CO2.** These values together with pH are routinely monitored in hospital inpatients.

   In patients with severe asthma the PaCO2 increases as a result of poor lung ventilation causing a reduction in gas exchange.
   Respiratory acidosis can occur because of accumulation of carbonic acid produced from excess CO2.
   PaCO2 can fall as a result of poor lung ventilation due to bronchospasm, and poor diffusion into the respiratory capillaries due to inflammation, edema and mucus plugging.

   Exercise ECG test because severe uncontrolled long-term asthma can cause COPD and Cor-pulmonale.

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<table>
<thead>
<tr>
<th></th>
<th>Daytime symptom</th>
<th>Night-time symptoms</th>
<th>Exacerbations</th>
<th>Spirometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>Less than weekly</td>
<td>Less than 2 per month</td>
<td>Infrequent</td>
<td>FEV\textsubscript{1} at least 80% predicted</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>More than weekly</td>
<td>More than 2 per month but not weekly</td>
<td>Occasional + may affect activity or sleep</td>
<td>FEV\textsubscript{1} at least 80% predicted</td>
</tr>
<tr>
<td>Moderate persis</td>
<td>Daily</td>
<td>Weekly or more often</td>
<td>Occasional + may affect activity or sleep</td>
<td>FEV\textsubscript{1} 60-80% predicted</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Daily with physical activity restriction</td>
<td>Frequent</td>
<td>Frequent</td>
<td>FEV\textsubscript{1} 60% predicted or less</td>
</tr>
</tbody>
</table>

From this table we can see that spirometry isn’t very sensitive as it can’t differentiate between intermittent and mild persistent.

Infrequent means less than once per 2 years.

Expiratory wheeze suggests asthma but isn’t pathognomonic.

The absence of physical signs doesn’t exclude a diagnosis of asthma.

Look for signs of allergic rhinitis with suspected asthma.

Don’t rely on peak flow meters for assessing airflow limitation in the diagnosis of asthma.

Practice points:

- Expiratory wheeze suggests asthma but isn’t pathognomonic.
- The absence of physical signs doesn’t exclude a diagnosis of asthma.
- Look for signs of allergic rhinitis with suspected asthma.
- Don’t rely on peak flow meters for assessing airflow limitation in the diagnosis of asthma.

Goals of asthma treatment:

- Prevent exacerbations
- Minimize symptoms
- Maximize lung function
- Minimize need for medications
- Minimize side effects
- Provide information to the patients
Chronic asthma

- The management of asthma depends on the frequency and severity of symptoms.
- Infrequent attacks can be managed by treating each attack when it occurs, but with more frequent attacks preventive therapy needs to be used.
- The preferred route of administration in the management of asthma is inhalation.
- This allows the drugs to be delivered directly to the airways in smaller doses with fewer side-effects than systemic or parenteral.
- Inhaled bronchodilators have faster onset of action than systemic ones and give better protection from bronchoconstriction. Treatment of chronic asthma can be given in a stepwise progression according to the severity of the condition.

Adrenoreceptor agonist bronchodilators

- They are main therapy of asthma (rescues)
- Selective agonists (Salbutamol and Terbutaline) have replaced the non-selective agents (adrenaline, Isoprenaline and Orciprenaline).
- Selective agents have fewer B1 mediated side effects, e.g. cardiotoxicity.
- B2 receptors are present in myocardial tissue; therefore, cardiovascular stimulation resulting in tachycardia and palpitations is still the main dose-limiting toxicity with these agents.
- Inhaled B2 agonist is the first line agent in the management of asthma. These are used as required by the patients for the symptomatic relief, e.g., Salbutamol 200ug prn.

Inhaled Anticholinergic Agent

- They block muscarinic receptors and can be added to the treatment regimen, e.g. Ipratropium (rescue) 80um four times/day or Oxitropium (controller) 200microg twice daily or tiotropium (controller) once daily.
- They have slower onset of action than agonists but last longer.
- They may be helpful in the elderly where asthma may be complicated by CoAD. Substitute LABA

Long-acting B-Agonist Bronchodilators (controllers)

- These (Salmeterol and efomoterol) should be used in conjunction with conventional agonists, rather than as replacements, as the latter have faster onsets of action.
- When low dose inhaled steroids fail to control asthma adequately, long-acting R2 agonists can be added instead of increasing the steroid dose.
- not preferred for elderly

High dose B2 agonists

- These are only considered if conventional dose doesn’t achieve adequate control. (in exacerbations)
- Nebulized drugs such as salbutamol 2.5-5 mg/dose are given.
- Multiple actuations of a MDI into a spacer can be used instead of nebulizer.
- Terbutaline has been given by subcutaneous infusion in the treatment of 'brittle' asthma, where there is an unpredictable and rapid onset of airway narrowing.
- side effects are tachycardia, tremors, and vivid dreams.
<table>
<thead>
<tr>
<th><strong>Inhaled Anti-inflammatory Agents</strong></th>
<th><strong>Oral Bronchodilators</strong> (not preferred due to systemic side effects)</th>
</tr>
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<tbody>
<tr>
<td>• Regular anti-inflammatory must be given to patients who require inhaled bronchodilator more than once a day or have nocturnal symptoms.</td>
<td>• Either B&lt;sub&gt;2&lt;/sub&gt; agonists or theophylline can be added for additional control.</td>
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<tr>
<td>• The agents used include corticosteroids, sodium cromoglycate and nedocromil sodium. Inhaled steroids are the drugs of choice.</td>
<td>• Slow-release should be used; they are especially useful in a single nighttime dose if nocturnal symptoms are troublesome although twice-daily dosing is more usual.</td>
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<tr>
<td>• Beclomethasone or budesonide are used at doses of 100-400 microg twice daily.</td>
<td>• They may be necessary in patients who are unable to use inhalers effectively.</td>
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<td>• Higher doses are used if symptoms persist.</td>
<td>• Theophylline should be started at a dose of 3mg/kg/day in adults and increased after 7 days to 6mg/kg/day (children 13 mg/kg/day).</td>
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<td>• If asthma is not controlled by the above dose, the dose can be increased to 1.5-2 mg/day. Adrenal suppression may occur at these doses. Candidiasis are common at the higher doses, but can be minimized by using spacer and rinse the mouth with water after inhalation.</td>
<td>• Its clearance is affected by a variety of factors. The dose used should take into account these factors (see table)</td>
</tr>
<tr>
<td>• When very high doses of steroids are recommended give them by oral but keeping an eye for the duration (tapering dose if TTT exceeded 2-3 weeks) and the side effects.</td>
<td>• Theophylline has a narrow therapeutic index, and its hepatic metabolism varies between individuals.</td>
</tr>
<tr>
<td>• <strong>All the time you have to know the conversion between different inhaled corticosteroids</strong></td>
<td>• Serum levels may be taken after 3-4 days at higher dose and it is normal practice to adjust the dose to keep the serum level within the therapeutic window of 10-20mg/L.</td>
</tr>
<tr>
<td>• Inhaled sodium cromoglycate and nedocromil could be used instead of steroids and are effective at controlling symptoms in mild to moderate asthma, aspirin induces asthma, and exercise-induced asthma but less effective in severe asthma.</td>
<td>• Patients should be monitored for the emergence of serious toxic effects, e.g., tachycardia and persistent vomiting.</td>
</tr>
<tr>
<td>• They can be used as an adjunct to inhaled steroids in those who are not fully controlled on steroids, in an attempt to reduce the amount of steroids required, or in children, especially those with exercise-induced or allergic asthma.</td>
<td>• Only modified release should be used, and once stabilized on a particular product the patient shouldn't be changed to another theophylline preparation as there are large differences in serum profile with the different preparations.</td>
</tr>
<tr>
<td></td>
<td>• Normal release theophylline shouldn't be used because of their rapid absorption and highly variable clearance, giving short and unpredictable duration of action.</td>
</tr>
</tbody>
</table>
### Oral Corticosteroids
- Should only be used if symptoms are not controlled with maximum doses of inhaled bronchodilators and steroids.
- The dose should be given as a single morning dose to minimize adrenal suppression.
- Alternate-day dosing produces fewer side effects but is less effective.
- Short courses of high-dose oral steroids, 40-60 mg can be used during exacerbation.

### Steroid Sparing Agents
- Some agents are being tried in patients who are dependent on systemic steroids in an attempt to reduce the steroid dose.
- Methotrexate, cyclosporin and gold have been shown to be effective.
- All have potentially toxic side effects and need to be closely monitored.

### Leukotriene (LK) Antagonists
- Two types of oral drugs were developed to attenuate the effect of LTs: The LT receptor blockers and the LT synthesis inhibitors (e.g. 5-lipoxygenase inhibitors).
- Both groups could be beneficial (especially in mild to moderate asthma when used alone or in combination with (B2 agonists, for exercise- or aspirin-induced asthma or in patients with poor compliance with inhaled drugs because of poor inhaler technique).

### IgE antibodies
- **Omalizumab** (FDA warning of anaphylactic reactions)
  - Asthma often has an allergic component resulting in over-production of human immunoglobulin E (IgE) in response to allergens, for example, pollen or house dust mite.
  - IgE binds to cell membrane receptors resulting in the release of inflammatory mediators. Omalizumab is a recombinant humanized monoclonal antibody, which selectively binds to IgE, forming an omalizumab-IgE complex.
  - This prevents IgE binding to receptor sites on mast cells and basophils. Consequently the cells do not release their inflammatory mediators and the allergic reaction and inflammation are prevented.
  - Omalizumab is a novel agent has a role in treatment-resistant asthma. It is a monoclonal antibody that is directed against free IgE, but not bound IgE, and prevents IgE from binding to immune cells that would otherwise lead to allergen-induced mediator release in asthma.

### Criteria for well controlled asthma (requiring step-down):
- No day time symptoms (less than two per week)
- No night time symptoms (less than two per month)
- No need for rescue drugs = no exacerbations (less than 2 attacks per year)
- No physical limitations
- Normalization of lung functions

Every drug trial should continue for at least 3 months