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Asthma

Asthma is a disease characterized by intermittent cough, chest tightness, shortness of breath, and wheezing. These symptoms result from airway obstruction, which is variable over a short period of time, or is reversible with treatment.

Chronic airway inflammation and airway hyperreactivity are the two cardinal features of asthma.

Epidemiology:

Asthma affects 5 – 10% of the adult population (around 300 million patients worldwide). The incidence is increasing especially in developed countries.

Pathophysiology:

Histologically, the asthmatic airways show evidence of inflammation characterized by inflammatory cell infiltrate (including eosinophils, lymphocytes, mast cells, and neutrophils), mucosal oedema, smooth muscle hypertrophy, mucus plugging, and epithelial damage. The inflammation is most intense during exacerbation.

Many patients are atopic (demonstrating skin prick test reactivity and elevated serum IgE), and in these atopic patients, inhaled allergens interact with mucosal mast cell, via IgE dependant mechanism, resulting in release of inflammatory mediators. Inhalation of the allergen is followed by two-phase (early and late) bronchoconstrictive response. Common examples of these allergens include house dust mites, pet's dander (such as cats and dogs), pests (such as cockroaches and fungi) and pollens.

In patients with persistent asthma, complex interaction between inflammatory cells is characteristic. Eosinophils are increased in the asthmatic airways during active disease. Neutrophils also increase during exacerbations and they tend to predominate in patients with severe persistent asthma. T lymphocytes are also involved in asthma pathogenesis, where Th_2 subtype predominates. These cells secrete cytokines that activate eosinophils and stimulate IgE synthesis, thus initiating an allergic reaction.

In aspirin-sensitive asthma, aspirin (or NSAID) inhibit cyclo-oxygenase, shunting arachidonic acid metabolism through lipo-oxygenase pathway, resulting in the production of leukotrienes (bronchoconstrictives and inflammatory mediators).

In exercise-induced asthma, hyperventilation result in water loss from the respiratory mucosa, triggering mediator release.

Airway hyperreactivity is related to airway inflammation, which means exaggerated (too easily and too much) bronchoconstriction in response to triggers that have little or no effect in normal individuals, like

histamine, methacholine and mannitol. Airway hyperreactivity is integral in the diagnosis of asthma.

Airway limitation (obstruction) results from both airway inflammation and airway hyperreactivity, and is typically reversible, spontaneously or with treatment.

Long standing severe disease is associated with airway remodeling, characterized by structural alteration of the airways, including airway fibrosis, and fixed narrowing of the airways, with reduced response to bronchodilators.

Aetiology:

The aetiology is complex involving environmental and genetic factors.

Hygiene hypothesis suggests that decreased infections in the early life shift the immune system towards Th_2 production (allergic phenotype). Childhood infections (including parasitic infections) increase Th_1 production with a reduction of the incidence of asthma. Living in large families and on farm appears to be protective.

In contrast to this hypothesis, respiratory syncytial virus infection tends to increase the incidence of asthma. Allergen exposure, indoor pollution and dietary deficiency of antioxidants may predispose to the disease.

Genetic predisposition is also important. It interacts with the environmental factors for disease expression.

Clinical picture:

Asthma is a disease of variable presentation. In its typical picture, the patient has recurrent episodes of breathlessness, wheezing, chest tightness and cough. The attacks are triggered by allergen exposure, exercise (particularly in cold weather), respiratory tract infections (commonly viral), dust and pollutants. Sometimes, no apparent trigger is identified. These attacks are reversible spontaneously or with treatment. Examination may show evidence of airway obstruction (prolonged expiration and wheezing). Nasal polyps and eczema may be present. Although some patients are asymptomatic in between the attacks (intermittent asthma), many others have continuous wheezing and breathlessness (persistent asthma), but variability is usually present with symptoms fluctuating is severity over time.

A characteristic feature of asthma is the diurnal pattern of symptoms that symptoms tend to worsen in the early morning (morning dipping). "Nocturnal asthma" is generally a feature of poorly controlled disease, where symptoms of cough and wheeze disturb sleep. Asthma may present with cough as a dominant feature, without other symptoms. So called "cough variant asthma" may be difficult to diagnose. "Drug induced asthma" may result from (or precipitated by) the use of β blockers (sometimes in eye drops), or aspirin (and NSAIDs). The classical aspirin-sensitive asthmatic is a middle aged female with associated rhinosinusitis and nasal polyps.

"Occupational asthma" is the most common occupational lung disease. It is defined as asthma which is related to work environment, and can

be caused by allergic sensitization or non allergic mechanism. Around 5% of all adult asthma is occupational and several hundred agents have been identified as potentially contributing to occupation asthma. Common examples include isocyanates, flour and wood dust, latex, paint spray and animals. Occupational asthma should be suspected if symptoms are worse during working hours and improves on weekends and holidays.

In general, asthma is classified according to severity into 4 categories; mild intermittent, mild persistent, moderate persistent, and severe persistent.

Regardless to severity, asthmatic patients are at risk of acute exacerbation of their disease, usually in association with viral respiratory infections, but also allergen exposure and air pollution.

Diagnosis:

The diagnosis of asthma is predominantly clinical and based on characteristic history, supported by demonstration of variable airway obstruction. This is done by **pulmonary function test**, which includes:

- Spirometry: measurement of FVC and FEV_1 by spirometry demonstrates airway obstruction and defines its severity. Improvement of FEV_1 by 15% (and 200ml) after bronchodilator administration (or trial of oral corticosteroids) confirms the diagnosis
- If spirometry is not available or if the patient has normal pulmonary function on spirometry at the time of examination, PEF (peak expiratory flowmeter) is an inexpensive and simple method of confirming airway obstruction. A diurnal variation of home record with more than 20% difference is diagnostic (the lowest value typically being recorded in the morning).
- If asthma is clinically suspected but the spirometry is normal, testing for airway hyperreactivity can be useful. Histamine or methacholine can be administered with sequential increase in concentration. The dose sufficient to cause 20% drop in FEV1 is called PC_{20}. Hyperreactivity is considered positive if PC_{20} is less than 8mg/ml. Absence of airway hyperreactivity practically excludes asthma (sensitivity of 90%), but positive results is seen in many other diseases, like COPD, bronchiectasis and allergic rhinitis.
- For patients whose symptoms are exclusively occurring after exercise, a 6-minute exercise test followed by a drop of FEV_1 by 15% is diagnostic.

In general, asthma can be diagnosed in the presence of compatible history and one of the followings:

1. $FEV_1 \geq 15\%$ (and 200 ml) increase after bronchodilator or trial of corticosteroids.
2. 20% diurnal variation in PEF daily records
3. $FEV_1 \geq 15\%$ decrease after 6 min. of exercise

Other investigations:

Chest X-ray is generally unhelpful in establishing the diagnosis of asthma (often normal or show hyperinflation of lung fields). However, it can exclude alternative diagnosis or coexistent problems. Complications like lobar collapse or pneumothorax are also diagnosed.

Allergy testing: Atopy can be confirmed by skin prick test, total and allergen specific IgE and peripheral oesinophilia.

Classification of asthma severity

Mild intermittent (Step 1)	Symptoms ≤ 2 times a week Asymptomatic between exacerbations	Nocturnal symptoms ≤ 2 times a month	FEV1 ≥ 80% predicted
Mild persistent (step 2)	Symptoms > 2 times a week, (but less than daily)	Nocturnal symptoms > 2 times a month (but less than weekly)	FEV1 ≥ 80% predicted
Moderate persistent (step 3)	Daily symptoms Exacerbations ≥ twice a week	Nocturnal symptoms ≥ 1 time a week	FEV1 60 – 80% predicted
Severe persistent (step 4 & 5)	Continual symptoms, frequent exacerbations	Nocturnal symptoms frequent	FEV1 ≤ 60% predicted

Management of stable patients:

Effective treatment is available for the majority of cases. The goal of management should be to obtain and sustain complete control. Unfortunately, studies found that most patients are actually poorly controlled.

Patient education: patients should be educated about the nature of their illness and its symptoms, the difference between various medications, the technique of inhaler use, and the use of PEF as a guide to severity and subsequent management. Whenever possible, patients should take responsibility in managing themselves.

Avoidance of aggravating factors:

This is most successful in patients with occupational asthma. To a lesser extent, removal of a household pet from homes can improve

asthma caused by animal dander allergy. It is less successful for house dust mite. Cockroaches and fungi have recently been noticed to be important sources of allergy and should be sought. Smoking cessation is particularly important. Smoking increases sensitization and induces corticosteroid resistance in the airways

Drug therapy:

A stepwise approach is followed in the drug therapy of asthma

Step 1: (Occasional use of inhaled short acting β_2 agonists)

Patients with mild intermittent asthma are treated with an inhaled short acting β_2 agonist (SABA) as salbutamol, to be used on as- required basis. Patients with history of acute exacerbation are not candidates for such form of therapy.

Step 2: (Introduction of regular (preventive) therapy)

Inhaled corticosteroids (ICS) given on regular basis (to act as anti-inflammatory), as well as SABA as-required to relieve symptoms, are prescribed to patients who:

- have experienced an exacerbation of asthma during the preceding two years
- experience asthma symptoms (or use SABA) three time weekly or more
- troubled by nocturnal asthma three times monthly or more

Beclomethasone or budesonide 500μg (low dose ICS) daily is reasonable. Fluticasone 250μg is equivalent.

Step3: (Add-on therapy)

If the patient is still symptomatic, a review of his adherence to treatment and the technique of inhaler use are essential. Attention should be focused on the presence of co-morbidities that can aggravate asthma (like gastro-oesophageal reflux disease and rhinosinusitis).The dose of ICS can be increased to 1000μg daily (moderate dose ICS). However an add-on therapy is considered in most patients. The choices include one of the followings

1. To add a long acting β_2 agonist (LABA) inhaler (like salmeterol or formoterol) to the previous therapy of low dose ICS and SABA is the preferred choice. ICS/LABA was shown to improve asthma control and reduce exacerbation compared with increasing ICS dose. Fixed combinations of ICS and LABA improves compliance and prevent the use of LABA as monotherapy by the patient because these medications lack an anti-inflammatory effect and there is an emerging concern of possible increase in the risk of death from life-threatening and fatal asthma if given alone.
2. Leukotreine receptor antagonists (montelukast 10 mg once daily or zafirlukast 20 mg twice daily) are orally administered drugs that can be added to low or moderate dose ICS.
3. Theophylline may be useful as add-on therapy to low or moderate dose ICS, but side effects and drug interaction limits its use

Step 4: (Poor control on moderate dose ICS and add-on therapy: addition of a fourth drug)

The dose of ICS can be increased to 2000 µg beclomethasone. A fourth drug is added when ICS and add-on therapy are not sufficient. This may include adding oral leukotreine modifier, theophylline or slow release β_2 agonist. Omalizumab (monoclonal antibodies against IgE) may be useful in some of these patients with moderate to severe allergic asthma. It inhibits the binding of IgE to mast cells.

Step 5: (Continuous or frequent use of oral corticosteroids)

Continuous (usually single morning dose) or frequent use of oral corticosteroids prescribed in the minimal dose necessary to control symptoms is added to the previous therapy. More than 3 months of oral steroid use or the need for more than 3 -4 courses per year is an indication to prescribe a bisphosphonate to prevent osteoporosis. Bronchial thermoplasty has been approved in selected patients with refractory asthma (heating the airway by special probes administered by bronchoscope). Newer approach using biological agents (monoclonal antibodies against IL5, IL4 and IL13) are showing encouraging results in refractory asthma.

Step down therapy:

Once control is achieved, a step down approach is followed every 3 months keeping the smallest dose sufficient to maintain effective control.

Asthma in pregnancy:

Asthma follows an unpredicted course in pregnancy (one third improve, one third worsen and one third remain unchanged). All drugs including oral prednisolone are safe. Prostaglandins are bronchoconstrictors and should not be used to induce labour. Breast feeding should continue. Uncontrolled asthma represents the greatest danger to the mother and foetus.

Acute exacerbation of asthma:

Mild to moderate exacerbation

Patients should be educated about features of mild to moderate exacerbation, which include:

1. Progressively worsening PEF records (or fall of PEF below 60% of best personal records)
2. Onset of nocturnal asthma
3. Persistence of morning dipping to midday
4. Diminished response to bronchodilators
5. Symptoms requiring nebulized therapy

Patients can be taught to start a short "rescue" course of oral corticosteroid (prednisolone 30 -60 mg daily is adequate). No need to taper the dose if used for less than 3 weeks.

Severe exacerbations

During these exacerbations (acute severe asthma), the patient gets severe dyspnoea, with tachypnoea (RR > 25/min), tachycardia (PR >

110/min), and is unable to complete a sentence in one breath. PEF is 33%-50% of predicted (less than 200 L/min). PaO_2 (and SpO_2) is usually normal, but $PaCO_2$ is low (CO_2 washed out by hyperventilation)
In more severe life threatening exacerbation, the patient may be unable to speak, is cyanosed, exhausted, and confused. There may be bradycardia, silent chest and coma may follow. PEF is less than 33% predicted (less than 100 L/min). SpO_2 <92% (PaO_2 <60 mmHg). $PaCO_2$: normal or raised.
Severe exacerbations (acute severe asthma and life threatening asthma) are treated in hospital as an emergency:

- High concentration oxygen is administered to maintain oxygen saturation (SpO_2) above 93%. High PCO_2 is not an indication to reduce oxygen concentration.
- High dose nebulized bronchodilators: β_2 agonist (salbutamol 2.5 – 5 mg) repeated within 30 minutes, which can be combined with nebulized ipratropium bromide (anticholenergic)
- Systemic corticosteroids as IV hydrocortisone 200 mg or oral prednisolone 40 -60 mg.
- Consider IV Magnesium sulphate (1.2 – 2.0 gm/20 min.), or aminophylline (5 mg/Kg over 20 minutes loading, then 1mg/Kg/min infusion)
- Ventilatory support (endotracheal intubation and mechanical ventilation) is needed if life threatening asthma persists despite adequate therapy. Indications include coma, respiratory arrest, extreme exhaustion and deterioration of blood gas results.

The patient is discharged when he is stable with PEF more than 75% predicted. Short course of oral corticosteroids should be prescribed with optimization of his medication and managing any possible trigger factors.
The outcome of acute severe asthma is generally good, death is rare. Failure to recognize the severity of an attack contributes to under-treatment or treatment delay.