"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all"
William Osler

Medicine

430

Bronchial Asthma

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-Red: Important notes
-Green: Team notes
-Blue: Extra information from books, websites, etc

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Normal Physiology of the Respiratory System: (Extra)

❖ Lung Volumes:

1. Tidal volume (TV): is the volume inspired or expired with each normal breath.
2. Inspiratory reserve volume (IRV): is the volume that can be inspired after the tidal volume (used in exercising)
3. Expiratory reserve volume (ERV): is the volume that can be expired after expiration of tidal volume.
4. Residual volume (RV): is the volume that remains inside the lungs after a maximal expiration. (It cannot be measured by spirometry)
5. Dead space:
   a. Anatomic dead space:
      - ➢ Volume of the conducting airways
      - ➢ Approximately 150mL normally
   b. Physiologic dead space:
      - ➢ Functional measurement
      - ➢ Volume of the lungs that doesn't participate in gas exchange
      - ➢ Approximately it's equal to anatomic dead space in normal lungs
      - ➢ In lung diseases associated with ventilation/perfusion (V/Q) defects, the physiologic dead space might increase
      - ➢ Equation:

$$V_D = V_T \times \frac{P_{ACO_2} - P_{ECO_2}}{P_{ACO_2}}$$

- ✓ V_D: Physiologic dead space
- ✓ V_T: Tidal volume
- ✓ P_{ACO_2}: P_{CO_2} of alveolar gas (mmHg) = P_{CO_2} of arterial blood
- ✓ P_{ECO_2}: P_{CO_2} of expired air (mmHg)

6. Ventilation Rate:
   a. Minute ventilation = TV x Breaths/min
   b. Alveolar ventilation = (TV - VD) x Breaths/min

Spirometry Test:

- Most common pulmonary function test.
- It measures the volume and flow of the inspired and expired air.
- Helpful in assessing conditions such as asthma, pulmonary fibrosis, cystic fibrosis and COPD.
- It is performed by the Spirometer

❖ Lung Capacities:

1. Inspiratory capacity = TV + IRV
2. Functional residual capacity (FRC) = ERV + RV
   - ➢ Is the volume remaining in the lungs after a tidal volume is expired
   - ➢ Includes the RV, so it cannot be measured by spirometry
3. **Vital capacity (VC),** or forced vital capacity (FVC) = TV + IRV + ERV
   - ➢ Is the volume of air that can be forcibly expired after a maximal inspiration
4. Total lung capacity (TLC) = all 4 lung volumes summed up (TV+IRV+ERV+RV)
   - ➢ Is the volume in the lungs after maximal inspiration
   - ➢ It includes the RV, so it cannot be measured by spirometry

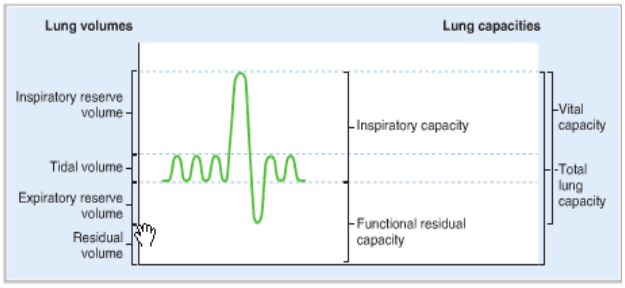


FIGURE 4-1 Lung volumes and capacities.

❖ Forced Expiratory Volume (FEV1):

- ➢ **FEV1** is the volume of the forced maximal expiration at the first second
- ➢ FEV1 normally is 80% of the forced vital capacity. It is expressed as: FEV1/FVC=0.8
- ➢ In obstructive lung diseases, e.g. asthma, **FEV1 is reduced more than FVC, so FEV1/FVC is decreased**

- In restrictive lung diseases, e.g. firbosis, both FEV1 & FVC are reduced, and FEV1/FVC is either normal or increased.

❖ The Airflow to The Lungs:

It is proportional to the pressure between the oral & nasal cavities and the alveoli, but is inversely proportional to airway resistance, so the higher the airway resistance the lower the airflow.

Poiseuille's law described the airway's resistance:

$$R = \frac{8\eta l}{\pi r^4}$$

where:
R = resistance
η = viscosity of the inspired gas
l = length of the airway
r = radius of the airway

Factors that affect the airway resistance:

1. Contraction or relaxation of bronchial smooth muscle: (Changes airway resistance by altering the radius of the airways)
   - Parasympathetic stimulation, irritant, and the slow-reacting substances of anaphylaxis (asthma) constrict the airways, decrease the radius, and increase the resistance to airflow
   - Sympathetic stimulation and sympathetic agonists (isoproterenol) dilate the airways via B_2 receptors, increase the radius, and decrease the resistance to airflow
2. Lung volume (alters airway resistance because of the radial traction exerted on the airways by surrounding lung tissue):
   - High lung volumes: associated with greater traction and decreased airway resistance (Asthmatic patients are trained to breath at higher lung volumes to decrease the high airway resistance associated with their disease)
   - Low lung volumes: associated with less traction and increased airway resistance (might cause airway collapse)
3. Viscosity or density of inspired gas:
   - During a deep-sea dive, the air density and resistance are increased
   - Airflow resistance decreases when a low-density gas, such as helium, is breathed

Airway resistance:

- The major site of airway resistance is the **medium-sized bronchi**
- The smallest airways do not offer the highest resistance because of their parallel arrangement

Bronchial Asthma: (Lecture Starts Here)

❖ Definition:

There is no universal agreed definition. Bronchial asthma can be described as chronic inflammatory disorder of the airways. It can also be described based on its clinical, physiological and pathological characteristics, stressing the central role of both chronic airway inflammation and increased airway hyper-responsiveness.

- Clinical Features:

  Typical symptoms of bronchial asthma include: (over short periods of time and are reversible with treatment)

  - ✓ Wheeze (Recurrent episodes)
  - ✓ Cough
  - ✓ Chest tightness
  - ✓ Dyspnea
  - ✓ Fatigue

  Patients with mild intermittent asthma are usually

  Asymptomatic between exacerbations.
  An inspection for nasal polyps and eczema should be performed on examination.
  Asthma characteristically displays as a diurnal pattern, with symptoms and lung function being worse in the morning. Particularly when poorly controlled, symptoms such as cough and wheeze disturb sleep, so when the disease is uncontrolled, symptoms are worst during the night.

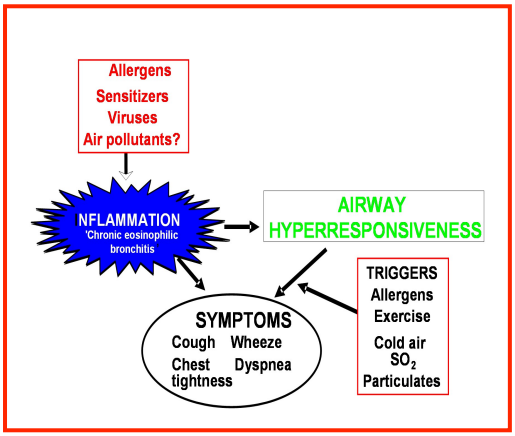
Exacerbations of asthma:

Exacerbations are characterized by:
- Increased symptoms
- Deterioration in lung function (gradually over several hours or days)
- Increase in airway inflammation.

Exacerbations are mostly precipitated by **viral infections**.

- Epidemiology:

  The prevalence of asthma increased steadily over the past couple of years, studies suggest that 300 million people world-wide have bronchial asthma.
  The rapid rise in the prevalence of asthma implies that environmental factors are critically important in terms of its expression.



- Triggers of Asthma:
  1. Allergens
  2. Irritants:
     - ✓ Infections
     - ✓ Chemicals
     - ✓ Diet/Medications
     - ✓ Emotional stress
     - ✓ Exercise
     - ✓ Cold temperature
     - ✓ Exposure to smoke

Examples:

- Allergens: cat dander, cockroach allergens, house dust mite allergens, dog dander, fungi/molds
- Infections: Rhinitis, sinusitis, and Viral infections
- Diet/Medications: Aspirin sensitivity, Sulfite sensitivity, Beta Blockers
- Irritants: Animal dander, Exposure to indoor chemicals, Dust, Outdoor pollutants (like ozone & PM), Mold, fungi, Pollen

Pathophysiology:

When exposed to an asthma trigger…

- Bronchioles constrict to limit exposure to the trigger.
- Mucous membrane becomes irritated and swells.
- Mucous is produced to trap the irritant.
- Coughing initiated to pop open bronchioles and expel the mucous build-up.
- Air retention volume in alveolar sacs increases – can't get air out or in.
- CO2 build-up in alveolar sacs and in system tissues, which can lead to acidosis.
- The body attempts to blow off the excess CO2 – rapid shallow breathing. (Hyperventilation)
- Hungry for O2 and trying to get rid of CO2 at the same time.
- Fatigued muscles in this effort.
- If this continues, the person with asthma can die.

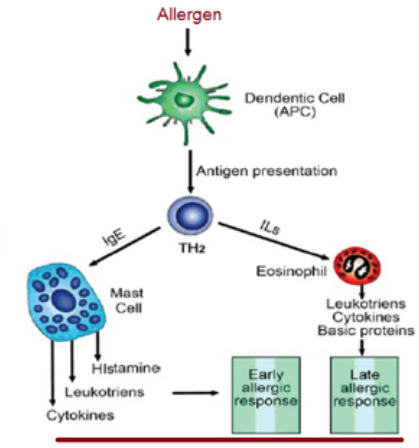
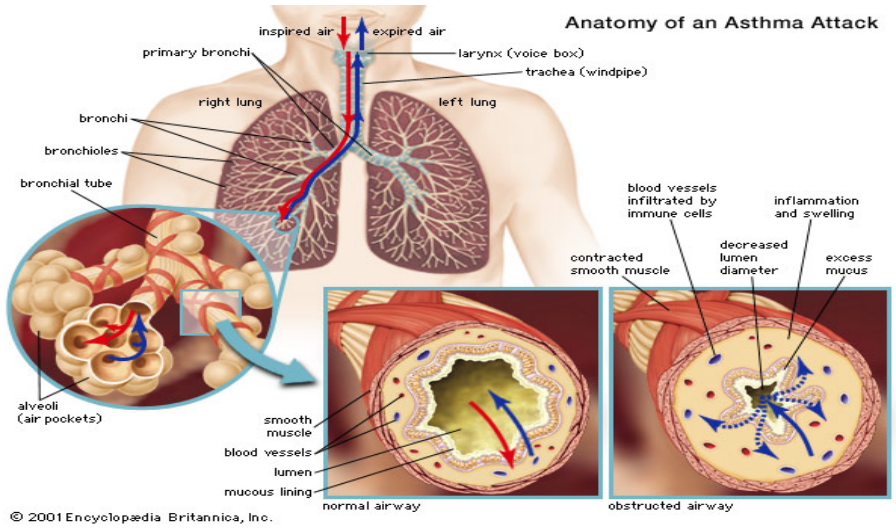
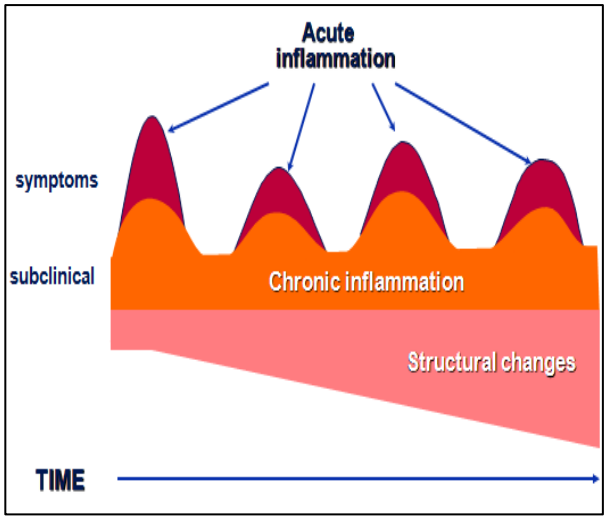


Fig. 1 : Pathophysiology of asthma
APC = Antigen presenting cell
ILs = Interleukins
TH2 = T-lymphocyte Helper cell 2

A person with asthma undergoes what is called "airway remodeling" – where there is permanent damage to the airways and decreased overall capacity and airway hyperactivity. A hyperactive airway is more susceptible to triggers.





Important figure

Asthma is a chronic inflammatory disease with a variable course characterized by episodic attacks of acute inflammation.[1] *Acute* inflammation in asthma is associated with bronchoconstriction, plasma exudation/edema, vasodilatation, and mucus hypersecretion. *Chronic* inflammation in asthma is associated with subepithelial fibrosis, smooth-muscle hyperplasia/hypertrophy, mucus gland hyperplasia, and new-vessel formation. If asthma remains uncontrolled or poorly controlled, the underlying chronic inflammation may lead to structural changes (remodelling) that reduce the extent of airway response to therapy.

1. Barnes PJ. New drugs for asthma. Clin Exp Allergy 1996;26:738-745.

More on the Pathophysiology:

It starts with an allergen entering the hyper-reactive airways (airways that have the tendency to contract easily to triggers that have little or no effect on normal airways) causing inflammation of the airways (Chronic eosinphilic bronchitis) which will lead to airway hyper-responsiveness and both the inflammation and airway hyper-responsiveness will lead to the symptoms of the bronchial asthma.

The inflammatory component is driven by Th2-type T lymphocytes which facilitate IgE synthesis through production of IL-4 and eosinophilic inflammation through IL-5. Infiltration of mast cells and lymphocytes will appear.

The hyper-responsiveness is presented through infiltration of blood vessels by immune cells, inflammation and swelling of the bronchus, contraction and hypertrophy of the smooth muscles and excess mucus production through profusion of mucus glands, which will, along with the contraction, cause narrowing of the lumen (decreasing lumen diameter) and wheezing sounds.

The course of Asthma:

- The Red waves: Patients present with Asthma symptoms
- The Orange wave: Subclinical phase, no symptoms are present but there is chronic inflammation of the airways
- The Pink wave: It represents the remodeling happening with time because of the chronic inflammation. (The structural changes happening in the remodeling phase will be explained below)

➢ Remodelling:

A characteristic feature of chronic asthma is an alteration of structure and functions of the formed elements of the airways. Together, these structural changes interact with the inflammatory cells and mediators to cause the characteristic features of the disease.

The remodeling is seen through changes in the epithelium, epithelial basement membrane, smooth muscles and nerves.

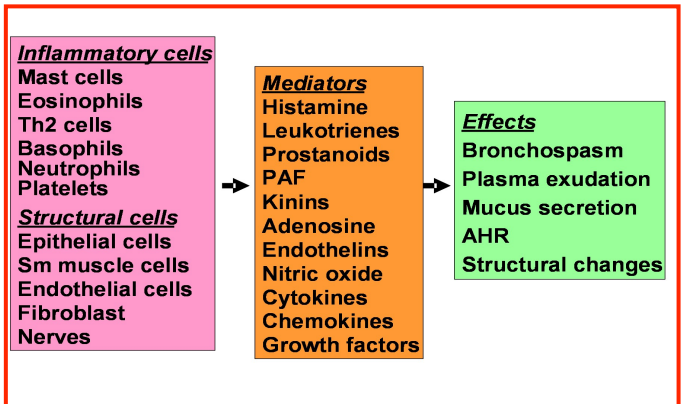
1. Epithelium:
   - ✓ Stressed and damaged epithelium with loss of ciliated columnar cells on to the lumen
   - ✓ Increase in the number & activity of mucus-secreting goblet cells
   - ✓ Increased in production of nitric oxide (NO) << It is useful as a non-invasive test of continuing inflammation.

   Damage of the epithelium make it more vulnerable to infection by common respiratory viruses (e.g. rhinovirus, coronavirus) and the effects of air pollutants.
2. Epithelial Basement Membrane:
   - ✓ Deposition of repair collagens (types I, III and V) and proteoglycans in the lamina reticularis beneath the basement membrane
   - ✓ Deposition of matrix proteins (e.g. Laminin, tenascin and fibronectin)

   These depositions together cause the appearance of a thickened basement membrane.

   Aberrant signaling between the epithelium and underlying myofibroblasts is thought to be the principal cause of airway wall remodeling.
3. Smooth Muscles:
   - ✓ Hyperplasia of the helical bands of airway smooth muscles (prominent feature of asthma)
   - ✓ Alteration in the function of the smooth muscles which make them easily contracted and stay contracted because of a change in actin-myosin cross-link cycling (The contraction happens too much and too easily at the least provocation)
   - ✓ Asthmatic smooth muscles also secret a wide range of cytokines, chemokines and growth factors that help sustain the chronic inflammatory response
4. Nerves:

   Neural reflexes, both central and peripheral contribute to the irritability of asthmatic airways.



❖ Diagnosis:

There is no single satisfactory diagnostic test for all asthmatic patients.

1. The diagnosis of Asthma is predominantly done through **clinical examination** (Characteristic History & Physical Examination)
   The characteristics of Asthma:
   - Wheeze/Rhonchi (No crackles)
   - Tachypnea
   - Any signs of allergy on the skin, nose or eyes

Remember:

Absence of symptoms at the time of examination **does not** exclude the diagnosis of Asthma

To confirm diagnosis:

2. **Lung function tests**
   Demonstrates the variable airflow obstruction, preferably done by using **Spirometry**. The measurement of FEV1 and VC identify the obstructive nature of the ventilatory defect, define its severity, and provide the basis of bronchodilator reversibility.
   If spirometry is not available, a **peak flow meter** is used. The diurnal variation in Peak Expiratory Flow Rate (PEFR) is a good measure of asthma activity; it is also helpful in the long-term assessment of the pt's disease and its response to treatment.
   Normally FEV1 = 600 mL in males & 500 mL in females (80% of predicted based on height, weight and race). Pts with asthma cannot reach the normal FEV1 because of the bronchial narrowing
   (In Asthma FEV1/FVC is reduced)
3. Exercise tests (used widely in children)
4. **Histamine or Methacholine bronchial provocation test:**
   Indicates the presence of airway hyper-responsiveness.
   It is useful in investigating patients whose main symptom is cough.
   *This test should not be performed on individuals with poor lung function (FEV1<1.5L) or a history of 'brittle' Asthma.
5. Trial of corticosteroids (A substantial improvement in FEV1 (>15%) after the corticosteroids administration, confirms the presence of a reversible element and indicates that the administration of inhaled steroids will prove beneficial to the pt)
6. Blood and sputum tests (Increase in eosinophils in blood and sputum, sputum is a more useful diagnostic tool)
7. Chest X-ray (may be helpful in excluding pneumothorax, but no diagnostic features of Asthma appear on the X-ray)
8. Skin-prick tests (Helpful in identifying the allergic causes)
9. Allergen provocation tests (required in suspected occupational asthma only)

Definitions:

1. **Histamine or Methacholine bronchial provocation test**: used to diagnose asthma, the patient breathes methacholine or histamine. Both drugs provoke bronchoconstriction, or narrowing of the airways. The degree of narrowing can then be quantified by spirometry. People with pre-existing airway hyperreactivity, such as asthmatics, will react to lower doses of drug.
2. **Occupational Asthma**: is an asthma due to causes and conditions attributable to a particular occupational environment and not stimuli encountered outside the workplace

❖ Management

The goal of management should be to obtain and sustain complete control.
Management options:

1. Avoid aggravating faction
2. Short-acting relievers
   - Inhaled β_2 agonists [Short-acting β_2 Agonists; SABA] (e.g. Salbutamol , terbutaline)

3. Long-acting relief/disease controllers
   - Inhaled long-acting β_2 agonists (Rapid acting: Formoterol, Non-rapid acting: Salmeterol)
   - Inhaled corticosteroids [ICS] (e.g. beclometasone, budesonide, fluticasone, cicleosenide, mometasone)
   - Compound inhaled salmeterol and fluticasone [Seretide]
   - Compound Budesonide and Formoterol [Symbicort]
   - Sodium cromoglicate
   - Leukotriene modifiers (e.g. montelukast, zafirlukast, zileuton)
4. Other agents with bronchodilator activity
   - Inhaled antimuscarinic agents (e.g. ipratropium, oxitropium)
   - Theophylline preparations
   - Oral cotricosteriods (e.g. prednisolone 40 mg daily)
5. Steroid-sparing agents
   - Methotrexate
   - Ciclosporin
   - Intravenous immunoglobulin
   - Anti-IgE monoclonal antibody – omalizumab
   - Etanercept
6. Combinations:
   - Symbicort: budesonide + formoterol
   - Seretide: fluticasone + salmeterol

Cicleosenide

Ciclosenide is an inhaled corticosteroid that is activated inside the lungs. It is useful in children with Asthma

The market names for some Asthma medications:

Scientific name	Market Name
Budesonide	Pulmicort
Fluticasone	Flixotide
Ciclosenide	Alvesco

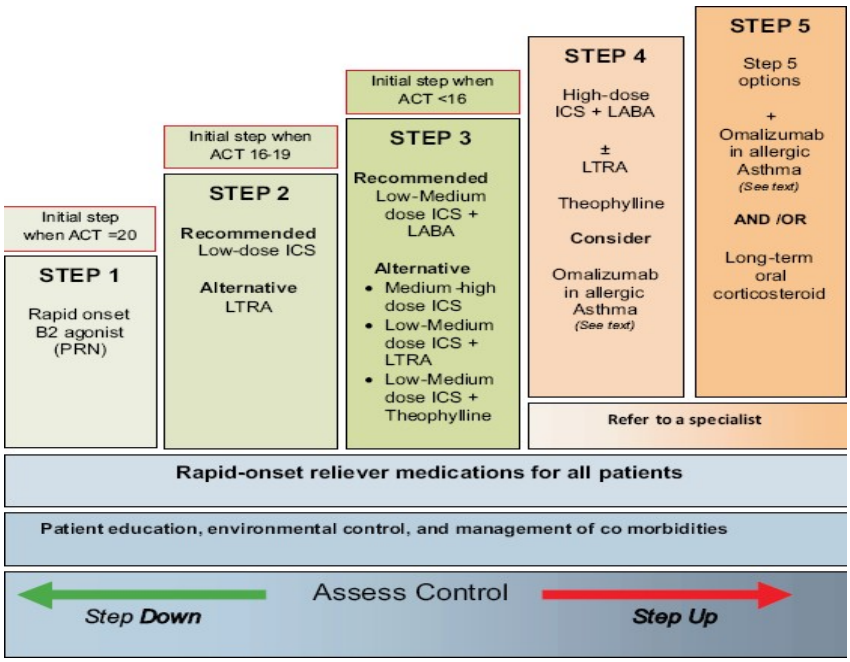
Another classification for Asthma medications:

Reliever/Rescue	**Salbutamol** Short acting B-agonist: SABA - Bronchodilator (β_2 agonist) - Quickly relieves symptoms (within 2-3 minutes) - Not for regular use (just to relieve symptoms, not used daily)
Preventer/Controller	**Anti-inflammatory** - Takes time to act (1-3 hrs) - Long-term effect (12-24 hrs) - Only for regular use (whether pt is feeling well or not)
Conroller Drugs	- **Inhaled steroids** - **Leukotriene modifiers (montelukast) singlair** - **Anti-IgE** - **Systemic Steroids**

The Rule of Two; When to prescribe controller

- Patient uses a quick-relief inhaler more than 2 times per week
- Patient is awaken at night due to asthma symptoms more than 2 times per month
- Patient consumes a quick-relief inhaler more than 2 times per year

Adult patients with Asthma; Management Course



Asthma Control Test (ACT):

ACT is test recommended for all asthmatic patients of the age 12 years old and above. The test is a 5-questions assessment tool.
The total ACT score is based on a range of 5 to 25

Before increasing medication in poorly controlled asthmas, check the following:

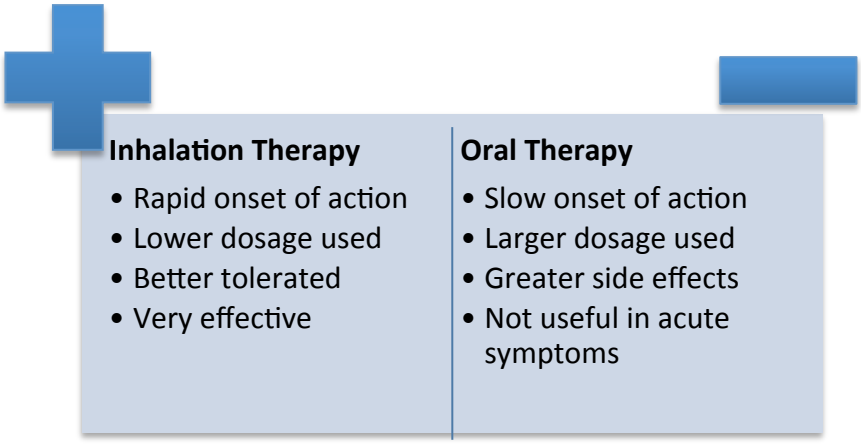
- Inhaler technique
- Patient's adherence to prescribed regimen
- Environmental changes
- Also consider alternative diagnosis

Treatment course is given to patients depending on the severity of disease, which is here determined by the Asthma Control Test (ACT).
If the patient is not improving, the management plan will step up to the next step, but if patient is improving there will be a step down in the management course.

- Step 1: *Occasional use of inhaled short-acting β_2 adrenoreceptor agonist bronchodilators* (used as relievers):
  Used in patients with mild intermittent asthma (ACT = 20).
  It is usually sufficient to prescribe an inhaled short-acting β_2 agonist (e.g. salbutamol)
- Step 2: *Introduction to regular 'Preventer' therapy*:
  Used in patients with moderate asthma, whom have experienced an exacerbation of asthma in the last 2 years, uses the inhaler 3 times a week or more, and might suffer from nocturnal asthma one night per week (ACT = 16-19)
  Regular Anti-inflammatory therapy (ICS is preferred) and β_2 agonists are prescribed
- Step 3: *Add on therapy:*
  Used in patients who remain poorly controlled despite regular use of ICS (ACT < 16)
  Increase in the ICS dose and Long-acting β_2 agonists (salmeterol, formoterol) are prescribed.
- Step 4: *Poor control on moderate dose of inhaled steroid and add-on therapy: addition of a fourth drug:*
  Used in patients with very poorly controlled asthmas. Some patients will also suffer from prominent upper airway symptoms (Nasal corticosteroids should be prescribed for these patients)
  Further increase in the ICS dose (up to 2000µg) and long-acting β_2 agonist along with leukotriene receptor agonists should be prescribed to the patient at this level.
  Theophyllines may be considered.
- Step 5: *Continuous or frequent use of oral steroids:*
  At this stage prednisolone therapy should be prescribed in the lowest amount necessary to control symptoms.

Patients on continuous or frequent use of oral steroids will be at risk of systemic side-effects. We might consider using steroid-sparing therapies (e.g. methotrexate,

Why is inhalation therapy more preferable than oral therapy?



Summary:

- Asthma can be controlled but not cured
- It can present at any age.
- It produces recurrent attacks of SOB , cough with or without wheeze
- Between attacks patients with asthma have normal lives
- In most cases there is some history of allergy in the family.
- Understanding the disease, learning the technique and compliance with medications is the key for good control of asthma
- The cells and mediators involved in Asthma:

Cells		Mediators	Effects
Inflammatory cells	Structural cells	Histamine	Bronchospasm
Mast cells	Epithelial cells	Leukotrienes	Plasma exudation
Eosinophils	Smooth muscle cells	Prostanoids	Mucus secretion
Th2 cells	Endothelial cells	PAF	AHR (Airway hyper-responsiveness)
Basophils	Fibroblasts	Kinins	Structural changes
Neutrophils	Nerves	Adenosine	
Platelet		Endothelins	
		Nitric oxide	
		Cytokines	
		Chemokines	
		Growth factors	

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