Drug Acting on Respiratory System

ANTI-ASTHMATIC DRUGS

Subject : Pharmacology-III
Code : BP602TP

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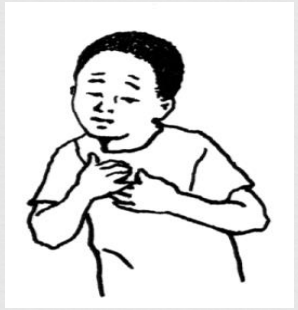
Overview

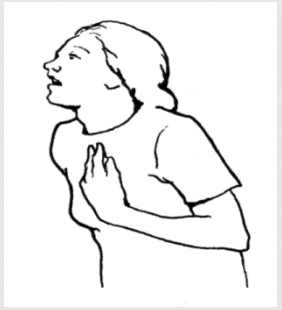
- What is asthma?
- Causes for asthma
- Types of asthma
- Epidemiology
- Pathophysiology
- Diagnosis
- Management

What is asthma?

- Asthma is a chronic inflammatory disorder of the airways.
- It involves complex interaction between many cells and inflammatory mediators, that results in inflammation, obstruction, increased airway responsiveness and episodic asthma symptom.
- In asthma many cells and cellular elements play a role, in particular masts cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells.

- Symptoms are
  - **Cough** (particularly at night or in the early morning)
  - **Wheeze**
  - **Chest tightness**
  - **shortness of breath**





Early warning signs:

- whistling sound during inspiration.
- shortness of breath
- Feeling very tired or weak when exercising
- Wheezing or coughing after exercise
- Decrease or changes in a peak expiratory flow
- Trouble sleeping
- Signs of cold, upper respiratory infection or allergy.

Causes

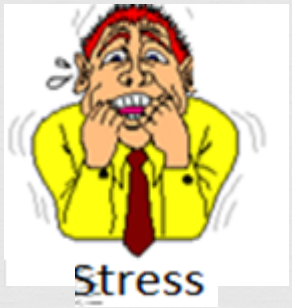

Pollution


Smoke


Dust

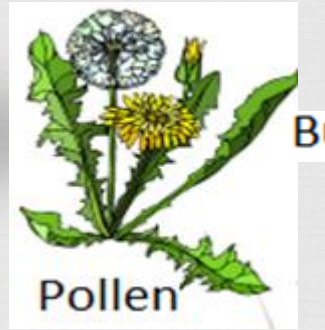

Cold air

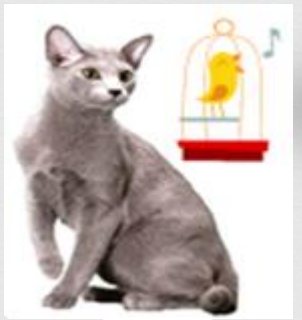

Strong odors


Stress


Chemical fumes


Bugs in the home


Pollen


Pets


Exercise

Types of asthma

- **Atopic asthma-classical type I IgE mediated hypersensitivity, allergen sensitization, seen from childhood, +ve history of asthma in family, skin test +ve**
- **Non-atopic asthma- no allergen sensitization, no such history, skin test –ve.**
- **Drug induced asthma-sensitive to certain drugs like aspirin, NSAIDS etc**
- **Occupational asthma- stimulants such as fumes, organic and chemical dusts(wood, cotton), gas(toluene), etc**
- **Exercise induced asthma- begins after exercise and stops after 30 minutes, worsen in cold and dry climate.**

Severity of Asthma

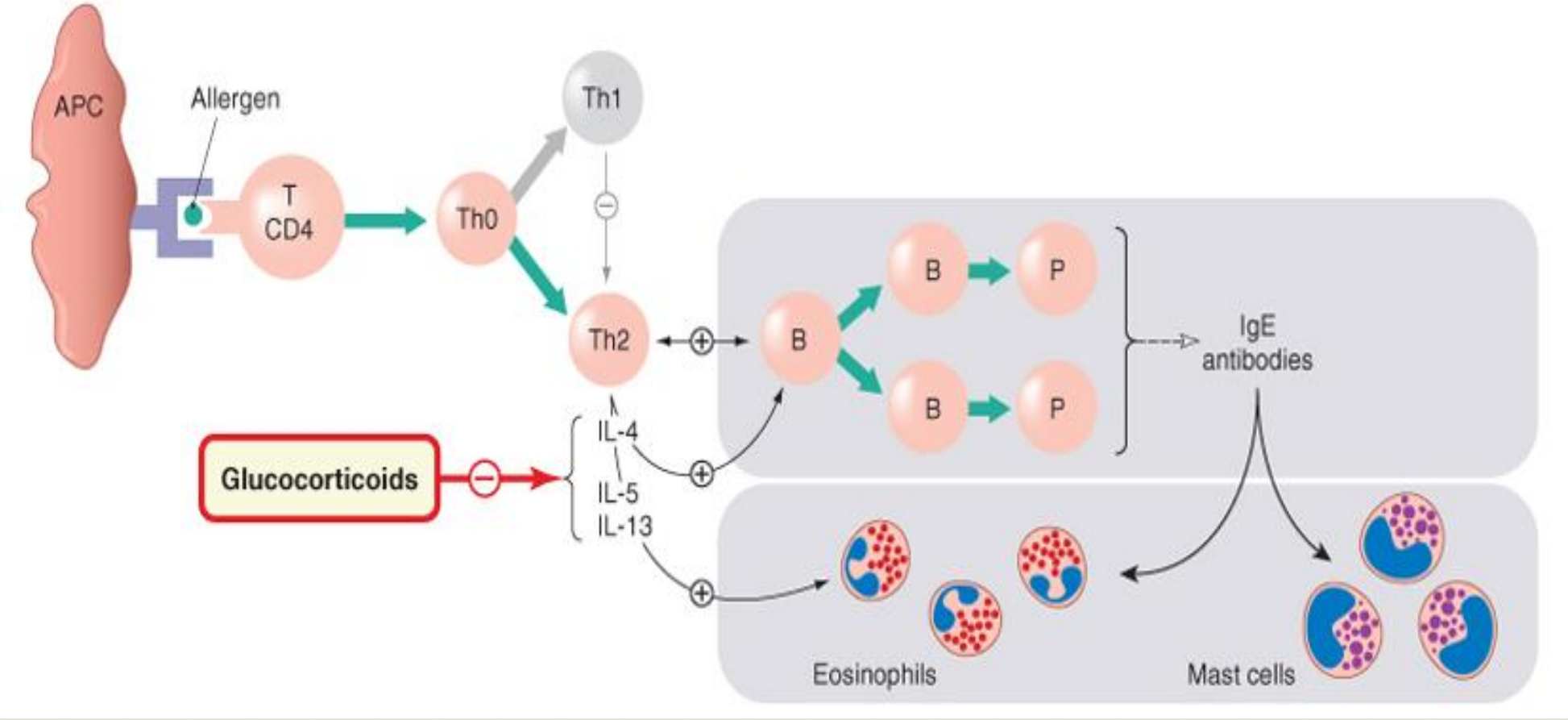
TYPE	CHARACTERISTICS
Mild intermittent (STEP-1)	Symptom ≤ 2times/week, many a time asymptomatic and intensity of exacerbation may vary and brief.
Mild persistent (STEP-2)	Symptom >2times/week but <1time/day. exacerbation may affect activity
Moderate persistent (STEP-3)	Daily symptom and exacerbation ≥ 2 times/ wk exacerbation affect activity
Severe persistent (STEP-4)	Continual symptoms. limited physical activity and shows frequent exacerbations.

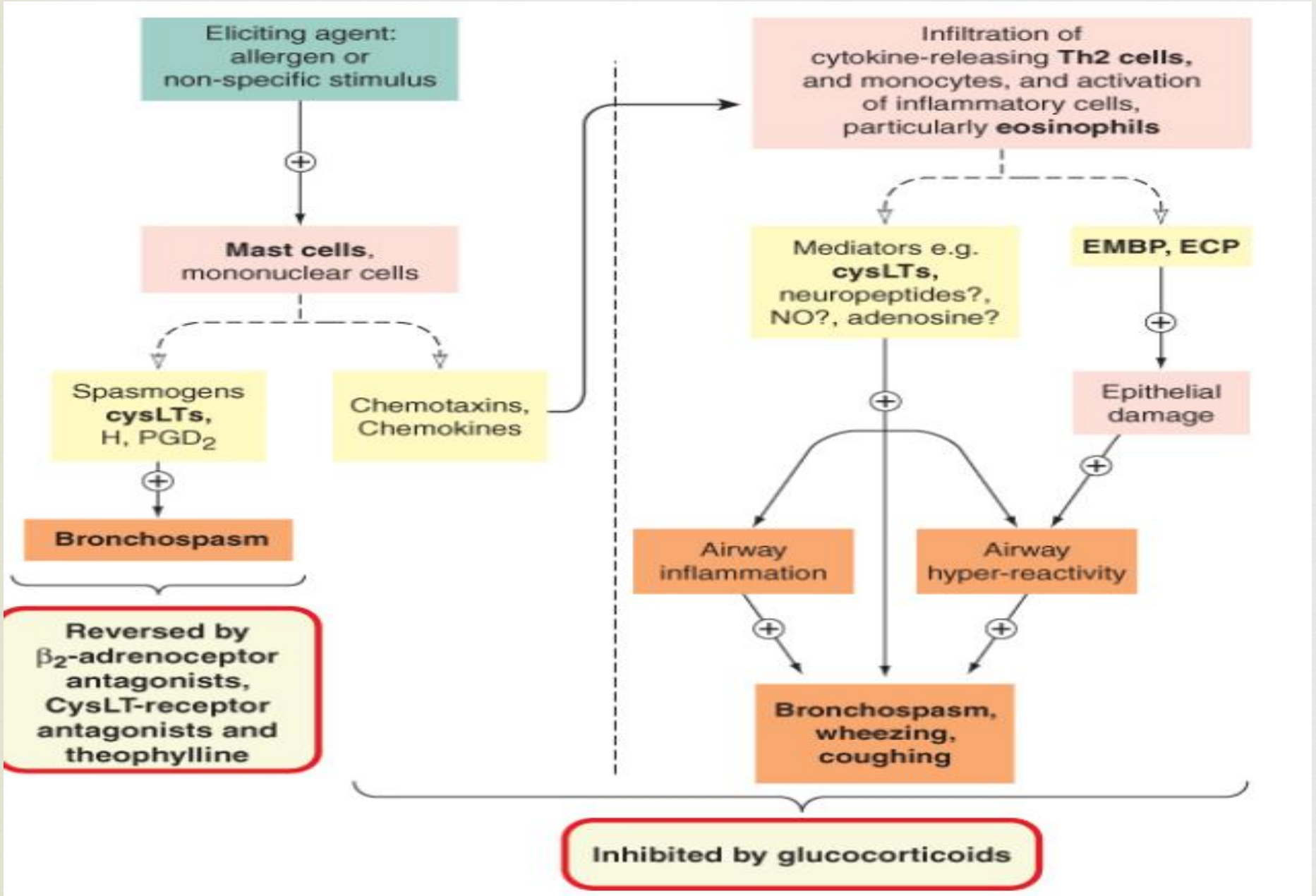
Epidemiology

- Worldwide, it is estimated that approximately 334 million people currently suffer from asthma, and 250,000 deaths are attributed to the disease each year. (According to global asthma report 2014)
- 30% of asthmatic patient are under 14 year.
- Children account for 35% of hospital admission.
- The prevalence of asthma increased steadily over the latter part of the last century in countries with a Western lifestyle and is also increasing in developing countries.

Pathophysiology

The part played by T lymphocytes in allergic asthma :





CysLTs: cysteinyl leukotrienes
ECP : eosinophil cationic protein
EMBP : eosinophil major basic protein
H : Histamine
Ino : induced nitric oxide

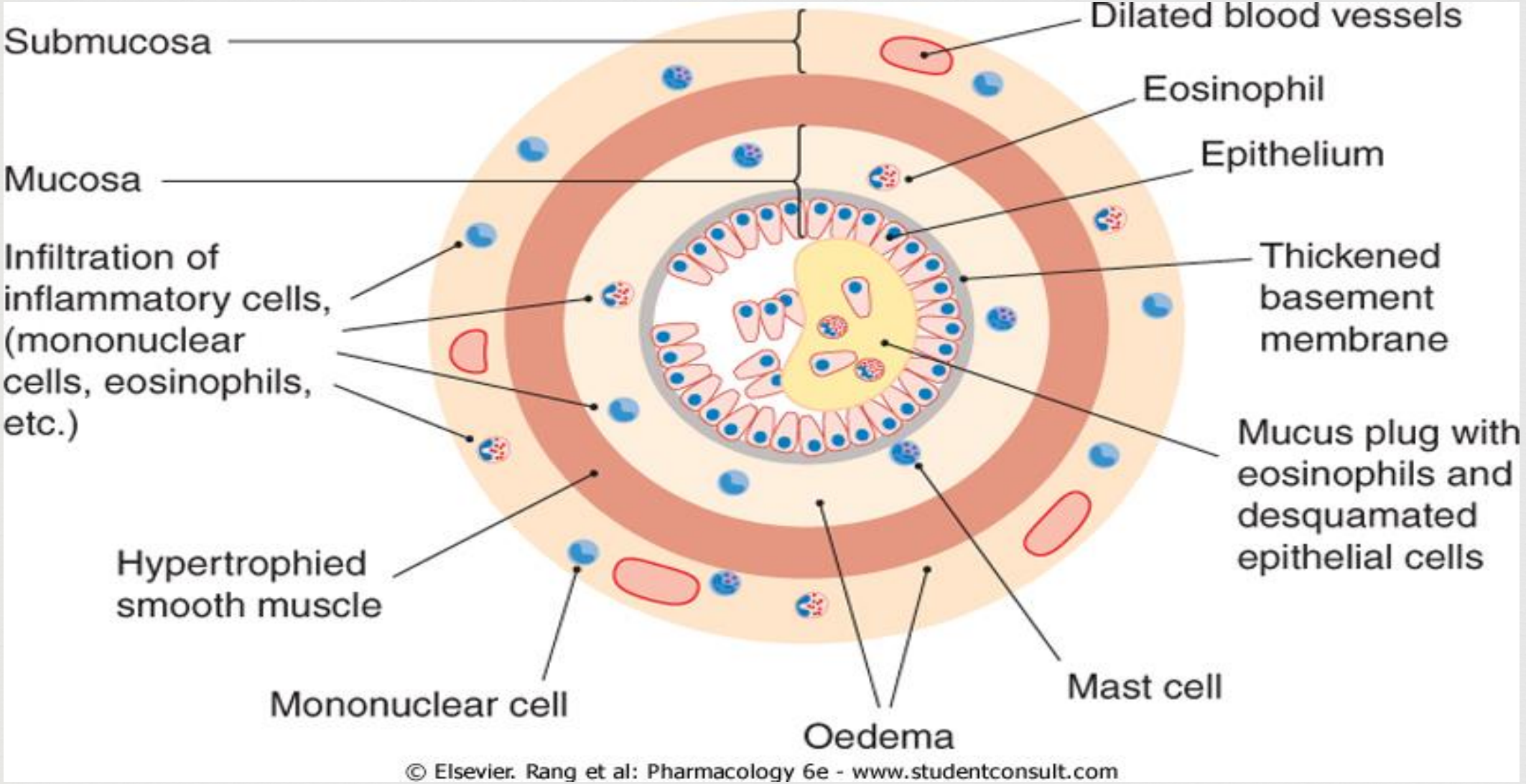
Key players in pathophysiology of asthma

- **Mast cell-activated by IgE dependant mechanism, initiate acute bronchoconstriction action by releasing histamine, prostaglandinD2,leukotrienes etc**
- **Macrophage-activated by low affinity IgE receptor, produce various inflammatory mediators**
- **Dendritic cell-macrophage like major APC in airways, chemokine release for TH2 cells**
- **T cell-release cytokines, causes recruitment of eosinophils, also causes maintenance of mast cells, in asthma TH2 cell produce IL-5(eosinophil recruitment) IL-4, IL-13(increase IgE production and mucus secretion).CD4+ cell also involved**

- **Eosinophils-infiltration is characteristic feature of asthma, activated by IL-5, causes exacerbation of asthma by producing mediators**
- **Neutrophil-activated and infiltration**

Effects of inflammation

- **Epithelium-dysfunction, damage, loss of enzyme, loss of relaxant factors, loss of barrier function**
- **Fibrosis- sub epithelial fibrosis, basement membrane thickening, (by factors release from eosinophil)**
- **Smooth muscle- increased responsiveness to constrictor mediators, in chronic cases hypertrophy/hyperplasia by growth factors released by inflammatory mediators**
- **Vascular response-vasodilation, angiogenesis, micro vascular leakage**
- **Mucus hypersecrection- by goblet cell hyperplasia, increase in mucus plug, leading to blocking of airway**


Submucosa
Mucosa
Infiltration of inflammatory cells, (mononuclear cells, eosinophils, etc.)
Hypertrophied smooth muscle
Mononuclear cell
Oedema
Mast cell
Mucus plug with eosinophils and desquamated epithelial cells
Thickened basement membrane
Epithelium
Eosinophil
Dilated blood vessels
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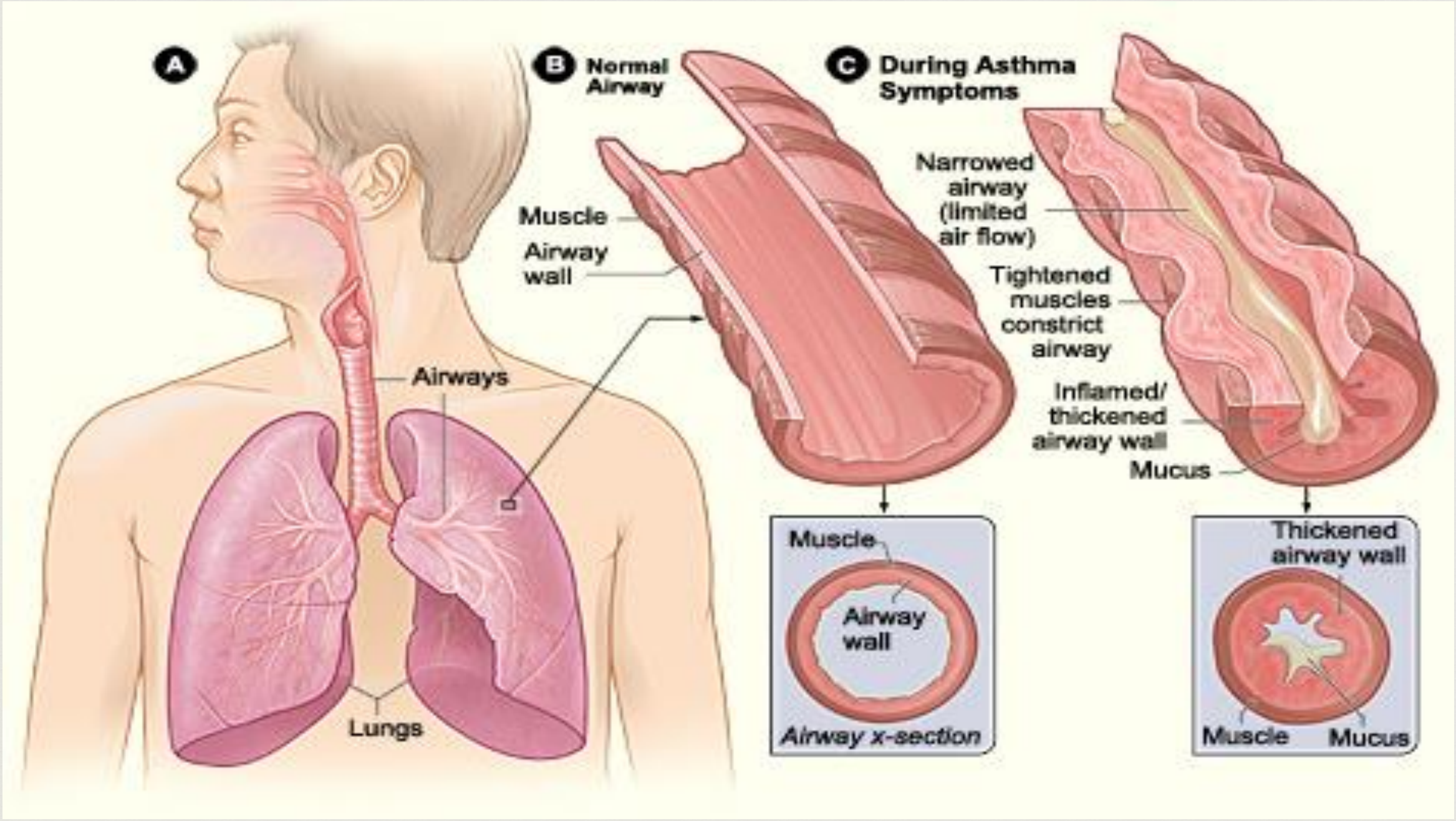

A
B Normal Airway
C During Asthma Symptoms
Muscle
Airway wall
Airways
Lungs
Narrowed airway (limited air flow)
Tightened muscles constrict airway
Inflamed/ thickened airway wall
Mucus
Muscle
Airway wall
Airway x-section
Thickened airway wall
Muscle
Mucus

Diagnosis of asthma :

- History and pattern of symptoms
- Physical examination
- Non specific diagnosis
- Specific diagnosis

  - Respiratory function test:

    1. peak expiratory flow.
    2. spirometry test.
    3. Arterial blood gases.

  - Exercise tests

- Other tests

History and Physical examination

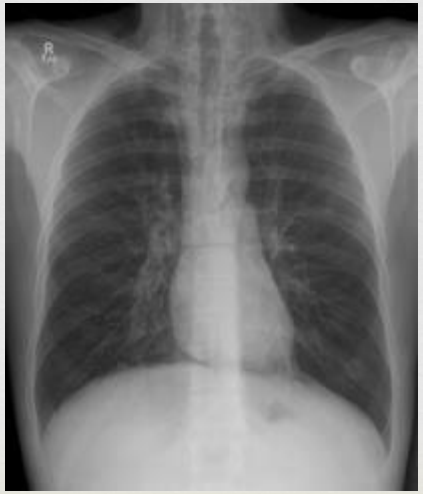
- The following information should be sought in the history:
  - Current symptoms
  - Pattern of symptoms (e.g. time course over 24 hours, a week, or year)
  - Precipitating or aggravating factors (trigger factors)
  - Present management
  - Hospital admissions (including Intensive Care Unit admissions)
  - Profile of typical exacerbation
  - Home and work environment
  - Impact of the disease on work and lifestyle
  - Family history
  - Response to prior treatment.

Non-specific investigation

Full blood count and differential count, increase number of eosinophils number.

- Sputum test: number of eosinophils

- Chest X-ray: Chest radiographs (posterior-anterior) may be normal in mild disease; signs of air trapping (hyperinflation) are more often present with severe, chronic asthma.



Peak flow measurement (specific)

- The **peak expiratory flow** (**PEF**), is a person's maximum speed of expiration, as measured with a **peak flow meter**, a small, hand-held device used to monitor a person's ability to breathe out air.
- A peak flow meter is a simple device that measures how hard you can breath out.
- Lower than usual peak flow readings are a sign your lungs may not be working as well and that your asthma may be getting worse.

Peak flow readings are often classified into 3 zones of measurement according to the American Lung Association; green, yellow, and red.

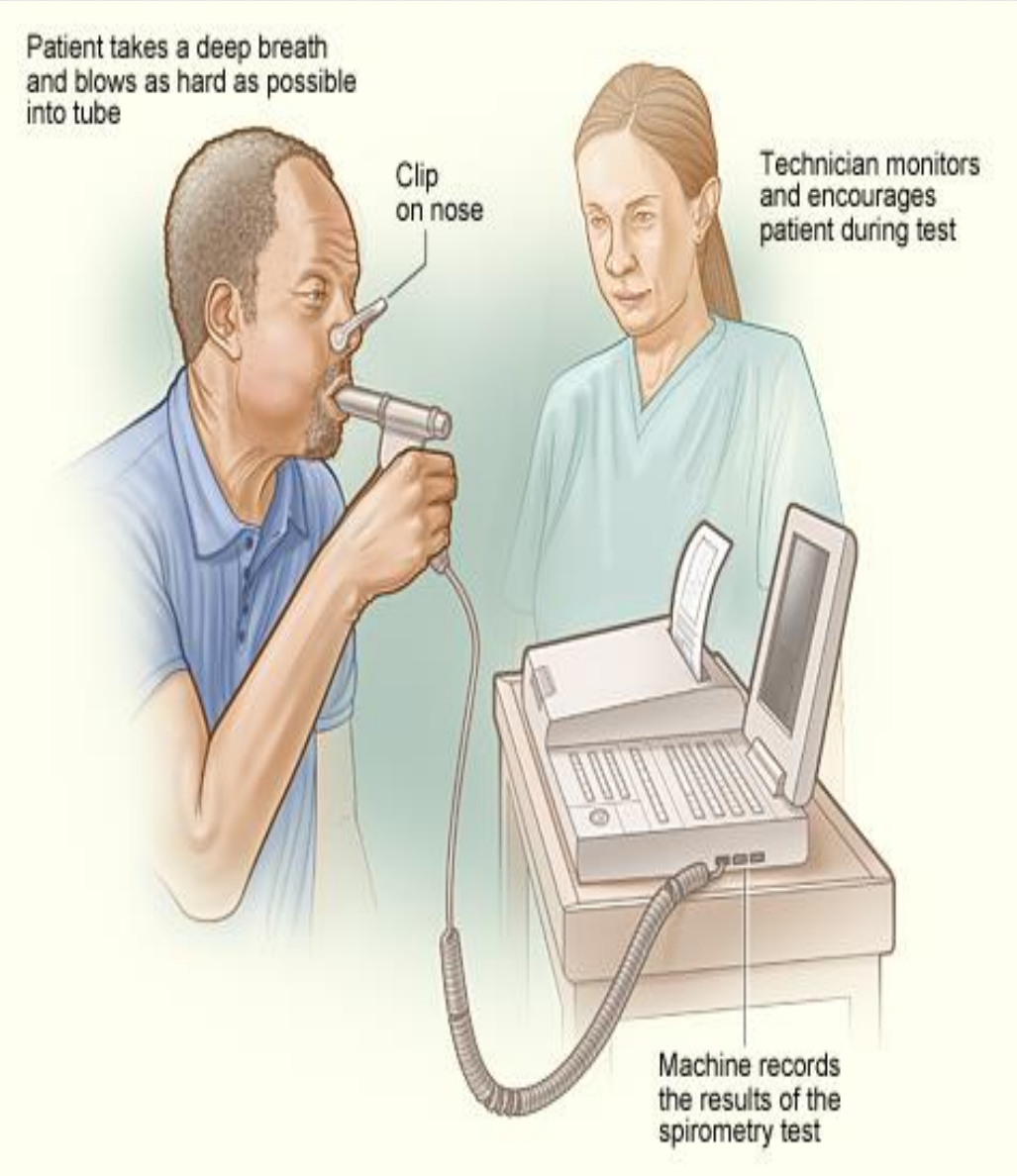
Zone	Reading	Description
Green Zone	80 to 100 percent of the usual or normal peak flow readings are clear.	A peak flow reading in the green zone indicates that the asthma is under good control.
Yellow Zone	50 to 79 percent of the usual or normal peak flow readings	Indicates caution. It may mean respiratory airways are narrowing and additional medication may be required.
Red Zone	Less than 50 percent of the usual or normal peak flow readings	Indicates a medical emergency. Severe airway narrowing may be occurring and immediate action needs to be taken. This would usually involve contacting a doctor or hospital.

- Lung function tests often are done before and after taking a bronchodilator, such as albuterol, to open your airways.
- If your lung function improves with use of a bronchodilator, it's likely you have asthma.

Spirometry Test :

- It is the **single best diagnostic test** for patients with airflow limitation.
- This test estimates the narrowing of your bronchial tubes by checking how much air you can exhale after a deep breath and how fast you can breathe out.
- A Spirometry Test
  - measures the volume of air blown out against time
  - gives more specific information about lung function.

- A value is calculated for the amount of air blown out in one second - "Forced Expiratory Volume" or FEV1).
- This is divided by the total amount of air blown out until all air is expired - Forced Vital Capacity or FVC).
- FEV1/FVC expressed as a percentage value.



- **Male Spirometry** reading range.
  - Normal: 4.3 lit
  - Mild reduction: 2.5 litres
  - Moderate reduction :1.5 to 2.49 litres
  - Severe reduction :Less than 1.5 litres
- **Female Spirometry** reading range
  - Normal: 3.1 lit
  - Mild reduction :2.0 litres
  - Moderate reduction: 1.0 to 1.99 litres
  - Severe reduction: Less than 1.0 litre

In asthma, the readings will be reduced, returning to normal between episodes

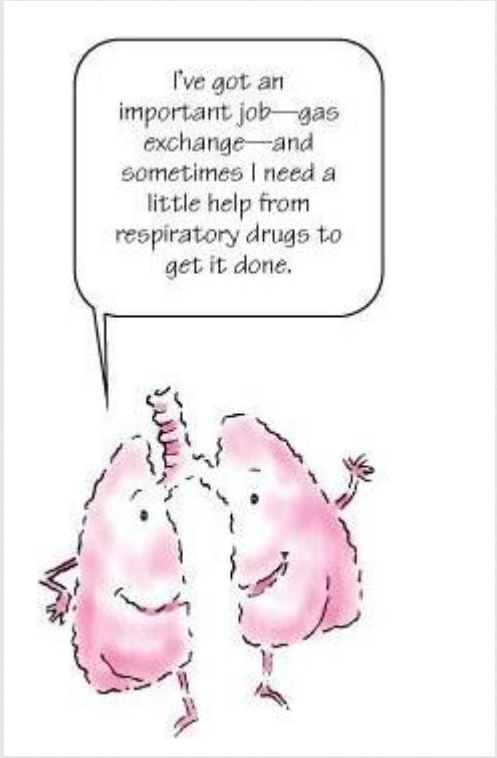
Arterial Blood Gases(ABG)

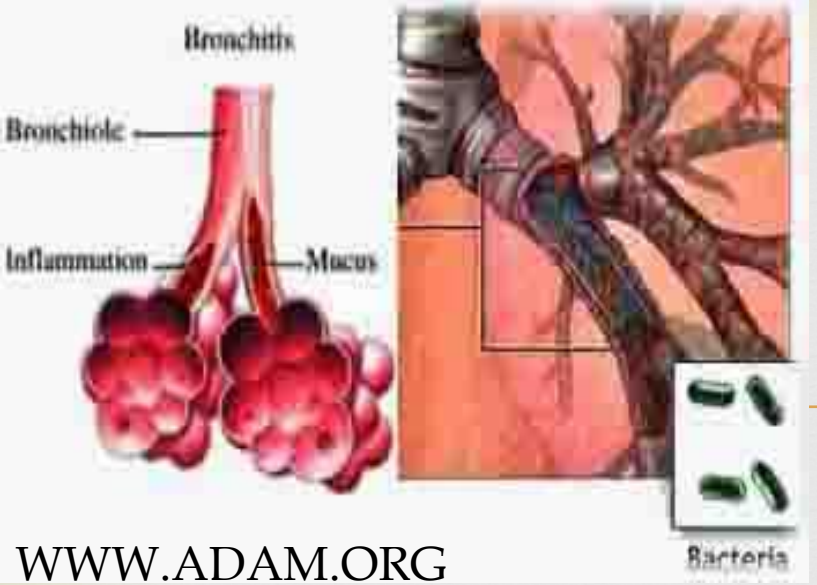
- An **arterial blood gas** (**ABG**) test is a blood gas test of blood from an artery; it is thus a blood test that measures the amounts of certain gases (such as oxygen and carbon dioxide) dissolved in arterial blood.
- An ABG test involves puncturing an artery with a thin needle and syringe and drawing a small volume of blood. The most common puncture site is the radial artery at the wrist,
- The blood can also be drawn from an arterial catheter.
- An ABG test measures the blood gas tension values of arterial oxygen tension (Pao_2=100mmHg) arterial carbon dioxide tension ($Paco_2$=40mmHg) and acidity (pH = 7.3- 7.4)

Exercise T

- Done especially in **children**
- Peak flow reading measured **before hand**
- Patient to **run for 5-6 min**, to increase **HR > 160** beats/min
- **After exercise** – take readings at intervals of 5, 10 and 15 minutes.
- **Diagnosed asthma - fall in peak flow of 15% or more, after exercise.**

Treatment


I've got an important job—gas exchange—and sometimes I need a little help from respiratory drugs to get it done.



Treatment

- Directly
  - Bronchodilators
    - Dilate / open up bronchi
  - Anti-inflammatory
    - ↓ inflamation inside airways
- Indirectly
  - Antibiotics in infection

BRONCHODILATORS

1. **β_2 –Adrenoceptor agonists**

Short acting**: salbutamol** or **terbutaline ,** Albuterol, Pirbuterol

Recent: Bitoterol

Long acting: Salmeterol

Recent: Formrterol

2. **Anticholinergics**

Muscarinic receptor (M_3) Antagonists

Ipratropium bromide(Quaternary Ammonium Comp.)

Tiotropium (Tiovan®)

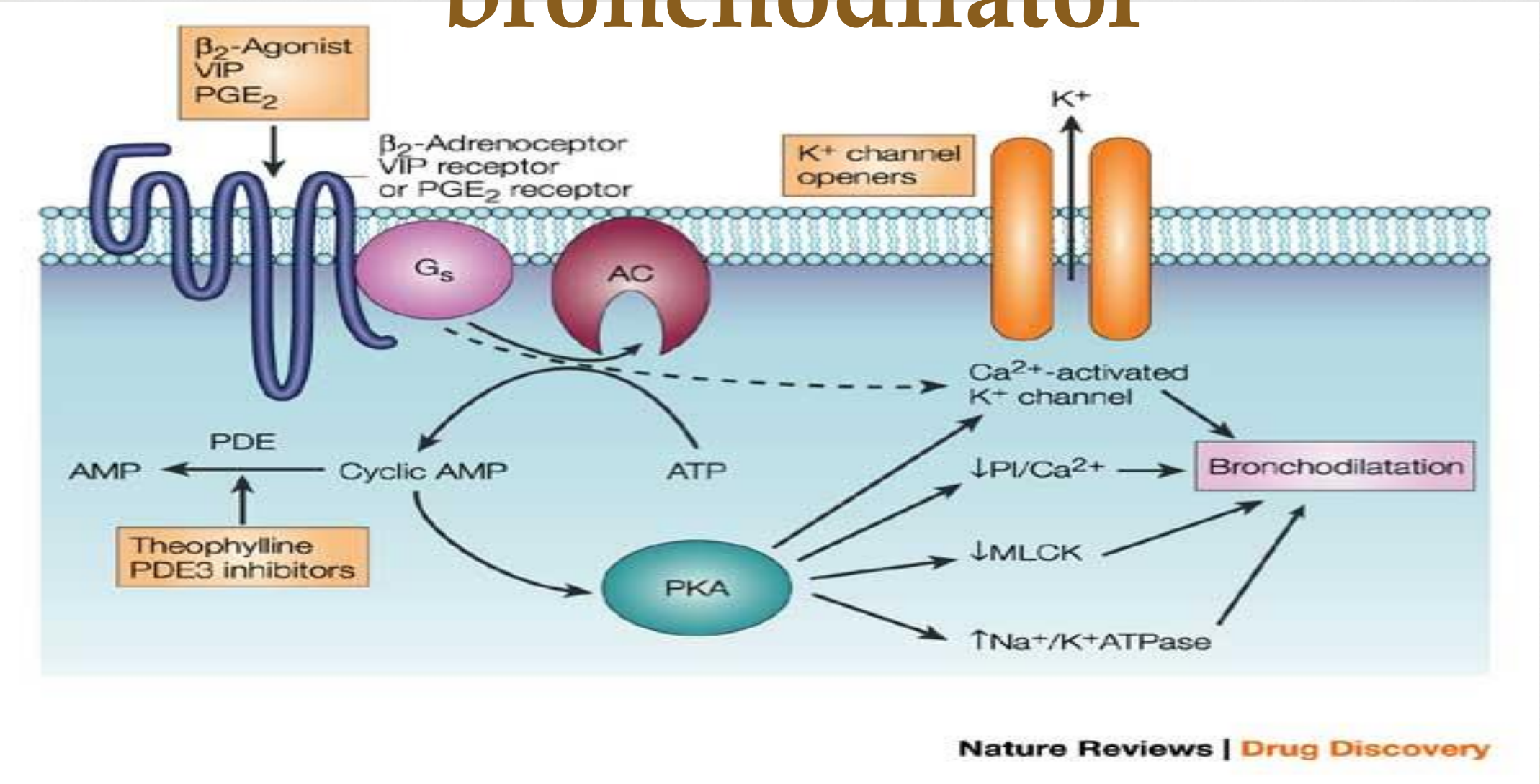
Recent -Oxicam, Evatropate, Derifenacin

3. **Methyl Xanthines** :

Theophylline

Recent: Aminophylline

Mechanism of action of bronchodilator



β_2 –Adrenoceptor agonists

- Their primary effect in asthma is to dilate the bronchi by a direct action on the β_2 adrenoceptors on the smooth muscle.
- Being physiological antagonists of bronchoconstrictors they relax bronchial muscle whatever the spasmogens involved.
- They also inhibit mediator release from mast cells and TNF-α release from monocytes, and increase mucus clearance by an action on cilia.
- The β_2-adrenoceptor agonists are usually given by inhalation of aerosol, powder or nebulised solution, but some may be given orally or by injection.
- A metered-dose inhaler is used for aerosol preparations.

short acting- **Salbutamol ,Terbutaline**

Recent: Bitoterol

- Given by inhalation, maximum effect within 30 min.
- Duration action is 3-5 hours.
- They are usually used on an 'as needed' basis to control symptoms.

Long acting- **salmeterol**

Recent: Formrterol

- Inhalation, duration of action is 8-12 hour.
- They are not used 'as needed' but are given regularly, twice daily, as adjunctive therapy in patients whose asthma is inadequately controlled by glucocorticoids.

Mechanism of action:

- Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing antagonism of bronchoconstriction. In vitro, inhibit mast cell mediator release, decrease vascular permeability, and increase mucociliary clearance.

Side effect: β2 selective agents cause

tachycardia

palpitation ,

Muscle tremor etc

Clinical use of β_2-adrenoceptor agonists as bronchodilators

- Short-acting drugs (**salbutamol** or **terbutaline**, usually by inhalation) to prevent or treat wheeze in patients with reversible obstructive airways disease.
- Long-acting drugs (**salmeterol, formoterol**) to prevent bronchospasm (e.g. at night or with exercise) in patients requiring long-term bronchodilator therapy.

Muscarinic receptor antagonists

- Cholinergic innervation important in regulation of airway
- smooth muscle tone
- **Bronchodilation**
- Reduces intrinsic vagal tone to the airways.
- Decrease mucus gland secretion.

Example:

- Ipratropium bromide (quaternary derivative of atropine)
- Additive benefit with inhaled beta 2-agonists in severe
- asthma exacerbations
- Effectiveness in long-term management not demonstrated

- Adverse effects such as blurred vision, urinary retention, nausea, and tachycardia.

- Unwanted effect of inhaled ipratropium bromide is dryness of mouth and throat, bitter taste, cough and nausea.

- Nebulized ipratropium bromide may precipitate glaucoma in elderly patients.

Methylxanthines(Theophylline , sustained-release tablets and capsules)

Mechanism of action: inhibition of phosphodiesterase, thereby increasing cAMP levels

- Inhibition of calcium ion influx into smooth muscle
- Prostaglandin antagonism
- Stimulation of endogenous catecholamines
- Adenosine receptor antagonism
- Inhibition of release of mediators from mast cells and leukocytes
- **EFFECTS:**
- Provides mild-moderate bronchodilation
- Low dose has mild anti-inflammatory action
- Sustained release form used as alternative **but not preferred** to long-acting beta2 agonists to control nocturnal symptoms

- The most common adverse effects are headache, nausea and vomiting, abdominal discomfort, and restlessness
- The gastrointestinal symptoms may be intolerable at therapeutically dose
- Infrequent adverse effects are diuresis, cardiac arrhythmia and seizure.
- Also theophylline has narrow therapeutic index and its hepatic metabolism greatly varied in individuals.

RECENT :

PDE_3 inhibitors :- Enoxamine, Benzafentrine

PDE_5 inhibitors : Zaprinast (degradation of cGMP in the corpus cavernosum)

Dual PDE3/4 inhibitors : Zardaverin

PDE_4 inhibitors : Rolipram, Denbufylline , **Roflumilast** LAS -31025, RP-73401

- PDE4 is the major cAMP-metabolizing enzyme found in inflammatory and immune cells.
- PDE4 inhibitors have proven potential as anti-inflammatory drugs, especially in inflammatory pulmonary diseases such as asthma, COPD, and rhinitis.
- They suppress the release of cytokines and other inflammatory signals, and inhibit the production of reactive oxygen species.

Corticosteroids(By inhalation or orally)

- Most potent and effective
- Reduction in symptoms, improvement in PEF and spirometry, diminished airway hyper responsiveness, prevention of exacerbations, possible prevention of airway wall remodeling
- **Suppresses: cytosine production, airway eosinophilic recruitment, chemical mediators**
- **Glucocorticoids also inhibit the generation of the vasodilators PGE_2 and PGI_2 by inhibiting induction of COX-2**
- **Reduced synthesis of IL-3** (the cytokine that regulates mast cell production)
  - Dose dependent on product and delivery device
  - 2 X/day use is common in moderate-to-severe persistent asthma
  - 1 or 2 X/day may be used in mild persistent asthma

Glucocorticoid resistance : Glucocorticoids are sometimes ineffective, even in high doses, for reasons that are incompletely understood.

Local adverse effects

- Oropharyngeal candidiasis
- Horseness and weakness of voice (dysphonia)

Other

- Decrease in bone mineral density specially in female received inhaled corticoids
- Fluid retention, increased appetite, weight gain, osteoporosis,
- Cushin's syndrome, hypertension, peptic ulceration, diabetes.
- Supperation of adrenal gland secretion at high dose on prolong use.

- Eg :- Hydrocortisone, prednisolone, Methyl prednisolone, Dexamethasone.

Recent : Triamcinolone acetonide, fluticasone porpionate, flunisolide , Budenoside

2. MEDIATOR RELEASE INHIBITORS:

M/A: Mast cell stabilizatior

e.g.**: Sodium cromoglicate, Nedocromil ,ketotifen.**

Mechanism

- Their mechanism of action is not fully understood. Cromoglicate is a 'mast cell stabiliser', preventing histamine release from mast cells.
- However, this is not the basis of its action in asthma, because compounds have been produced that are more potent than cromoglicate at inhibiting mast cell histamine release
- It may inhibit the release of T-cell cytokines. Various other effects on the inflammatory cells and mediators involved in asthma have been described.

Leukotriene modifiers

- Leukotrienes are potent biochemical mediators released from mast cells, eosinophils, and basophils.
- Two receptors have been cloned, $CysLT_1$ and $CysLT_2$
  - Contract bronchial smooth muscle
  - Increase vascular permeability
  - Increase mucus secretions
  - Attract & activate inflammatory cells in
- **Pharmacokinetic aspects :**

Both drugs are given orally, montelukast once daily, zafirlukast twice.

- **Clinical use :**

  They are used in combination with an inhaled corticosteroid, usually at step 3, when regular long-acting β_2 agonists are inadequately effective.

RECENT: ZD- 2138, ABt :761, Prunlukast

Anti-IgE

- Omalizumab is a blocking antibody that neutralizes circulating IgE without binding to cell-bound IgE; it thus inhibits IgE-mediated reactions. This treatment has been shown to reduce the number of exacerbations in patients with severe asthma and may improve asthma control.
- However, the treatment is very expensive and only suitable for highly selected patients who are not controlled on maximal doses of inhaler therapy and have a circulating IgE within a specified range.
- Omalizumab is usually given as a subcutaneous injection every 2–4 weeks and appears not to have significant side effects.

- **Histamine H_1-receptor antagonists**

- Although mast cell mediators play a part in the immediate phase of allergic asthma and in some types of exercise-induced asthma,
- They may be modestly effective in mild atopic asthma, especially when this is precipitated by acute histamine release in patients with concomitant allergy such as severe hay fever.

- **ALLERGIC EMERGENCIES**

- *Anaphylaxis* and *angio-oedema* are emergencies involving acute airways obstruction; **adrenaline** is potentially life-saving.
- It is administered intramuscularly (or occasionally intravenously, as in anaphylaxis occurring in association with general anaesthesia).
- Patients at risk of acute anaphylaxis, for example from food or insect sting allergy.

DRUGS IN THE PHASE –II/IIICLINICLE TRIALS

- **Newer Inhaled Corticosteroids (ICS)** :-

Ciclesonide - outline in-vitro data.

- It is a prodrug which can delivered directly into the airways can be transformed by esterase cleavage into the active metabolite producing high local anti-inflammatory activity.
- The precise mechanism through which ciclesonide affects allergic rhinitis symptoms is not known.
- Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic inflammation.

GLIMPSE OF FUTURE DRUGS

- Leukotrine inhibitors & single isomer agents which are available for clinical use.
- Antiinterleukin agents & PDE inhibitors are in the stage of clinical trials.
- Antisense therapy & pharmacogenetics are the on horizons for treatment of asthma.
- Long acting 2 – agonist (LABAs) Salbutamol & Formoterol are currently positioned as ‘add-on’ therapy ,where combination with inhaled steroids results in better lung function .

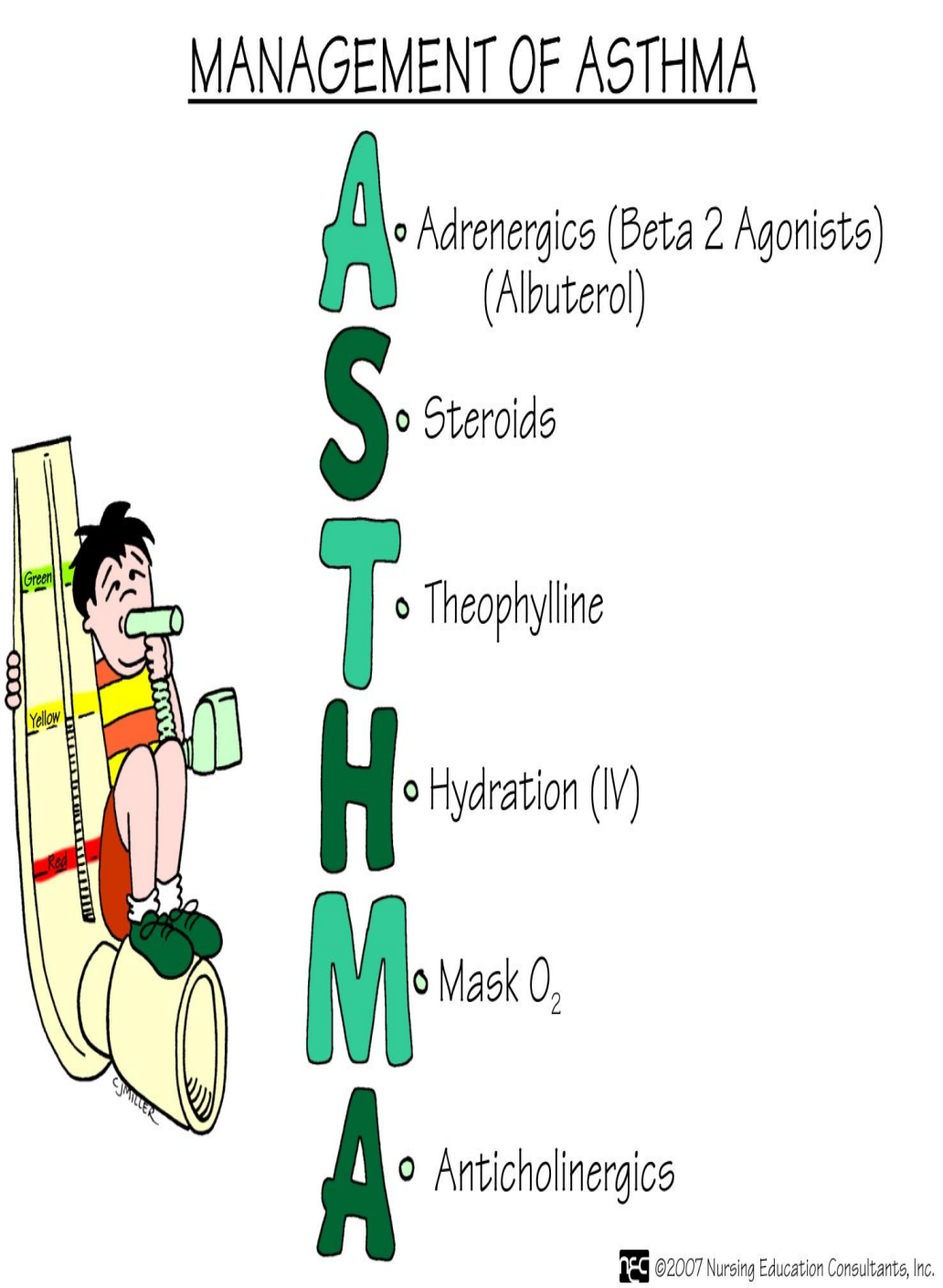
- Soft steroids are active by it self ,has therapeutic efficacy at site of application & inactivated during its systematic uptake .e.g.: Loteprednol, Etabonate & lactone derivatives.
- "An orange a day!":- Eating citrus fruits (vit. C) even 1-2 times /week proved significantly.
- Research have identified ,the expression profile of ADAM33 gene & its possible etiological /hereditary roll in asthma.

Herbs Therapy

- **Gingiber officinale** :- Expectorant
- **Piper nigrum/longum** :- Antiinflammatory
- **Elleteria cardamom** :- Imflammation
- **Adhatoda vasaka** :- To relieve ashma
- **W. Somniferous** :- Antiinflammatory
- **Cuminum cyminum** :- Bronchodilator
- **Terminalia chebula** :- Antiasthmatic
- **Aloe barbadensis** :- Antibiotic, astringent, and pain reliever and beneficial to asthma
- **Tragacanth gum** :- Elimination of toxins causing allergies and asthma.

Management

- Pharmacological
- Non pharmacological



	Long-term control	Quick relief	Education
Step-1 **Mild intermittent**	***No daily medication*** is needed	• SABA- inhaled β_2 agonists as needed for symptoms • Intensity of treatment depends on severity of exacerbation	• Teach basic facts about asthma • Teach inhaler, spacer or holding chamber technique • Discuss appropriate measures to avoid exposure to allergen and irritants
Step-2 **Mild persistent**	***One daily medication-*** **Anti-inflammatory-** either inhaled **corticosteroid(low dose)** or **cromolyn** or **nedocromil**	• SABA- inhale β_2 agonists as needed for symptoms • Intensity of treatment depends on severity of exacerbation • Use of SABA- inhaled β_2 agonists on daily basis or increasing use indicates the need for additional long-term therapy.	Step-1 action plus- • Teach self monitoring • Refer to group education if available • Review and update self-management plan

	Long-term control	Quick relief	Education
Step-3 **Moderate persistent**	***Daily medication-*** **Anti-inflammatory-**either inhaled **corticosteroid (low dose) or (medium dose)** and a **LABA** or sustained release **Theophylline**	• SABA- inhale β_2 agonists as needed for symptoms • Intensity of treatment depends on severity of exacerbation • Use of SABA on daily basis or increasing use indicates the need for long-term therapy.	Step-1 action plus- • Teach self monitoring • Refer to group education if available • Review and update self-management plan
Step-4 **Severe persistent**	***Daily medication-*** • **Anti-inflammatory-** inhaled **corticosteroid (high dosage)** and a LABA or sustained release **Theophylline** • **Corticosteroid tablets** or **syrup** long term (2mg/kg/day) generally do not exceed 60mg per day.	• SABA- inhale β_2 agonists as needed for symptoms • Intensity of treatment depends on severity of exacerbation • Use of SABAon daily basis or increasing use indicates the need for long-term therapy.	Steps 2 and 3 action plus- Refer to individual education and counselling

Assess Severity

Measure PEF: Value <50% personal best or predicted suggests severe exacerbation.

Note signs and symptoms: Degrees of cough, breathlessness, wheeze, and chest tightness correlate imperfectly with severity of exacerbation. Accessory muscle use and suprasternal retractions suggest severe exacerbation.

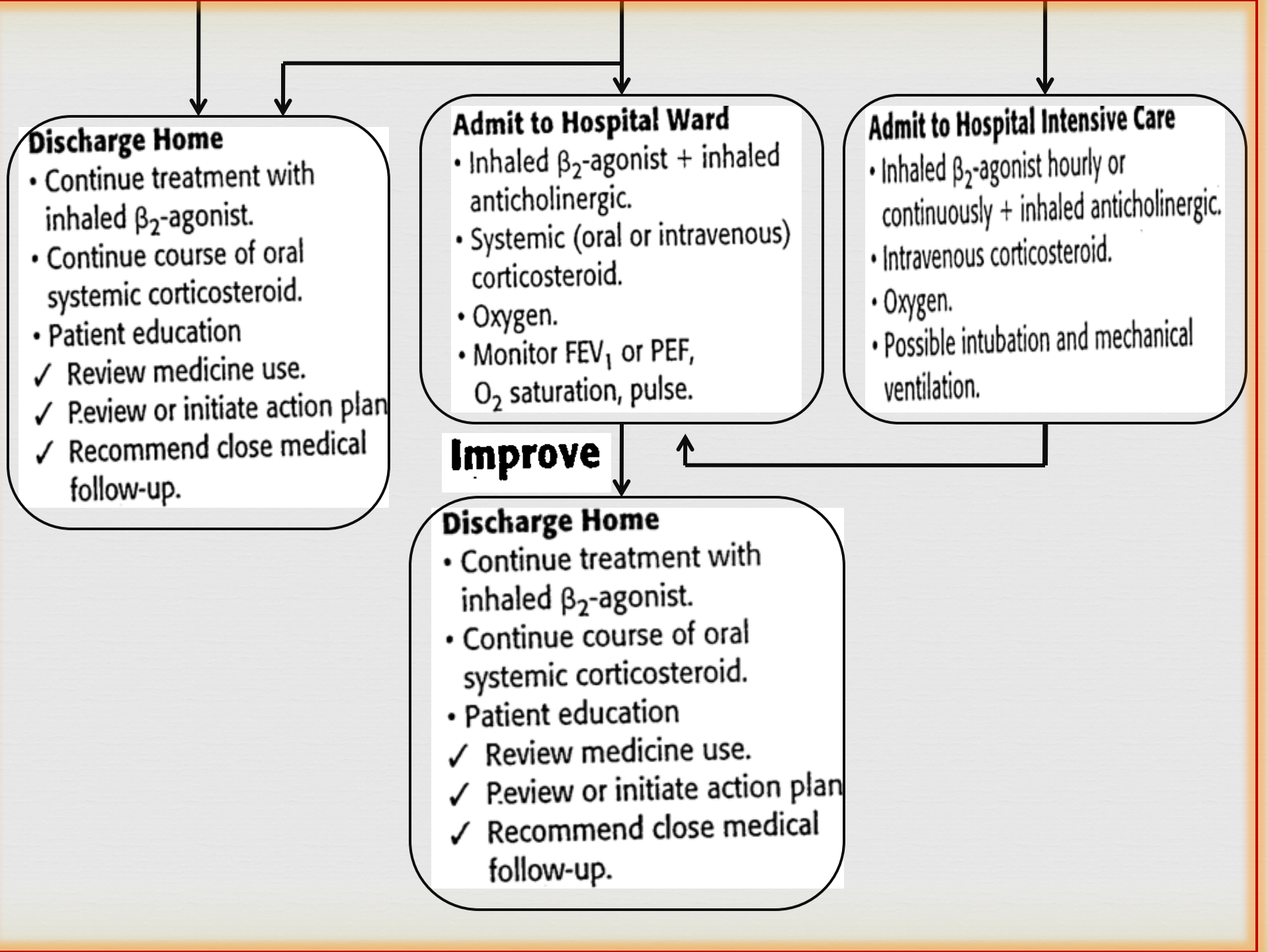
Initial Treatment

- Inhaled short-acting β_2-agonist: up to three treatments of 2–4 puffs by MDI at 20-min intervals or single nebulizer treatment.

Good response
- Mild exacerbation
- PEF> 80%
- No wheezing or shortness of breath
- Response to β_2 agonist sustained for 2 hours
- May continue β_2 agonist every 3-4 hour

Incomplete response
- Moderate exacerbation
- PEF> 50-80%
- Persistent wheezing and shortness of breath
- Add **oral corticosteroid**
- Inhaled short acting

Poor response
- Severe exacerbation
- PEF< 50%
- Marked wheezing or shortness of breath
- **Systemic corticosteroid**
- Inhaled short acting β_2 agonist hourly or continuously
- Oxygen supply


Discharge Home
• Continue treatment with inhaled β_2-agonist.
• Continue course of oral systemic corticosteroid.
• Patient education
✓ Review medicine use.
✓ Review or initiate action plan
✓ Recommend close medical follow-up.
Admit to Hospital Ward
• Inhaled β_2-agonist + inhaled anticholinergic.
• Systemic (oral or intravenous) corticosteroid.
• Oxygen.
• Monitor FEV_1 or PEF, O_2 saturation, pulse.
Admit to Hospital Intensive Care
• Inhaled β_2-agonist hourly or continuously + inhaled anticholinergic.
• Intravenous corticosteroid.
• Oxygen.
• Possible intubation and mechanical ventilation.
Improve
Discharge Home
• Continue treatment with inhaled β_2-agonist.
• Continue course of oral systemic corticosteroid.
• Patient education
✓ Review medicine use.
✓ Review or initiate action plan
✓ Recommend close medical follow-up.

Non pharmacological

- Quite smoking
- Education
- Take a mouth mask when go to the out side
- At a regular interval go for doctor visit.
- Take regular medicines
- Always take inhaler when out side

THANK YOU