ANTI ASTHMA
ANTI TUBERCULAR DRUGS
FIRST YEAR MBBS

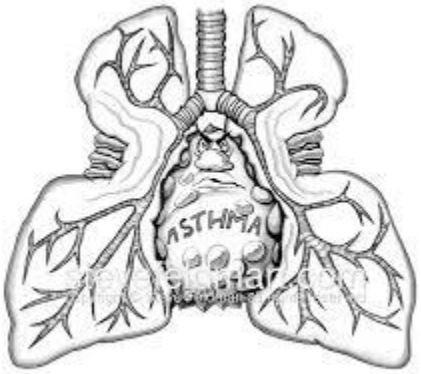
DR SHAMS SULEMAN

LEARNING OBJECTIVES

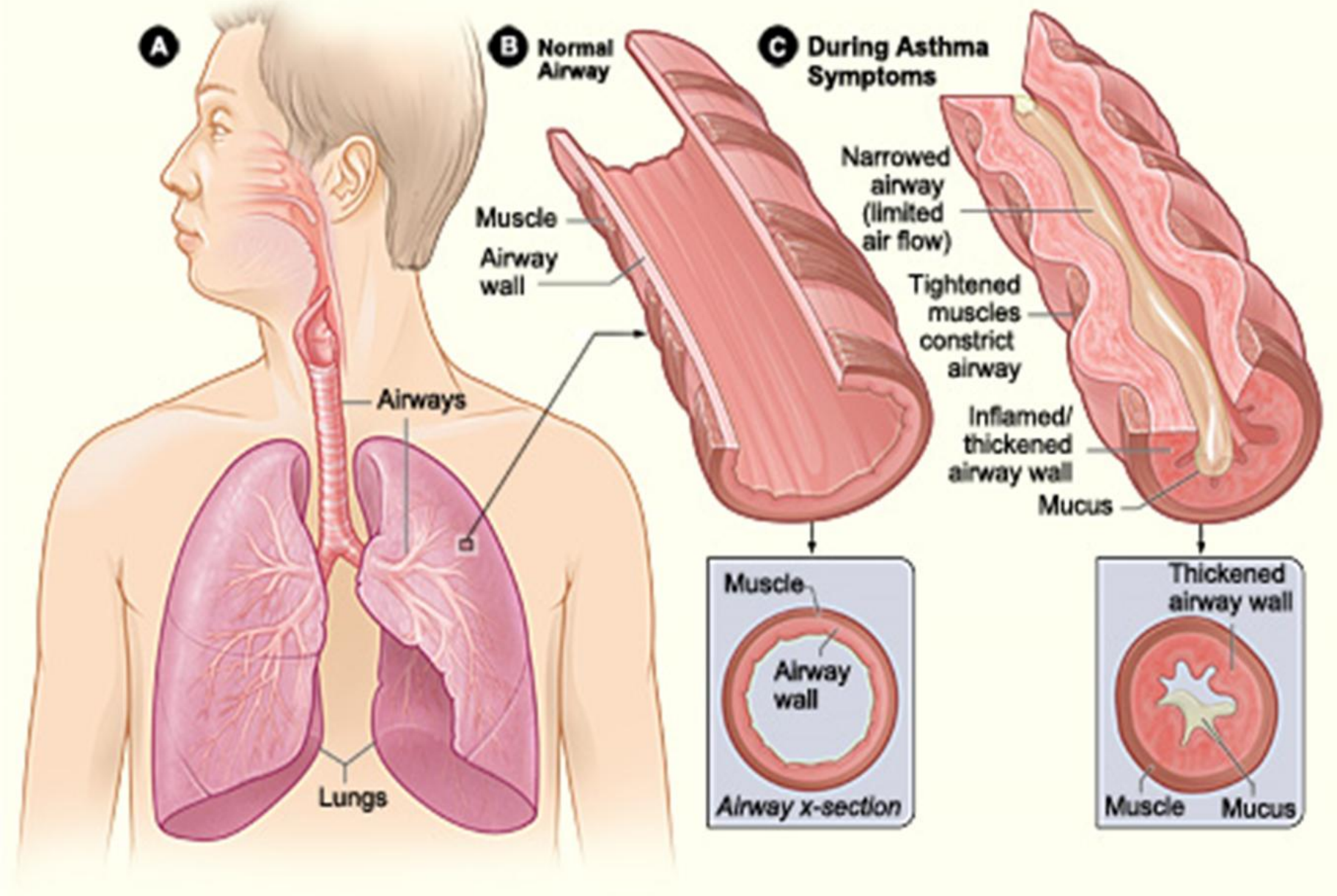
- Classify on anti asthma drugs
- Briefly describe Basic Pharmacology of anti asthma drugs
- Classify on First-line antitubercular drugs
- Briefly describe Basic Pharmacology of antitubercular drugs

Pharmacotherapy

Definition:



- Asthma is defined as an acute inflammatory disease characterized by bronchial hyper responsiveness that resolves spontaneously or with treatment
- A common chronic disorder of airways characterized by variable and recurring symptoms


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

AIMS OF TREATMENT

- Identify and reduce the exposure to risk factors
- Manage asthma exacerbations
- Achieve and maintain control of symptoms
- Maintain normal activity/ exercise level
- Prevent asthma mortality

- ***Relief medications:***
- Short acting bronchodilators
- Systemic corticosteroids
- Anticholinergics
- ***Control agents:***
- Inhaled corticosteroids
- Long acting bronchodilators
- Mast cell stabilizers
- Leukotriene modifiers

CLASSIFICATION

a- SYMPATHOMIMETICS:

i. α & β adrenoceptor Agonists:

- Adrenaline
- Ephedrine

ii. β - adrenoceptor Agonists:

- Albuterol
- Terbutaline
- Salmeterol
- Formeterol
- Isoprenaline
- Orciprenaline

CLASSIFICATION

b- Methylxanthines:

- Aminophylline
- Theophylline
- Theobromine
- Caffeine

c- Muscarinic Antagonists:

Ipratropium Bromide

Tiotropium

CLASSIFICATION

d. corticosteroids

- Hydrocortisone Sodium Succinate
- Methyl Prednisolone
- Betamethasone Valerate
- Beclomethasone Dipropionate

e. Mast cell stabilizers

- Nedocromil
- Na Chromoglycate (Cromolyn)

CLASSIFICATION

f. LEUKOTRIENE PATHWAY INHIBITORS:

- **Leukotriene Receptor Antagonist:**

  Montelukast

- **5-lipooxygenase inhibitor (synthesis inhibitor)**

  Zileuton

g. Anti IgE monoclonal antibodies:

Omalizumab

β_2-AGONISTS:

Mechanism Of Action:

β_2 receptors in airway smooth muscles

↓

Stimulate adenylyl cyclase

↓

↑ cAMP in airway tissue

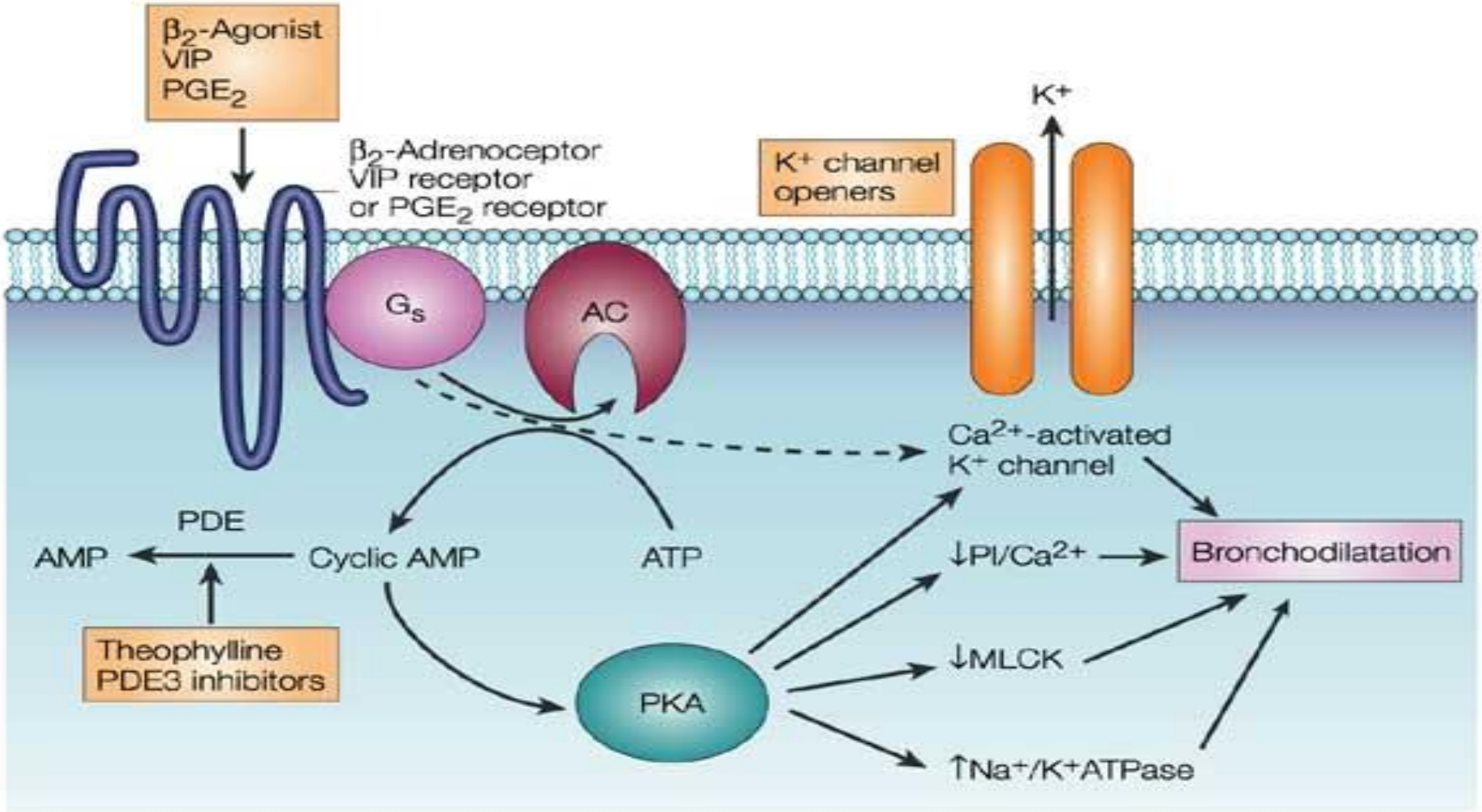
↓

Relaxation of smooth muscle

↓

Bronchodilation

Mechanism of action



Nature Reviews | Drug Discovery

METHYLXANTHENES

MECHANISM OF ACTION

Phosphodiestrase Inhibition

↓

Increased intracellular cAMP

↓ ↓

Smooth muscle relaxation Decreases Histamine release

ANTICHOLINERGICS

- ✓ Relief/rescue medication
- ✓ Relieves acute asthma
- ✓ Often paired with a short-acting β2-agonist
- ✓ Used where β2-agonist are intolerable

CORTICOSTEROIDS

- ***Mechanism of action:***

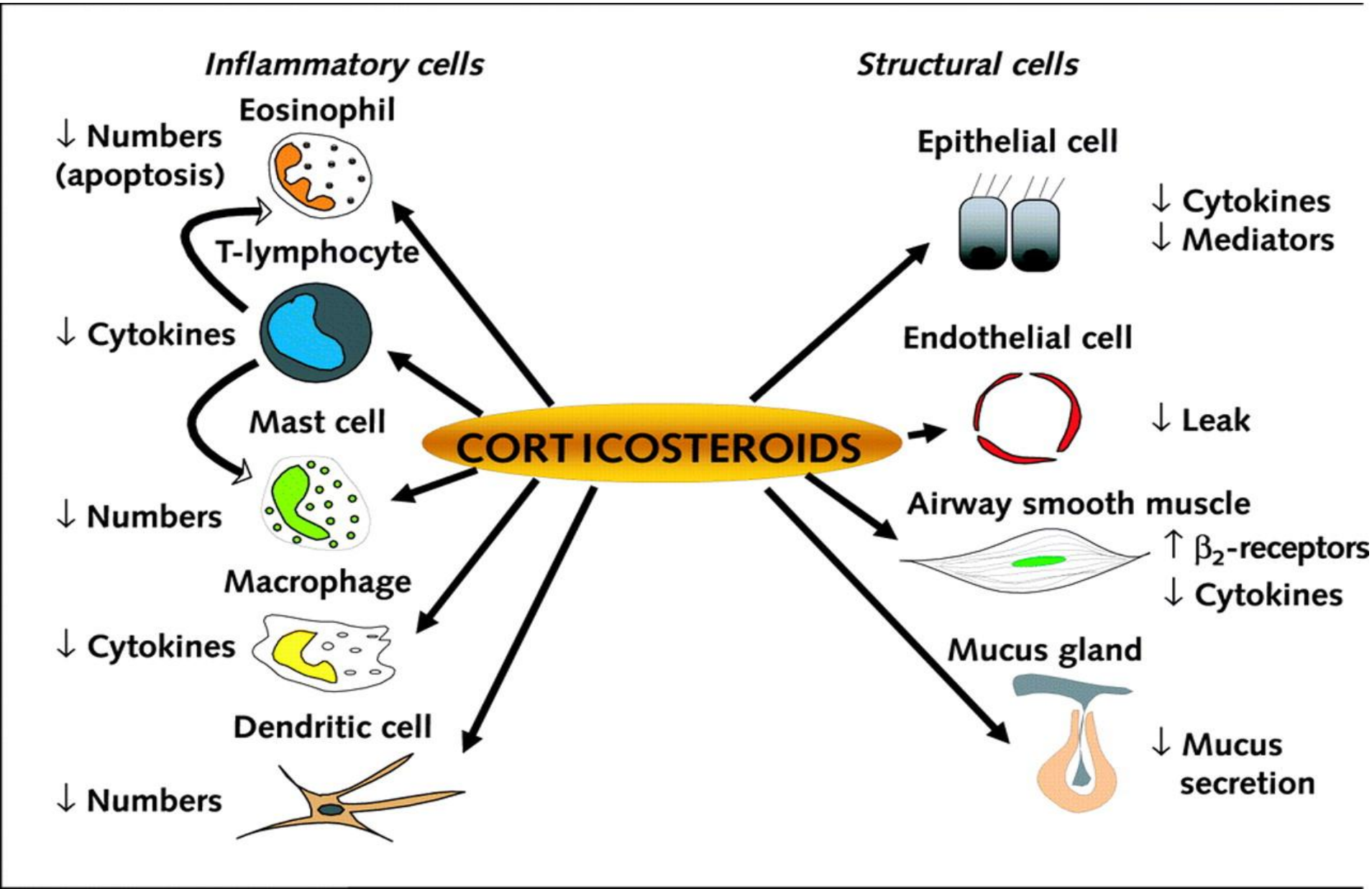
✓ Inhibit multiple cell types involved in asthmatic response e.g.

- Mast cells, Eosinophils, Basophils, Lymphocytes, Macrophages, Neutrophils

✓ Mediate secretion of

- Histamine, Eicosanoids, Leukotrienes, Cytokines

Steroids: Mechanism of action



✓ ***Routes:***

- Intranasal, I/V
- Inhaled, oral

❖ ***Adverse effects:***

- Osteoporosis
- Growth retardation
- Oral candidiasis
- Immunosuppression

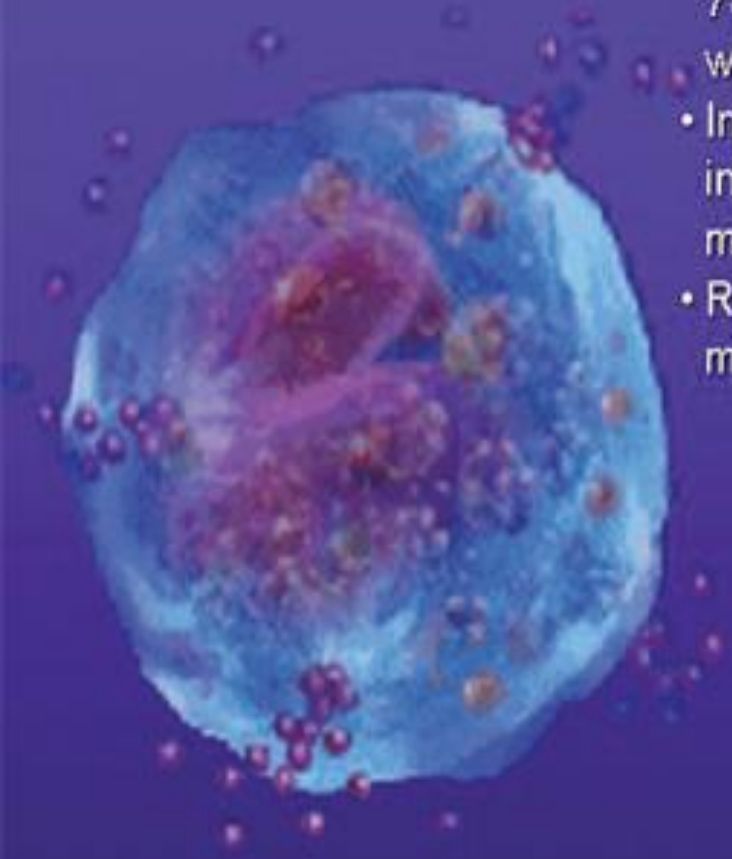
MAST CELL STABILIZERS

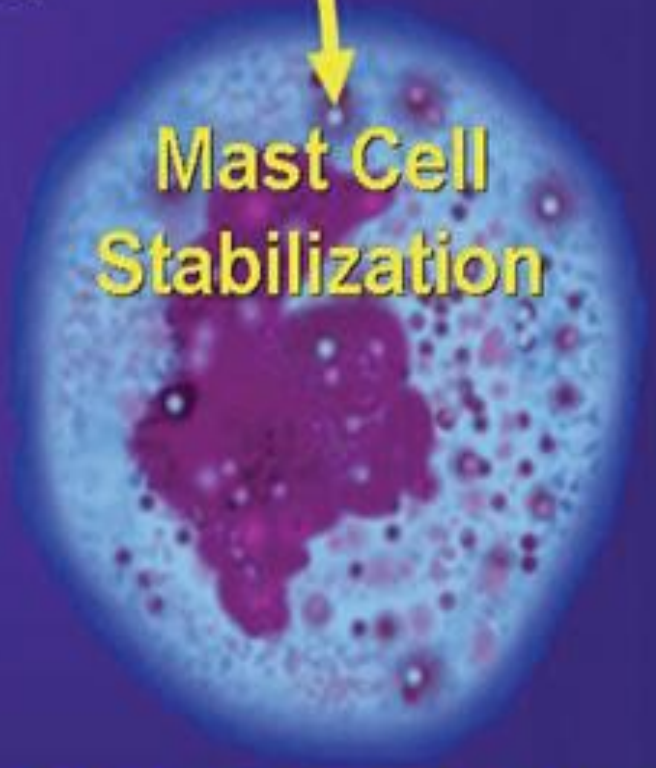
- Alteration in function of delayed chloride channels in the cell membrane inhibiting cell activation, stabilizing cell – prevent release of histamine/related mediators
- ✓ Prophylactic anti-inflammatory agents
- ✓ ***Route:***
- ✓ inhalational

Mast Cell Stabilizers

Possible Mechanisms

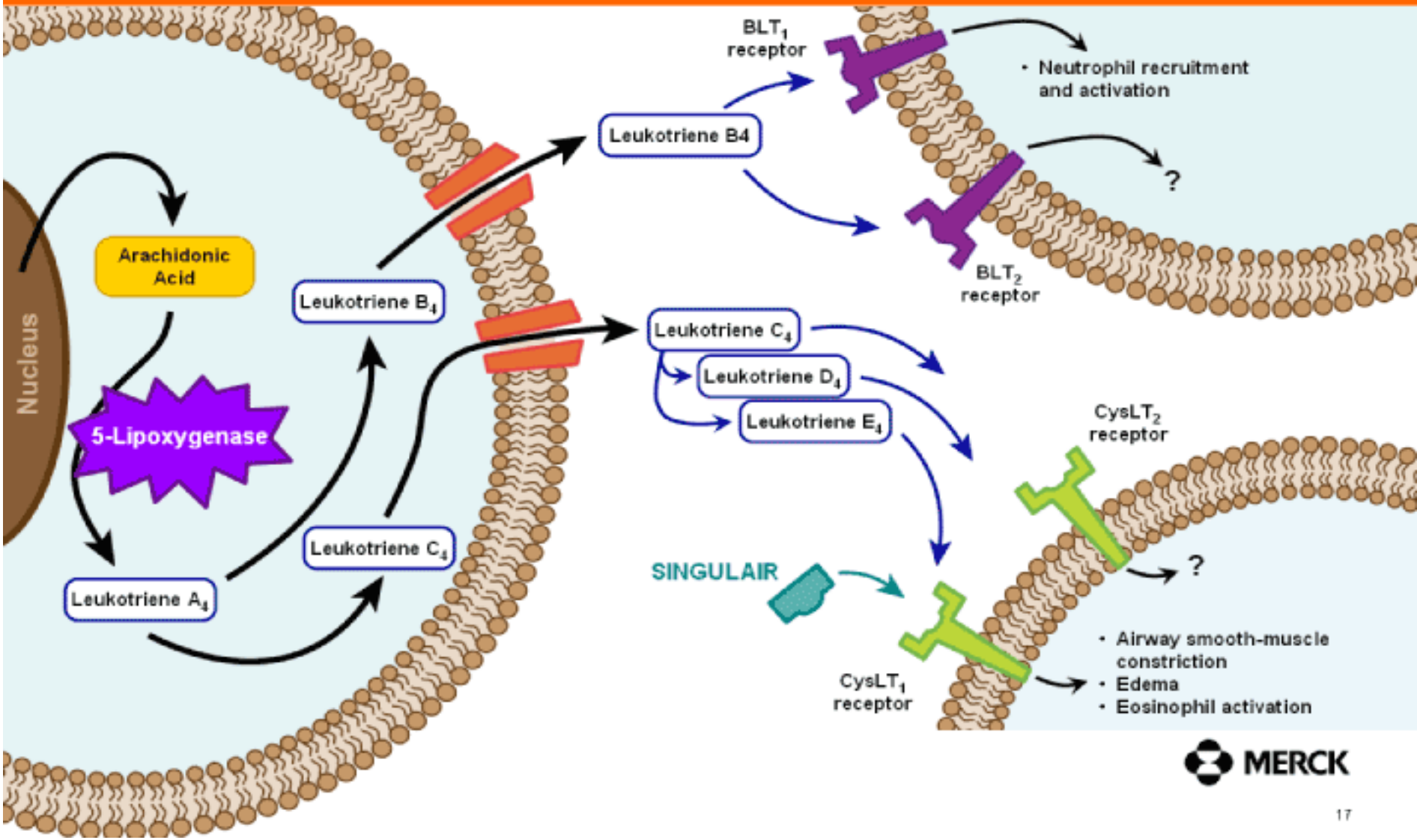
- Phosphorylation of a 78,000-dalton protein which terminates secretion
- Inhibition of Ca^{++} influx into cell, preventing membrane changes
- Reduces pre-secretion membrane fluidity





Membrane Changes Halted

5-Lipoxygenase Inhibition: Targets Pathway Responsible for Production of All Leukotrienes



MERCK

LEUKOTRIENE SYNTHESIS INHIBITOR

SYNTHESIS

5- Lipooxygenase

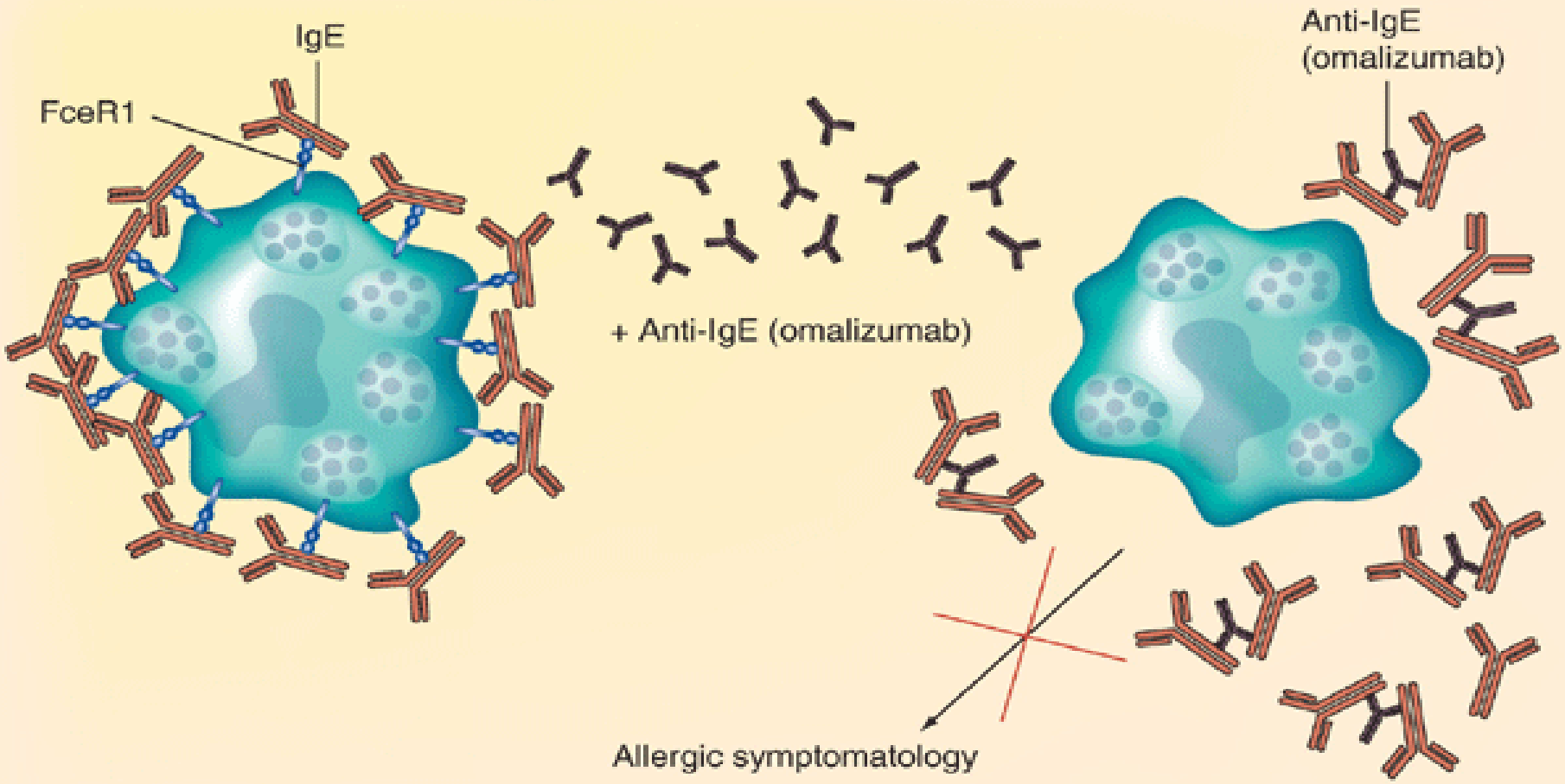
↓

Arachidonic acid ⟶ Leukotrienes

- ✓ Synthesized from
  - Eosinophils
  - Mast cells
  - Macrophages
  - Basophils

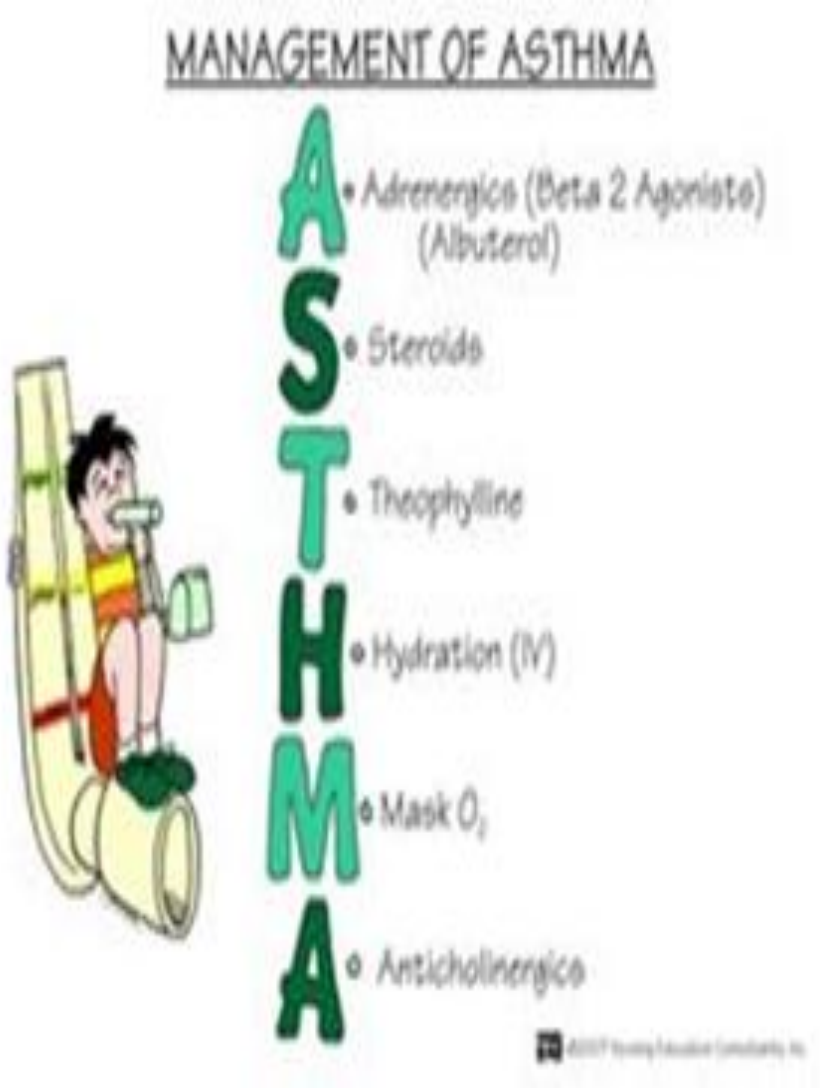
ANTI IGE ANTIBODIES

- ✓ Recombinant DNA – derived monoclonal antibody
- ✓ Selectively binds to IgE → ↓ binding to IgE receptors on surface of mast cells/basophils → inhibit degranulation
- ✓ High cost
- ✓ Useful in
  - o Moderate – severe asthma not responding to conventional therapy



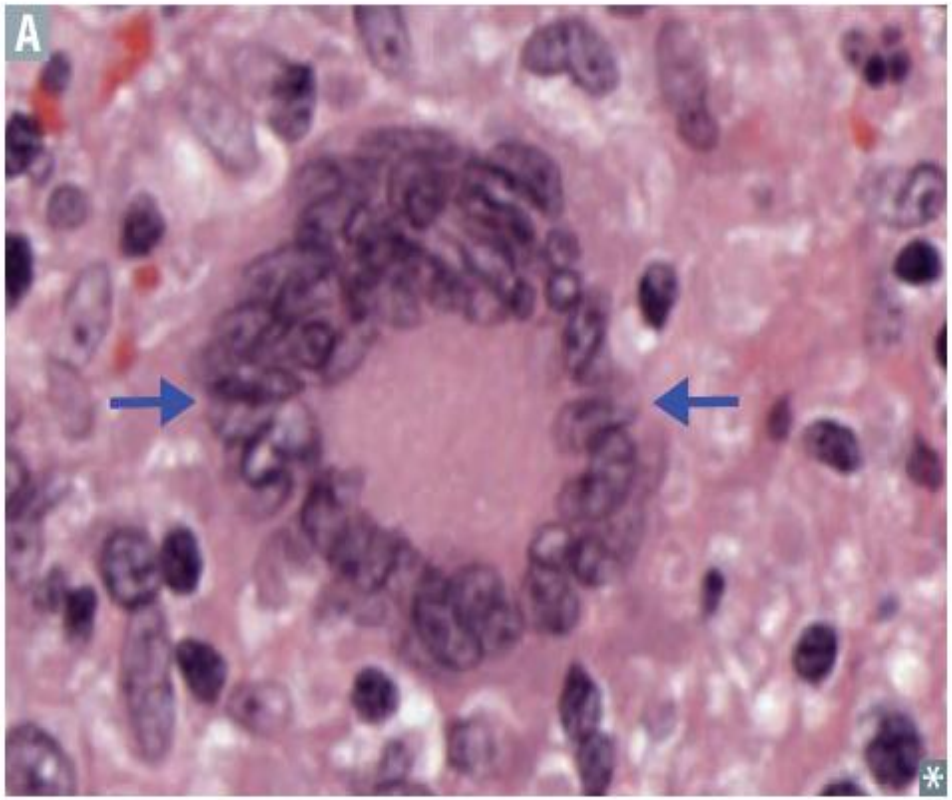
ACUTE SEVERE ASTHMA

- Oxygen
- Goal :saO2 > 92%
- Inhaled bronchodilators
- Short acting β2 agonist
- Systemic corticosteroids
- Intravenous fluids



TUBERCULOSIS

- Is a chronic infectious disease caused by Mycobacterium Tuberculosis
- Requires prolonged treatment
- Consists of excessive fibrous tissue with central necrosis



TUBERCULOSIS

- Poor vascularity of lesion
- poor penetration of the drug to lesion site

- Mycobacterial species are mostly intracellular pathogens
- Bacteria residing within macrophages are inaccessible to drugs that penetrate these cells poorly

- Mycobacteria are notorious for their ability to develop resistance.

ANTIMYCOBACTERIAL DRUGS CLASSIFICATION

First line antitubercular drugs (standard drugs)

1. Isoniazid (H)
2. Rifampicin (R)
3. Pyrazinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

ANTIMYCOBACTERIAL DRUGS CLASSIFICATION

Second-Line antitubercular drugs (Reserve/ Alternative drugs)

1. Para-amino salicylic acid
2. Thiacetazone
3. Cycloserine
4. Ethionamide
5. Kanamycin
6. Capreomycin
7. Amikacin

ANTIMYCOBACTERIAL DRUGS CLASSIFICATION

Second-Line antitubercular drugs (Reserve/ Alternative drugs)

8. Levofloxacin
9. Moxifloxacin
10. Ofloxacin
11. Clarithromycin
12. Rifabutin
13. Rifapentine
14. Bedaquiline
15. Linezolid

Isoniazid (H) ,Rifampicin (R) , Pyrazinamide (Z), Ethambutol (E), Streptomycin (S)

FIRST-LINE ANTI TUBERCULAR DRUGS

CHEAP
MORE EFFECTIVE
ROUTINELY USED
LESS TOXIC

ISONIAZID (INH)

- Active against both, intracellular and extracellular bacilli
- Mechanism of action: Inhibits biosynthesis of Mycolic acids, which are essential constituents of the mycobacterial cell wall
- Tuberculocidal
- Metabolized by acetylation (in liver) – either slow or fast acetylation – under genetic control
- Metabolites are excreted in urine

RIFAMPIN/ RIFAMPICIN

- A derivative of rifamycin
- It rapidly kills intracellular and extracellular bacilli including spurters (those rising in caseous lesion)
- It is the only agent that can act on all types of bacillary subpopulation, hence rifampicin is called as sterilizing agent

RIFAMPIN/ RIFAMPICIN

- It is active in vitro against
  - Mycobacteria
  - Gram-positive and gram-negative cocci
  - Some enteric bacteria
  - Chlamydia
- Mechanism of action

Binds to the B-subunit of bacterial DNA-dependent RNA polymerase and inhibits RNA synthesis

ETHAMBUTOL

- Bacteriostatic
- Mechanism of action

  It inhibits Arabinosyl transferase that are involved in synthesis of Arabinolgycan in the mycobacterial cell wall

- Adverse effects: Optic neuritis
  - Characterized by – decreased visual acuity and color-vision defects (red-green)
  - The toxicity is reversible if the drug is discontinued early following onset of symptoms

PYRAZINAMIDE

- A synthetic analogue of nicotinamide
- Active in acidic pH (of lysosomes) –effective against intracellular bacilli (has sterilizing activity)
- Has Tuberculocidal activity
- Pyrazinamide is converted to Pyrazinoic acid—the active form of the drug—by mycobacterial pyrazinamidase
- Pyrazinoic acid disrupts mycobacterial cell membrane metabolism and transport functions.

STREPTOMYCIN

- An aminoglycoside antibiotic
- A bactericidal drug
- Active against extracellular bacilli in alkaline pH
- Pharmacokinetics: Not effective orally and must be injected intramuscularly
- Adverse Effects: Ototoxicity, nephrotoxicity and neuromascular blockade

SECOND-LINE / ALTERNATIVE ANTI TUBERCULOSIS DRUGS

SECOND-LINE / ALTERNATIVE ANTI TUBERCULOSIS DRUGS

The alternative drugs are usually considered only

- In case of resistance to first-line agents;
- In case of failure of clinical response to conventional therapy; and
- In case of serious treatment-limiting adverse drug reactions

ETHIONAMIDE

- Structurally similar to INH but less efficacious
- Mechanism of action: It inhibits the synthesis of mycolic acid
- Spectrum: A bacteriostatic drug effective against both extracellular and intracellular bacilli
- Resistance to ethionamide as a single agent develops rapidly in vitro and in vivo.
- There can be low-level cross-resistance between isoniazid and ethionamide.

CYCLOSERINE

- Bacteriostatic activity
- Mechanism of action: It inhibits bacterial cell wall synthesis
- Widely distributed in the body including CSF
- Side Effects:
  - Related to CNS and include headache, tremor, depression, psychosis and convulsions
  - Peripheral neuropathy (the most serious side effect)

CAPREOMYCIN

- A peptide protein synthesis inhibitor antibiotic
- Injectable agent
  - Used for treatment of drug-resistant tuberculosis
- Side Effects:
  - Nephrotoxicity
  - Ototoxicity
  - Tinnitus, deafness, and vestibular disturbances
  - Local pain, and sterile abscesses

AMINOSALYCYLIC ACID

- Structurally similar to Sulphonamides
- Mechanism of action:
  - Competitively inhibits folate synthetase enzyme and thus prevents the formation of tetrahydrofolic acid (THFA)
  - A bacteriostatic effect
- Uses:
  - A reserve drug for the management of MDR-tuberculosis

*MDR – multidrug-resistant

KANAMYCIN & AMIKACIN

- Amikacin is useful against atypical mycobacteria
- There is no cross-resistance between streptomycin and amikacin
- But kanamycin resistance often indicates resistance to amikacin as well
- Amikacin is indicated for treatment of tuberculosis suspected or known to be caused by streptomycin-resistant or multidrug-resistant strains

FLUOROQUINOLONES

- Also helpful in treating atypical mycobacteria
- Useful for strains resistant to first-line antitubercular drugs
- Resistance: may result from one of several single point mutations in the Gyrase A subunit, if a Fluoroquinolone is used as a single agent

LINEZOLID

- Used in combination with other antitubercular drugs for the treatment of multidrug resistant strains
- Adverse effects: bone marrow suppression and irreversible peripheral and optic neuropathy

RIFABUTIN/RIFAPENTINE

- Rifabutin is derived from rifamycin and is related to rifampin
- It has significant activity against *M tuberculosis*, MAC, and *Mycobacterium fortuitum*
- Indicated in place of rifampin

  Because it is a less potent inducer of hepatic enzymes

BEDAQUILINE

- A diarylquinoline, with a novel mechanism of action
- Mechanism of action:
  - Inhibits adenosine 5’-triphosphate (ATP) synthase in mycobacteria,
  - has in vitro activity against both replicating and non replicating bacilli
- Has bactericidal and sterilizing activity
- No cross-resistance with other medications used to treat tuberculosis.

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