DRUGS ACTING ON RESPIRATORY SYSTEM
ANTI ASTHMATIC

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

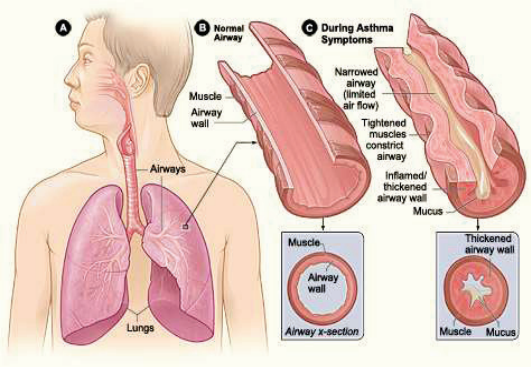
Bronchial Asthma

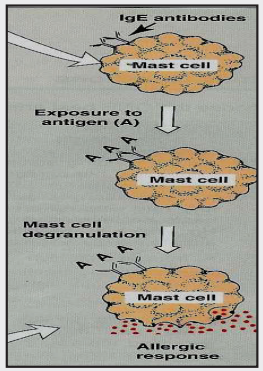
Asthma is a chronic inflammatory disorder of bronchial airways that result in airways obstruction in response to external stimuli (as pollen grains, cold air and tobacco smoke).

Characters of airways in asthmatic patients :

- **Airway hyper-reactivity:** abnormal sensitivity of the airways to any external stimuli.
- **Inflammation**
  - ↑ edema, swelling
  - ↑ Thick mucus production.
- **Bronchospasm** (constriction of the bronchial smooth muscles).

Airway hyper-reactivity





Symptoms of asthma

Asthma produces recurrent episodic attack of

- Acute bronchoconstriction
- Shortness of breath
- Chest tightness
- Wheezing
- Rapid respiration
- Cough

Symptoms can happen each time the airways are irritated by inhaled irritants or allergens.

Causes

- Infection
- Stress
- Exercise (cold air)
- Pets
- Seasonal changes
- Emotional conditions
- Some drugs as aspirin, β-bockers

Asthma drug targets

- **Parasympathetic supply**

  M3 receptors in smooth muscles and glands.

  - **Bronchoconstriction**
  - **Increase mucus secretion**

- **No sympathetic supply but B_2 receptors in smooth muscles and glands.**

  - **Bronchodilation**
  - **Decrease mucus secretion**

Anti asthmatic drugs:

1) Quick relief medications:

Bronchodilators used to relieve acute episodic attacks of asthma.

2) Control therapy (prophylactic drugs):

Glucocorticoids; anti-inflammatory drugs used to reduce the frequency of attacks, and nocturnal awakenings

Anti asthmatic drugs

Bronchodilators (Quick relief medications)	Anti-inflammatory Agents (Prophylactic therapy)
treat acute attack of asthma	reduce the frequency of attacks
• Short acting β2-agonists	• Corticosteroids
• Antimuscarinics	• Mast cell stabilizers
• Xanthine preparations	• Leukotrienes antagonists
	• Anti-IgE monoclonal antibody
	• Long acting ß2-agonists

Bronchodilators

These drugs can produce rapid relief of broncho constriction.

Bronchodilators:

- **β2 - adrenoreceptor agonists**
- **Antimuscarinics**
- **Xanthine preparations**

Sympathomimetics

β- adrenoceptor agonists

Mechanism of Action

➢direct β_2 stimulation ⟶ stimulate adenyl cyclase ⟶ ↑ cAMP → bronchodilation.

➢Increase mucus clearance by (increasing ciliary activity).

➢Stabilization of mast cell membrane.

Classification of β agonists

- **Non selective β agonists:**
  - **epinephrine - isoprenaline**
- **Selective β2 – agonists (Preferable).**
  - **Salbutamol (albuterol)**
  - **Terbutaline**
  - **Salmeterol**
  - **Formeterol**

Non selective β-agonists.

Epinephrine

- **Potent bronchodilator**
- **Given subcutaneously, S.C.**
- **rapid action (maximum effect within 15 min).**
- **Has short duration of action (60-90 min)**
- **Drug of choice for acute anaphylaxis *(hypersensitivity reactions).***

Disadvantages

- **Not effective orally.**
- **Hyperglycemia**
- **Skeletal muscle tremor**
- **CVS side effects:**
  - tachycardia, arrhythmia, hypertension
- **Not suitable for asthmatic patients with hypertension or heart failure.**

Contraindications:

- **CVS patients, diabetic patients**

Selective β2 –agonists

- Are mainly given by **inhalation** by (metered dose inhaler or nebulizer).
- Can be given orally, parenterally.
- Short acting ß2 agonists

  e.g. salbutamol, terbutaline
- Long acting ß2 agonists

  e.g. salmeterol, formoterol

Short acting $ß_2$ agonists

Salbutamol, inhalation, orally, i.v.

Terbutaline, inhalation, orally, s.c.

- **Have rapid onset of action (15-30 min).**
- **short duration of action (4-6 hr)**
- **used for acute attack of asthma (drugs of choice).**

Long acting selective $ß_2$ agonists

Salmeterol & formoterol

- are given by inhalation
- Long acting bronchodilators (12 hours) due to high lipid solubility (creates depot effect).
- are not used to relieve acute episodes of asthma
- used for nocturnal asthma.
- combined with inhaled corticosteroids to control asthma (decreases the number and severity of asthma attacks).

Advantages of ß$_2$ agonists

- Minimal CVS side effects
- suitable for asthmatic patients with

CV disorders as hypertension or heart failure.

Disadvantages of ß$_2$ agonists

- Skeletal muscle tremors.
- Nervousness
- Tolerance (β-receptors down regulation).
- Overdose may produce tachycardia due to

$\beta_1$stimulation.

Muscarinic antagonists

Ipratropium – Tiotropium

- Act by blocking muscarinic receptors .
- given by aerosol inhalation
- Have delayed onset of action.
- Quaternary derivatives of atropine (polar).
- Does not diffuse into the blood
- Do not enter CNS.
- Have minimal systemic side effects
- **Ipratropium** has short duration of action 3-5 hr
- **Tiotropium** has longer duration of action (24 h).

Pharmacodynamics

- Inhibit bronchoconstriction and mucus secretion
- Less effective than β_2-agonists.
- No anti-inflammatory action only bronchodilator

Uses

- Main choice in chronic obstructive pulmonary diseases (COPD).
- In acute severe asthma combined with β_2 agonists & corticosteroids.

Methylxanthines

- Theophylline - aminophylline

Mechanism of Action

- are phosphodiestrase inhibitors
- ↑ cAMP → bronchodilation
- Adenosine receptors antagonists (A1) (not very significant in asthma)
- Increase diaphragmatic contraction
- Stabilization of mast cell membrane

Pharmacological effects :

- Bronchial muscle relaxation
- ↑contraction of diaphragm→ improve ventilation

CVS: ↑ heart rate, ↑ force of contraction

GIT: ↑ gastric acid secretions

Kidney: ↑renal blood flow, weak diuretic action

CNS stimulation

* stimulant effect on respiratory center.
* decrease fatigue & elevate mood.
* overdose (tremors, nervousness, insomnia, convulsion)

Pharmacokinetics

- **Theophylline** is given orally
- **Aminophylline**, is given as slow infusion
- **metabolized by Cyt P450 enzymes in liver**

T ½= 8 hours

- **has many drug interactions**
  - **Enzyme inducers:**
    - as phenobarbitone & rifampicin
    - ↑ metabolism of theophylline → ↓ T ½.
  - **Enzyme inhibitors:**
    - as erythromycin

↓ metabolism of theophylline → ↑ T ½.

Uses

- Second line drug in asthma (theophylline).
- For status asthmatics (aminophylline, is given as slow infusion).

Side Effects

- Low therapeutic index **(narrow safety margin)** monitoring of theophylline blood level is necessary.
- CVS effects: hypotension, arrhythmia.
- GIT effects: nausea & vomiting
- CNS side effects: tremors, nervousness, insomnia, convulsion

Prophylactic therapy

Anti - inflammatory drugs include:

- Glucocorticoids to be discussed in (COPD)
- Leukotrienes antagonists
- Mast cell stabilizers
- Anti-IgE monoclonal antibody

  e.g. omalizumab

Anti - inflammatory drugs:

(control medications / prophylactic therapy)

- ↓ bronchial hyper-reactivity.
- ↓ reduce inflammation of airways
- ↓ reduce the spasm of airways

Glucocorticoids

Mechanism of action

Anti-inflammatory action due to:

- Inhibition of phospholipase A2
- ↓ prostaglandin and leukotrienes
- ↓ Number of inflammatory cells in airways.
- Mast cell stabilization →↓ histamine release.
- ↓ capillary permeability and mucosal edema.
- Inhibition of antigen-antibody reaction.
- **Upregulate β_2 receptors** (have additive effect to B_2 agonists).

Routes of administration

- **Inhalation:**

e.g. Budesonide & Fluticasone, beclometasone

Given by inhalation (metered-dose inhaler).

Have first pass metabolism

Best choice in asthma, less side effects

- **Orally:** Prednisone, methyl prednisolone (for acute asthma attack)
- **Injection:** Hydrocortisone, dexamethasone

Glucocorticoids in asthma

- Are **not** bronchodilators
- Reduce bronchial inflammation
- Reduce bronchial hyper-reactivity to stimuli
- Have delayed onset of action (effect usually attained after 2-4 weeks).
- Maximum action at 9-12 months.
- Given as prophylactic medications, used alone or combined with β_2 agonists.
- Effective in allergic, exercise, antigen and irritant-induced asthma,

Inhalation has very less side effects:

Oropharyngeal candidiasis (thrush).

Dysphonia (voice hoarseness).

(to reduce these effects, Instruct patient to rinse mouth properly after inhalation).

Withdrawal

Abrupt stop of corticosteroids should be avoided and dose should be tapered (*to avoid exacerbation of asthmatic attack and adrenal insufficency*).

Mast cell stabilizers

e.g. Cromoglycate – Nedocromil (not commonly used)

- act by stabilization of mast cell membrane.
- given by inhalation (aerosol, nebulizer).
- Have poor oral absorption (10%)

Uses

- Prophylactic therapy in asthma especially in children.
- Allergic rhinitis.
- Conjunctivitis.

Side effects

- Bitter taste
- minor upper respiratory tract irritation (burning sensation, nasal congestion)

Leukotrienes antagonists

Leukotrienes

- synthesized by inflammatory cells found in the airways (eosinophils, macrophages, mast cells).
- produced by the action of 5-lipoxygenase on arachidonic acid.

- **Leukotriene B4:** chemotaxis of neutrophils
- **Cysteinyl leukotrienes C4, D4 & E4:**
  - bronchoconstriction
  - increase bronchial hyper-reactivity
  - ↑ mucosal edema, ↑ mucus secretion

Uses of leukotriene receptor antagonists

- **Not** effective in acute attack of asthma.
- **Prophylaxis** of mild to moderate asthma.
- Aspirin-induced asthma
- Antigen and exercise-induced asthma
- Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).

Side effects:
Elevation of liver enzymes, headache, dyspepsia

Anti-IgE monoclonal antibody

e.g. Omalizumab

- is a monoclonal antibody directed against human IgE – given by injection (s.c.)
- prevents IgE binding with its receptors on mast cells & basophiles.
- ↓ release of allergic mediators.
- Expensive-not first line therapy.
- used for treatment of moderate to severe allergic asthma which does not respond to high doses of corticosteroids.

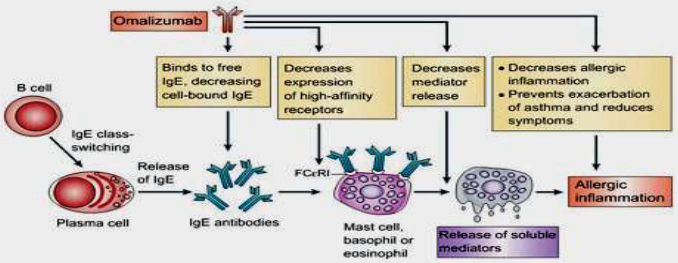


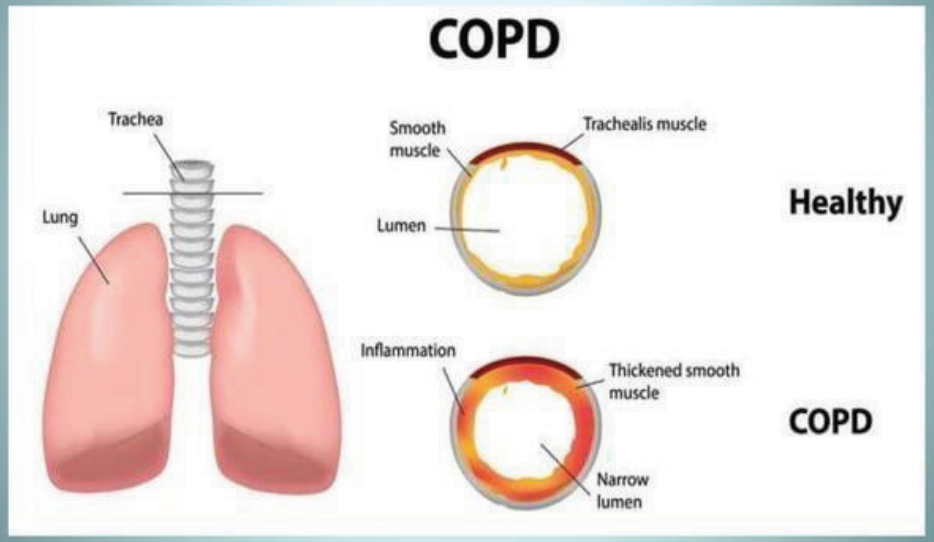
Figure 1. Mechanisms of action of omalizumab in allergic asthma.
Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Immunol,[14] copyright 2008.
Abbreviation: Fc RI, high-affinity IgE receptor.

SSIP

DRUGS ACTING ON RESPIRATORY SYSTEM
DRUGS- COPD

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

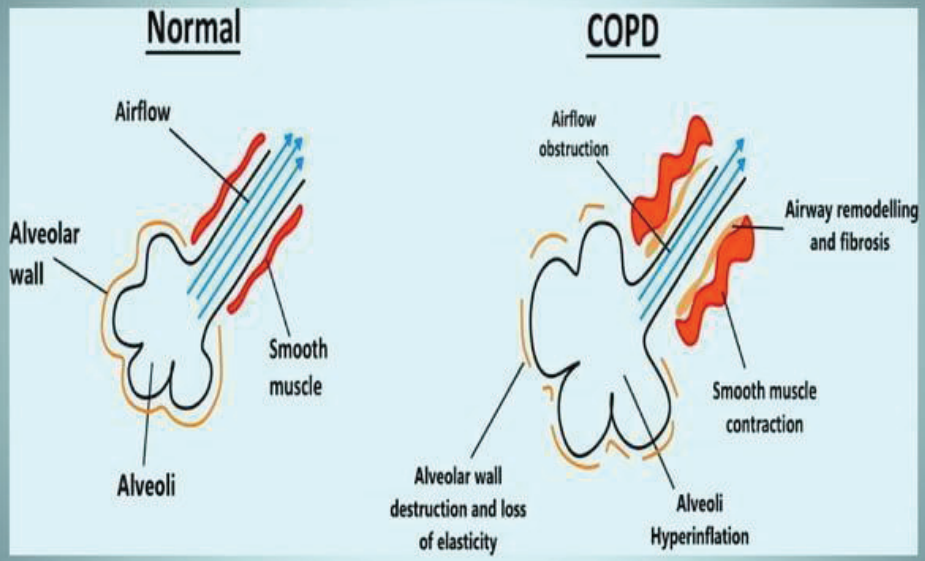
Chronic Obstructive Pulmonary Disease or Chronic Obstructive lung disease.



- **Chronic obstructive pulmonary disease (COPD)is a disease state characterized by airflow limitation that is not fully reversible.**
- **COPD may include diseases that cause airflow obstruction (e.g., emphysema, chronic bronchitis) or a combination of these disorders.**

- COPD includes chronic bronchitis and emphysema. Asthma is not considered part of COP due its reversibility.

1. **Chronic bronchitis**: is a chronic inflammation of the lower respiratory tract characterized by excessive mucous secretion, cough, & dyspnea associated with recurrent infections of the lower respiratory tract.
2. **Emphysema:** is a complex lung disease characterized by damage to the gas- exchanging surfaces of the lungs (alveoli)

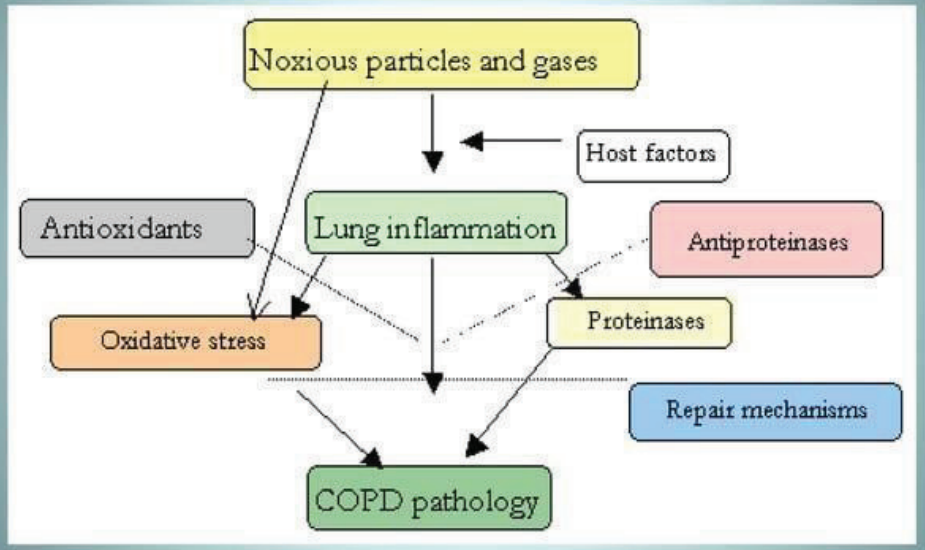


Risk Factors for COPD

1. Exposure to tobacco smoke accounts for an estimated 80% to 90% of COPD cases. (smoking)
2. Passive smoking
3. Occupational exposure
4. Ambient air pollution
5. Genetic abnormalities, including a deficiency of **alpha1-antitrypsin** enzyme.

SMOKING

PATHOPHYSIOLOGY



Clinical Manifestations

- COPD is characterized by three primary symptoms:

1. **Cough**
2. **Sputum production and**
3. **Dyspnea on exertion (DOE)**

Dyspnea may be severe and often interferes with the patient's activities. Weight loss is common because dyspnea interferes with eating.

Assessment and Diagnostic Findings

1. **History collection** (The nurse should obtain a thorough health history for a patient with known or potential COPD).

Key Factors to Assess in the COPD Patient's Health History

1. Exposure to risk factors—types, intensity, duration.
2. Past medical history—respirator diseases/problems, including asthma, allergy, sinusitis, nasal polyps, history of respiratory Infections.
3. Family history of COPD or other chronic respiratory diseases.
4. Pattern of symptom development.
5. History of exacerbations or previous hospitalizations for respiratory problems.

6. Presence of comorbidities
7. Appropriateness of current medical treatments
8. Impact of the disease on quality of life
9. Available social and family support for patient
10. Potential for reducing risk factors (e.g., smoking cessation).

2. **Pulmonary function studies** are used to help confirm the diagnosis of COPD, determine disease severity, and follow disease progression.
3. **Spirometry** is used to evaluate airflow obstruction.
4. **Arterial blood gas (ABGs)** measurements may also be obtained to assess baseline oxygenation and gas exchange.

5. **Chest x-ray**
6. **alpha1antitrypsin deficiency screening** may be performed for patients under age 45 or for those with a strong family history of COPD.

Complications

1. **Respiratory insufficiency and Respiratory failure** are major life-threatening complications of COPD.
2. Pneumonia & respiratory infection
3. Right-sided heart failure
4. Pulmonary hypertension
5. Pneumothorax
6. Skeletal muscle dysfunction
7. Depression and anxiety disorders

The objective of Management client with COPD

The main objective of COPD management are Following:

1. Relieve symptoms
2. Prevent disease progression
3. Reduce mortality & improve exercise tolerance
4. Prevent and treat complications

Medical Management

1. **Risk reduction**: **Smoking cessation** is the single most effective intervention to prevent COPD or slow its progression. (**smoking cessation** is major essential to reduce disease progression and improve survival rate)

Nurses play a key role in promoting smoking cessation and educating patients about ways to do so. Patients diagnosed with COPD who continue to smoke must be encouraged and assisted to quit.

PHARMACOLOGIC THERAPY

- **Bronchodilators**: Bronchodilators relieve bronchospasm and reduce airway obstruction by allowing increased oxygen distribution throughout the lungs and improving alveolar ventilation.
- These medications, which are **central in the management of COPD** are delivered through a **metered-dose inhaler (MDI) by nebulization**, or via the oral route in pill or liquid form.

A metered-dose inhaler(MDI) is a pressurized device containing an aerosolized powder of medication.

Metered-dose inhaler(MDI)

Corticosteroids

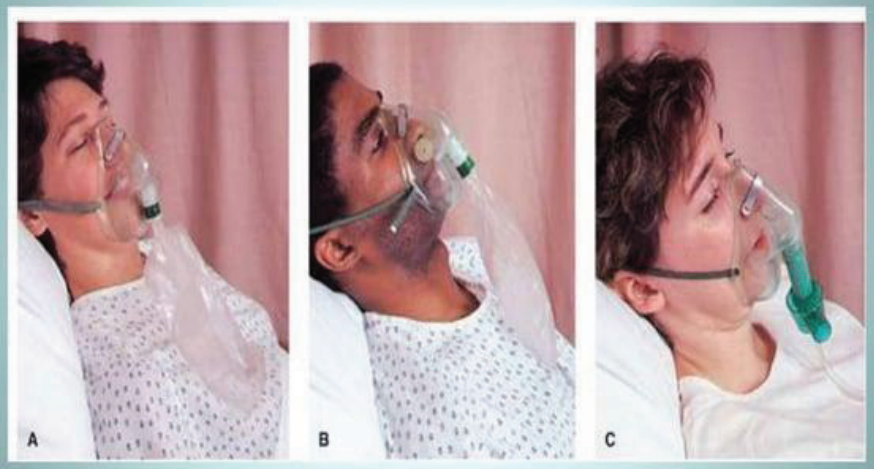
- **Corticosteroids**. Inhaled and systemic corticosteroids (oral or intravenous) may also be used in COPD but are used more frequently in asthma.
- Although it has been shown that corticosteroids do not slow the decline in lung function, these medications may improve symptoms.

- **Other Medications** including Patients should receive a yearly influenza vaccine and the **pneumococcal vaccine** every 5 to 7 years as preventive measures.

MANAGEMENT OF EXACERBATION

- An exacerbation of COPD is difficult to diagnose, but signs and symptoms may include increased dyspnea, increased sputum production and purulence, respiratory failure, changes in mental status, or worsening blood gas abnormalities.
- Primary causes for an acute exacerbation include tracheobronchial infection and air pollution.

OXYGEN THERAPY



OXYGEN THERAPY

- Oxygen therapy can be administered as long-term continuous therapy, during exercise, or to prevent acute dyspnea.
- Long-term oxygen therapy has been shown to improve the patient's quality of life and survival.

SURGICAL MANAGEMENT

- **bullectomy**

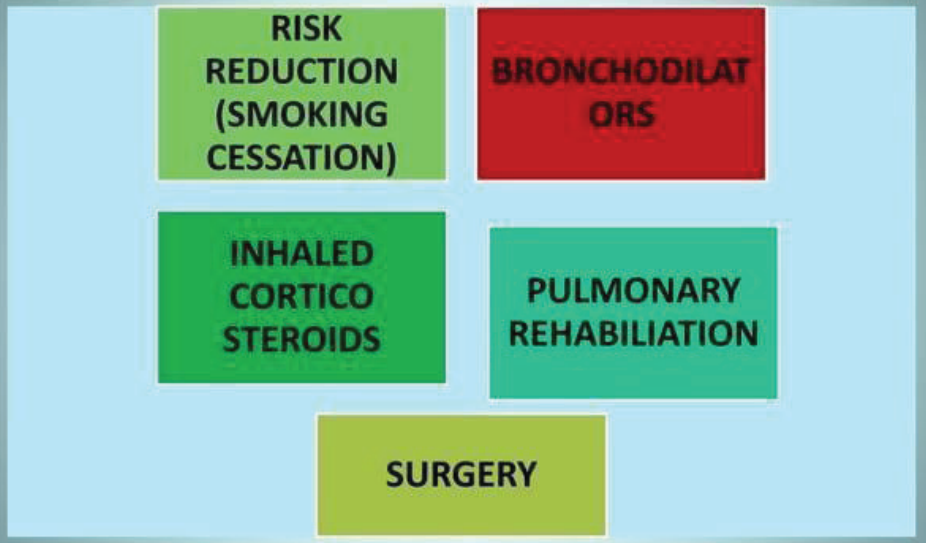
  bullae are enlarged airspaces that do not contribute to ventillation but occupy space in the thorax,these areas may be surgically excised
- **lung volume reduction surgery**
- it involves the removal of a portion of the diseased lung parenchyma.this allows the functional tissue to expand.
- **lung transplantation**

PULMONARY REHABILITATION

- The primary goal of rehabilitation is to restore patients to the highest level of independent function possible and to improve their quality of life.
- A successful rehabilitation program is individualized for each patient, is multidisciplinary, and attends to both the physiologic and emotional needs of the patient.

Components of pulmonary Rehabilitation

The treatment concept of COPD



Nursing Management client with COPD

1. Assess the Clint status ask detail about smoking (pack per year history), occupational exposure history, positive family history of respiratory disease etc.)
2. Note amount, color and consistency of sputum.
3. The nurse should be inspect for use of accessory muscles during respiration and use of abdominal muscles during expirations.
4. The nurse plays a key role in identifying potential candidates for pulmonary rehabilitation and in facilitating and reinforcing the material learned in the rehabilitation program.

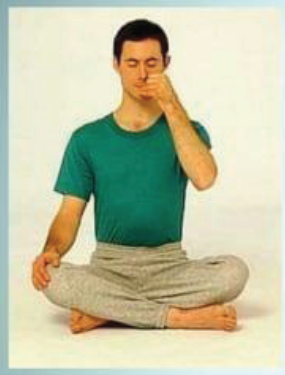
Nursing Management client with COPD

- The nurse should teach to patient and family as well as facilitating specific services for the patient (e.g., respiratory therapy education, physical therapy for exercise and breathing retraining, occupational therapy, medications using e.g. MDI, Nebulization for conserving energy during activities of daily living, and nutritional counseling)

PATIENT EDUCATION

- Patient education is a major component of pulmonary rehabilitation and includes a broad variety of topics.
- Depending on the length and setting of the program, topics may include normal anatomy and physiology of the lung, pathophysiology and changes with COPD, medications and home oxygen therapy, nutrition, respiratory therapy treatments, symptom alleviation, smoking.

Breathing Exercise



Inspiratory muscle training is defined as a course of therapy consisting of a series of breathing exercises that aim to strengthen the bodies' respiratory muscles making it easier for people to breathe. Inspiratory muscle training is normally aimed at people who suffer from asthma, bronchitis, emphysema and COPD

- **Self-Care Activities**.As gas exchange, airway clearance, & the breathing pattern improve, the patient is encouraged to assume increasing participation in self-care activities.

Oxygen Therapy. Oxygen supplied to the home comes in compressed gas, liquid, or concentrator systems. Portable oxygen systems allow the patient to exercise, work, and travel.

Nutritional Therapy. Nutritional assessment and counseling are important aspects in the rehabilitation process for the patient with COPD.

Nursing diagnosis

1. Ineffective breathing pattern related to chronic airflow limitation.
2. Ineffective airway clearance related to bronchoconstriction, increased mucus production, ineffective cough, possible bronchopulmonary infection.
3. Risk for infection related to compromised pulmonary function, retained secretions and compromised defense mechanisms.

Nursing diagnosis

4. Imbalanced nutrition: less than body requirements related to increased work of breasting, presenting dyspnea & drug effects.

5. Deficient knowledge of self-care strategies to be performed at home.

DRUGS ACTING ON RESPIRATORY SYSTEM
EXPECTORANTS & ANTITUSSIVE

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

Expectorants : Introduction

Definition: "Expectorants are oral drugs that are increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing simply they enhance the clearance of mucus.".

Also called as **Mucokinetics.**

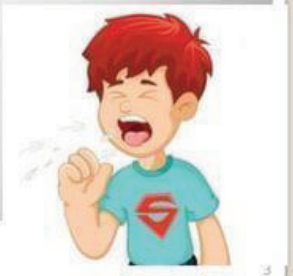
FDA has removed most expectorants from the market in a review of over the-counter drugs; only **guaifenesin** is approved as expectorants in the U.S.

Classification of Expectorants

The drugs used as expectorants are classified as follows;

1. **Bronchial secretion enhancers**:
   Ex- Sodium or Potassium citrate,
   Potassium iodide,
   Guaiphenesin
   (Glyceryl guaiacolate),
   balsum of Tolu & Vasaka,
   Ammonium chloride.

2. **Mucolytics**:
   Ex- Bromhexine,
   Ambroxol,
   Acetyl cysteine,
   Carbocisteine



1. Bronchial secretion enhancers:

Potassium iodide secreted by bronchial glands and can irritate the airway mucosa are considered to increase bronchial secretion by salt action If potassium iodide given externally for prolong use can affect thyroid function and produce iodism.

Guaiphenesin, vasaka, tolu balsum are plant products enhance bronchial secretion and mucociliary function.

Ammonium salts are nauseating—reflexly increase respiratory secretions so US-FDA has stopped marketing of all expectorants, except guaiphenesin.

Now a days steam inhalation and proper hydration may be more helpful in clearing airway mucus

2. Mucolytics:

Several agents can reduce the viscosity of sputum in vitro but clinical studies in chronic bronchitis, asthma, and bronchiectasis not showing much activity.

Mucolytic drugs (ex-derivatives of cysteine) reduce the disulfide bridges that bind glycoproteins to other proteins such as albumin and secretory IgA.

These drugs also act as antioxidants and may therefore reduce airway inflammation.

Only N-acetylcysteine (MUCOMYST, others) is available in the U.S.; carbocysteine, methylcysteine, erdosteine, and bromhexine are available elsewhere.

COPD patients if not treated with inhaled corticosteroids or other medications shows symptomatic relief after treatment with carbocysteine .

But N-acetylcysteine is not currently recommended for COPD management.

Various triggers like oxidative stress, cigarette smoke, inflammatory cytokines, and activated TLRs stimulates the epidermal growth factor receptor (EGFR) which plays a critical role in airway mucus secretion from goblet cells and submucosal Glands.

Small molecule inhibitors of EGFR kinase, such as gefitinib and erlotinib (anticancer drugs) are currently used for treatments of mucus hypersecretion in COPD patients.

Sr No	Drug Name	Use	Dose
1	Bromhexine	A derivative of the alkaloid vasicine obtained from Adhatoda vasica (Vasaka). It is particularly useful if mucus plugs are present. Potent mucolytic and mucokinetic. It depolymerises mucopolysacchrides directly as well as by liberating lysosomal enzymes network of fibres in tenacious sputum is broken	**Adults** 8 mg TDS, **children** 1–5 years 4 mg BD, 5–10 years 4 mg TDS. **Side effects :** Rhinorrhoea and lacrimation, nausea, gastricirritation, hypersensitivity.
2	Ambroxol	Metabolite of bromhexine having similar mucolytic action, uses and side effects.	15–30 mg TDS. AMBRIL, AMBROLITE, AMBRODIL, MUCOLITE
3	Acetylcysteine	It opens disulfide bonds in mucoproteins present in sputum—makes it less viscid, but has to be administered directly into the respiratory tract.	MUCOMIX 200 mg/ml inj in 1,2,5 ml amps; injectable solution may be nebulized/instilled through trachiostomy tube.
4	Carbocisteine	It liquefies viscid sputum in the same way as acetylcysteine. Some patients of chronic bronchitis have been shown to benefit. It may break gastric mucosal barrier; is contraindicated in peptic ulcer patients. Side effects are gastric discomfort and rashes.	MUCODYNE 375 mg cap, 250 mg/5 ml.

Antitussives: Introduction

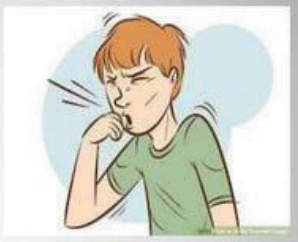
Definition: " These are drugs that act in the CNS to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussal impulses, or both these actions."

Actually cough is a common symptom of airway disease, but its mechanisms are poorly understood. Viral infections of the upper respiratory tract are the most common cause of cough; postviral cough is usually self-limiting and commonly patient-medicated.

Antitussives should be used only for dry nonproductive cough or if cough is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).

Before treatment with antitussives, it is important to identify underlying causal mechanisms that may require therapy.

Classification of Antitussives



1. Opioids: Ex- Codeine,
Ethylmorphine,
Pholcodeine.

2. Nonopioids: Ex- Noscapine,
Dextromethorphan,
Chlophedianol.

3. Antihistamines: Ex- Chlorpheniramine,
Diphenhydramine,
Promethazine.

4. Peripherally acting: Ex- Prenoxdiazine.

5. Adjuvant antitussives/ Bronchodilators:
Ex- Salbutamol,
Terbutalin.

1. Opioids derivatives:

Definition: "Opiates have a central mechanism of action on μ opioid receptors in the medullary cough center, they may have additional peripheral action on cough receptors in the proximal airways."

Codeine and pholcodine are commonly used derivatives in postviral cough but they produces side effects like sedation and constipation.

Morphine and methadone are effective but indicated only for intractable cough associated with bronchial carcinoma.

Sr No	Drug Name	Use	Dose
1	Codeine	An opium alkaloid, less potent than morphine, but is more selective for cough centre. Codeine is standard antitussive; suppresses cough for about 6 hours. The antitussive action is blocked by naloxone indicating that it is exerted through opioid receptors in the brain. **Side effect:** Low Abuse liability and constipation. At higher doses specially in children respiratory depression and drowsiness can occur.	10–30 mg; **children** 2–6 years 2.5–5 mg, 6–12 years 5–10 mg, used as syrup codeine phos. 4–8 ml. CODINE 15
2	Ethylmorphine	It is closely related to codeine which is methylmorphine, and has antitussive, respiratory depressant properties like it, but is believed to be less constipating.	DIONINDON 16 mg tab
3	Pholcodeine	It has practically no analgesic or addicting property, but is similar in efficacy as antitussive to codeine and is longer acting—acts for 12 hours.	dose: 10–15 mg.

2. Nonopioids derivatives:

Definition: " These are the agents used in reducing cough without causing any hallucinations or narcotic action it less abuse potential ."

Sr No	Drug Name	Use	Dose
1.	Noscapine (Narcotine)	An opium alkaloid of the benzoisoquinoline series. It depresses cough but has no narcotic, analgesic or dependence inducing properties. It is nearly equipotent antitussive as codeine, especially useful in spasmodic cough. Side effect: Headache and nausea. It can release histamine produce bronchoconstriction in asthmatics.	Dose: 15–30 mg, children 2–6 years 7.5 mg, 6–12 years 15 mg. COSCOPIN 7 mg/5 ml syrup, COSCOTABS 25 mg tab.

Sr No	Drug Name	Use	Dose
2	Dextro-methorphan	A synthetic central NMDA (N-methyl D-aspartate) receptor antagonist; also antagonize opioid receptors; The d-isomer - antitussive action l-isomer - analgesic. Non-addicting. The antitussive action of dextromethorphan has been rated equivalent to codeine. **Side effect:** Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur.	Dose: 10–20 mg, children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg.
3	Chlophedianol	It is a centrally acting antitussive with slow onset and longer duration of action. **Side effect:** Dryness of mouth, vertigo, irritability.	Dose: 20–40 mg;

3.Antihistamines:

Many H1 antihistamines have been conventionally added to antitussive/ expectorant formulations .

They relieves cough due to their sedative and anticholinergic actions, but lack selectivity for the cough centre.

They have no expectorant property, may even reduce secretions by anticholinergic action. They have been specially promoted for cough in respiratory allergic states, though their lack of efficacy in asthmatic conditions.
Chlorpheniramine (2–5 mg),
Diphenhydramine (15–25 mg) and
Promethazine (15–25 mg; PHENERGAN 5 mg/5 ml elixir)
Second generation antihistamines like fexofenadine, loratadine, etc. are ineffective.

4. Peripherally acting antitussives:

Prenoxdiazine In contrast to other antitussives, it acts peripherally; desensitizes the pulmonary stretch receptors and reduces tussal impulses originating in the lungs.

It is indicated in cough of bronchial origin.

Efficacy, however, is not impressive.

5. Bronchodilators:

Bronchospasm can induce or aggravate cough. Stimulation of pulmonary receptors can trigger both cough and bronchoconstriction, especially in individuals with bronchial hyperreactivity.

Bronchodilators relieve cough in such individuals and improve the effectiveness of cough in clearing secretions by increasing surface velocity of airflow during the act of coughing.

Fixed dose combinations of a centrally acting antitussive with a bronchodilator or with an antihistaminic having high atropinic activitivity.

SOME ANTITUSSIVE-EXPECTORANT COMBINATIONS

Sr. No	Brand Name	Drugs	Dosage form
1	ASTHALIN EXPECTORANT	Salbutamol 2 + guaiphenesin 100 mg /10ml	syrup
2	ASCORIL-C	Codeine 10mg+chlorpheniramine 4 mg/5ml	
3	AXALIN	Ambroxol 15 mg+guaiphenesin 50 mg+salbutamol 1 mg+ menthol 1 mg / 5 ml	
4	BRONCHOSOLVIN	Guaiphenesin 100 mg+ terbutalin 2.5mg + bromhexine 8 mg /10 ml	suspension
5	CADICOFF, GRILINCTUS	Dextromethorphan 5 mg+ chlorpheniramine 2.5 mg+ guaiphenesin 50 mg+ Amm.chloride 60 mg/ 5 ml	
6	BENADRYL	Diphenhydramine 14 mg+ amm. chlor. 138 mg + sod. citrate 57 mg+ menthol 1.1 mg/ 5 ml	syrup
7	BRO-ZEDEX	Bromhexine 8 mg+ guaiphenesin 100 mg+ terbutaline 2.5 mg+ menthol 5 mg /10 ml	syrup

Sr. No	Brand Name	Drugs	Dosage form
8	CADISTIN EXPECTORANT	Chlorpheniramine 2 mg+ glyceryl guaiacolate 80 mg+ amm. chlor. 100 mg+ sod. citrate 44 mg+ menthol 0.8 mg+ terpin hydrate 4 mg+ tolu balsum 6 mg+ Vasaka syrup 0.13 ml.	syrup
9	CHERICOF	Dextromethorphan 10 mg+ chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg/ 5 ml.	Monophasic liquid
10	CLISTIN	Carbinoxamine 4 mg+ amm. chlor. 240 mg+ sod. citrate 240 mg/ 10 ml	Syrup
11	COREX	Chlorpheniramine 4 mg+ codeine phos. 10 mg+ menthol 0.1 mg/ 5 ml	syrup
12	COSCOPIN LINCTUS	Noscapine 7 mg+ chlorpheniramine 2 mg+ citric acid 29 mg+ sod. citrate 3 mg+ amm. chlor. 28 mg/5 ml;	syrup
13	COSOME	Dextromethorphan 10 mg+ phenylpropanolamine 25 mg+ chlorpheniramine 4 mg /10 ml	
14	GRILINCTUS	Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, ammon. chlor. 60 mg/5 ml	

Sr. No	Brand Name	Drugs	Dosage form
15	GRILINCTUS SOFTCAPS:	Dextromethorphan 10 mg+ chlorpheniramine 2 mg+ phenylpropanolamine 12.5 mg.	Softcapsule
16	SOLVIN EXPECTORANT	Bromhexine 4 mg+ pseudoephedrine 30 mg	Tablet
17	SOLVIN EXPECTORANT:	Bromhexine 4 mg+ pseudoephedrine 30 mg	Tablet & Liquid
18	TOSSEX:	Codeine phos 10 mg+ chlorpheniramine 4 mg.+menthol 1.5 mg+sod. citrate 75	Liquid
19	VENTORLIN EXPECTORANT	Salbutamol 2 mg+guaiphenesin 100 mg	syrup
20	ZEET LINCTUS:	Dextromethorphan 10 mg+ guaiphenesin 50 mg+ phenylpropanolamine 25 mg	

Reference:

- Rang H.P. and Dale M.M.: Pharmacology, Churchill Livingstone, Edinbergh.
- Katzung B.G.: Basic and Clinical Pharmacology, Lange Medical Publications, California.
- Craig C.R. and Stitzel R.E.: Modern Pharmacology, Little Brown and Co., Boston.
- Bowman W.C. and Rand M.J.: Textbook of Pharmacology, Blackwell Scientific Publications, Oxford.
- P.N Bennett & M J Brown: Clinical Pharmacology, Churchill Livingstone, Edinburgh.
- Tripathi K.D.: Essentials of Medical Pharmacology, Jaypee Brothers, Medical Publishers, New Delhi.

SSIP

DRUGS ACTING ON RESPIRATORY SYSTEM
NASAL DECONGESTANTS

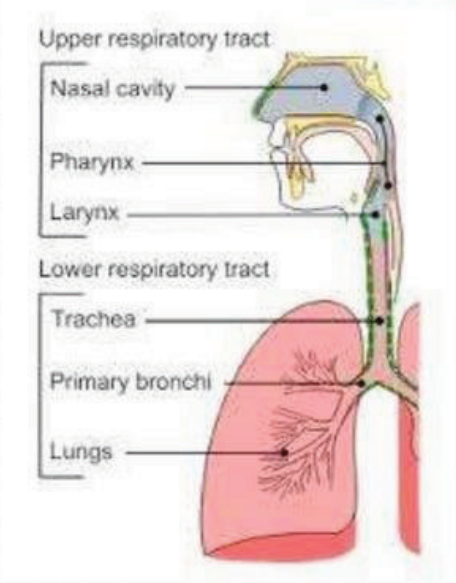
MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

Nasal congestion :-

- Nasal congestion can be caused by anything that irritates or inflames the nasal tissues .
- Infections such as cold , flu or sinusitis and allergies are frequent causes of nasal congestion and runny nose .
- Sometimes a congested and runny nose can be caused by irritants such as tobacco , smoke etc...

Nasal decongestants :-

- Nasal decongestants are pharmaceutical drugs that are used to relieve nasal congestion in the upper respiratory tract .



Mechanism of action :-

The mechanism of nasal decongestants are activation of postjunctional alpha-adrenergic receptors found on precapillary and postcapillary blood vessels of the nasal mucosa.

CLASSIFICATION :-

The active ingredients in most decongestants is either pseudoephedrine or phenylepherine .

a) Adrenalin release agents :-
Ex:- Ephedrine , Levo methamphitamine , phenyl propional amine , pseudoephedrine .

b) Alpha-adrenergic receptor agonist:-
Ex:-Naphazoline , oxymetazoline , phenylephrine.

c) Corticosteroids :-
Ex:- Beclomethasone dipropionate , pregnisolone.

- **Mechanism of action :-**
  Ephedrine , the principle mechanism of action relies on its indirect stimulation of the adrenergic receptor system by increasing the activity of norepinephrine at the postsynaptic alpha and beta receptors .
- Ephedrine stimulates alpha-adrenergic receptors in blood veseels of nasal mucosa , producing vasoconstriction and nasal decongestion .

Pharmacological actions :-

- **Heart :-**
  On heart ephedrine action on beta-adrenergic receptors in the heart produces a positive ionotropic effect .
- **Brain :-**
  Ephedrine activates pathways in human brain that are responsible for weight loss mediated through ß2 receptors .

- **Smooth muscle :-**
  Ephedrine relaxes the smooth muscles of gastro-intestinal tract by stimulating the α1 and ß1 receptors .
- **Blood pressure :-**
  Ephedrine shows biphasic response . If ephedrine at low doses taken by iv and sc routes causes decreasing in BP mediated through ß2 receptors . When ephedrine at high doses increases BP .

PHARMACOKINETICS :-

- Ephedrine is absorbed through orally , iv , im and sc.
- Bioavailability :- 85%
- Metabolism :- In liver by oxidative deamination .
- Onset of action :- IV[seconds] , IM[10min to 20min] , orally [15min to 60min] .
- Duration of action :- IV/IM[60min] , orally[2 to 4hrs].
- Elimination half-life :- 3h to 6 hrs .
- Excretion :- 22% to 99% through urine .

Adverse reactions :-

CNS :- Insomnia , euphoria , dizziness,headache, confusion, nervosness and excitation with nasal solution .

CV:- palpitations, hypertension, tachycardia with nasal solution .

EENT:- Drynose and throat , rebound nasal congestion with excessive use , mucosal irritation with nasal solution .

GI:- Nausea, vomiting, anorexia .

Contraindications :-

- Ephedrine is containdicated to the patients with severe hypertension , cardiac arrhythmias , organic heart disease , coronary artery disease , angina or other cardiac disease .
- Ephedrine is contraindicated in patients with closed-angle glaucoma .

Levomethamphetamine :-

- It is a sympathomimetic vasoconstrictor which is the active ingredient in some over-the-counter nasal decongestants inhalers in the united states .

MOA :-

It temporarily relieves nasal congestion by constricting bloodvessels in the nasal mucosa .

ALPHA-ADRENERGIC RECEPTOR AGONIST:-

- Phenylephrine :-
- Phenylephrine was approved in 1976 for nasal congestion .
- It is a medication primarily used as a decongestant , to dilate the pupil , to increase blood pressure .

- MOA :-

Phenylephrine is an agonist of α1-adrenoceptors.Nasal decongestant action is mediated by activation of α1-adrenoceptors in the arterioles of the nasal mucosa . This causes vasoconstriction, which leads to decreased edema and increased drainage of the sinus cavities .

Pharmacokinetics :-

- Metabolism through liver by oxidative deamination.
- Onset of action very rapid through iv, within 20min by mouth .
- Duration of action :- upto 20min[iv], 4hrs [by mouth] .
- Elimination half-life :-2.1 – 3.4hrs .
- Protein binding :- 95%
- Bioavailability :- 38% through GI tract .

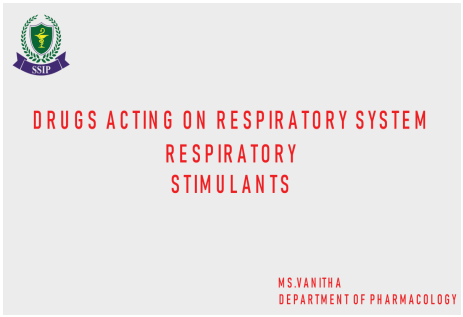
OXYMETAZOLINE :-

- MOA :-

  Oxymetazoline binds to activates α2 adrenergic receptors .upon nasal administration , oxymetazoline constricts the arterioles in the nose decreasing nasal congestion .

  USES :- Oxymetazoline is available over the counter as a nasal decongestant in the form of oxymetazoline hydrochloride in nasal sprays such as a otrivin , afrin , vicks sinex .....

THANK YOU .....



RESPIRATORY STIMULANTS

(ANALEPTICS)

These are drugs which stimulate respiration and can have resuscitative value (property to restore the consciousness) in coma or fainting.

•9 They may also help by stimulating coughing and thus helping the patient to expel secretions.

* At low doses they stimulate respiration, but margin of safety is narrow; at high dose the patient may get convulsions while still in coma.

+ Mechanical support to respiration and other measures to improve circulation are more effective and safe.

➢ **Role of Analeptics:**

Overdose with sedatives or hypnotic untill mechanical ventilation is instituted.

✓ Suffocation on drowning, acute respiratory insuffciency or in post-anaesthetic respiratory depression,
Apnoea in premature infante

✓ Failure to ventilate spontaneously after general anaesthesia.

✓ Idiopathic hypoventilation.

1) Doxapram
2) Prethcamide
3) Niketha mide 4) Almitrine

I) Doxapram :

•9 Shon acting analeptic.

❖Acts by promoting excitation of central neurons.

❖ At low doses it is more selective for the respiratory centre than other analeptics.

❖The respiratory stimulant action is manifested by an increase in tidal volume associated with a slight increase 111 respiratory rate.

❖A pressor response may result following doxapram administration.

❖Provided there is no Impairment of cardiac function, the pressor effect is more marked in hypovolemic than in normovolemic states.

•9 The pressor response is due to the improved cardiac output rather than peripheral vasoconstriction.

❖Following doxapram administration, an increased release of catecholamines has been noted.

MOA:

- Doxapram produces respiratory stimulation mediated through the peripheral carotid chemoreceptors.
- It is thought to stimulate the carotid body by inhibiting certain potassium channels.

•3 Route of administration: I.V./ I,M.

•9 Excreted rapidly,

❖Continuous I.V. infusion of doxapram has been found to abolish episodes of apnoea in the premature infant not responding to Theophylline.

ADR:

- Nausea
- Coughing
- Restlessness
- Disorientation
- Headache
- Fever etc., , ➢ DOSE:
- 40-80 mg I.M.
- 0.5-2 mg/kg/hr I.V. infusion.

➢ USES:

- Acute respiratory failure
- Acute hypercapnia
- COPD

2) Prethcamide :

❖ It is a respiratory stimulant composed of two related drugs, cropropamide and crotethamide. # Briefduration of action,

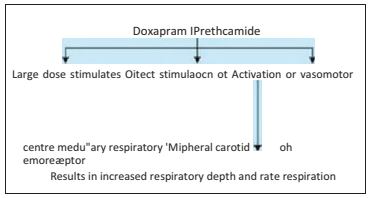
MOA:

+ Acts by stimulation of peripheral chemoreceptors and centrål respiratory centers,

❖ It has pressor effects and may also increase catecholamine release.

➢ ADR:

- Dyspnea
- Muscular and GI effects.



3) Nikethamide :

❖ It is a stimulant which mainly affects the respiratory cycle.

❖ It is known as nicotinie acid diethylamide.

+ Antidotes to barbiturate overdose.

Essentials of Medical Pharmacology by K D Tripathi , 8th edition, Page no:S15.

➢ Pharmacology and Pharmacotherapeutics by R S Satoskar, Nirmala N. Rege, S D Bhandarkar , 24 th edition, Page no: 322 & 593.

➢ Pubchem

Drugbank.

It increase the stimulation of CNS, especially stimulate medulla oblongata respiratory center, carotid body and aortic chemoreceptor and then stimulate respiratory center reflectivity.

A single IN, bolus can maintain 5-10 mins.

➢ ADR .

- Overdose : BPt
- Tachycardia
- Cough
- Vomiting
- Perspiration

Convulsion, ➢ USES :

- Neonatal asphyxia
- C02 intoxication
- Respiratory depression.

4) Almitrine :

It enhances respiration by acting as an agonist of peripheral chemoreceptors located on the carotid bodies,

•9 The drug increases arterial oxygen tension while decreasing arterial carbon dioxide tension in patients with chronic obstructive pulmonary disease.

❖ It may also prove useful in the treatment of nocturnal oxygen desaturation without impairing the quality of sleep.

THANK YOU

DRUGS ACTING ON G.I TRACT
ANTI ULCER AGENTS

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

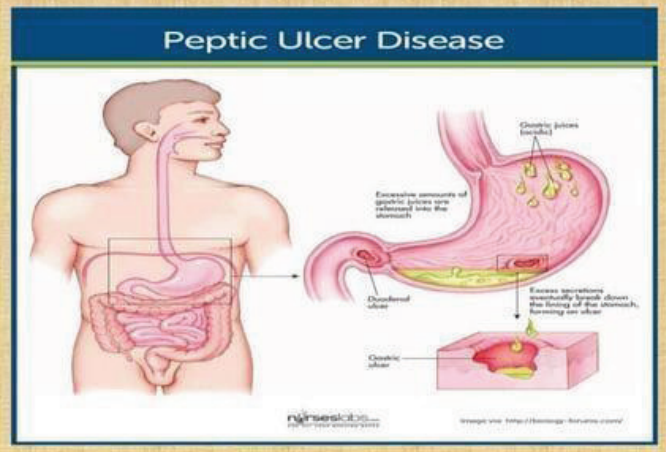
Content

➢ Introduction

- **Peptic ulcers** form when cells on the surface of the lining become inflamed and die.
- Peptic ulcers are sores that develop in the lining of the stomach, lower esophagus, or small intestine.
- They're usually formed as a result of inflammation caused by the bacteria *H. pylori*, as well as from erosion from stomach acids.

- **Antiulcer drugs** are the drug which is used to treat or prevent ulcer of intestine or stomach.
- These drugs act by either inhibiting acid production
- or by killing the microorganism responsible for ulcer.

➢ PHYSIOLOGY



➢ Etiology

- H. pylori
- Drugs such as NSAID'S
- Life style factors
- Severe emotional or physiological stress
- Having family history

➢ Classification Of Antiulcer Agent

1) Reduction of gastric acid secretion

- H2 antihistamines: Cimetidine, ranitidine, famotidine, roxatidine.
- PPI's : Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole
- Anticholinergics: Pirenzepine, propantheline, ox phenonium
- Prostaglandin analogues:- Misoprostol.

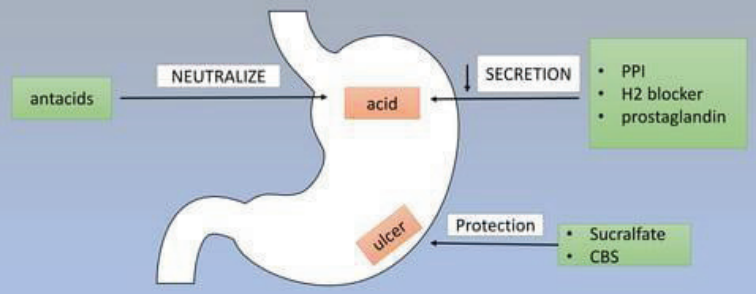
2) Neutralization of gastric acid (Antacids)

- Systemic : Sodium bicarbonate, sodium citrate
- Non-systemic (Local) : Mg hydroxide, Mg trisilicate, Al hydroxide gel, calcium)

3) Ulcer protectives: Sucralfate, CBS (Colloidal Bismuth Sub-citrate)

4) Anti-H. pyloric drugs: Amoxicillin, clarithromycin, metronidazole, tinidazole, tetracycline

Fig: DRUGS USED IN PEPTIC ULCER



A . REDUCE GASTRIC SECRETION

• H2- RECEPTOR BLOCKER

(Cimetidine, Ranitidine, Famotidine, roxatidine)

- MOA:inhibit acid secretion by blocking H2 receptors on the parietal cell
- These agents inhibit gastric acid secretion by competitively blocking the binding of histamine to H2 receptors. decreases gastric acid secretion

- They are taken orally and are well absorbed in the gastrointestinal tract.
- They undergo first-pass metabolism in the liver.
- Oral bioavailability : 50%

- Use:

a) in peptic ulcer
b) Zollinger-Ellison syndrome
c) GERD

- Adverse effects:

- Diarrhoea, dizziness, muscle pain, hypotension, gynaecomastia

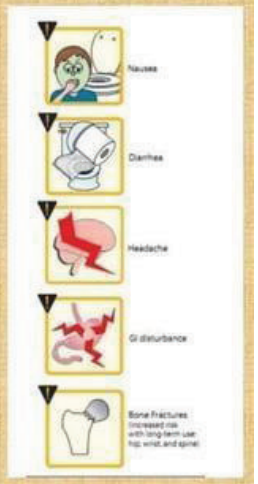
• PROTON PUMP INHIBITOR

(Omeprazole, Rabeprazole, pantoprazole)

- MOA: act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme (H+K+ATPase) system of the gastric parietal cells.(sulfenamide)

- USE: in peptic ulcer, GERD, Zollinger-Ellison syndrome.

- Adverse effects: Nausea, abdominal pain, constipation, flatulence, Subacute myopathy, headaches, and skin rashes.



- Anticholinergic

(pirenzepine, telenzepine)

MOA: Inhibit acetylcholine action on muscarinic receptor-Decreases HCl secretion(M1 receptor blocker)

(Have low efficacy and anticholinergic side effect)

- Prostaglandin analogous

(Misoprostol, Enprostol)

MOA: Increase mucous and bicarbonate secretion, increase blood supply, Decrease HCl secretion

- Contraindications:
- It is contraindicated during pregnancy because it can increase uterine contractility.
- Adverse effects:
- Diarrhea and nausea are the most common adverse effects

B. Neutralization of gastric acid

- (Systemic: sod. Bicarbonate, Sod. Citrate)
- (Non- systemic: Al(OH)3, Mg(OH)2
- MOA: Antacids are weak bases that react with (neutralize) gastric acid to form water and a salt, thereby diminishing gastric acidity.

- They reduce gastric acidity and increase gastric mucosal protection. A single dose of antacid (taken 1 hour after meal) can neutralize the acid for 2 hours.
- Sucralfate
- CBS

- Sodium bicarbonate

-Effective, rapid action onset but short acting . And has some disadvantages.
-Used in acidosis. Contraindicated in patient with CCF and hypertension.

$$NaHCO3 + HCl = Co2 + NaCl$$

- Magnesium hydroxide and aluminum hydroxide

-They react slowly with HC1. They are combined together, because Aluminum causes constipation and Magnesium causes osmotic diarrhea. They can interact with other drugs, inhibiting their absorption.

- Adverse effects.
- Drug interaction.

C. ULCER PROTECTIVE

- (SUCRALFATE, CBS)
- MOA: These compounds, known as cytoprotective compounds, have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.
- Adverse effects: Constipation, dryness of mouth, abdominal discomfort.

D. Anti h. pylori drugs

(Amoxicillin, metronidazole)

- MOA: The antimicrobial agents acts on bacterial cell wall synthesis and bacterial protein synthesis.
- Resistance to metronidazole occurs rapidly but not with amoxicillin.
- Adverse effects: Epigastric pain, Hypersensitivity reactions,

References

- Rang and Dale,Pharmacology, 6th edition, 2007, pg.385 – 390.
- Bertram G.Katzung, Basic & Clinical pharmacology, 11th edition, 2009, pg.1070 – 1076.
- Goodman & Gilman's The Pharmacological Basis of Therapeutics. 5th edition, pg 1008-1010.
- Lippincott's Illustrated Reviews Pharmacology, 4th Edition, pg.329 – 335.
- K.D.Tripati, Essentials of Medical pharmacology, 6th edition,2008, pg.627 – 638.

Thank you

DRUGS ACTING ON G.I TRACT
CONSTIPATION & DIARRHOEA

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

Constipation

- Constipation is a condition in which one may have
- Fewer than three bowel movements a week
- Stools that are hard, dry, or lumpy
- Stools that are difficult or painful to pass
- A feeling that not all stool has passed.

- Unsatisfactory defecation, characterized by infrequent stools and/or difficult stool passage.
- Patients may define constipation as passing hard stools or straining, incomplete or painful defecation.
- **Constipation is a symptom, NOT a disease.**
- Constipation has many causes and may be a sign of undiagnosed disease

Types of Constipation:

1. Primary Constipation: Slow colonic transit time, Pelvic floor/anal sphincter dysfunction

- Secondary Constipation: Endocrine dysfunction (DM, hypothyroid), Metabolic disorder (↑ Ca,↓ K), Mechanical (obstruction, rectocele), Pregnancy, Neurologic disorders (spinal cord injuries)

Risk Factors

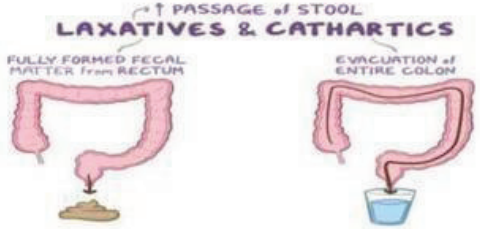
- ↓ ***fiber :***(most common)
- ↓ ***liquid:*** (8 glasses/day is needed for constipated)
- ↓ ***Exercise*** : bedridden, coma
- ***Ignoring urge to defecate***
- ***Disease:*** Hypothyroidism, DM, hypercalcemia, Hypokalemia Stroke, Parkinsonism,
- ***Pregnancy***
- ***Medication therapy:*** Opioid, Aluminum hydroxide, Anti- hypertensives, Muscle Relaxants
- ***Obesity***

Treatment:

- ***High fiber diet.***
- ***Increased fruit intake:*** Apple, Pear, Guava, Papaya etc.
- ***Exercise***
- ***Weight loss.*** (BMI between 19.0-24.9)
- Drugs therapy.

Drugs Therapy (Cathartics)

- These are drugs that promote *evacuation of bowels*. A distinction is sometimes made according to the intensity of action.
- *Laxative or aperient: milder action,* elimination of soft but formed stools.
- *Purgative or cathartic: stronger action* resulting in more fluid evacuation.
- Many drugs in low doses act as laxative and in larger doses as purgative.



Classification of Drugs:

Bulk forming: **Dietary fibre:** Bran, Psyllium , Ispaghula, Methylcellulose

Stool softener: Docusates (DOSS), Liquid paraffin

Stimulant purgatives:

- **Diphenylmethanes:** Phenolphthalein, Bisacodyl
- **Anthraquinones (Emodins):** Senna, Cascara sagrada
- **5-HT4 agonist:** Prucalopride
- **Fixed oil:** Castor oil

Osmotic purgatives:

- **Magnesium salts:** Sulfate, hydroxide
- **Sodium salts:** sulfate, phosphate, Lactulose

Bulk Forming Agents:

- It absorbs water in the intestines, swells, increases water content of faeces—softens it and facilitates colonic transit.
- Osmotically, active products may be formed in the colon by bacterial degradation of pectins, gums, etc. which act to retain water
- Binds with bile and promote emulsification of fats.
- Long term use relieve the symptoms of IBS.

Drawbacks: Large Quantity is needed (30-40gms)

- Action produced after 3-4 days use.
- Does not soften feces already present in colon
- Shouldn't be used on patients with peptic ulcer.

Stool Softeners:(DOSS)

- An anionic detergent
- softens the stools by net water accumulation in the lumen by an action on the intestinal mucosa.
- Emulsifies the colonic contents and increase penetration of water into the faeces
- Mild Laxative
- 100-300 mg/day acts in 1-3 days.

Drawbacks: Bitter

- Cause cramps and abdominal pain
- Long term use may cause hepatotoxicity.
- Cant be given with liq. Paraffin, may cause disruption of mucosa

Stool Softeners:(Liquid Paraffin)

- Viscous liquid
- Mixture of petroleum hydrocarbons
- Taken for 2–3 days, it softens stools and is lubricates hard scybali by coating them.
- *Dose: 15–30 ml/day—oil as such or in emulsified form.*

Drawbacks: very unpleasant to swallow

- While swallowing it may trickle into lungs—cause lipid pneumonia.
- Carries away fat soluble vitamins with it into the stools:

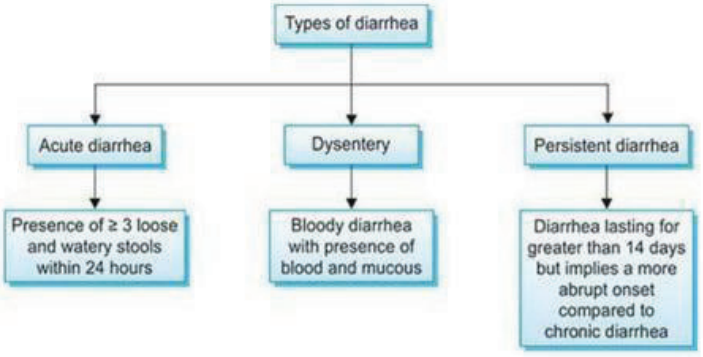
Stimulant Purgatives:

- Bisacodyl (5- 15mg), PTHP (60-130 mg)
- Powerful
- May produce griping
- Act by accumulation of water and electrolytes in the lumen by altering absorptive and secretory activity of the mucosal cell.
- Enhance NO release into the colon
- Larger doses of stimulant purgatives can cause excess purgation resulting in fluid and electrolyte imbalance.
- Hypokalaemia can occur on regular intake.
- contraindicated during pregnancy.

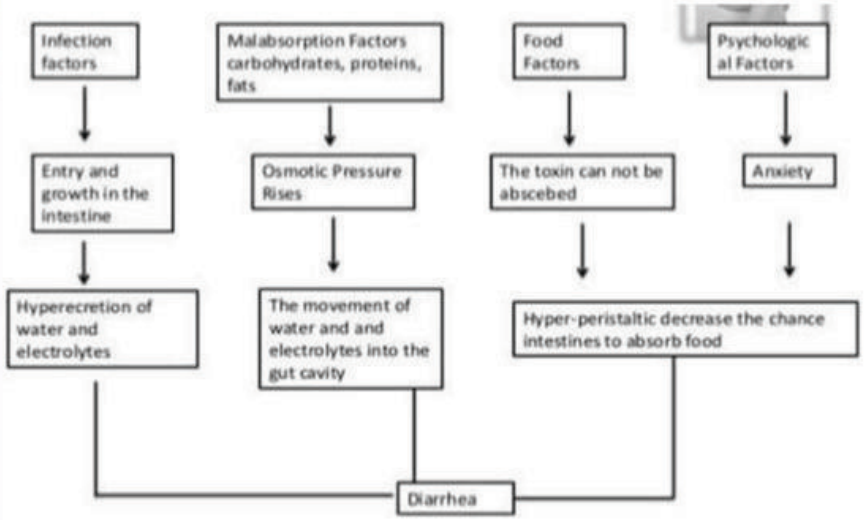
Osmotic Cathartics:

- Solutes that are not absorbed in the intestine retain water osmotically and distend the bowel—increasing peristalsis indirectly.
- Magnesium ions release cholecystokinin which augments motility and secretion, contributing to purgative action.
- Saline purgatives are not used now for the treatment of constipation because they are inconvenient/ unpleasant, produce watery stools and after constipation.
- Should be taken along 150-200ml water

- It is defined by WHO as 3 or more loose or watery stools in a 24 hour period. May be due to:
- Decreased electrolyte and water absorption.
- Increased secretion by intestinal mucosa.
- Increased luminal osmotic load.
- Inflammation of mucosa and exudation into lumen.



Pathophysiology:



Treatment:

- Therapeutic measures may be grouped into:
- Treatment of fluid depletion, shock and acidosis. (Rehydration)
- Maintenance of nutrition: chicken soup, banana, sago, etc. should be given as soon as the patient can eat.
- Drug therapy.
- *Rotavirus is an important pathogen of acute* diarrhoea,

Rehydration

Oral Rehydration

- ORS therapy.
- NaCl : 2.6 g Na+-75 mM, KCl : 1.5 g K+ — 20 mM, Trisod. citrate : 2.9 g Cl^- — 65 mM, Glucose : 13.5 g Citrate — 10 mM, Water : 1 L Glucose — 75 mM (WHO 2002)
- Patients are encouraged to drink ORS at ½–1 hourly intervals

I.V. Therapy

- It is needed only when fluid loss is severe, i.e. > 10% body weight
- is unable to take enough oral fluids due to weakness, vomiting.
- NaCl 85 mM = 5 g, KCl 13 mM = 1 g, $NaHCO_3$ 48 mM = 4 g in 1 ltr water or 5% glucose solution
- oral rehydration can be instituted after the initial volum replacement.

Drugs:

- Specific antimicrobial drugs
- Probiotics
- Drugs for inflammatory bowel disease (IBD) :- Sulfasalazines
- Nonspecific anti diarrhoeal drugs

Ofloxacins

- Flouroquinolone derivative
- Act by inhibiting the bacterial topoisomerase IV and DNA gyrase enzynme.
- In acute diarrhoea & dysentry
- 200mg oral BD
- Travellers' diarrhoea: mostly due to ETEC, *Campylobacter or virus: cotrimoxazole, norfloxacin,* doxycycline reduce the duration of diarrhoea and total fluid needed only in severe cases
- Rifaximin for 3 days 200mg TDS
- Side effects are flatulence, abdominal pain, defecation urgency and headache.

Probiotics

- microbial cell preparations, either live cultures or lyophillised powders
- Intended to restore and maintain healthy gut flora
- lactic acid forming bacteria and yeast. Organisms like- *Lactobacillus sp., Bifidobacterium, Streptococcus faecalis, Enterococcus sp. and the yeast Saccharomyces boulardii.*
- loudly promoted
- Natural curd/yogurt is an abundant source of lactic acid producing organisms, which can serve as probiotic

Non- specific anti- diarrheal drugs: Absorbants and adsorbants

- These are colloidal bulk forming substances like ispaghula, methyl cellulose, carboxy methyl cellulose which absorb water and swell.
- *Adsorbants like kaolin, pectin, attapulgite are believed to* adsorb bacterial toxins in the gut and coat/protect the mucosa, but banned in india due to no proof of efficacy.

Antisecretory drugs

- *Racecadotril*
- prodrug
- Is rapidly converted to *thiorphan, an enkephalinase inhibitor.*
- Racecadotril decreases intestinal hypersecretion, without affecting motility
- It is indicated in the short term treatment of acute secretory diarrhoeas

Antimotility drugs

- *Loperamide*
- Opiate analogue with major peripheral μ opioid and additional weak anticholinergic property.
- constipating agent
- Longer DOA (12 hrs)
- Faecal continence is improved by enhancement of anal sphincter tone

Dose: 4 mg followed by 2 mg after every motion

Drawback: Abdominal cramps and rashes

DRUGS ACTING ON G.I TRACT
APPETITE STIMULANTS& SUPPRESANTS

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

APPETITE STIMULANTS

Appetite stimulants act by increasing food intake in people who have lost weight abnormally or have cachexia (loss of weight due to diseased conditions like cancer, AIDS etc.)

This condition is termed as *Anorexia*.

Anorexia is most commonly seen in the following conditions,

- Emotional upset,Nervousness,Loneliness,Boredom
- Tension,Anxiety,Depression
- Acute and Chronic infections
- Pregnancy
- Hypothyroidism
- Usage of chemotherapeutic agents
- HIV and advanced Cancer

Drugs used as Appetite stimulants;

- Alcohol
- Megestrol
- Dronabinol
- Vitamin B12,zinc
- Dexamethasone
- Cyproheptadine

Alcohol (10%)

- Given in small quantities before meals
- It act primarily by increasing the gastric secretions both reflex and also by stimulating the taste buds.
- Alcohol stands as a major constituent in many appetite stimulants and tonics.
- Repeated ingestion leads to gastritis and diminution in appetite.
- Use of alcohol as an appetite stimulant is limited because of its abuse.

Magestrol

- It is a progesterone derivative.
- Commonly used as an appetite stimulant in people with cancer.
- Weight gain with megestrol is because of water or fat gain but not because of gain lean body mass.
- After prolonged therapy patients become unresponsive to megestrol and develop anorexia.

Dronabinol

- It is an FDA approved tetrahydrocannabinol derivative
- It posses antiemetic properties and serves as an appetite booster.

Dexamethasone

- It is found to be effective as an appetite stimulant. If used as an appetite stimulant, dexamethasone exhibits many side effects such as immunosuppression, steroids induces myopathy, etc.

Vitamin B12,zinc

- Loss of appetite is a symptom of vitamin B12 deficiency,
- Zinc, vitamins are the major ingredients in appetite boosters.

APPETITE SUPPRESSANTS / ANOREXIANTS

- Anorexiants, anorexigenics or Appetite suppressants are dietary supplements or drugs that act primarily by reducing the appetite.
- These are used in the treatment of obesity
- Anorexiants generally act by reducing the food intake.

CLASSIFICATION: centrally acting,

ANOREXIANTS

- Adrenergic agents
  E.g.: Amphetamine
  Mephenteramine
- 5-HT agonists
  E.g.: Fenfluramine,
- Drugs acting on both adrenergic and 5-HT receptors
  E.g.: Sibutramine
- Cannabinoid receptor antagonist
  E.g.: Rimonabant

CLASSIFICATION: Drugs acting on GIT;

ANOREXIANTS

- Bulk anorexiants
  E.g.: Methylcellulose, Dietary fibre.
- Non-absorbable fat substitutes
  E.g.: Olestra.
- Lipase inhibitors
  E.g.: Orlistat

CENTRALLY ACTING ANOREXIANTS:

Adrenergic agents;

This class of drugs act by enhancing the release of dopamine and norepinephrine from adrenergic cells.

Amphetamine

- Amphetamine is also known as Benzedrine.
- Which is an indirectly acting sympathomimetic.
- It acts either by stimulating NE release or blocking its reuptake.
- Amphetamine is known to exhibit anorexiant effect, i.e., body weight decreases as a result of less food intake.
- Amphetamine cannot used in the treatment of obesity due to rapid development of tolerance.

5-HT Agonists;

This class of drugs act by enhancing 5-HT levels in brain, by stimulating their release and reducing reuptake.

Fenfluramine

- Fenfluramine in combination with phenteramine is widely used as an anti-obesity medication. This combination is known as "FEN-PHEN".
- It is found to be effective in the management of exogenous obesity and as an adjunct in the treatment of weight reduction based on caloric restriction.
- Most common adverse effects of fenfluramine includes drowsiness, diarrhoea and dry mouth.
- It is no longer used because of wide profile of unwanted effects which include heart valve disease, pulmonary hypertension and cardiac fibrosis.

Drugs acting on both Adrenergic and 5-HT Receptors;

This class of drugs exhibit their action by inhibiting the reuptake of serotonin and norepinephrine.

Sibutramine

- Sibutramine exerts its action by inhibiting the reuptake of the neurotransmitters like serotonin, norepinephrine and dopamine leading to enhanced levels of the neurotransmitters in the synaptic cleft. Enhanced level of neurotransmitters stimulates satiety centre. Anorexiant effect of sibutramine is due to its serotonergic action.
- It is rapidly metabolized by cytochrome P450 isozyme CYP3A4 to yield secondary (M1) and primary (M2) metabolites which are pharmacologically active in nature.
- Side effects include headache, insomnia, dry mouth, nausea, constipation, tachycardia, rise in BP and rarely arrhythmias.
- It is contraindicated in uncontrolled hypertension, stroke, hepatic failure and obesity of endocrine and psychiatric origin.

Cannabinoid Receptor Antagonists;

This class of drugs exhibit their action by selectively antagonizing cannabinoid (CB1) receptors.

Rimonabant

- It acts by inhibiting lipogenesis and increasing the production of adinopectin, resulting in decreased food intake and consequent weight loss. It also enhances high density lipid (HDL-C) levels and decrease low density lipids (LDL-C).
- It is also found to be effective in improving short term memory.
- Side effects include dizziness, nausea, diarrhoea, upper respiratory tract infections, depression etc.
- The drug is still under FDA consideration.

ANOREXIANT ACTING ON GIT:

Bulk Anorexiant;

This class of drugs act by increasing the bulk in diet.

Methylcellulose

- MC is a non-digestible polysaccharide which swells in the stomach, their by increasing the bulk in the diet. It is used as a low calorie diet.
- It is an important ingredient of many commercial preparations used for the treatment of obesity.
- It is also used in the treatment of constipation and diarrhoea.

Non-Absorbable Fat Substitutes;

Olestra

- It consist of a mixture of sucrose and fatty acid esters which is neither digested nor absorbed from the GIT.
- It enhances bowel function and forms bulky faeces.
- It is recommended as a fat substitute in cooking.
- It is expensive and its long term health effects are yet to be explored.

Lipase Inhibitors;

Orlistat

- It exerts its action by suppressing pancreatic and other lipases thereby preventing the degradation and subsequent absorption of 1/3rd of the dietary fat.
- It also reduces total cholesterol and LDL cholesterol in plasma.
- Most common side effects are abdominal pain and augmented defecation of fatty stools with anal leaking.
- It is contraindicated in chronic diarrhoea.

DRUGS ACTING ON G.I TRACT
CARMINATIVE& DIGESTANTS

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

CARMINATIVES

These are drugs which promote the expulsion of gases from the g.i.t. and

Give a feeling of warmth and comfort in the epigastrium.

- Commonly used drugs are:

Sodium bicarbonate : 0.6—1.5 g
Oil Peppermint : 0.06-0.1 ml
Tincture Cardamom Co. : 1—2 ml
Oil of dil : 0.06--0.2 ml
Tincture ginger : 0.6—1 ml

- Sodium bicarbonate reacts with gastric I-ICI and
- Evolves C02 which rapidly distends stomach,
- Relaxes LES and brings about erructation.
- The others are condiments and spices, contain volatile oil
- Which by their mild irritant action and flavour relax LES and increase g.i.t. motility.
- They give a feeling of warmth and comfort in the abdomen,

Used for: flatulent dyspepsia.

DIGESTANTS

- These are substances intended to promote digestion of food.
- A number of proteolytic, amylolytic and lipolytie enzymes are marketed in combination formulations and are vigorously promoted for dyspeptic symptoms, and as appetite stimulants or health tonics.
- They are occasionally beneficial, only when their elaboration in g.i.t. is deficient.
- Their routine use in tonics and appetite improving mixtures is irrational.

Hydrochloric acid

- It may be used in achlorhydria
- 5—10 ml of dilute HCI (10%) should be further diluted to 100— 200 ml with water and sipped with a straw (to prevent contact with teeth) during meals,

Pepsin

- May be used along with HCI in gastric achylia due to atrophic gastritis, gastric carcinoma, pernicious anaemia, etc.

Papain

- It is a proteolytic enzyme obtained from raw papaya.
- Its efficacy after oral ingestion is doubtful.

Pancreatin

- It is a mixture of pancreatic enzymes obtained from hog and pig pancreas.
- Tt contains amylase, trypsin and lipase
- Indicated in chronic pancreatitis and other exocrine pancreatic deficiency states.
- Fat and nitrogen content of stools may be reduced and diarrhoea/ steatorrhoea may be prevented.
- It has to be used as enteric eoated tablets or capsules

W To protect the enzymes from being themselves digested in stomach by pepsin.

Side effects

- Nausea, diarrhoea and hyperuricaemia are the occasional side effects.

Diastase and Takadiastase

- These are amylolytic enzymes obtained from the fungus Aspergillus oryzae.
- They have been used in pancreatic insufficiency, but efficacy is equivocal.

DRUGS ACTING ON G.I SYSTEM
EMETICS & ANTIEMETICS

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

Emetics

Drugs which evoke vomiting

They are life savers when toxic substances are ingested

Powdered mustard suspension/strong salt solutions used in emergency (act by reflexly irritating stomach) **Drugs are:**

1. **Act on CTZ**: Apomorphine
2. **Act reflexly and on CTZ**: Ipecacuanha

Apomorphine

Semi synthetic derivative of morphine

Acts as a **Dopaminergic agonist on CTZ**

Injected IM/SC (not orally as dose required is high and acts slowly)

Dose :6mg (IM) –induces within 5 min

Has therapeutic effect in parkinsonism (not used due to side effects)

Contraindicated in respiratory and CNS depressants

Emetics Contraindicated in

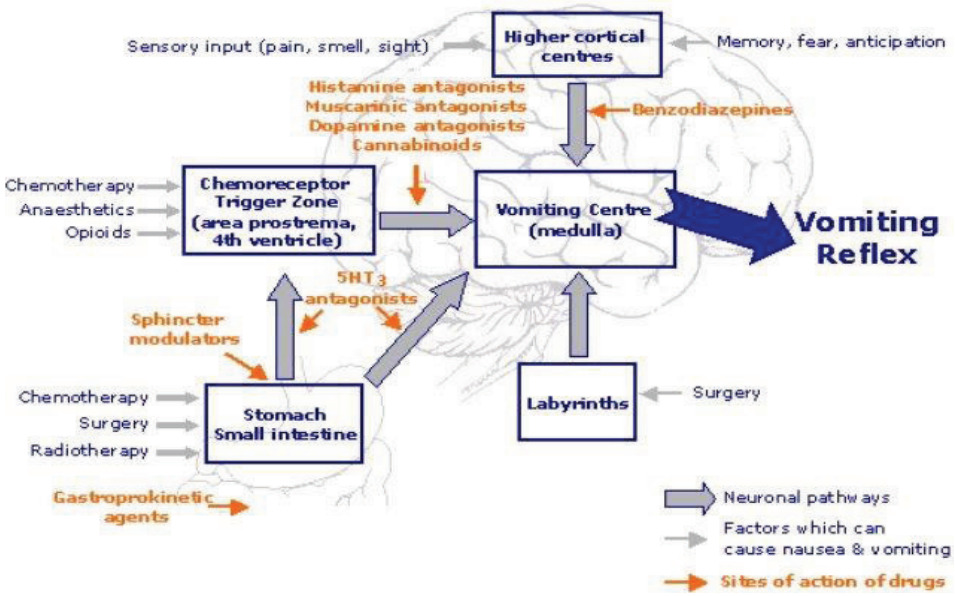
- **Acid or alkali poisoning**: perforation & esophageal injury
- **CNS stimulant poisoning** : convulsions.
- **Kerosene (Petroleum) poisoning**: aspiration Pneumonia.
- **Unconscious patients** :aspiration of vomitus.
- **Morphine or Phenothiazine poisoning**: Ineffective.

ANTI-EMETICS

Emesis is treated mainly by antagonising the receptors

CLASSIFICATION

1. **Anticholinergics :**Hyoscine, Dicyclomine
2. **Antihistaminics:** Promethazine, Diphenhydramine, Dimenhydrinate, Cyclizine, Meclizine
3. **Neuroleptics:** Chlorpromazine, Prochlorperazine , Haloperidol
4. **Prokinetic agents**: Metocloperamide, Domperidone, Cisapride, Mosapride
5. **5HT3 receptor antagonist**: Ondansetrone, Granisetrone, Topisetrone
6. **Adjuvant antiemetics:** Corticosteroids ,Cannabinoids ,Benzodiazepines



Process of vomiting

Stimulation of the CTZ leading to activation of the motor, parasympathetic and sympathetic nervous system

Stimulation of the parasympathetic nervous system leading to increased salivation

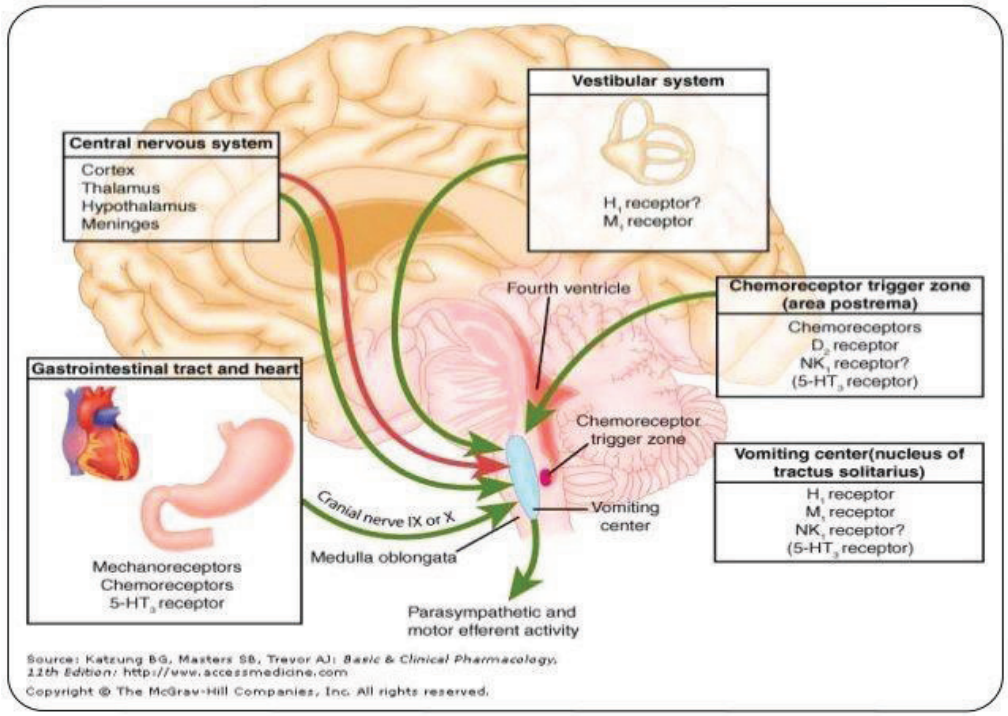
Deep breathing preceding the actual vomiting to protect the lungs from aspiration

Heaving or retching before the actual vomiting

Relaxation of the pyloric sphincter that guards the lower end of the stomach to bring up content from the gut

The pressure within the abdomen rises and the pressure within the chest or thorax is lowered. The abdominal muscles contract to expel the contents of the stomach

Activation of the sympathetic nervous system leads to sweating, palpitation and rapid heart rate



ANTICHOLINERGICS

Act by inhibition of cholinergic transmission from the vestibular nucei to higher centres with in the cerebral cortex.

Hyoscine

Dicyclomine

SE: drowsiness, dry mouth, dilated pupils and blurred vision, decreased sweating, GI motility, GI secretions and difficulty with micturition, may precipitate closed angle glaucoma.

ANTICHOLINERGICS

Hyoscine:

- ✓ Dose: 0.2-0.4 mg Oral/IM
- ✓ Short Duration of Action
- ✓ AE: sedation
- ✓ Used in motion sickness
- ✓ Transdermal patches (applied behind pinna) with mild side effects.

DICYCLOMINE:

- ✓ Dose ;10-20-mg Oral
- ✓ Used for prophylaxis of motion sickness and for morning sickness

ANTIHISTAMINICS

Motion sickness, morning sickness, Post operative N&V
Anticholinergic, Antihistaminic & Sedative action

❖ **Promethazine:**

Afford protection of motion sickness for 4-6 hrs
Sedation, dryness of mouth

❖ **Doxylamine:**

Sedative H1 anti histaminic
Morning sickness (combined with vit B6)
Oral absorption is slow
T1/2 : 10 hrs
SE: drowsines ,drymouth, vertigo, abdominal upset
Dose :10-20 mg

Cyclizine/meclizine:

Less sedative and less anti cholinergic
Meclizine long acting, protects against sea sickness for 24 hrs

Cinnarizine:

Anti vertigo drug
Protective for motion sickness
Inhibits influx of Ca^{+2} from endolymph into the vestibular sensory cells which mediates labyrinthine refluxes.

NEUROLEPTICS

Broad spectrum antiemetics

Acts by blocking D2 receptor in CTZ

Useful for: - drug induced - disease induced - malignancy associated - radiation induced vomiting. Avoided in morning sickness except hyperemesis gravidarum.

SIDE EFFECTS :-

- ✓ Significant degree of sedation
- ✓ Acute muscle dystonia
- ✓ Extrapyramidal effects

NOT EFFECTIVE FOR :-

❖ Motion sickness as vestibular pathway does not involve dopaminergic pathway

Prochlorperazine:

D2 blocking phenothiazine

Labyrinthine supressant, selective anti vertigo and antiemetic action

SE:acute dystonia ,tardive dyskinesia, parkinsonism

DOSE:10-20mg tid

Incontrast

Metoclopramide:

Acts through D2, 5HT4 & 5HT3 receptors

D2 antagonism leads to - increased gastric emptying -enhances LES tone

Central D2 antagonism leads to - extrapyramidal effects - hyperprolactinemia

Metoclopramide crosses BBB ----Movement disorder, fatigue, spasmodic torticollis, occulogyric crises,

Increased prolactin release ----galactorrhea , menstrual irregularities

- **DOSE**:10mg IM/IV Q 6hr Increase the motility of esophagus, stomach, and intestine

Domperidone

D2 antagonist with low antiemetic & prokinetic actions

Poorly crosses BBB (Rare extrapyramidal

effects) Hyperprolactinemia can occur **Pk:**

PROKINETIC DRUGS

- ❖ Increase gastric peristalisis
- ❖ Relaxes pylorus & 1st part of duodenum
- ❖ Hastens gastric emptying
- ❖ Lower esophageal sphincter tone is increased ❖

Gastro esophageal reflux is opposed.

Metoclopramide and Domperidone

D2 receptor antagonist in CTZ.

Peripheral prokinetic activity: Increase the motility of esophagus, stomach, and intestine.

Domperidone does not cross BBB.

- ✓ Absorbed orally
- ✓ Low bioavailability due to first pass metabolism
- ✓ T1/2 : 7.5 hrs
- ✓ Dose :10-40mg

SE: dry mouth, loose stools, head ache,rashes, galactorhoea,cardiac arrythmia (rapid IV)

Used: Chemotherapy induced N& V &drug induced

Cisapride:

Mainly has 5HT4 activity (Acts by releasing Ach), Also has 5HT3 antagonistic effects

No effects on D2 receptors

Restores & facilitate motility throughout GIT including colon therefore used for chronic constipation

Used for:- non-ulcer dyspepsia - impaired gastric emptying - chronic constipation

Serious drug interaction with CYP3A4 (antifungals, macrolide antibiotics, etc.) leads to ventricular arrhythmias & death (Withdrawn in USA & other countries)

MOSAPRIDE : (same as Cisapride) - No arrythmia **Tegaserod:**

Selective 5HT4 partial agonist

Colonic motility, promotes gastric emptying, Intestinal transit

Colonic Cl- & water secretion

5HT3 antagonism

5HT3 antagonism leads to - minor increase in Ach release (Central action appears only in large doses)

5HT4 antagonism leads to increased release of Ach leading to - gastric hurrying - LES tonic effects

Pk:

- ✓ Rapidly absorbed orally
- ✓ Enter brain , crosses placenta, secreted in milk so leads to
- ✓ - Sedation, Dizziness, Parkinsonism, Galactorrhea, Gynecomastia, Loose motions, dystonia & myoclonus in suckling infants

USES :-

Antiemetic

Gastrokinetic - in emergency post vagotomy or diabetes associated gastric stasis to facilitate duodenal intubation

Dyspepsia

Gastroesophageal reflux

5HT3 Antagonists

- ❖ Blocks the depolarising action of serotonin through 5HT3 receptors on vagal afferents in **GIT as well as NTS & CTZ .**
- ❖ **Useful for**
  - ❖ - cytotoxic drug induced
  - ❖ - radiation induced
  - ❖ - inflammation induced vomiting

SE: Well tolerated with minor side effects like headache, constipation or diarrhoea, abdominal discomfort & rash on iv injection.

Ondansetron:

- ✓ Oral BA is 60 -70 %
- ✓ Eliminated in urine
- ✓ T1/2 :3-5 times
- ✓ DOA: 4-12 hrs
- ✓ Week 5HT4 blockade
- ✓ First choice of antiemetic.

Granisetron:

✓ 10-15 times more potent , plasma T1/2 is: 8-12 hrs ✓ Doses:

- Ondansetron 32 mg / day
- Granisetron 10 mg / kg / day
- Dolasetron 1.8 mg / kg / day

ADJUVANT ANTI EMETICS

Cortico steroids:

may act on steroid receptors in area postrema

Dexamethasone (8-20mg)

Augment metachlopramide & ondansetron for cisplatin induced delayed emesis.

Reduces side effects of 10 anti emetics.

Benzodiazepenes:

Week anti emetics (sedation)

Adjuvant to metachlopramide and ondansetron

Diazepam/lorazepam (oral/IV)

Relieve anxiety, anticipatory vomiting and produce amnesia for the unpleasant procedure, supress dystonic SE of metachlopramide

Cannabinoids

- ∆9 tetra hydro cannabinol (∆9THC) active principle of cannabis indica
- Acts at higher centres / VC by activating CB1 receptors.

Dronabinol:

- (synthetic ∆9THC)
- Less hallucinogenic ,More anti emetic

- CINV
- Used as appetite stimulant in AIDS patient

SE: drowsiness ,dizziness, drymouth,mood changes, postural hypotension

Nabilone is a closely related THC analog that has been available in other countries and is now approved for use in the USA

NEWER ANTI EMETIC THERAPY

Neurokinin antagonist:

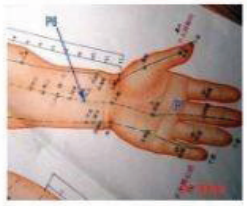
NK1 receptors in area postrema & nucleus tractus solitarus (NTS)

The tachykinin substance P is localized within both the gastrointestinal vagal afferent nerve fibers and in the neural pathways

Adjuvant to dexamethaone & 5HT 3 antagonist oral aprepitant 125 mg

The drug is metabolized by CYP3A4 and may inhibit the metabolism of other drugs.

ALTERNATIVE THERAPY



- Stimulate wrist accupuncture point p6 (PONV)

- Ginger (1g pre operatively)

Motion sickness and pregnancy induced N & V

DRUG TREATMENT IN SELECTED CIRCUMSTANCES

PONV

Prophylactic : Dexamethasone before surgery.

5HT3, H1 antagonist, phenothiazines at end. Opioid – atropine/hyoscine.

CINV

Acute – 5HT3 antagonist(high) , metachlopramide (low)

Delayed -5HT3+dexa ,Meta +dexa

✓ anti cholinergic ,anti histaminic, benzodiazepines, phenothiazines ✓ Severe - meclizine

MOTION SICKNESS: anti cholinergic (hyoscine)

Anticipatory-low doses of benzodiazepine (avoid previous cycles)

PREGNANCY

CHO rich meal

Ginger /acupuncture

Severe –promethazine ,second line prochlorperazine, metachlopramide

USA: vitB6 + doxylamine

Hyperemesis gravidarum: fluid and electrolyte replacement

MIGRAINE: metachlopramide

LABYRINTHITIS:

CHEMOTHERAPHY GENERAL PRINCIPLES OF CHEMOTHERAPHY

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

Chemotherapy

Chemotherapy: chemo + therapy

The use of drug (chemical entity/ substance derived form microorganisms) with selective toxicity against infections/ viruses, bacteria, protozoa, fungi and helminthes is called as chemotherapy.

History of chemotherapy

Antibiotics and Antimicrobials

- ***Antibiotics:*** Antibiotics are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentration.

- ***Antimicrobials:*** (chemotherapeutic agent + Antibiotics)

  Any substance of natural, synthetic or semisynthetic origin which at low concentrations kill or inhibits the growth of microorganisms but causes little or no host damage.

History of chemotherapy

Before Ehrlich's period (till 1900)

- Chaulmoogra oil by Hindus in leprosy
- Cinchona bark for fever
- 'Mouldy curd' by chines on boils
- Mercury by Paracelsus for syphilis

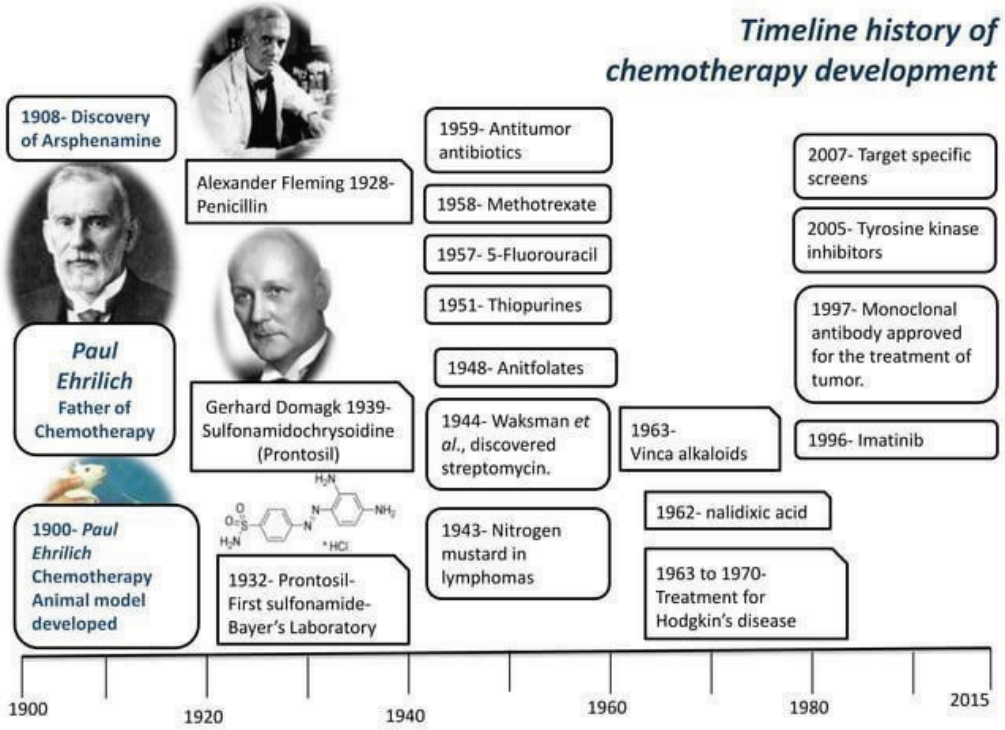
Ehrlich's period (1900 to 1930)

- Organometallic dye for treatment for cane

After Ehrlich's period (1930 to till date)

- discovery of sulfonamide (*Prontosil)*

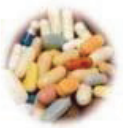
Timeline history of chemotherapy development



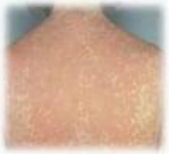
Principles of antimicrobial therapy

Principles of antimicrobial therapy

- Diagnosis: Site of infection, responsible organism, sensitivity of drug
- Decide- chemotherapy is necessary: Acute infection require chemotherapy whilst chronic infections may not. The chronic abscess respond poorly, although chemotherapy cover is essential if surgery is undertaken to avoid a flare-up of infection.
- Select the drug: Specificity (spectrum of activity, antimicrobial activity of drug), pharmacokinetic factors (physiochemical properties of the drug) , patient related factors (allergy, renal disease)



Sulfonamide: gram (+) / (-)
Quinolones: gram (-)
Penicillin-G: gram (+)
Tetracyclines: Broad spectrum
Aminoglycosides: gram (-)
Erythromycin: gram (+)



Principles of antimicrobial therapy

Cont.,

- Frequency and duration of drug administration: Inadequate dose may develop resistance, intermediate dose may not cure infection, optimize dose should be used for therapy.
- Continue therapy: Acute infection treated for 5-10 days. But some of the bacterial infection exceptions to this. E.g.: Typhoid fever, tuberculosis and infective endocarditis (after clinical cure, the therapy is continued to avoid relapse).
- Test for cure: After therapy, symptoms and signs may disappear before pathogen eradicated.
- Prophylactic chemotherapy: To avoid surgical site infections.

Classification of antimicrobials

Classification of antimicrobials

A. Chemical structure
B. Mechanism of action
C. Type of organisms (against which primarily active)
D. Spectrum of activity
E. Type of action (bacteriostatic and bactericidal)
F. Source of antibiotics

A. Chemical structure

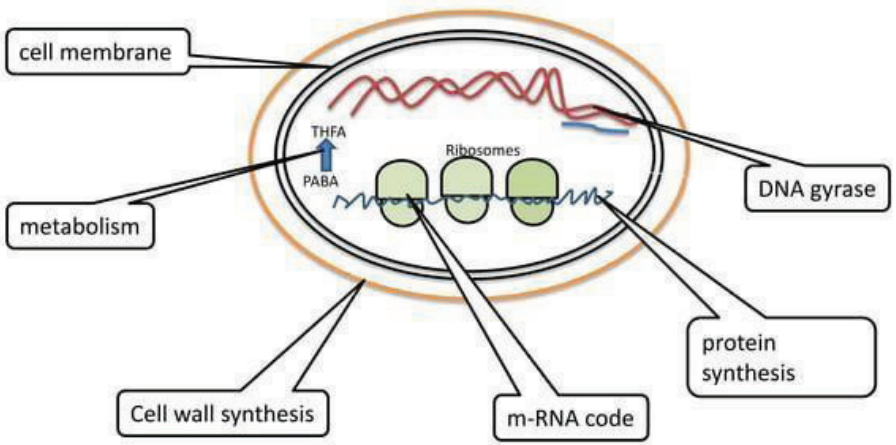
- Sulfonamides and related drugs: Dapsone (DDS), Sulfadiazine, Paraaminosalicylic acid (PAS)
- Diaminopyrimidines: Trimethoprim, Pyrimethamine
- Quinolones: Nalidixic acid, Norfloxacin, Ciprofloxacin
- Beta lactam antibiotics: Penicillins, Cephalosporins
- Tetracyclines: Oxytetracycline, Doxycycline
- Nitrobenzene derivative: Chloramphenicol
- Aminoglycosides: Streptomycin, Gentamycin, Amikacin, Neomycin
- Macrolides antibiotics: Erythromycin, Clanthromycin, Azithromycin

A. Chemical structure

Cont.,

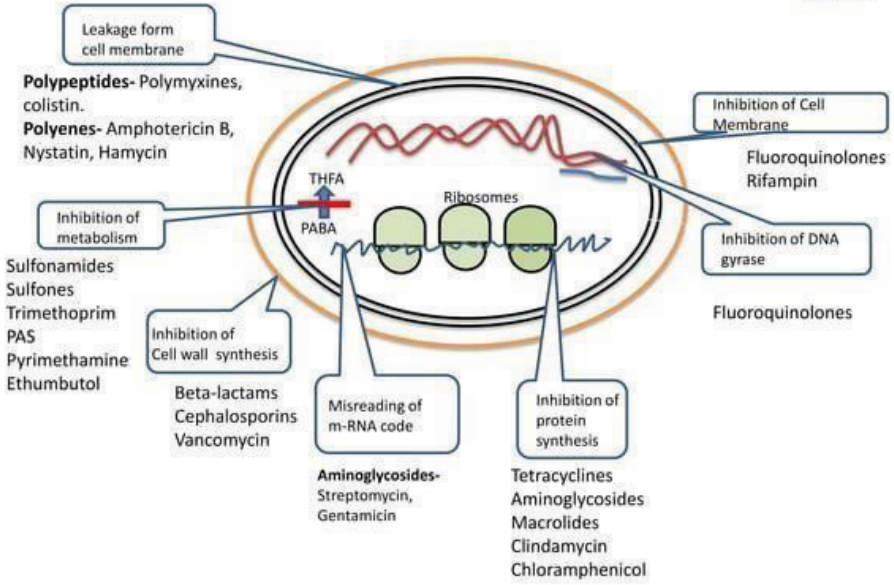
- Lincosamide antibiotics: Clindamycin
- Glycopeptide antibiotics: Vancomycin
- Polypeptide antibiotics: Polymyxin-B, Bacitracin, Tyrothricin
- Nitrofuran derivatives: Nitrofurantoin
- Nitroimidazoles: Metronidazole, Tinidazole
- Nicotinic acid derivatives: Isoniazid, Pyrczinamide, Ethionamide
- Polyene antibiotics: Amphotericin-B, Nystatin, Hamycin
- Azole derivatives: Miconazole, Clotrimazole, Ketoconazole, Fluconazole
- Others: Rifampin, Ethambutol, Griseofulvin

B. Mechanism of action



B. Mechanism of action

Cont.,



C. Type of organisms *(against which primarily active)*

- *Antibacterial:* Penicillins, Aminoglycosides, Erythromycin, etc.
- *Antiviral:* Acyclovir, Amantadine B, Zidovudine, etc.
- *Antifungal:* Griseofulvin, Amphotericin B, Ketoconazole, etc.
- *Antiprotozoal:* Chloroquine, Pyrimethamine, Metronidazole, etc.
- *Anthelminthic:* Mebendazole, Niclosamide, Diethyl carbamazine, etc.

D. Spectrum of activity

Narrow-spectrum
Penicillin G, Streptomycin, Erythromycin

effective against specific type of bacteria ***either*** gram-positive ***or*** gram-negative

Broad-spectrum
Tetracyclines, Chloramphenicol

effective against a wide range of bacteria, ***both*** gram-positive ***and*** gram-negative

D. Type of action (bacteriostatic and bactericidal)

Bacteriostatic:

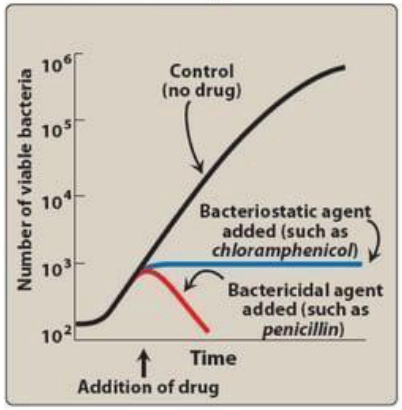
Inhibit the growth of Bacteria.

E.g.: Sulfonamides, Tetracyclines, Chloramphenicol, Erythromycin, Ethambutol

Bactericidal:

Kill the microbes.

E.g.: Penicillins, Aminoglycosides, Polypeptides, Rifampin, Isoniazid, Vancomycin, Ciprofloxacin, Metronidazole, Cotrimoxazole



Note: Some b'static drugs may act b'cidal at high concentration (Sulfonamides, nitrofurantion)

E. Source of antibiotics

- ***Fungi:*** Penicillin, Griseofulvin, Cephalosporin
- ***Bacteria:*** Polymyxin B, Tyrothricin, Colistin, Aztreonam, Bacitracin
- ***Actinomycetes:*** Aminoglycosides, Macrolides, Tetracyclines, Polyenes, Chloramphenicol

Problems with AMAs

- Hypersensitivity reaction
- Drug resistance
- Toxicity
- Drug tolerant
- Superinfection

Toxicity

Local irritancy:

- exerted site of administration. E.g.: Gastric irritation, pain and abscess formation at the site of i.m. inection, thrombophlebitis of injected vein.

Systemic toxicity:

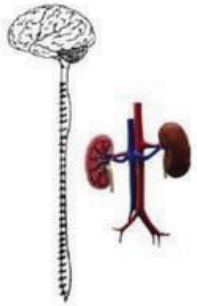
- Dose related organ damage.
  - High therapeutic index agents may not damage host cells, E.g.: penicillin, erythromycin.

Toxicity

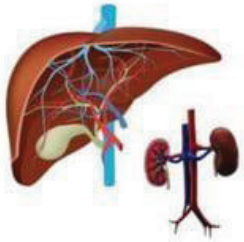
Cont.,

Systemic toxicity:

- The agent which have low therapeutic index exhibits more toxicity. E.g.:,



aminoglycosides
(renal and CNS toxicity)



tetracycline
(liver and renal toxicity)

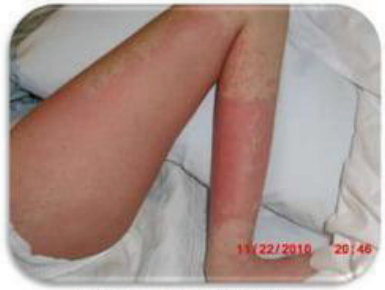
chloramphenicol
(bone marrow depression)

Toxicity

Cont.,

Systemic toxicity:

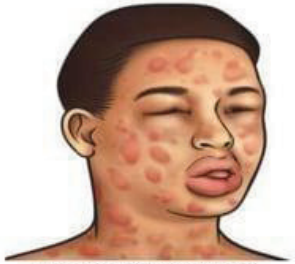
- Very low therapeutic index drug is used when no suitable alternative AMAs available,
- E.g.: Vancomycin
  (hearing loss, kidney damage,
  "red man' syndrome)
- polymyxin B
  (neurological and renal toxicity)



Vancomycin toxicity

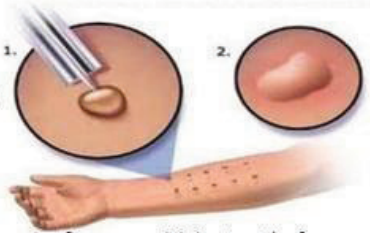
Hypersensitivity reaction

- All AMAs are capable to causing hypersensitive reaction, and this this reactions are unpredictable and unrelated to dose. E.g.: Penicillin induced anaphylactic shock (prick skin testing)



Inj. Penicillin induced
anaphylactic shock

To avoid



Perform sensitivity test before
administering penicillin Inj.

Resistance

- Unresponsiveness of a microorganism to an AMA, and is similar to the phenomenon of drug tolerance.
  - Natural resistance
  - Acquired resistance
- ***Natural resistance:*** Some microbes have resistant to certain AMAs. E.g.: Gram negative bacilli not affected by penicillin G; M. tuberculosis insensitive to tetracyclines.
- ***Acquired resistance:*** Development of resistance by an organism (which was sensitive before) due to the use of AMA over a period of time. E.g.: Staphylococci, tubercle bacilli develop resistance to penicillin (widespread use for >50 yr). Gonococci quickly developed resistant to sulfonamides in 30 yr.

Resistance

Cont.,

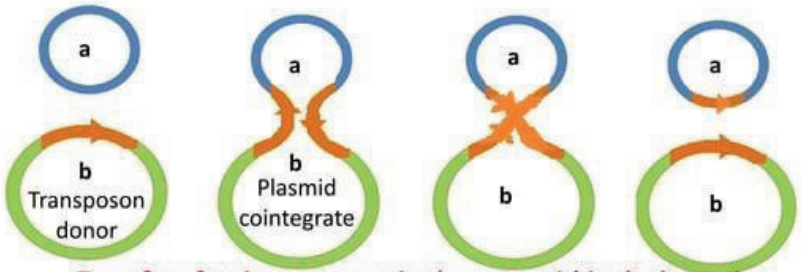
Development of resistance

- Resistance mainly developed by mutation or gene transfer.
- Mutation: Resistance developed by mutation is stable and heritable genetic changes that occurs spontaneously and randomly among microorganism (usually on plasmids).
- Mutation resistance may be single step or multistep.
  - Single gene mutation may confer high degree of resistance. E.g.: enterococci to streptomycin
  - Multistep mutation may modify the more number of gene that will decreases the sensitivity of AMAs to pathogens.

Resistance

Cont.,

- ***Development of resistance***
- Gene transfer (Infectious resistance): From one organism to another organism.
  - Conjugation
  - Transduction
  - Transformation



Transfer of resistance genetic elements within the bacterium

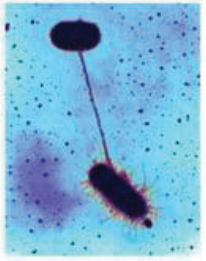
Resistance

Cont.,

Development of resistance

Gene transfer - Conjugation:

- cell-to-cell contact; transfer of chromosomal or extrachromosomal DNA from one bacterium to another through sex pili. The gene carrying the resistance or 'R' factor is transferred only if another "resistance transfer factor" (RTF) is present. This will frequently occurs in gram negative bacilli.
- The nonpathogenic organisms may transfer 'R' factor to pathogenic organisms, which may become wide spread by contamination of food and water.
- The multidrug resistance has occurred by conjugation.
  - Chloramphenicol resistance to typhoid bacilli
  - Penicillin resistance to *Haemophilus*, gonococci
  - Streptomycin resistance to *E.coli*

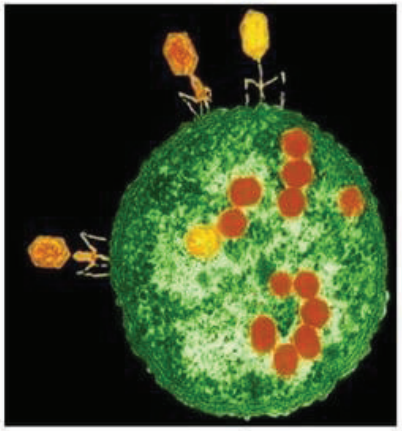


Resistance

Cont.,

Development of resistance Gene transfer- Transduction:

- Transfer resistance gene through bacteriophage (bacterial virus) to another bacteria of same species.
  - E.g.: Transmission of resistance gene between strains of staphylococci and between strains of streptococci.



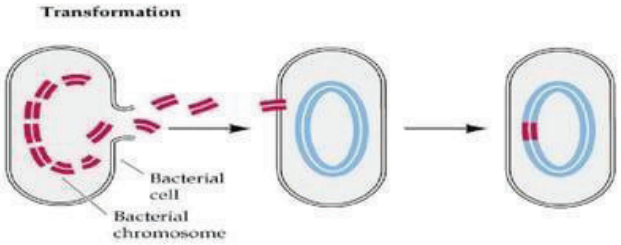
Resistance

Cont.,

Development of resistance

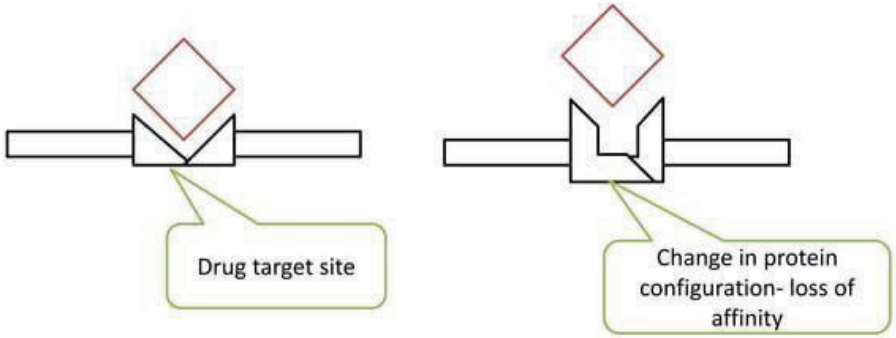
Gene transfer - Transformation:

- It will occur in natural conditions.
- Bacteria taking up naked DNA form its environment and incorporating it into its genome through the normal cross-over mechanism.



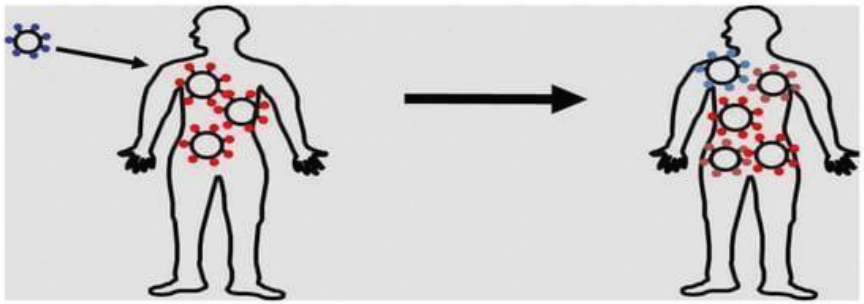
Drug Tolerant

- Loss of affinity of target biomolecule of the microorganism with particular AMAs, E.g.: Penicillin resistance to *Pneumococcal* strain (alteration of penicillin binding proteins)



Superinfection (Suprainfection)

- A new infection occurring in a patient having a preexisting infection. Superinfections are most difficult to treat.



Superinfection

Cont.,

- Development of superinfection associated with the use of broad/ extended-spectrum of antibiotics, such as tetracyclines, chloramphenicol, ampicillin and newer cephalosporins.
- Superinfections are more common when host defence is compromised.
- Superinfections are generally most difficult to treat.
  - bacterial superinfection in viral respiratory disease
  - infection of a chronic hepatitis B carrier with hepatitis D virus
  - Piperacillin-tazobactam may cause superinfection with candida

Superinfection

Cont.,

- Treatment for superinfection
  - *Candida albicans*: Monilial diarrhoea, Candidal vulvovaginitis or vaginal thrush (an infection of the vagina's mucous membranes) treat with nystain or clotrimazole
  - Resistant *Staphylococci*: treat with coxacillin or its congeners
  - *Pseudomonas:* Urinary tract infection, treat with carbenicillin, piperacillin or gentamicin.

- Superinfections minimized by
  - using specific (narrow-spectrum) AMA (whenever possible)
  - avoid using (do not use) antimicrobials to treat self limiting or untreatable (viral) infection
  - avoid prolong antimicrobial therapy.

Choice of an antimicrobial agents

Patient related factors

Drug factors

Organism-related considerations

Choice of an antimicrobial agents

Patient related factors:

- Patient age (chloramphenicol produce gray baby syndrome in newborn; Tetracyclines deposition in teeth and bone-below the age of 6 years)
- Renal and hepatic function (aminoglycoside, vancomycin-renal failure; erythromycin, tetracycline- liver failure)
- Drug allergy (History of known AMAs allergy should be obtained) .
  - Syphilis patient allergic to penicillin – drug of choice is tetracycline
  - Fluoroquinolones cause erythema multiforme
- Impaired host defence

Choice of an antimicrobial agents

Cont.,

Drug factor:

- Pregnancy
  - All AMAs should be avoided in the pregnant
  - many cephalosporins and erythromycin are safe, while safety data on most others is not available.

- Genetic factors
  - Primaquine, sulfonamide fluoroquinolones likely to produce haemolysis in G-6-PD deficient patient)

Choice of an antimicrobial agents

Cont.,

Organism-related considerations:

- A clinical diagnosis should first be made, and the choice of the AMAs selected
- Clinical diagnosis itself directs choice of the AMA
- Choice to be based on bacteriological examination (Bacteriological sensitivity testing)

Choice of an antimicrobial agents

Cont.,

Drug factor:

- Spectrum of activity (Narrow/ broad spectrum)
- Type of activity
- Sensitivity o f the organism (MIC)
- Relative toxicity
- Pharmacokinetic profile
- Route of administration
- Cost

Combined use of antimicrobials

Combined use of antimicrobials

- To achieve synergism, Rifampin+ isoniazid for tuberculosis
- To reduce severity or incidence of adverse effects, Amphotericin B + rifampin (rifampin enhance the antifungal activity of amphotericin B)
- To prevent resistance (Concomitant administration of rifampin and ciprofloxacin prevents *Staph. aureus* resistance ciprofloxacin)
- To broaden the spectrum of antimicrobial action (cotrimoxazole: Trimethoprim/sulfamethoxazole)

Prophylactic use of antimicrobials

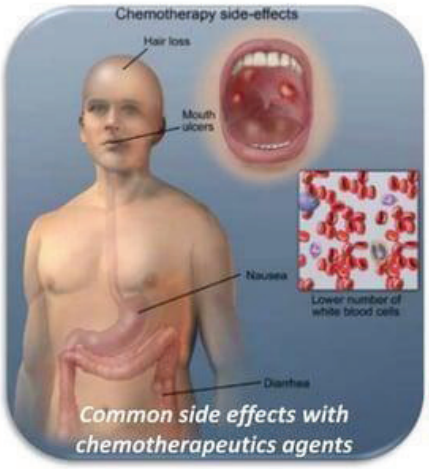
Prophylactic use of antimicrobials

- Prophylaxis against specific organisms (Cholera: tetracycline prophylaxis; Malaria: for travelers to endemic area may take chloroquine/ mefloquine)
- Prevention of infection in high risk situations
- Prophylaxis of surgical site infection
- Prophylaxis against specific organisms
- Prevention of infection in high risk situations
- Prophylaxis of surgical site infection

Failure of antimicrobial therapy

Failure of antimicrobial therapy

- Improper selection of AMAs, dose, route or duration of treatment.
- Treatment begun too late
- Failure to take necessary adjuvant measures
- Poor host defence
- Trying to treat untreatable (viral) infections
- Presence of dormant or altered organisms which later give risk to a relapse



Thank U

CHEMOTHERAPHY SULPHONAMIDES& COTRIMOXAZOLE

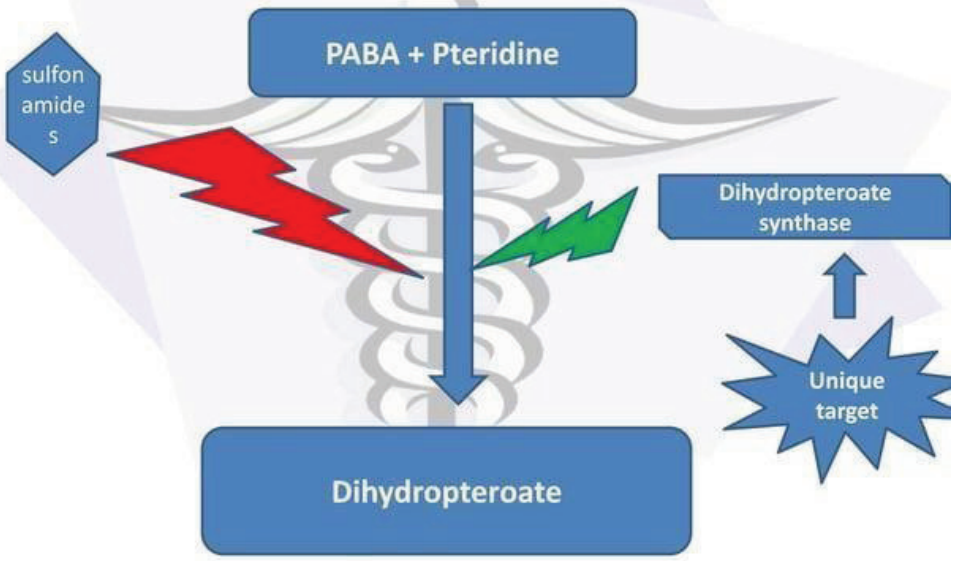
MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

INTRODUCTION

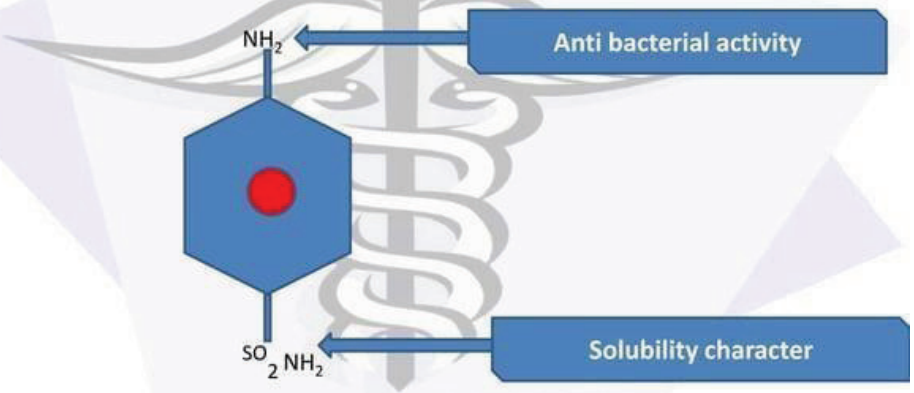
- These are a class of anti- biotics which acts by inhibition/ interrupting the synthesis of nucleic acids
- Although they interfere in the bio-synthesis of nucleic acids they are not genotoxic due to it`s specificity of target

Prontosil rubrum → Sulphanilamide

Mechanism of action



Chemical properties



CLASIFICATION

Based upon duration of action:-

- Short acting (Sulfadiazine)
- Intermediate acting (Sulfamethaxozole)
- Long acting (Sulfamethopyrazine)

Based on chemical properties:-

- Sulfanilamide derivatives (Sulfadiazine)
- Sulfones (DAPSONE)
- Miscellaneous (Sulfacetamide)

Pharmacokinetics

Absorption:-

- ✓ Better absorption orally and also taken through IV route

Distribution:-

- ✓ Large volume of distribution
- ✓ Can cross all barriers
- ✓ Highly protein bound → Phenytoin toxicity

Metabolism:-

- ✓ Metabolism in liver by N-Acetyl trasferase enzyme

Excretion:-

- ✓ Through kidney by urine

Resistance

- ➢ Alterations in the DHPS enzyme & PABA binding site
- ➢ ⬆ Production of PABA by Bacterial strains
- ➢ ⬇ Cell membrane permeability of Sulfonamides

Anti microbial spectrum

- G-ve entero bactor sps affect intestine
- Sulfadiazine used as *Silver ointment used to treat infection of open wound & burns
- Sulfasalazine is not absorbed orally due to this used as suppositories

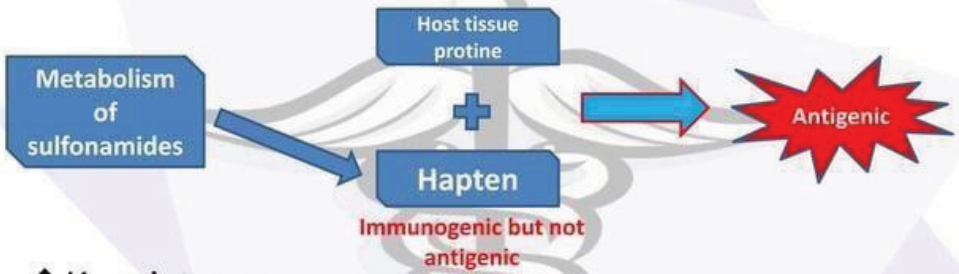
- Genrally given in combination therapy

Pyrimithamine + Trimethoprim → Protozoal infection

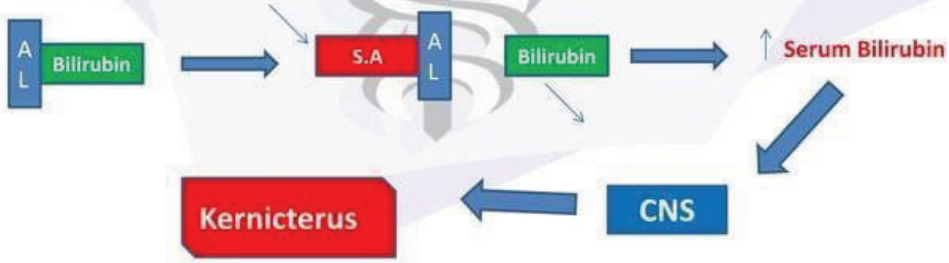
Sulfamethaxozole + Trimethoprim → Bacterial infection

Adverse effects

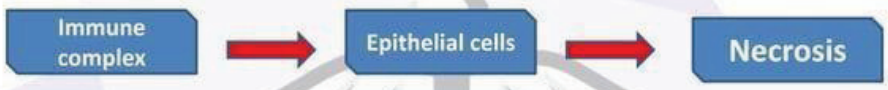
❖ Hypersensitivity reactions



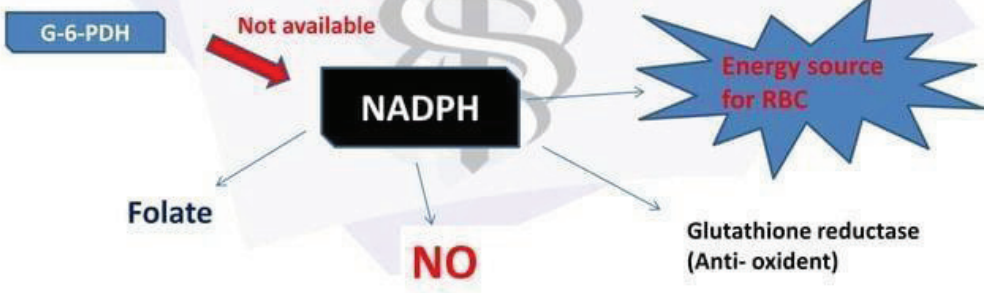
❖Kernicterus



❖Steven Jonson syndrome (separation of epidermal layers)



❖Non immune haemolytic anaemia in G-6-PDH deficiency patients



Cotrimoxazole

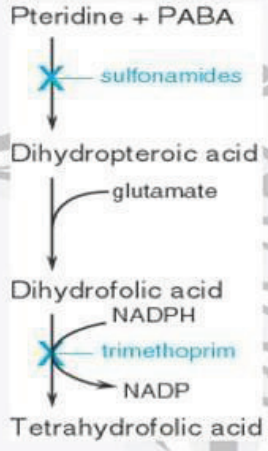
[TRIMETHOPRIM-SULFAMETHOXAZOLE]

- **Introduction**
- **Sulfamethoxazole is a close congener of sulfisoxazole**
- **A pyrimidine inhibitor of dihydrofolate reductase, it is an antibacterial related to PYRIMETHAMINE**
- **Trimethoprim in combination with sulfamethoxazole constitutes an important advance in the development of clinically effective antimicrobial agents**
- **Popularly this combination is various names such as cotrimoxazole , Bactrim , Septran**

Composition

- **Cotrimoxazole is an combination of trimethoprim and sulphamethoxazole in the ratio of 1:5**
- **The reason for selecting these drugs is they have an equal $t_{1/2}$ of approximately 10 hours**
- **Their mechanism of action help in sequential blockade in the pathway of an obligate enzymatic reaction in bacteria**

Mechanism of action



Steps in folate metabolism blocked by sulfonamides and trimethoprim

Antibacterial Spectrum and Efficacy

- Antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole
- Resistance can develop easily when the individual drugs are used alone
- A synergistic interaction between the components of the preparation is apparent even when microorganisms are resistant to sulfonamide with or without moderate resistance to trimethoprim activity.

- However, a maximal degree of synergism occurs when microorganisms are sensitive to both components.
- The activity of trimethoprim-sulfamethoxazole *in vitro* depends on the medium in which it is determined;
- *e.g.,* low concentrations of thymidine almost completely abolish the antibacterial

Spectrum

- **G + VE**
- *S. pneumoniae* [susceptible, there has been a disturbing increase in resistance]
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *S. pyogenes*
- S. *viridans*
- MRSA

- **G –VE**
- *E. coli*
- *Proteus mirabilis*
- *Proteus morganii*
- *Proteus rettgeri*
- *Enterobacter* spp
- *Salmonella*
- *Shigella*
- *Pseudomonas pseudomallei*
- *Serratia*
- *Klebsiella* spp.
- *Brucella abortus*
- *Pasteurella haemolytica*
- *Yersinia pseudotuberculosis*
- *Yersinia enterocolitica*

Bacterial Resistance

- Resistance often is due to the acquisition of a plasmid that codes for an altered dihydrofolate reductase

Pharmacokinetics

- **Absorption** ; Orally and intravenously well absorbed sulfamethoxazole and trimethoprim are closely but not perfectly matched to achieve a constant ratio of 20:1 in their concentrations in blood and tissues.
- The ratio in blood is often greater than 20:1, and that in tissues is frequently less.
- After a single oral dose of the combined preparation, trimethoprim is absorbed more rapidly than sulfamethoxazole.
- The concurrent administration of the drugs appears to slow the absorption of sulfamethoxazole.
- Peak blood concentrations of trimethoprim usually occur by 2 hours in most patients, whereas peak concentrations of sulfamethoxazole occur by 4 hours after a single oral dose.
- The half-lives of trimethoprim and sulfamethoxazole are approximately 11 and 10 hours, respectively

Pharmacokinetics

- **Distribution** ; Distributed well in all body fluids Trimethoprim is distributed and concentrated rapidly in tissues, and about 40% is bound to plasma protein in the presence of sulfamethoxazole.
- The volume of distribution of trimethoprim is almost nine times that of sulfamethoxazole.
- The drug readily enters cerebrospinal fluid and sputum, About 65% of sulfamethoxazole is bound to plasma protein
- **Metabolism** ; By liver
- **Execration** ; About 60% of administered trimethoprim and from 25% to 50% of administered sulfamethoxazole are excreted in the urine in 24 hours

Adverse reactions

- **Similar to that of sulphonamides**

Therapeutic uses

- **Uncomplicated lower urinary tract infections**
- ***Bacterial Respiratory Tract Infections***
- ***Infection by Pneumocystis jiroveci***
- ***In G-VE rods infection's***
- ***Gastrointestinal Infections***
- ***MRSA infections –skin and soft tissue infections***

Contraindications'

- Contraindicated to patients with hypersensitivity
- Sever renal or hepatic insufficiency
- Infants less than 4 weeks
- Megaloblastic anemia pregnancy and lactating mother's

Available doses

- BACTRIM -TAB [S-400mg T-80 mg] APHL
  -TAB [S-100mg T-20mg]
  -TAB [S-200mg T-40mg]

- SEPTRAN -TAB [S-400mg T-80 mg] GSK
  -TAB [S-100mg T-20mg]
  -TAB [S-200mg T-40mg]

SSIP

CHEMOTHERAPHY
ANTI BIOTICS

MS.VANITHA
DEPARTMENT OF PHARMACOLOGY

What is an antibiotic?

"Antibiotic" is from antibiosis, meaning against life.

Substances derived from a microorganism or produced synthetically (Sulfonamides & Quinolones) to kill or suppress the growth of other microorganisms.

Classification of Antibiotics

Antibiotics are classified by several ways:

- On the basis of mechanism of action
- On the basis of spectrum of activity
- On the basis of mode of action

Mechanism of action of antimicrobial agents

1. Inhibition of cell wall synthesis:
- Penicillins, Cephalosporins, Bacitracin & Vancomycin

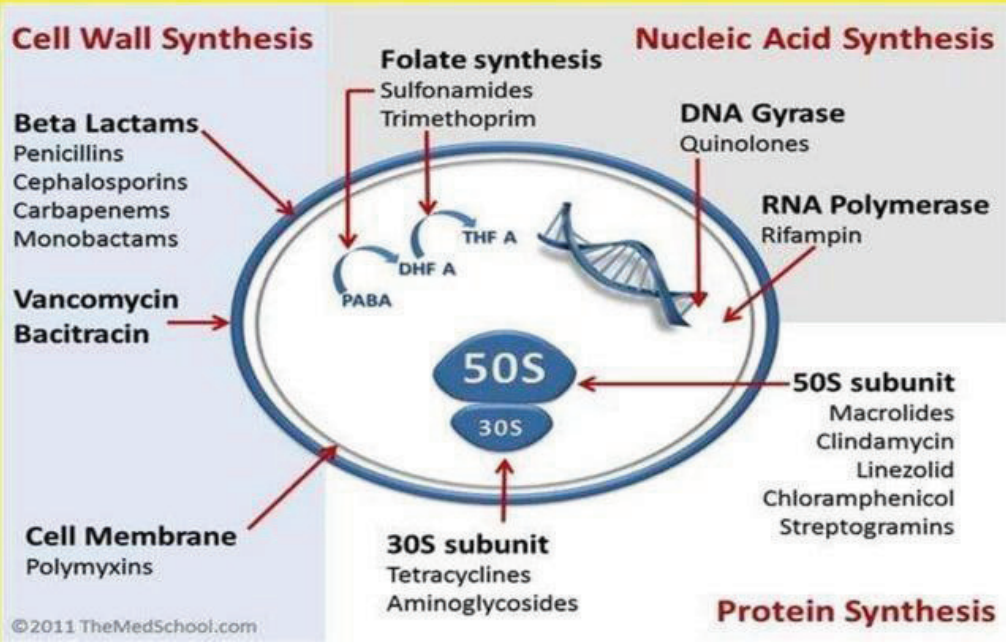
2. Inhibition of functions of cellular membrane:
- Polymyxins

3. Inhibition of protein synthesis:
- Chloramphenicol, Macrolides & Clindamycin
- Tetracyclines & Aminoglycosides

4. Inhibition of nucleic acid synthesis:
- Quinolones
- Rifampin

5. Inhibition of folic acid synthesis:
- Sulfonamides & trimethoprim

On the basis of mechanism of action



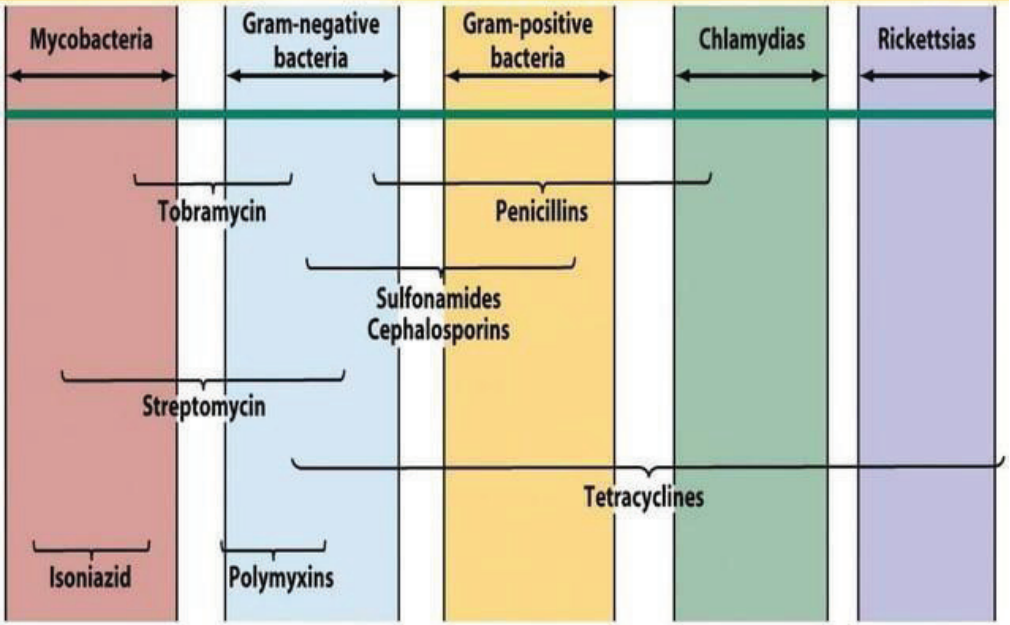
Antimicrobial Spectrum

Antimicrobial spectrum: the scope that a drug kills or suppresses the growth of microorganisms.

Narrow-spectrum: The drugs that only act on one kind or one strain of bacteria.(Isoniazide)

Broad-spectrum: The drugs that have a wide antimicrobial scope.(Tetracycline & Chloramphenicol)

On the basis of spectrum of activity



On the basis of mode of action

Bacteriostatic antibiotics:

- Tetracycline
- Chloramphenicol
- Erythromycin
- Lincomycin

Bacteriocidal antibiotics:

- Cephalosporin
- Penicillin
- Erythromycin
- Aminoglycosides
- Cotrimoxazole

Misuse of Antibiotics

Antibiotic misuse, sometimes called antibiotic abuse or antibiotic overuse

The misuse or overuse of antibiotics, may produce serious effects on health.

It is a contributing factor to the creation of multidrug-resistant bacteria, informally called "super bugs".

Antibiotic Resistances and Cross Resistances

Antibiotic resistance is the phenomenon that susceptibility of pathogenic microorganisms to antibiotic becomes lower or even loses after the microorganisms contact with antibiotic many times.

When the bacteria show resistance to one antibiotic, they are also resistant to some other antibiotics. This phenomenon is called cross antibiotic resistance.

Mechanisms of Antibiotic Resistance

1. Alteration of the target site of the antibiotic

- One of the most problematic antibiotic resistances worldwide, methicillin resistance among Staphylococcus aureus

2. Enzyme inactivation of the antibiotic

- β-lactam antibiotics (Penicillins & Cephalosporins) can be inactivated by β-lactamases.

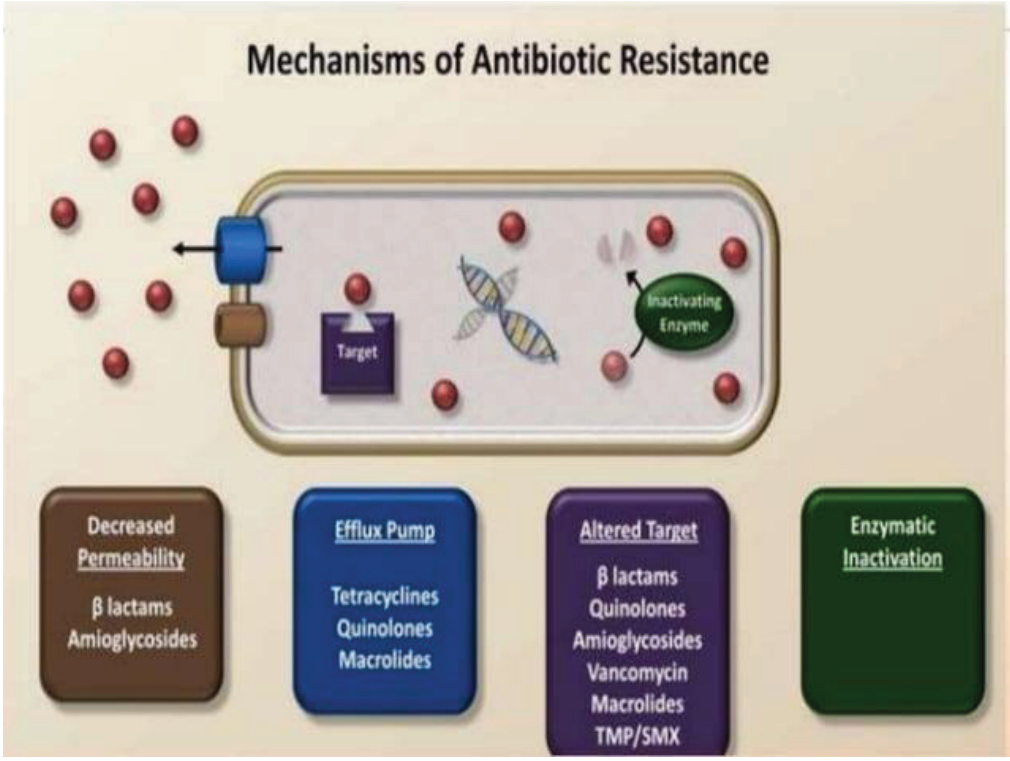
Mechanisms of Antibiotic Resistance Cont.

3. Active transport of the antibiotic out of the bacterial cell

- Active transport of the antibiotic out of the bacterial cell (efflux pumps) as removal of some antibiotics e.g. Tetracyclines, Macrolides & Quinolones

4. Decreased permeability of the bacterial cell wall to the antibiotic

- Alteration in the porin proteins that form channels in the cell membrane e.g. Resistance of Pseudomonas aeruginosa to a variety of Penicillins & Cephalosporins



General Principles of Antimicrobial Therapy

- Identification of the infecting organism should precede antimicrobial therapy when possible.
- The pathogenic microorganism susceptibility to antimicrobial agents should be determined, if a suitable test exists.
- Factors that influence the choice of an antimicrobial agent or its dosage for a patient include the age, renal & hepatic function, pregnancy status and the site of infection, etc.

Selection of Antimicrobial Agent

- Empiric therapy - prior to identification of Organism - critically ill patients
- Organism's susceptibility to the antibiotic
- Patient factors - immune system, renal/hepatic function
- Effect of site of infection on therapy - blood brain barrier
- Safety of the agent
- Cost of therapy

Ideal Antimicrobial Agent

- Have highly selective toxicity to the pathogenic microorganisms in host body
- Have no or less toxicity to the host
- Low propensity for development of resistance
- Not induce hypersensitive reactions in the host
- Have rapid and extensive tissue distribution
- Be free of interactions with other drugs
- Be relatively inexpensive

Complications of Antibiotic Therapy

- Resistance due to inappropriate use of antibiotics
- Hypersensitivity (Penicillin)
- Direct toxicity (Aminoglycosides = ototoxicity)
- Super infections (broad spectrum antimicrobials cause alteration of the normal flora; often difficult to treat)

Antimicrobial Combination

Results of Combination Therapy:

- Additive (indifferent) effect: the activity of two drugs in combination is equal to the sum (or a partial sum) of their independent activity when studied separately.
- Synergistic effect: the activity of two drugs in combination is greater to the sum of their independent activity when studied separately.
- Antagonistic effect: the activity of two drugs in combination is less to the sum (or a partial sum) of their independent activity when studied separately.

Indications for the Clinical Use of Antimicrobial Combinations

- Prevention of the emergence of resistant organisms
- Polymicrobial infection
- Initial therapy
- Decreased toxicity
- Synergism

Prevention of the Emergence of Resistant Organisms

- Decreased resistant mycobacterium tuberculosis with combination
- Reduction of β-lactamase induction with combination β-lactam agents and Aminoglycosides

Polymicrobial Infection

- Intra-abdominal infection
- Pelvic infection
- Mixed aerobic and anaerobic organism

Initial Therapy

- Neutropenic patients
- In patients where the nature of infection is not clear yet

Decreased Toxicity

- Decrease the toxic drug required for treatment and thus reduce the dose related toxicity

Synergism

Enhanced Uptake of Aminoglycosides when Combined with β-lactam agents

- Treatment of enterococcal endocarditis: ampicillin & gentamicin
- Viridans streptococcal endocarditis: penicillin & gentamicin
- Staphylococcal bacteremia: vancomycin & gentamicin
- Treatment of pseudomonas infections: β-lactam agent & Aminoglycosides

Inhibition of Sequential Steps

- Sulfonamide with trimethoprim
- Treatment and prevention of chronic urinary tract infection, typhoid fever, shigellosis caused by organisms resistant to ampicillin

Inhibition of enzymatic activation

Disadvantages of the Inappropriate Use of Antimicrobial Combination

- Antagonism
- Increased cost
- Adverse effects
- Super infections (alteration of the normal flora; often difficult to treat)

Classes of Antibiotics

The main classes of antibiotics are:

- Beta-Lactams
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams
- Macrolides & Ketolides
- Aminoglycosides
- Fluoroquinolones
- Tetracyclines, Amphenicols

Penicillins

- The penicillins are the oldest class of antibiotics. Penicillins have a common chemical structure which they share with the Cephalosporins.
- Penicillins are generally bactericidal, inhibiting formation of the cell wall. Penicillins are used to treat skin infections, dental infections, ear infections, respiratory tract infections, urinary tract infections, gonorrhea.

Types of penicillins

- ***The natural penicillins***
  Penicillin G
- ***Penicillinase-resistant penicillins***
  Methicillin & Oxacillin
- ***Aminopenicillins***
  Ampicillin & Amoxicillin

Penicillins side effects

- Diarrhea, nausea, vomiting, and upset stomach
- In rare cases Penicillins can cause immediate and delayed allergic reactions - specifically skin rashes, fever & anaphylactic shock.
- Penicillins are classed as category B during pregnancy.

Cephalosporins

- Cephalosporins have a mechanism of action identical to that of the Penicillins.
- Interferes with synthesis of the bacterial cell wall and so are bactericidal.

- Cephalosporins are used to treat pneumonia, strept throat, staph infections, tonsillitis, bronchitis, otitis media, various types of skin infections, gonorrhea, urinary tract infections.

- Cephalosporins antibiotics are also commonly used for surgical prophylaxis. Cephalexin can also be used to treat bone infections.

The first generation Cephalosporins

- They possess generally excellent coverage against most Gram-positive pathogens and variable to poor coverage against most Gram-negative pathogens.

- The first generation includes:

  Cephradine (Velosef)

  Cephalexin (Ceporex)

  Cefadroxil (Biodroxil, Duricef)

The second generation Cephalosporins

- In addition to the Gram-positive spectrum of the first generation Cephalosporins, these agents have expanded Gram-negative spectrum.
- Cefoxitin and Cefotetan also have good activity against Bacteroides fragilis.

- The second generation includes:

  Cefaclor (Bacticlor)

  Cefuroxime (Zinnat)

The third generation Cephalosporins

- They have much expanded gram negative activity. However, some members of this group have decreased activity against gram-positive organisms. They have the advantage of convenient administration, but they are expensive.
- The third generation includes:

  Ceftazidime (Fortum)

  Cefixime (Suprax)

  Cefoperazone (Cefobid)

  Cefotaxime (Claforan, Cefotax)

  Ceftriaxone (Ceftriaxone, Rociphen)

  Cefdinir (Omnicef)

The fourth generation Cephalosporins

- They are extended-spectrum agents with similar activity against Gram-positive organisms as first-generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins.
- Many fourth generation cephalosporins can cross blood brain barrier and are effective in meningitis.

- The fourth generation includes:

  Cefepime (Maxipime)

The Fifth generation Cephalosporins

- Used to treat MRSA (methicillin-resistant Staphylococcus aureus), penicillin-resistant Streptococcus pneumoniae, Pseudomonas aeruginosa, and enterococci.

- The fifth generation includes:

  Ceftaroline (Teflaro)

  Ceftobiprole (Zeftera)

Cephalosporins side effects

- Diarrhea, nausea, mild stomach upset
- Approximately 5–10% of patients with allergic hypersensitivity to penicillins will also have cross-reactivity with cephalosporins.
- Cephalosporin antibiotics are classed as pregnancy category B.

Carbapenems

- A class of β-Lactam antibiotics with a broad spectrum of antibacterial activity.
- Highly resistant to most β-lactamases.
- Active against both Gram-positive and Gram-negative bacteria, and anaerobes, with the exception of intracellular bacteria (atypical), such as the *Chlamydia*.

- Agents:

  Imipenem/Cilastatin (Tienem)

  Meropenem (Meronem)

- Adverse effects to Carbapenems include headache, rash, GI upset, phlebitis, hypotension, seizures in patients with renal dysfunction.

Monobactams

- They are β-lactam compounds.
- They work only against aerobic Gram negative bacteria (Neisseria, Pseudomonas).
- The only commercially available Monobactams antibiotic is Aztreonam (Azactam).
- Adverse effects to Monobactams can include skin rash and occasional abnormal liver functions.

Macrolides

- Macrolides are bacteriostatic, binding with bacterial ribosomes to inhibit protein synthesis.
- Macrolides antibiotics are used to treat respiratory tract infections (such as pharyngitis, sinusitis, and bronchitis), genital, gastrointestinal tract & skin infections.

- Macrolides antibiotics are:
  Erythromycin (Erythrocin)
  Clarithromycin (Klacid)
  Azithromycin (Zithromax)
  Roxithromycin (Roxicin)

Macrolides side effects

- Nausea, vomiting, diarrhea; infrequently, there may be temporary auditory impairment.
- Oral Erythromycin may be highly irritating to the stomach and when given by injection may cause severe phlebitis.
- Macrolides antibiotics should be used with caution in patients with liver dysfunction.
- Pregnancy category B: Azithromycin, Erythromycin.
  Pregnancy category C: Clarithromycin

Ketolides

- Antibiotics belonging to the Macrolides group.
- Much broad spectrum than other Macrolides.
- Ketolides are effective against Macrolides-resistant bacteria, due to their ability to bind at two sites at the bacterial ribosome as well as having a structural modification that makes them poor substrates for efflux-pump mediated resistance.
- The only Ketolide on the market at this moment is telithromycin, which is sold under the brand name of Ketek.

Lincosamides (e.g. lincomycin, clindamycin)

- Lincosamides prevent bacteria replicating by interfering with the synthesis of proteins.

- They are normally used to treat staphylococci and streptococci, and have proved useful in treating Bacteroides fragilis and some other anaerobes.

- They are used in the treatment of Toxic Shock Syndrome.
- Lincosamides antibiotics are one of the classes of antibiotics most associated with pseudomembranous colitis caused by C. difficile.

Aminoglycosides

- The Aminoglycosides are bactericidal and work by stopping bacteria from making proteins.
- Aminoglycosides antibiotics are used to treat infections caused by Gram-negative bacteria.
- Aminoglycosides may be used along with penicillins or cephalosporins to give a two-pronged attack on the bacteria.
- Since Aminoglycosides are broken down easily in the stomach, they can't be given by mouth and must be injected.

- Generally, Aminoglycosides are given for short time periods.
- Aminoglycosides group includes:

  Amikacin (Amikin)

  Gentamicin (Garamycin)

  Neomycin (Neomycin)

  Streptomycin (Streptomycin)

  Tobramycin (Nebcin)

Aminoglycosides side effects

- Ototoxicity
- Nephrotoxicity
- Aminoglycosides are classed as pregnancy category D.

Fluoroquinolones

- They are synthetic antibiotics, not derived from bacteria.
- Fluoroquinolones are broad-spectrum bactericidal drugs that are chemically unrelated to the penicillins or the cephalosporins.
- Fluoroquinolones inhibit bacteria by interfering with their ability to make DNA. This effect is bactericidal.
- Because of their excellent absorption Fluoroquinolones can be administered not only by intravenous but orally as well.

- Fluoroquinolones are used to treat most common urinary tract infections, skin infections, and respiratory infections (such as sinusitis, pneumonia, bronchitis).
- Fluoroquinolones group includes:
  Ciprofloxacin (Ciprobay, Ciprocin)
  Levofloxacin (Tavanic, Alfacef)
  Norfloxacin (Noracin)
  Ofloxacin (Tarivid)
  Moxifloxacin (Avalox)

Fluoroquinolones side effects

- Nausea, vomiting, diarrhea, abdominal pain
- Irreversible damage to central nervous system (uncommon)
- Tendinosis (rare)
- Fluoroquinolones are classed as pregnancy category C.

Trimethoprim/sulfamethoxazole or Co-trimoxazole

- An antibiotic used in the treatment of a variety of bacterial, fungal and protozoal infections.
- Co-trimoxazole is generally considered bactericidal, although its components are individually bacteriostatic.
- Its actions are antifolate in nature, inhibiting both *de novo* folate biosynthesis and metabolism.

Co-trimoxazole side effects

- Nausea, vomiting
- An allergic reaction and infection with Clostridium difficile, a type of diarrhea
- Co-trimoxazole is classed as pregnancy category C.
- Some state it should not be used during breastfeeding while others say it is okay.

Tetracyclines

- Broad-spectrum bacteriostatic agents and work by inhibiting the bacterial protein synthesis.
- Tetracyclines may be effective against a wide variety of microorganisms, including Rickettsia and Amoebic parasites.
- Tetracyclines are used in the treatment of infections of the respiratory tract, sinuses, middle ear, urinary tract, skin, intestines.

- Tetracyclines also are used to treat Gonorrhea, Rocky Mountain spotted fever, Lyme Disease, Typhus.
- Their most common current use is in the treatment of moderately severe acne and rosacea.
- Tetracycline antibiotics are:

  Tetracycline

  Doxycycline (Vibramycin)

  Minocycline

  Oxytetracycline (Oxytetracid)

Tetracyclines side effects

- Cramps or burning of the stomach, diarrhea, sore mouth or tongue
- Skin photosensitivity
- Allergic reactions
- Tetracycline antibiotics should not be used in children under the age of 8 and specifically during periods of tooth development.
- Tetracyclines are classed as pregnancy category D. Use during pregnancy may cause alterations in bone development.

Chloramphenicol

- It is a bacteriostatic.
- It is considered a prototypical broad-spectrum antibiotic, alongside the tetracyclines, and as it is both cheap and easy to manufacture, it is frequently an antibiotic of choice in the developing world.
- Effective against a wide variety of Gram-positive and Gram-negative bacteria, including most anaerobic organisms.

- Due to resistance and safety concerns, it is no longer a first-line agent for any infection in developed nations, with the notable exception of topical treatment of bacterial conjunctivitis.

Chloramphenicol side effects

- The most serious adverse effect associated with chloramphenicol treatment is bone marrow toxicity.
- Use of intravenous chloramphenicol has also been associated with gray baby syndrome.
- Other less serious reactions include fever, rashes, headache, confusion.

Glycopeptides (e.g. vancomycin, teicoplanin)

- These antibiotics are effective principally against Gram-positive cocci.
- This class of drugs inhibit the synthesis of cell walls in susceptible microbes by inhibiting peptidoglycan synthesis.
- Vancomycin is used if infection with methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected.

- Due to their toxicity, use of glycopeptides antibiotics is restricted to patients who are critically ill, who have a demonstrated hypersensitivity to the β-lactams, or who are infected with β-lactam-resistant species.
- They exhibit a narrow spectrum of action, and are bactericidal only against the enterococci.

- Oral preparations of vancomycin are available, however they are not absorbed from the lumen of the gut, formulated for the treatment of infections within the gastrointestinal tract, Clostridium difficile, for example.

Vancomycin side effects

- Vancomycin is usually given intravenously, as an infusion, and can cause tissue necrosis and phlebitis at the injection site.
- Red man syndrome, an idiosyncratic reaction to bolus dose caused by histamine release
- Nephrotoxicity including renal failure and interstitial nephritis
- Blood disorders including neutropenia, and deafness, which is reversible once therapy has stopped
- Risk of accumulation in patients with renal impairment

Streptogramins

- Effective in the treatment of vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE), two of the most rapidly growing strains of multidrug-resistant bacteria.

- Members include:
  - Quinupristin/dalfopristin
  - Pristinamycin
  - Virginiamycin

Adverse effects include:

Related to administration via peripheral vein

Inflammation, pain, edema, infusion site reaction, thrombophlebitis

Non-venous adverse effects

- Nausea, vomiting, diarrhea
- Rash
- Headache
- Pain, ill-defined focal or generalized discomfort
- Pruritus
- Arthralgia, myalgia
- Asthenia
- Conjugated hyperbilirubinaemia

Oxazolidinones (e.g. linezolid)

- Linezolid inhibits ribosomal protein synthesis by inhibiting formation of the initiation complex.
- It is used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics.
- Linezolid is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).

- The main indications of linezolid are infections of the skin & soft tissues and pneumonia (particularly hospital-acquired pneumonia).
- Common adverse effects of short-term use include headache, diarrhea & nausea. Long-term use, however, has been associated with serious adverse effects; linezolid can cause bone marrow suppression and low platelet counts, particularly when used for more than two weeks. If used for longer periods still, it may cause sometimes irreversible chemotherapy-induced peripheral neuropathy and optic nerve damage, and lactic acidosis.

Ansamycins

- A family of secondary metabolites that show antimicrobial activity against many Gram-positive and some Gram-negative bacteria and includes various compounds, among which: streptovaricins and rifamycins.
- Rifamycins are a subclass of ansamycins with high potency against mycobacteria. This resulted in their widespread use in the treatment of tuberculosis, leprosy, and AIDS-related mycobacterial infections.

- The antibacterial activity of rifamycins relies on the inhibition of bacterial DNA-dependent RNA synthesis. This is due to the high affinity of rifamycins for the prokaryotic RNA polymerase.

Adverse effects include:

- Hepatotoxic - hepatitis, liver failure in severe cases
- Respiratory - breathlessness
- Cutaneous - flushing, pruritus, rash, redness and watering of eyes
- Abdominal - nausea, vomiting, abdominal cramps with or without diarrhea
- Flu-like symptoms - with chills, fever, headache, arthralgia, and malaise, rifampin has good penetration into the brain, and this may directly explain some malaise and dysphoria in a minority of users.

Rifaximin is a semisynthetic antibiotic based on rifamycin. It has poor oral bioavailability, meaning that very little of the drug will be absorbed into the blood stream when it is taken orally. Rifaximin is used in the treatment of traveler's diarrhea and hepatic encephalopathy, for which it received orphan drug status* from the U.S. Food and Drug Administration in 1998.

Rifaximin interferes with transcription by binding to the β-subunit of bacterial RNA polymerase.

* An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition.

Metronidazole

- A nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa.
- It is antibacterial against anaerobic organisms, an amoebicide and an antiprotozoal.
- It inhibits nucleic acid synthesis by disrupting the DNA of microbial cells. This function only occurs when Metronidazole is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria.

- Metronidazole is primarily used to treat: bacterial vaginosis, pelvic inflammatory disease (along with other antibacterials like ceftriaxone), pseudomembranous colitis, aspiration pneumonia, rosacea (topical), fungating wounds (topical), intra-abdominal infections, lung abscess, gingivitis, amoebiasis, giardiasis, trichomoniasis, and infections caused by susceptible anaerobic organisms such as *Bacteroides.*

- It is also often used to eradicate *Helicobacter pylori* along with other drugs and to prevent infection in people recovering from surgery.

- Adverse effects include:

  Discolored urine, headache, metallic taste , nausea

  Metronidazole is classed as pregnancy category B.

For more information:

- http://www.emedexpert.com/classes/antibiotics.shtml
- http://en.wikipedia.org/wiki/List_of_antibiotics
- http://www.orthobullets.com/basic-science/9059/antibiotic-classification-and-mechanism
- http://www.nlm.nih.gov/medlineplus/antibiotics.html
- https://www.youtube.com/channel/UCvl8mk9dKfhidf8oVhYkaOg