2.Chemotherapy & Antimicrobial Agents

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  - Broad Spectrum
- Antimicrobial agents

CHEMOTHERAPY

- Treatment of disease by chemicals that kill the cells or microorganism or cancer cells
- If directed to cancer cells→ cancer chemotherapy
- If directed to micro-organism→ Antibiotics

General Principles of Chemotherapy

- Diagnosis
- Indication of chemotherapy
- Selections of drugs , dose and route of administration
- Duration of therapy
- Drug therapy
- Test for cure
- Prophylactic drug

Diagnosis:

- Site of Infections
- Responsible organism
- Sensitivity of drug

Indication of chemotherapy

- May or may not need the antibiotics medicine →so, need to identify
- Sore throat, common cold may not need the antibiotics
  - If viral→ no need antibiotics, will recover within 5-7 days
  - But if bacterial →may need of antibiotics

Selection of Drugs

- Is based on the cost effectiveness of drug, safety and toxicity .
- Can be targeted and empirical chemotherapy
  - Targeted chemotherapy
    - Chemotherapy according to culture sensitivity
    - Cancer drugs, treatment after confirmation of organism
  - Empirical chemotherapy
    - According to practice of doctors
    - According to epidemiological pattern to disease
    - Extent of disease in community

Selection of dose

- Should be enough to achieve minimum inhibitory concentration(MIC)
- MIC
  - Minimum effect of antibiotics require to suppress microorganism or to achieve therapeutic effect

Route of administrations

- In order to achieve MIC and drug reaches the site of action
- Different routes has its own benefits

aminoglycoside like streptomycin if given orally its not effective(a polar compound)

Route for administration
-Time until effect-

intravenous	30-60 seconds
intraosseous	30-60 seconds
endotracheal	2-3 minutes
inhalation	2-3 minutes
sublingual	3-5 minutes
intramuscular	10-20 minutes
subcutaneous	15-30 minutes
rectal	5-30 minutes
ingestion	30-90 minutes
transdermal (topical)	variable (minutes to hours)

Duration of therapy

- Depends of type of disease
- Most drug → minimum 48 hours even after symptoms subsides
- Antibiotics—>5-10 days

Acute -5-10 days
Subacute-2-3 wks
Chronic – several months

Some chronic disease
Tuberculosis → 6-9 months
Extra pul tuberculosis > 9-12-18 months...
Leprosy > one 1yr

Drug therapy

- **Mono drug therapy**
  - Better tolerated
  - Cost effective
  - Chance of drug interaction less
- **Combination drug therapy**
  - Eg. Tuberculosis
  - Advantage
    - Achieve synergism,less side effect,inscrease spectrum

Change of drug during therapy

- Frequent change is not good
- Enough time give so that it can be goodly absorbed, reach site of action and produce pharmacological effects

Removal of barriers for site of administration

- Remove the pus or necrotic tissue
- Drainage of pus incase of abscess

Chemoprophylaxis(Prophylaxis)

- Prevention of disease or infections by chemotherapy
  - Non Surgical prophylaxis
    - Rheumatic fever →long acting penicillin
    - Person travelling endemic area of malaria → mefloquinine or primaquine
    - DVT prophylaxis in bed ridden patient
  - Surgical
    - Purpose is to decrease the adverse effect
    - Prevent further infection
    - Given if surgical hours is two or more hours(esp. GI surgery, musculoskeletal surgeries etc

Adverse effect of antimicrobial agents(AMAs)

- Toxicity
- Hypersensitivity
- Drug resistance
- Super infection
- Nutritional deficiency
- Masking of infection

Toxicity

- Selective toxicity or no toxicity
  - ability to kill an invading microorganism without harming the cells of host
- Local toxicity
  - Local irritation at site of administration
    - → pain and abscess by i/m drug
    - Thrombophlebitis on iv drug
- Systematic toxicity
- agent which have low Therapeutic index exhibit more toxicity
  - Aminoglycoside→ototoxicity
  - Chloramphenicol→bonemarrow suppression

tetracycline
(liver and renal toxicity)

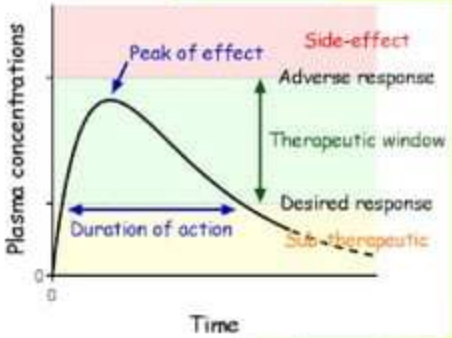
chloramphenicol
(bone marrow depressio

Therapeutic index

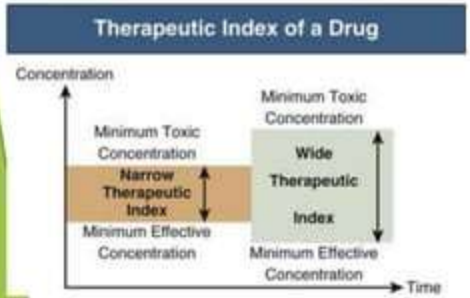
- The therapeutic index of a drug is the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals:

$$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$

- where TD50 = the drug dose that produces a toxic effect in half the population and ED50 = the drug dose that produces a therapeutic or desired response in half the population.

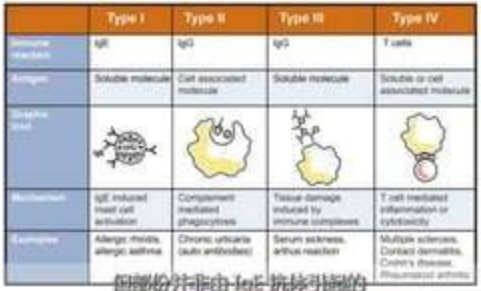


Therapeutic Window : Drug effect between desired response and adverse respone



- High therapeutic index
  - NSAIDs
    - Aspirin
    - Tylenol
    - Ibuprofen
  - Sedative/hypnotics
    - Benzodiazepines
  - Most antibiotics
  - Beta-blockers
- Low therapeutic index
  - Lithium
  - Neuroleptics
    - Phenytoin
    - Phenobarbital
  - Some antibiotics
    - Gent/Vanco/Amikacin
  - Digoxin
  - Immunosuppressives

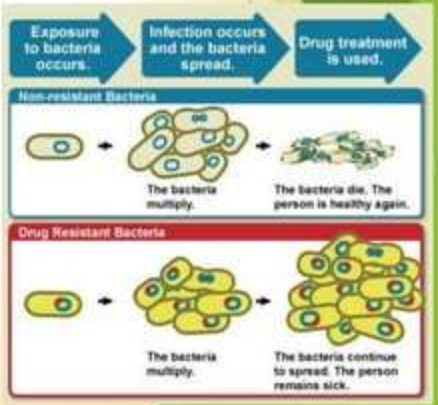
Hypersensitivity Reaction



- 4 types of reaction (EGGT)
- Skin rash and anaphylactic shock
- Usually seen penicillin and cephalosporin

Drug Resistance

- Unresponsiveness of microorganism to antibiotics
- Two types
  - Natural resistance
    - g positive--not affected g negative
    - existed before antibiotic use
  - Acquired resistance
    - Resistance by prolong use of antibiotics
    - mutation in gene(conguation, transduction, transformation of gene



Super Infection

By using more antibiotics

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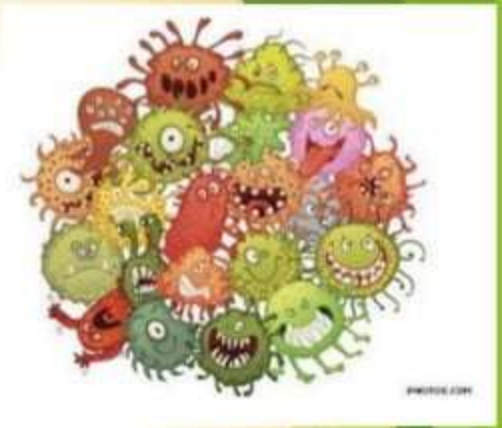
Change to flora of bacteria

↓

Leads to superinfection



Nutritional deficiency

- Prolong use of antibiotics alters the normal flora
- Cause different deficiency of vitamins and minerals

Different Drugs induced nutritional deficiency

Drug Category	Action	Name	Nutrient Depletion
Proton-Pump Inhibitor	Reduce Stomach Acid	Prevacid, Omeprazole	Vitamin B12, D, Folic Acid, Calcium, Iron, Zinc
Statin	Lower Cholesterol	Lipitor, Simivistatin, Lovastatin	CoQ 10
Birth Control	Prevent Pregnancy	Yaz, Alesse, Loestrin	Vitamin B6
Anti-Inflammatory/ Corticosteroid	Reduce Inflammation, Arthritis, Pain	Prednisone, Cortisone, Budesonide	Calcium, Magnesium Vitamin B6, B12 C, D,
Diuretic	Reduce High Blood Pressure	Hydrochlorothiazide, Furosemide, Triam-terene	Calcium, Magnesium, Vitamin B1, B6, C, CoQ 10, Zinc
Diabetic Drugs	Lower Blood Sugar	Metformin	Vitamin B1, B6 CoQ10, Zinc

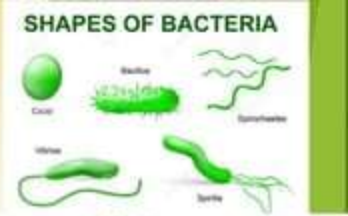
masking of infection

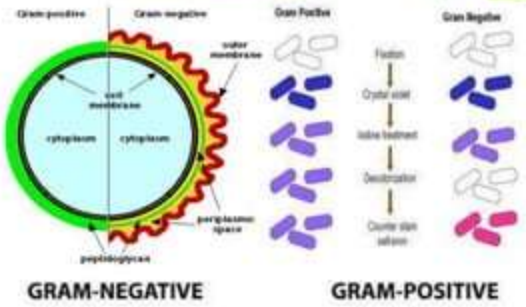
- Short course of antibiotics may be sufficient to treat one infection
- but suppresses other
- other will mask for short time and cause severe form

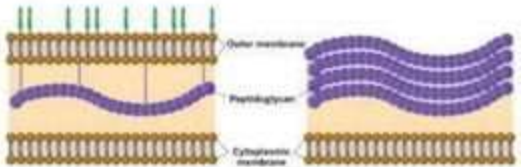
- Examples are:
- (i) Syphilis masked by the use of a single dose of penicillin which is sufficient to cure gonorrhoea.
- (ii) Tuberculosis masked by a short course of streptomycin given for trivial respiratory infection.

Bacteria

- Gram Positive Bacteria
  - Takes gram stain
- Gram Negative Bacteria
  - Don't take gram stain





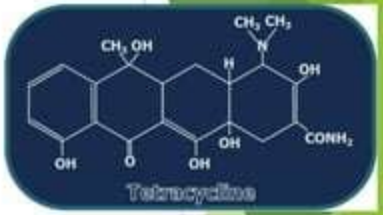


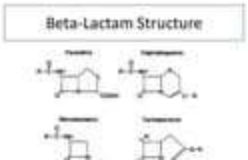
Classification of antimicrobials

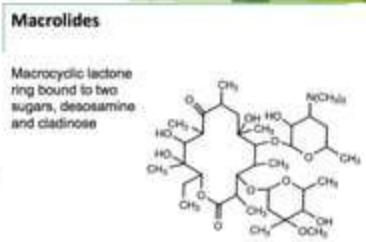
A. Chemical structure
B. Mechanism of action
C. Type of organisms (against which primarily active)
D. Spectrum of activity
E. Type of action (bacteriostatic and bactericidal)
F. Source of antibiotics

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

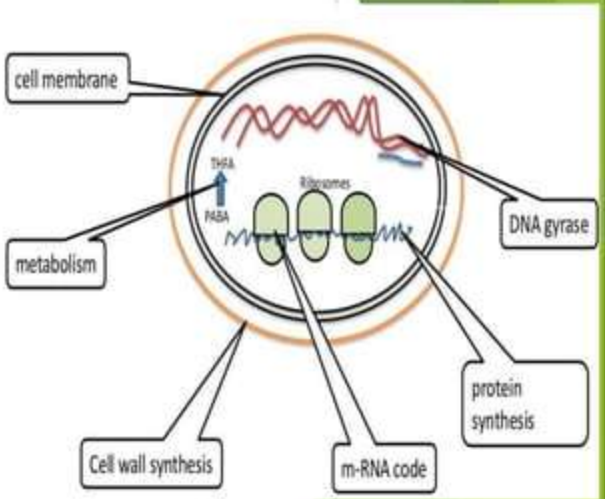






B. Mechanism of Action

- Inhibition of cell wall synthesis
- Inhibition of protein synthesis
- Inhibition of nucleic acid synthesis
- Inhibition of metabolic pathways
- Interference with cell membrane integrity



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
  - Only effective against certain specific family of bacteria
  - gram positive or Negative only
  - eg. streptomycin, erythromycin
- Broad Spectrum
  - Effective against wide range of microorganism
  - Both Gram Positive and Negative
  - Tetracycline, chloramphenicol, cephalosporin
- Extended Spectrum
  - Gram positive and negative with other microbes
  - Tazobactam, meropenam

E. Type of Action

- Bacteriostatic
  - inhibit growth of Bacteria
    - Clindamycin, tetracyclines
- Bactericidal
  - Kill the microbes
    - Penicillins, amminogycosides, ciprofloxacin, metronidazole

F. Source of antibiotics

- ***Fungi:*** Penicillin, Griseofulvin, Cephalosporin

- ***Bacteria:*** Polymyxin B, Tyrothricin, Colistin, Aztreonam, Bacitracin

- ***Actinomycetes:*** Aminoglycosides, Macrolides, Tetracyclines, Polyenes, Chloramphenicol