Basic Principles of Chemotherapy

Dr. R. B. Pandhare

Associate Professor & Head , Dept. of Pharmacology

M.E.S's College of Pharmacy, Sonai , Ahmednagar

Learning Outcomes

At the end of the session student should be able to:

1) Define terms: Chemotherapy, antibiotics, antimicrobials, bacteriostatic and bactericidal.
2) Classify antimicrobial drugs
3) Explain the problems that arise with the use of antimicrobial agents
4) Define bacterial resistance and explain mechanisms involved in acquiring drug resistance

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.

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

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

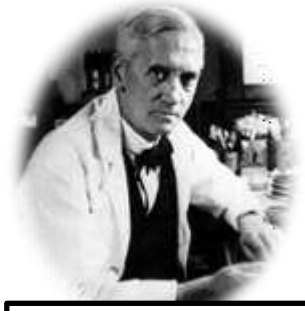
Ehrlich's period (1900 to 1930)

- Organometallic dye for treatment for cane

After Ehrlich's period (1930 to till date)

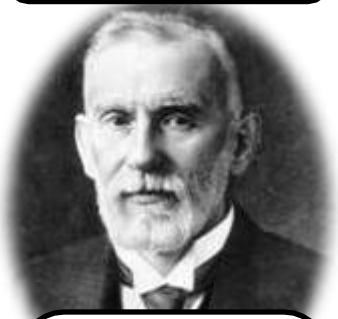
- discovery of sulfonamide (*Prontosil)*

Timeline history of chemotherapy development



1908- Discovery of Arsphenamine

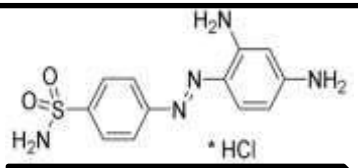
Alexander Fleming 1928- Penicillin



Paul Ehrilich
Father of Chemotherapy

Gerhard Domagk 1939- Sulfonamidochrysoidine (Prontosil)

1900- *Paul Ehrilich* Chemotherapy Animal model developed



1932- Prontosil- First sulfonamide- Bayer's Laboratory

1959- Antitumor antibiotics

1958- Methotrexate

1957- 5-Fluorouracil

1951- Thiopurines

1948- Anitfolates

1944- Waksman *et al*., discovered streptomycin.

1943- Nitrogen mustard in lymphomas

1963- Vinca alkaloids

1962- nalidixic acid

1963 to 1970- Treatment for Hodgkin's disease

2007- Target specific screens

2005- Tyrosine kinase inhibitors

1997- Monoclonal antibody approved for the treatment of tumor.

1996- Imatinib

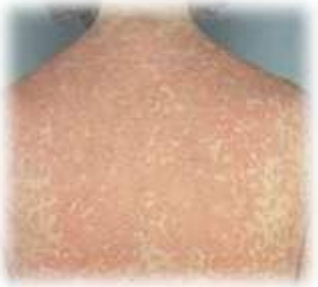
1900 1920 1940 1960 1980 2015

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

1) Chemical structure
2) Mechanism of action
3) Type of organisms (against which primarily active)
4) Spectrum of activity
5) Type of action (bacteriostatic and bactericidal)
6) Source of antibiotics

1) Chemical structure

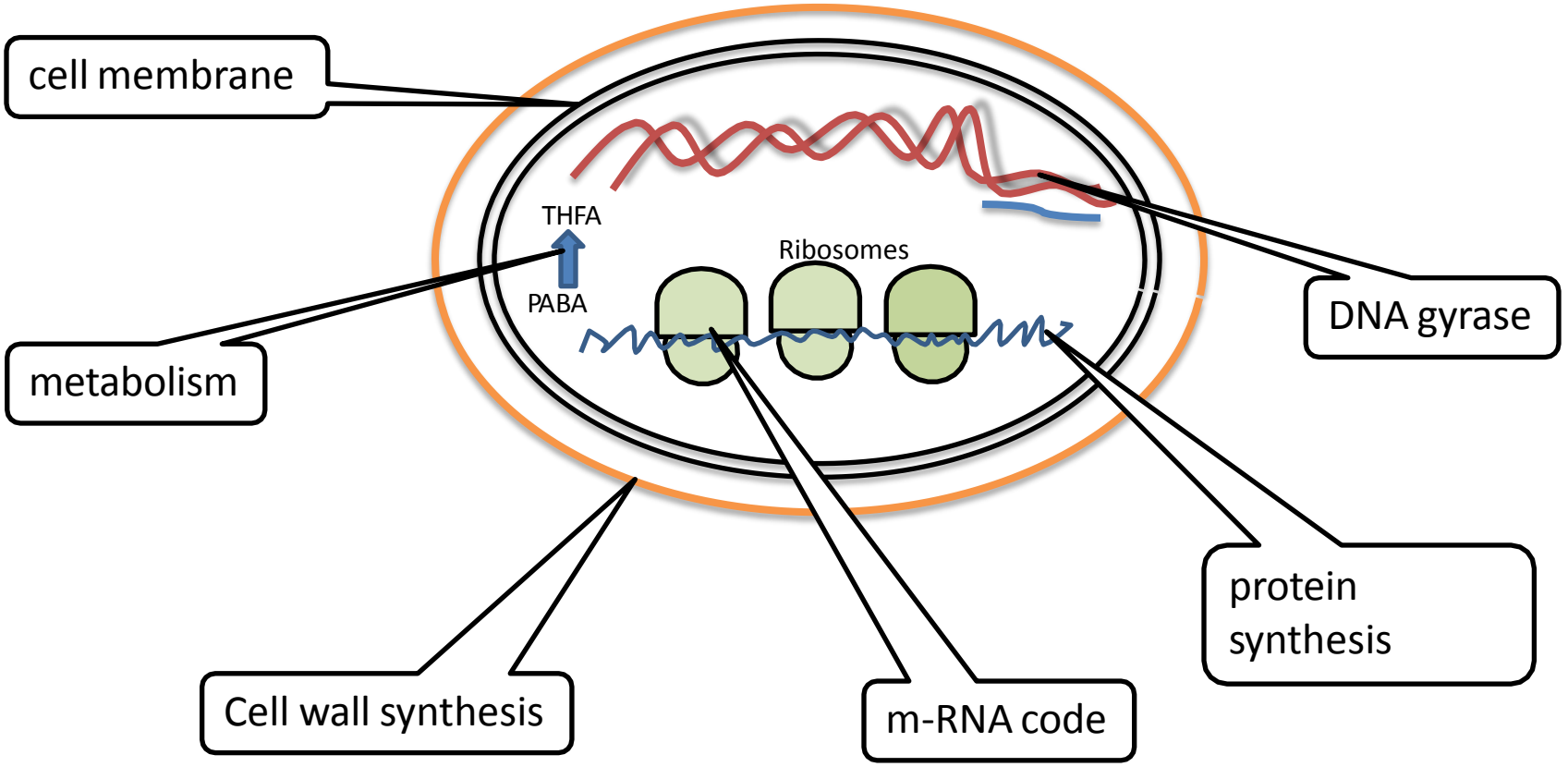
- Sulfonamides and related drugs: Dapsone (DDS), Sulfadiazine, Paraaminosalicylic acid (PAS)
- Diaminopyrimidines: Trimethoprim, Pyrimethamine
- Quinolones: Nalidixic acid, Norfloxacin, Ciprofloxacin
- Beta lactam antibiotics: Penicillins, Cephalosporins
- Tetracyclines: Oxytetracycline, Doxycycline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

1) 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

2) Mechanism of action



2) Mechanism of action

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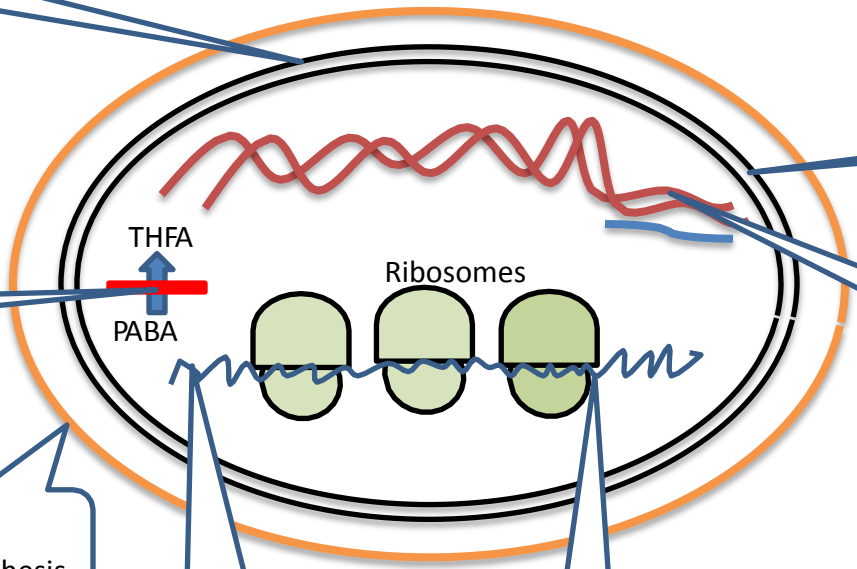


Leakage form cell membrane

Polypeptides- Polymyxines, colistin.

Polyenes- Amphotericin B, Nystatin, Hamycin

Inhibition of Cell Membrane

Fluoroquinolones
Rifampin

Inhibition of metabolism

Sulfonamides
Sulfones
Trimethoprim
PAS
Pyrimethamine
Ethumbutol

Inhibition of DNA gyrase

Fluoroquinolones

Inhibition of Cell wall synthesis

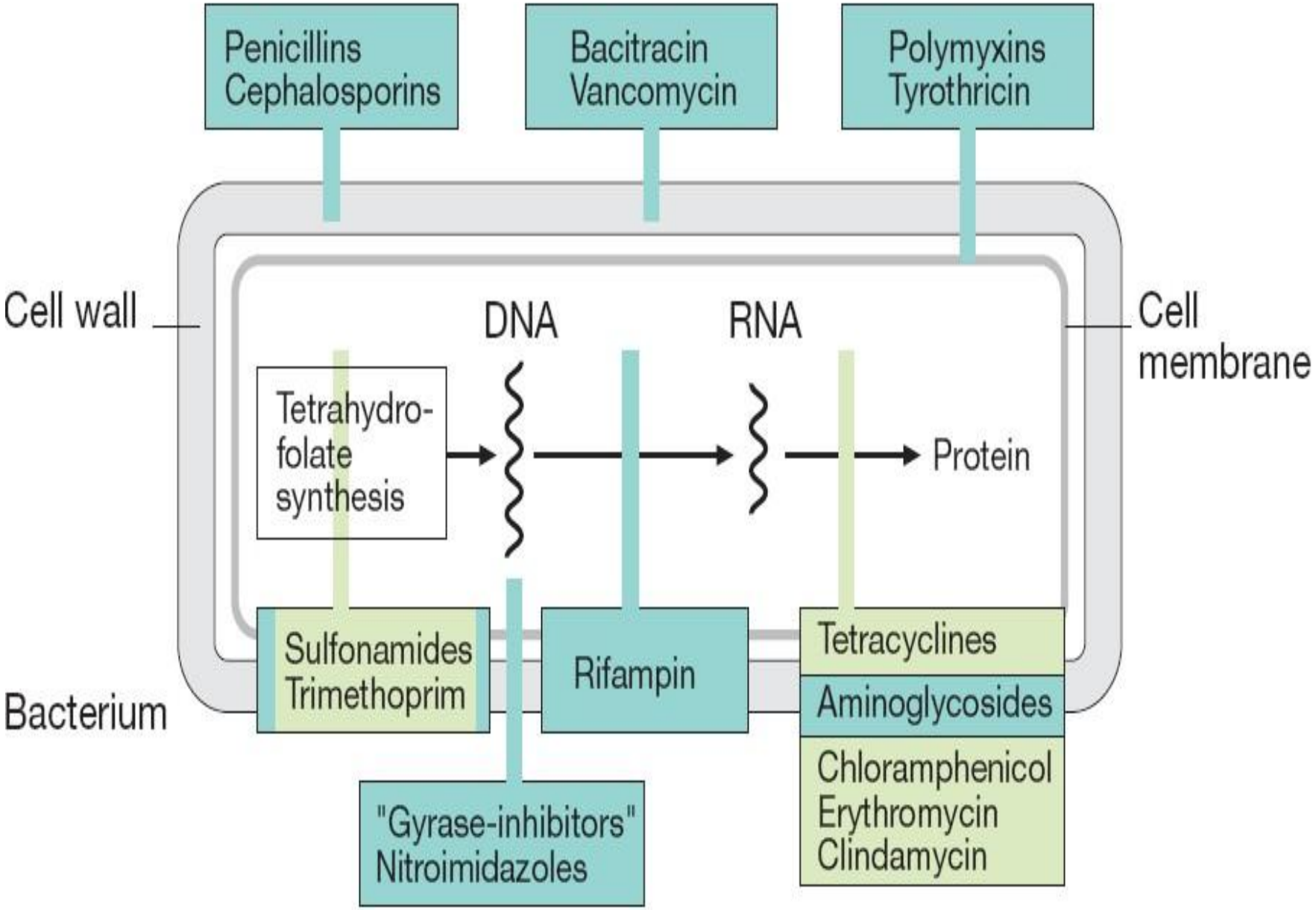
Beta-lactams
Cephalosporins
Vancomycin

Misreading of m-RNA code

Aminoglycosides- Streptomycin, Gentamicin

Inhibition of protein synthesis

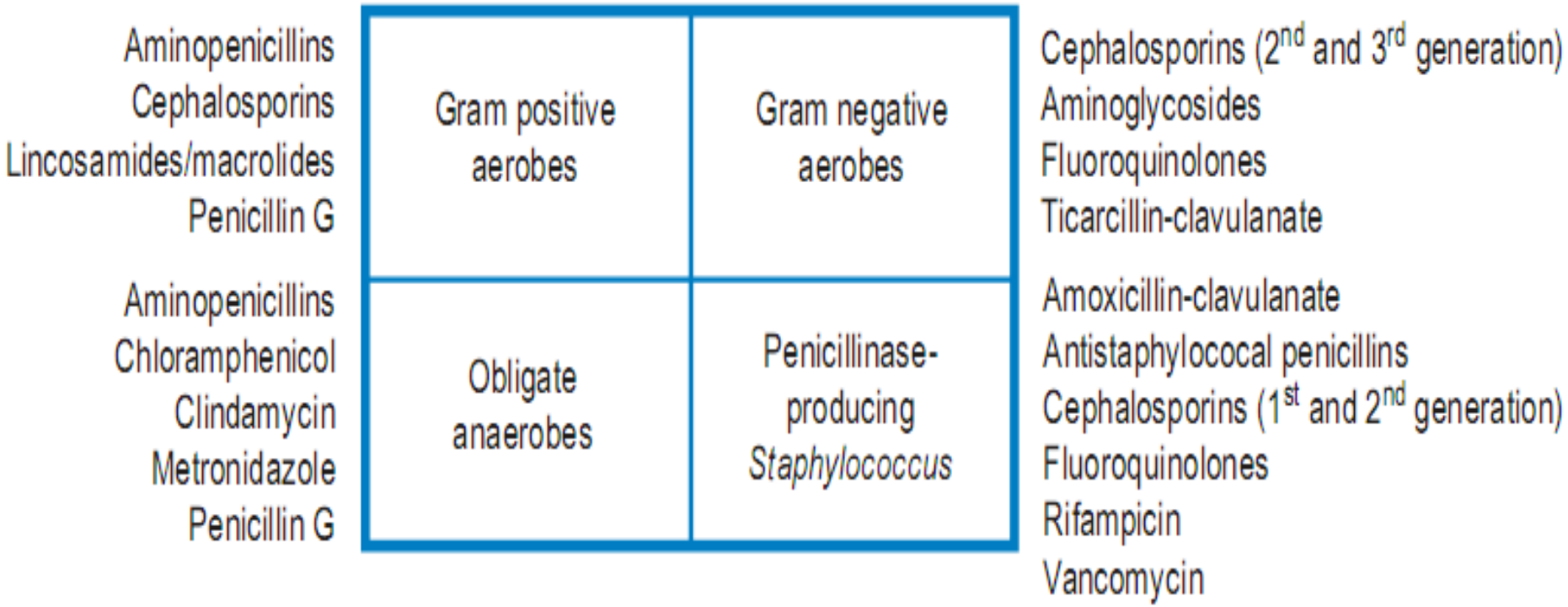
Tetracyclines
Aminoglycosides
Macrolides
Clindamycin
Chloramphenicol


Penicillins
Cephalosporins
Bacitracin
Vancomycin
Polymyxins
Tyrothricin
Cell wall
DNA
RNA
Cell membrane
Tetrahydro-folate synthesis
Protein
Sulfonamides
Trimethoprim
Rifampin
Tetracyclines
Aminoglycosides
Chloramphenicol
Erythromycin
Clindamycin
Bacterium
"Gyrase-inhibitors"
Nitroimidazoles

3) 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.

3) Type of organisms (against which primarily active)



4) 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

Antibiotic Spectrum of Activity

TABLE 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

Prokaryotes				Eukaryotes			
Mycobacteria*	Gram-Negative Bacteria	Gram-Positive Bacteria	Chlamydias, Rickettsias†	Fungi	Protozoa	Helminths	Viruses
		←Penicillin→		←Ketocon-azole→		←Niclosamide→ (tapeworms)	
←Streptomycin→					←Mefloquine→ (malaria)		
							←Acyclovir→
						←Praziquantel→ (flukes)	
	←Tetracycline→						
←Isoniazid→							

*Growth of these bacteria frequently occurs within macrophages or tissue structures.
†Obligately intracellular bacteria.

No antibiotic is effective against all microbes

4) Type of action (bacteriostatic and bactericidal)

Bacteriostatic:

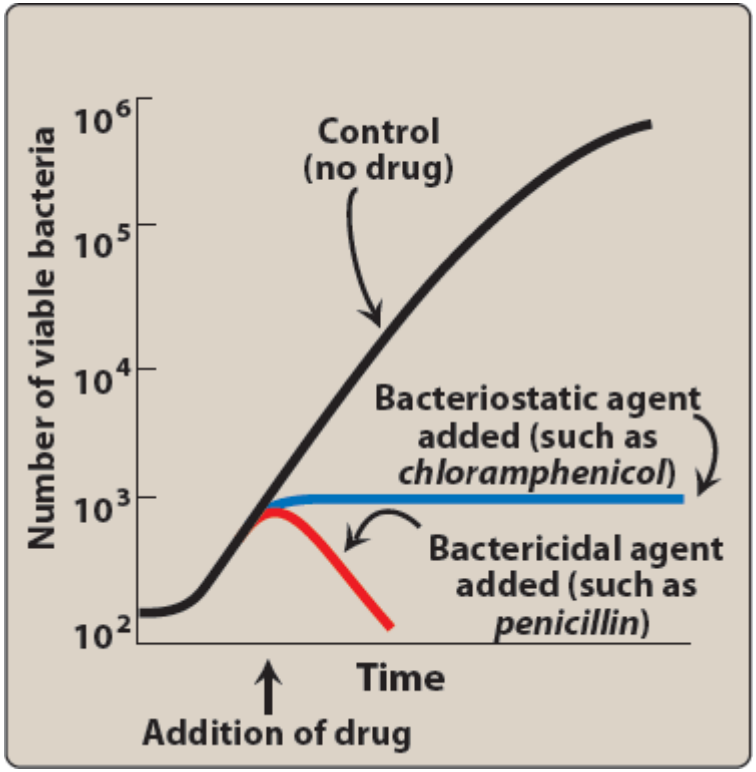
Inhibit the growth of Bacteria.

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

Bactericidal:

Kill the microbes.

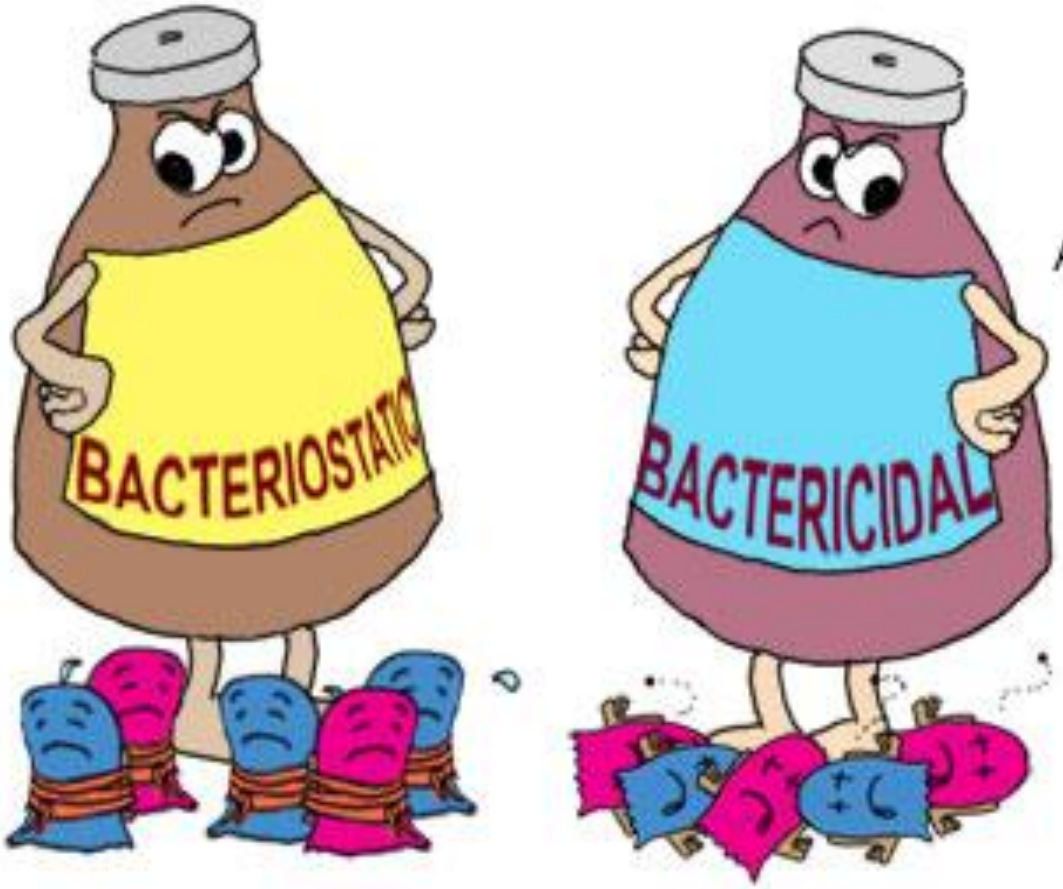
E.g.: Penicillins, Aminoglycosides, Polypeptides, Rifampin, Isoniazid, Vancomycin, Ciprofloxacin, Metronidazole, Cotrimoxazole



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

4) Type of action (bacteriostatic and bactericidal)

EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines



EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole

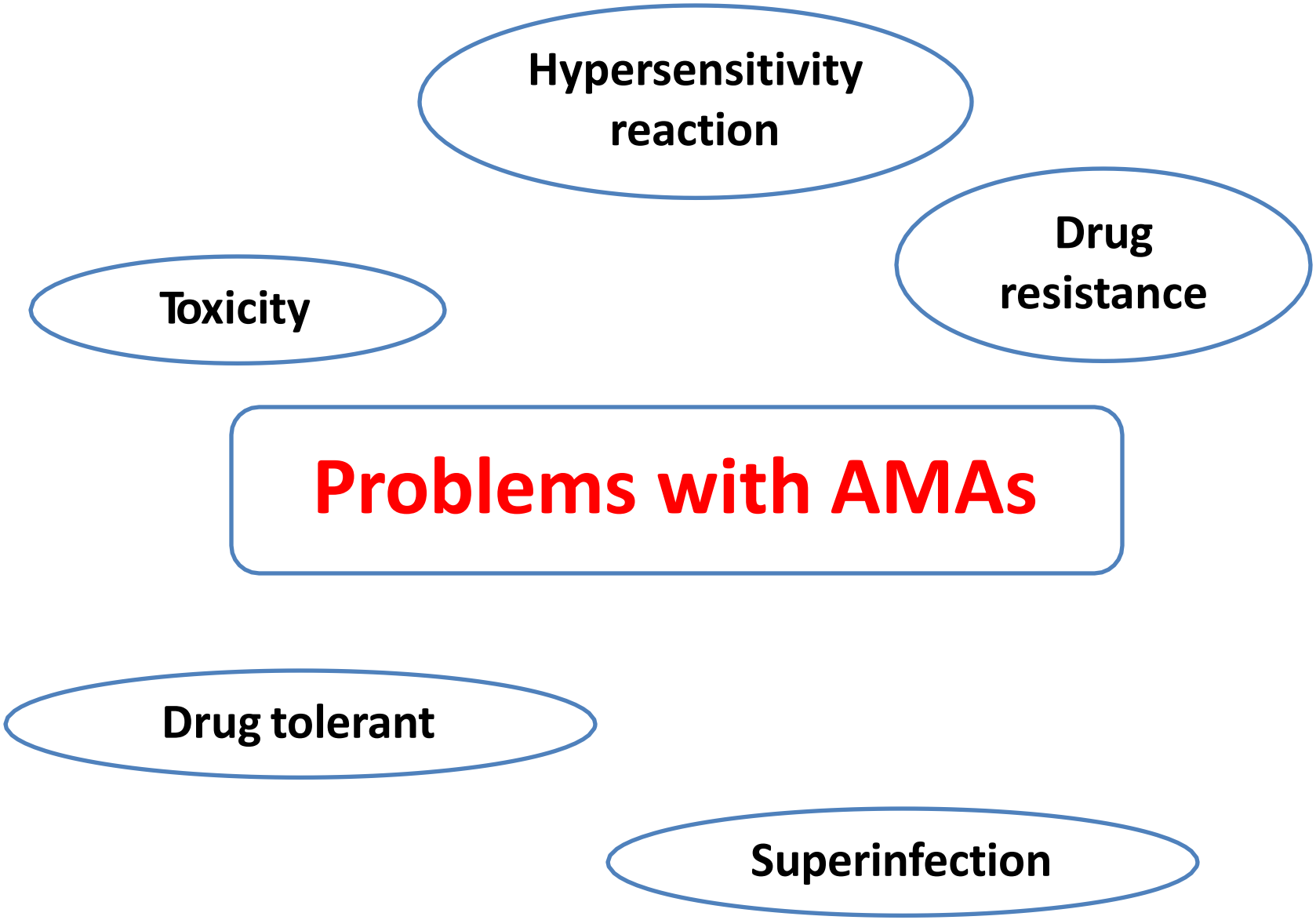
5) Source of antibiotics

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

Microbial Sources of Antibiotics

TABLE 20.1 Representative Sources of Antibiotics

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Streptomyces erythraeus	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpureae	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium notatum	Penicillin


Hypersensitivity reaction
Drug resistance
Toxicity
Problems with AMAs
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,

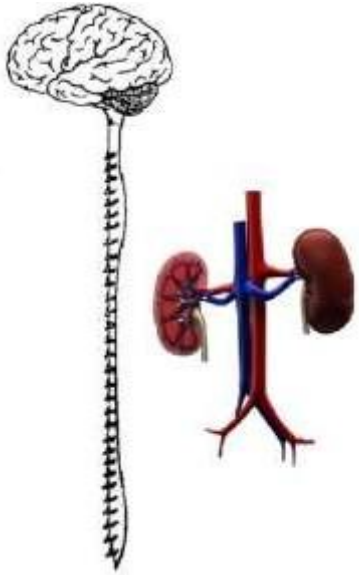
  E.g.: penicillin, erythromycin.

Toxicity

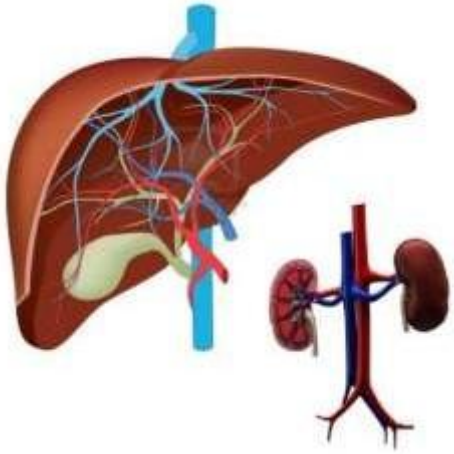
Cont.,

Systemic toxicity:

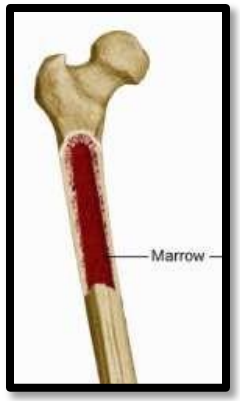
- The agent which have low therapeutic index exhibits more toxicity.
  E.g.:,



aminoglycosides
(renal and CNS toxicity)



tetracycline
(liver and renal toxicity)



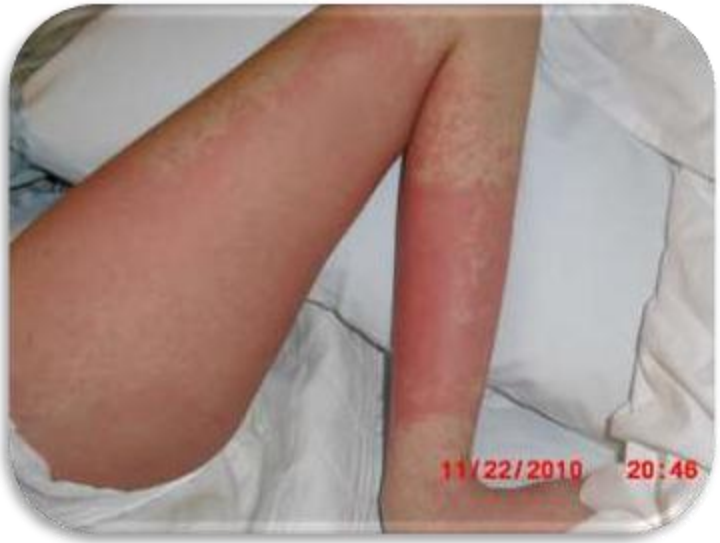
chloramphenicol
(bone marrow depression)

Toxicity

Cont.,

Systemic toxicity:

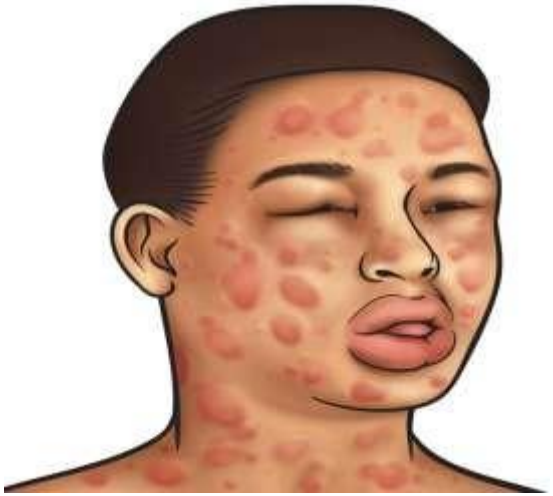
- Very low therapeutic index drug is used when no suitable alternative AMAs available,
- E.g.: Vancomycin
  (hearing loss, kidney damage,
  "red man' syndrome)
- polymyxin B
  (neurological and renal toxicity)



Vancomycin toxicity

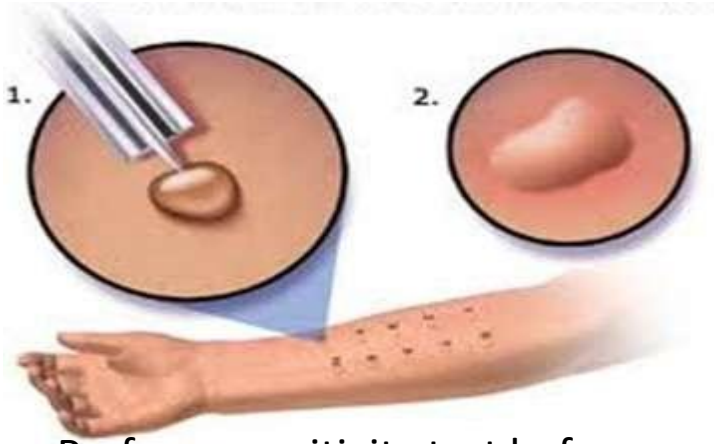
Hypersensitivity reaction

- 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.,

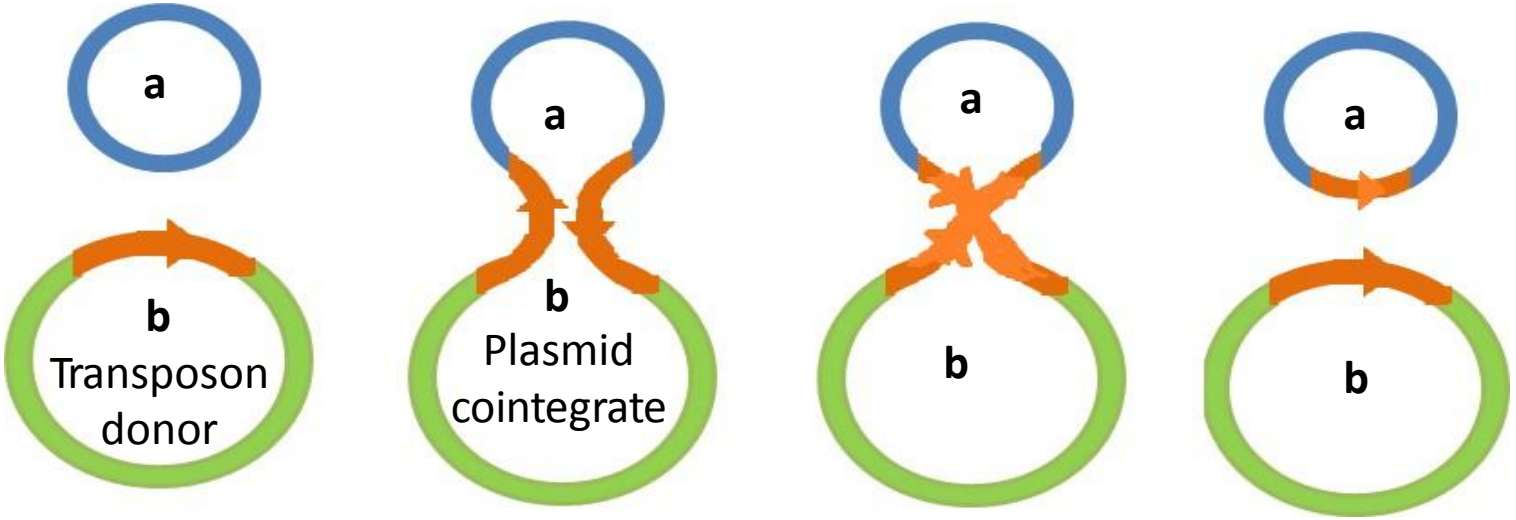
Development of resistance

- 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

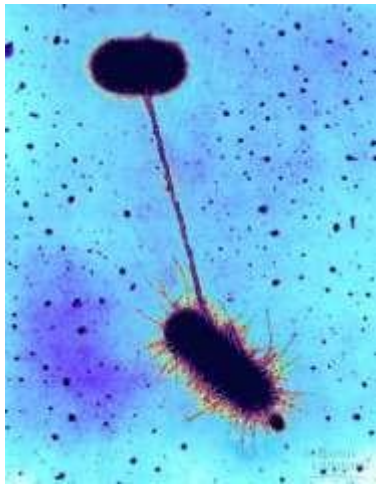
Resistance

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*

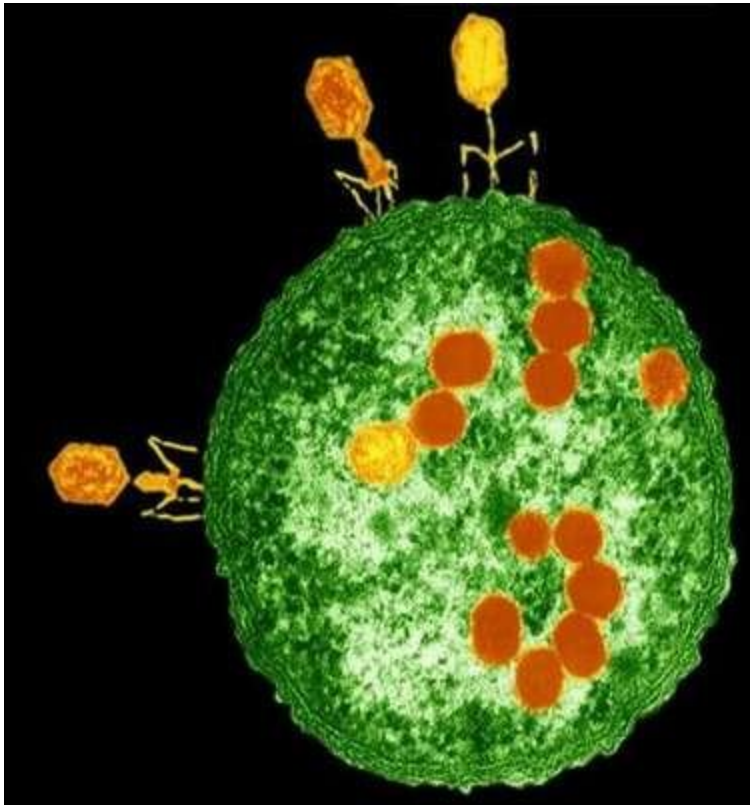


Resistance

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.



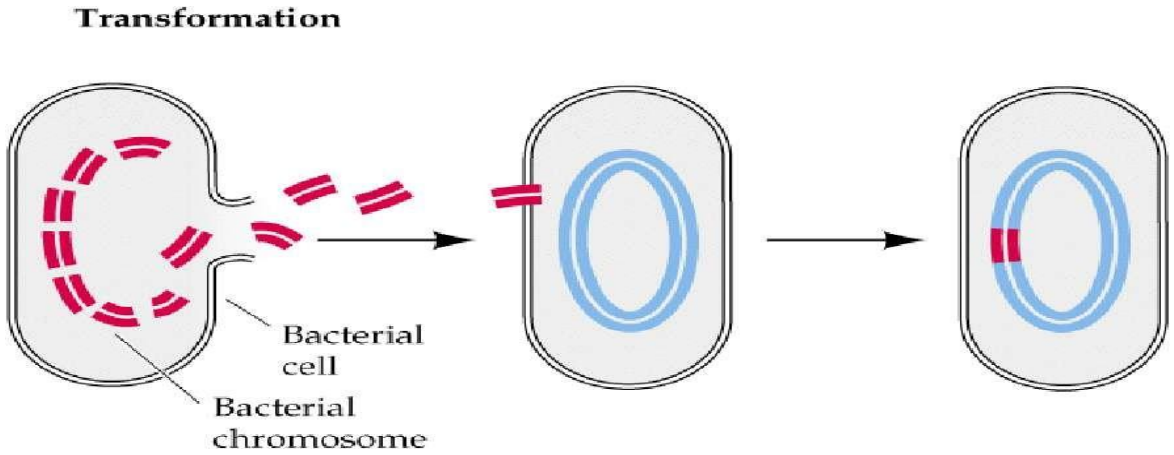
Resistance

Cont.,

Development of resistance

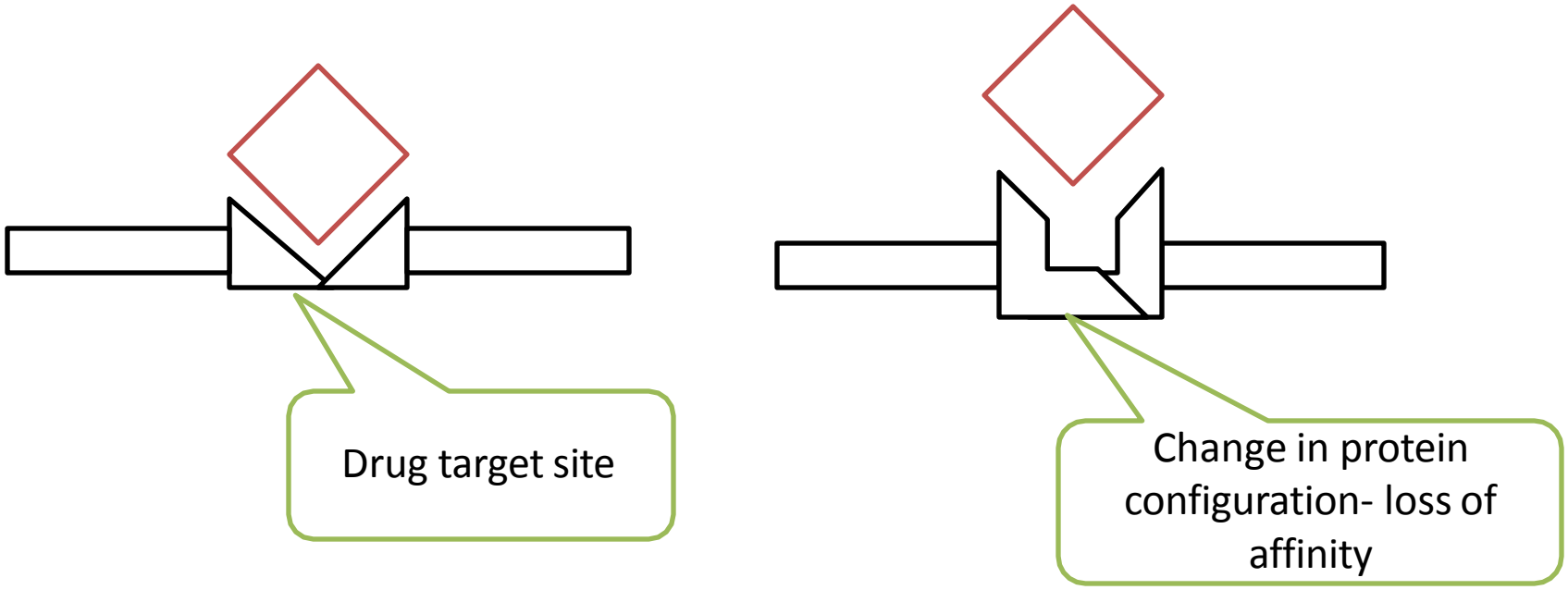
Gene transfer - Transformation:

- 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.



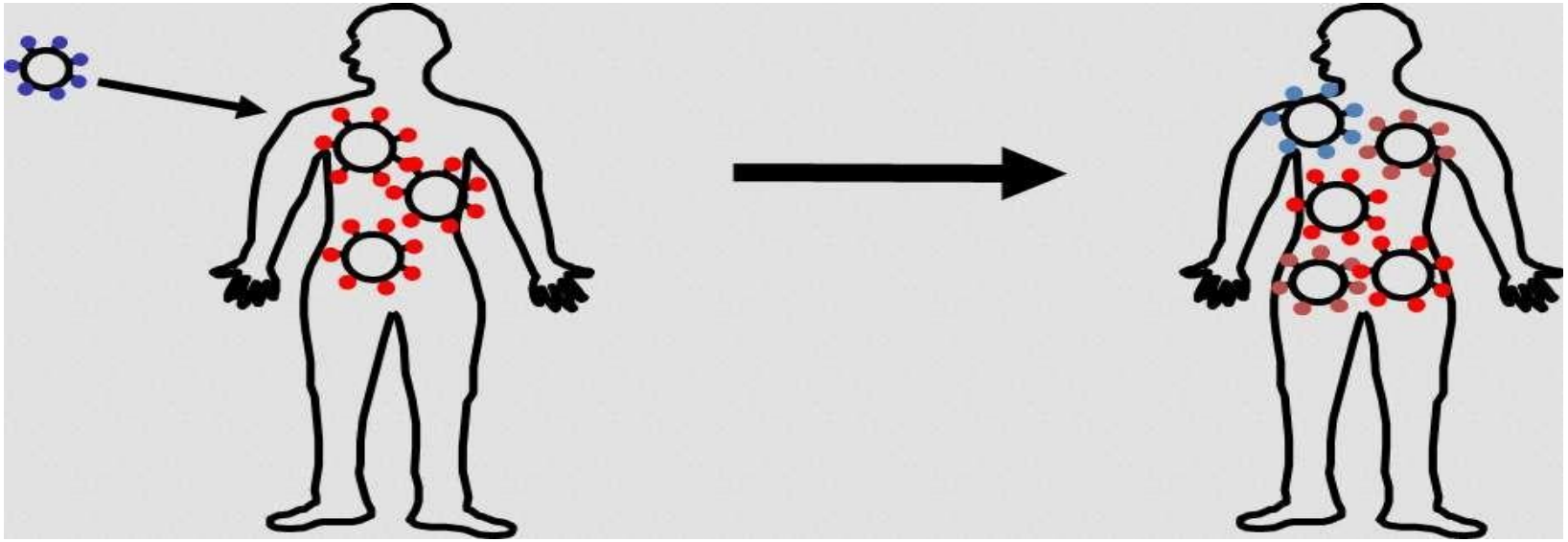
Drug Tolerant

- 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 nystatin 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

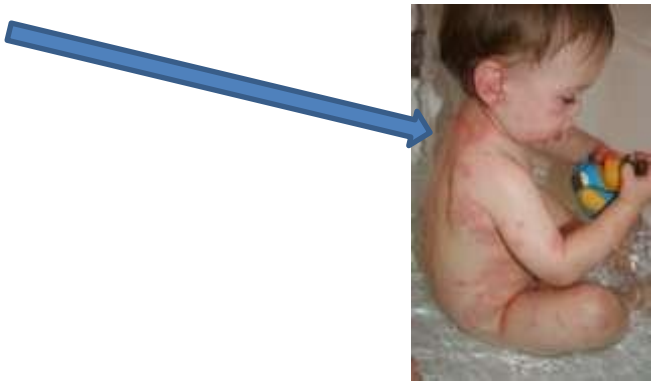
Drug factors

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 mothers
  - 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

Combination of antimicrobials

Combination 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

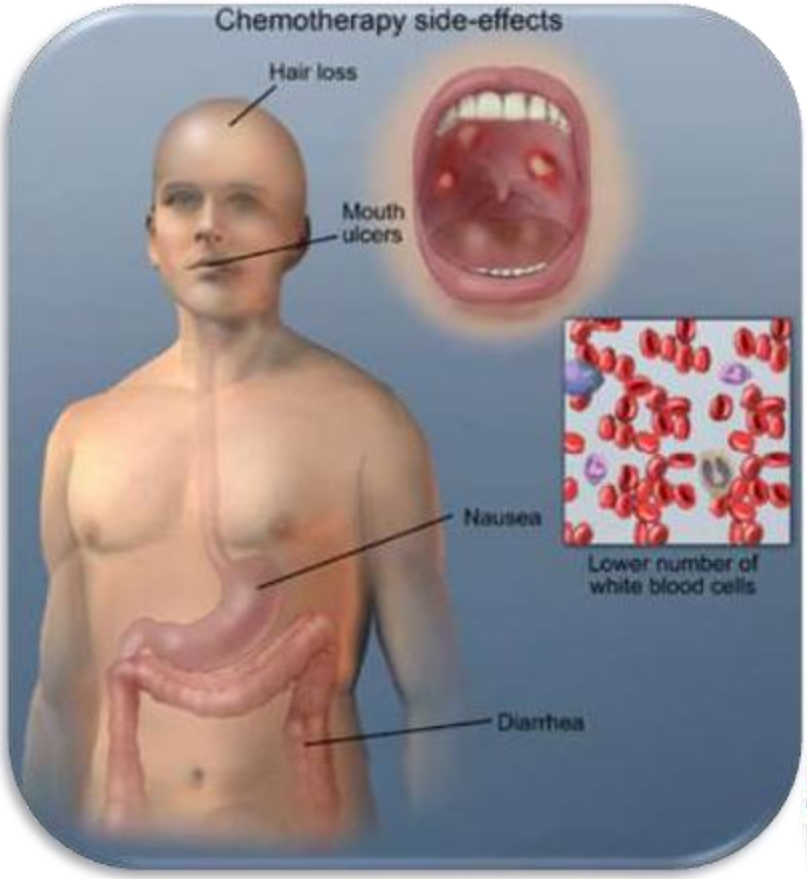
- Prophylaxis against specific organisms
  (Cholera: tetracycline prophylaxis;
  Malaria: for travelers to endemic area may take chloroquine/ mefloquine)

- Prevention of infection in high risk situations
- Cotrimoxazole or Norfloxacin.
- Surgical prophylaxis- Penicillin + Gentamicin injected single dose at the Dental extraction , Tonsillectomy, endoscopies,⇒Endocarditis- Few hour before give Amoxicillin.
- Catheterization- beginning of surgery have been found to effectively reduce the incidence of wound infection, how ever Cefazolin 1 gm iv is most favoured drug.
- 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



Common side effects with chemotherapeutics

Think before dispensing

Thank U