General Principles of Antimicrobial therapy

Dr. Omar Salim Ibrahim

Department of Pharmacology

- **Chemotherapy:** is the drug treatment for the diseases caused by bacteria and the other pathologic microorganisms, parasites, fungal and other.

- The objective of chemotherapy is to study and to apply the drugs that have highly selective toxicity to the pathogenic microorganisms in host body and have no or less toxicity to the host, so as to prevent and cure infective diseases caused by pathogens.

- **Antimicrobial agents:** chemical substances that can kill or suppress the growth of microorganisms

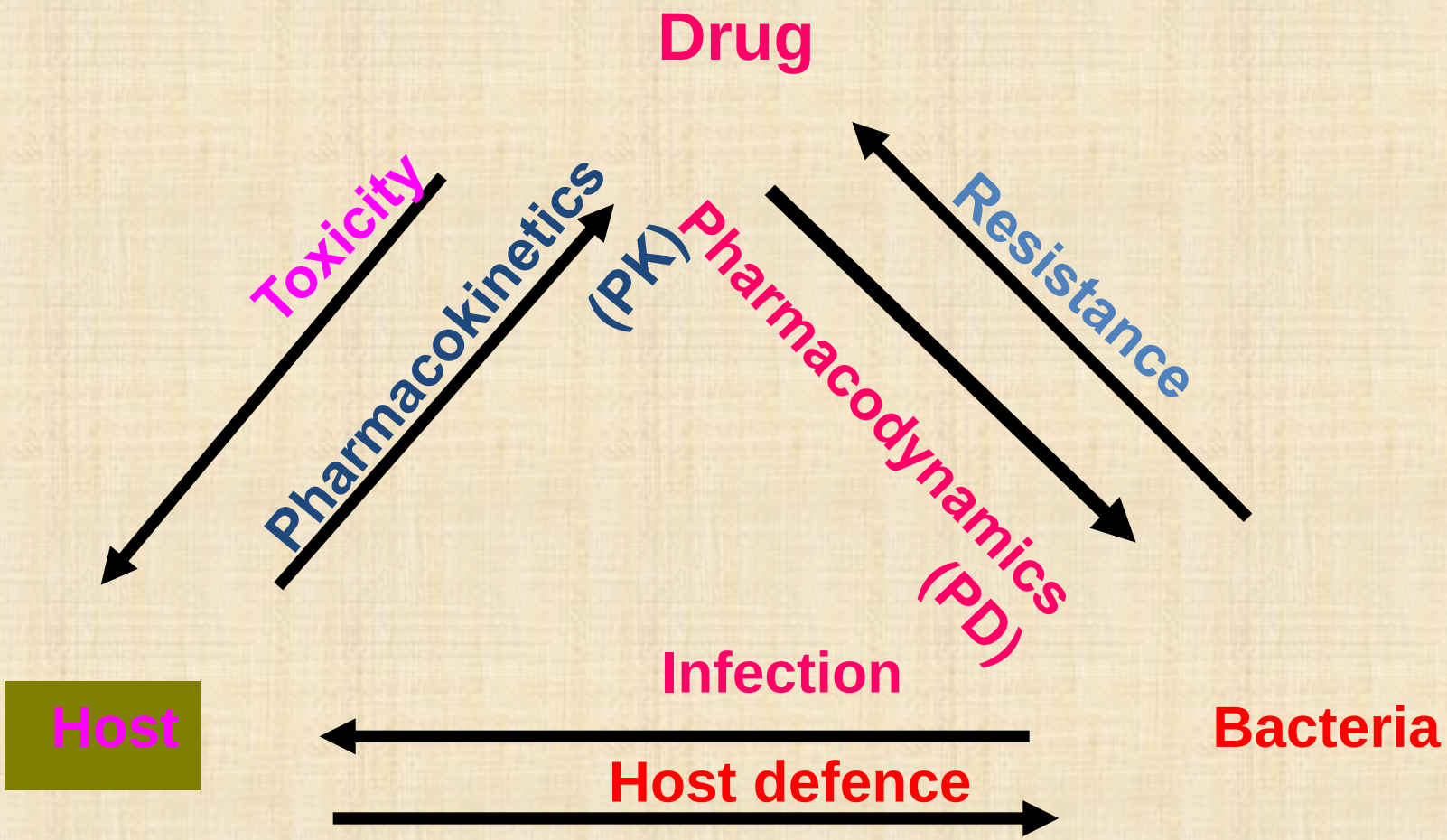
What is an Antibiotic?

- "Antibiotic" is from antibiosis, meaning **against life**.
- Substances produced by various species of microorganisms: bacteria, fungi— ***to kill or suppress the growth of other microorganisms*. It soluble substance.**
- Today the term antibiotic extends to include **synthetic antibacterial agents**: sulfonamides and quinolones.

History of Antimicrobial Therapy

- 1929 Penicillin discovered by Alexander Fleming
- 1940 Florey and Chain mass produce penicillin for war time use, becomes available to the public.
- 1935 Sulfa drugs discovered
- 1944 Streptomycin discovered by Waksman from *Streptomyces griseus*

There are Three in this Relationship

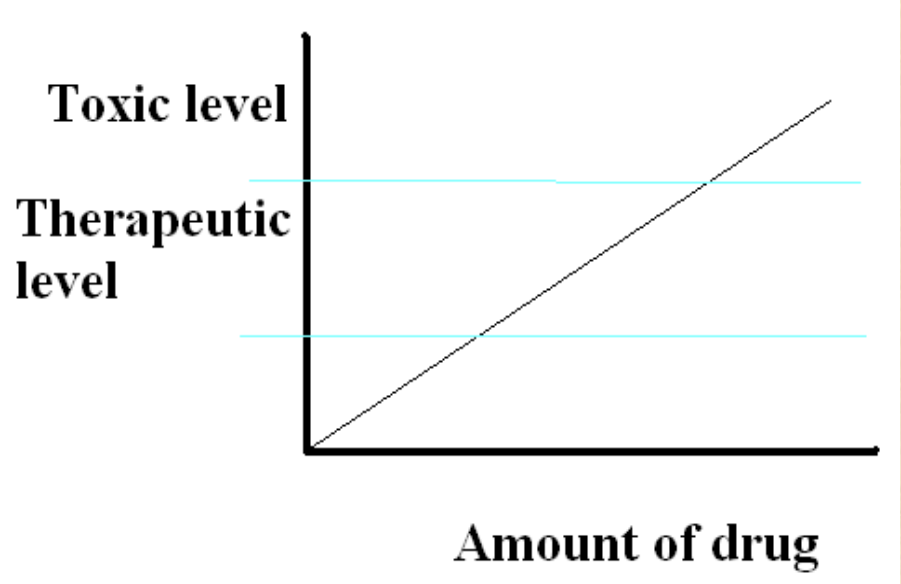


Selective toxicity means safer for host

- Antibiotics generally have a low MIC
  - Minimum inhibitory concentration
  - Effective at lower doses
- Good therapeutic index (Ti).
  - Safer; larger quantity must be administered before harmful side effects occur.

e.g. $Ti = LD_{50} / ED_{50}$

Where LD = lethal dose
ED = effective dose



- **Many infectious diseases once considered incurable and lethal are now amenable to treatment with a few pills.**

- Antimicrobial drugs are effective in the treatment of infections because of their ***selective toxicity***; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host.

- **The minimal inhibitory concentration (MIC)**

the minimum amount of a drug required to inhibit the growth of bacteria in vitro.

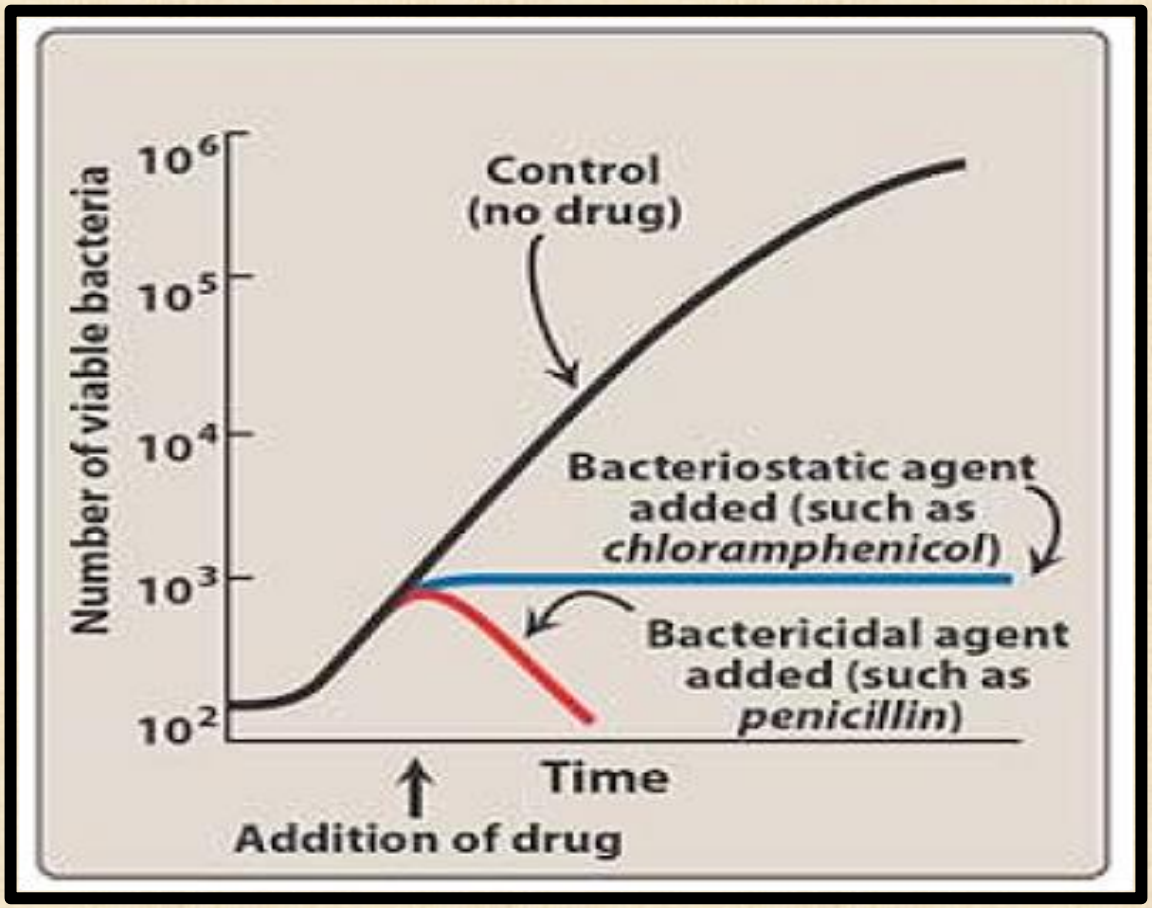
- **The minimal bactericidal concentration (MBC)**

the minimum amount of a drug required to kill bacteria in vitro.

Types of infection and their treatment

- Bacterial infections- antibacterial that can be ***bacteriostatic*** (they inhibit the growth susceptible bacteria) or ***bactericidal*** (they kill susceptible bacteria).

- Fungal infections- *antifungal*
- Mycobacterial infections- *antimycobacterial*
- Helminthiasis- *antihelminthic*
- Protozoal infections- *antiprotozoal*
- Viral infection- *antiviral*



Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

Bacteriostatic	Bactericidal
Macrolides	Beta-lactams
Tetracyclines	Penicillins, Cephalosporins
Chloramphenicol	Monobactams, Carbapenems
Sulphonamides	Aminoglycosides
Trimethoprim	Bacitracin
Lincomycin, clindamycin	Isoniazid
Ethambutol	Metronidazol
Nitrofurantoin	Polymyxines
	Pyrazinamid
	Quinolons, Rifampicin
	Vancomycin, teicoplanin

Types of Bacteria

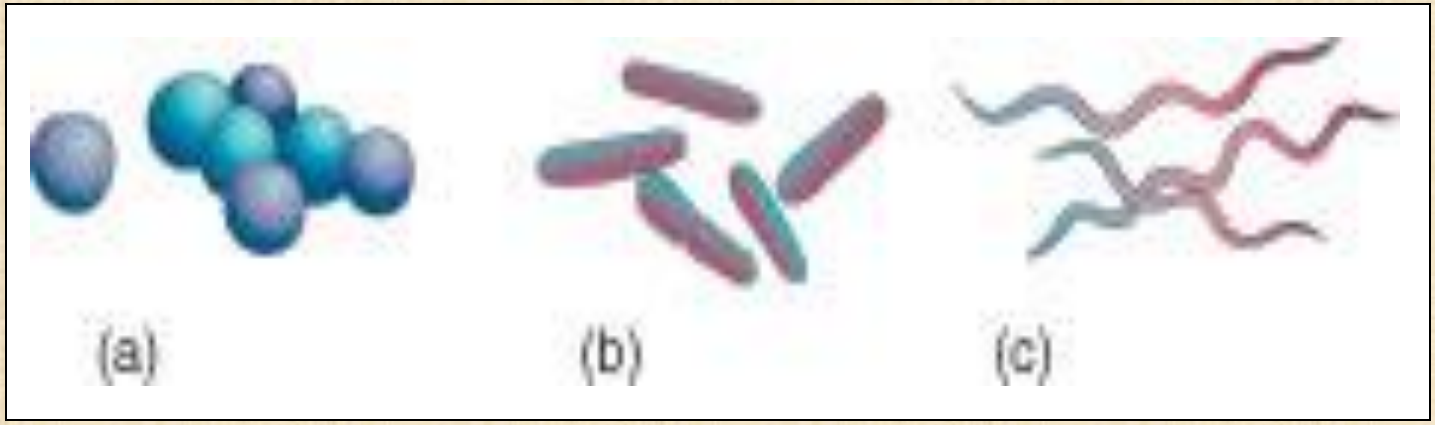
- **Aerobic bacteria**

  needs oxygen to survive

- **Anaerobic bacteria**

  survives in the absence of oxygen

Bacteria Shapes



(a) Round cocci

(b) Rod-like bacilli

(c) Spiral-shaped spirochetes

SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowing:-

1) the organism's identity.
2) the organism's susceptibility to a particular agent.
3) the site of the infection.
4) patient factors e.g. age, weight, pregnancy or breast-feeding, hepatic and renal status, etc.
5) the safety of the agent.
6) the cost of therapy.

However, some patients require empiric therapy (umbrella therapy)—that is, immediate administration of drug(s) prior to bacterial identification and susceptibility testing.

Effect of the site of infection on therapy:

(*The blood-brain barrier*)

- **Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated.**
- **Lipid solubility of the drug: lipid-soluble drugs, such as chloramphenicol and metronidazole, have significant penetration into the CNS.**
- **Molecular weight of the drug: high molecular weight (for example, vancomycin) penetrate poorly, even in the presence of meningeal inflammation.**
- **Protein binding of the drug.**

Safety of the agent

- **Many of the antibiotics, such as the penicillins, are among the least toxic of all drugs because they interfere with a site unique to the growth of microorganisms.**

- **Other antimicrobial agents (for example, *chloramphenicol) are less microorganism specific and are reserved for* life-threatening infections because of the drug's potential for serious toxicity to the patient.**

Cost of therapy

- **Often several drugs may show similar efficacy in treating an infection, but vary widely in cost.**
- Standard treatment of Helicobacter pylori includes various combinations of two or three antimicrobial agents along with a proton pump inhibitor.

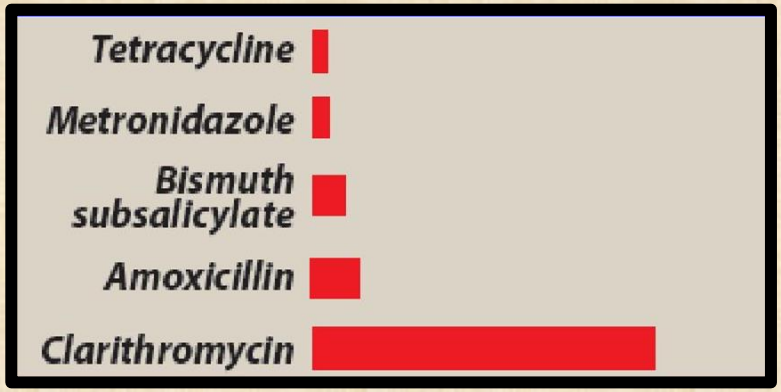


Figure illustrates relative cost of some drugs used for the treatment of peptic ulcers caused by H. pylori.

- It also demonstrates that a triple therapy regimen including clarithromycin is significantly more expensive than the bismuth subsalicylate based quadruple therapy.

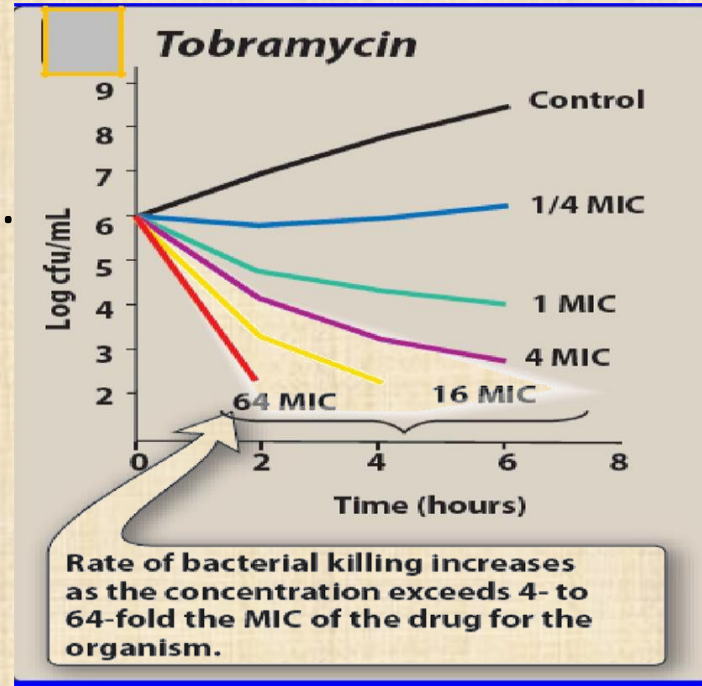
ROUTE OF ADMINISTRATION

- The oral route of administration is chosen for infections that are mild and is favourable for treatment on an outpatient basis.
- In patients requiring a course of i.v therapy initially, the switch to oral agents should occur as soon as possible.
- However, some antibiotics, such as *vancomycin, the aminoglycosides,* and *amphotericin B, are so poorly absorbed from the GIT* that adequate serum levels cannot be obtained by oral administration.
- Parenteral administration is used for drugs that are poorly absorbed from the GIT and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents than can be reliably obtained by the oral route.

DETERMINANTS OF RATIONAL DOSING

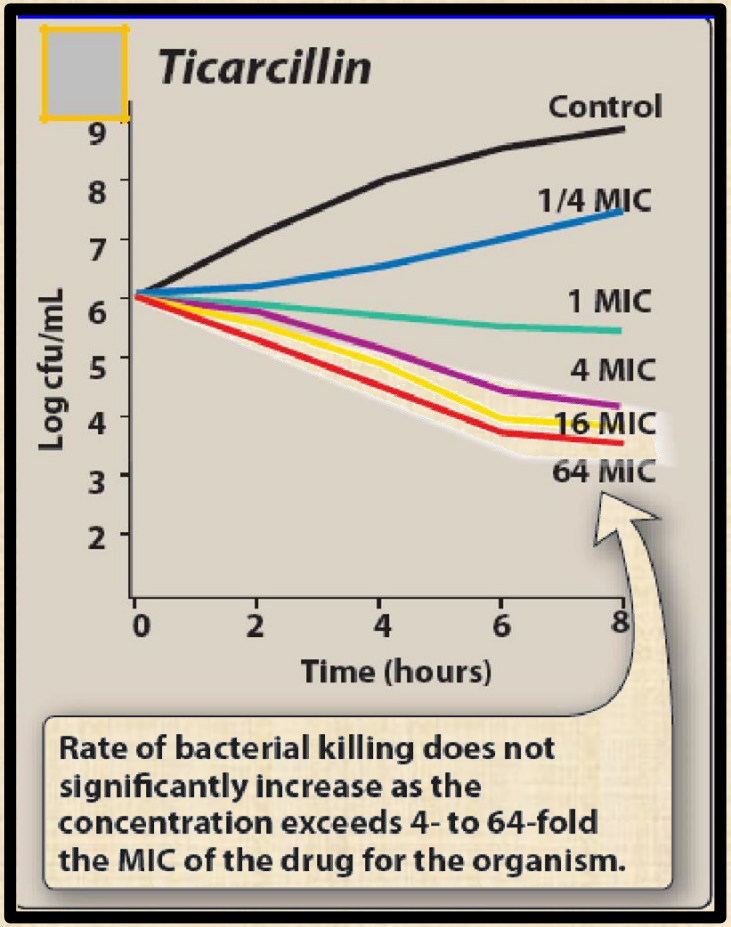
- **Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (the absorption, distribution, metabolism and elimination of the drug by the body).**

1-Concentration-dependent killing: Certain antimicrobial agents, including **aminoglycosides**, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism.



2-Time-dependent (concentration-independent) killing:

By contrast, β-lactams, glycol peptides, macrolides, *clindamycin, and linezolid* do not exhibit this concentration-dependent property; that is, increasing the concentration of antibiotic to higher multiples of the MIC does not significantly increase the rate of kill.



CHEMOTHERAPEUTIC SPECTRA

1-Narrow-spectrum antibiotics

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. E.g., *isoniazid* is active only against mycobacteria.

2-Extended-spectrum antibiotics

Extended spectrum is the term applied to antibiotics that are effective against gram-positive organisms and also against a significant number of gram-negative bacteria.

For example, ampicillin is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria.

3-Broad-spectrum antibiotics

- Drugs such as *tetracycline and chloramphenicol affect a wide variety of* microbial species and are referred to as broad-spectrum antibiotics.

COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism.

This strategy:-

1-reduces the possibility of superinfection.

2-decreases the emergence of resistant organisms.

3- Synergistic: action of one drug enhances the activity of another

4- To provide broad coverage (when the infection is due to more than one organism).

5- For initial therapy (when the patient is seriously ill and the results of culture are pending).

6- **Decreased toxicity**: The addition of flucytosine to amphotericin B in the treatment of fungal meningitis makes it possible to reduce the dose of amphotericin B, thus, reduced risk of renal damage.

- For example, the treatment of tuberculosis benefits from drug combinations.

- However, situations in which combinations of drugs are employed do exist.

B. Disadvantages of drug combinations:-

Antagonism (A number of antibiotics act only when organisms are multiplying. Thus, co-administration of an agent that causes bacteriostatic plus a second agent that is bactericidal may result in the first drug interfering with the action of the second.

1. Increased risk of toxic and allergic reactions
2. An increase in the number or severity of adverse effects.
3. Increased cost to the patient.

Good Combination

-**Two bactericidal** e.g. Cell wall inhibitor and amionglycosides

-**Two bacteriostatic** e.g. Quinupristin and dalfopristin

DRUG RESISTANCE.

- Bacteria are said to be resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth.
- Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are inherently resistant to *vancomycin.*
- When the bacteria show resistance to one drug, they are also resistant to some other drugs. This phenomenon is called cross drug resistance.
- The emergence of bacteria that are resistant to several drugs is the major cause of failure in the treatment of infectious diseases.

- **Over use and inappropriate use of antibiotics has fueled or play a major increase in prevalence of multidrug-resistant pathogens, leading some to speculate that we are nearing the end of the antibiotic era.**

- **Drug resistance: is the phenomenon that susceptibility of pathogenic microorganisms to drugs becomes lower or even loses after the microorganisms contact with drugs many times.**

Types of resistance.

- **Intrinsic or natural resistance.(e.g. no target site in the bacteria).**
- **Acquired resistance.**

–Resistance acquired by mutation,

–Resistance acquired by R-factors on plasmids is common, very rapid method of acquiring resistance that often involves resistance to many antibiotics. (*R factor contains genes coding for enzymes that make the cell resistant to antibiotics*)

Mechanisms of antibacterial resistance.

- ✓ **Produce *enzymes* that destroy the chemical structures of drugs.**
- ✓ **Change their cell membrane and cell wall *permeability* to the drug.**
- ✓ **Develop an *altered structural target* for the drug.**

Antibiotic inactivation.

– bacteria acquire genes encoding enzymes that inactivate antibiotics

- **Examples include:**

– b-lactamases
– aminoglycoside-modifying enzymes
– chloramphenicol acetyl transferase

Bacterial Drug Resistance

The origin of drug resistance may be non-genetic or genetic.

1. **Non genetic Origin**:

- Bacteria may be sensitive to certain antibiotics *in vitro* but may appear to be resistant *in vivo*. This may be true with infections with intracellular microorganisms such as in brucellosis, salmonellosis, and tuberculosis. In these cases, drugs may fail to reach the **intracellular** site of action and therefore resulting in failure of treatment.

2. Genetic Origin:

-Most drug-resistant microbes emerge as a result of genetic change and subsequent selection processes by antimicrobial drugs.

a. Chromosomal Resistance:

This develops as a result of spontaneous mutation, the presence of the antimicrobial drug serves as a selecting mechanism to suppress susceptible organisms and favour the growth of drug-resistant mutants.

Antibiotic resistance can arise from a number of mechanisms involving mutation of chromosomal genes. Such mechanisms, usually involving mutations in genes encoding drug targets or systems that affect drug accumulation, are defined as endogenous resistance mechanisms, to distinguish them from the exogenous resistance mechanisms that are typically mediated by the acquisition of plasmids and transposons.

b. Extra chromosomal Resistance:

Bacteria often contain extra chromosomal genetic elements called **plasmids.**

- **R factors** are a class of plasmids that carry genes for resistance to one and often several antimicrobial drugs and heavy metals.
- Plasmid genes for antimicrobial resistance often control the formation of enzymes capable of destroying the antimicrobial drugs.

Genetic material and plasmids can be transferred by the following mechanisms:

- **Conjugation:**

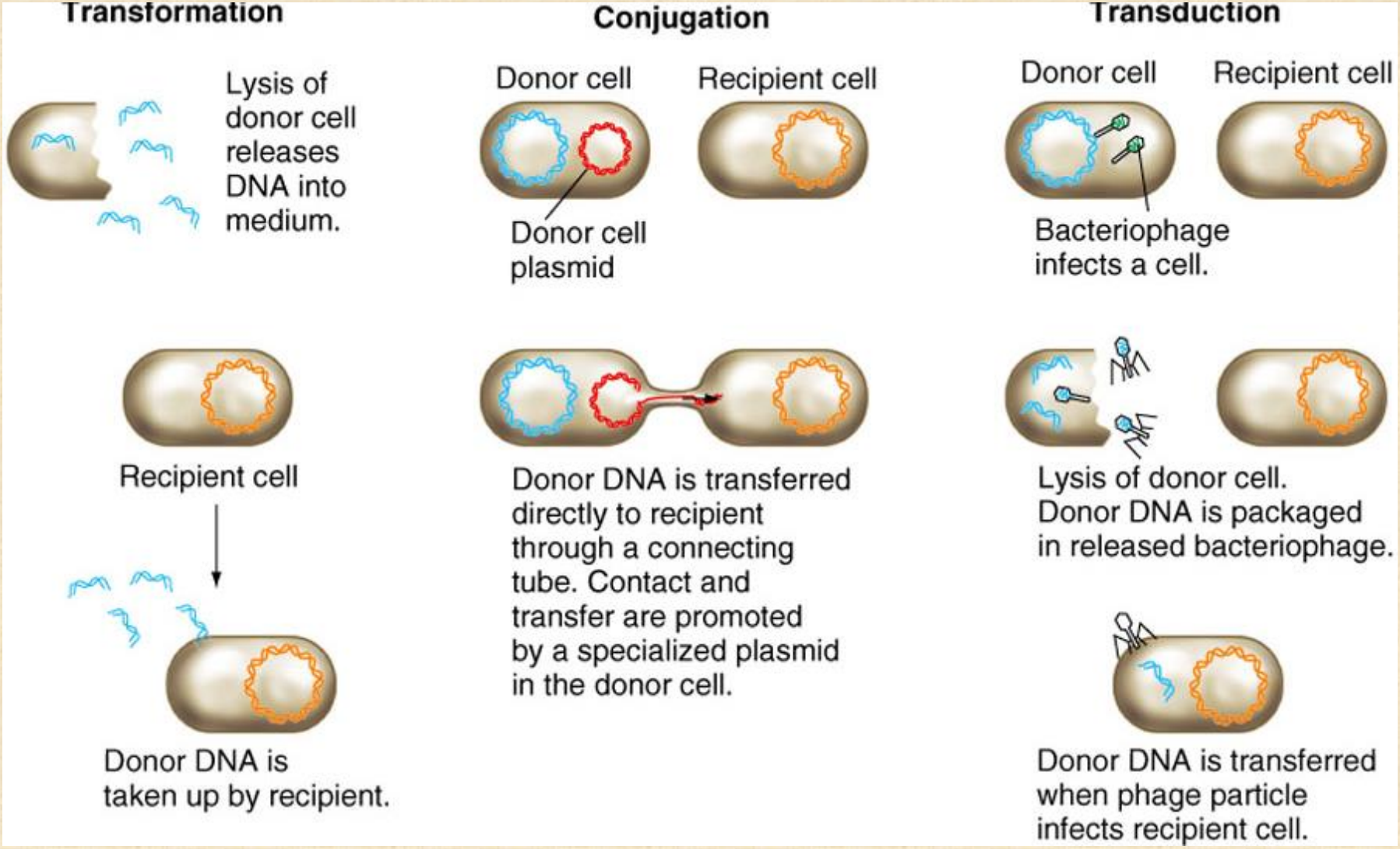
A unilateral transfer of genetic material between bacteria of the same or different genera occurs during a mating (conjugation) process. **Plasmid or other DNA is transferred through these protein tubules from the donor to the recipient cell**. A series of closely linked genes, each determining resistance to one drug, may thus be transferred from a resistance to a susceptible bacterium. This is the commonest method by which multidrug resistance spreads among different genera of gram-negative bacteria.

· **Transduction**: Plasmid DNA is enclosed in a bacterial virus (bacteriophage) and transferred by the virus to another bacterium of the same species (as in the case of staphylococci).

· **Transformation:** Naked DNA passes from one cell of a species to another cell thus altering its genotype.

· **Transposition:** A transfer of short DNA sequences (transposons, transposable elements) occurs between one plasmid and another or between a plasmid and a portion of the bacterial chromosome within a bacterial cell.

Mechanisms of bacterial gene transfer



PROPHYLACTIC ANTIBIOTICS

- Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections.
- **Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and super infection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks.**
- **The duration of prophylaxis should be closely observed to prevent unnecessary antibiotic exposure.**

COMPLICATIONS OF ANTIBIOTIC THERAPY

A. Hypersensitivity

- Hypersensitivity reactions to antimicrobial drugs or their metabolic products frequently occur.
- For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity

- High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host.
- For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the hair cells of the organ.

C. Super infections

- Drug therapy (with broad-spectrum antimicrobials or combinations of agents) can lead to alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms. These infections are often difficult to treat.

Post antibiotic effect (PAE).

The **persistent suppression** of bacterial growth after short antimicrobial exposure.

– Shows the capacity of an antimicrobial drug to inhibit the growth of bacteria after **removal** of the drug from the culture.

– **Serum concentrations** - below MIC.

– **Aminoglycosides**, **fluoroquinolones**, **tetracyclines**, **clindamycin**, **ketolides**, **rifampicin**, **azithromycin**.

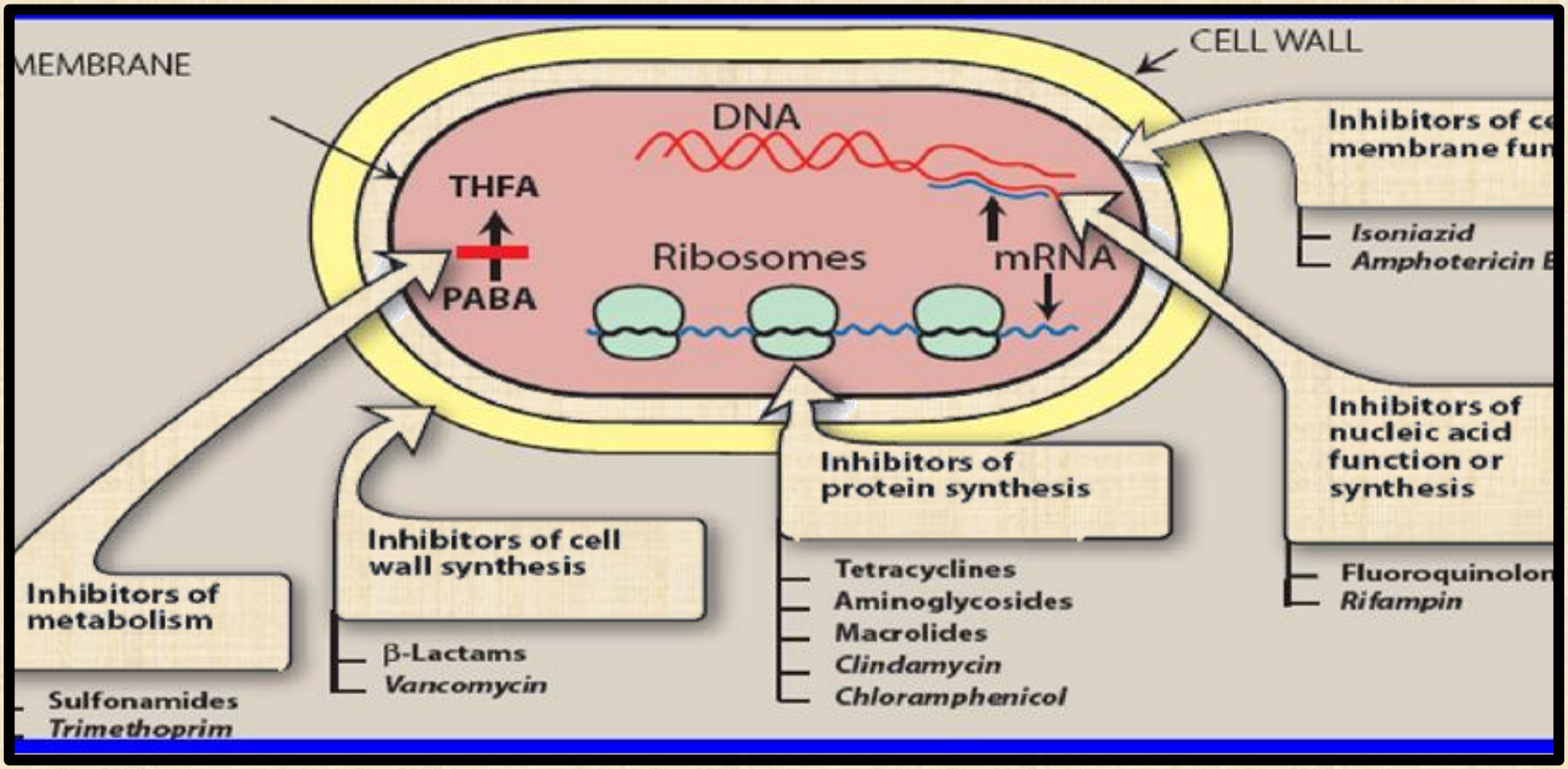
SITES OF ANTIMICROBIAL ACTIONS

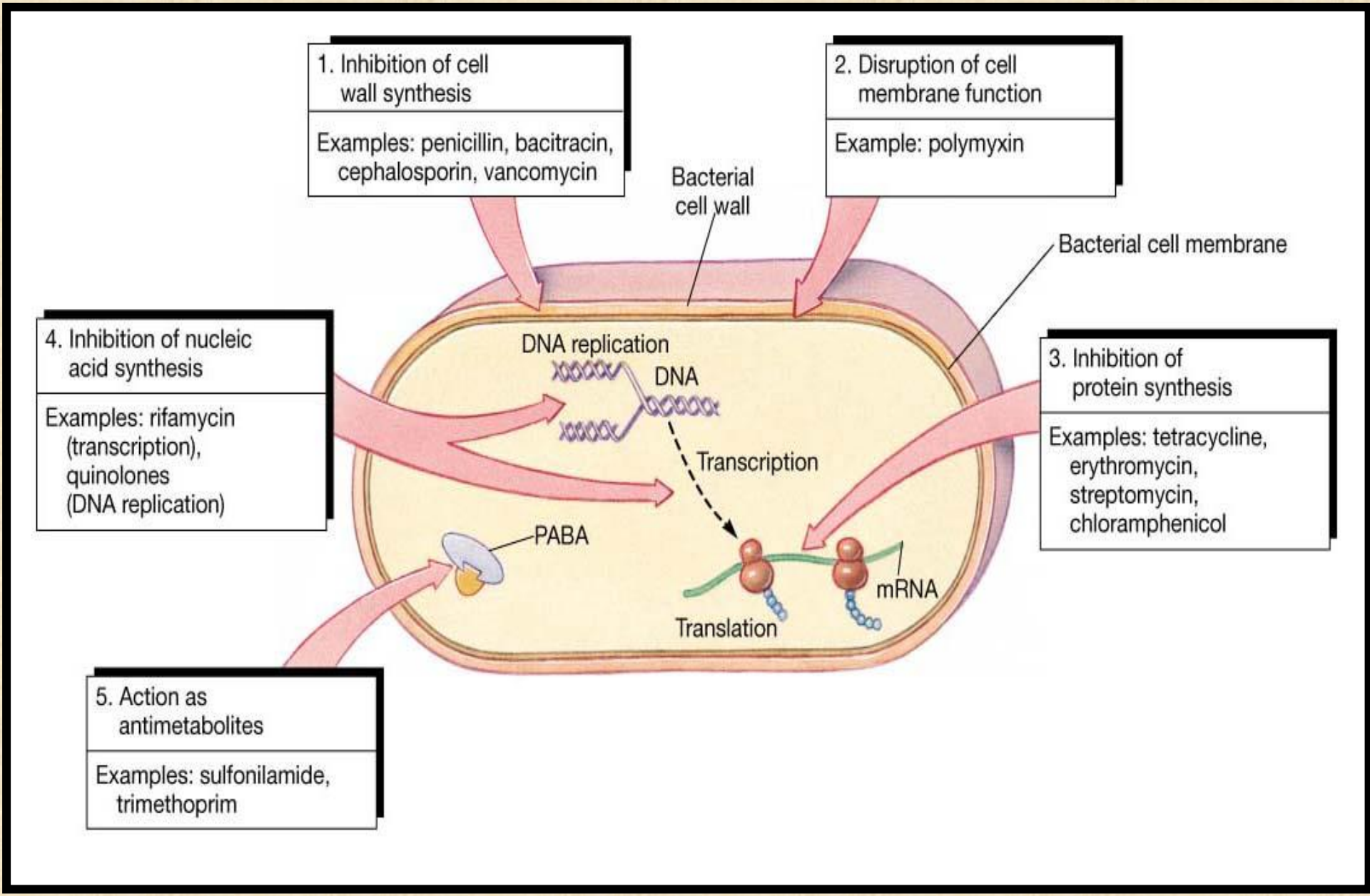
Antimicrobial drugs can be classified in a number of ways:

- by their chemical structure (e.g. β-lactams or aminoglycosides).
- by their mechanism of action (e.g., cell wall synthesis inhibitors).
- by their activity against particular types of organisms (e.g., bacteria, fungi, or viruses).

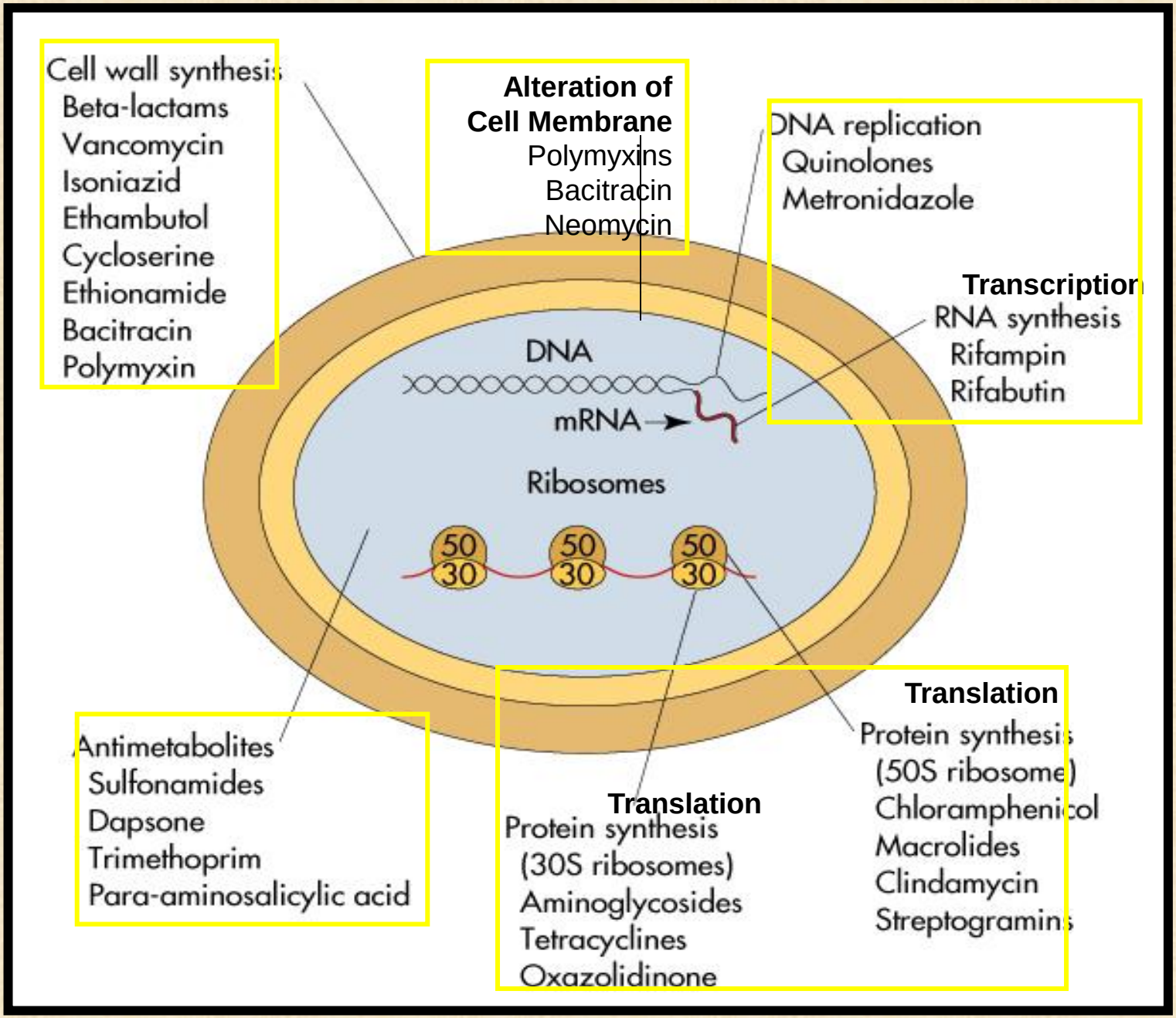
classification of the most important antimicrobial agents according to their mode of action.

Drug	Mode of Action	Activity
Sulphonamide	Folic acid synthesis inhibition	Bacteriostatic
Trimethoprim	Folinic acid synthesis inhibition	Bacteriostatic
Penicillins Cephalosporins Imipenem Vancomycin Aztreonam	Cell wall damage	Bactericidal
Tetracyclines Chloramphenicol Erythromycin Clindamycin Spectinomycin	Protein synthesis inhibition	Bacteriostatic
Aminoglycosides		Bactericidal
Polymixin B Amphotericin B Nystatin	Membrane damage	Bactericidal
Rifampicin Ciprofloxacin Metronidazole Nalidixic acid	Nucleic acid synthesis inhibition	Bactericidal

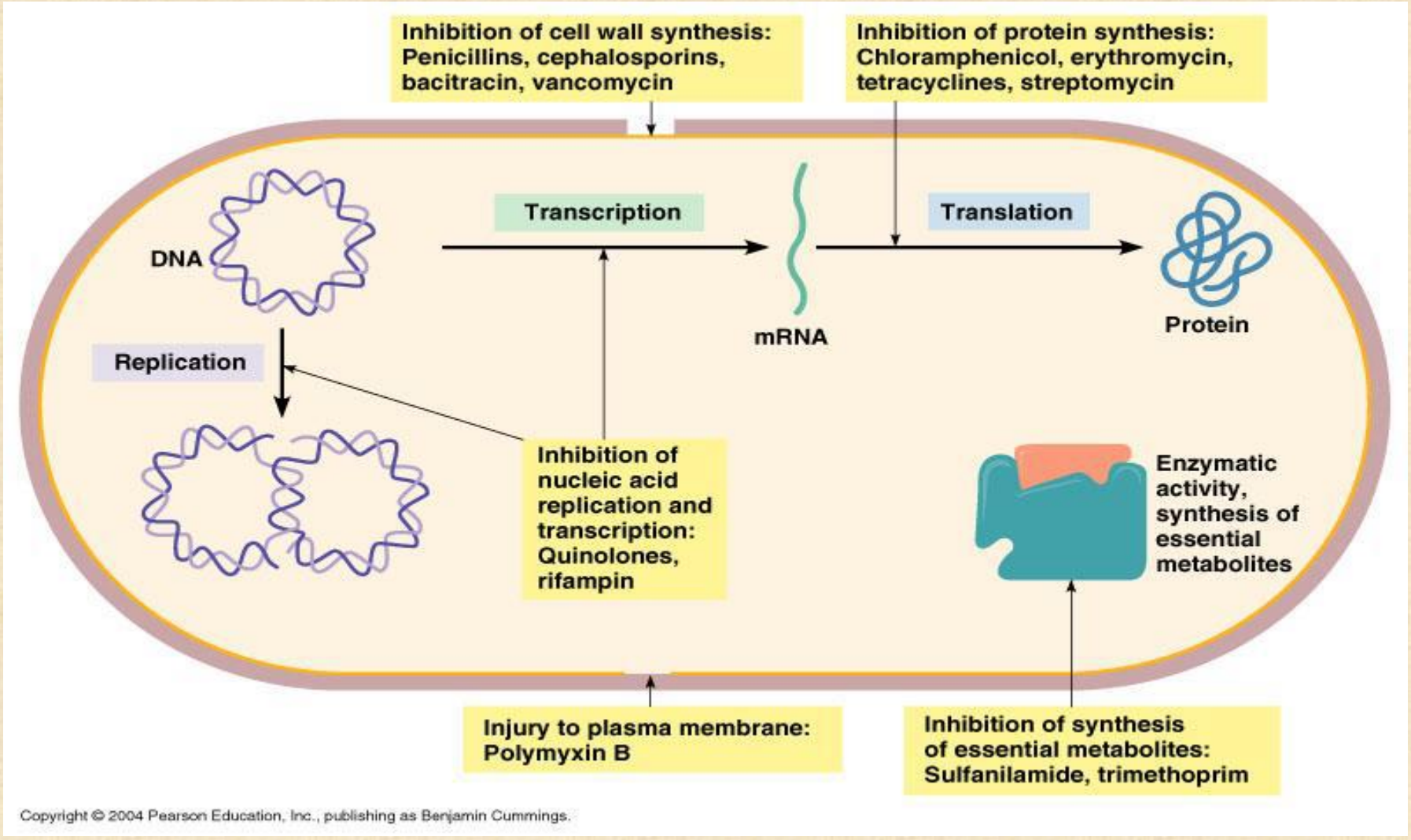

MEMBRANE
CELL WALL
DNA
THFA
PABA
Ribosomes
mRNA
Inhibitors of cell membrane fun
Isoniazid
Amphotericin B
Inhibitors of nucleic acid function or synthesis
Fluoroquinolon
Rifampin
Inhibitors of protein synthesis
Tetracyclines
Aminoglycosides
Macrolides
Clindamycin
Chloramphenicol
Inhibitors of cell wall synthesis
β-Lactams
Vancomycin
Inhibitors of metabolism
Sulfonamides
Trimethoprim


1. Inhibition of cell wall synthesis
Examples: penicillin, bacitracin, cephalosporin, vancomycin
2. Disruption of cell membrane function
Example: polymyxin
Bacterial cell wall
Bacterial cell membrane
4. Inhibition of nucleic acid synthesis
Examples: rifamycin (transcription), quinolones (DNA replication)
DNA replication
DNA
Transcription
3. Inhibition of protein synthesis
Examples: tetracycline, erythromycin, streptomycin, chloramphenicol
PABA
mRNA
Translation
5. Action as antimetabolites
Examples: sulfonilamide, trimethoprim

Antibiotic Mechanisms of Action



Modes of ATB Action



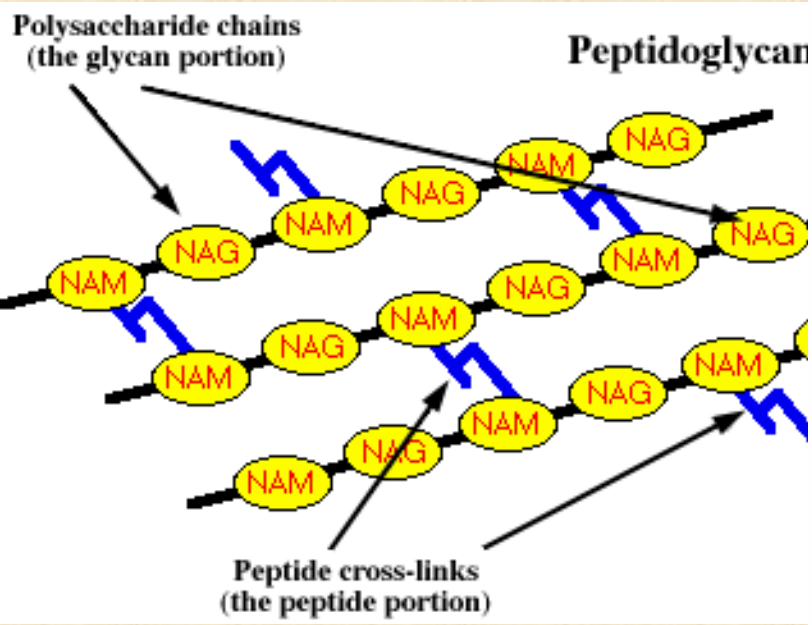
Classification of the important antimicrobial drugs based on principal therapeutic objectives by susceptible organisms.

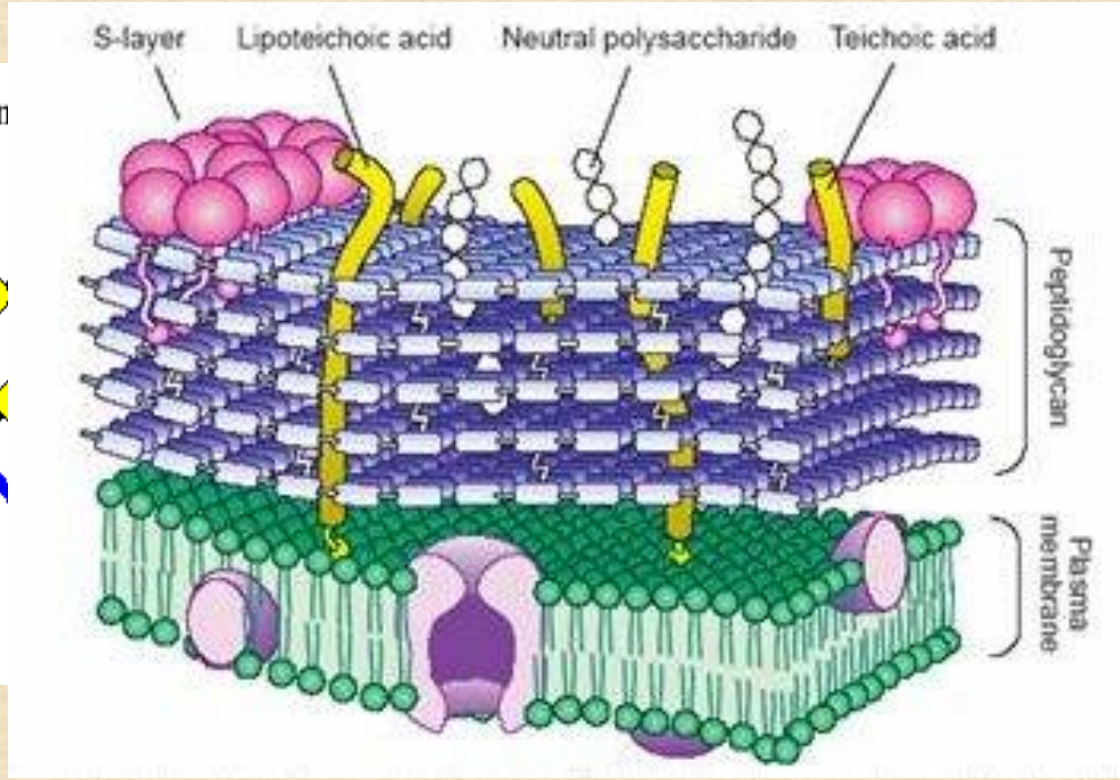
Antibacterial Drugs	Susceptible Organisms
Narrow Spectrum Agents Penicillin G Penicillinase-Resistant Penicillin Erythromycin Clindamycin Vancomycin Sodium fusidate	Primarily gram positive cocci and gram positive bacilli
Cephalosporins (1^{st} & 2^{nd} generation)	Primarily gram positive cocci
Aminoglycosides	Primarily gram negative aerobes
Metronidazole	Anaerobic bacilli
Isoniazid (Rifampicin) Ethambutol Pyrazinamide Dapsone	Mycobacteria
Broad Spectrum Agents Broad spectrum penicillins (e.g. ampicillin, amoxicillin) Cephalosporins (3^{rd} generation, e.g. cefotaxime) Tetracyclines Chloramphenicol Trimethoprim Sulphonamides Ciprofloxacin Imipenem	Gram positive cocci and gram negative bacilli

cell walls continued

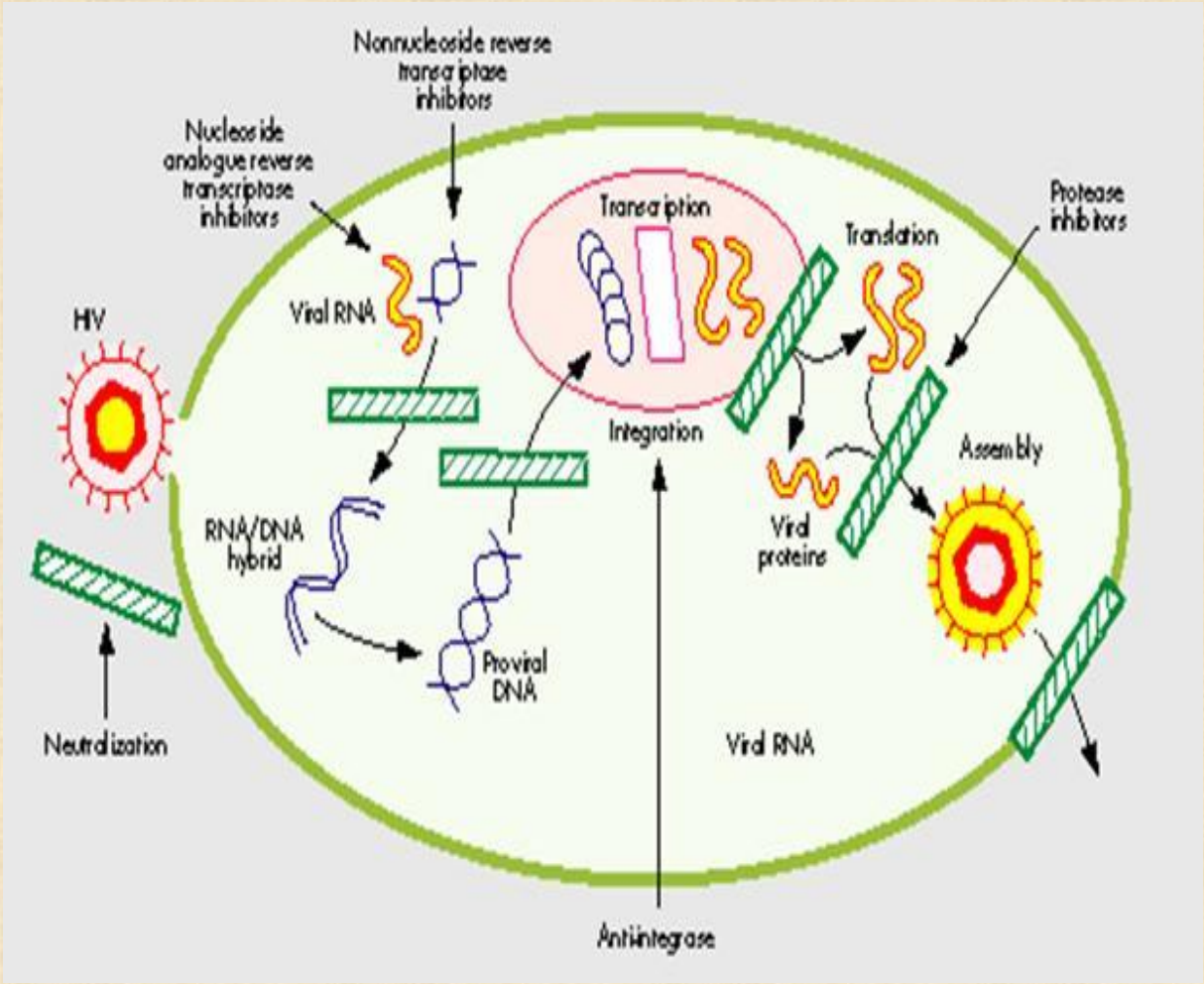
- Chemical structure of peptidoglycan contributes to its function
  - Polysaccharide chains composed of 2 alternating sugars, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM)
  - Cross-linked in 3 dimensions with amino acid chains
  - A breach in peptidoglycan endangers the bacterium

Peptidoglycan Molecule





Cross links are both horizontal and vertical between glycan chains stacked atop one another.


Nonnucleoside reverse transcriptase inhibitors
Nucleoside analogue reverse transcriptase inhibitors
Transcription
Translation
Protease inhibitors
HIV
Viral RNA
Integration
Assembly
RNA/DNA hybrid
Viral proteins
Proviral DNA
Neutralization
Viral RNA
Antiintegrase

Gram positive & Gram Negative

- Gram positive bacteria have a thick cell wall
  - Peptidoglycan directly accessible from environment
- Gram negative bacteria have a different wall
  - Thin layer of peptidoglycan
  - Surrounded by an **outer membrane** composed of lipopolysaccharide, phospholipids, and proteins
  - Outer membrane is a barrier to diffusion of molecules including many antibiotics
    - Some hydrophobic antibiotics may diffuse in.
    - Porins allow passage of only some antibiotics