Antimicrobials (2)

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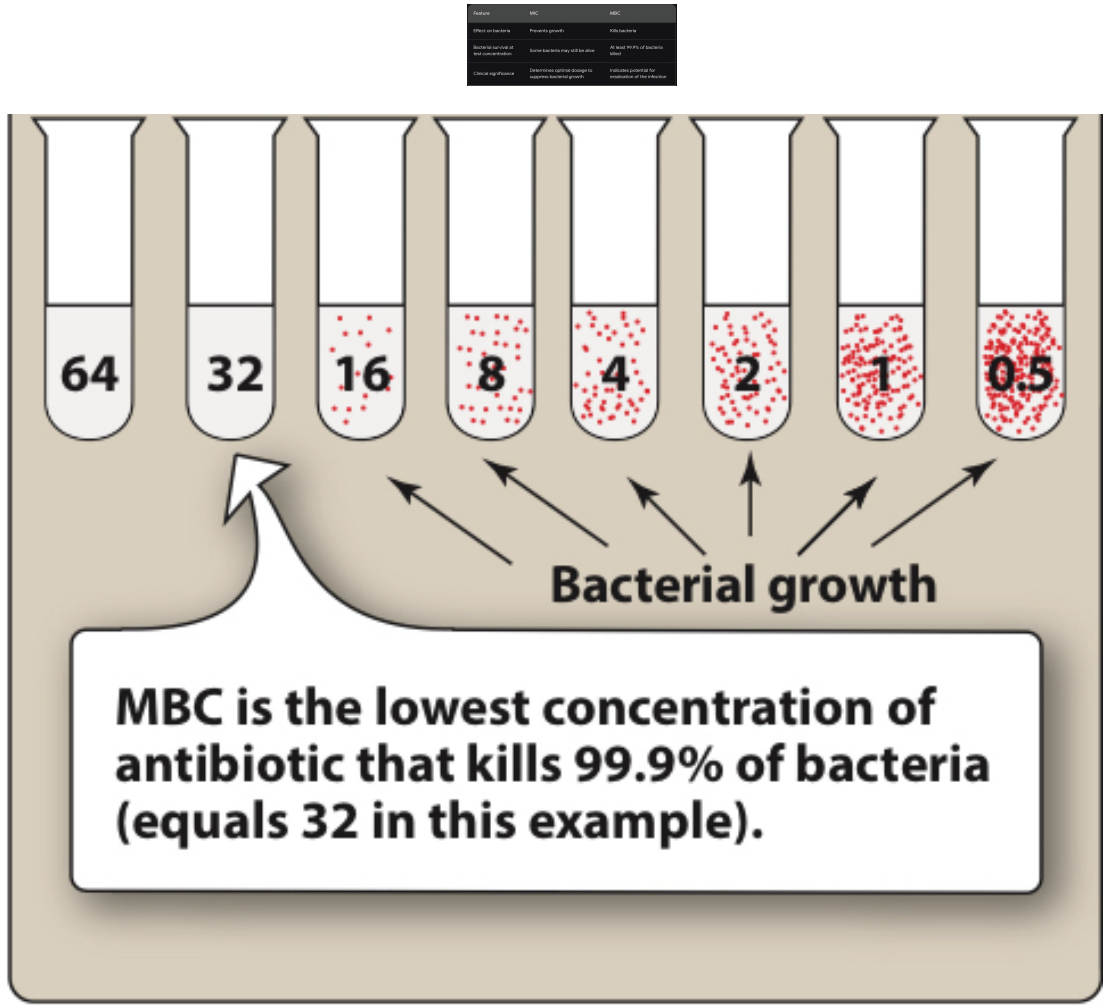
MBC and ALL

MBC: (Minimal Bactericidal Concentration) Lowest concentration of antibiotic that reduces the number of viable cells by at least 1000-fold.

The MBC of a truly bactericidal agent is equal to or just slightly above its MIC.

AAL: The Attainable Antibiotic level is the concentration of the drug that can be reached in the target tissues without causing toxic or side-effects.

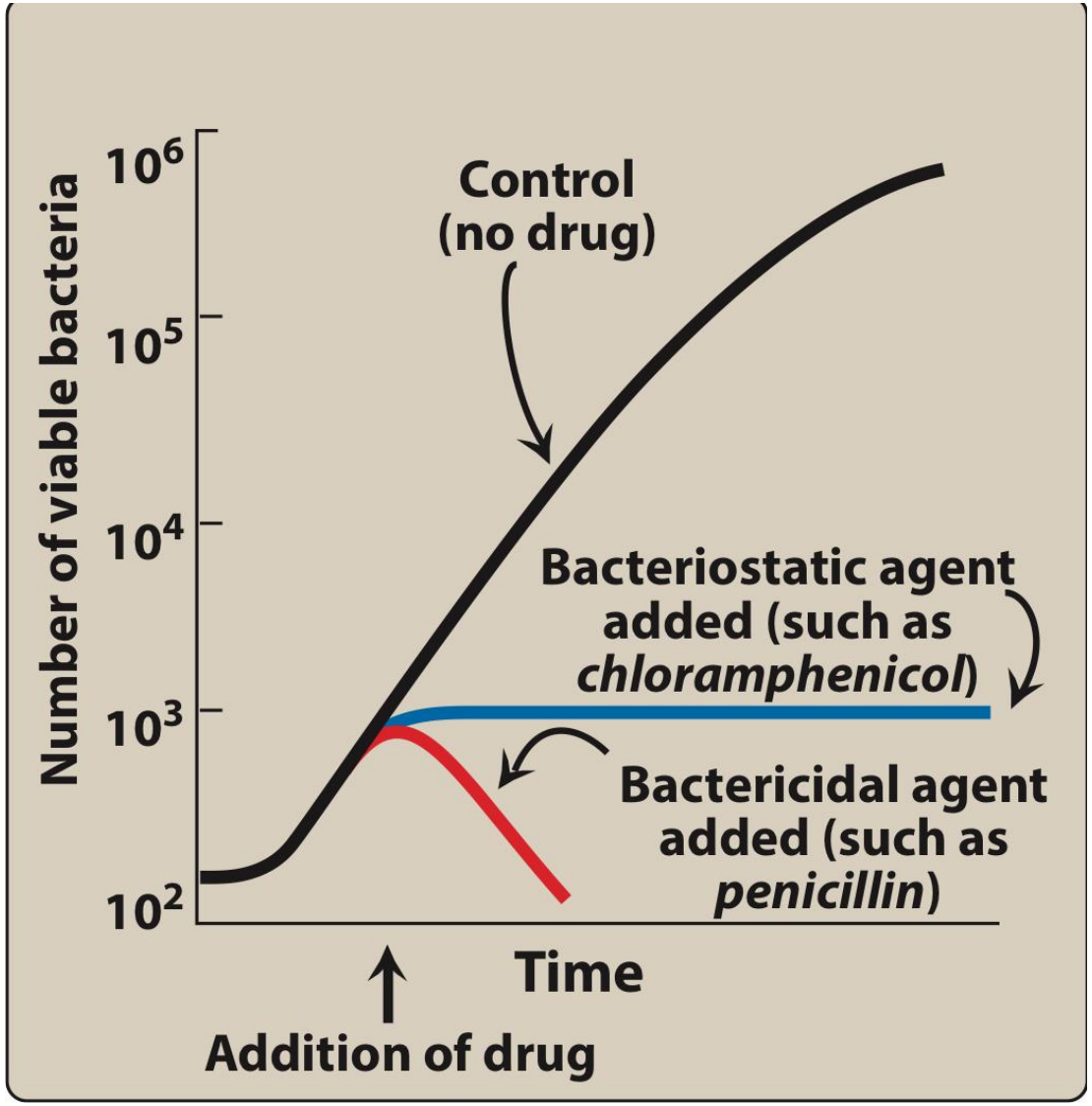


Cidal VS. Static

If you grow bacteria in a medium and observe the number of viable bacteria without using a drug, their number is going to increase as they multplicate and reproduce continuously.

Bacteriostatic is going to decrease the number and bacteriocidal is going to reduce it further.

Bacteriostatic can lead to the same effect of bacteriocidal if the drug is used and along with a good immune system, so it will lead to a complete end of the infection.



Trough Levels:

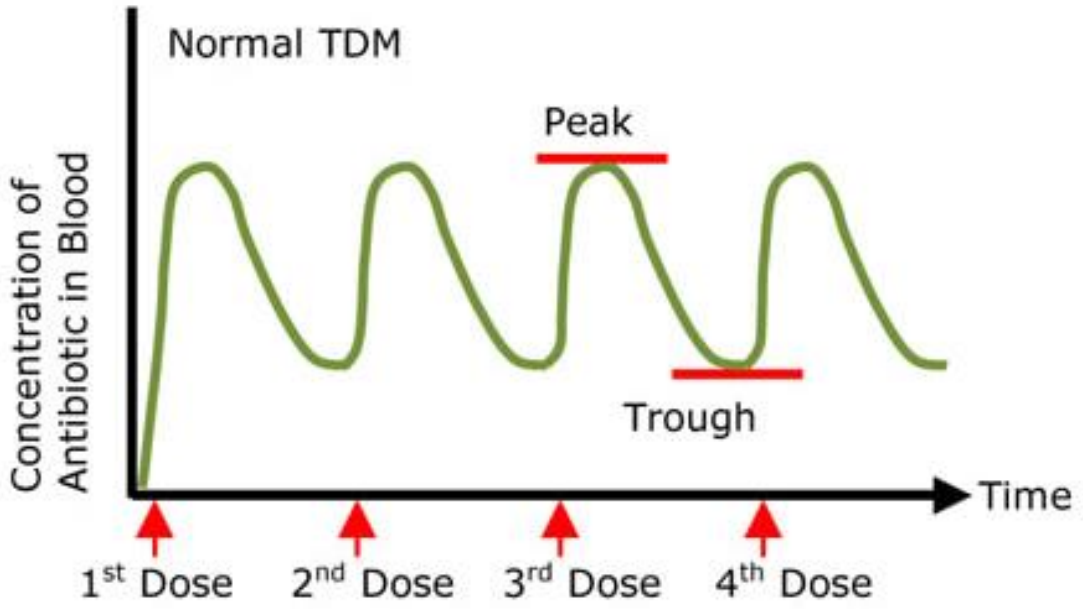
Levels of antibiotics reach minimal levels (troughs) at roughly predictable times after administration .

The troughs may be at, or below the MIC.

This may or may not be a problem because of two factors:

Post Antibiotic Effect, a prolonged period before bacteria resume growth.

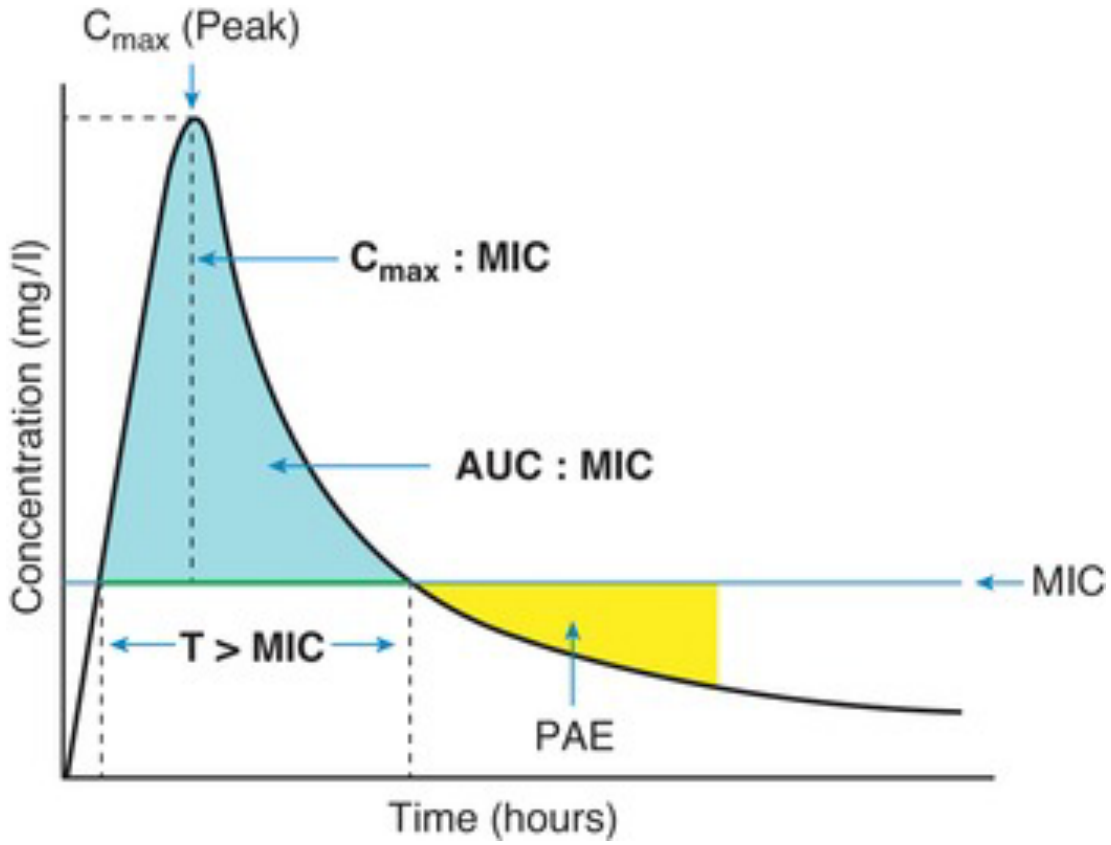
Synergism between host defenses and sub-MIC levels of antibiotics.



Post-antibiotic effect (PAE)

PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.

Antimicrobial drugs exhibiting a long PAE (several hours) require only one dose per day (e.g. Aminoglycosides & Fluroquinolones).



MIC and drug resistance

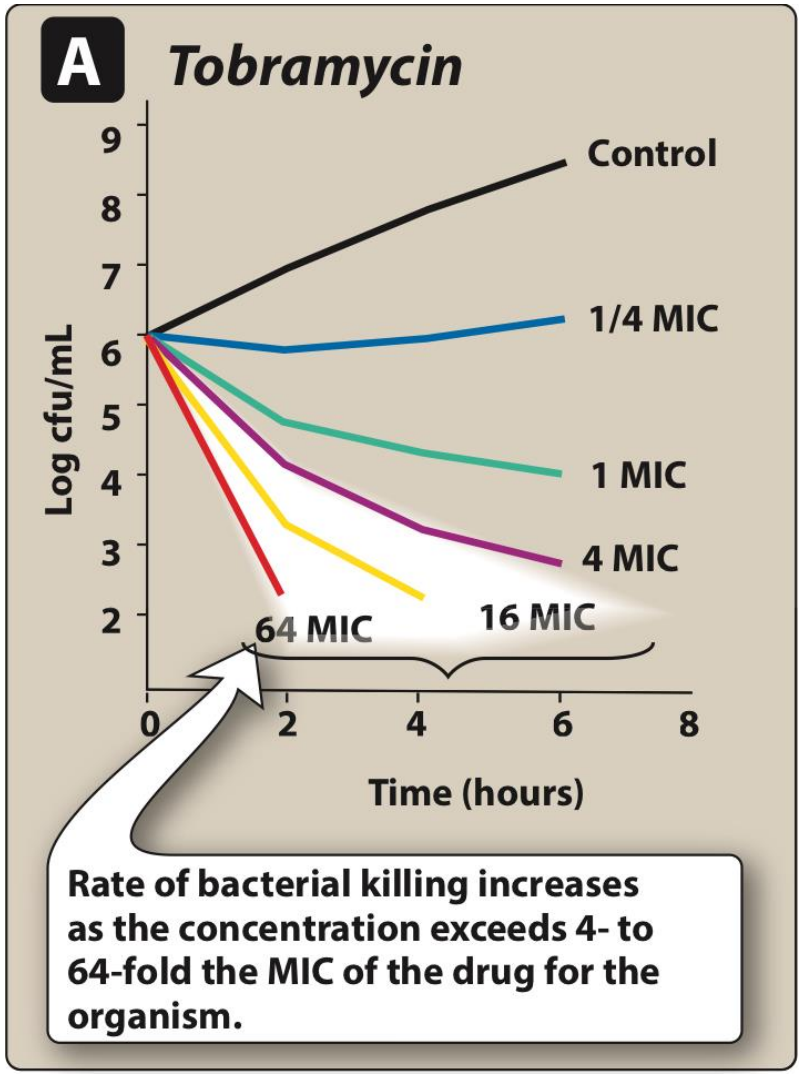
Trough levels may increase the frequency of drug-resistant bacteria.

Frequency of developing resistance is greatly increased at levels below, at or little bit above the MIC.

Development of resistance to ciprofloxacin is 10,000 times more frequent at 2 times the MIC compared to 8 times the MIC.

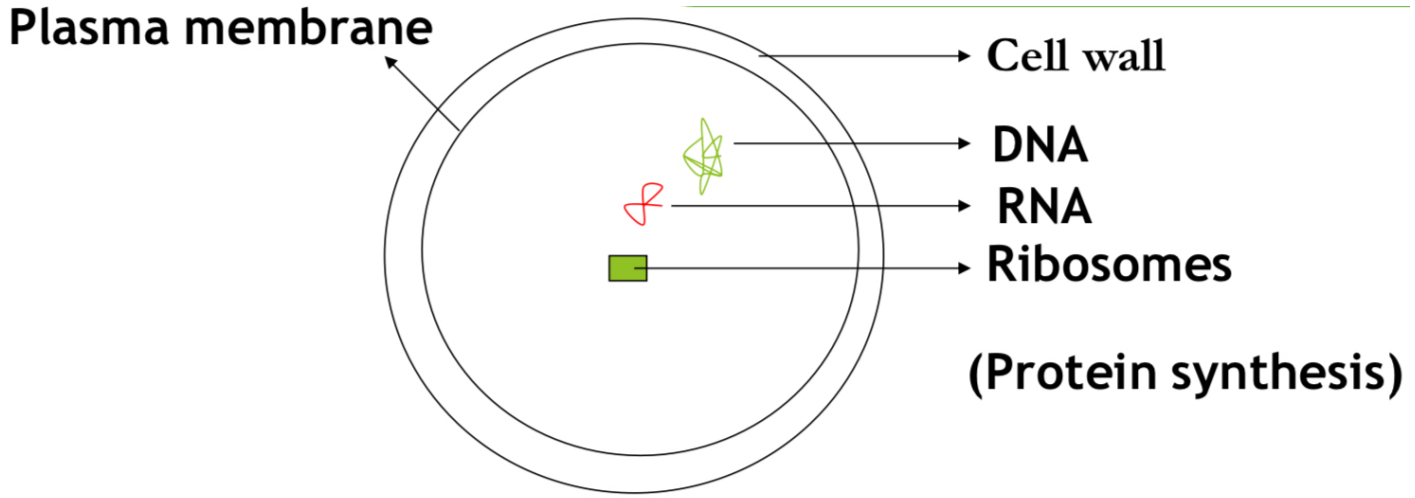
NOTE: major problem for using antibiotics, it could bear resistance by the bacteria.

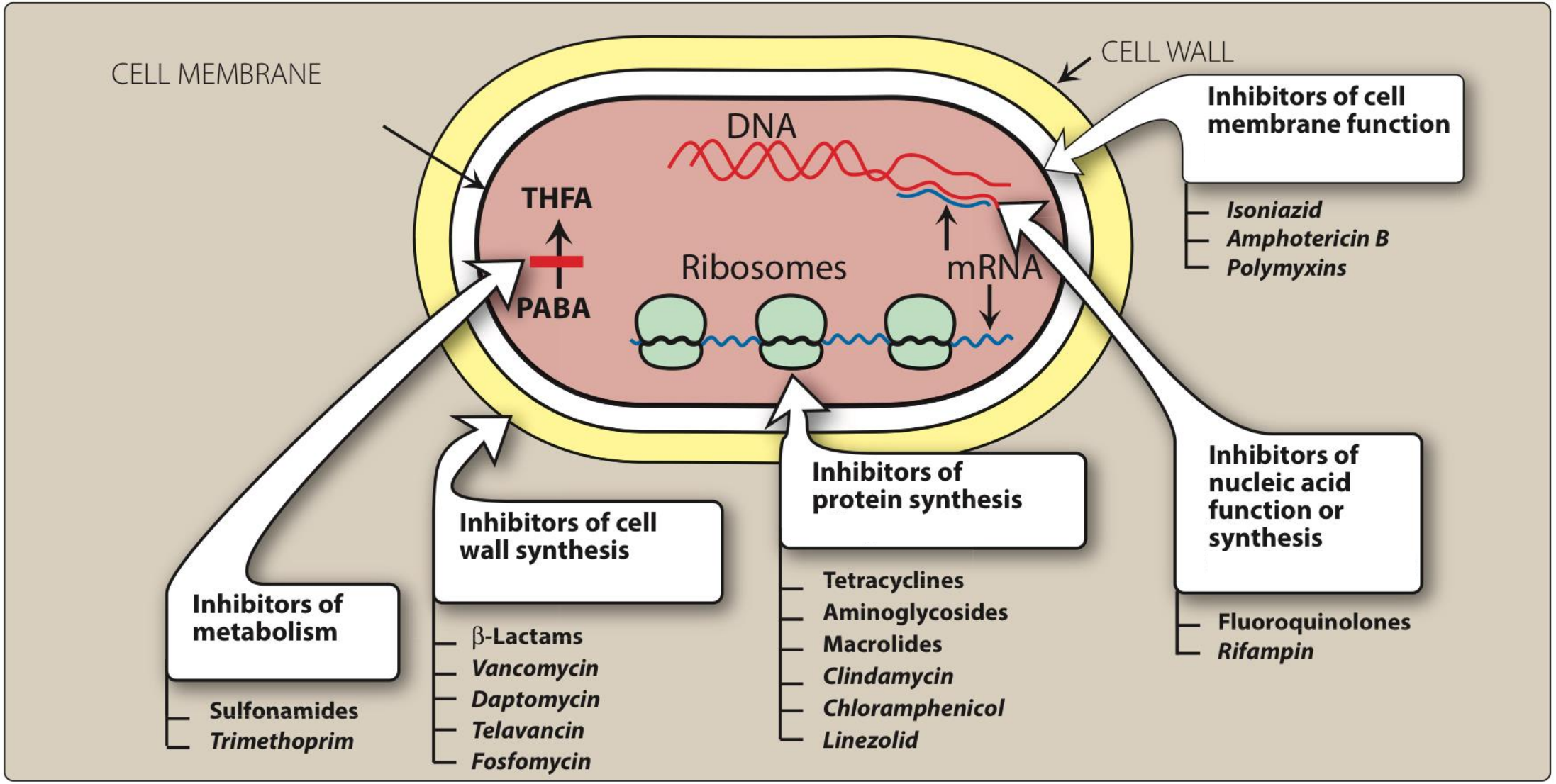
Inadequate trough levels of antibiotics may increase the risk of drug-resistant bacteria, emphasizing the importance of maintaining proper drug concentrations for effective treatment and resistance prevention.



Mechanism of action

- Bacteria is prokaryotic cell, it has characteristics not found in our cells, which gives selectivity for the given antibiotic to act on. Like cell wall of the bacteria.
- Then , the antibiotics would target these unique structures.




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

MOA of Antibiotics

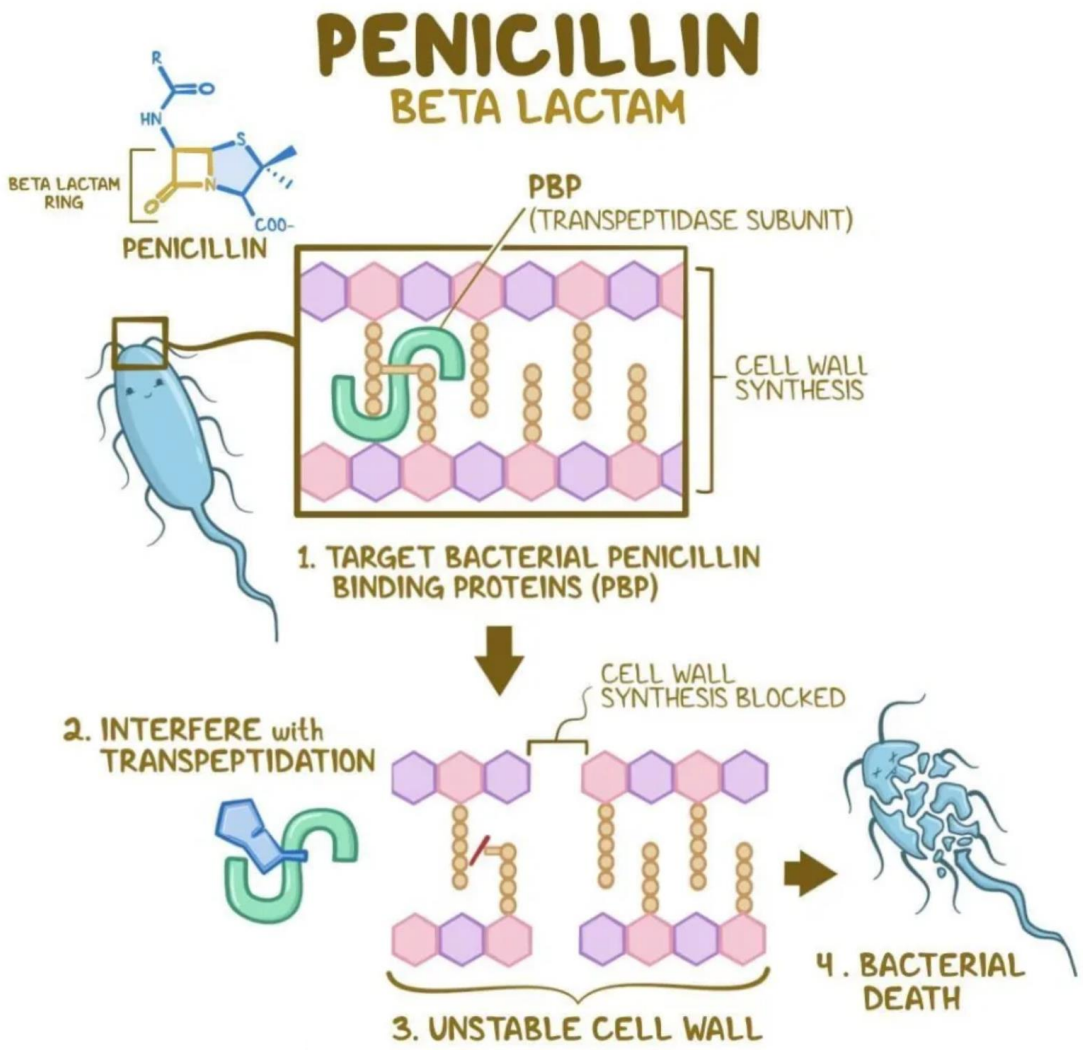
Inhibitors of cell wall synthesis:

Penicillins, Cephalosporins, Bacitracin, Vancomycin, Cycloserine…etc-

Most bacteria have rigid cell walls that are not found in host cells (selective toxicity).

Cell wall inhibitors work by inhibiting the formation of peptidoglycans that are essential in cell wall formation.

Disruption of the cell wall causes death of the bacterial cell (Bactericidal).



MOA of Antibiotics

Interference with permeability or function of plasma membrane:

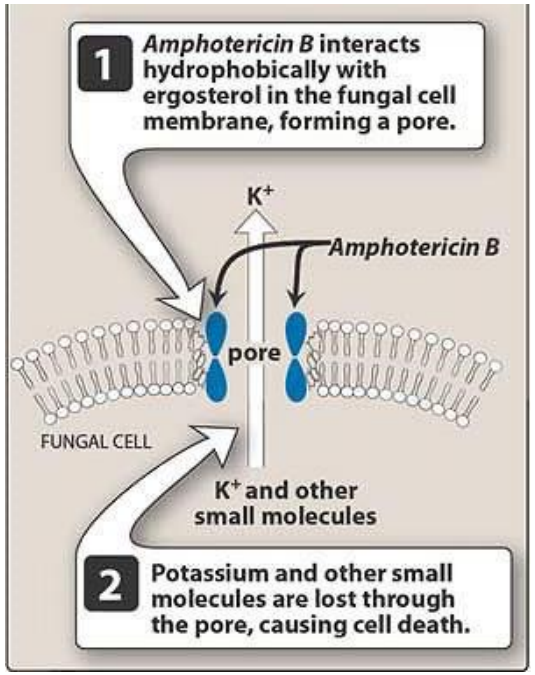
Antifungal agents (Colistin, Nystatin, Amphotericin B, Polymyxin B).

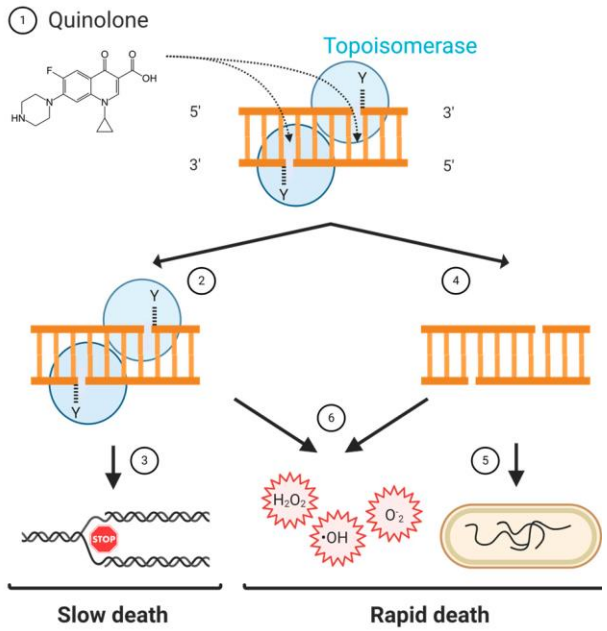
Inhibitors of DNA synthesis or replication (DNA disturbers):

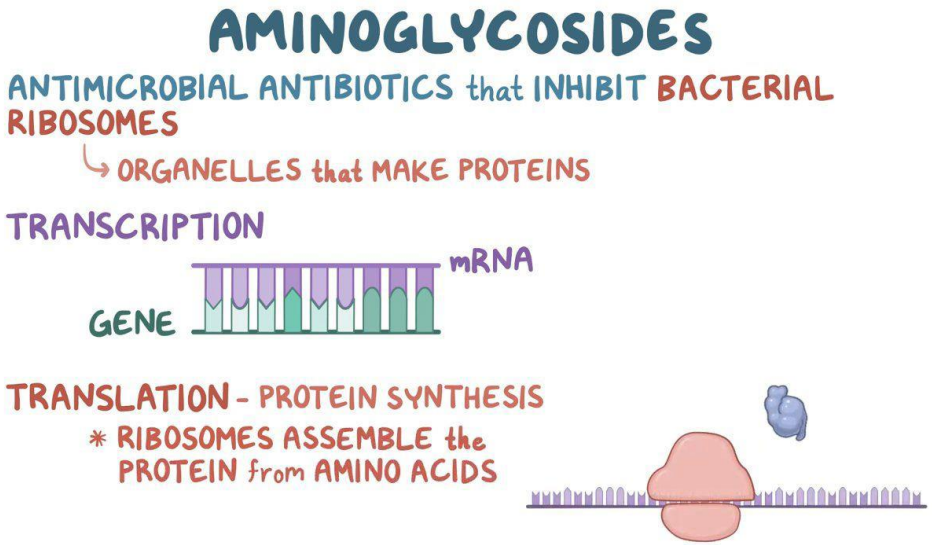
Quinolones (Nalidixic acid), Fluoroquinolones, Griseofulvin, Novobiocin…etc-

Inhibitors of RNA synthesis:

Rifampicin







MOA of Antibiotics

Inhibitors of protein synthesis:

Aminoglycosides (Streptomycin, Gentamicin…), Chloramphenicol, Tetracyclines, Lincomycin, Clindamycin…etc

Interference with metabolism of microorganisms:

Bacteria requires PABA for synthesis folic acid.Sulfonamides (static) which inhibits the 1st step added with trimethoprim (static) which inhibits the 2nd step, leading to Bactericidal effect with wide spectrum activity.

Classification of antimicrobials

According to:

Mechanism of action (eg. cell wall inhibitors).

Chemical structure: the best criteria of classification.

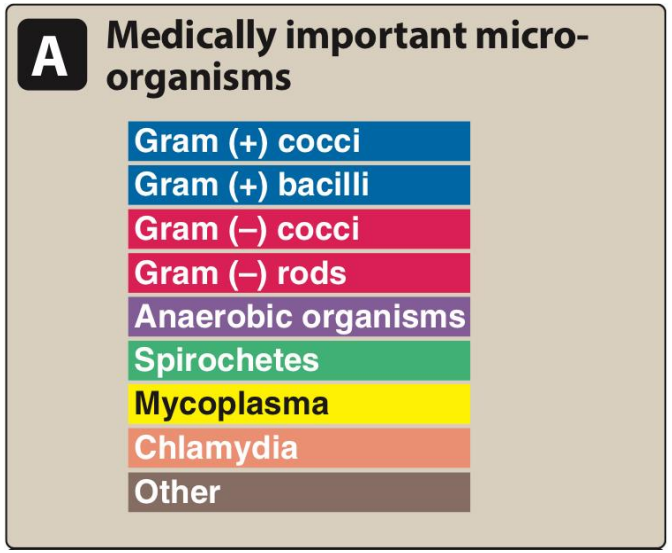
Antimicrobial activity (spectrum of activity):

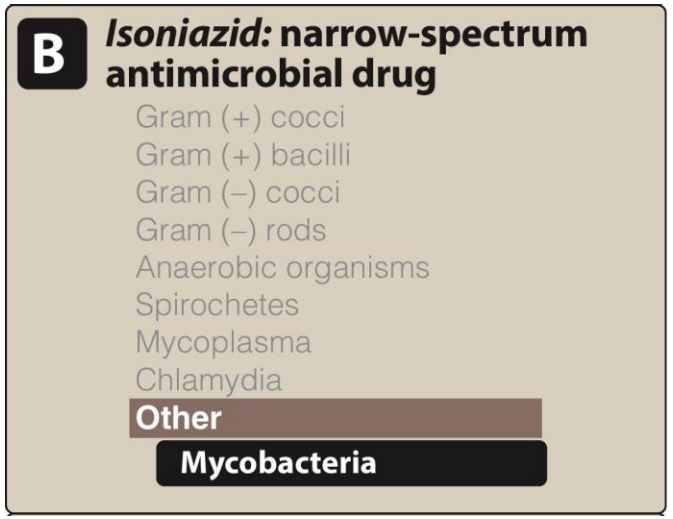
Narrow spectrum (effective in G+ve cocci & bacilli):

Drugs effective in G-ve bacilli (Aminoglycosides), drugs only effective in specific infections (Isoniazid is only active against mycobacteria T.B).

NOTE: spectrum: the more microorganisms covered by the antibiotic, the higher its spectrum.

Always start with low spectrum antibiotics, there are some exceptions for this rule. The narrower the spectrum the more specific is the antibiotic.





Classification of antimicrobials

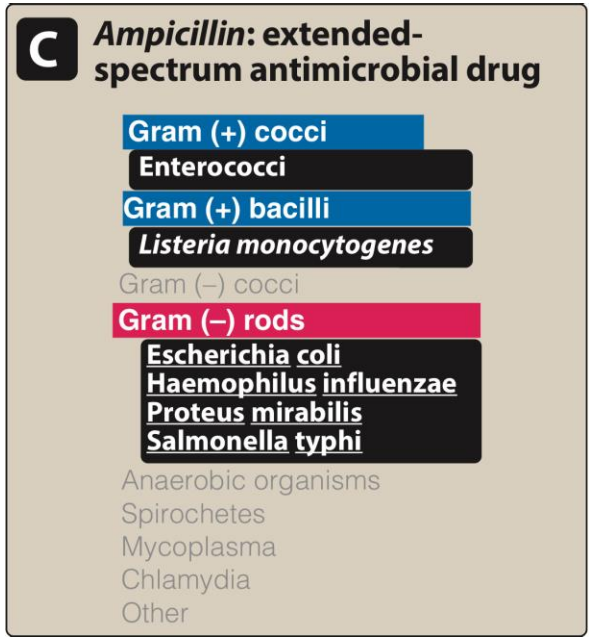
Broad spectrum (effective in G+ve & -ve cocci & bacilli):

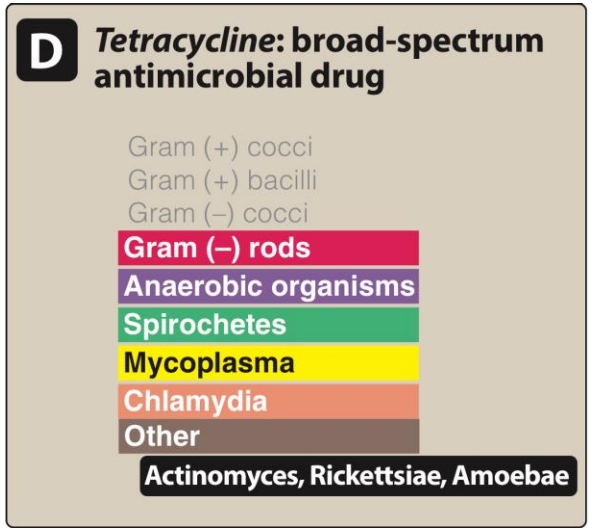
Affect a wide variety of microbial species (this type could alter the nature of the normal flora & precipitate a superinfection).

NOTE: antibiotics can affect the useful bacteria in our bodies.

Extended-spectrum antibiotics:

Agents that are effective against gram-positive organisms & also against a significant No. of gram-negative bacteria or against specific microorganisms e.g. Antipseudomonal penicillin's.





General considerations in the usage of antimicrobials:

- Is the antimicrobial agent indicated? Aim if indicated is to achieve a level of antimicrobial activity at the site of infection that is sufficient enough to inhibit or kill microorganisms without affecting host cells.
- Antimicrobials are harmful drugs.
- New drugs are not necessarily better than old ones.
- Major consideration is identification of the causative microorganism and the use of proper dose for adequate duration, otherwise it will gain resistance to the antibiotic.
- Sometimes there is a need to combine more than one antimicrobial.

Which antibiotic should we use?

Selection of an antimicrobial agent

- Factors affecting selection:
- 1. Causative microorganism (susceptibility):the most important factor. The lack of susceptibility guarantees therapeutic failure).
- Determined from:
- Clinical picture (Empiric therapy: the use of an antibiotic prior to identification of organism in critically ill patients.
- NOTE: clinical picture, which includes the patient's symptoms, signs, and the likely source of infection.
- Identifying the causative microorganism and its susceptibility helps ensure the selection of an appropriate antibiotics.
- Bacteriological examination (culture and sensitivity).
- Serology-measures antibody levels.
- Polymerase Chain Reaction (PCR) detects the specific DNA for a specific organism.

Selection of an antimicrobial agent

- 2. Pharmacokinetic factors:
- Site of infection CNS, prostate, vitreous body of the eye..
- NOTE: site of infection is important in determination of the drug, like in the CNS infection we need drug can penetrate the BBB(blood brain barrier).
- Renal disease (poor kidney function causes antibiotics that ordinarily secreted by this route to accumulate & lead to serious adverse effects e.g. aminoglycosides) do you need to decrease the given dose.
- Liver disease (antibiotics that are concentrated or eliminated by liver are contraindicated)in liver diseases (e.g. erythromycin & tetracycline.
- Route of administration.
- NOTE: Oral antibiotics are typically avoided for individuals experiencing vomiting because the medications may not be effectively absorbed.

Selection of an antimicrobial agent

- 3. Toxicity and side effects to antibiotic.
- 4. Interactions with other drugs.
- 5. Cost.
- 6. Host factors:
- Age (newborn & old pts have less kidney and liver function compared to adults).
- Allergic reaction to a given antimicrobial agent.
- Host defense mechanisms (alcoholism, DM, HIV, malnutrition, poor hygiene, advanced age, neutropenia, & the use of immunosuppressive drugs can affect a patient's immuno-competency.
- Such patients need higher-than-usual doses or longer courses of treatment)so you should give them a cidal rather than static.

Selection of an antimicrobial agent

- 7. Genetic factors:
- Sulfonamides, Chloramphenicol, Nitrofurantoin → severe hemolysis in G6PD deficient individuals (hemolytic anemia)
- 8. Pregnancy:
- Streptomycin → Deafness; during pregnancy, the drug can potentially cross the placenta and affect the developing fetus.
- 9. Lactation:
- Sulfonamides → hemolysis in G6PD deficient newborn due to the passage of sulfonamides into breast milk.
- 10. Local factors at site of infection:
- In Abscess, Systemic antibiotics may Have Limited penetration into abscesses, so they are treated by drainage, not antibiotics, But they can be given to control the spread of bacteria.