PHARMACOLOGY

Modified slides no.2
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Trough Levels

- **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:**

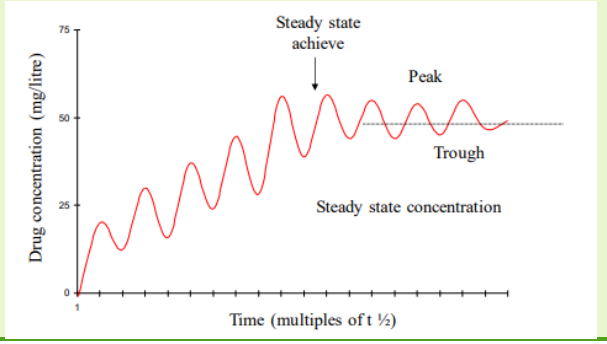
  - Post Antibiotic Effect, a prolonged period before bacteria resume growth

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

■ **Additional information**:
Trough levels in antibiotics are the lowest concentrations in the blood before the next dose, vital for optimal drug efficacy. They help **ensure** the concentration remains **above** the Minimum Inhibitory Concentration **(MIC)**, **preventing bacterial growth and minimizing resistance**.

■ **NOTE**: we need our drug concentration to be within therapeutic level.
Exceeding level → toxicity
Lowering level → ineffective & cause resistance to bacteria

■ **Attachment**:



■ **Additional information**:
However, antimicrobial stills effective , even if its level drops below the MIC , due to :
Post-Antibiotic Effect and collaboration between host defenses and sub- MIC levels of antibiotics; where the **host's immune system, when working together with lower antibiotic concentrations**, can produce a more effective response than either acting alone.

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)

■ **NOTE**: continued effect of an antibiotic on bacteria after the drug has been removed from the system.

Trough levels may increase the frequency of drug-resistant bacteria

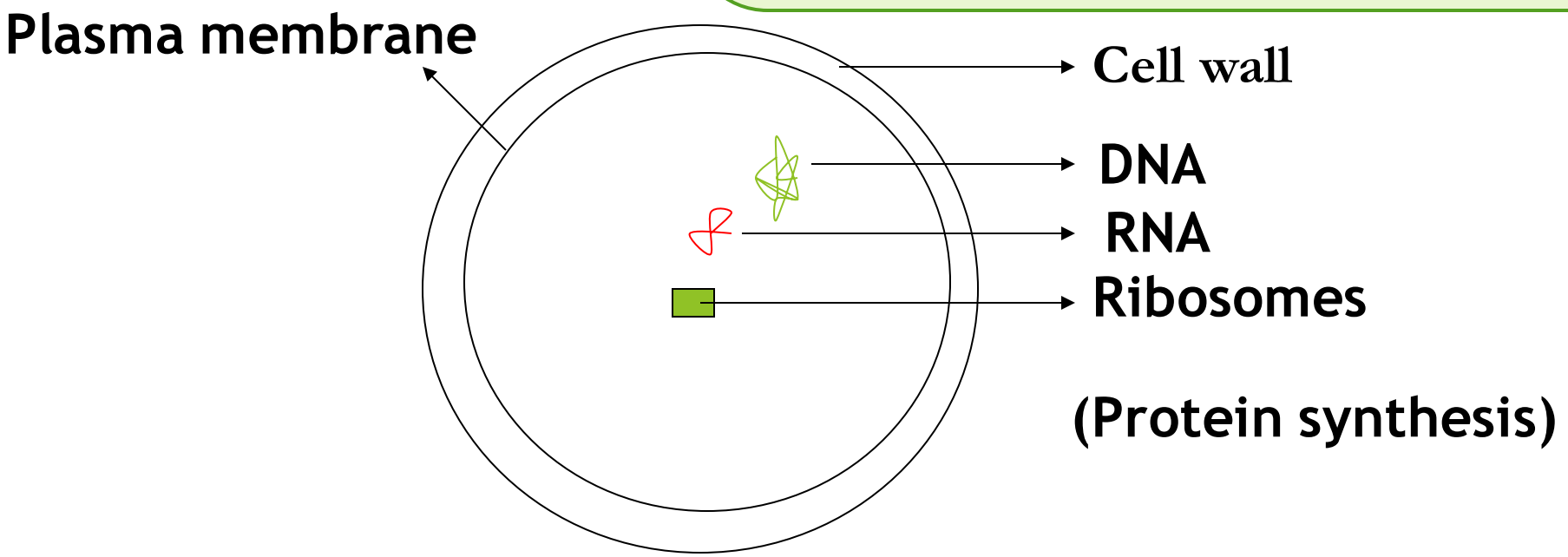
- Frequency of developing resistance is greatly increased at levels below, at or little bit above the MIC
- Development of resistance to ciprofloxacin is 10,000 times more frequent at 2 times the MIC compared to 8 times the MIC

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

■ **Additional information**:
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

■ **NOTE:** 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.



- 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)

!! **NOTE:**

The classification of antibiotics as static (inhibitory) or cidal (killing) is not determined by their mechanism of action. While some antibiotics acting on the cell wall are static, the distinction between static and cidal antibiotics is based on their overall impact on bacterial growth, not just their mechanism of action.

- 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

■ **NOTE:** against TB microorganisms

- **Inhibitors of protein synthesis**

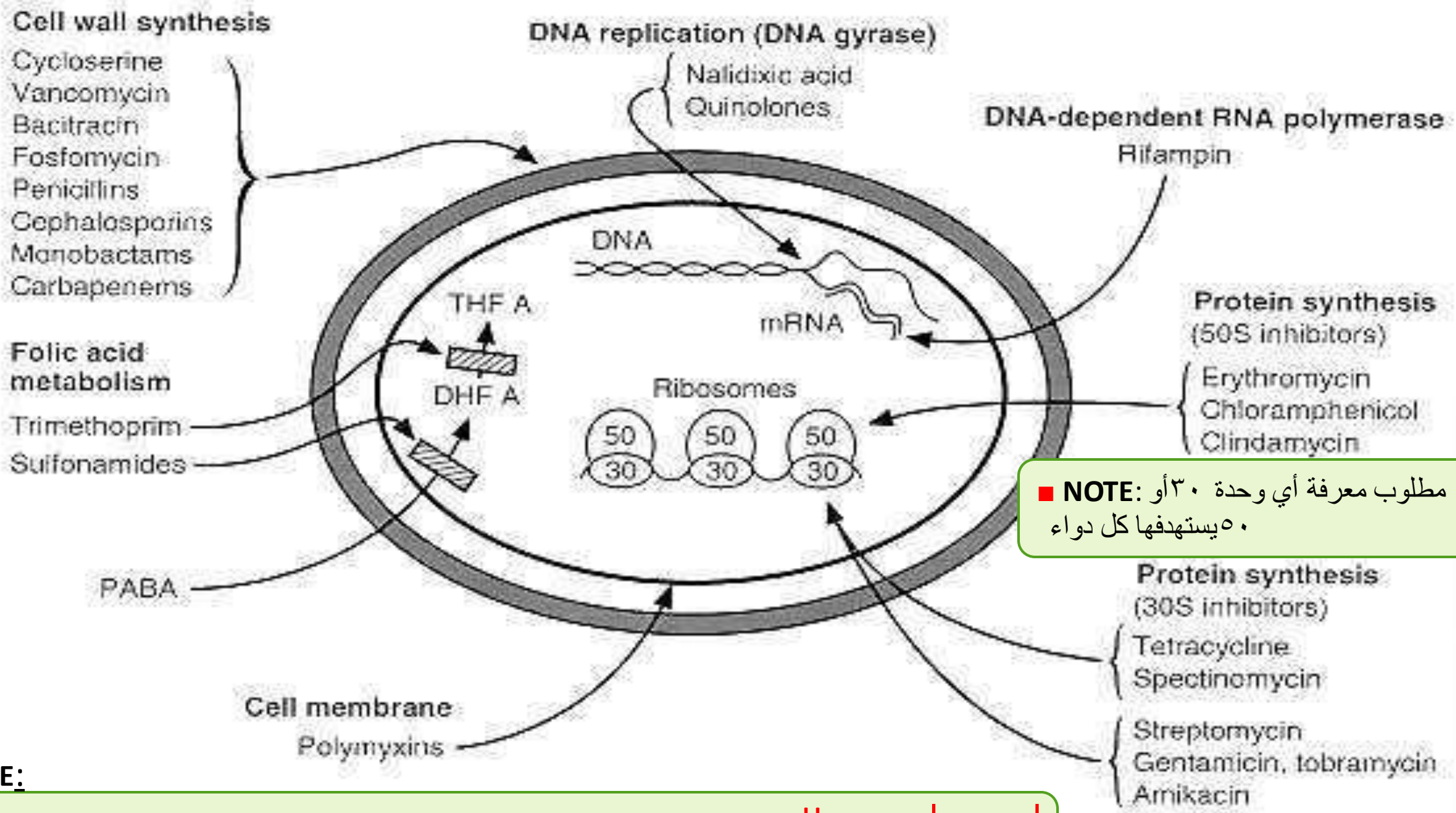
Aminoglycosides (Streptomycin, Gentamicin…), Chloramphenicol, Tetracyclines, Lincomycin, Clindamycin…etc

- Interference with metabolism of microorganisms

■ **Additional information**:
The folic acid pathway in bacteria involves the synthesis of tetrahydrofolate (THF), a crucial coenzyme for nucleotide synthesis.

■ **NOTE:**
bacteria requires PABA for synthesis folic acid.
Sometimes, we give 2 drugs to clear the bacteria (combination will be discussed later on)
Sulfonamides (static) which inhibits the 1st step added with trimethoprim (static) which inhibits the 2nd step , leading to Bactericidal effect with wide spectrum

PABA: Para-aminobenzoic acid (PABA) is a precursor molecule crucial in the bacterial synthesis of folate DHF: dihydrofolate, THF : tetrahydrofolate



■ **NOTE**: غير مطلوب معرفة أي وحدة ٣٠أو ٥٠يستهدفها كل دواء

■ **NOTE:**

ابصم واستمتع!!

سوف يتم شرحهم بالتفصيل في المحاضرات القادمة إن شاء الله

Classification of antimicrobial:

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. Simple !!

Always start with low spectrum antibiotics, there are some exceptions for this rule.

The narrower the spectrum the more specific is the antibiotic.

* 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

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 (قبل) 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 antibiotic

   - Bacteriological examination (culture and sensitivity)
   - Serology-measures antibody levels
   - Polymerase Chain Reaction (PCR) detects the specific DNA for a specific organism

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 does**
- **Liver disease (antibiotics that are concentrated or eliminated by liver are contraindicated** **يمنع استخدامه** **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, reducing their utility in treating the infection.

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

7. Genetic factors

Sulfonamides, Chloramphenicol, Nitrofurantoin → severe hemolysis in G6PD deficient individuals (hemolytic anemia) for more explanation check the next slide

7. Pregnancy

Streptomycin → Deafness

during pregnancy, the drug can potentially cross the placenta and affect the developing fetus.

8. Lactation

Sulfonamides → hemolysis in G6PD deficient newborn

the passage of sulfonamides into breast milk

8. Local factors at site of infection

e.g. Abscesses

Systemic antibiotics may have limited penetration into abscesses , so they are treated by drainage, not antibiotics. But can be given to control the spread of bacteria.

■ **Additional information**:

Glucose 6 p dehydrogenase is in the pentose phosphate pathway, providing a source of NADPH, which is crucial for protecting cells from oxidative damage .

Sulfonamides, chloramphenicol, and nitrofurantoin can increase hemolysis in individuals with G6PD deficiency by inducing oxidative stress on red blood cells

In **G6PD deficiency**, the decreased capacity to handle oxidative stress makes RBCs more susceptible to damage induced by these antibiotics, resulting in hemolysis.

The end