بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 17

Antibiotics Pt.9

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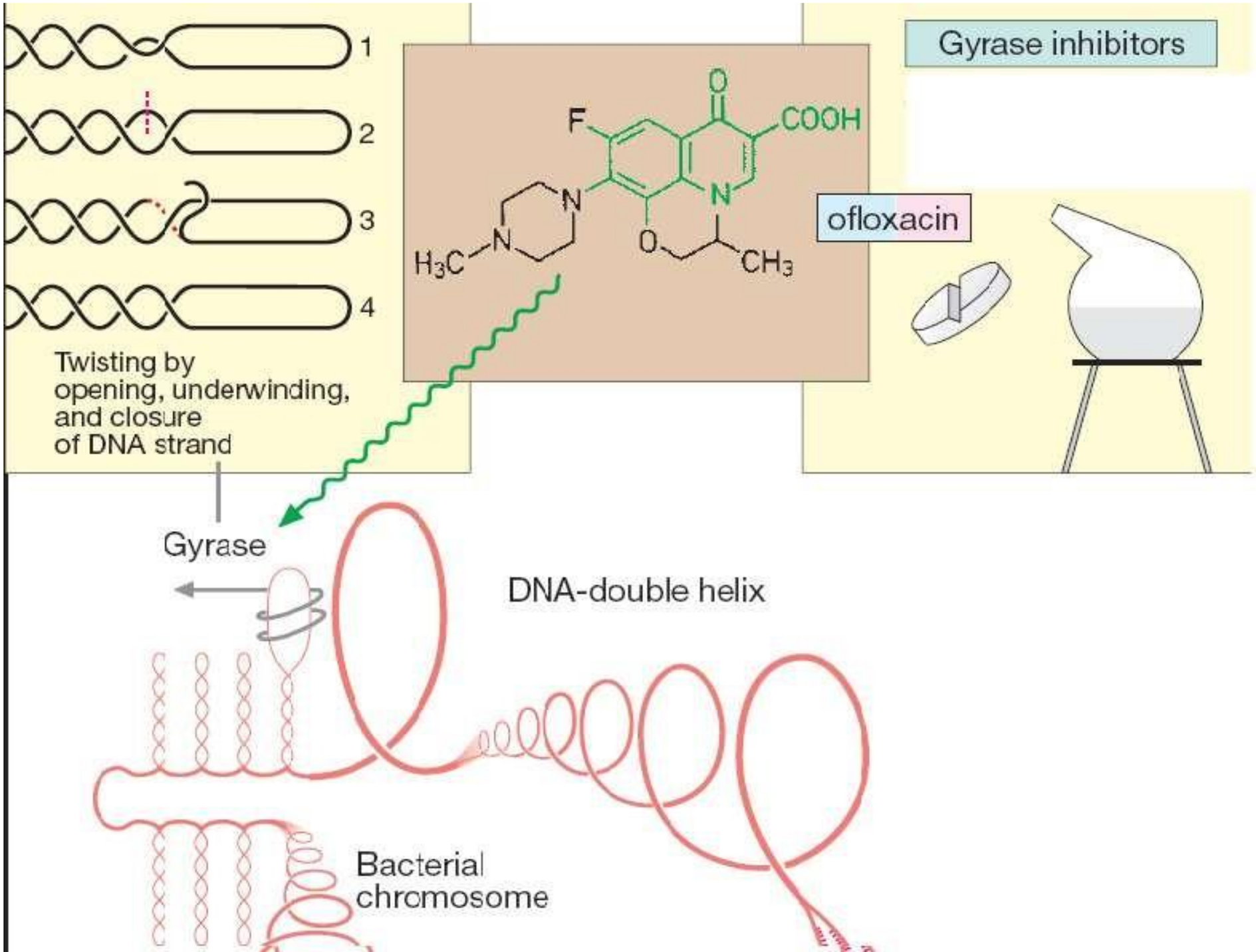
Inhibition of DNA Gyrase

- bacterial DNA gyrase is a type II topoisomerase that produces transient double strand breaks in DNA.
- The best example is the fluoroquinolones, which are specific inhibitors of DNA gyrase that trap the enzyme in its cleavable complex.
- Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.
- Its a broad spectrum antibiotic active against both Gram-negative and Gram-positive bacteria. It is more active against Gram-negative species.


Gyrase inhibitors
1
2
3
4
Twisting by
opening, underwinding,
and closure
of DNA strand
F
O
COOH
N
N
H_3C
N
O
CH_3
ofloxacin
Gyrase
DNA-double helix
Bacterial
chromosome

DNA Gyrase (Topoisomerase/Floroquinolone)

Now we are going to talk about DNA Gyrase (Fluoroquinolones or Topoisomerase inhibitors).
They have 5 generations (not required from us).

DNA Gyrase vs Topoisomerase

❖ Topoisomerase:
- Present in our body
- Its function is to cut and rejoin DNA during replication

❖ DNA Gyrase:
- Present only in bacteria
- It is the main target of fluoroquinolones

Types of Drugs Acting on DNA Gyrase

We have DNA Gyrase inhibitors and DNA Gyrase poisons.

1. DNA Gyrase Inhibitors

- They **inhibit** the function of the enzyme.
- **Similar to** inhibition of any other enzyme

2. DNA Gyrase Poisons

❖ They use the enzyme itself to kill the bacteria.
❖ The enzyme cleaves DNA and rebound it, but the drug:
- Traps the cleavable complex.
- Prevents re-ligation of DNA.
- This results in double-strand DNA breaks.

Example: Quinolones
Effect: Bactericidal

Important note:

If you read from books like Lippincott, you will find that they describe fluoroquinolones as “inhibitors”.
This description is conceptually wrong. They are actually enzyme poisons, not simple inhibitors.

DNA Gyrase (Topoisomerase/Floroquinolone)

Resistance to Fluoroquinolones

❖ Can resistance happen here?
✓ **Yes, it is difficult, but it can occur.**

❖ Resistance happens by:
- Changing the shape of the enzyme.
- Formation of another enzyme subtype.

✓ Because of this, newer drugs were designed to:
- Poison other subtypes of gyrase/topoisomerase.

The rule is:
The more subtypes of gyrase (topoisomerase) a drug can poison and inhibit, the stronger the drug.

Selective Toxicity (Why They Are Safer for Humans)

❖ Fluoroquinolones are very toxic to bacteria but not to us because:
- The toxicity is dose dependent
- The dose given is:
  - Enough to kill bacteria.

→ This applies even to sensitive tissues like bone marrow. This concept is called dose selection.

Spectrum of Activity

❖ Fluoroquinolones are broad-spectrum antibiotics.

❖ Active against:
- Gram-positive bacteria
- Gram-negative bacteria (more activity on Gram-negative)

❑ ***Ciprofloxacin***

❖ **General Information :**

- Ciprofloxacin is the first quinolone
- The most common fluoroquinolone.
- The first oral antibiotic effective against Gram-negative bacteria.

Important point:
Ciprofloxacin is **orally active against Pseudomonas aeruginosa.**

DNA Gyrase (Topoisomerase/Floroquinolone)

Clinical Uses of Ciprofloxacin

❑ **Drug of choice for:**
- Urinary tract infections
- Abdominal infections

Exception:
Weak activity against anaerobes.

It is also the first drug we mention that is active against:
Staphylococcus saprophyticus

Empirical Use in UTI

Can ciprofloxacin be used empirically for UTI?
Yes, especially in Jordan, since :
- 80% caused by E. coli.
- 15% caused by Staph. Saprophyticus.

What About Enterococcus (we didn't cover it and it is one of the causes of UTI?
Ciprofloxacin **does not** have good activity against Enterococcus.

So how can we still use it empirically?

The reality is:
Enterococcus is mainly an **intestinal organism.** It can contaminate the urinary tract from feces (exit with feces and enter through urethrea).

In our countries:
We use water in bathrooms (استنجاء بالماء)
Therefore, **Enterococcus UTIs are less common.**

In the USA:
Enterococcus **causes about 20-25% of UTIs.**
In this case, **the drug of choice is Ampicillin.**

Use in Abdominal Infections

Can ciprofloxacin be used empirically in abdominal infections?
Yes, but:
It must be combined with another drug that covers Bacteroides (anaerobes).

DNA Gyrase (Topoisomerase/Floroquinolone)

II. Targeted Therapy: Pseudomonas aeruginosa

P. aeruginosa is an opportunistic, Gram-negative pathogen that is notoriously difficult to treat due to its intrinsic resistance mechanisms.

1. Fluoroquinolones for Pseudomonas

- **Ciprofloxacin:** The **gold standard** oral agent for Pseudomonas. It was the first oral antibiotic effective against this pathogen.
- **Potency:** It is significantly more potent in vitro than levofloxacin (lower MICs).
- **Limitation:** It has poor activity against S. pneumoniae. Using it for respiratory infections is dangerous because it kills competitors but leaves S. pneumoniae behind (**selection pressure**).
- **Levofloxacin:** Also active against Pseudomonas but **less potent** than Ciprofloxacin. To achieve therapeutic levels against Pseudomonas, higher doses (e.g., 750 mg) are typically required.
- **Moxifloxacin & Gemifloxacin:** These have **no reliable activity** against Pseudomonas.
- **Mechanism of Failure:** They cannot effectively penetrate the Pseudomonas outer membrane and are easily pumped out by the bacteria's efflux systems.

2. Alternative Antipseudomonal Agents

If we can’t use any of the following options we use fluoroquinolones:

1) **Antipseudomonal Cephalosporins: Ceftazidime** (3rd gen) and **Cefepime** (4th gen).
2) **Antipseudomonal Penicillins: * Carboxypenicillins:** (e.g., Ticarcillin).
3) **Ureidopenicillins:** (e.g., Piperacillin/Tazobactam).
4) **Aminoglycosides:** (e.g., Amikacin, Gentamicin). Usually used in **combination therapy** with a \beta-lactam for synergy and to prevent resistance.

DNA Gyrase (Topoisomerase/Floroquinolone)

4th Generation Fluoroquinolones (Respiratory Quinolones)

These drugs are grouped as "respiratory quinolones" because they are highly effective against common Upper and Lower Respiratory Tract Infection (URTI/LRTI) agents, specifically **S. pneumoniae**.

1. Key Medications & Activity

Drug Name	Anaerobic Activity	Pseudomonas aeruginosa Activity	Target Mechanism
Levofloxacin	No	Active	Topoisomerase 2
Moxifloxacin	Active	Not Active (cannot penetrate)	Topoisomerase 2 & 4
Gemifloxacin	Active	Not Active	Topoisomerase 2 & 4

2. Clinical Usage & Guidelines

· **Spectrum of Activity:** Extremely broad-spectrum. They are active against Gram-positive, Gram-negative, and atypical bacteria.

· **Prescribing Principle:** Always prescribe the **narrowest possible antibiotic** that covers the suspected bacteria.

· **Status:** Due to their broad spectrum, they are often "kept aside" and used as a **last resort drug** to prevent resistance.

3. Treatment of Respiratory Infections

· **Upper Respiratory Infections (URTI):** Despite being effective, respiratory fluoroquinolones are **not** the first choice because they are unnecessarily broad for most cases.

· **S. pneumoniae (Penicillin-Resistant):**

· **1st Line Therapy:** Azithromycin.

· **2nd Line Therapy:** Levofloxacin (Fluoroquinolones).

· **Best Overall Activity:** Levofloxacin is noted as the best drug against all respiratory tract infections (upper and lower).

Quinolones

- **First oral antibiotics effective against gram-negative bacteria.**
- **Ciprofloxacin is the most commonly used fluoroquinolone.**
- **Ciprofloxacin most active agent against gram-negatives, *Pseudomonas aeruginosa* in particular**
- **Levofloxacin, gemifloxacin, and moxifloxacin: improved activity against gram-positive organisms, particularly *S. pneumoniae* and some staphylococci.**

Quinolone

- **Their main uses are:**

(1) complicated urinary tract infections

(2) respiratory infections in patients with cystic fibrosis

Levofloxacin,, gemifloxacin, and moxifloxacin, so-called respiratory fluoroquinolones, with their enhanced gram-positive activity and activity against atypical pneumonia agents (eg, chlamydia, mycoplasma, and legionella), are effective and used increasingly for treatment of upper and lower respiratory tract infections.

(3) Infections of soft tissues, bones, and joints and in intra-abdominal

(4) bacterial prostatitis (takes 28, day in order for the drug to built an adequate concentration) and cervicitis (takes14 days)

(5) Also used in bacterial diarrhoea caused by shigella, salmonella, *E. coli*.

Quinolone

- **Side-effects are infrequent and usually mild. They consist mainly of GI disorders (nausea, vomiting, and diarrhea) and skin rashes.**

- **Arthropathy (this is the primary side effect), Fluoroquinolones may damage growing cartilage and cause an arthropathy. particularly in young individuals.**

  So contraindicated in children (under 18) except in special Cases (Cystic Fibrosis).

- If a patient have cystic fibrosis then we should give him Flouroquienoloes (the ones that are active agansit anaerobes **since cystic fibrosis involves the thick secretion which is a suitable environment for anaerobic bacteria to grow an cause infection.**

Perturbation of nucleic acid synthesis

- **Sulphonamides have a similar structure to p-aminobenzioc acid (PAPA), which is a precursor of Folic acid.**

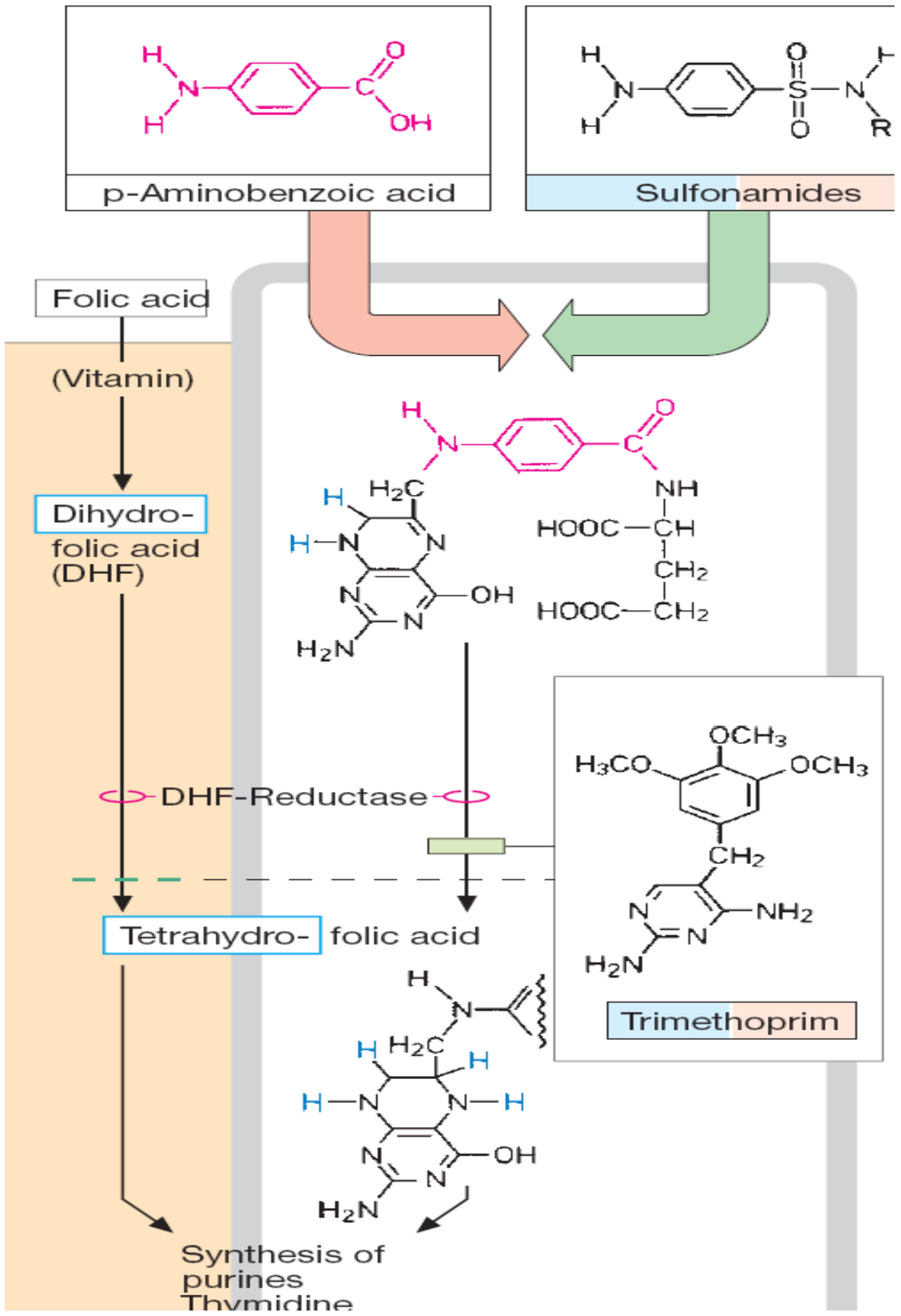
- **These agents compete with PAPA for the bacterial enzyme, dihydropteroate synthetase. Thus, they inhibit the synthesis of the bacterial folic acid (which is used in the synthesis of purines) and the end result is interfering in nucleic acid synthesis**

- **The sulphonamides are bacteriostatic rather than bacteriocidal so the host must have effective immune function.**

- **Resistance is common, mainly via up-regulation of the synthesis of PABA and by mutations in dihydropteroate synthetase.**

- **As a result, Sulphonamide alone is not being used.**

- Trimethoprime is the only sulphonamide drugs that is still available.
- It inhabit DHF- Reductase, which result in inhabiting Tetrahydro folic acid synthesis which result in purine synthesis inhabition.



Sulphonamides are available as:

(1) Oral Absorbable Agents:
Sulfisoxazole and sulfamethoxazole. almost exclusively to treat urinary tract infections.

(2) Oral Nonabsorbable Agents

Sulfasalazine (salicylazosulfapyridine) is widely used in ulcerative colitis, enteritis, and other inflammatory bowel disease

(3) Topical Agents

Silver sulfadiazine (sulfadizine – Augmented with silver) is used for prevention of infection of burn wounds.

Sulphonamides

- ~~Sulphonamides have mild to moderate side-effects including, nausea, vomiting, headaches, and depression.~~

- **More serious side-effects include hepatitis, hypersensitivity reactions, bone marrow depression** (purine synthesis inhibition, because these drugs are not selective by their nature, but we make them selective to the bacteria by managing the doses so it's not enough to damage our own cells except in cases of already present genetic disease, like : G6P-Dehydrogenase deficiency) **and aplastic anemia.**

- **Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency.**

Oral Trimethoprim-Sulfamethoxazole (TMP-SMZ)

- **is the drug of choice for infections such as *Pneumocystis jiroveci* (formerly *P carinii*) pneumonia, toxoplasmosis, nocardiosis, and occasionally other bacterial infections.**

- **effective treatment for urinary tract infections (cased by E.coli especially the ones sensitive to Ciprofloxacin and prostatitis.**

- **prophylaxis in recurrent urinary tract infections of some women.**

- Child that has recurrent UTI, with resistance toward cephalosporins, we can't give her cephalosporins and penicillins, we are going to prescribe **oral Trimethoprim-Sulfamethoxazole.**
- What about Ceripropholxine ? No, it is contraindicated, it causes Arthropathy.

VRE and more

- **Teicoplanin** **(an alternative of Vancomycin for children, kidney problems)** is used in the prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including **methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*.**
- Enterococcus –> Penicillin Resistant Enterococcus –> Vancomycin Resistant Enterococcus –> Linezolid.

- S.aureus–> penicillin resistant s.aureus–> methicillin resistant S.aureus–> Vancomycin Resistant S. aureus–> Linezolid.
- **Linezolid (oral, injectable, protein synthesis inhibitor, inhabit the initiation of the synthesis-binding of the 50 S toward RNA)** is approved for **vancomycin-resistant *E faecium* infections**; nosocomial pneumonia; community-acquired pneumonia; and skin infections, complicated or uncomplicated. (Should not be taken for more than 2 weeks, since it cases platelet count decrease (platelets cytopemia), Dose dependent side effect).

  It should be **reserved for treatment of infections caused by multidrug-resistant gram-positive bacteria.**
- **Daptomycin** is active against **vancomycin-resistant strains of enterococci and *S aureus*.**

VRE and more

- **Daptomycin** is active against **vancomycin-resistant strains of enterococci and *S aureus*.**
- It binds to Ca+2 channels on the surface of gram positive and make efflux of material present inside the bacteria.
- Its mechanism of action is related to calcium pores opening and depolarization.
- Can't be used in pneumonia, since it is deactivated by the respiratory secretions.

Common Bacteria by Site of Infection

Mouth
Peptococcus
Peptostreptococcus
Actinomyces

Skin/Soft Tissue
S. aureus
S. pyogenes
S. epidermidis
Pasteurella

Bone and Joint
S. aureus
S. epidermidis
Streptococci
N. gonorrhoeae
Gram-negative rods

Abdomen
E. coli, Proteus
Klebsiella
Enterococcus
Bacteroides sp.

Urinary Tract
E. coli, Proteus
Klebsiella
Enterococcus
Staph saprophyticus

Upper Respiratory
S. pneumoniae
H. influenzae
M. catarrhalis
S. pyogenes

Lower Respiratory Community
S. pneumoniae
H. influenzae
K. pneumoniae
Legionella pneumophila
Mycoplasma, Chlamydia

Lower Respiratory Hospital
K. pneumoniae
P. aeruginosa
Enterobacter sp.
Serratia sp.
S. aureus

Meningitis
S. pneumoniae
N. meningitidis
H. influenza
Group B Strep
E. coli
Listeria

رسالة من الفريق العلمي:

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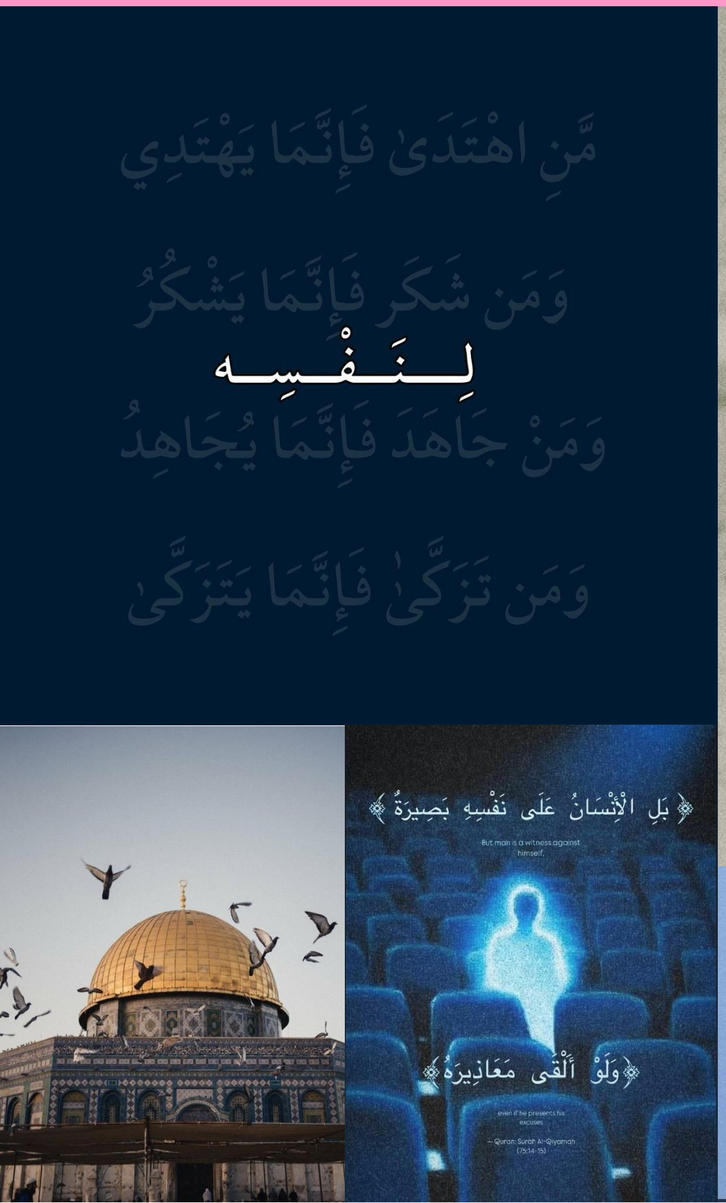

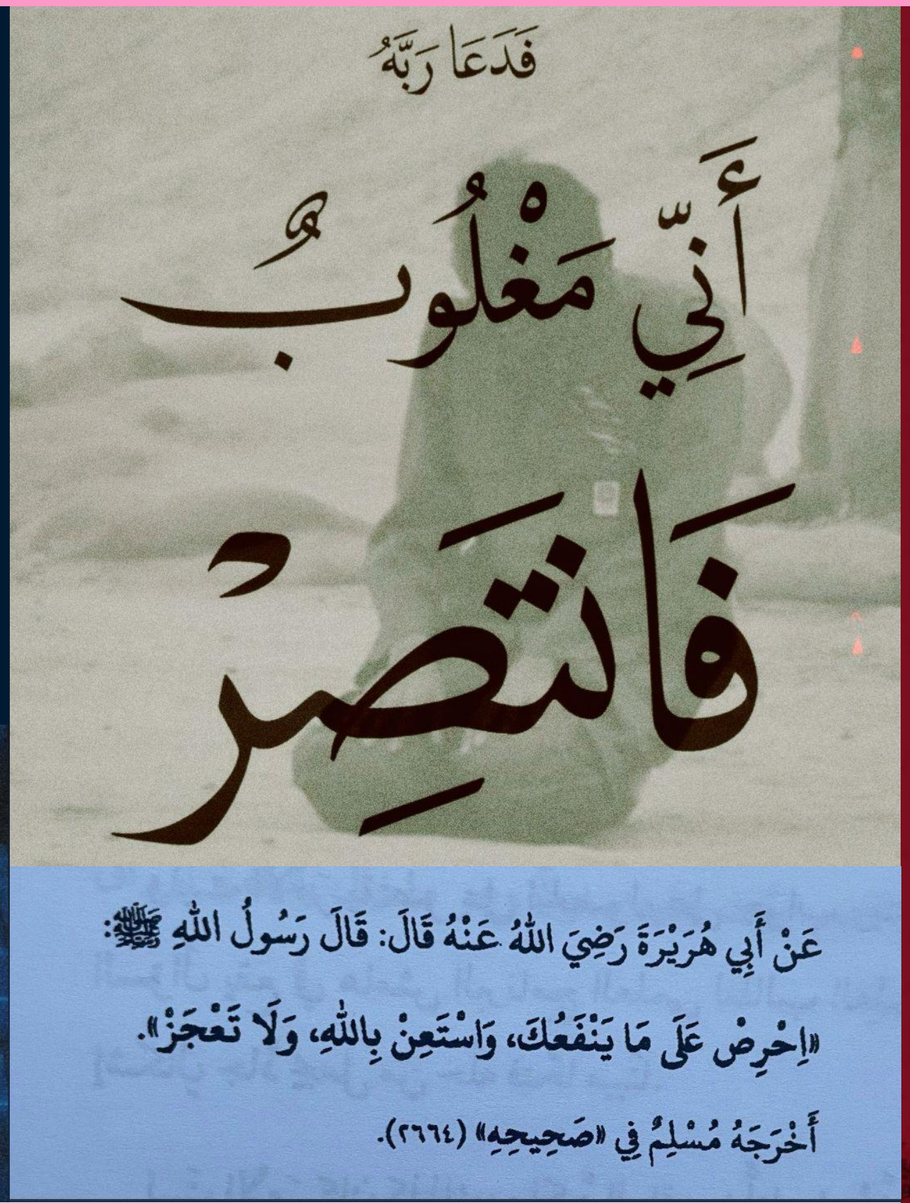

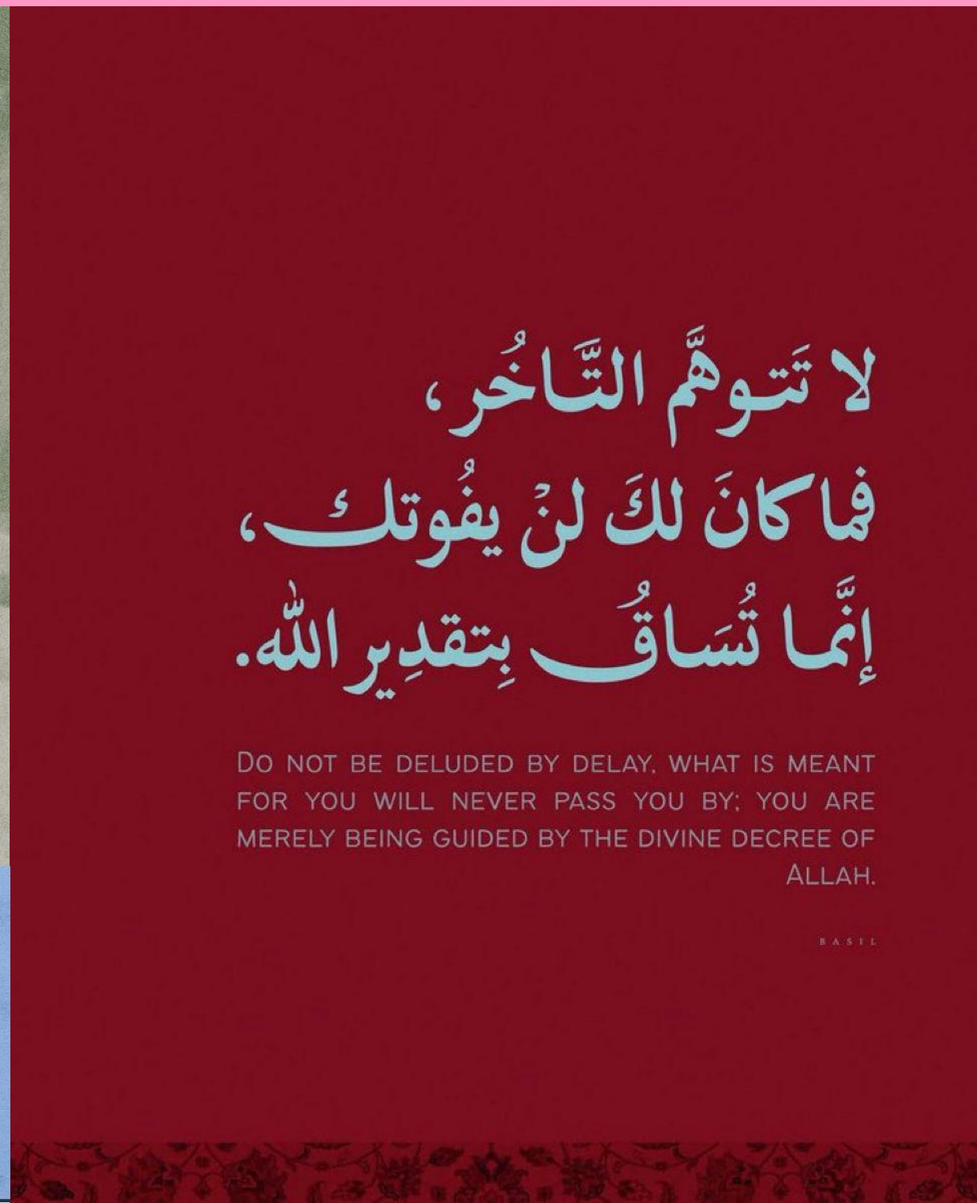

رسالة من الفريق العلمي:


بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

فَتَبَسَّمَ ضَاحِكًا مِّن قَوْلِهَا وَقَالَ

رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ

الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَىٰ وَالِدَيَّ

وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ

وَأَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ

النمل : ١٩

وبهذا نُنهي موديفايدات الفارما بحمد الله تعالى

أكرموا الفريق العلميّ بدعواتكم، لعلّ الله أن يكتب بها التوفيق لكم ولهم

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Corrections from previous versions:

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