بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 16

# Antibiotics Pt.8

Written by : NST
NST

# Azithromycin

- azithromycin penetrates intomost tissues (except cerebrospinal fluid), with tissue concentrations exceeding serum concentrations by 10- to 100-fold.

- The drug is slowly released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days.

# Macrolides

- **Ototoxicity: Transient deafness has been associated with erythromycin, especially at high dosages.**

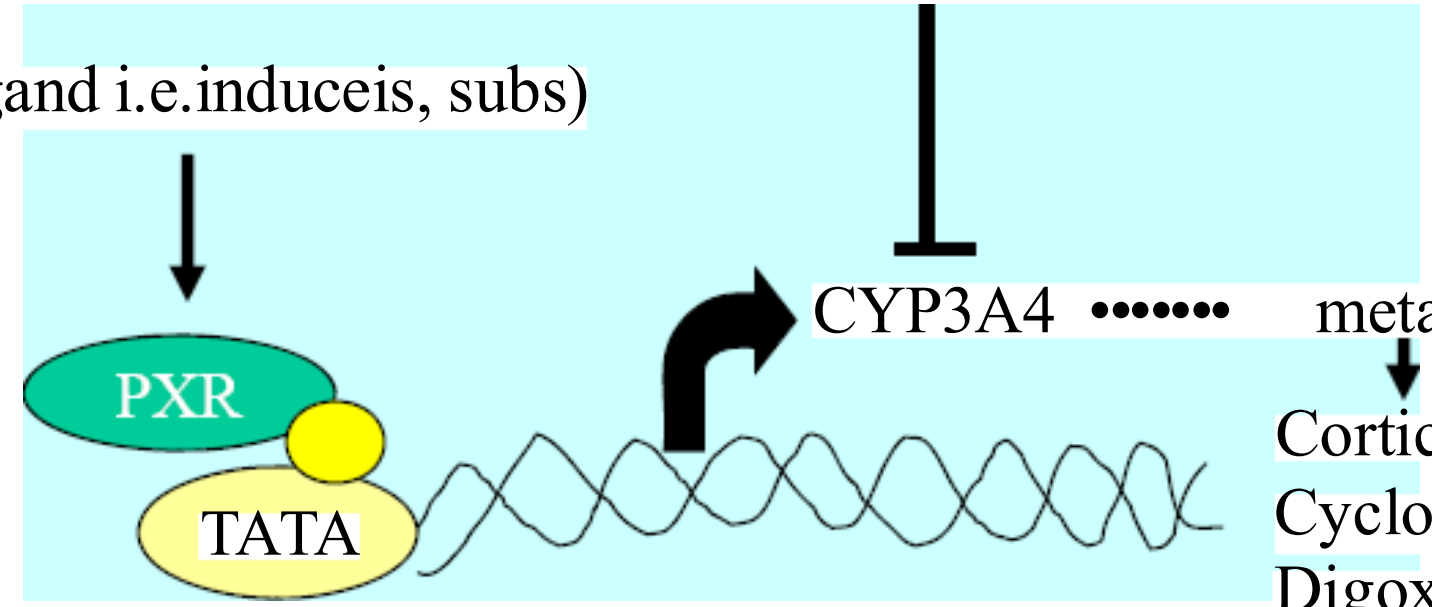
- **Cholestatic jaundice especially with the estolate form of erythromycin**

﴿ وَاذْكُر رَّبَّكَ إِذَا نَسِيتَ ﴾

- لآ آلهَ الا الله.
- سبحَان الله وَبحمده.
- سبحَآن الله العظيم.
- استغفرالله واتوب إليه

# Drug Interactions of Macrolides

Mainly Erythiomycin
and (to a lesser extent Clarithromycin)
(use caution with Azithiomycin)



**The Mechanism:** CYP3A4 is responsible for breaking down many drugs. If a Erthromyocin "blocks" this enzyme, other drugs that rely on it for clearance will stay in the body longer.

**The Result:** This leads to increased plasma concentrations and potential toxicity.

**Ranking:** Erythromycin is the strongest inhibitor, Clarithromycin is moderate, and Azithromycin is generally considered the "safest" in this regard because it has minimal effect on CYP enzymes

**Narrow Therapeutic Index: The Digoxin Case**

Digoxin as a "narrow therapeutic index" (NTI) drug. This is a critical clinical point.
Definition: An NTI drug has a very small window between a dose that is effective and a dose that is toxic.

The Interaction: Digoxin is not just affected by CYP enzymes; it is also metabolized by gut bacteria ).

Tetracyclines: These antibiotics kill the gut bacteria. When the bacteria are gone, less Digoxin is broken down in the gut, leading to higher absorption and potential Digoxin toxicity (which can cause dangerous heart arrhythmias).

Even Fenatol is
smaller in does
Trump enemy

## Telithromycin & Hepatotoxicity

Telithromycin is historically and clinically accurate.
purpose: It was developed to overcome resistance in Streptococcus pneumoniae.

Safety Issue: Its use was severely restricted (and largely stopped) because it was found to cause severe, sometimes fatal, hepatotoxicity (liver damage).

## Approval of Antibiotic Worried Safety Officials

"How does one justify balancing the risk of fatal liver failure against one day less of ear pain?“

David Ross and Rosemary Johann-Liang

- http://www.nytimes.com/2006/07/19/health/19fda.html?_r=0 اقرأ (للقراءة فقط)

# Aminoglycosides
# (only bactericidal protein synthesis inhibitor)

- **bind to the ribosomal 30S subunit**
- **inhibit initiation of peptide synthesis and cause mis-reading of the genetic code.**
- **Streptomycin is the best known member of the group which also includes amikacin, Gentamicin, *Tobramycin*, Netilmycin, and Neomycin.**
- **They are effective against many aerobic Gram-negative and some Gram-positive bacteria, finding their greatest use against Gram-negative enteric organisms and in sepsis.**

**Dose Independent**
**In the 70s and 80s, we left the Aminoglycosides because we produced Monobactam and Ceftazidime (only Gram-negative).**
**I put with those 3 drugs one of these 3 drugs: Amikacin, Gentamicin, Tobramycin.**
**(Only Gram-negative) / they can work on Nosocomial infection.**

# Aminoglycosides

**Target: They only work against Gram-negative bacteria.**

**The Main Clinical Problem**

**The primary concern with these drugs is Non-dose dependent toxicity (which causes deafness).**
**What does this mean? It means toxicity can occur even if you give the drug without increasing the dose.**

**Types of Adverse Drug Reactions (ADRs)**

- Type A: (Augmented) Dose-dependent.
- **Type B: (Bizarre) "We are now here" – This is where non-dose dependent toxicity falls.**
- Type C: (Chronic) Related to cumulative dose.
- Type D: (Delayed) Occurs after treatment.
- Type E: (End-of-use) Withdrawal.

## Types of Toxicity (Ototoxicity & Nephrotoxicity)

### 1. Dose-Dependent Toxicity:

Effect: Can cause Nephrotoxicity (kidney damage).

Management: It can be managed/controlled by monitoring doses.

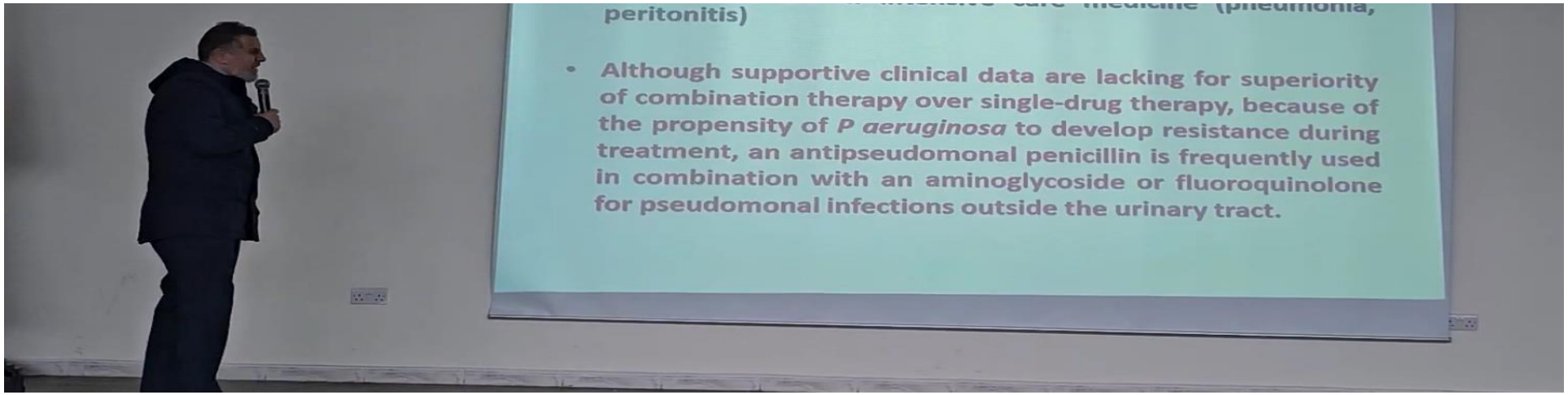
### 2. Dose-Independent (Non-Dose Dependent) Toxicity:

Effect: Causes Ototoxicity (permanent deafness).

Characteristic: Unpredictable; happens regardless of the dose amount.

In your slides, there is a sentence...

عشان ما تضيعوا وترجعوا مية صفحة لورا ✨



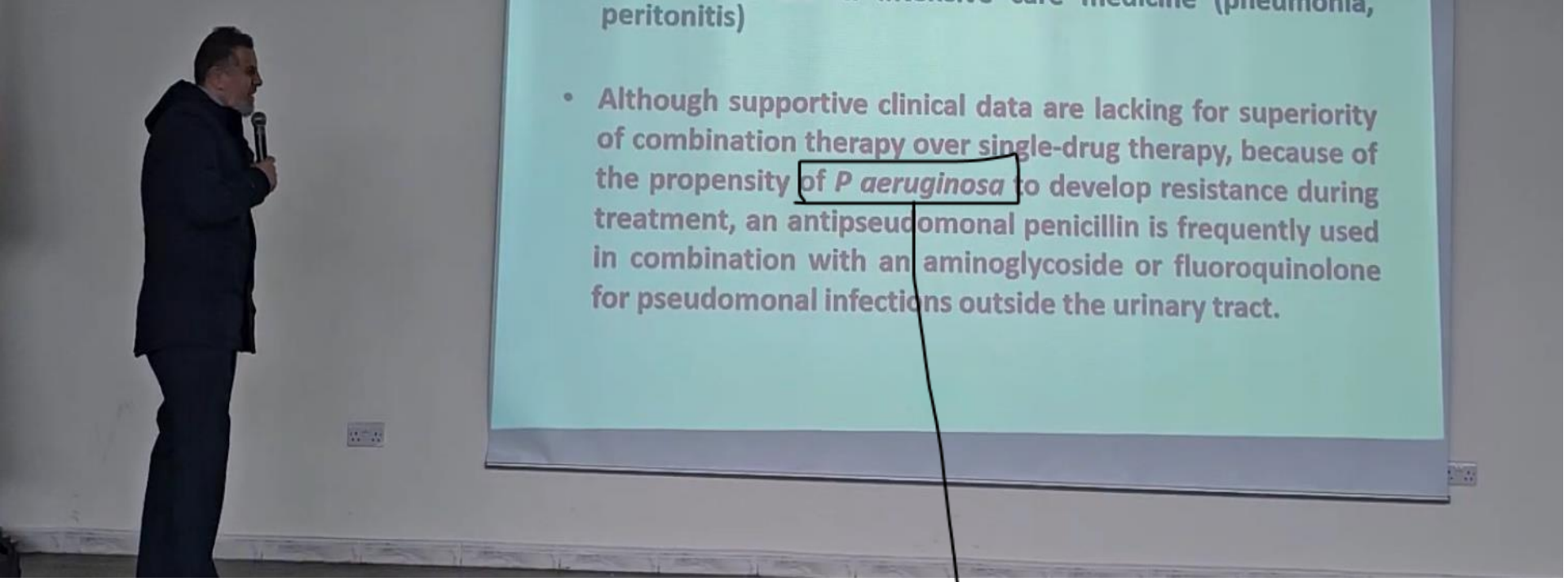

For less severe Pseudomonas infections, these agents can be used alone. You have categorized them by their mechanism of action:

Cell Wall Inhibitors

- Tazocin (Piperacillin + Tazobactam): An antipseudomonal penicillin combined with a beta-lactamase inhibitor.
- Ceftazidime: A 3rd generation cephalosporin with specific activity against Pseudomonas.
- Cefepime (written as "Cifamex"): A 4th generation cephalosporin.
- Aztreonam: A monobactam, often used if a patient has a penicillin allergy.

Protein Synthesis Inhibitors

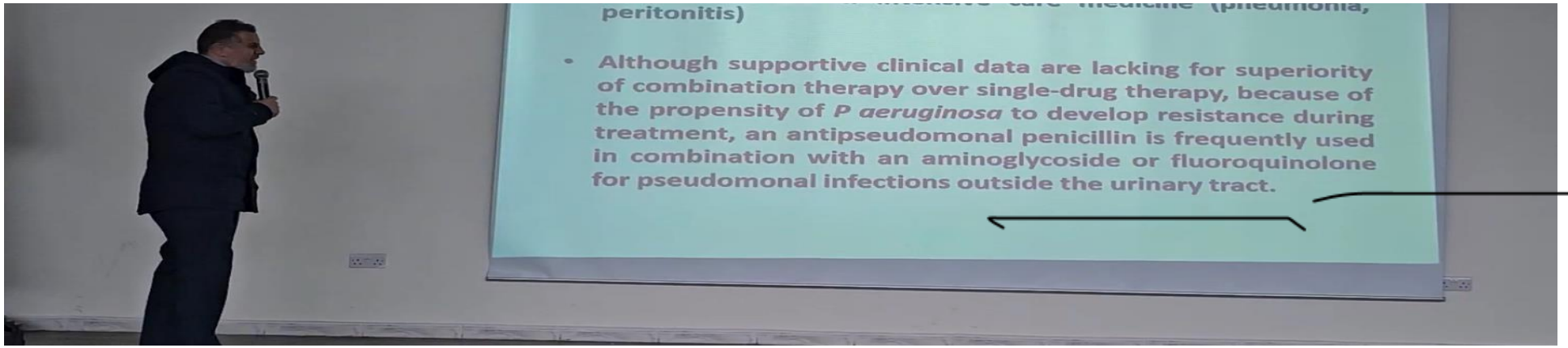
- Aminoglycosides: Such as Gentamicin or Amikacin.




The Rule of Combination Therapy

Do not combine two drugs with the same mechanism of action (e.g., do not give two cell wall inhibitors together).
Why use two mechanisms? To prevent resistance and ensure "double coverage" for severe infections.

The Strategy: If you are worried about the bacteria "mutating" ( ,(تطورyou must pair a Cell Wall Inhibitor with a drug from a different class, such as an Aminoglycoside or a Fluoroquinolone (e.g., Ciprofloxacin).



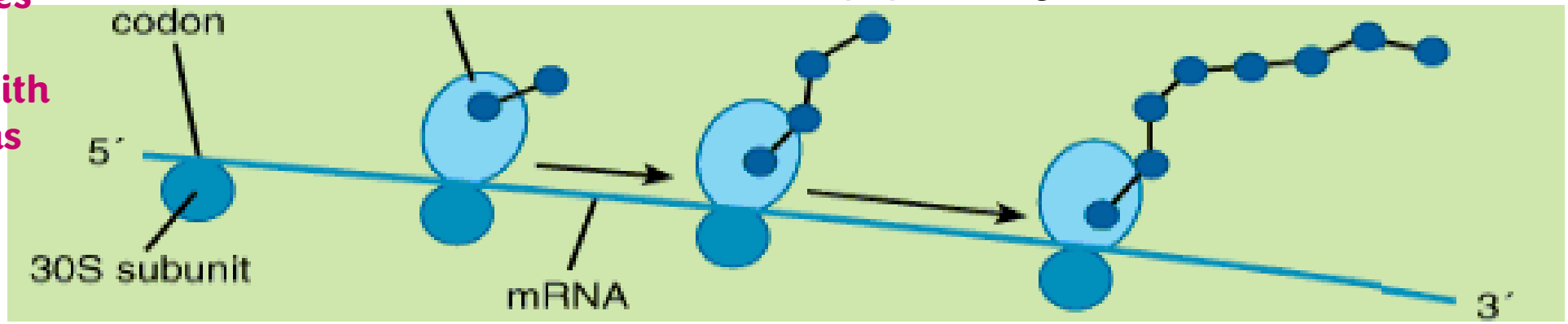

The strategy for treating Pseudomonas aeruginosa depends heavily on the location and severity of the infection. If the infection is located in the urinary tract, it can be treated with a single agent. In this case, you can give a high dose of the medication without a problem because the drug concentrates effectively in the urine.

However, the approach changes for more severe or systemic conditions. If the patient has pelvic sepsis, hospital-acquired pneumonia, or bacteremia, you must choose two drugs with two different mechanisms of action. This combination therapy is necessary for these high-risk infections to ensure clinical success and overcome potential bacterial resistance.

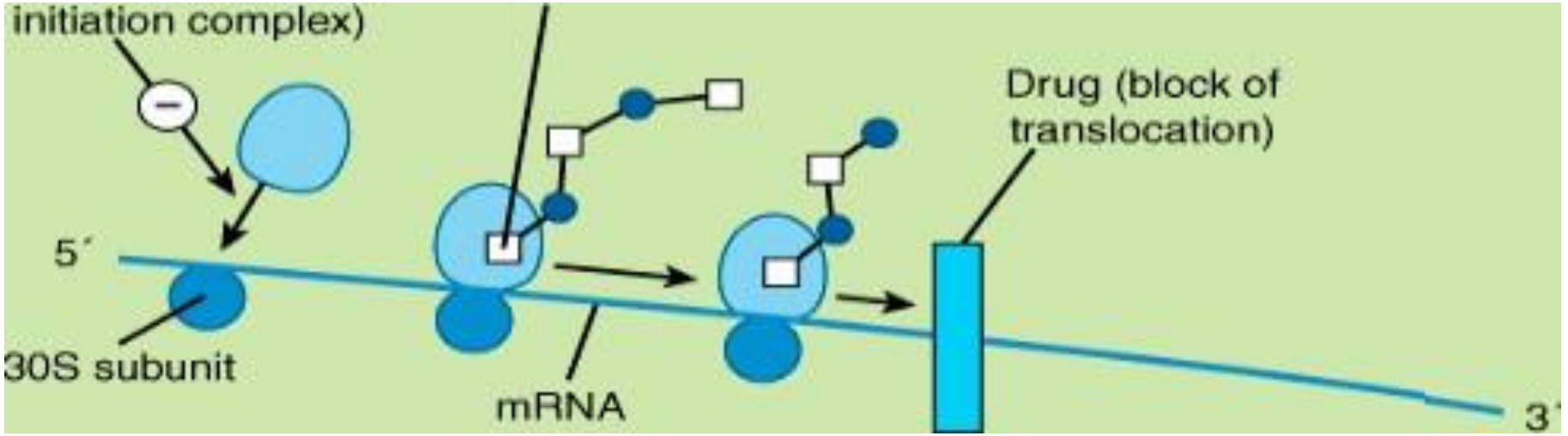
كتب هذا الموديفايد تحت ضغط ومواد
وأصابعي وجعوني من سخونة شاشة الايباد لا تنسونا من دعائكم ❤️

**Aminoglycosides work on the 30S ribosomes And the membrane with 2 mechanisms explained in slide 16**

Normal bacterial cell




Aminoglycosicle-treated bacterial cell




Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition; http://www.accessmedicine.com

# Aminoglycosides
# (only bactericidal protein synthesis inhibitor)

- **bind to the ribosomal 30S subunit**
- **inhibit initiation of peptide synthesis and cause mis-reading of the genetic code.**
- **Streptomycin is the best known member of the group which also includes amikacin, Gentamicin, *Tobramycin*, Netilmycin, and Neomycin.**
- **They are effective against many aerobic Gram-negative and some Gram-positive bacteria, finding their greatest use against Gram-negative enteric organisms and in sepsis.**

**Dose Independent**
**In the 70s and 80s, we left the Aminoglycosides because we produced Monobactam and Ceftazidime (only Gram-negative).**
**I put with those 3 drugs one of these 3 drugs: Amikacin, Gentamicin, Tobramycin.**
**(Only Gram-negative) / they can work on Nosocomial infection.**

**Mechanisms:**

**1) Bind to the ribosome irreversibly that's why they are bacterocidal ?**

**They are glycoside with AMINO group so the cells recognize them as amino acids so they open their membranes to them by creating pores. They enter through the outer membrane of the gram –ve membrane and become part of the membrane acting on the fidelity. This way the membrane is more loose and the cell can burst. This is theoretical only**

**2)miscoding:**

**which can interfere with human cells causing ototoxicity**

**Patients with mitochondrial mutation are most susceptible might lead to complete deafness.**

**We changed the membrane fidelity at the same time we are acting on the protein synthesis(by binding to the ribosome) producing different proteins which the cell doesn't recognize leading the cell to choose to die by apoptosis**

Treating gram-ve
Hospital acquired infection(except MRSA use vancomycin)

# Clinical uses

1) Gram –ve bacillary infection – septicemia, pelvic & abdominal sepsis

2) Bacterial endocarditis – enterococcal, streptococcal or Staphylococcal.

3) Pneumonias, Tuberculosis

4) Plague, Brucellosis

These are gram +ve and the aminoglycosides are not supposed to be active on them which is clinically right
The doctor explains that doctors usually prescribe aminoglycosides with other antibiotics like ampgent or vancgent (خراريف فاضية) because they thought that antibiotics work with another cell wall inhibitor on gram positive and this is actually true but *only* in vitro (in the lab) not in vivo (in the body) hence there is no actual clinical use so in vivo does not equal in vitro

5) To sterilize the bowel of patients who receive immunosuppressive therapy, before surgery & in hepatic coma

Go to slide 23

# Aminoglycosides
# (only bactericidal protein synthesis inhibitor)

- **bind to the ribosomal 30S subunit**
- **inhibit initiation of peptide synthesis and cause mis-reading of the genetic code.**
- **Streptomycin is the best known member of the group which also includes amikacin, Gentamicin, *Tobramycin*, Netilmycin, and Neomycin.**
- **They are effective against many aerobic Gram-negative and some Gram-positive bacteria, finding their greatest use against Gram-negative enteric organisms and in sepsis.**

**Which one to use?**

**-Gentamicin & tobramycin:**

**Both are natural, coming from bacteria and there is resistance towards them but not a lot. The bacteria is smart, it developed this resistance by adding methyl or acetyl groups to the drugs which have 6 sides to be added on, this modification changes the structure and activity of these drugs**

**The resistance in these drugs is 13%. Gentamicin is older**

**Tobramycin is the strongest on pseudomonas aeruginosa**

**-Amikacin (nickname king):**

**This isn't natural. To prevent resistance, we evolved this drug By blocking the 2 sites which can be modified by the bacteria. Resistance is not more than 3%**

**Please as a doctor save this drug**

# Points

- **First choice gentamycin due to low cost, reliable activity and long experience of use.**
- **Used in infected burns, otitis externa, acute pyelonephritis**
- **Tobramycin is the most active against Pseudomonas infections**
- **Amikacin is the Broadest antibacterial spectrum Preferred in serious nosocomial G –ve bacillary infection in hospitals where Tobramycin & Gentamicin have developed resistance**

# Aminoglycosides

- **They are effective in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli.**

- **Neomycin is reserved for topical applications because of their systemic toxicity.**

# Aminoglycosides

Explained below 3 important points about using aminoglycosides:
1) only use aminoglycosides when necessary
2) don't use for more than one week
3) when using it trough the medication

- Aminoglycosides are not absorbed from the GI tract.
- They are usually administered intramuscularly or intravenously.
- Serious dose-related side-effects occur with the aminoglycosides, The main hazards and nephrotoxicity.

Remember that aminoglycosides are non-dose dependent so to prevent toxicity & keep the drug within the normal range we need to trough the medication by: monitoring the level of the drug in blood before giving the next dose. If the level in blood is high, we decrease the next dose and if it is low we increase the next dose. Although we troughed the medication Aminoglycosides accumulate in tissues that is why we should never use this medication for more than one week. It accumulates in kidneys and adipose tissues, and we won't see this accumulation

- Ototoxicity

Part of ototoxicity is dose dependent and part is not

**Neomycin:**
**Only given orally or topically because if given IV it kills the patient.**
**Why we use it?**
**To sterilize the GI tract flora before abdominal surgery to decrease the load of the flora.**
***if patient has a problem in liver (cirrhosis) he can't metabolize the ammonia leading to accumulation in brain leading to encephalopathy**
**That's why we want to decrease the load of flora which produce ammonia, so we use Neomycin**

| Subclass | Mechanism of Action | Effects | Clinical Applications | Toxicities, Interactions |
|---|---|---|---|---|
| **Aminoglycosides & Spectinomycin** | | | | |
| **Gentamicin** | **Prevents bacterial protein synthesis by binding to the 30S ribosomal subunit** | **Bactericidal activity against susceptible bacteria. synergistic effects against gram-positive bacteria when combined with lactams or vancomycin. demonstrate concentration-dependent killing and a significant postantibiotic effect** | **Sepsis caused by aerobic gram-negative bacteria synergistic activity in endocarditis caused by streptococci, staphylococci, and enterococci** | **once-daily dosing at 5–7 mg/kg as effective and may have less toxicity than conventional dosing *Toxicity:* Nephrotoxicity (reversible), ototoxicity (irreversible), neuromuscular blockade** |
| ***Tobramycin: Intravenous; more active than gentamicin versus pseudomonas; may also have less nephrotoxicity*** | | | | |
| ***Amikacin: Intravenous; resistant to many enzymes that inactivate gentamicin and tobramycin; higher doses and target peaks and troughs than gentamicin and tobramycin*** | | | | |
| ***Neomycin: Oral or topical, poor bioavailability; used before bowel surgery to decrease aerobic flora; also used to treat hepatic encephalopathy*** | | | | |

This drug is mostly used by dentists.

We still haven't solved the problem of patients who have odontogenic infection along with penicillin allergy (we used Pen. V or G for patients without Pen, allergy)

# Clindomycin

- Binds to the 50S ribosomal subunit and inhibit the correct attachment of the amino acid end of aminoacyl-tRNA.
- Is active against Gram-positive cocci, including penicillin-resistant staphylococci, and many anaerobic bacteria.
- Clindomycin finds its main clinical use in infections caused by *Bacteroides* organisms and for staphylococcal infections of bones and joints.
- Clindamycin is also indicated for treatment of anaerobic infection caused by bacteroides and other anaerobes that often participate in mixed infections.

This is the best drug for anaerobes.
Active against: Gram +ve (strep. Staph.) & anaerobic bacteria
Its characteristic: Penetration, Penetrates through bones in a magnificent way hence It is the best treatment used in osteomyelitis. And it penetrates through teeth.
It is also active on fragilis it's an alternative to 2nd generation cephalosporins Cefoxitin and Cefotetan which are not found in Jordan.
It is used for upper and lower diaphragm anaerobes ( abdominal infection)
Once a patient died from this antibiotic due to pseudomembranous colitis by
Cl. Difficile. ;now there isa warning on this drug
So we only use it in odontogenic infection and special cases

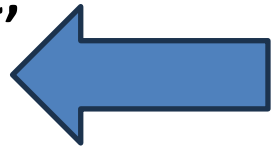
Used in osteomyelitis because of its good penetration

# Clindomycin

- Clindamycin, sometimes in combination with an aminoglycoside or cephalosporin, is used to treat

(1) penetrating wounds of the abdomen and the gut;

So the drug of choice here is Clindamycin



When someone gets injured with a sharp object, they might get strep/staph inside. A mixed infection might occur by anaerobes &strep & staph

(2) infections originating in the female genital tract, eg, septic abortion.

(3) and aspiration pneumonia.

When you choke on food, you might get anaerobes from the oral cavity into the lungs--> aspiration pneumonia. Use Clindamycin

- Side-effects generally are limited to GI upsets.

However, a potentially lethal psuedomembranous colitis can occur.

we have talked about this in the previous slide

# Dental pharmacologic features of clindamycin

*not required*

1. Wide spectrum of in vitro antimicrobial activity that includes those species implicated as pathogens in dental infections
2. Achievement of high levels in saliva, gingival crevicular fluid, and bone
3. Reduction of the expression of virulence factors (M protein, capsule, and toxins)
4. Increased bacterial phagocytosis and killing
5. Activity in conjunction with the host defense system
6. Suppression of the adherence of bacteria to the mucosal epithelial cells and the expression of virulence factors
7. Postantibiotic effect

# Additional Resources:

# رسالة من الفريق العلمي:

# For any feedback, scan the code or click on it.

**Corrections from previous versions:**

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V0 → V1 | | | |
| V1 → V2 | | | |