بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 14

Antibiotics Pt.6

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Quick Revision

1. Carbapenems

Drugs: Imipenem, Meropenem, and Ertapenem.

Overview: These are the broadest-spectrum antibiotics currently available.

Ertapenem: Has a slightly narrower spectrum compared to Imipenem and Meropenem; it lacks activity against Enterococci and Pseudomonas.

General Spectrum: Covers most bacteria except:

1) **MRSA and Coagulase-negative Staphylococci.**
2) **Clostridioides difficile.**
3) **Nocardia.**
4) **VRE (Vancomycin-Resistant Enterococci).**

Resistance: Some bacteria produce **carbapenemases (enzymes that degrade the drug).** This is most common in Klebsiella pneumoniae (KPC), but also seen in E. coli, Serratia, Enterobacter, Pseudomonas, Proteus, and Salmonella. Currently, very few drugs effectively cover carbapenemase-producing organisms.

Clinical Use (Febrile Neutropenia): In immunocompromised patients (e.g., chemotherapy patients) with an unknown infection and persistent fever despite empirical treatment, Meropenem is often used. If Meropenem fails, Colistin may be used, though it is highly toxic.

Vancomycin

2. <u>Glycopeptides: Vancomycin</u>

Spectrum: Exclusively Gram-positive bacteria, particularly cocci. It is the gold standard for MRSA and is effective against Enterococcus and Clostridium.

- Mechanism of Action: Like Penicillins, it is a cell wall inhibitor, **<u>but it works differently.</u>** While Penicillins bind to Penicillin-Binding Proteins (PBPs/transpeptidases), and MRSA is resistant since it has mutated these receptors.
The penicillin-binding sites are crucial for the action of penicillin, but in the case of MRSA, these sites have undergone mutations, making penicillin ineffective. Therefore, we need new drugs that don't rely on binding to these mutated sites. Vancomycin, for example, doesn't bind to penicillin-binding proteins; instead, **it works by integrating into the peptidoglycan structure and disrupting its formation**, rather than inhibiting transpeptidases. **This action makes vancomycin effective mainly against Gram-positive bacteria, as it's difficult for the drug to penetrate Gram-negative bacteria. Therefore, vancomycin is primarily used for Gram-positive infections.**

➢ **Clinical Applications:**

Nosocomial Infections: Used empirically when MRSA is suspected (responsible for ~25% of hospital-acquired infections).

Enterococcal Endocarditis: Used if the strain is resistant to Ampicillin.

C. difficile: Administered orally because it is not absorbed into the bloodstream, allowing it to act directly within the GI tract. For systemic infections, it must be injected (IV).

Administration & Toxicity:

Adverse Effects: Nephrotoxicity and ototoxicity (more common in children).

Vancomycin

Safety Protocol: Vancomycin is highly irritating and can damage renal tissues if concentrations are too high. To mitigate this, it must be administered in a diluted solution via slow IV infusion (at least 60 minutes). This slow administration helps maintain safe plasma levels and reduces the risk of direct toxicity to the kidney tubules during excretion.

Vancomycin

- **Vancomycin is bactericidal and acts by inhibiting cell wall synthesis.**
- **it is active only against gram-positive bacteria, particularly staphylococci.**
- **Its special clinical use is in treating methicillin-resistant staphylococci, resistant enterococci and *Clostridium difficile* (which causes psuedomembranous colitis).**
- **The main indication for parenteral vancomycin is sepsis or endocarditis caused by methicillin-resistant staphylococci.**

Vancomycin

- It is also valuable in severe staphylococcal infections in patients allergic to penicillins and cephalosporins.
- Vancomycin in combination with gentamicin is aused for treatment of enterococcal endocarditis in a patient with serious penicillin allergy.
- It is not absorbed from the gut and is only given orally for treatment of GI infections. It is generally administered intravenously.
- Resistance can be caused by changing the permeability to the drug and by decreasing the binding of Vancomycin to receptors.

Vancomycin

- **Vancomycin must be administered in a dilute solution slowly, over at least 60 minutes.**

This is due to the high incidence of pain and thrombophlebitis and to avoid an infusion reaction known as the red man syndrome or red neck syndrome.

- **Unwanted effects are a series problem and include fever, rashes and local phlebitis.**

- **Ototoxicity and nephrotoxicity can occur and hypersensitivity reactions are occasionally encountered.**

Monobactams

3. Monobactams

➢ **Drug: Aztreonam :**

- **Spectrum:** Strictly Gram-negative aerobes (e.g., Pseudomonas aeruginosa, Enterobacter, Serratia, Klebsiella pneumoniae, and Proteus).
- Activity Gaps: No activity against Gram-positive bacteria or anaerobes.
- Clinical Niche: It is the primary alternative for patients with severe Penicillin or Cephalosporin allergies, as it does not cross-react with most beta-lactams. It is often used as a bridge before escalating to Carbapenems.

Monobactams

Their spectrum of activity is limited to aerobic gram-negative rods (including pseudomonas). Unlike other beta-lactam antibiotics, they have no activity against gram-positive bacteria or anaerobes.

- The main monobactam is Aztreonam which is a monocyclic b-lactam resistant to most b-lactamases.

- Penicillin-allergic patients tolerate aztreonam without reaction.

In which used to treat serious infections such as pneumonia, meningitis, and sepsis caused by susceptible gram-negative pathogens.

- Its unwanted side-effects are similar to the other b-lactam antibiotics.

Monobactams

Spectrum of Activity

Aztreonam bind preferentially to PBP 3 of gram-negative aerobes; has little to no activity against gram-positives or anaerobes

Gram-negative

E. coli, *K. pneumoniae*, *P. mirabilis*, *S. marcescens*

H. influenzae, *M. catarrhalis*

Enterobacter, *Citrobacter*, *Providencia*, *Morganella*

Salmonella, *Shigella*

Pseudomonas aeruginosa

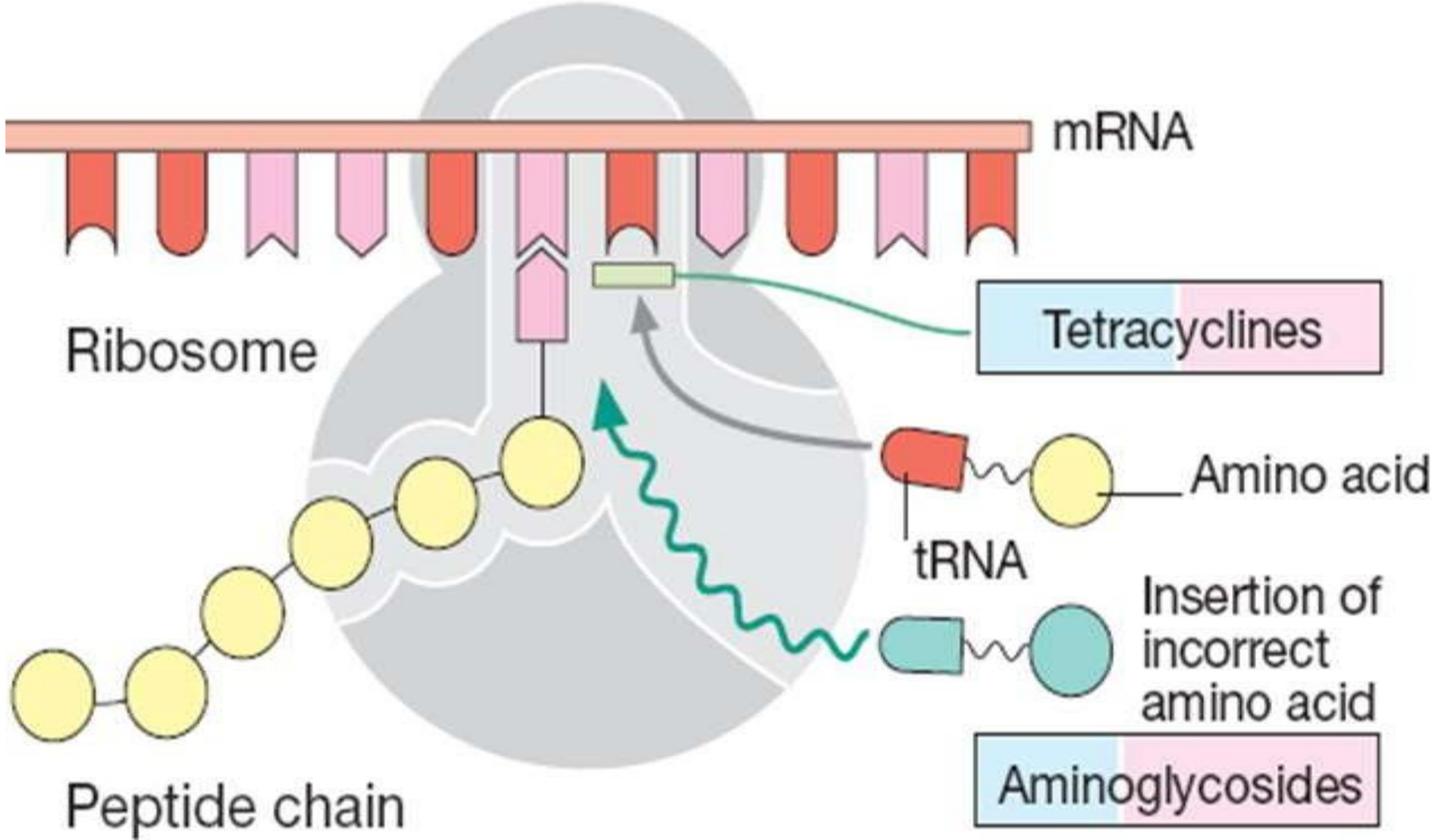
Protein Synthesis Inhibitors

- They are active against a wide variety of organisms (broad spectrum).
- Most are bacteriostatic but a few are bactericidal against certain organisms.
- Because of overuse, resistance is common.

- Bacterial ribosomes differ in molecular detail from eukaryotic ones enabling antibiotics to exhibit selective toxicity.

- The main ribosomal processes they interfere with are :
  (1) binding of aminoacyl-tRNA
  (2) normal codon:anticodon recognition
  (3) transpeptidation


DNA
mRNA
ribosomes
50
30
50
30
50
30
proteins


mRNA
Ribosome
Tetracyclines
Amino acid
tRNA
Insertion of incorrect amino acid
Aminoglycosides
Peptide chain

Tetracycline

4. Tetracyclines

Drugs: Doxycycline, Minocycline, and Tigecycline.

- Mechanism of Action: These are bacteriostatic drugs that inhibit protein synthesis by binding irreversibly to the 30S ribosomal subunit, causing mRNA misreading or preventing protein assembly.

- Resistance: Many common bacteria (Staph, Strep) have developed efflux pumps that actively pump the tetracycline out of the bacterial cell.

- **Tigecycline**: A newer, expensive glycylcycline designed to overcome resistance. It is not recognized by the multi-drug resistant efflux pumps that affect older tetracyclines. It has a very broad spectrum (Gram-positive and Gram-negative).

Tetracyclines

- Tetracycline, Methacycline, Moxycycline, **doxycycline minocycline** and **Tigecycline**.

- They bind to both mRNA and the ribosomal 30S subunit where they prevent the binding of aminoacyl-tRNA.

- They are **bacteriostatic not bacteriocidal.**

- Their spectrum of activity is very wide and includes Gram-positive and Gram-negative bacteria, some spirochaetes and some protozoa (eg amoebae).

CHLAMYDIAL INFECTIONS

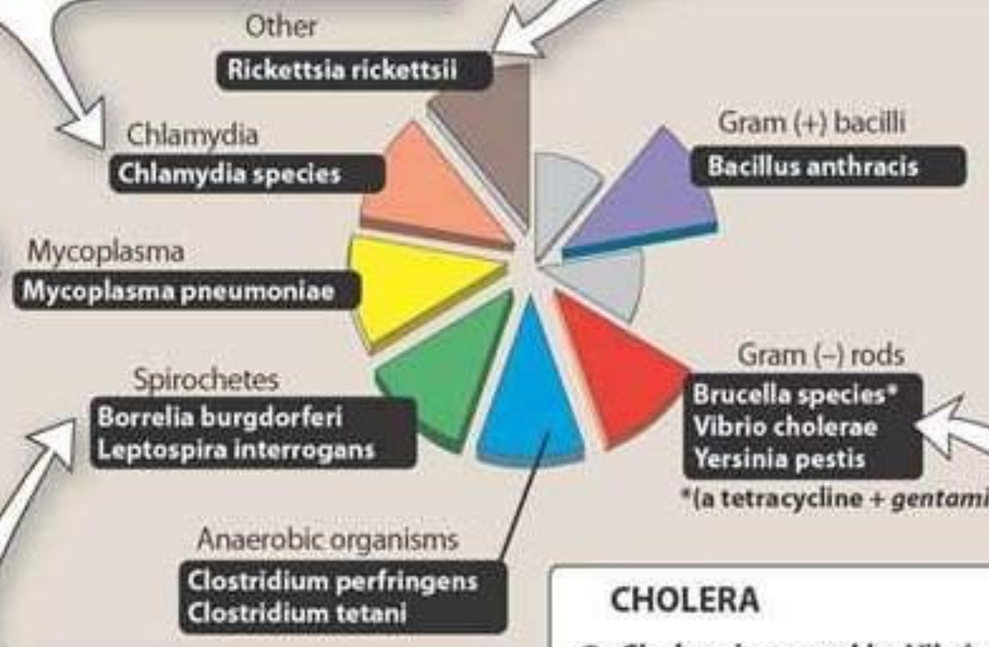
- Chlamydia trachomatis is the major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
- Chlamydia psittaci causes psittacosis, which usually takes the form of pneumonia. Other clinical forms include hepatitis, myocarditis, and coma.
- *Doxycycline* or *azithromycin* is used to treat chlamydial infections.

ROCKY MOUNTAIN SPOTTED FEVER

- This disease, caused by Rickettsia rickettsii, is characterized by fever, chills, and aches in bones and joints.
- Response to tetracyclines is prompt if the drug is started early in the disease process.

MYCOPLASMA PNEUMONIA

- Mycooplasm pneumoniae is a common cause of pneumonia in young adults and in people who live in close confines, such as in military camps.
- Treatment leads to a shorter duration of fever, cough, and malaise.
- Treatment with marcrolides is also effective.



LYME DISEASE

- This is a spirochetal infection caused by Borrelia burgdorferi. The disease is transmitted by the bite of infected ticks.
- Infection results in skin lesions, headache, and fever, followed by meningoencephalitis and, eventually, arthritis.
- A single, 200–mg dose of *doxycycline*, given within 72 hours after a tick bite, can prevent development of the disease.

CHOLERA

- Cholera is caused by Vibrio cholerae ingested as part of fecally contaminated food or water.
- The organism multiplies in the gastrointestinal tract, where it secretes an enterotoxin that produces diarrhea.
- Treatment includes *doxycycline*, which reduces the number of intestinal vibrios, and fluid replacement.

Explanation of the previous figure Pt.1

Disease	Pathogen	Clinical Role
Chlamydial Infections	Chlamydia trachomatis & C. psittaci	Used as second-line therapy (Macrolides are usually first-line). Effective for pneumonia and STDs.
Mycoplasma Pneumonia	Mycoplasma pneumoniae	Used for definitive therapy in young adults or those in close quarters.
Cholera	Vibrio cholerae	Drug of choice. Usually effective as a single dose to reduce intestinal vibrios.
Rocky Mountain Spotted Fever	Rickettsia rickettsii	Drug of choice. Treatment must be started early to be effective against tick-borne rickettsia.
Lyme Disease	Borrelia burgdorferi	Used to treat the spirochetal infection transmitted by tick bites.
Brucellosis	Brucella species	One of the few active drugs because it can penetrate the cell to reach this intracellular pathogen.
Q Fever	Coxiella burnetii	Specifically treated with Doxycycline.
Syphilis	Treponema pallidum	Used as an alternative for patients allergic to Penicillin.
Acne	Propionibacterium acnes	Commonly used for dermatological management.

Explanation of the previous figure Pt.1

- **Chlamydial Infections**

Caused by Chlamydia trachomatis and Chlamydia psittaci. Doxycycline is used as a second-line therapy since macrolides are better. It is used empirically when signs suggest chlamydia.

- **Mycoplasma Pneumonia**

Caused by Mycoplasma pneumoniae. While Azethromax is the first-line therapy, Doxycycline is used as definitive therapy.

- **Vibrio Cholera**

Doxycycline is the drug of choice for cholera. A single dose is enough for treatment.

- **Rocky Mountain Spotted Fever**

Caused by Rickettsia rickettsii transmitted by ticks. Tetracycline is the drug of choice.

- **Q Fever**

Treated with Doxycycline.

- **Brucellosis**

Doxycycline is used because it is one of the only drugs active against Brucella, which is an intracellular pathogen.

- **Acne**

Tetracyclines are used in the treatment of acne.

- **Syphilis**

The primary treatment is Benzathine Penicillin, but Tetracycline is used as an alternative.

- **Lyme Disease**

A spirochetal infection caused by Borrelia burgdorferi transmitted by tick bites. It is treated with Doxycycline.

Tetracyclines

- **Their main clinical uses are :**

(1) mycoplasma and chlamydia infections

(2) A tetracycline—usually in combination with an aminoglycoside—is indicated for brucellosis

(3) They are used in combination regimens to treat gastric and duodenal ulcer disease caused by *Helicobacter p*

(4) Acne

(5) syphilis

Tetracyclines

- Resistance is common and is mainly due to a plasmid-mediated energy-dependent efflux pump, (typical of the multiple drug resistance type). Mutations in the tetracycline target site are also found.

- The Tetracyclines are usually administered orally but can be given parenterally.

- Absorption from the gut is irregular and better in the absence of food.

- Since Tetracyclines chelate di- and trivalent metal ions, forming insoluble complexes, absorption is decreased in the presence of milk, certain antacids and iron preparations.

Tetracyclines

- **The most Common side-effects are GI disturbances, due initially to direct irritation and later to modification of gut flora.**

- **They are deposited in growing bones and teeth, causing staining and sometimes dental hypoplasia and bone deformities.**

- **Phototoxicity: for example, severe sunburn, occurs when the patient receiving a tetracycline is exposed to sun or ultra-violet rays.**

- **They shouldn’t be given to children, pregnant women or nursing mothers. (may causes hepatotoxicity in pregnant women).**

Tetracyclines

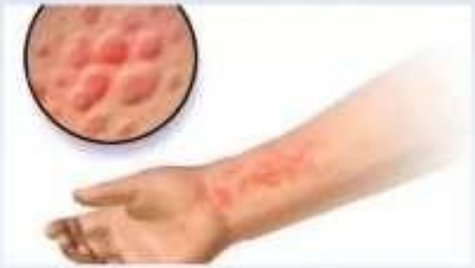
- **Tetracycline is a broad spectrum antibiotic that is occasionally used in Dentistry to treat bacterial infections.**

- **This antibiotic has a natural tendency to concentrate in the gingival fluids around the teeth so it is often used to treat gingivitis and gum disease.**

- **It is one of the first choices for the treatment of ANUG.**

- **Acute Necrotizing Ulcerative Gingivitis appears with stress. College students can get it during finals and people breaking up can get it.**

Tigecycline



Escherichia coli, Enterococcus faecalis (vancomycin-susceptible only),
Staphylococcus aureus (MRSA and methicillin-susceptible and resistant isolates),
Streptococcus pyogenes,
Streptococcus anginosus grp,
Streptococcus agalactiae,
or Bacteroides fragilis

E coli,
Enterococcus faecalis (vancomycin-susceptible only),
S aureus (methicillin-susceptible only),
Citrobacter freundii,
Enterobacter cloacae,
Klebsiella pneumoniae,

Streptococcus pneumonia (penicillin-susceptible isolates)
Haemophilus influenzae,
Legionella pneumophila

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

1. Doctor’s lecture
2. Gemini was used to organise the file

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			