PHINMA EDUCATION

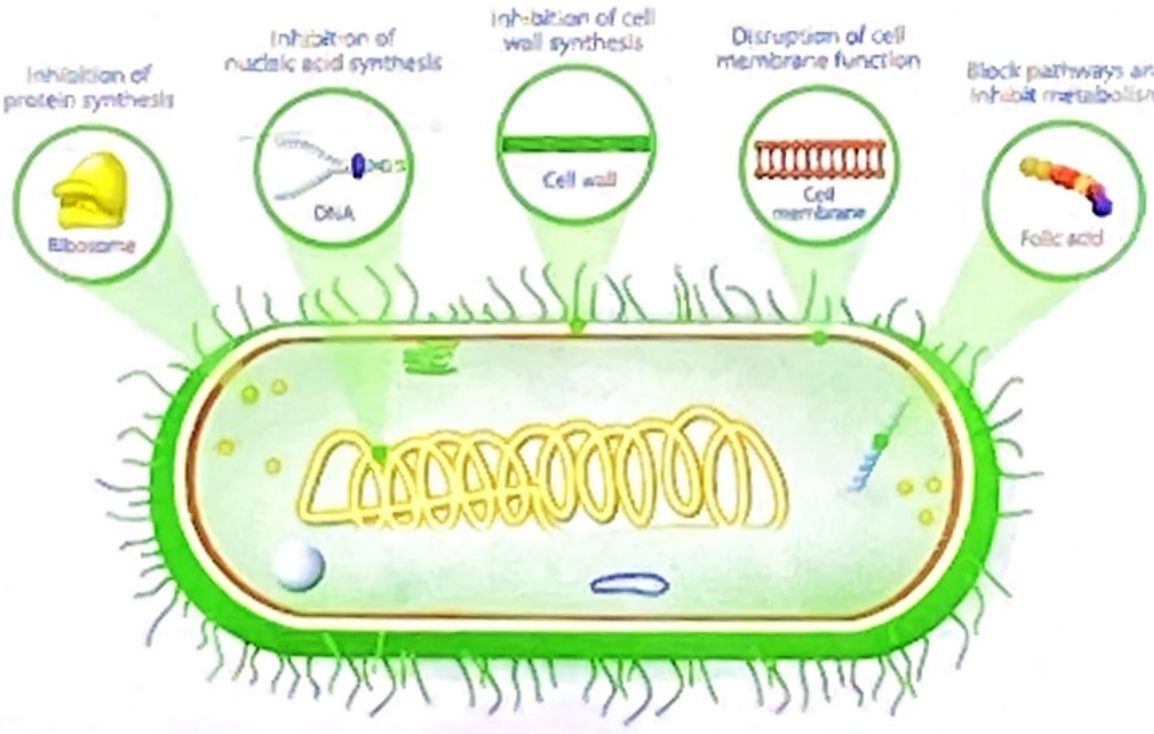
Antibacterial Agents:

An **antibiotic** or **antibiotic substance** is defined as a compound produced by microorganisms that can **inhibit the growth** of, or **destroy, other microorganisms** (Selman Waksman, 1942).

The discovery of antibiotics began with **Sir Alexander Fleming in 1929**, who identified *Penicillin* from *Penicillium* mold. Later, **Selman Waksman and his associates** isolated *Streptomycin* from *Streptomyces griseus*, marking a major milestone in antimicrobial therapy.

ANTIBACTERIAL AGENTS WORKS BY:

PHINMA EDUCATION



CELL WALL INHIBITOR

PHINMA EDUCATION

BETA-LACTAM ANTIBIOTICS

β-lactam antibiotics represent one of the most important classes of antimicrobial agents in clinical medicine. These compounds are characterized by their **four-membered lactam ring structure**, which is essential for their antibacterial activity. They **prevent bacterial cell wall synthesis** by binding to and **inhibiting cell wall transpeptidation.**

Major β-Lactam Classes

1. **Penicillins** - 6-aminopenicillanic acid
2. **Cephalosporins** - 7-aminocephalosporanic acid
3. **Carbapenems** - Penem ring
4. **β-lactamase inhibitors (Clavulanic Acid)** - Protect other β-lactams from enzymatic degradation

NOTE! Expect **cross-sensitivity reactions** between drugs under these classes.

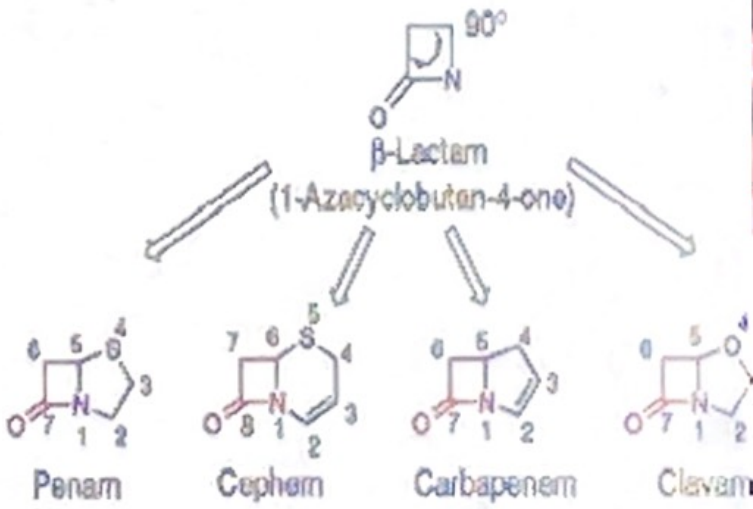
BETA-LACTAM ANTIBIOTICS

PHINMA EDUCATION

The **β-lactam ring (azetidinone)**, along with additional ring substituents, determines the **spectrum of antibacterial activity**.

Mechanism of Action (MOA):

- **Irreversible inhibition** of bacterial **cell wall transpeptidase** (also called transamidase), an enzyme responsible for **cell wall cross-linking**.
- Cross-linking is essential for the **structural integrity** of both **Gram-positive and Gram-negative bacteria**. Without it, bacterial cells undergo **lysis and destruction**.



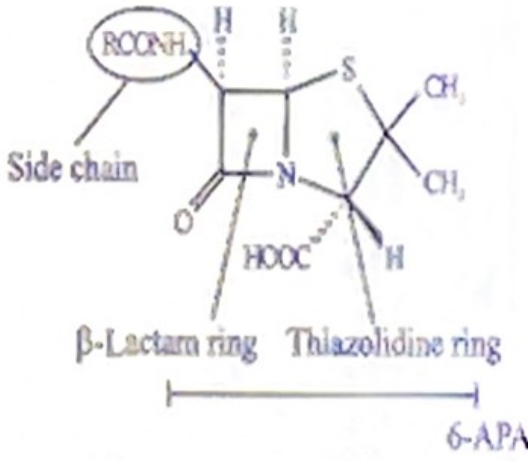
A.PENICILLIN

PHINMA EDUCATION

- Source: Penicillium Chrysogenum
- Contains: *Beta-Lactam Ring* and *Thiazolidine Ring*
- Discovered by: Alexander Fleming
- Easily degraded by **BETA-LACTAMASE** → bacterial enzyme that **degrades the beta-lactam ring**, inactivating the drug

In **Gram-positive bacteria**, β-lactamases are **secreted outside the cell**.

In **Gram-negative bacteria**, β-lactamases are located in the **periplasmic space**.



A.PENICILLIN

PHINMA EDUCATION

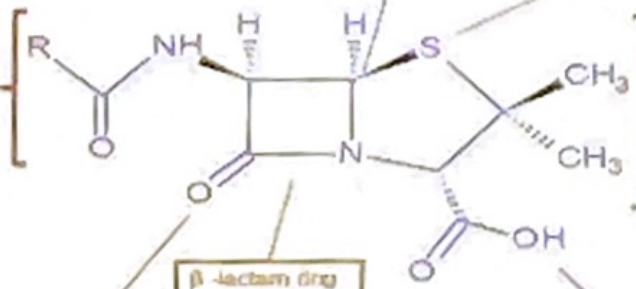
STRUCTURE ACTIVITY RELATIONSHIP OF PENICILLIN

Cis-stereochemistry
-essential

No substitution allowed

Sulphur is usual but not essential

Acylamino side chain
Electron withdrawing group render amide oxygen less nucleophilic.
Bulky group provides steric hindrance to β-lactamase.
Incorporation of polar group makes it more hydrophilic.



Thiazolidine ring
-5-membered nitrogen saturated ring

β -lactam ring
-strained

Carbonyl group
-lone pair electron located on nitrogen atom not fed to carbonyl group to form a stabilized resonance structure, thus more electrophilic for nucleophilic attack.

Bicyclic system
-confers further strain on β -lactam ring.
-the greater the strain, the greater the activity, the greater the instability of the molecule to other factors.

Carboxylic acid
-Usually ionized and administered as sodium/potassium salt
-Carboxylate ions bind to charged nitrogen of a lysine residue in the binding site.
-Activity reduces when modified to alcohol/ ester.

A.PENICILLIN

PHINMA EDUCATION

1. **Benzyl penicillins** (Pen G) **Phenoxymethyl penicillin** (Pen V) – Gram-positive cocci; URTI, LRTI, and Gastric Ulcer infections.
2. **Aminopenicillins (ampicillin, amoxicillin)** – Extended Gram-negative coverage (*H. influenzae, N. gonorrhoeae*) + Gram-positive Infections.
3. **Methicillin group (dicloxacillin, nafcillin, oxacillin)** – Penicillinase-producing bacteria; less potent on Gram-positive; Methicillin-Resistant Staphylococcus aureus.
4. **Carboxypenicillins (ticarcillin)** – Gram-negative coverage; used for *Pseudomonas aeruginosa*.
5. **Ureidopenicillin (piperacillin)** – Broad-spectrum (Gram-positive & Gram-negative).

Adverse Effects:

- Hypersensitivity reactions and Stevens–Johnson syndrome

B. BETA-LACTAMASE INHIBITORS "Suicide Substrate"

PHINMA EDUCATION

- Protect β-lactam antibiotics from bacterial enzymes
- Mechanism: POTENTIATION (protect active drug, but don't directly kill)

PENICILLIN	BETA-LACTAMASE INHIBITOR	NAME
Amoxicillin	Clavulanic Acid	Co-Amoxiclav (Augmentin®)
Ampicillin	Sulbactam	Unasyn®
Piperacillin	Tazobactam	Piptaz®, Tazocin®

B. BETA-LACTAMASE INHIBITORS "Suicide Substrate"

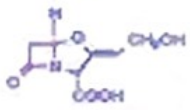
PHINMA EDUCATION

Clavams, Penams, Diazabicyclocarbamoyl Sulfate

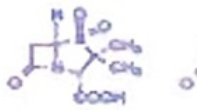
- **Clavulanic acid, sulbactam, tazobactam, avibactam** – minimal antimicrobial activity but **strong β-lactamase inhibitors**.
- **Clavulanic acid, sulbactam, tazobactam** – bind **irreversibly** to β-lactamase (serine-OH).
- **Avibactam** – binds **reversibly** to β-lactamase.

Clinical Use:

- Combined with **penicillins** to extend coverage against **β-lactamase–producing organisms**:
  - **Augmentin** [amoxicillin/clavulanic acid],
  - **Timentin** [ticarcillin/clavulanic acid],
  - **Unasyn** [ampicillin/sulbactam],
  - **Zosyn** [piperacillin/tazobactam]).
- Also combined with *cephalosporins*:
  - **Zerbaxa** [ceftolozane/tazobactam]
  - **Avycaz** [ceftazidime/avibactam])



Clavulanic acid



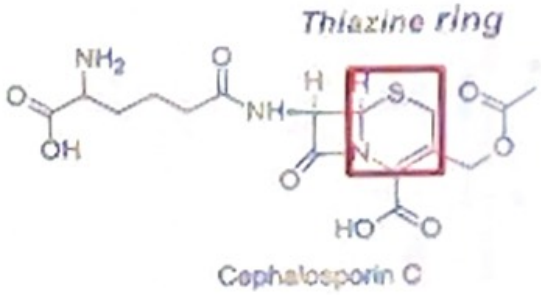
Tazobactam

Avibactam

Expands activity, especially against **β-lactamase–producing Gram-positive bacilli**.

C. CEPHALOSPORINS

- More stable to bacterial β-lactamases than penicillins
- Broader spectrum of activity
- Source: **Cephalosporium Acremonium**
- Contains: *Beta-lactam ring* and *Dihydrothiazine ring*.
- Cross-sensitivity with Penicillin
- ↑ Generation = ↑ Activity against **GRAM NEGATIVE** bacteria
- ADR: **HYPOPROTHROMBINEMIA**



Cephalosporin C

C. CEPHALOSPORINS

PHINMA EDUCATION

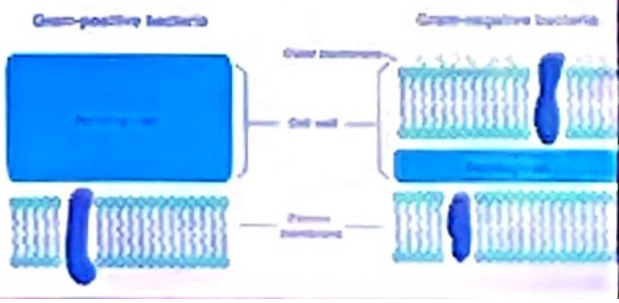
MOA: Inhibit **peptidoglycan synthesis** by binding to **penicillin-binding proteins (PBPs)**. Block final **transpeptidation step**, weakening the bacterial cell **wall** → **cell lysis**.

Clinical Applications (Oral Cephalosporins)

- **Phenylglycyl substituent** → ↑ acid stability → oral activity.
- **Broad-spectrum** and **more β-lactamase resistant than ampicillin**.
- Strong activity vs **Klebsiella**.
- **Cefuroxime** and **cefpodoxime** – orally active ester prodrugs; β-lactamase–resistant.
- Generational classification (1st–5th/6th) has **limited clinical relevance**.

Mnemonic: "LAME" (No Activity Against)

- Listeria
- Atypicals (*Mycoplasma, Chlamydia*)
- MRSA
- Enterococci



C. CEPHALOSPORINS

PHINMA EDUCATION

Antipseudomonal Cephalosporins

Active agents:

- **Cefoperazone**
- **Cefotaxime**
- **Ceftizoxime**
- **Ceftriaxone**
- **Ceftazidime**

✓ Penetration into *Pseudomonas* due to polar groups (carboxy, N-acylureido).

Adverse Effects

- Hypersensitivity reactions (similar to penicillins)
- Possible cross-reactivity with penicillins (less common than previously thought)
- Skin testing unreliable

C. CEPHALOSPORINS

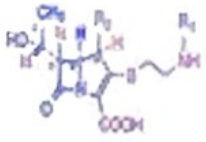
PHINMA EDUCATION

1st Generation	2nd Generation	3rd Generation
Cephalothin	Cefuroxime	Ceftibuten
Cephaperin	Cefonicid	Cefditoren
Cephalexin	Cefoxitin	Ceftazidime
Cephradine	Cefotetan	Cefixime
Cefadroxil	Cefprozil	Cefotaxime
Cefazolin	Cefmetazole	Cefpodoxime
	Cefaclor	Ceftizoxime
	Cefamandole	Ceftriaxone (DOC for gonorrhea)
	Loracarbef	Cefoperazone
		Moxalactam
		Cefdinir

4th Generation	5th Generation
Cefepime	Ceftaroline
Cefpirome	Ceftobiprole
	Ceftolozane

D. CARBAPENEM

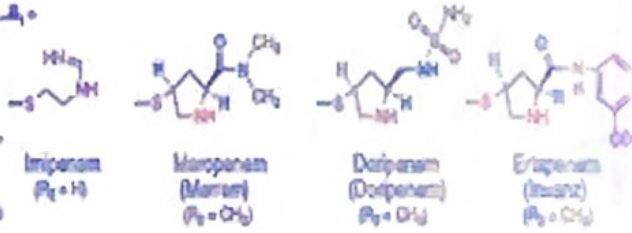
- Synthetic derivatives of **thienamycin**
- Same **MOA as other β-lactams** (inhibit cell wall synthesis)
- **Thienamycin**- sourced from **Streptomyces Cattleya** and the First discovered carbapenem



Carbapenem

PK Properties

- Soluble at **alkaline pH** → **suitable for IV use**
- **Imipenem** given with **cilastatin** to prevent β-lactam hydrolysis



Clinical Use

- **Broad-spectrum**: Gram-negative bacilli, anaerobes, *S. aureus*
- Used for: **UTIs, LRTIs, intra-abdominal, gynecologic, skin/soft tissue, bone, and joint infections**

D. CARBAPENEM

PHINMA EDUCATION

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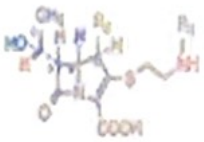

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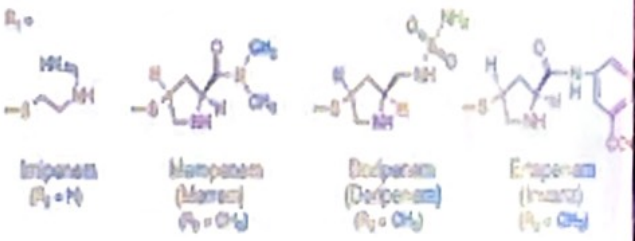

Imipenem (R_1 = H)

Meropenem (Merrem) (R_1 = CH_3)

Doripenem (Doripenem) (R_1 = CH_3)

Ertapenem (Invanz) (R_1 = CH_3)

Clinical Use

- **Broad-spectrum**: Gram-negative bacilli, anaerobes, *S. aureus*
- Used for: **UTIs, LRTIs, intra-abdominal, gynecologic, skin/soft tissue, bone, and joint infections**

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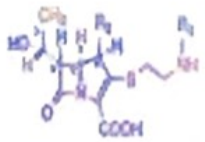

Carbapenem

PK Properties

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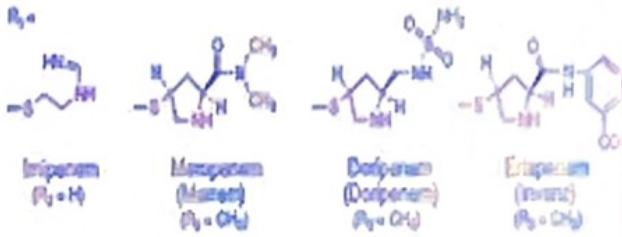

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Clinical Use

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- Used for: **UTIs, LRTIs, intra-abdominal, gynecologic, skin/soft tissue, bone, and joint infections**

PROTEIN SYNTHESIS INHIBITOR

PHINMA EDUCATION

RIBOSOMAL TARGETS

30S Inhibitor:

- **Aminoglycosides** (streptomycin, gentamicin): Cause misreading of mRNA
- **Tetracyclines** (doxycycline, minocycline): Block tRNA binding to A site

50S Inhibitor:

- **Chloramphenicol**: Blocks peptidyl transferase
- **Macrolides** (erythromycin, azithromycin): Block translocation
- **Lincosamides** (clindamycin): Block peptide bond formation
- **Streptogramins** (quinupristin/dalfopristin): Block peptide elongation

A.AMINOGLYCOSIDES (30s inh.)

PHINMA EDUCATION

Source:

- Micromonospora (-micin)
- Streptomyces (-mycin)

Aminoglycoside	Source
Streptomycin	*S. griseus*
Neomycin	*S. fradiae*
Paromomycin	*S. rimosus*
Kanamycin	*S. kanamyceticus*
Amikacin	Semisynthetic Kanamycin A

Aminoglycoside	Source
Gentamicin	*M. purpurea*
Netilmicin	*M. inyoensis*
Tobramycin	*S. tenebrarius*
Spectinomycin	*S. spectabilis*

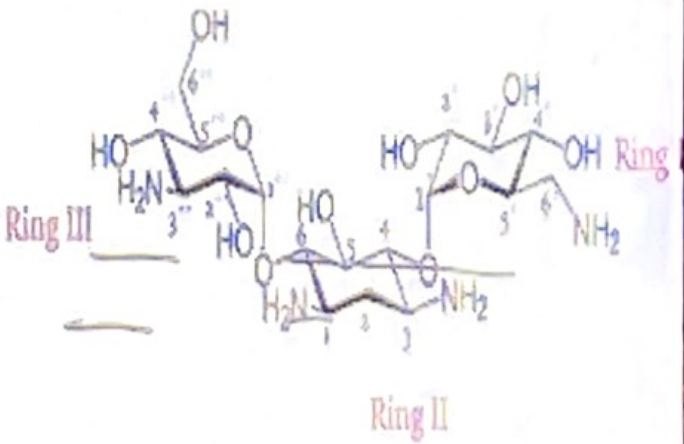
A.AMINOGLYCOSIDES (30s inh.)

PHINMA EDUCATION

MOA: Bind 16S rRNA of 30S ribosomal subunit. Cause irreversible inhibition of protein synthesis → formation of nonsense proteins → bactericidal. Enter Gram-negative bacteria via passive & active transport

SAR:

- Ring I – essential for broad-spectrum activity; main site of enzymatic inactivation
- 6' and 2' amino groups – important for activity
- Phosphorylation of 3'-OH ↓ ribosomal binding
- Ring II – tolerates minor modifications
- Ring III – less sensitive; 3" amino group (1° or 2°) needed for max activity



A.AMINOGLYCOSIDES (30s inh.)

Clinical Use

- Reserved for **serious Gram-negative infections**
- **Streptomycin** – first aminoglycoside antibiotic to be used in **chemotherapy** and mainly for **mycobacterial** infections
- **Gentamicin** – broad Gram+ and Gram−
- **Tobramycin** – strong vs *P. aeruginosa*
- **Amikacin** – resistant to most inactivating enzymes
- **Netilmicin** – similar potency to gentamicin

Chemical Incompatibility

- Do **NOT mix with β-lactams** (aminoglycoside amino group hydrolyzes β-lactam ring)

A.AMINOGLYCOSIDES (30s inh.)

PHINMA EDUCATION

- Not considered as first-line agent
- Low oral bioavailability → PO route not recommended
- Has a narrow therapeutic index

Topical/Oral Aminoglycosides

- **Neomycin** and **Paromomycin** – used **orally** to suppress intestinal flora or treat **amebiasis**, and **topically** for skin infections.
- Toxicity may occur if absorbed through **ulcerated intestines** or large denuded skin areas

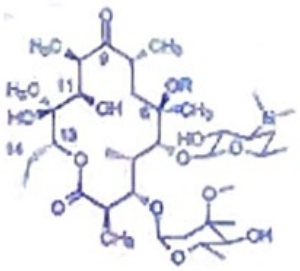
ADR:

TOXICITY	EXAMPLE
Vestibulotoxicity	Streptomycin, Gentamicin
Ototoxicity	Neomycin, Amikacin, Kanamycin
Nephrotoxicity	Neomycin, Tobramycin, Gentamicin

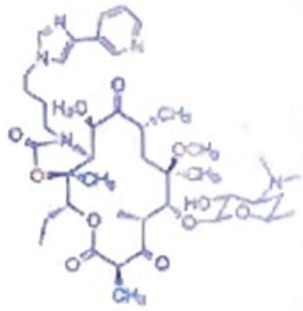
B. MACROLIDES (50s inh.)

PHINMA EDUCATION

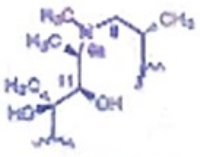
- 14–16 membered lactone ring (Derived from **Actinomycetes)**
- **Erythromycin** – prototype (1952)
- **Clarithromycin & Azithromycin** – synthetic analogues



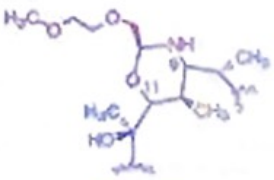
Erythromycin A (R = H)
Clarithromycin (R = CH_3)
(Biaxin)



Telithromycin
(Ketek)



Azithromycin
(Zmax, Zithromax)



Dirithromycin
(discontinued)

MOA

- Bind **23S rRNA of 50S ribosomal subunit**
- Inhibit **translocation** → bacteriostatic

Adverse Effects

- GI disturbance (common with erythromycin)
- QT prolongation

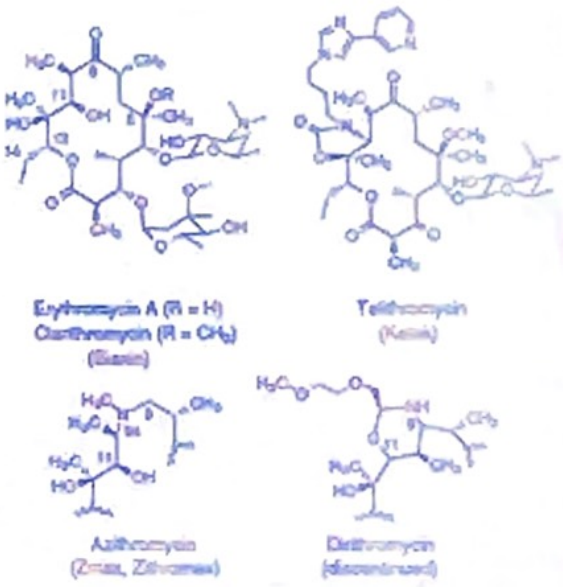
B. MACROLIDES (50s inh.)

PHINMA EDUCATION

Clinical Uses:

- **Gram-positive cocci** (URTI, LRTI, otitis media)
- **Atypicals** (*Mycoplasma, Legionella, Chlamydia*)

1. **Erythromycin**- prototype of macrolides and was isolated in 1952 (Ilosone) by Dr. Abelardo Aguilar. *DOC for diphtheria, pertussis, and Legionnaires disease*
2. **Clarithromycin**- Aka "Methylated Erythromycin", for used for of H. pylori causing peptic ulcer disease.
3. **Azithromycin**- long half-life, given for only *3-5 days of treatment*



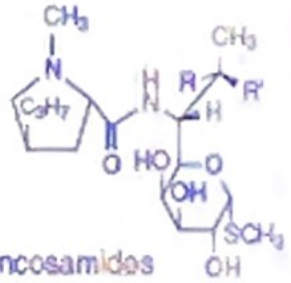
C. LINCOSAMIDE (50s inh.)

PHINMA EDUCATION

Lincomycin(natural) **Clindamycin** (semisynthetic)

MOA

- Bind to **50S ribosomal subunit**
- Inhibit **protein synthesis**
- Binding site similar to macrolides → **cross-resistance possible**



Lincosamides

Lincomycin (Lincocin) (R = OH, R' = H)

Clindamycin (Cleocin) (R = H, R' = Cl)

Clinical Uses

- **Gram-positive cocci & anaerobes**
- Alternative when **β-lactams cannot be used**
- **Skin, soft tissue, respiratory infections**
- **Topical clindamycin** – acne treatment
- **Lincomycin** – reserved for serious infections

ADR: Pseudomembranous colitis (Clostridium difficile overgrowth)

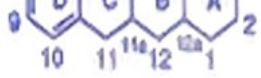
D. TETRACYCLINE (30s inh.)

PHINMA EDUCATION

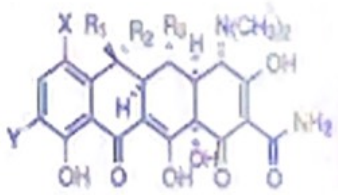
- Naturally occurring antibiotics with **four fused rings**
- **Broadest spectrum** of all the antibacterial agents

MOA

- Bind **30S ribosomal subunit**
- Block **aminoacyl-tRNA attachment to A site**
- Primarily **bacteriostatic**
- Minor binding to 50S



Tetracycline



Tetracycline derivatives

SAR (High-Yield)

- **C4 dimethylamino (α-configuration)** → essential for activity
- **C1–C3, C10–C12, and D ring** → required for binding

D. TETRACYCLINE (30s inh.)

PHINMA EDUCATION

Chlortetracycline
- Aka "Aureomycin"
- First discovered (Source: Streptomyces aureofaciens)

Demeclocycline
- Former DOC for SIAD (Syndrome of inappropriate antidiuretic hormone secretion)

Doxycycline
- DOC for **Leptospirosis**

Minocycline
- most Potent

E. AMPHENICOLS (CHLORAMPHENICOL)

PHINMA EDUCATION

Chloramphenicol sodium succinate – prodrug (limited use due to toxicity)

MOA:

- Reversibly bind **50S ribosomal subunit**
- Inhibit **protein synthesis**
- Similar mechanism to macrolides and clindamycin

Clinical Use:

- **Typhoid fever**
- **Haemophilus infections**
- **Rickettsial infections** (when alternatives unavailable)

Adverse Effects:

- **Fatal pancytopenia**
- Bone marrow suppression → **anemia, leukopenia, thrombocytopenia, aplastic anemia**

PEPTIDE ANTIBIOTICS

PHENMA EDUCATION

A. GLYCOPEPTIDE

Vancomycin, Telavancin, Dalbavancin, Oritavancin

MOA

- Bind **D-Ala–D-Ala** , inhibits cell wall synthesis
- Inhibit **transglycosylation & transpeptidation**
- Bactericidal (↑ membrane permeability + ↓ cross-linking)

PK

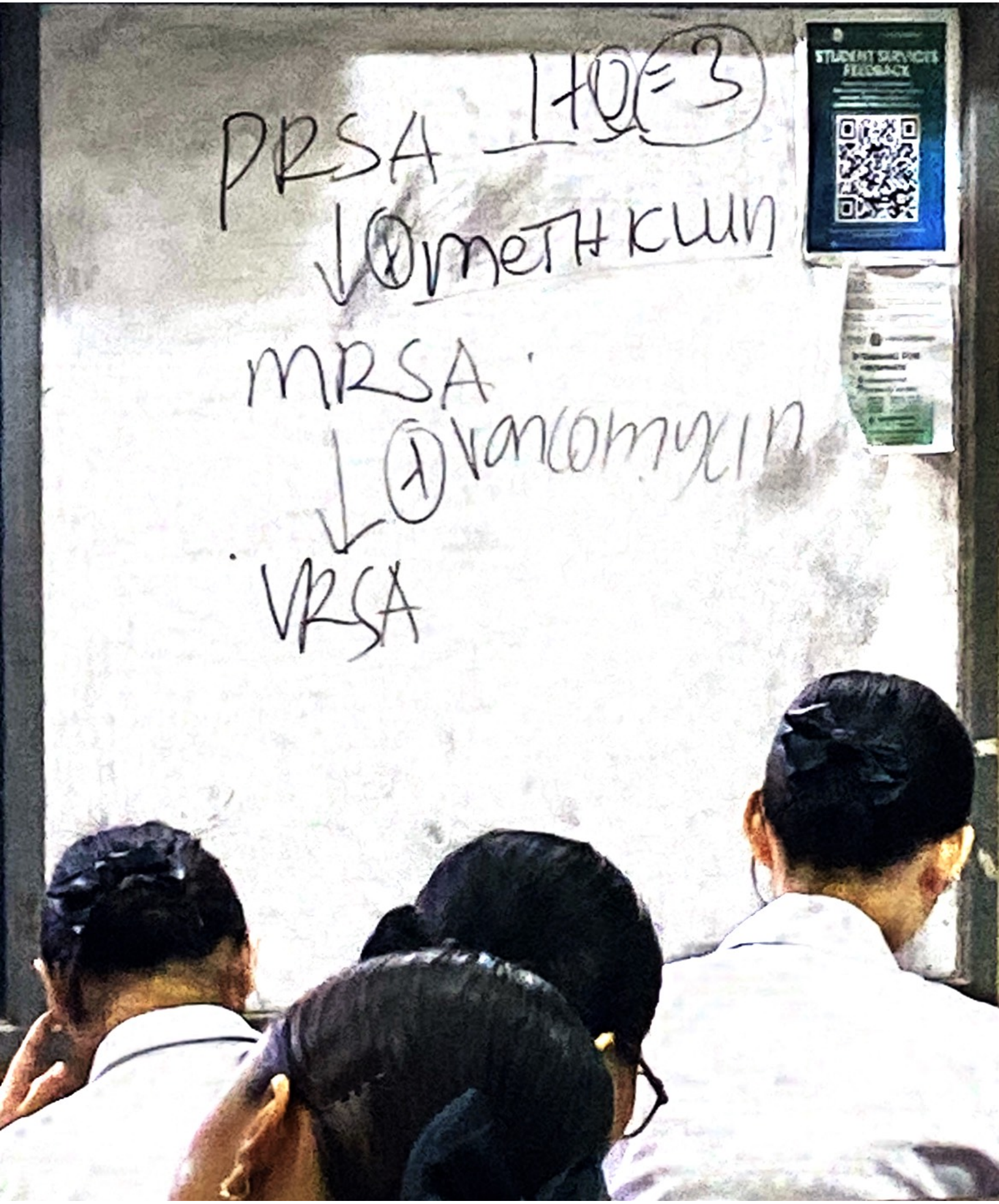
- **IV only**
- Dalbavancin: very long half-life (~12 days)
- Telavancin: once daily
- Vancomycin: q6–12h

Clinical Use

- **Gram-positive only**
- **MRSA**, S. pyogenes (skin infections)
- Vancomycin:
  - IV → MRSA, meningitis
  - Oral → C. difficile

Adverse Effects (Vancomycin)

- **Red Man Syndrome**
- Nephrotoxicity
- Ototoxicity


PRSA
1 to 3
methicillin
MRSA
vancomycin
VRSA
STUDENT SERVICES FEEDBACK

A. GLYCOPEPTIDE

PHINMA EDUCATION

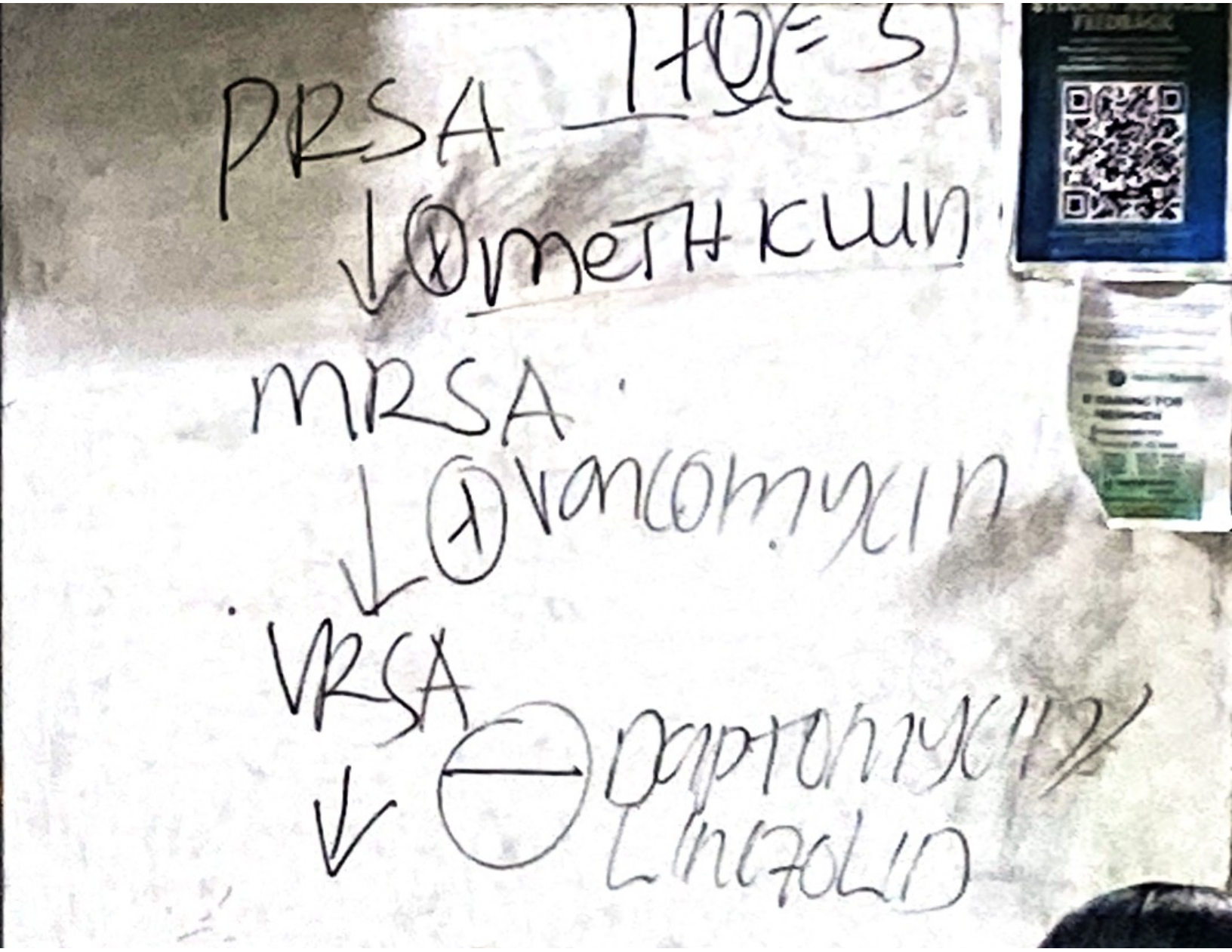
Vancomycin

- Effective for **gram-positive bacteria only**
- DOC: Methicillin Resistant Staphylococcus Aureus (MRSA)
- Source: Streptomyces Orientalis

B. LIPOPEPTIDE

Daptomycin

- Binds cell membrane → depolarization → rapid cell death
- Similar to vancomycin, work against vancomycin-resistant strains (VRSA) DOC: Linezolid


PRSA
methicillin
MRSA
vancomycin
VRSA
daptomycin
Linezolid

C. POLYMYXINS & BACITRACIN

PHINMA EDUCATION

Polymyxin B (B1, B2) and Bacitracin – cyclic peptides

- Commonly found in **OTC topical and ophthalmic preparations** (e.g., conjunctivitis)
- MOA: Disrupt bacterial **cytoplasmic membrane**

Clinical Use

- **Polymyxin B** – severe **Gram-negative infections** (meningitis, pneumonia, sepsis, UTI)
- **Colistimethate sodium** – serious infections caused by resistant aerobic Gram-negative bacteria, used when options are limited

D. OXAZOLIDINONES

PHINMA EDUCATION

Linezolid, Tedizolid

MOA

- Bind **23S rRNA (50S)**
- Bacteriostatic

PK

- Excellent oral absorption (90–100%)

Clinical Use

- **MRSA**
- VRE (*E. faecium*)
- Pneumonia (nosocomial & community)
- Skin infections
- Not active vs Gram-negative
- *Tedizolid* → approved for acute skin infections

Adverse Effects

- **MAO inhibition** → avoid tyramine-rich foods

SUMMARY OF ANTIBACTERIAL AGENTS

PHINMA EDUCATION

Bactericidal	
TARGET	EXAMPLE
Cell Wall	BETA-LACTAMS • Penicillins • Cephalosporins • Monobactams • Carbapenems GLYCOPEPTIDES • Teicoplanin • Vancomycin
Cell Membrane	POLYPEPTIDES • Bacitracin • Colistin • Polymyxin B

SUMMARY OF ANTIBACTERIAL AGENTS

PHINMA EDUCATION

Bacteriostatic		
TARGET	EXAMPLE	
Protein	30s inhibitors • Tetracyclines • Aminoglycosides (bactericidal)	50s inhibitors • Pleuromutilins • Chloramphenicol • Lincosamides • Oxazolidinones • Macrolides • Streptogramins