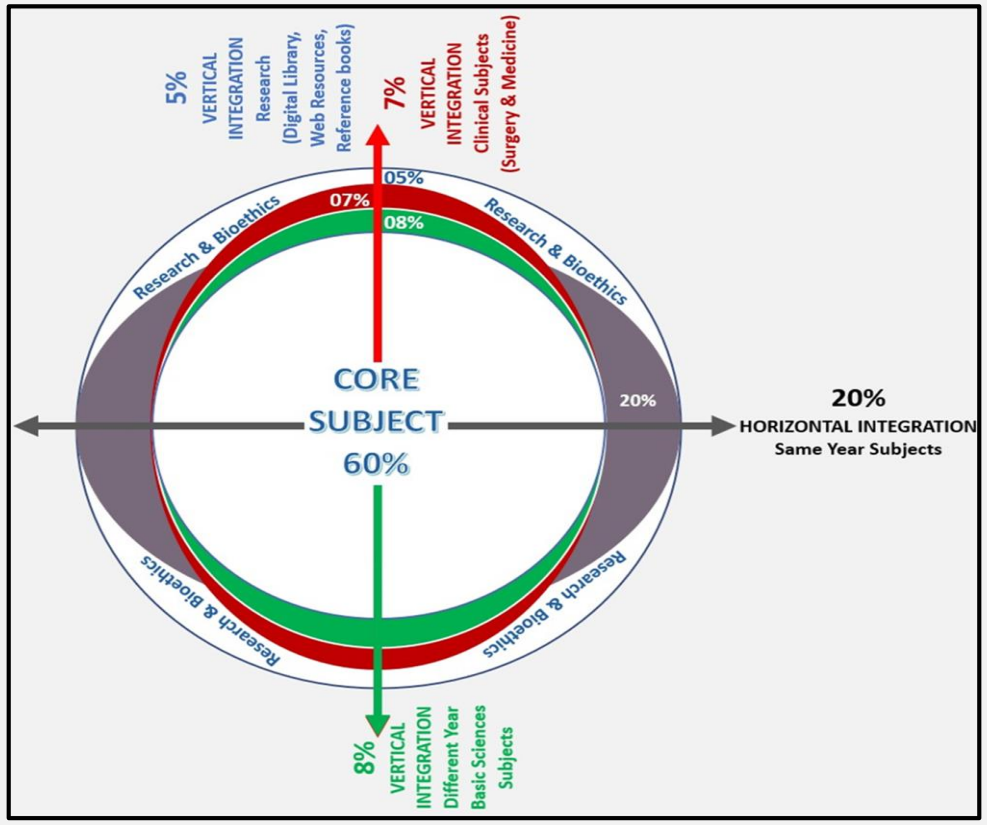
Cell wall synthesis inhibitors

UMAR'S MODEL OF INTEGRATION



3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	

Learning objectives

At the end of the lecture, the students will be able to;

- Enumerate antibacterial drugs acting at cell wall & cell membrane
- Describe the mechanism of action,clinical indications & adverse effects of different classes of cell wall synthesis inhibitors

GLYCOPEPTIDES

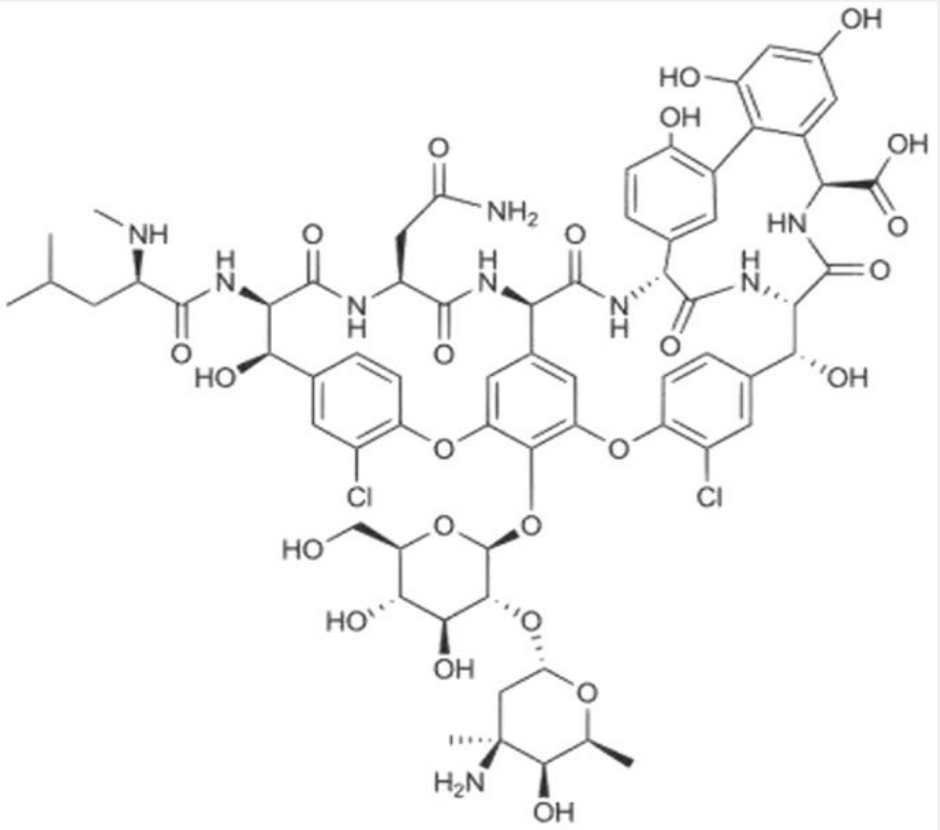
Vancomycin

Source & Structure

- Teicoplanin (mixture of glycopeptides)
- Dalbavancin
- Telbavancin
- Oritavancin

Lipoglycopeptide semisynthetic

Stage of development and Purification
(*Streptococcus orientalis*)



Structure of Vancomycin

Vancomycin

Mechanism of Action

- Bactericidal via interrupting proper cell wall synthesis in the susceptible bacteria
- Vancomycin can form five hydrogen bond with the terminal D-alanyl-D-alanine (D-Ala–D-Ala) moieties of the peptidoglycan precursor
- Binding of vancomycin leads to conformational alteration that prevents the incorporation of the precursor to the growing peptidoglycan chain and the subsequent transpeptidation, thereby leading to cell wall decomposition and bacterial lysis
- **Telavancin & oritavancin:** Disrupts the cell membrane potential & increases membrane permeability (rapid bactericidal activity)
- Inhibit RNA synthesis

Vancomycin

Anti-microbial spectrum

Narrow ,against resistant micro-organisms

G +ve bacteria, specially *Staphylococcus*, even MRSA

Clostridium difficile
clostridium tetani
clostridium perfringens
Bacillus anthracis
Corynebacterium diphtheriae

Jens Martensson

Vancomycin
Pharmacokinetics

- Poor oral absorption yielding high fecal concentrations
- Administered through intravenous, intraperitoneal, intrathecal or intraventricular, and intraocular routes (NOT IM because of severe local pain)
- The elimination half- life is 6 hrs and dependent upo
- CSF penetration is minimal in absence of meningeal inflammation (high dose continuous infusion , intrathecal and intaventricular)
- There is transplacental passage during second trimester and at time of delivery
- It is excreted in breast milk
- Primarily excreted unchanged via the kidneys by glomerular filtration,

Tiecoplanin can be given both IM/IV

Teicoplanin t1/2 100hrs (4 days)
Dalbavancin & oritavancin t1/2 10 days

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Vancomycin

Therapeutic Uses

- Sepsis or endocarditis by MRSA, streptococci, enterococci / severe penicillin allergy. **I/V**
- Pneumococcal Meningitis with 3rd gen Cephalosporins (Cefotaxine, Ceftriaxone) or Rifampin. **I/V**
- Antibiotic induced Enterocolitis(pseudomembranous colitis by *C .difficile)*Orally
- Skin/soft tissue & bone/joint infections (MRSA osteomyelitis)
- Respiratory tract infections(MRSA nosocomial pneumonia)
- Endophthalmitis (postoperative and post traumatic)
- Prophylaxis of endocarditis in cardiac patients

Telavancin : Complicated skin & soft tissue infections
Hospital-acquired pneumonia

Dalbavancin & oritavancin: Skin & soft tissue infections

Vancomycin

Adverse reactions

- **Infusion site reactions:**
  Redman or Red neck syndrome (erythematous or urticarial reactions, flushing, tachycardia, and hypotension)
  Can be prevented by pretreatment with antihistamine
  Reducing the infusion rate and dose
- **Nephrotoxicity** (oxidative effects on cells of the proximal renal tubule leading to renal tubular ischemia) **(Telavancin)**
- **Ototoxicity**
- **Hematological disturbances** (neutropenia, thrombocytopenia)
- **Skin reactions** (maculopapular or erythematous rash, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome)
- **Teratogenic and QT interval prolongation (telavancin)**

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Fosfomycin

Analogue of phosphoenolpyruvate

- Bactericidal cell wall synthesis inhibitor
- Inhibit enolpyruvate transferase and block synthesis of N-acetylmumaric acid
- Resistant due to inadequate accumulation
- Active against both **gram+tive** & **gram –tive** organisms
- Oral & parenteral administration (IV)
- Used in uncomplicated UTI & prostatitis
- Well tolerated, can cause GIT distress, headache & vaginitis
- Considered safe in pregnancy

Bacitracin

- **Source: *Bacillus subtilis***
- Group of polypeptide antibiotics; the major constituent is bacitracin A.
- Inhibits cell wall synthesis by binding to lipid carrier that transports cell wall precursors to the growing cell wall

- Gram-positive cocci and bacilli, *Neisseria, H. influenzae, T. pallidum, Actinomyces* & *Fusobacterium*
- No cross resistance with other antimicrobial drugs
- Markedly nephrotoxic
- **Th. Uses: <u>Not used systemically</u>**
- Used topically as ointment on skin, with polymyxin & neomycin for mixed bacterial flora
- Eradication of nasal carriage of staphylococcal
- Saline solutions for irrigation of joints, wounds or pleural cavity
- Suppurative conjunctivitis & infected corneal ulcers (ophthalmic ointment)
- Gut decontamination

Cycloserine

Source: *Streptomyces orchidaceous*

- Second line anti TB drug

MOA: Cycloserine & D –alanine are structural analogues
Inhibit incorporation of D alanine into the growing peptidoglycan by inhibiting

i) Alanine racemase
ii) D alanyl D alanine ligase

PK: Good oral absorption with t1/2 of 9 hours

Wide distribution including CNS (same as that of plasma)
Renal elimination

A/E: Dose dependent CNS toxicity (headaches, tremors, acute psychosis, and convulsions)

Psych-serine

Drugs Acting on Bacterial Cell Membrane

Daptomycin

Source: *Streptomyces roseoporus*

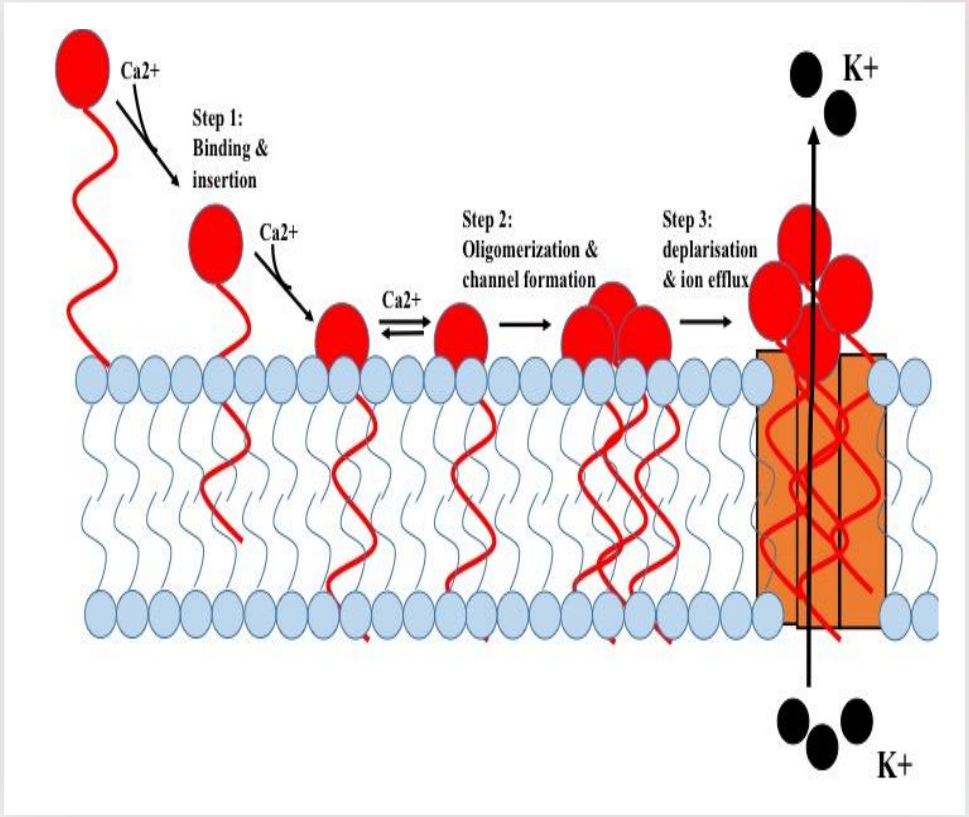
- Bactericidal activity against gram +tive similar to vancomycin, even effective against **vancomycin resistant strains of enteroccoci & S aureus**

MOA: Binds to & depolarizes the cell membrane, potassium efflux & cell death

PK: Only intravenous administration
Degraded by pulmonary surfactant (not used in pneumonia)
Renal elimination

Th. Uses: Alternative to vancomycin (skin& soft tissue infections, bacteremia& endocarditis)

A/E: Myopathy & rhabdomyolysis
Allergic pneumonitis(> 2 weeks of use)



Polymyxins

A group of closely related antibiotics i-e Polymyxin B_1 and Polymyxin E (colistin)

Source : *Bacillus polymyxa, Bacillus colistinus*

- **Spectrum of activity:** Gram –tive bacteria (aerobes)
- **Mechanism of action:** Surface active amphipathic agents
  Bind to phospholipid and disrupts the structure of cell membrane
  Bind & inactivate endotoxin
- **Pharmacokinetics:** Poor absorption orally and from mucous membranes
- **Therapeutic uses:**
  1. Skin,mucous membrane,ear and eye infections
  2. Serious infections by resistant organisms (revisiting)
- **Adverse effects:** Nephrotoxicity,neurological reactions

RESEARCH

Zhou, J., Cai, Y., Liu, Y., An, H., Deng, K., Ashraf, M.A., Zou, L. and Wang, J., 2022. Breaking down the cell wall: Still an attractive antibacterial strategy. *Frontiers in Microbiology*, *13*, p.952633.

BIOETHICS

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Jamrozik E, Heriot GS. Ethics and antibiotic resistance. Br Med Bull. 2022 Mar 21;141(1):4-14. doi: 10.1093/bmb/ldab030. PMID: 35136968; PMCID: PMC8935610.

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ARTIFICIAL INTELLIGENCE

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END OF LECTURE ASSESSMENT

1. The drug of choice for treatment of methicillin resistant Staphylococcus aureus infection is:

A. Vancomycin
B. Oxacillin
C. Tobramycin
D. Ticarcillin
E. Imipenem

2. *Oral vancomycin is indicated in the following condition:*

A. Appendicitis
B. Campylobacter diarrhea
C. Bacillary dysentery
D. Pseudomembranous enterocolitis
E. Traveler's diarrhea

3. *'Red man syndrome' has been associated with rapid intravenous injection of the following antibiotic*:

A. Vancomycin
B. Clindamycin
C. Cefoperazone
D. Piperacillin
E. Aztreonam

REFERENCE

- Katzungand Betram's Basic and Clinical Pharmacology, 15thEdition
  Chapter 43 : Beta Lactam & other cell wall & membrane active antibiotics
  Page No: 823-830

- Goodman & Gilmans, The Pharmacological Basis of Therapeutics, 13thEdition
  Chapter 59: Protein synthesis inhibitors & miscellaneous Antibacterial agents
  Page No:1049-1062