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**Pharmacology of
antibacterial drugs
Cell wall and cell
membrane inhibitors**

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Carbapenems

Imipenem, meropenem, doripenem and ertapenem

- ❑ This class of antibiotics has a broad spectrum of activity.
- ❑ Carbapenems bind to PBP, disrupt bacterial cell wall synthesis.
- ❑ Carbapenems **resist** hydrolysis by **most β -lactamases** except carbapenemase-producing **Enterobacteriaceae**.
- ❑ Some combination (**meropenem-vaborbactam** or **imipenem - relebactam**) retains activity against these highly drug-resistant organisms.

1- Imipenem:

-It is marketed in combination with **cilastatin**, a drug that inhibits the degradation of imipenem by a renal tubular **dehydropeptidase**.

Antimicrobial activity

- ❑ Imipenem has antibacterial activity against penicillinase producing *S. aureus* although some strains of **MRSA** are **resistant**.
- ❑ Most strains of **Pseudomonas** are sensitive.
- ❑ Activity is excellent against the Enterobacteriaceae except carbapenemase-producing bacteria.

Pharmacokinetics

- Given **i.v.** & is hydrolyzed by **dehydropeptidase** in renal tubule.
- Cross BBB.
- Cleared renally, dose must be ↓ in patients with renal insufficiency.

Therapeutic uses

- 1- **Urinary tract infection**
- 2- **Lower respiratory tract infection**
- 3- **Intra-abdominal** and **gynecological** infection
- 4- **Soft tissue, bone** and **joint** infection.
- 5- Cephalosporin-resistant **nosocomial infection**

Side effects:

- 1- Nausea and **vomiting**
- 2- Possibly **seizures** (in CNS lesions & renal failure).
- 3- Patients with penicillin allergy are liable to **allergy** from imipenem also.

2- Meropenem and Doripenem

- Adding cilastatin is not required as these 2 drugs are less sensitive to renal dehydropeptidase compared to imipenem.
- **less likely to cause seizure.**
- Active against some imipenem-resistant *P. aeruginosa*.
- Same therapeutic uses of imipenem.

3- Ertapenem

- ❑ It has a **broad spectrum of antibacterial actions** but is licensed only for a limited range of indications.
- ❑ Unlike the other carbapenems, ertapenem does not have appreciable activity against *P. aeruginosa* and *acinetobacter* species.
- ❑ Ertapenem is **not degraded** by renal dehydropeptidase.
- Carbapenems penetrate body tissues and fluids well, including the cerebrospinal fluid except ertapenem

Monobactams

Aztreonam is a monocyclic β -lactam (structure like ceftazidime).

-**Aztreonam** has antimicrobial activity against gram negative aerobes (e.g., *E.coli*, *P aeruginosa*, *H. influenza*, *N.meningitidis* & Enterobacteriaceae).

-**It has no action against gram-positive organisms or anaerobes.**

-It resists β -lactamases except those of Enterobacteriaceae.

-**Aztreonam is available in a combination with avibactam.**

-**Patients who are sensitive to penicillins or cephalosporins do not react to aztreonam** (except ceftazidime).

-**Pharmacokinetics:**

-**Given IV, or IM (but painful) and by inhalation (but irritant and cause wheezes and cough)**

- **Cross BBB, eliminated renally.**

-**Safe in pregnancy.**

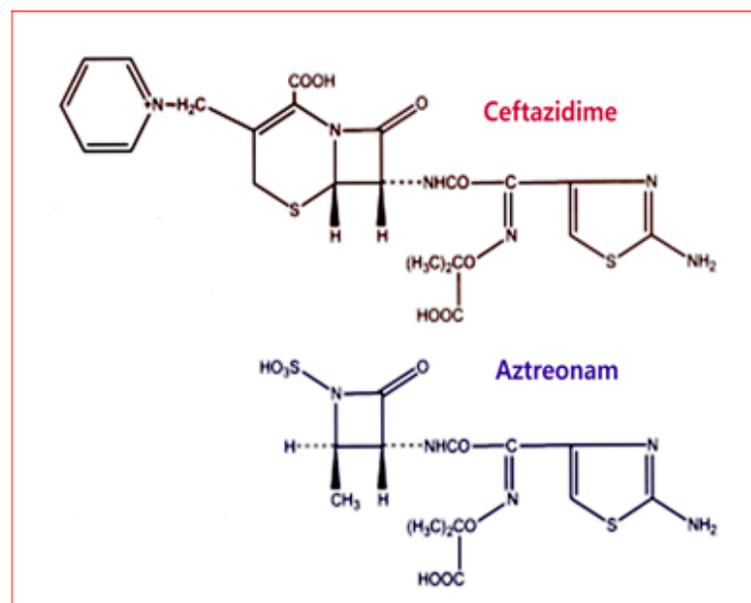
Uses of Aztreonam

1- In patients with a history of penicillin anaphylaxis, aztreonam can be used to treat **serious infections** such as **pneumonia**, **meningitis**, **bone infections**, **endometritis**, **urinary tract infections** and **sepsis** caused by gram-negative organisms.

2- Inhalation forms for treating chest infections in **cystic fibrosis**, **bronchiectasis**, after lung transplant and in certain **mycobacterium** diseases.

Adverse effects:

1. Allergic reactions (skin rash, eosinophilia) and rarely anaphylaxis or **toxic epidermolytic necrolysis (TIN)**
2. Elevation of liver enzymes
3. Nausea, diarrhea and Cl. Difficile infection.
4. Seizures in renal failure.



Non beta lactam cell wall inhibitors

1- Glycopeptides

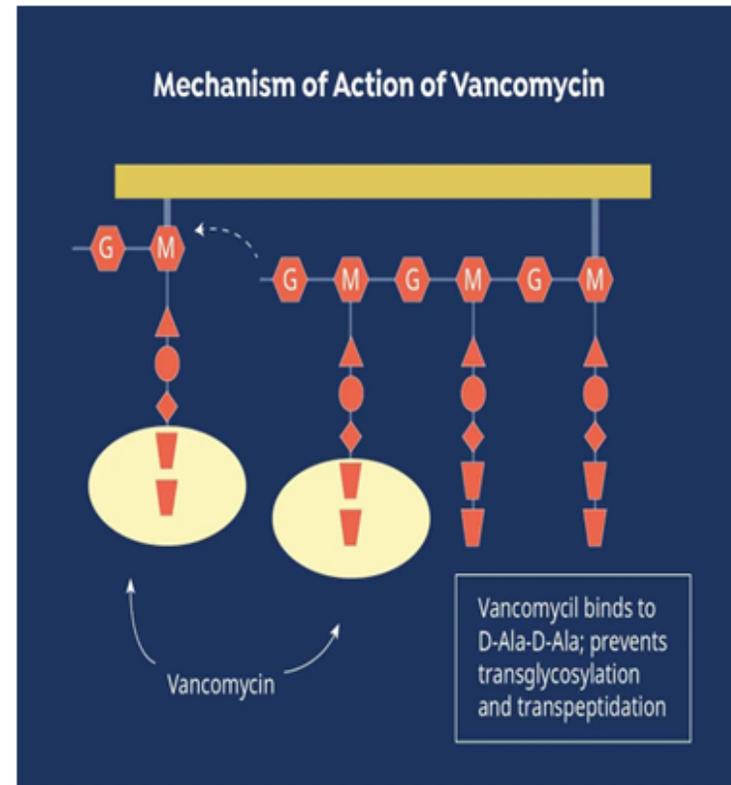
❑ **Glycopeptides are not beta lactams**

➤ **Mechanism of action:**

Vancomycin & teicoplanin inhibit the synthesis of the cell wall in sensitive bacteria by binding to **D -alanyl-D-alanine** terminus of cell wall precursor units and thus inhibits the transglycosylase, preventing further elongation of peptidoglycan.

The peptidoglycan is thus weakened, and Lysis occur.

The cell membrane also is damaged, which contributes to the antibacterial effect.



Antibacterial Activity

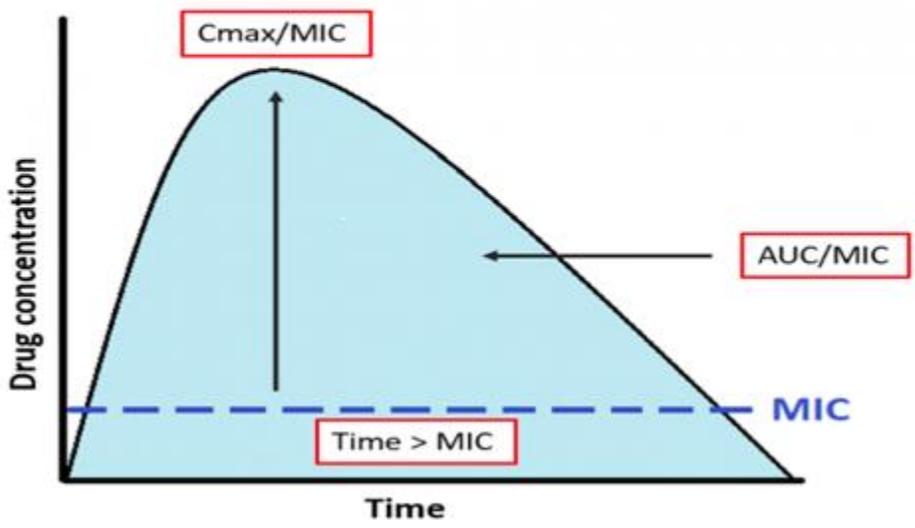
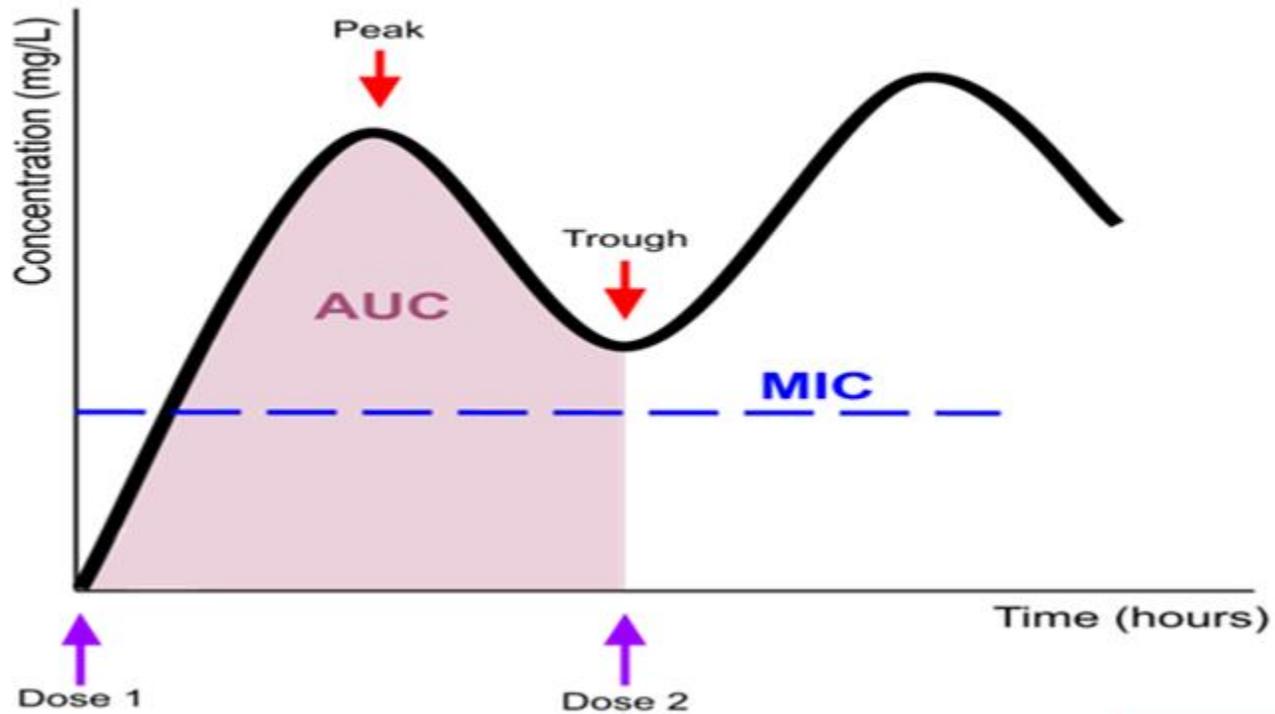
- Vancomycin (0.5–10 ug/mL) is bactericidal for **gram-positive bacteria**.
- **It is not effective against gram negative bacilli or mycobacteria.**
- Most pathogenic staphylococci, including those producing β -lactamase and those resistant to nafcillin and methicillin, are killed by **2 mcg/mL** or less.
- Vancomycin kills staphylococci relatively slowly than penicillins
- Vancomycin kills only actively dividing cells.
- Vancomycin is synergistic in vitro with gentamicin or streptomycin against **enterococci**
- Vancomycin is active against many **gram-positive anaerobes** including **Cl. difficile**.
- A minimum target **trough concentration of 10 μ g/ml** is recommended.

Therapeutic adjustment of glycopeptides

Glycopeptides (vancomycin and teicoplanin) are bactericidal drugs, and their activity is predicted by the **AUC/MIC ratio**.

- ❑ Calculating AUC (area under the curve) through measuring **trough levels*** of vancomycin via therapeutic-drug monitoring.
- ❑ MIC (minimum inhibitory concentration) of the infecting organism is obtained from bacteriological testing.
- **A ratio of 400-600** is targeted for efficacy in patients with **MRSA** pneumonia without causing major nephrotoxicity.
- Increase in organism MIC (i.e. resistance) without substantial increase in drug dosage can make achieving this target ratio difficult.
- Some tools such as online vancomycin calculators or pharmacokinetic software have become available to optimize vancomycin dosing.

*serum trough concentrations within 30 minutes prior to a dose at steady state



The AUC/MIC is the most important parameter for vancomycin efficacy

-Pharmacokinetics:

- Vancomycin is poorly absorbed orally, and is given **I.V.** (not I.M).
- On the other hand, teicoplanin can be given I.M. or I.V.
- A 1-hour intravenous infusion of 1 gram of vancomycin produces blood levels of **15–30 mcg/mL** for 1–2 hours.

- Vancomycin is administered orally only for the treatment of colitis caused by *Cl. difficile*.

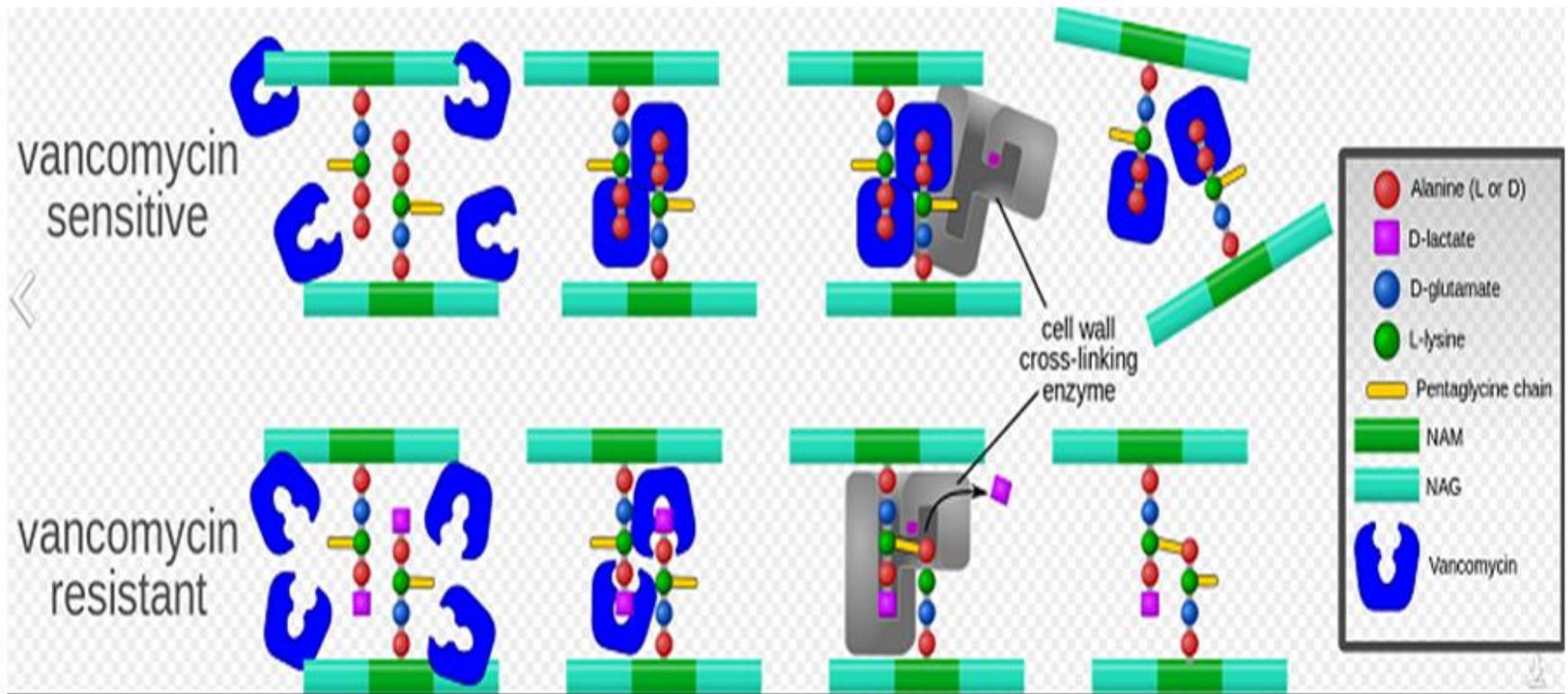
Plasma protein binding: 30% for Vancomycin & 90% for teicoplanin.

- Vancomycin is widely distributed in the body, including Cerebrospinal fluid if there is meningitis.

- Vancomycin** has an elimination half-life of about **6 hours** while **teicoplanin** half life is long; **about 100 hours**. They both depend on the kidney in elimination (90% is excreted by glomerular filtration).

Resistance to glycopeptides:

- Enterococcal resistance to glycopeptides is developed by **substituting a terminal D-lactate for D-alanine**, reducing Vancomycin binding affinity by 1000 times.
- *S. aureus* resistance may be intermediate when **MIC required of vancomycin is 4-8 $\mu\text{g/ml}$** or high-level resistance when **MIC $\geq 16 \mu\text{g/ml}$** and it may be related to abnormally thick cell wall.



Therapeutic uses:

1. **Pneumonia** when **MRSA** is suspected.
2. **Skin, soft tissue, bone and joint infection** especially when **MRSA** is suspected
3. Vancomycin (in combination with ceftriaxone or rifampin) is recommended for treatment of **meningitis** suspected or known to be caused by a penicillin-resistant strain of pneumococci.
4. **Endocarditis** by **MRSA**.
 - Vancomycin in combination with gentamicin is used for treatment of **enterococcal endocarditis** in a patient with serious penicillin allergy.
5. **Pseudomembranous colitis** caused **Clostridium difficile** (Vancomycin is given orally)

❑ Clinical data suggest that vancomycin is associated with higher initial response rates than metronidazole in treating C. difficile.

❑ Therefore, oral **vancomycin** or oral **Fidaxomicin** (macrolide) is now preferred as first-line therapy compared with metronidazole for treatment of C. difficile colitis.

📌 First-Line Treatment (2026):

- **Vancomycin** 125 mg every 6 hours for 10 days
- **Fidaxomicin** 200 mg twice daily for 10 days
- Metronidazole NO longer first-line in adults
- Stop triggering antibiotic if possible

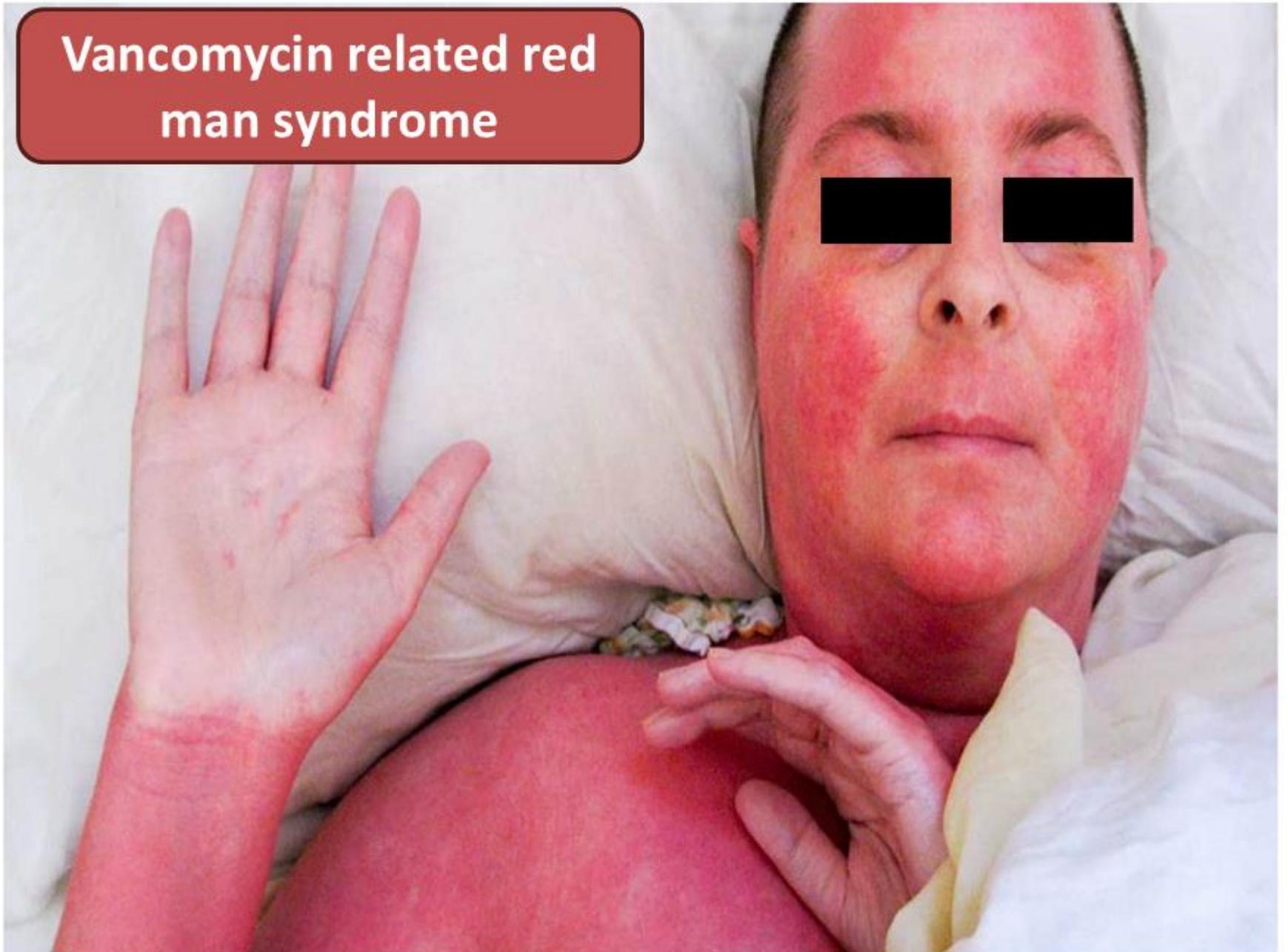
❑ For Recurrences:

- Fidaxomicin or vancomycin taper regimen
- **Bezlotoxumab** for high-risk patients
- **Fecal transplant** after multiple recurrences
- Success rates >90% with proper management

Adverse effects of glycopeptides

- 1- **Hypersensitivity** reactions as skin rash and **anaphylaxis**.
- 2- **Red man syndrome**: Rapid I.V. infusion of vancomycin may cause extreme flushing in the body, hypotension, and tachycardia due to a toxic effect of vancomycin on mast cell causing **histamine release**. **It does not occur with Teicoplanin**. It can be prevented by ↓ the infusion period to 1–2 hours (preferred) or pretreatment with diphenhydramine (antihistamine).
- 3- Vancomycin is irritating to tissue, resulting in **phlebitis** at the site of injection. **Chills and fever** may occur.
- 4- **Nephrotoxicity** especially with trough serum vancomycin concentration > 20 ug/ml.
- 5- **Ototoxicity is rare**

Vancomycin related red man syndrome



2- Topical cell wall inhibitors

1- Bacitracin

It is polypeptide antibiotic that **inhibits bacterial cell wall synthesis**. It is used **topically** for **ophthalmic** and **dermatological** infections with gram positive cocci and bacilli. It is also used by neurosurgeons to irrigate the meninges intraoperatively as an alternative to vancomycin.

2- Mupirocin

It is used **topically** for treatment of **dermatological** infections, like traumatic skin lesions and **impetigo** caused by Staph. aureus and Strept. pyogenes.

The **nasal ointment** of the drug is used for **eradication of S aureus nasal carriage**

3- Fosfomycin

- Fosfomycin is a **bactericidal** agent that **inhibits cell wall synthesis**.
- It is used for the **treatment of uncomplicated cystitis** by E coli and Enterococcus faecalis.
- Little cross-resistance between Fosfomycin and other antibiotics exists.
- It is excreted unchanged in the urine, and concentrations remain high for 24-48 hours after a single dose of 3 grams.

Common side effects include **diarrhea**, nausea, headache, and **vaginal yeast** infections. Severe side effects may include **anaphylaxis** and ***Clostridioides difficile*-associated diarrhea**.

4- Miscellaneous cell wall inhibitors

A- Cycloserine: inhibits mycobacterial cell wall synthesis and used with other drugs for treatment of **tuberculosis**.

B- Tunicamycin is a natural antibiotic mixture of nucleosides that inhibit glycoprotein synthesis (thus inhibit cell wall synthesis in Gram positive bacteria and inhibits viral coating), it has antifungal activity, and it **induces endoplasmic reticulum stress** and **arrest of cell cycle** in different cancers including **breast carcinoma**.

C- Ramoplanin inhibits early stages of bacterial cell wall.

It is absorbed in the gastrointestinal tract, although it is unstable in the bloodstream, so can be taken only **orally** against **multiple antibiotic-resistant *C. difficile*** and ***E. faecalis*** infections of the gastrointestinal tract.

D- Type B Lantibiotics.

- Lantibiotics produced by Gram-positive bacteria and inhibit peptidoglycan biosynthesis in other **Gram-positive bacteria**.
- They are active in **very low concentrations**.
- Lantibiotics have become attractive candidates for use in **food preservation** (by inhibiting pathogens that cause food spoilage) and the **pharmaceutical industry** (to prevent infections in humans or animals).

Antibacterial drugs inhibiting bacterial cell membrane functions

1-Polymyxins

Mechanism of action: polymyxins **disrupt both the outer and inner bacterial membranes**.

The combination (**trimethoprim/polymyxin**) broaden the effective spectrum of polymyxin. It is used for **topical treatment of acute bacterial conjunctivitis**.

- Polymyxins B are not absorbed from the gastrointestinal tract, so they are only administered **orally** if the goal is to **disinfect the GI tract**.
- For systemic effects; the intravenous or inhalation routes are used.
- They are also used externally as a **cream or drops** to treat **Otitis externa** (swimmers' ear), and to treat and prevent **skin infections**.
- Polymyxin antibiotics are relatively **neurotoxic** and **nephrotoxic**, so are usually used only as a last resort if other antibiotics are ineffective or are contraindicated.
- Typical uses are for infections caused by strains of multiple drug-resistant Pseudomonas aeruginosa or carbapenemase producing Enterobacteriaceae.
- Polymyxins **have less effect on Gram-positive organisms**.

Daptomycin

- It is a **lipopeptide antibacterial** drug (bactericidal) used to treat **vancomycin resistant gram-positive bacterial infection**.
- It binds to bacterial membranes resulting in depolarization, loss of membrane potential and cell death.
- It is given by **I.V. route**.
- **Myopathy** is a side effect.



Thank You

