Athar Batch

Pharmacology

Lecture: 29

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LECTURE 5- DR. TAREQ PART 1

Other β-Lactams

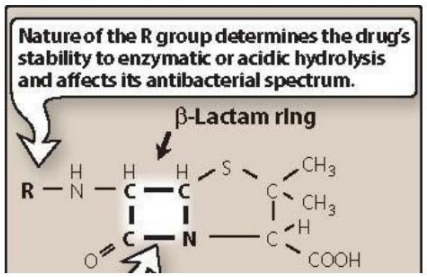
- These drugs are more advanced than penicillins and cephalosporins.
- They are the last resort

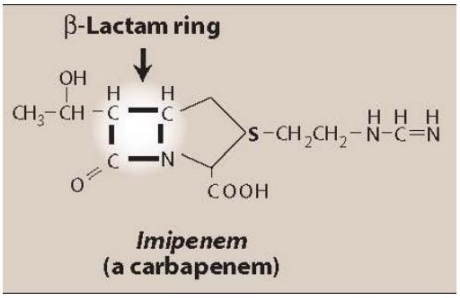
نستخدمهم في حال ان ال Initial therapy ما اعطت نتيجة و السب انه لو صار في Resistance لهاي الادوية،

مش راح نقدر نعالج ال Infection اللي بتسببه ال Resistant bacteria

Carbapenems

CARBAPENEMS
Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM



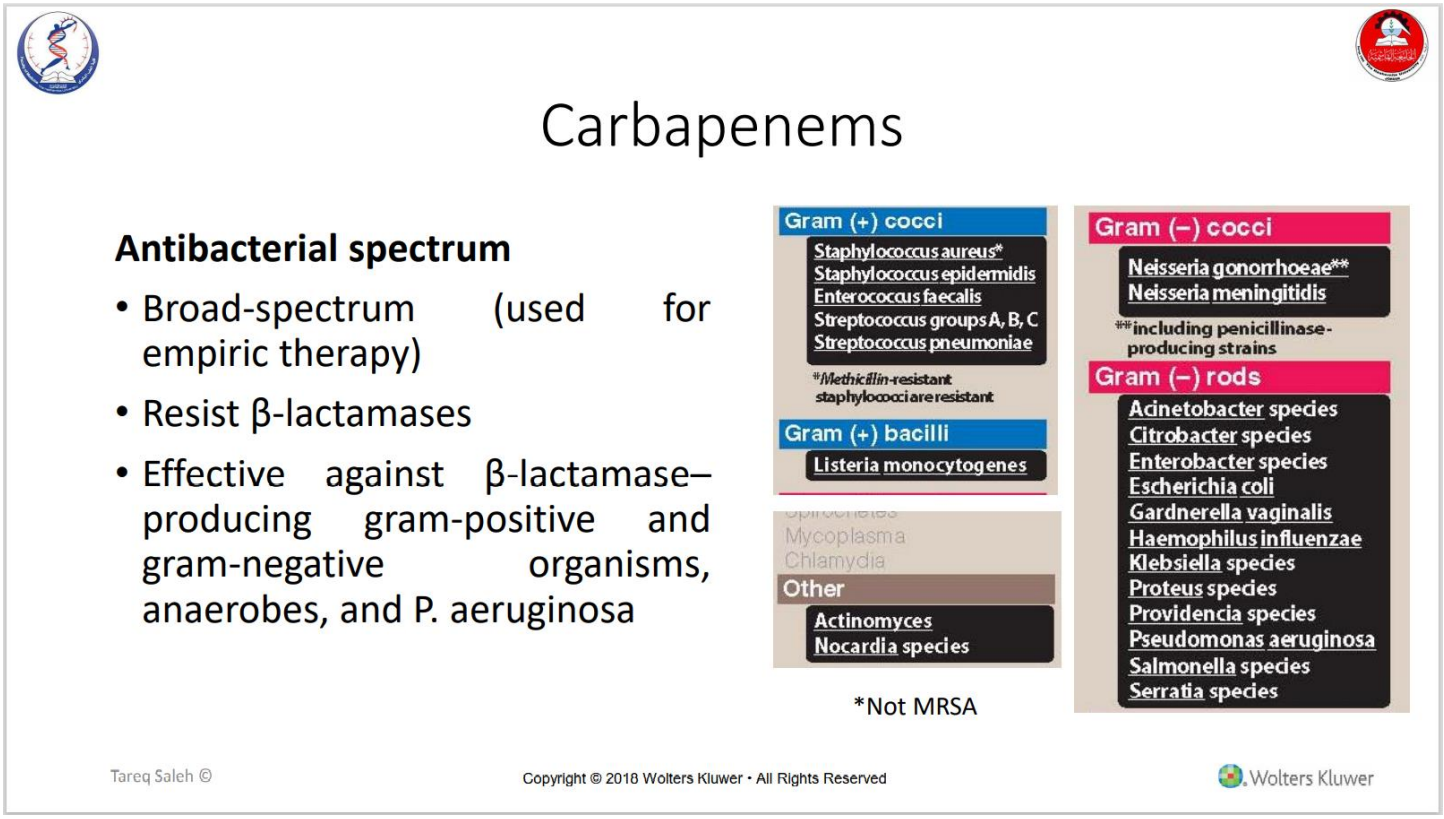


Imipenem
(a carbapenem)

Carbapenems:

- They have beta lactam ring (that consists of three atoms of carbon and one atom of nitrogen).
- The figure above shows that:
  1) The sulfa group of carbapenems is externalized in carbapenems and attachs to a side chain.
  2) The structure of carbapenems is simpler than cephalosporins and penicillin (which are bulky compounds).
- Examples:
  1) Imipenem: the most well-known carbapenem.

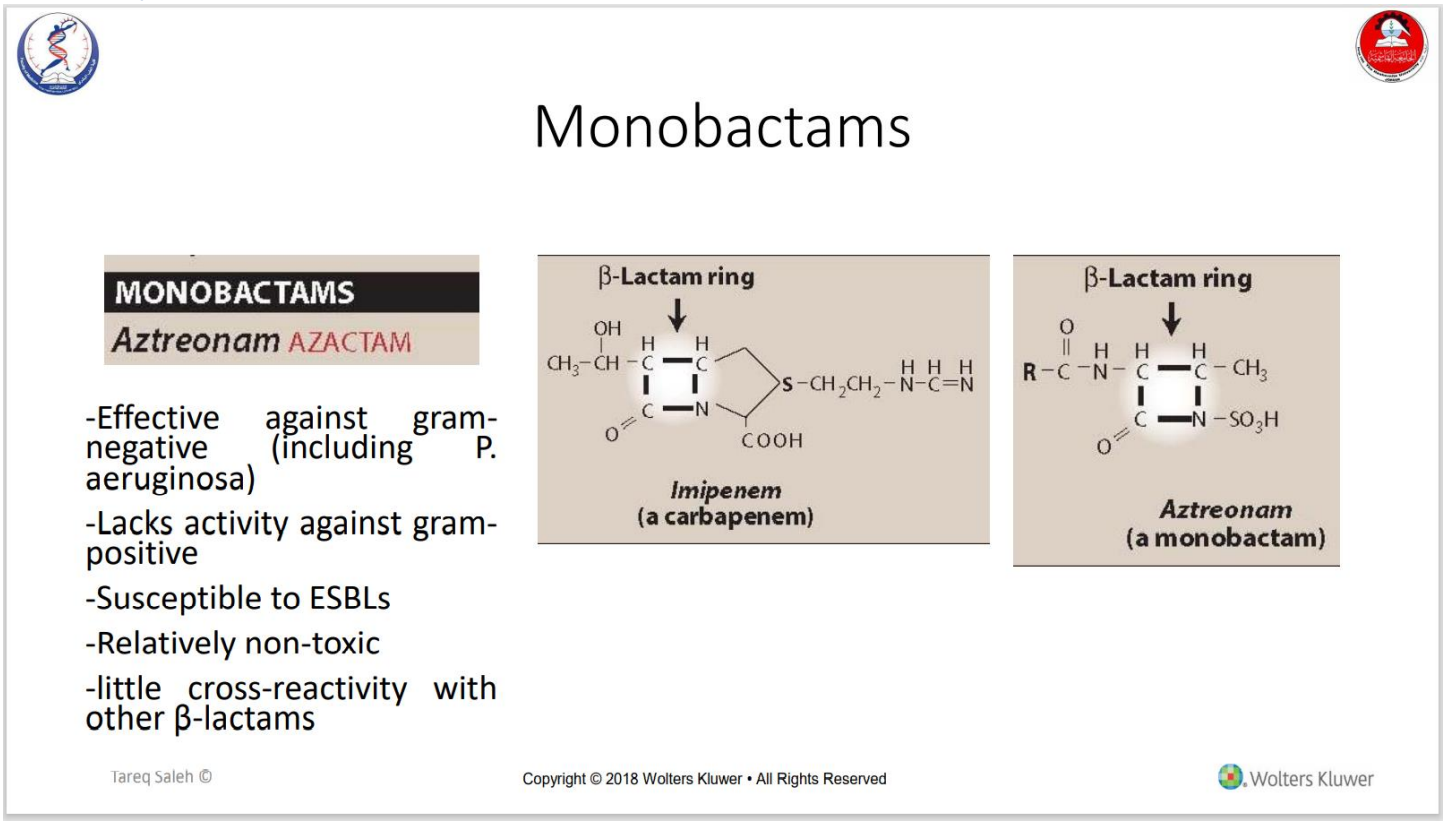
2) Meropenem: the second known carbapenem
3) Doripenem
4) Ertapenem



- ♣ Carbapenems have verry wide antibacterial spectrum (the most broad-spectrum antibiotics that we know so far)
- ♣ They are used in empiric therapy.
- ♣ They cover wide variety of gram-negative and gram-positive bacteria.
- ♣ Note: streptococcus pneumonia is the most common cause of community acquired pneumonia.
- ♣ Carbapenems cover penicillin resistant Neisseria gonorrhoeae.
- ♣ Carbapenems are not effective against MRSA.
- ♣ Carbapenems are resistant to beta lactamases. That is why they cover wide variety of bacteria species.
- ♣ Exception: metalolactamases → a group of enzymes secreted by resistant bacteria. These enzymes can hydrolyze carbapenems.
- ♣ Imipenem (the trade name is Tienam) is given in combination with another drug called cilastatin… why??
    - Imipenem is minimally metabolized by the liver and majorly excreted by the kidney. Dehydropeptidase enzyme is found in the proximal tubules of the kidney. This enzyme is able to breakdown imipenem rapidly.
      The presence of this enzyme will increase the elimination and excretion of imipenem.

Cilastatin can inhibit the action of dehydropeptidase enzyme delaying the breakdown of imipenem → decrease the elimination of the drug → increase the concentration in the blood → requiring less frequent doses.

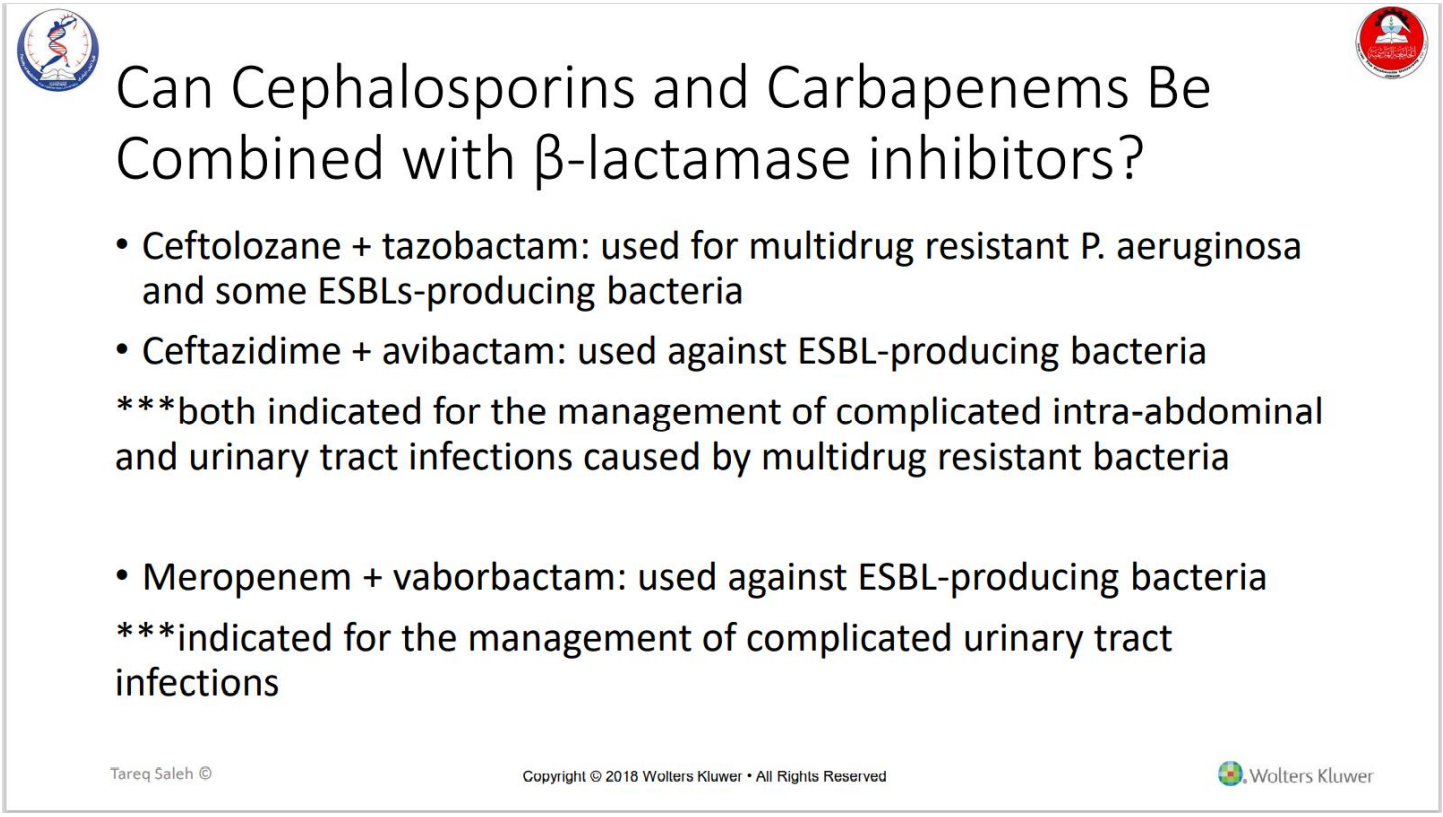
- ♣ This combination technique is not available for other carbapenems.
- ♣ Carbapenems are relatively safe, but they cause adverse effects:
  1) Gastrointestinal adverse effects such as nausea, vomiting and diarrhea.
  2) They have hematologic adverse effects similar to penicillin → they cause neutropenia
  3) Sometimes, high concentration of imipenem can cause seizures in patients who are susceptible or have epilepsy.
- ♣ Since carbapenems have beta lactam ring in their structure and have similar structure to penicillins and cephalosporins, there is a risk of cross allergy. (If the patient is allergic to penicillin, there is a chance for carbapenem allergy)
- ♣ Fortunately, only 1% of patient with allergy t penicillin are allergic to carbapenem.
- ♣ Note: in the middle east, there are reports show that there are resistant bacterial strains to imipenem.



Monobactams:

- ♣ The only example of monobactams is aztreonam.
- ♣ The structure of monobactam is similar to other β-lactams (have the β-lactam ring in their structures).
- ♣ The structure of monobactam is simpler than carbapenems.

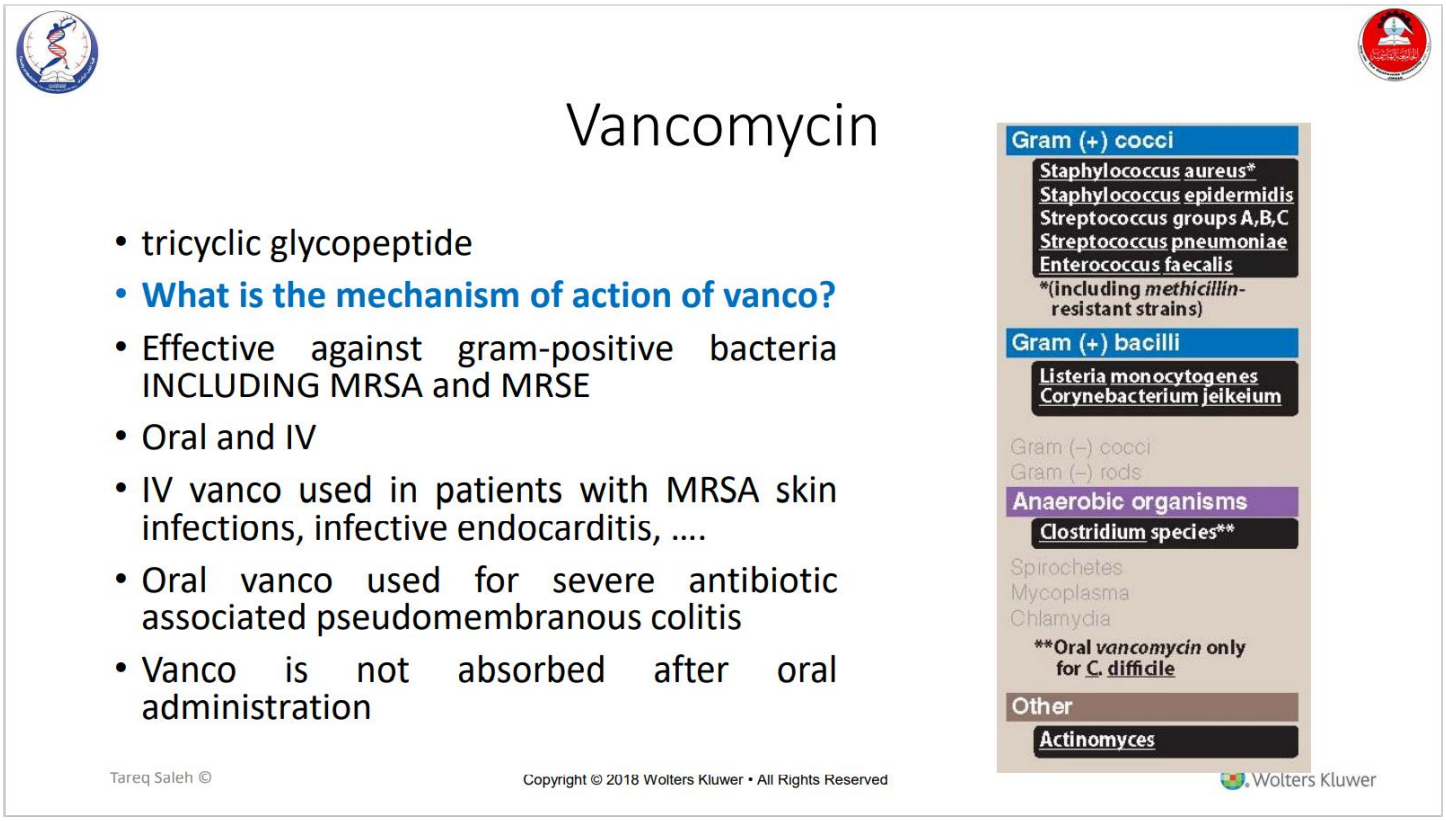
- ♣ Aztreonam is very effective against gram-negative bacteria including multi-drug resistant pseudomonads aeruginosa.
- ♣ It lacks the activity against gram-positive bacteria.
- ♣ ESBLs: Extended Spectrum Beta Lactamases producing bacteria.
- ♣ ESBLs can hydrolyze aztreonam.
- ♣ Aztreonam is very safe drug, but it has some adverse effects.
- ♣ Less cross-reactivity: means that the chance of aztreonam allergy in patients with penicillin allergy is little.



- ♣ The main mechanism of resistance to β-lactams is to produce β-lactamases enzymes.
- ♣ Combination of β-lactams with β-lactamases inhibitors → effective against β-lactamases producing bacteria.
- ♣ β-lactamases inhibitors have no antibiotic effect, but they protect β-lactams from hydrolysis by β-lactamases.
- ♣ Examples of Combination:

1) Ceftolozane + tazobactam:
   - ♣ Ceftolozane is a third-generation cephalosporin.
   - ♣ Tazobactam is β-lactamase inhibitor.
   - ♣ This combination is very powerful and can be used in treatment of multi-drug resistant gram-negative bacteria (including pseudomonads aeruginosa) and some extended spectrum β-lactamase producing bacteria.

2) Ceftazidime + avibactam:
   - ♣ Ceftazidime is a third-generation cephalosporin.
   - ♣ Avibactam is a β-lactamase inhibitor.
   - ♣ This combination is effective against ESBLs producing bacteria.
   - ♣ Note: the two examples above are indicated for the management of the intra-abdominal and urinary tract infections caused by multi-drug resistant gram-negative bacteria.
3) Meropenem + vaborbactam:
   - ♣ Meropenem is a carbapenem.
   - ♣ vaborbactam is a β-lactamase inhibitor.
   - ♣ This combination is more effective against ESBLs producing bacteria than the use of meropenem only.
   - ♣ Used in very complicated urinary tract infections caused by multi-drug resistant gram-negative bacteria.



Vancomycin:

- ♣ Cell wall inhibitors but not β-lactam
- ♣ The structure of vancomycin is: tricyclic glycopeptide
- ♣ As we mentioned previously, the target of β-lactams is PBP (penicillin binding protein). the mechanism of action of vancomycin is different…

- The first step in cell wall synthesis is the synthesis of peptidoglycans, vancomycin binds to peptidoglycan precursors before they start to be cross linked in the evolving cell wall (prevent the precursors to bind to each other).

Transpeptidation يعني قبل عملية ال

- Vancomycin is effective against gram-positive bacteria including many cocci and bacilli such as *Staphylococcus aureus*, *Staphylococcus epidermidis, streptococci*, … etc.
- Vancomycin is effective against MRSA and MRSE (vancomycin is the drug of choice to treat infections caused by MRSA).
- MRSE: Methicillin Resistant *Staphylococcus Epidermidis*
- So until now, the two effective types of antibiotics that are effective against MRSA are:
  1) Advanced generation cephalosporins
  2) Vancomycin
- Vancomycin can cover certain anaerobic organisms such as *Clostridium difficile.*
- *Clostridium difficile*: can cause a severe colonic infection.
- This infection is usually caused by the frequent use of broad-spectrum antibiotics that kill the pathogenic bacteria and the normal flora (which protect the body from the pathogens) in the GUT, this allows to pathogenic bacteria (including *Clostridium* difficile) to grow and cause pseudomembranous colitis. Vancomycin is used to treat this infection.
- Vancomycin is not effective against gram-negative bacteria, but it is very powerful against gram-positive bacteria.
- It can be given orally or intravenously.
- Orally administered vancomycin is not absorbed from the gastrointestinal tract → which means that we cannot use vancomycin for systemic infections.
- E.g: in patients with pneumonia caused by MRSA, we can use vancomycin and it must be given intravenously not orally.
- We use oral vancomycin to treat infections limited to the gastrointestinal tract (e.g: pseudomembranous colitis caused by *Clostridium difficile*).

Vancomycin

- Bactericidal
- Time- and concentration-dependent

Homework: What is the best predictor of vacomycin's antistaph activity?

Adverse effects

- Nephrotoxicity
- Red man syndrome
- Ototoxicity

Mechanisms of resistance:

- Alteration in binding affinity to peptidoglycan precursors

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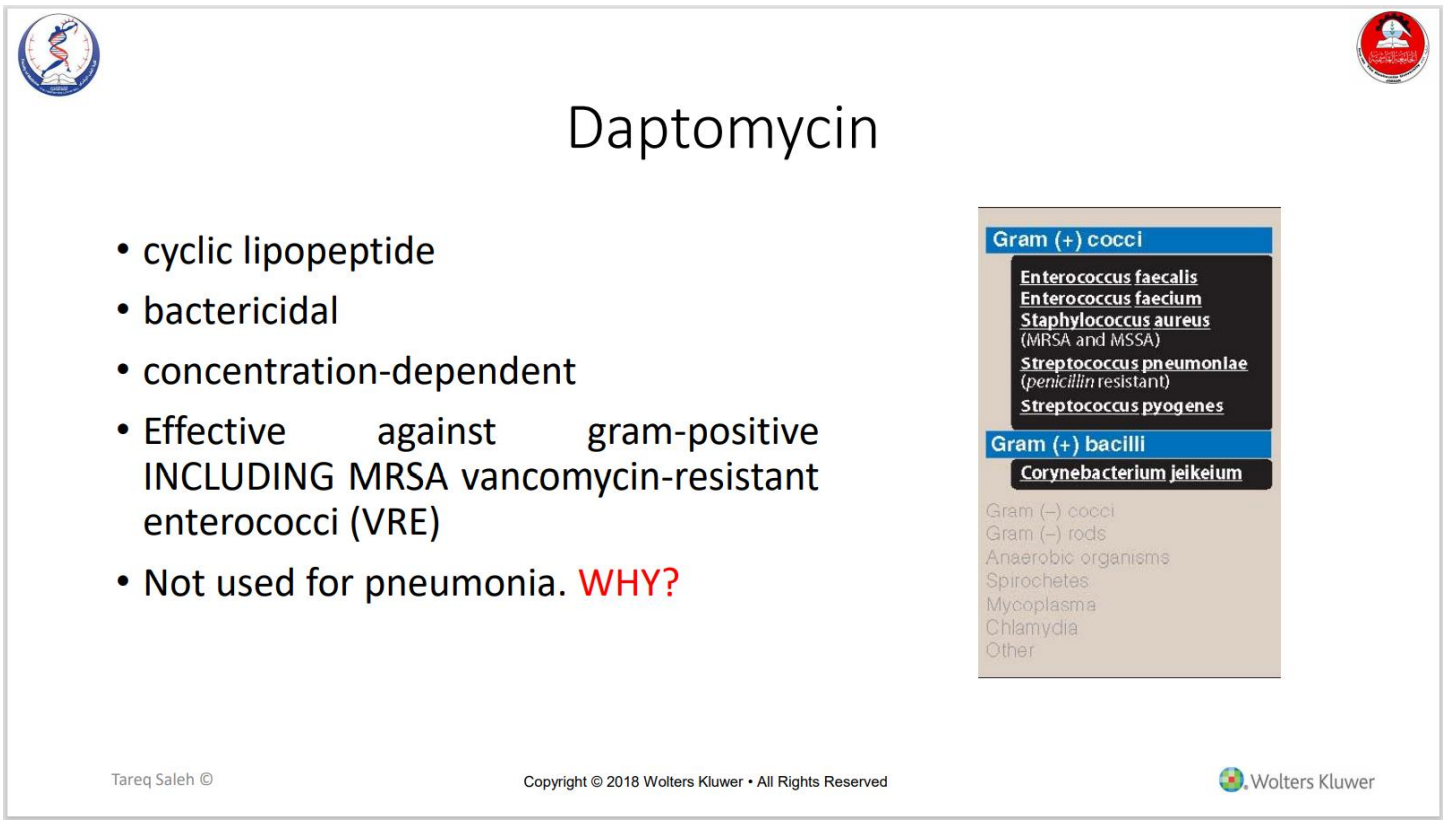
- Vancomycin is bactericidal since it interferes with cell wall synthesis.
- It has mainly a time-dependent killing manner, but there may be an element of concentration dependence (which means that the increase of concentration sometimes increases the bacterial killing).
- Since vancomycin is mainly time-dependent antibiotic, monitoring of vancomycin level in the blood is very important during therapy.
- Vancomycin therapy requires frequent infusions (almost every 60-90 mins)
- In case of high concentration in the blood, vancomycin causes toxicity.
- Adverse effects:
  1) Nephrotoxicity: because vancomycin is mainly eliminated by the kidney and causes injury to the kidney.
  2) Vancomycin when administrated intravenously, could cause inflammation in the site of injection or of blood vessels (this type of inflammation is called phlebitis)
  3) Red man syndrome: hypersensitivity reaction
  4) Ototoxicity: injury to the hearing system.
- Vancomycin is not susceptible to β-lactamases because it lacks β-lactam ring → β-lactamases production is not a mechanism of resistance against vancomycin.
- Vancomycin does not bind to PBP → alteration of PBP is not a mechanism of resistance against vancomycin.
- The mechanism of resistance against vancomycin is the alteration of binding affinity to peptidoglycan precursors → leading to inability of vancomycin too bind with peptidoglycan precursors.

- Some strains (e.g: vancomycin resistant enterococci) have started to develop resistance against vancomycin.



Daptomycin:

- Very similar to vancomycin
- Its structure: cyclic lipopeptide
- Daptomycin is concentration-dependent→ it requires less frequent doses.
- Daptomycin covers gram-positive bacteria including MRSA.
- Three types of antibiotics are effective against MRSA so far:
  1) Vancomycin
  2) Advanced generation cephalosporins
  3) Daptomycin
- Daptomycin is used as an alternative in case of no response to vancomycin.
- It is used in treatment of severe skin infections caused by MRSA.
- Daptomycin cannot be used to treat pneumonia even if caused by MRSA or streptococcus pneumonia, why?
  - Daptomycin is inactivated by enzymes in pulmonary surfactant.
  - Note: surfactant is a thin layer of fluids lines the alveoli

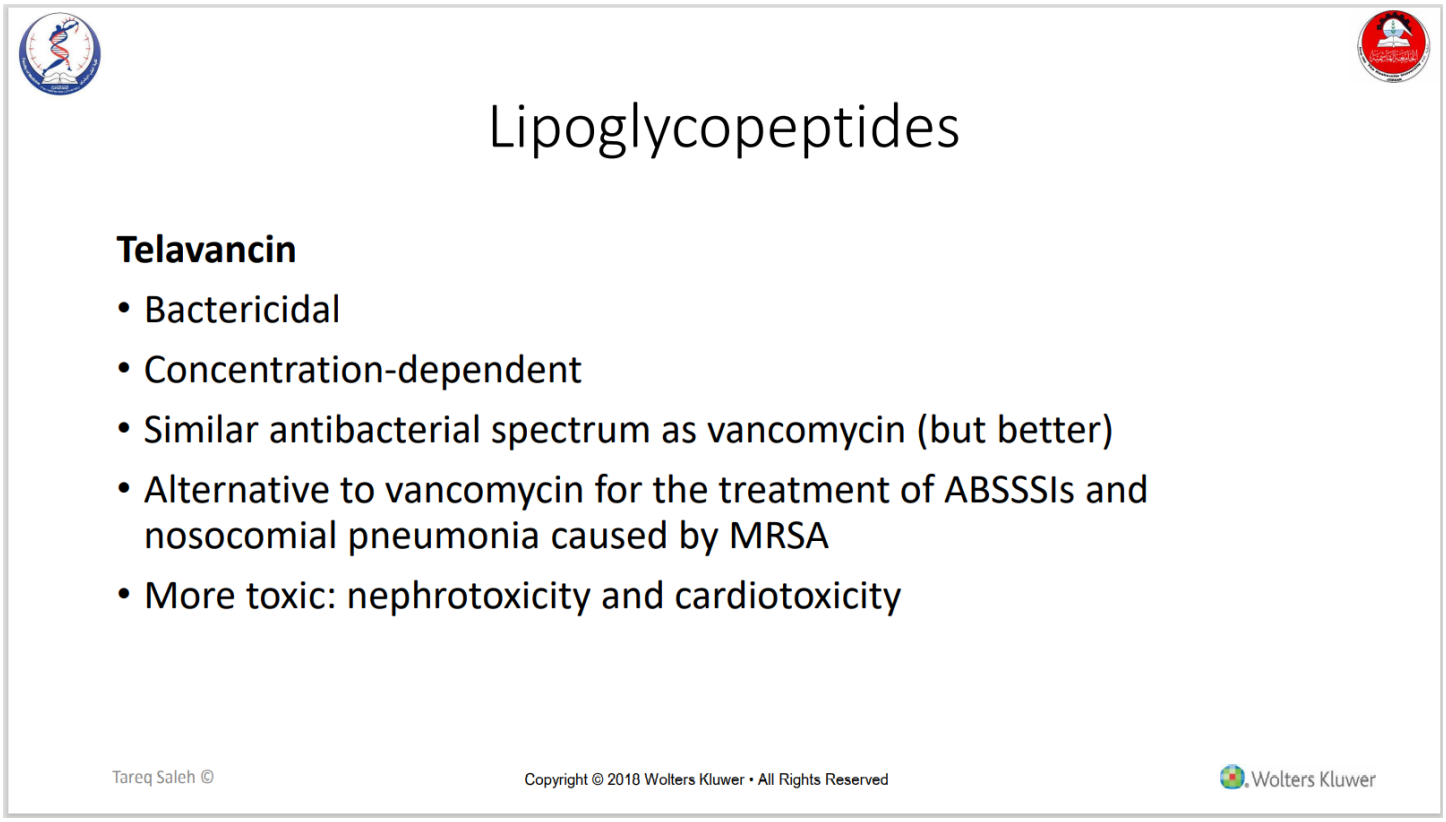
	VANCOMYCIN	DAPTOMYCIN
Mechanism of Action	Inhibits bacterial cell wall synthesis	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein
Pharmacodynamics	Combination of time and concentration-dependent Bactericidal	Concentration dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MI S. agalactiae, penicillin-resistant S. pneumoniae, Corynebacterium jeikeium, *vanc* faecalis, and E. faecium	
Unique Antibacterial Spectrum	Clostridium difficile (oral only)	*Vancomycin*-resistant E. faecalis and E. faecium (VRE)
Route	IV/PO	IV

- In addition to cell wall synthesis inhibition, daptomycin can cause depolarization of the bacterial cell membrane (in gram-positive bacteria). It also interferes with the synthesis of bacterial DNA, RNA and proteins → so, the mechanism of action of daptomycin is broader than vancomycin or beta lactams.

	VANCOMYCIN	DAPTOMYCIN
Typical Administration Time	60- to 90-minute IV infusion	2-minute IV push 30-minute IV infusion
Pharmacokinetics	Renal elimination Normal half-life: 6–10 hours Dose is adjusted based on renal function and serum trough levels	Renal elimination Normal half-life: 7–8 hours Dose is adjusted based on renal function
Unique Adverse Effects	Infusion related reactions due to histamine release: Fever, chills, phlebitis, flushing (red man syndrome); dose-related ototoxicity and nephrotoxicity	Myalgias, elevated hepatic transaminases and creatine phosphokinases (check weekly), and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while on therapy)
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for C. difficile infection; resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules; monitor serum trough concentrations for safety and efficacy	*Daptomycin* is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia

- Vancomycin is the first line therapy against MRSA infections, and it is one of the best therapies to treat *C.difficile* infections when it is given orally.

- Daptomycin is very effective against MRSA and other gram-positive bacteria but is inactivated by pulmonary surfactant.



Lipopolypeptides:

- E.g: telavancin
- Telavancin is bactericidal and concentration-dependent
- Telavancin is more powerful than vancomycin and daptomycin.
- Resistance to telavancin if there is no response to vancomycin because telavancin is more toxic.

Fosfomycin

- Derivative of phosphoric acid
- Bactericidal
- **MOA**: blocks cell wall synthesis by inhibiting the enzyme UDP-N-acetylglucosamine *enolpyruvyl transferase* (*first step* in peptidoglycan synthesis)
- First line therapy for acute cystitis
- Cross-resistance is unlikely

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Wolters Kluwer

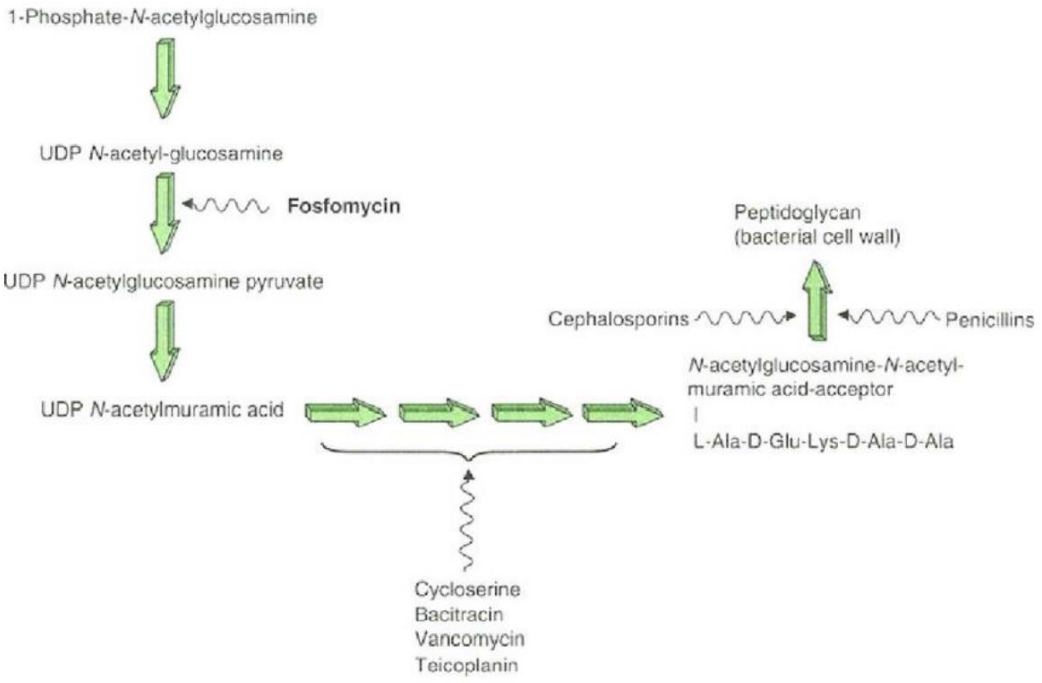
Fosfomycin:

- This antibiotic is different from all previous cell wall inhibitors.
- Fosfomycin is naturally derived from phosphoric acid.
- Fosfomycin does not interfere with cross-linking or transpeptidation, yet it interferes with the first step of cell wall synthesis (interferes with one of the enzymes catalyze the synthesis of peptidoglycans which is called UDP-N-acetylglucosamine enolpyruvyl transferase.
- The mechanism of resistance against Fosfomycin is different from other mechanisms against other cell wall inhibitors.

Polymyxin B

- Cation polypeptides
- **MOA**: bind phospholipids on the bacterial cell membrane of gram-negative bacteria (disrupt cell membrane not cell wall)
- Active against most gram-negative bacteria including P. aeruginosa
- Bactericidal
- Concentration-dependent
- Limited use because of nephrotoxicity/neurotoxicity
- Spared for multi-drug resistant infections

- ♣ Polymyxin B is another polypeptide, it is a large molecule
- ♣ Polymyxin B is not a cell wall inhibitor, its target is the bacterial cell membrane.
- ♣ It binds to the phospholipids in the cell membrane especially in gram-negative bacteria → disruption of the cell membrane and leakage of the intracellular contents of the bacteria.
- ♣ Gram-negative bacteria have 2 membranes that is why polymyxin B is effective against them.



Quick Exercise

Name five cell wall synthesis inhibitors that have antipseudomonal activity.

1. _____

2. _____

3. _____

4. _____

5. _____

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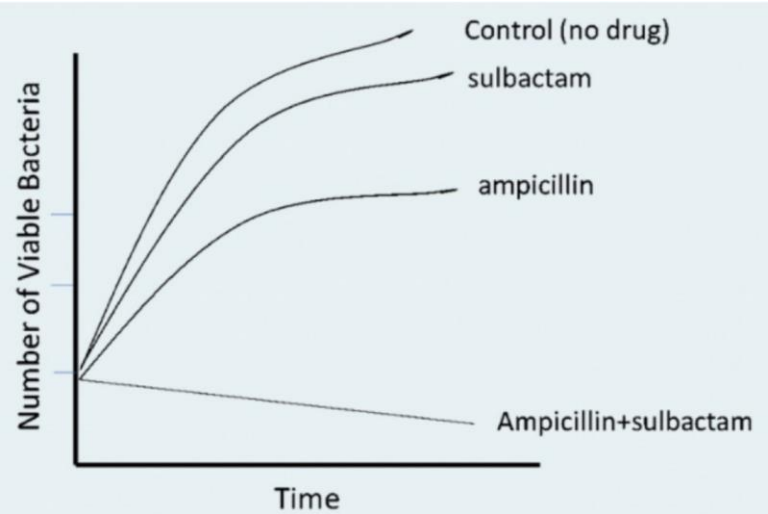
Wolters Kluwer

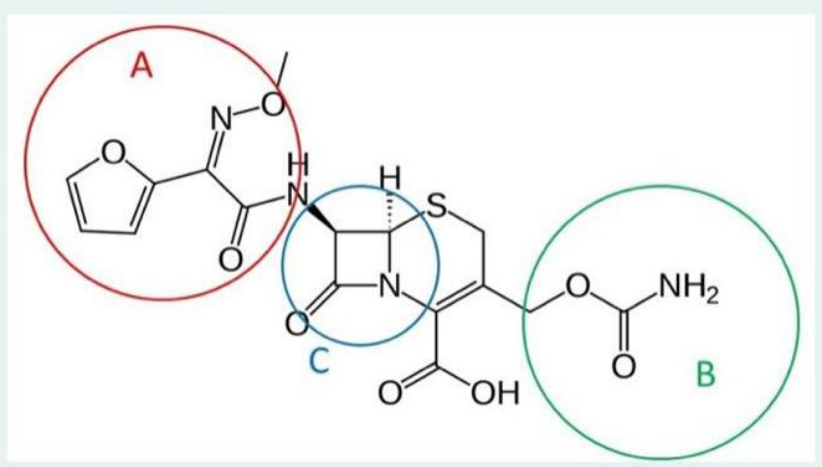
حل اسئلة الكويز:

1) The diagram represents viability results from an experiment testing the antibacterial effects of the indicated drugs against *E. coli* in vitro. The synergistic effect observed in the drug combination group is most likely due to:
    a) Upregulation of penicillin-binding proteins
    b) Inhibition of cytosolic proteoglycan synthesis
    c) Inhibition of proteoglycan membrane transport
    d) Activation of gram-negative cell wall porins
    e) Inhibition of bacterial beta-lactamase activity

    ANSWER: E

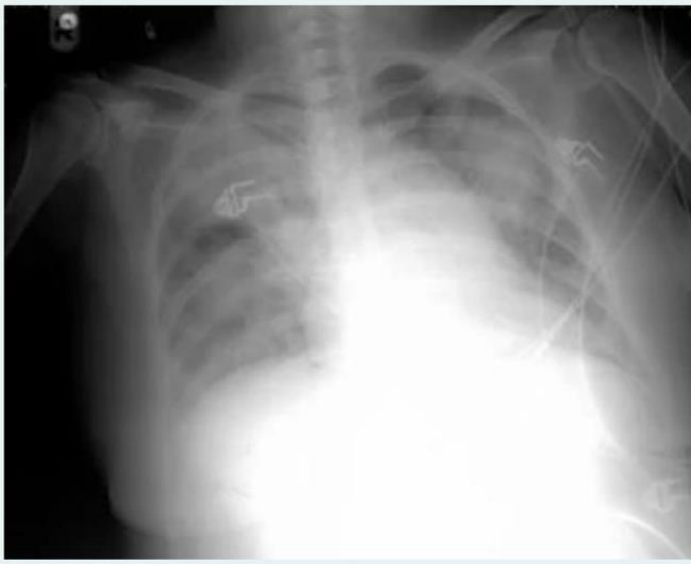


2) The following diagram depicts the chemical structure of cefuroxime. Based on your understanding of the structure-effect relationship of cephalosporins, which of the following statements is correct?
    a) Group A is responsible for determining the antibacterial spectrum of cefuroxime
    b) Group A is responsible for the pharmacokinetic properties of cefuroxime.
    c) Group B is responsible for the susceptibility of cefuroxime to beta-lactamases
    d) Group C is responsible for the activity of cefuroxime against MRSA
    e) Group C is responsible for the extent of hepatic metabolism of cefuroxime.
    ANSWER: A



3

A 55-year-old male patient has been hospitalized for the last 3 days after suffering from severe upper gastrointestinal bleeding. While in the hospital, and possibly due to aspiration, the patient started developing fever, dyspnea, and productive cough, with pleuritic chest pain. On examination, the patient had purulent sputum and auscultatory signs of pulmonary consolidation. Radiography showed widespread pulmonary infiltrates suggestive of MRSA infection. Your initial evaluation highly favors the possibility of nosocomial aspiration pneumonia. Which of the following antibiotics must be included in your empiric therapy regimen? *



- ○ Daptomycin
- ○ Cefepime
- ○ Nafcillin
- ○ Linezolid
- ○ Ceftriaxone

ANSWER: D