Pharmacology

Subject :

Lec no : 25

Done By : Raneem Azzam

وَقُل رَّبِّ زِدْنِي عِلْمًا

Other β-Lactams

They have beta lactam ring (that consists of three atoms of carbon and one atom of nitrogen)

① These drugs are more advanced than penicillins and cephalosporins.

② They are the last resort → multi drug resistant to bacteria اخر سلاح منستخدمو في علاج

منخبيهم لهاي الحالة

نستخدمهم في حال ان ال Initial therapy ما اعطت نتيجة و السبب انه لو صار في Resistance لهاي الأدوية، مش راح نقدر نعالج ال Infection اللي بتسببه ال Resistant bacteria

* خليني فيي بالك ال newantibiotic منخبيها كسلاح وما منيجي عليها غير وقت ظهور resistent

عشان هيك ال (other β-lactams) منخبيها كسلاح لوقت ظهور resistent

While MRSA and MBLs involve different mechanisms of resistance (MRSA involves altered PBP production, while MBLs involve enzymatic degradation), both are examples of bacteria that have developed resistance against important classes of antibiotics. These types of antibiotic resistance pose significant challenges in the treatment of infections and require alternative treatment approaches.

معلومة خارجية لا نحتاجها في دراستنا

Carbapenems

The most well-known

CARBAPENEMS (Family)

- *Doripenem* DORIBAX
- *Ertapenem* INVANZ
- *Imipenem/cilastatin* PRIMAXIN ← يؤخذ معها
- *Meropenem* MERREM

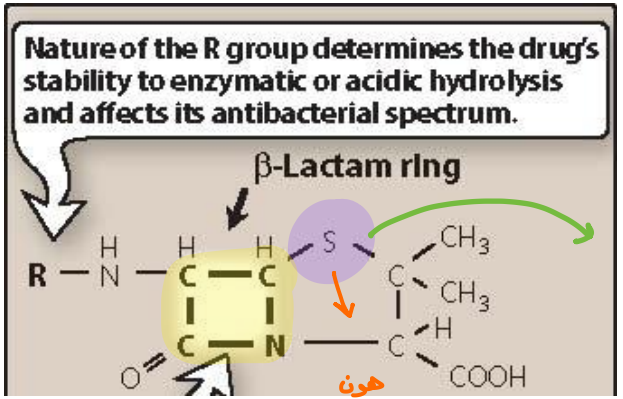
↳ second well-known

هسا imipenem لا يؤخذ لحالو لازم ناخذ مع cilastain، ليه؟

بسبب وجود انزيم dehydropeptidase الي بكسر ال imipenem،كيف نحل هاي المشكلة ؟بعطي cilastain بعمل inhibition لعاد الانزيم ف بستفيد من ال antibiotic

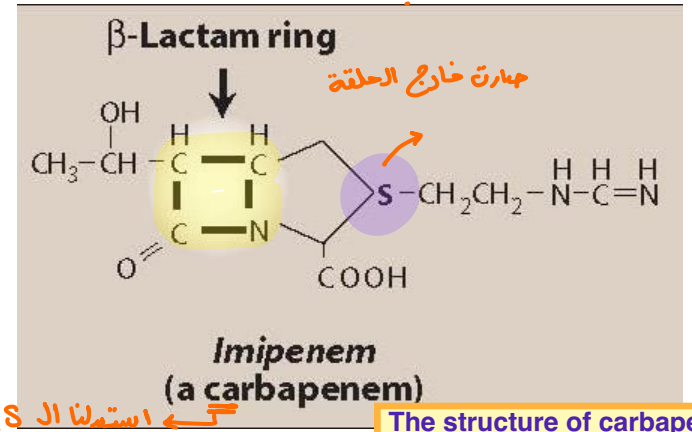
ما إلو تأثير كتأثير antibiotic

لـ هاد احتهار الحكي تحت 😊



غيرنا مكانها

هون جوا الحلقة



استبدلنا الـ S بـ ذرة كربون

The structure of carbapenems is simpler than cephalosporins and penicillin (which are bulky compounds).

Carbapenems

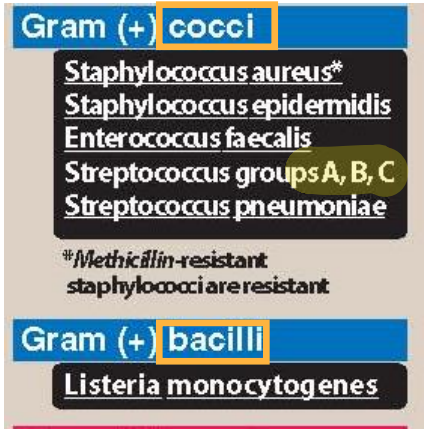
imp

* Carbapenems have verry wide antibacterial spectrum (the most broad-spectrum antibiotics that we know so far)

synthetic drug

Antibacterial spectrum

- Broad-spectrum (used for empiric therapy)
- Resist β-lactamases : Carbapenems are resistant to beta lactamases. That is why they cover wide variety of bacteria species.
- Effective against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa * very powerful against it



* 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 except *Not MRSA methicillin-resistant Staphylococcus aureus

Exception: metalolactamases → a group of enzymes secreted by resistant bacteria,These enzymes can hydrolyze carbapenems except @

* الجداول بتبين الكميات الكبيرة من البكتريا إلي بتغطيها

Resist β-lactamases

الدكتور حكى معلومة عن

*carbapenems still not effective at extended spectrum b-lactames producing gram negative bacteria such as (((These enzymes are responsible for resistance to β-lactam antibiotics in certain bacterial species such as Escherichia coli, Klebsiella pneumoniae, and ,,)))....... → ** بس فيه حل ؟

الحل → انو نحل

Combination of β -lactams with β -lactamases inhibitors → effective against β -lactamases producing bacteria.

مثل Meropenem

ترجيعي ← yes

ESBL

فيه شغلة حكاها الدكتور :انو انا بقدر احل مشكلة ELSB عن طريق ال B-lacatmase inhibitor combined مش زي حل MRSA لانو مشكلتنا معها في ال genetic بحيث قللت ال affinity of PBP

1. Genetic determinants: MRSA is resistant to methicillin and other β-lactam antibiotics due to the acquisition of the mecA gene, which encodes penicillin-binding protein 2a (PBP2a). PBP2a has a low affinity for β-lactam antibiotics, making them ineffective. Inhibiting PBP2a directly is challenging because it differs in structure from other penicillin-binding proteins found in susceptible bacteria.

2. Persistence and survival: MRSA has the ability to survive in different environments, including hospitals and communities. It can colonize the skin and mucous membranes of individuals without causing symptoms. This persistence and ability to rapidly spread make it difficult to control and eliminate MRSA infections.

→ إضافة

مشان هيك أفضل حل لقتل MRSA (best way) ألاقي inhibator ثاني يكون هدفو ال cell wall بتشتغل بطرق مختلفة وما عندها ال Target PBP

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.

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

دوا واحد

MONOBACTAMS

Aztreonam AZACTAM

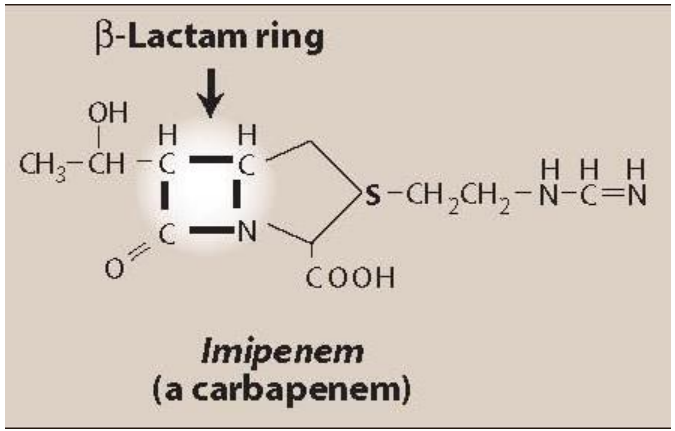
mainly for

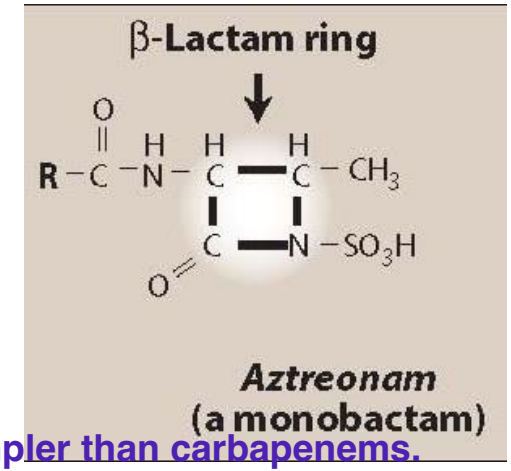
- -Effective against gram-negative (including P. aeruginosa)
- -Lacks activity against gram-positive
- -Susceptible to ESBLs

ESBLs can hydrolyze aztreonam. → حكينا عن العلل فوق

- -Relatively non-toxic
- -little cross-reactivity with other β-lactams

له بقدر اعطيه لواحد عنده حساسية من البنسلين مثلاً





The structure of monobactam is simpler than carbapenems.

- **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.**

Can Cephalosporins and Carbapenems Be Combined with β-lactamase inhibitors?

- Ceftolozane + tazobactam: used for multidrug resistant P. aeruginosa and some ESBLs-producing bacteria
- Ceftazidime + avibactam: used against ESBL-producing bacteria

***both indicated for the management of complicated intra-abdominal and urinary tract infections caused by multidrug resistant bacteria

- Meropenem + vaborbactam: used against ESBL-producing bacteria

***indicated for the management of complicated urinary tract infections

في البداية نتذكر ليه اعمل combined:

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.

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.

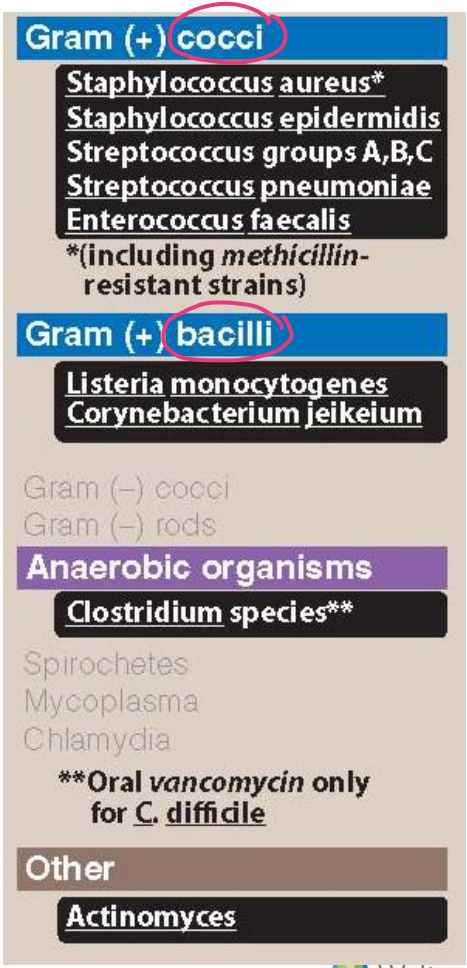
3) Meropenem + vaborbactam:
* Meropenem is a carbapenem.
* vaborbactam is a β -lactamase inhibitor.
*This combination is more effective against ESBLs producing bacteria than the use of meropenem only.
** Used in very complicated urinary tract infections caused by multi-drug resistant gram-negative bacteria.

* لقينا حل لل ESBL بس ضلت MRSA
(ارجع للمعلومة الاخيرة اخر سلايد ٣)
فضل لاخر نضع مضاد للموضوع فعطنا

Cell wall inhibitors but not β -lactam

Vancomycin

- tricyclic glycopeptide
- **What is the mechanism of action of vanco?**
- Effective against gram-positive bacteria INCLUDING MRSA and MRSE → cocci, bacilli
- Oral and IV
- why? IV vanco used in patients with MRSA skin infections, infective endocarditis, ….
- Oral vanco used for severe antibiotic associated pseudomembranous colitis (GIT في) → in this case okay we can use it orally
- Vanco is not absorbed after oral administration



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).

يعني قبل عملية ال Transpeptidation

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

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).

systemic
Like → Lung infection
→ Meningitis

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.

+شرح السلايد الي تحت

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.

Vancomycin

- Bactericidal
- Time- and concentration-dependent

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

Adverse effects

- Nephrotoxicity
- Red man syndrome
- Ototoxicity

Mechanisms of resistance:

- Alteration in binding affinity to peptidoglycan precursors

Vancomycin الـ resistance ← ظهرت عنا مشكلة الـ

لـ بس لسا قادرين نحل المشكلة عن طريق ↓

Daptomycin is used as an alternative in case of no response to vancomycin.

Daptomycin

Very similar to vancomycin

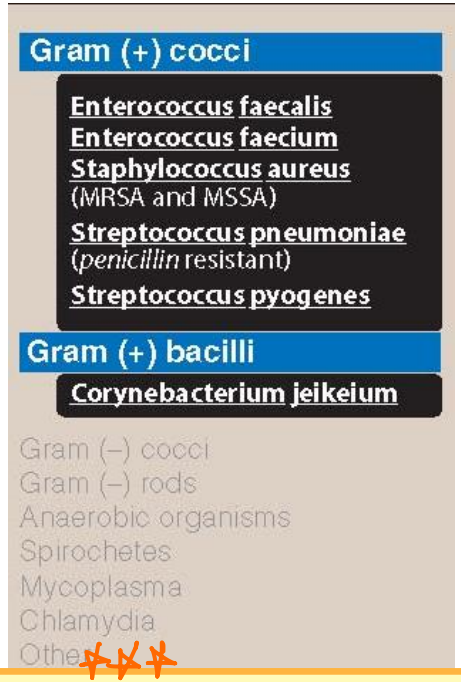
structure:

- cyclic lipopeptide
- bactericidal killing
- concentration-dependent → it requires less frequent doses.
- Effective against gram-positive INCLUDING MRSA vancomycin-resistant enterococci (VRE)
- Not used for pneumonia. WHY?

pharmaco kinetic ↑ المشكلة هون بـ ←

عشان انو هو عشن فعال للـ MRSA بالعكس فعال جيدًا. ←

Daptomycin is inactivated by enzymes in pulmonary surfactant.
• Note: surfactant is a thin layer of fluids lines the alveoli



Three types of antibiotics are effective against MRSA so far:
1) Vancomycin
2) Advanced generation cephalosporins
3) Daptomycin

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.

comparison	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

	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

These are injury that directly affect the SM

Vancomycin is the first line therapy against MRSA infections, and it is one of the best therapies to treat C.difficle infections when it is given orally. **Daptomycin is very effective against MRSA and other gram-positive bacteria but is inactivated by pulmonary surfactant.

Lipoglycopeptides

مثال → **Telavancin** → bactericidal and concentration-dependent / have broad spectrum

- Bactericidal
- Concentration-dependent
- Similar antibacterial spectrum as vancomycin (but better)
- Alternative to vancomycin for the treatment of ABSSSIs and nosocomial pneumonia caused by MRسA
- More toxic: nephrotoxicity and cardiotoxicity

kidny damaged

حدوث مثلاً cardic Attack

Resistance to telavancin if there is no response to vancomycin because telavancin is more toxic.

* بسببها ما بقدر استخدمها

first choice

للتوضيح

ABSSSIs stands for Acute Bacterial Skin and Skin Structure Infections. This term refers to a group of infections that affect the skin and underlying soft tissues, caused by bacteria such as Staphylococcus aureus (including MRSA) and Streptococcus pyogenes. Examples of ABSSSIs include cellulitis, wound infections, and abscesses. These infections can range from mild to severe and typically require antibiotic treatment.

This antibiotic is different from all previous cell wall inhibitors
Very unique

phase 3 الـ وش الـ Target الـ ←
cell wall inhibitors زي معظم cell wall من الـ

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 (inflammation of the urinary bladder التهاب المثانة)
- Cross-resistance is unlikely

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 mechanism's against other cell wall inhibitors.

* Polymyxin B is not a cell wall inhibitor, its target is the bacterial cell membrane.

Polymyxin B (Colistin)

* This is your last resort of all antibiotic
↳ when you lose hope with every other antibiotic

- Cation polypeptides large molecule
- **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** → for treatment

نفس العكس

لماذا السبب

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.

In Jordan

هاي البكتيريا ما كانت كثير ظاهرة او منشوفها بالمستشفى (ما كان الها resistant هون)قبل ٢٠ سنة ولكن انتشر الاصابة فيها في ال middle East بسبب الحروب زي مثلا العراق و ظهر الها resistance ل majority of antibiotic فعملت infection in areas that were complicated by war
عدد كبير مش قليل وطلع الها
resistant to the most commonly used antibiotic, including carbapenams like (meropenem and ertapenem) and these are the most powerful b-lactams cell wall inhibitor،،،
وهاد الايشي شفناه منتشر عنا بالاردن والاصابة بهاي البكتيريا مميت ممكن يعمل pneumonia وما ننسى انو عامل resistant لكثير انواع من ال antibiotic

- We are starting to see bacterial infections (mainly gram-negative) that are resistant to almost all antibiotics except for colistin.
- 76.8% of Acetinobacter *baumannii* isolates were MDR and 99.2% were carbapenem-resistant.
- Resistance patterns indicated
  - **high resistance** for most cephalosporins, carbapenems, and fluoroquinolones
  - **moderate resistance** for trimethoprim/sulfamethoxazole and ampicillin/sulbactam,

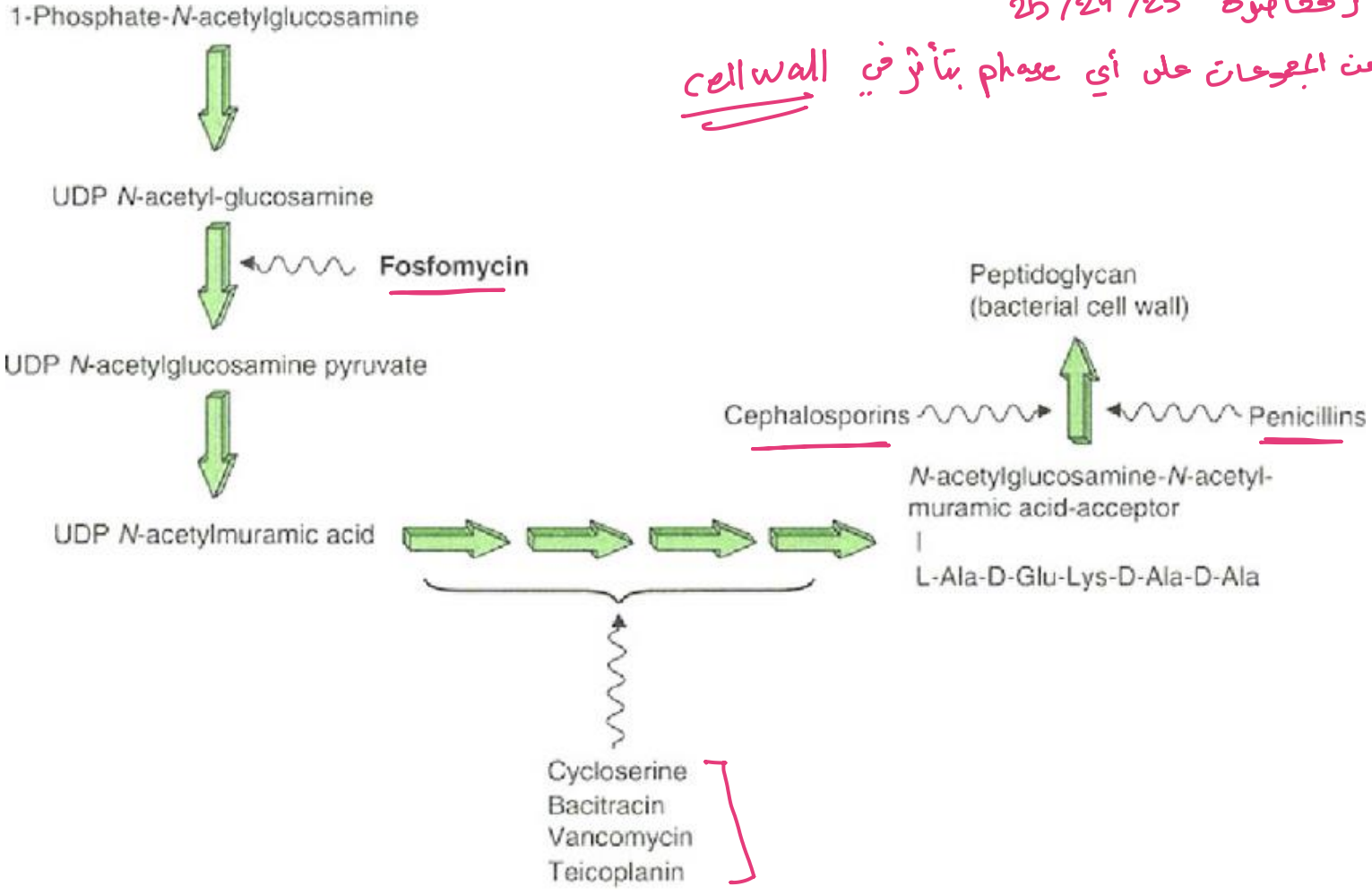
طيب مين ال sensitive الها؟
colistin, unfortunately, this will be the last resort for the treatment of this multi drug resistant infection،
على الرغم من هيك فهي بتعمل مرض قاتل وكثير من الناس بتخسر حياتها لانو علاجها مش سهل ،ومن هون بدنا نعرف قديش مشكلة MDR كثير خطيرة وخصوصا عنا في الاردن لانو لو هاي البكتيريا قدرت تعمل resistance to Polymyxin "سلم على الشهدا الي معاك " لانو من غير شر مافي ولا مضاد لحد هسا effective لهاى البكتيريا

Acinetobacter baumannii commonly exhibits resistance to various members of the carbapenem family. This includes resistance to drugs such as meropenem and ertapenem

Al-Tamimi *et al*. 2022

*ملخص لمحاضرة 25/24/23

كل وحدة من المجموعات على أي مرحلة بتأثر في الـcell wall



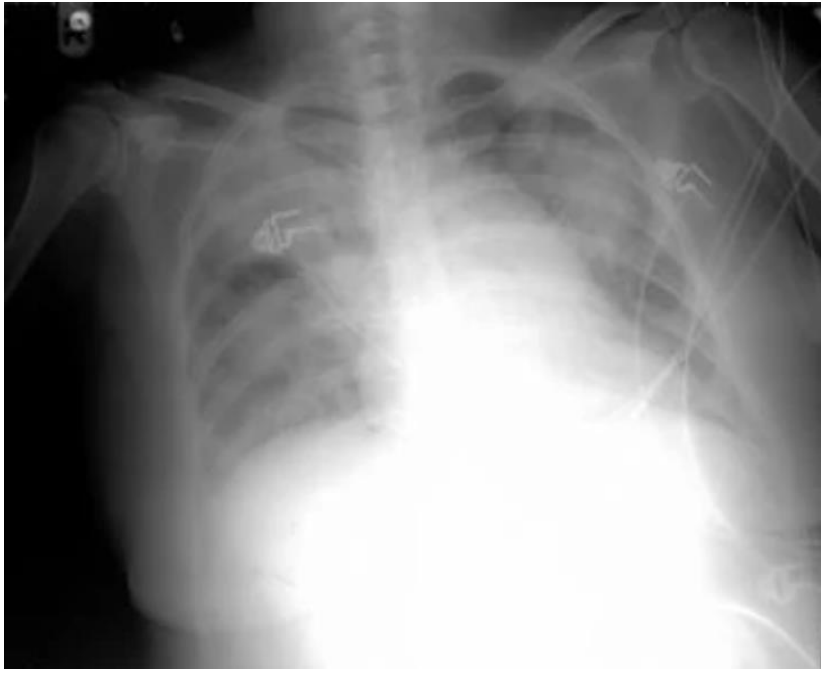
Quick Exercise

Name five cell wall synthesis inhibitors that have antipseudomonal activity.

1. _____
2. _____
3. _____
4. _____
5. _____

Here are five cell wall synthesis inhibitors with antipseudomonal activity:
1. Penicillins: Penicillins like piperacillin and ticarcillin inhibit cell wall synthesis in Pseudomonas aeruginosa.
2. Cephalosporins: Cephalosporins such as ceftazidime and cefepime are effective against Pseudomonas aeruginosa by targeting cell wall synthesis.
3. Carbapenems: Carbapenems like imipenem and meropenem inhibit cell wall synthesis in Pseudomonas aeruginosa and have broad-spectrum activity.
4. Monobactams: Monobactams like aztreonam specifically target cell wall synthesis in Pseudomonas aeruginosa.
5. Glycopeptides: Vancomycin, a glycopeptide antibiotic, can have activity against Pseudomonas aeruginosa when used in combination with other antibiotics.

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?



Linezolid

Daptomycin

Ceftriaxone

Cefepime

Nafcillin

الجواب

A