B-lactam drugs and other cell wall and membrane-active agents

Pharmacology 3

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Cell wall active agents

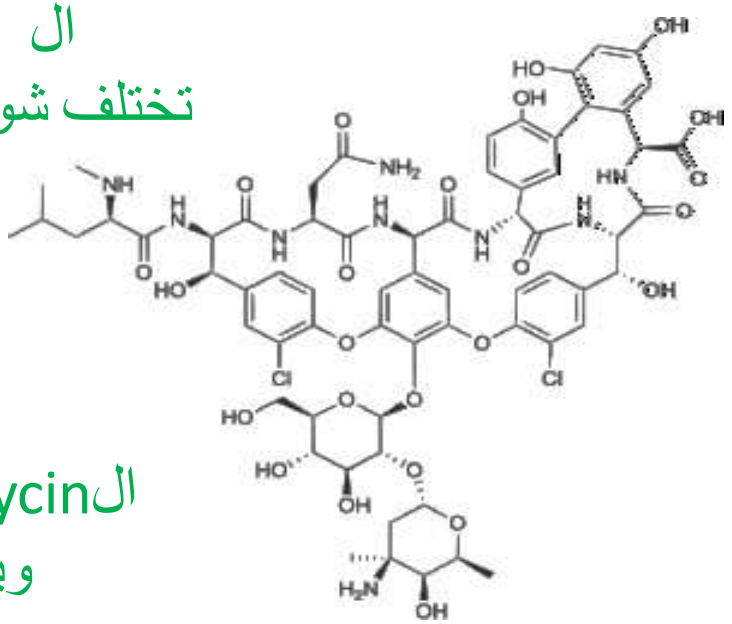
- B-lactam ABs
- Glycopeptides
- Others

Glycopeptide ABs

- Vancomycin
- Tiecoplanin
- Telavancin
- Dalbavancin

احنا بس حنوخذ عن ال Vancomycinومتوقع
من حجمه الكبير انه ما يكون orally active
حيكون parenteral

هيvancomycin للmechanism of action ال
تختلف شوي عن الb-lactam اذا ذاكرين الb-lactam كانت
تشتغل على ''pbp''وتعمل للINHIBITION
وبهاي الطريقة توقف الTranspeptidation
بينcrosslinking الpeptidoglycan لكن
كانvancomycinالpeptidoglycan يدخل بهاض ال
ويشبك عطول مع اخر D-ALA-D-ALA و يوقف ال
CROSSLINKING



Vancomycin

- Vancomycin inhibits synthesis of bacterial cell wall by binding to the D-Ala-D-Ala terminus preventing further crosslinking.

- Vancomycin is bactericidal for gram-positive bacteria including those producing β lactamase and those resistant to nafcillin and methicillin (**MRSA (methicillin-resistant staph. Aureus))** as well as enterococcal infections.

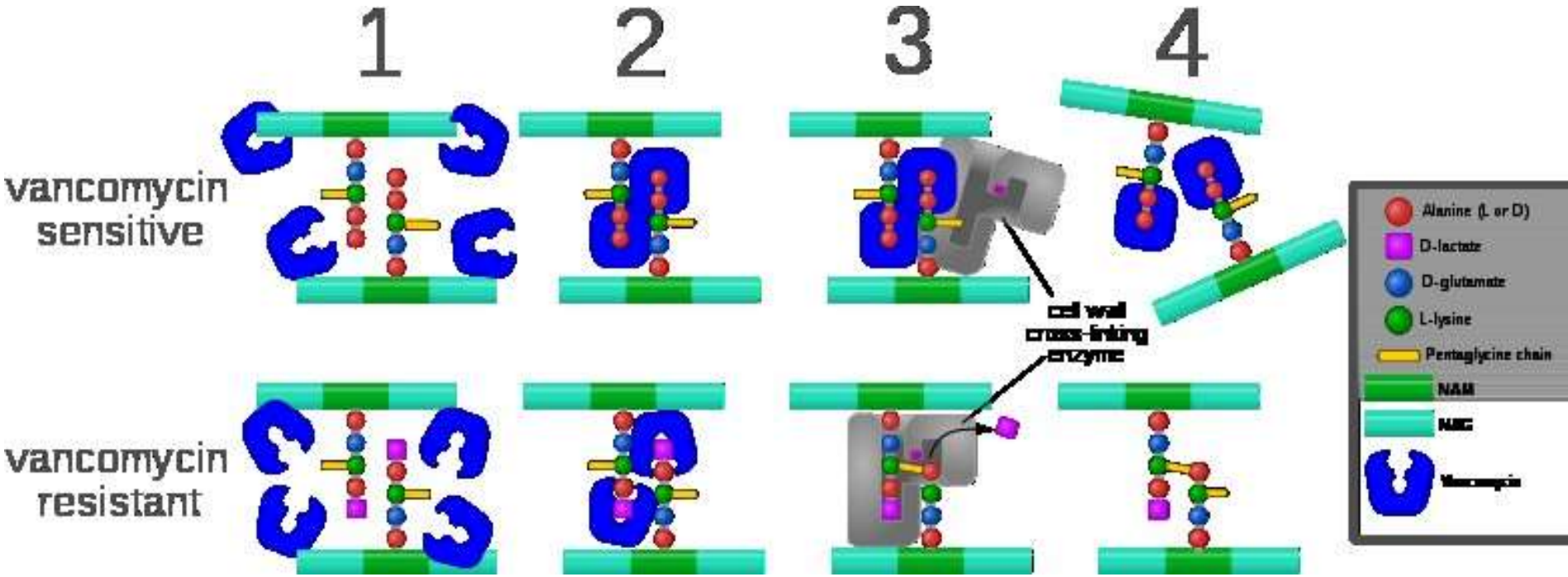
- With the emergence of vancomycin-resistant strains(for example, Enterococcus faecium and Enterococcus faecalis….daptomycin can be used), it is important to restrict the use of vancomycin to the treatment of serious infections caused by β-lactam resistant, gram-positive microorganisms or gram-positive infections in patients who have a serious allergy to the β-lactams.

بشتغل ال vancomycinعلى g+ وهو قاتل له
(bactericidal)وبشتغل كمان على MRSA
(METHICILLIN- resistant staph aureus) , لكن الدكاترة
والاستخدام الخاطئ لاله عمللهresistance البكتيريا كانت ذكية
عملت اشي بحيث انه ما يأثر على cell wall synthisisوبنفس
الوقت يعمل Inhibitin for vancomycinاجت البكتيريا
ومسكت اخر D-ALAوعملتله تبديل ب D-LACTATE

Vancomycin

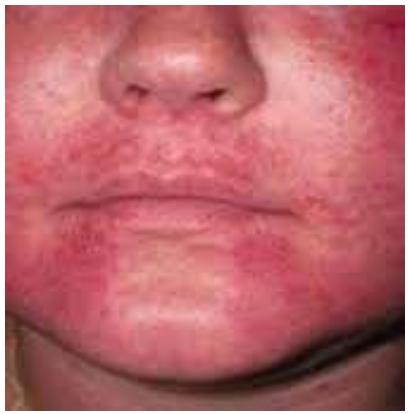
- Resistance

- Change in permeability to the drug or by decreased binding of receptor molecules (by replacing the terminal D- vancomycin to Ala by D-lactate)



Vancomycin

- systemic infectionsIV for
- Not absorbed after oral administration (the use of the oral formulation is limited to the treatment of severe antibiotic-associated C. difficile colitis.)
- Combined with ceftriaxone for meningitis
- **Adverse Reactions**
  - Irritating to tissue
  - “red man” or “red neck” syndrome.
    - This is infusion-related flushing and caused by release of histamine.
    - Prevented by:
      - ORprolonging the infusion period to 1-2 hours
      - pretreatment with an antihistamine such as diphenhydramine.



  - (Mostly minor).10% of cases

- ال vancomycinبينعطى ivاذا اعطيته oralما رح يمتص لكن اذا بدي اعطيه oralراح اعطيه فحالة كان localالي هو ال giومثل C.difficile colitis
- For meningitis فيcombined (vancomycin+ceftriaxone)
- ال adverse reaction
1-red nick 2-red man ,they caused by release of histamin
- الحل انه يا اما نخليها infusionونطول العلاج من ١- ٢ساعة او اعطيه ببساطة antihistamin

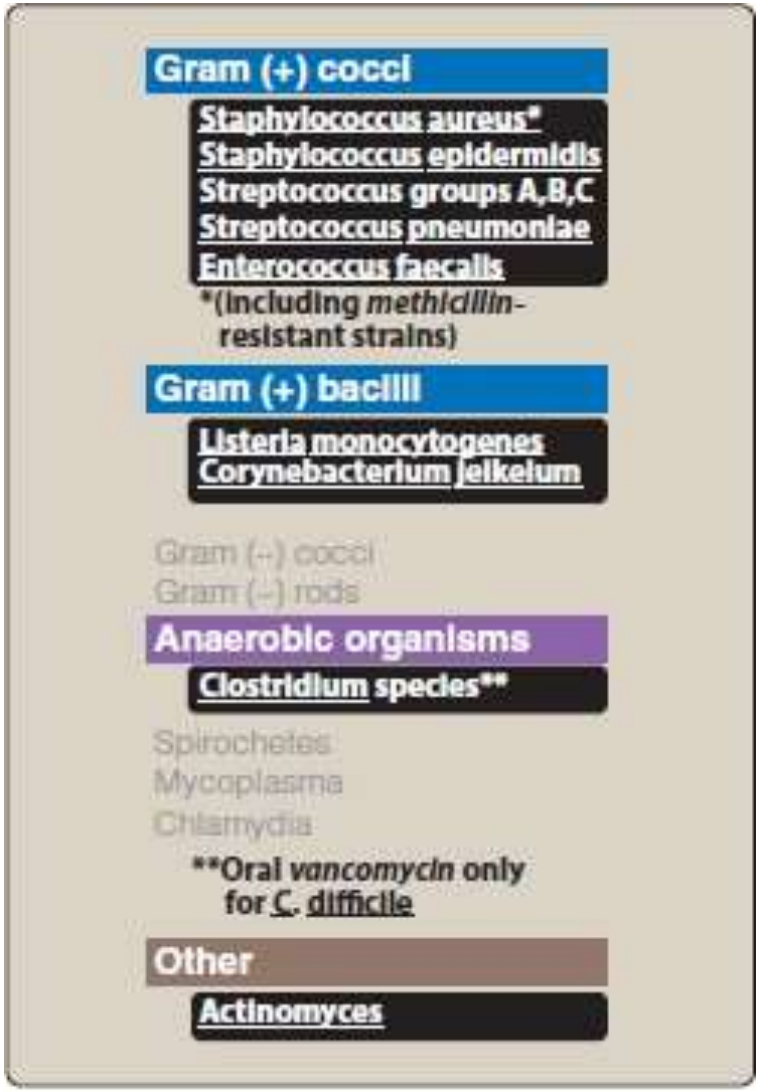


Figure 38.16
Antimicrobial spectrum of *vancomycin*.

Cell wall and cell membrane active agents

- B-lactam Abs
- Glycopeptides
- Others
  - Daptomycin
  - Fosfomycin
  - Bacitracin
  - Cycloserine
  - Polymyxines

Daptomycin:

- Cyclic lipopeptide, binds to cell membrane (Ca^{+2} – dependent) causing depolarization and rapid cell death (doesn't work on cell wall).
- Its spectrum of activity is similar to that of vancomycin except that it may be active against vancomycin-resistant strains of enterococci and S aureus.

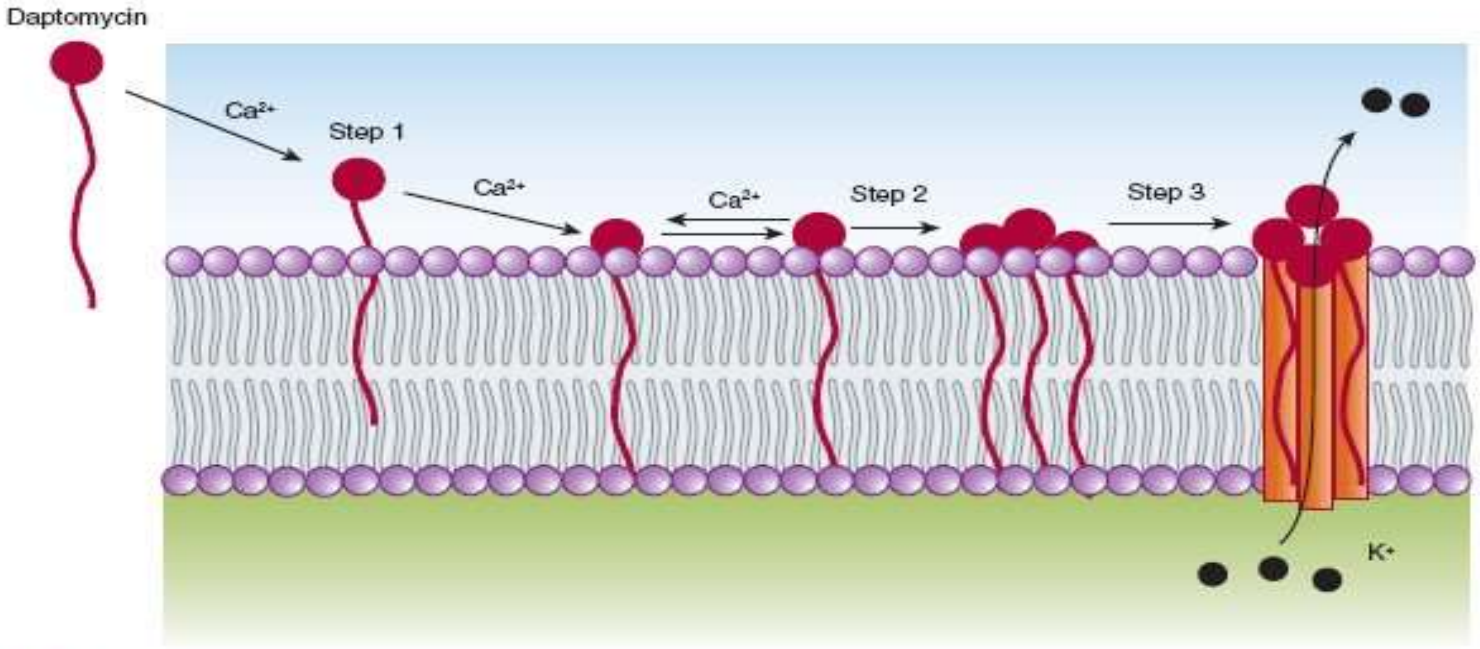


FIGURE 43–9 Proposed mechanism of action of daptomycin. Daptomycin first binds to the cytoplasmic membrane (step 1) and then forms complexes in a calcium-dependent manner (steps 2 and 3). Complex formation causes a rapid loss of cellular potassium, possibly by pore formation, and membrane depolarization. This is followed by arrest of DNA, RNA, and protein synthesis resulting in cell death. Cell lysis does not occur.

- هسا زي ما نحنا عارفين انه للبكتيريا cell membranاو حتى موجود بكل الخلايا prokaryotic and eukaryotic
- ال cell membraneهاض مهم ...ليش؟ لانه بده يحافظ عندي على electrochemical gradiant.
- ال Daptomycinهو عبارة عن lipopeptideبشبه شكل ال phospholipidعنده القدرة انه يتعرف على certain phospholipidبال cell membranب certain bacteria
- بتصل بال bacteriaوبعمل ثقوب بال cell membranبسببلي depolarization and rapid cell death.
- ال spectrumتاعه زي ال vancomycinبقدر يشتغل على g+ لكن الفرق انه بقدر يشتغل كمان على vancomycin- s.aureus,enterococcig resistant strains(vrs).
- في ادوية ثانية كمان بتشتغل على ال mrsa&vrsالي هم linezolid,qunipristin,dalfopristin.
- لا يستعمل ال daptomycinفي علاج الpneumoniaلانه بصيرله inactivation بواسطة ال pulomonary surfactantيعني مش البكتيريا الي بتخربه لا جسمنا نفسه بخربه .

Daptomycin

- Is an alternative to other agents, such as linezolid and quinupristin/dalfopristin, for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycinresistant enterococci (VRE).
- Daptomycin is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia.

Figure 38.17
Antimicrobial spectrum of *daptomycin*. MRSA = *methicillin* resistant S. aureus; MSSA = *methicillin* susceptible S. aureus.

Fosfomycin •

- Aanalog of phosphoenolpyruvate (PEP)
- Inhibits the cytoplasmic enzyme enolpyruvate transferase which inhibits the formation N -acetylmuramic acid precursor.
- Active against both G+ & G-
- The active drug is excreted by the kidney, with urinary concentrations exceeding MICs (minimum inhibitory concentrations) for most urinary tract pathogens.
- Fosfomycin is approved for use as a single 3-g dose for treatment of uncomplicated lower urinary tract infections in women.

- Fosfomycin هو analog of phosphoenolpyrovate
- في عندي انزايم اسمه enolpyrovate transferase بعملي formation of N-acetylemuramic acid precursor (NAP), ال fosfomycin بعملي inhibition اله.
- بشتغل على g+,g-
- وبوصل ال urinary tract بتراكيز اعلى من ال MIC فا من استخداماته كمان uncomplicated lower tract infection

- يعتبر ك first choice

- **Bacitracin**
- Mixture of related cyclic polypeptides
- *Active against G+*
- Inhibits cell wall formation by interfering with dephosphorylation of the lipid carrier that transfers peptidoglycan subunits to the growing cell wall.
- Indicated **topically** for skin and eye infections.
- Bacitracin in parenteral (IM) therapy may cause renal failure. Its use should be restricted to infants with staphylococcal pneumonia and empyema due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible.

- Renal failure: **[US Boxed Warning]: IM use may cause renal failure due to tubular and glomerular necrosis; monitor renal function daily.** Avoid concurrent use with other nephrotoxic drugs; discontinue use if toxicity occurs; maintain adequate fluid intake and urine output throughout therapy. Do not exceed recommended doses

- ال bactracin هو كمان بشتغل على ال cell wall , inhibitor Carrier protein transfers peptidoglycan to growing cell wall .
- بشتغل على g+
- ال bactracin كثير يستخدم topicalاكثر استخداماته هيك مثل skin and eye infection
- ما بينعطى parenteral لانه عليه risk و warning كبير , يمكن يعمل renal failure
- بقدر اعطيه لطفل مصاب ب staphylococcal pneumonia واعطاني انه susceptible to bactracin بقدر اعطيه اياه بس بضل الخطر الاصابة ب renal failure موجود عشان هيك لازم يضل monitoring

Cycloserine :

- Cycloserine inhibits many gram-positive and gram-negative organisms, but it is used almost exclusively to treat tuberculosis caused by strains of *Mycobacterium tuberculosis* resistant to first-line agents.
- Structural analog of D-alanine and inhibits the incorporation of D-alanine into peptidoglycan by inhibiting alanine racemase, which converts L-alanine to D-alanine.
- The dosage for treating tuberculosis is 0.5 to 1 g/d in two or three divided doses.
- Cycloserine causes serious dose-related central nervous system toxicity with headaches, tremors, acute psychosis, and convulsions. If oral dosages are maintained below 0.75 g/d, such effects can usually be avoided.

- ال cycloserin بعمل inhibit لخطوة تحويل الl-alanine الى D-ALANINE, بعمل INHIBITION للانزايم الي بعمل هاي العملية واسمه....ANALNINE RACEMASE

- بعالج MYCOBACTERIUM TUBERCULOSIS RESISTANCE , بعالج كمان G+, G- لكن حاليا هو شغال على الاولى

- في حال زادت الDOSE عن المفروض تنعطاه بصير عنا SIDE EFFECT مثل , CENTRAL NERVOUS SYSTEM TOXICITY HEADACHE , acute psychosis, and convulsion

Polymyxines :

- The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and ultimately cell death.
- Polymyxins are concentration-dependent bactericidal agents with activity against most clinically important **gram-negative bacteria.**
- Only two forms of polymyxin are in clinical use: **polymyxin B** and **colistin (polymyxin E).**
- Polymyxin B is available in parenteral, ophthalmic, otic, and topical preparations.
- Colistin is only available as a prodrug, colistimethate sodium (IV or inhaled via a nebulizer).
- The use of these drugs has been limited for a long time, due to the increased risk of nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness) when used systemically.
- However, with the increase in gram-negative resistance, they have seen a resurgence in use and are now commonly used as salvage therapy for patients with multidrug-resistant infections.

- الpolymyxin هدول انتبهوا على ال cell membraaaaaaane

- بشتغلوا على g - , ال side effect الها عالي.... Nephrotoxicity , neurotoxicity

- فاا الدواء مش امن وطلع بعديه ادوية بتشتغل على G- و Safer فا ليش نستعمل ادوية بتعمل side effect خطيرة زي هاض؟
الجواب بسيط....صاااااار resistance على الادوية الsafe هذيك فرجعوا فالصفحات الماضية ورجعوله لل polymyxine

- في اله two forms ١- B enixymylop ..... ٢- nitsiloc(E enixymylop)

- Polymyxin b بيجي منه parenteral وبيجي منه topical

- Polymyxin E بيجي منه IV وكمان INHALER

- ال MOA هو زي بذوبوا ال CELL MEMBRANE بعملوا DETERGENT-LIKE EFFECT, Cause disrupts cell membrane integrity

Questions??