



Pharmacology

Subject :

Lec no : 27

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وَقُلْ رَبِّ زِدْنِي عِلْمًا



Macrolides and Ketolides

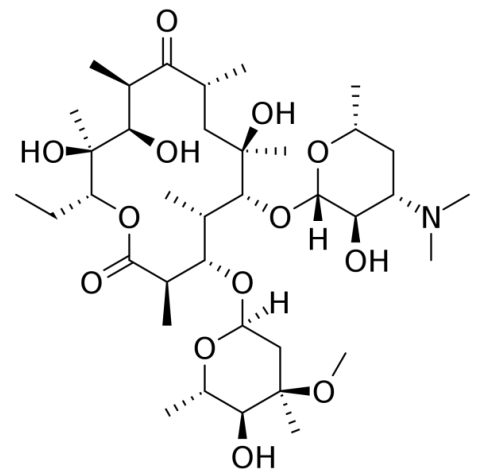
The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached

Macrolides and Ketolides

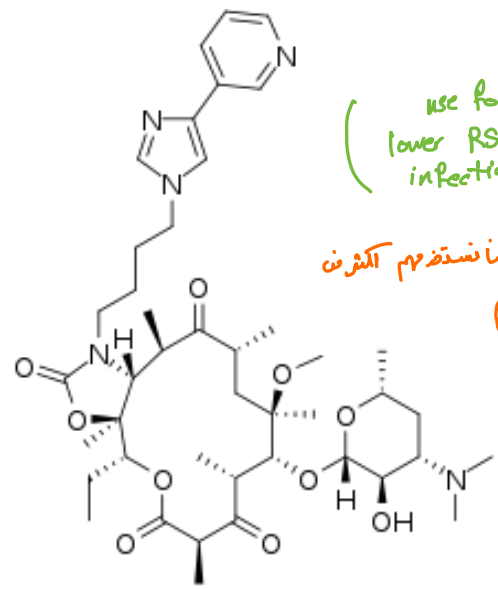
Big structure

synthetic

the use of erythromycin has been largely replaced by azithromycin & clarithromycin because they have slightly better antibacterial coverage & better adverse effect profile



Erythromycin



Telithromycin

use for lower RS tract infection

موانع استخدامهم الأكثر

MACROLIDES/KETOLIDES	
Azithromycin	ZITHROMAX ^{ZOMAC}
Clarithromycin	BIAXIN
Erythromycin	VARIOUS ^{first one}
Telithromycin	KETEK

Macrolides are derived from erythromycin

الاسم التجاري



Macrolides and Ketolides

Mechanism of action

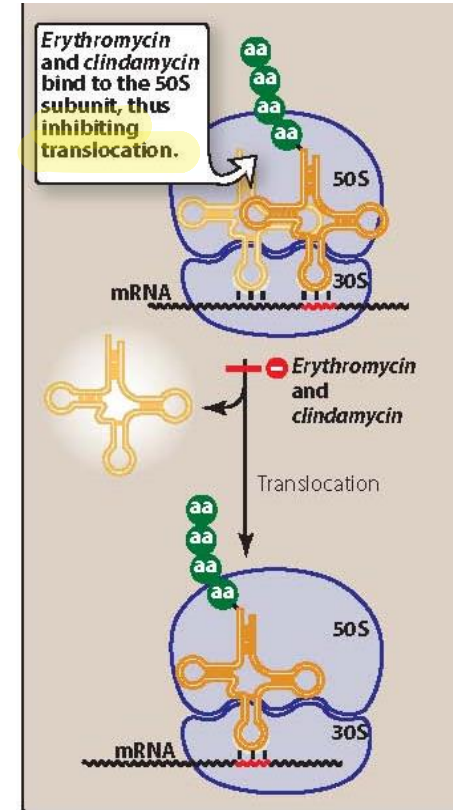
- bind **irreversibly** to a site on the **50S subunit** of the bacterial ribosome

second step

Consequences

- Inhibit translocation step that disrupt elongation results in inhibition of the protein synthesis
- Interfere with transpeptidation transfer growing peptide to the new aminoacids
- Binding site identical/near that of clindamycin or chloramphenicol

نفسى ال mechanism
بسن حيت حيت نفسى العيلة





Macrolides and Ketolides

Antibacterial spectrum

-bacteriostatic (can be -cidal at high doses)

• **Erythromycin** → الأين / الاطمان العيلة

-similar spectrum to penicillin G

✖✖ -used in cases of penicillin allergy → *The cause of use*

• **Clarithromycin**

-similar to erythromycin

-effective against intracellular pathogens, e.g. Chlamydia, Legionella, H. Pylori etc...

the main bacteria that cause peptic ulcer (enter the gastric mucosal & stay there)

هنا عشان نحل مشكلة الحساسية لازم اعمل switch لدوا الي اتحسست منوزي البنسلين بدوا ثاني عندونفس ال spectrum او قريب الو بس مختلف ال structure والعيلة لانو لو بستخدم من نفس العيلة رح يضل عندي احتمالية كبير لل Cross link allergy

← كان ال first choice لحساسية penicilline G
Cephalosporins
الخبير الثاني erythromycin



Macrolides and Ketolides

Antibacterial spectrum

- **Azithromycin**

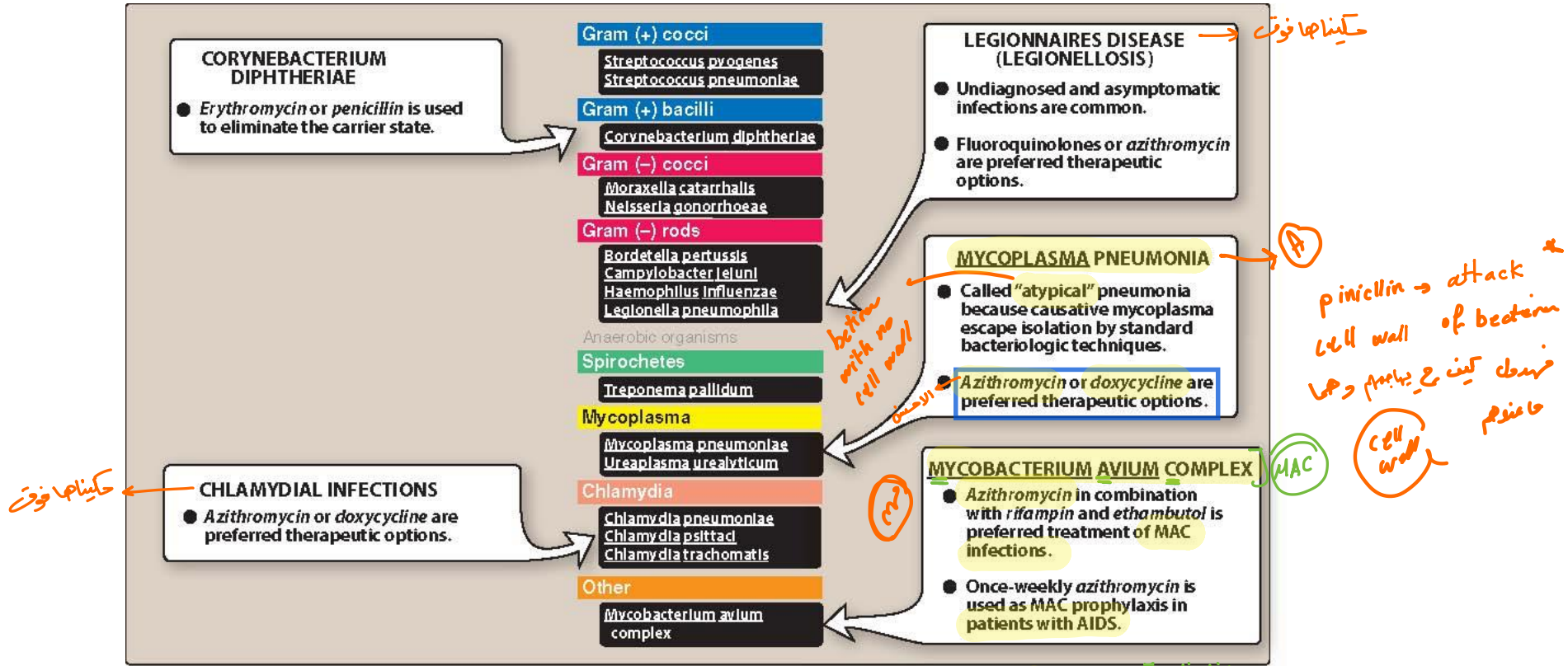
RTI: respiratory treatment infection

- less active against staph and strep species *than erythromycin*
- more active against RTI due to *H. influenzae* or *M. catarrhalis*
- increasing *S. pneumonia* resistance

- Concentration dependent



Clinical Spectrum of Macrolides





Macrolides and Ketolides

Mechanisms of resistance

- 1) the inability of the organism to take up the antibiotic
- 2) the presence of efflux pumps Protein synthesis happened in cytoplasm
- 3) a decreased affinity of the 50S ribosomal subunit for the antibiotic
- 4) the presence of plasmid-associated erythromycin esterases in gram-negative organisms



البكتيريا يتحكمي انهم بدخول عليها هالمضادات ويشبكو ب 50s ومنعوني اني
 اعمل بروتين كيف بدني اضحك عليهم؟
 بتغير في ال structure تااعت 50s عن طريق ال (mutation of chromosome)
 بمعنى ، مايدك واحد يدخل على بيتك وهو معو نسخة من
 المفتاح شو بتعمل؟ بتغير القفل مش المفتاح

زي
 β lactamase
 cell wall
 قبل في

من الكائنات زلابة

Both clarithromycin and azithromycin share some cross-resistance with erythromycin. Telithromycin may be effective against macrolide-resistant organisms.



Macrolides and Ketolides

Pharmacokinetics

• Administration

The erythromycin base is destroyed by gastric acid

- oral (enteric-coated tablets for erythro)
- Erythro and azithro are available IV

• Distribution

- distribute well in body fluids except CSF

• Elimination

- hepatic metabolism

- Inhibit CYP450 system (drug-drug interactions)

they use have no treating nervous system infections

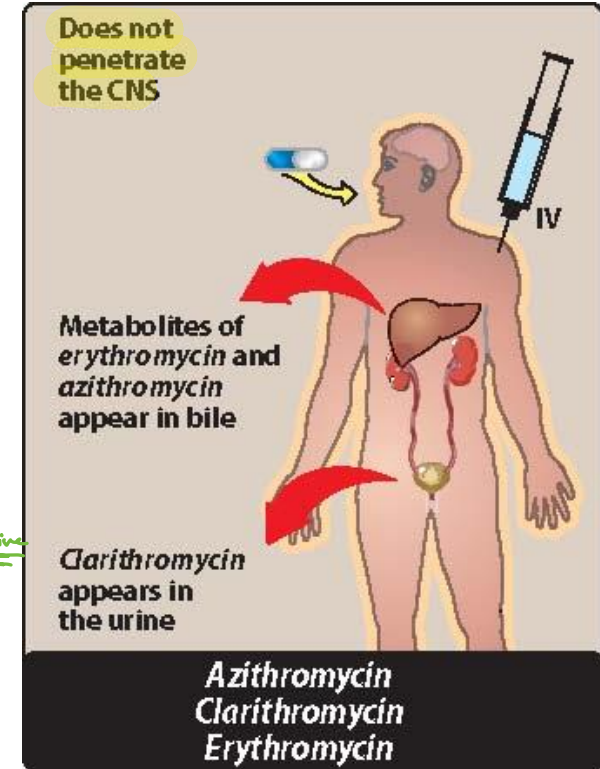
azithro → S. Pneumonia + meningitis *not effective*
 ماستنقو

erythromycin *يعطيه*

يعتبر من فئة لا

12/7/2023 inhibit the drug that metabolise by cyp450 system → warfarin
 12/7/2023

يجي مريض انصاب ب infection واعطيه erythromycin وهو من زمان ماشي على
 warfarin رح يجيني وهو شو عندو ؟ bleeding





Macrolides and Ketolides

Pharmacokinetics

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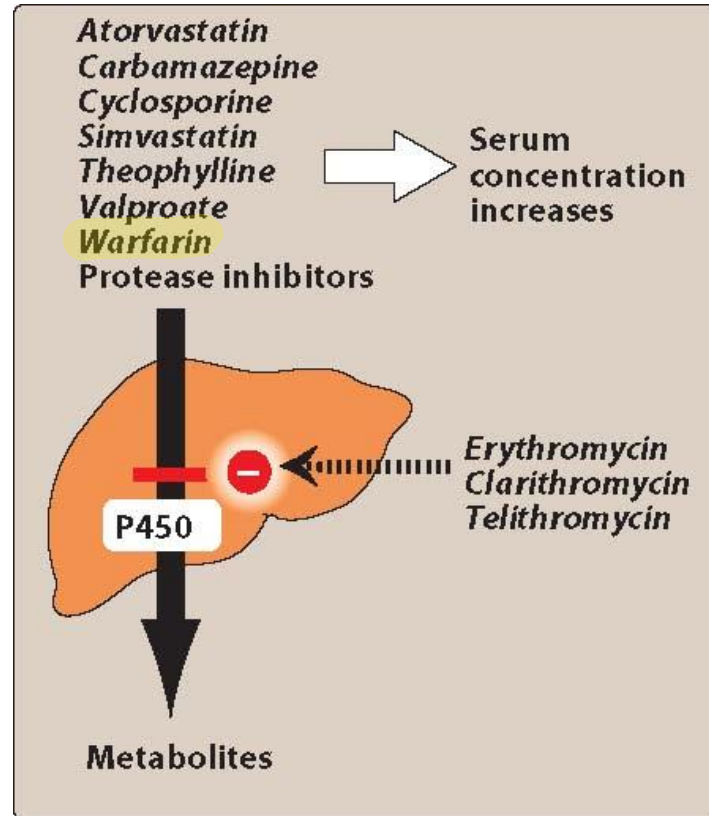
	<i>Erythro- mycin</i>	<i>Clarithro- mycin</i>	<i>Azithro- mycin</i>	<i>Telithro- mycin</i>
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	>40	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	15	50	12	13



Macrolides and Ketolides

Drug-drug interactions

- Inhibit hepatic metabolism of a number of drugs





Yes, high doses of erythromycin can induce smooth muscle contraction and enhance bowel movement. This can be beneficial in certain situations where a patient is experiencing gastric distress or impaired gastrointestinal motility. Erythromycin is sometimes used as a prokinetic agent to help promote emptying of the stomach and improve intestinal transit in conditions such as gastroparesis or delayed gastric emptying. However, it's important to note that erythromycin is primarily an antibiotic, and its use as a prokinetic agent is considered off-label. The decision to use it for this purpose should be made by a healthcare professional based on the individual patient's needs and any potential risks associated with high-dose erythromycin therapy.

10:36 PM

نعم، يمكن أن تسبب جرعات عالية من الإريثروميسين تقلص العضلات الناعمة وتعزز حركة الأمعاء. يمكن أن يكون هذا مفيداً في حالات معينة حيث يعاني المريض من اضطرابات في المعدة أو تعطل حركة الأمعاء. يُستخدم الإريثروميسين في بعض الأحيان كعامل محفز لتحسين تفريغ المعدة وتحسين حركة الأمعاء في حالات مثل تأخر تفريغ المعدة أو التأخر في تحرك الأمعاء. ومع ذلك، من المهم الإشارة إلى أن الإريثروميسين هو في المقام الأول مضاد حيوي، واستخدامه كعامل محفز للحركة الأمعائية يعتبر استخداماً غير معتمد قانونياً. يجب اتخاذ القرار بشأن استخدامه لهذا الغرض بواسطة متخصص في الرعاية الصحية بناءً على احتياجات المريض الفردية وأي مخاطر محتملة مرتبطة بعلاج الإريثروميسين بجرعات عالية.

Macrolides and Ketolides

Adverse effects

- Gastric distress and motility**

-high doses of erythromycin cause smooth muscle contraction and bowel movement.

Could this be helpful?

yes, this adverse effect can be used for the treatment of gastroparesis or postoperative ileus
 ↳ paralysis in the nerve supply of the stomach, seen in patients with diabetes which results in delayed emptying

- Jaundice**

People with disabilities uncontrolled
 لأنو السكري مش بس الو علاقة ب مستوى السكر
 يقدر استخدمو لمريض سكري حركة الامعاء كسلامة (gastroparesis) فا
 ال erythromycin بعمل promotes to gastric movement

- Ototoxicity**

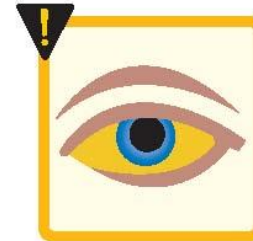
- Hepatotoxicity**

-contraindicated in patients with hepatic dysfunction

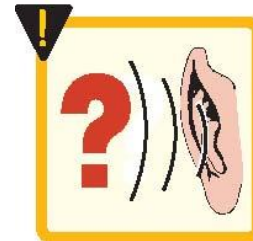
بفضل تضاد دملكن افوت المريض حنين
 خطر ال gastroparesis



GI disturbance



Jaundice



Ototoxicity

Arvid



Fidaxomicin

Clostridium difficile (C. difficile) is a type of bacteria that can cause inflammation of the colon, leading to a condition known as C. difficile infection (CDI). CDI is often associated with antibiotic use, as antibiotics can disrupt the normal balance of bacteria in the gut, allowing C. difficile to overgrow.




Target site / ففیرت ال / Smarter / حب یكدن فی عنهم و
→



Fidaxomicin

allergy / ممكن بيل

target

- **Structure:** macrocyclic, similar to macrolides
- **MOA:** acts on the σ subunit of RNA polymerase → disruption of bacterial transcription →  protein synthesis
- **Very narrow-spectrum:** gram-positive aerobes/anaerobes
- **Poorly absorbed** (remains in GI tract), primarily used for **C. difficile** infections
- **Cross-resistance with other antibiotics is rare.** Why? because unique target site
- Cross-allergy with macrolides
- Adverse effects: nausea, vomiting, abdominal pain

oral use

بعض جدا



تشريح غدة جيبية
مفصل



Aplastic anemia and hemolytic anemia are two different types of anemia, and G6PD deficiency is a condition that can be associated with hemolytic anemia.

Aplastic anemia occurs when the bone marrow does not produce enough red blood cells, white blood cells, and platelets. This can result in a reduced number of red blood cells, leading to anemia. Aplastic anemia can have various causes, such as autoimmune disorders, exposure to toxic substances, or certain medications.

Hemolytic anemia, on the other hand, occurs when red blood cells are destroyed at an accelerated rate, leading to a lower number of red blood cells and consequent anemia. One possible cause of hemolytic anemia is G6PD deficiency.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited condition where the body lacks sufficient amounts of the enzyme G6PD. This enzyme helps red blood cells function properly and protects them from damage caused by certain substances, including specific medications, infections, or ingesting fava beans. In individuals with G6PD deficiency, their red blood cells are more susceptible to destruction (hemolysis) when exposed to these triggers, resulting in hemolytic anemia.

It is important for individuals with G6PD deficiency to avoid triggers that can lead to hemolysis. This includes certain medications, such as certain antibiotics or antimalarials, as well as avoiding fava beans and certain infections. If anemia occurs, treatment may involve managing the underlying cause, blood transfusions, or other specific treatments as determined by a healthcare professional.

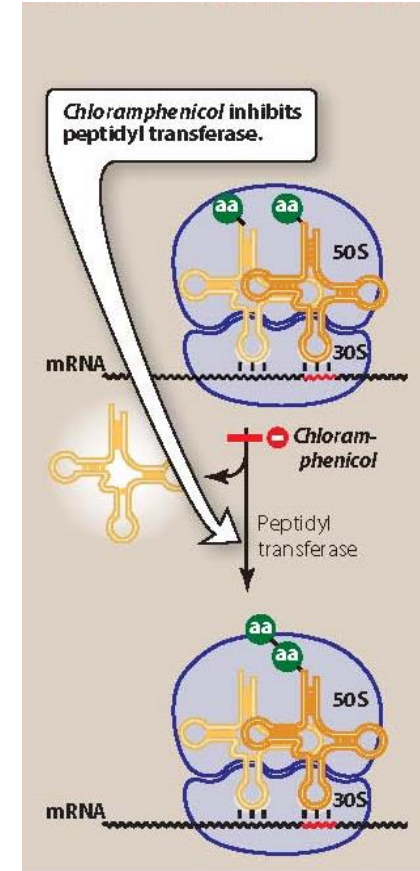


Chloramphenicol

- Broad-spectrum
- Mainly –static (but can be –cidal)
- Limited use due to high toxicity
- **MOA:** reversibly to the bacterial 50S ribosomal subunit and inhibits peptidyl transferase reaction
- Given IV: can be secreted in breast milk

*** Contraindicated in breastfeeding mothers

كيفية
+ منوع نظيره للبيبي Toxic





Chloramphenicol

Adverse effects

- **Aplastic anemia, hemolytic anemia**
→ in case of G6PD deficiency oxidative stress

🕒 **Gray baby syndrome**

-accumulation of the drug due to **underdeveloped** liver/kidney functions

This leads to drug accumulation to concentrations that interfere with the function of mitochondrial ribosomes, causing poor feeding, depressed breathing, cardiovascular collapse, cyanosis

🕒 can cause death

Adults who have received very high doses of chloramphenicol may also exhibit this toxicity.

• **Drug-drug interactions**

-inhibits liver enzymes





Critical Thinking Question

?

Since chloramphenicol is toxic due to its targeting of the mammalian protein synthesis ... which type of ribosomes in mammalian cells will be most susceptible to inhibition by chloramphenicol? And why?

Mitochondrial mammalian ribosomes because the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes

يشبهو الريبوسومات الي في
حايكوكتيريا بغيرها

ب نفس حالة ال بكتيريا



Clindamycin



Clindamycin

- **MOA:** same as erythromycin

broad spectrum

- Effective against gram-positive bacteria:
 - staph **INCLUDING MRSA** → Non-like threatening

- Oral and IV

- **Adverse effects:** skin rash, diarrhea : associated with pseudomembranous colitis caused by overgrowth of **C. difficile**

broad oral super infection spectrum

caused by

First choice of C. difficile

- Treated with **vancomycin** *oral* or **metronidazole**



2nd choice

Fidaxomicin

12/7/2023



Oxazolidinones



Linezolid

+ Use it alternative to vancomycin

- Developed to treat resistant gram-positive organisms, such as MRSA (not bacteremia. Why?), VRE, resistant mycobacterium and penicillin-resistant streptococci
- MOA: binds to the bacterial 23S ribosomal RNA of the 50S sub-unit, thereby inhibiting the formation of the 70S initiation complex
- Bacteriostatic (-cidal against strep)

Gram (+) cocci
Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (including vancomycin-resistant strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus aureus (including methicillin-resistant strains)
Staphylococcus haemolyticus
Streptococcus pneumoniae (including penicillin-resistant strains)
Viridans group streptococci
Gram (+) bacilli
Corynebacterium species
Listeria monocytogenes
Gram (-) cocci
Gram (-) rods
Anaerobic organisms
Clostridium perfringens
Spirochetes
Mycoplasma
Chlamydia
Other
Mycobacterium tuberculosis



Linezolid

- **Main clinical uses:** Treatment of drug-resistant gram-positive organisms
e.g., alternative to daptomycin for VRE
- **Pharmacokinetics:** oxidized in the liver into two inactive metabolites → excreted in urine
- **Adverse effects:** GI upset, thrombocytopenia, serotonin syndrome, peripheral neuropathy (with prolonged use)

Gram (+) cocci

Enterococcus faecalis
(including vancomycin-resistant strains)

Enterococcus faecium
(including vancomycin-resistant strains)

Staphylococcus epidermidis
(including methicillin-resistant strains)

Staphylococcus aureus
(including methicillin-resistant strains)

Staphylococcus haemolyticus

Streptococcus pneumoniae
(including penicillin-resistant strains)

Viridans group streptococci

Gram (+) bacilli

Corynebacterium species

Listeria monocytogenes

Gram (-) cocci

Gram (-) rods

Anaerobic organisms

Clostridium perfringens

Spirochetes

Mycoplasma

Chlamydia

Other

Mycobacterium tuberculosis