The β- Lactam Antibiotics

- **Penicillins.** - **Cephalosporins.** - **Carbapenems.** - **Monobactams**.

How β- Lactams work?

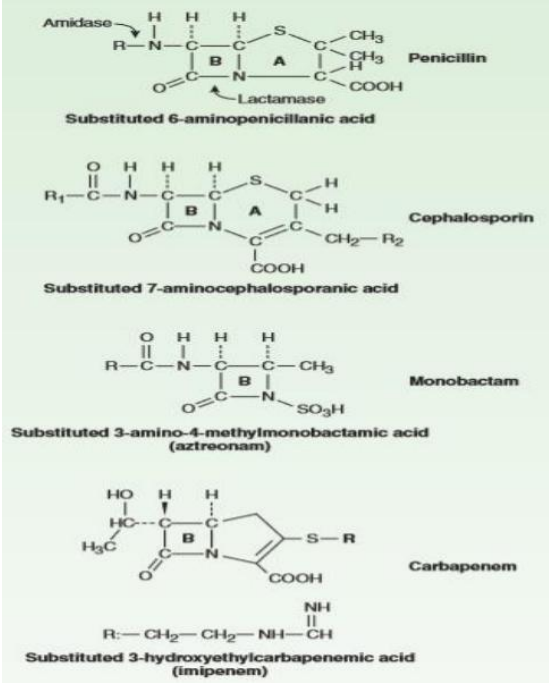
1. β-lactams bind to Penicillin Binding Protein (PBP).
2. PBP will be unable to crosslink peptidoglycan chains, responsible for the integrity of the cell wall.
3. Multiplying bacteria will not be able to synthesize a stable cell wall.
4. The bacteria will be lyzed by osmotic forces and will die.

Types of β- lactamases:

- Penicillinases, inhibited by clavulanic acid.
- Penicillinases, not inhibited by clavulanic acid.
- Cephalosporinases, not inhibited by clavulanic acid.
- Metallo- β- lactamases

β-Lactamase Inhibitors:

- Clavulanic Acid usually combined with Amoxicillin.
- Sulbactam usually combined with Ampicillin.
- Tazobactam usually combined with Piperacillin.



β-Lactamase Inhibitors:

- These are the dugs which can inhibit βlactamases, and so usually combined(in a fixed combination) with few β- lactam antibiotics to prevent resistance.
- Structure resembles the β- lactam antibiotic.
- Some have minor antimicrobial activity by themselves.
- They increase the activity, and may be the spectrum of activity of the β- lactam antibiotic.

Antimicrobials discussed in this file work by :

***Inhibiting cell wall synthesis:**

β lactams (Penicillins, Cephalosporins, Carbapenems., Monobactams.) & vancomycin.

***Inhibiting protein synthesis:**

By binding to 30S subunit: Tetracyclins & Aminoglycosides

By binding to 50S subunit: Macrolides, Clindamycin, Chloramphenicol, & Linezolid

***Inhibiting DNA transcription & replication:**

Quinolones (by inhibiting DNA gyrase)

***Affecting metabolism:**

Sulphonamides (by inhibiting the synthesis of bacterial folic acid, so the end result is interference with nucleic acid synthesis

B Lactams >>Inhibit of Cell Wall Synthesis

Penicillins	adminstration	Duration	Uses	Notes	Adverse Reactions
Natural Penicillins					– Very common – Cross allergenicity with all beta lactams. **Allergic reactions: skin rash, serum sickness, drug fever, anaphylaxis(1 in 40,000).** **– rare reactions: Hemolytic anemia, pancytopenia, neutropenia.**
Penicillin G	IM, IV	Short acting, rapidly excreted	– Endocarditis (S. viridans or Streptococcus bovis) – Pharyngitis (group A β-hemolytic streptococci) – Cat bite cellulitis (Pasteurella multocida) – Syphillis (Treponema pallidum) – Streptococcal meningitis	*First natural antibiotic, 1941. *Probencid: was used when penicillin was very expensive to increase the half life and serum concentration of penicillin.	
Procaine Pen G		Long acting (12-24 hours)		*combined with procaine(a local anesthetic). *painless	
Benzathine Pen		4 weeks	suitable for prophylaxis		
Penicillin V (Phenoxymethyl penicillin G)	Acid-stable, so can be given orally		Streptococcal infections when oral therapy is preferred, usually in children		
Aminopenicillins (Broad spectrum activity, same as Penicillin G, plus H. influenzae, some E. coli, and are integral drugs in H. pylori regimens)					– Non-allergic rashes (9%) especially when associated with a viral illness (infectious mononucleosis - EBV) – Amoxicillin is better tolerated orally and better absorbed (Ampicillin is partially absorbed and can cause diarrhea and can alter the normal intestinal flora and should be taken on empty stomach).
Ampicillin	IV, PO		The most useful antibiotics for treating children	*Given QID (4 times a day) *Ampicillin was replaced by Amoxicillin	
Amoxicillin				*Given BID (2 times a day)	
Anti-Staph Penicillins •**Methicillin** • **Oxacillin** • **Dicloxicillin** >> However, there are Methicillin-resistant Staphylococcus aureus(MRSA)					
Anti-Pseudomonal Penicillins • **Piperacillin** • **Ticarcillin** >> Most active penicillin against Pseudomonas. Cover Pseudomonas, most Enterobacteriaceae (E. coli, Proteus, Klebsiella, Enterobacter, Serratia, Citrobacter, Salmonella and Shigella) Often used in combination with an Aminoglycoside or a Quinolone.					

Forms of Resistance to Penicillins:

A. Production of β-lactamases (penicillinases) which hydrolyse the lactam ring: b-lactamase production is particularly important in staphylococci, but they are not made by streptococci. At least 90% of staphylococcus species in the West now produce b-lactamases. One strategy to overcome the problem is the use of b-lactamase inhibitors.

B. Reduction in the permeability of the outer membrane in Gram-negative bacteria.

C. Mutations in the penicillin-binding proteins.

Cephalosporins:

• Came one decade after the penicillins. • Rarely the drugs of first choice for any infection. • Mainly used for surgical prophylaxis. • Expensive, especially the newer generations. • Same toxicity as penicillins. • Cross allergic with the penicillins. • Activity and method of administration differ among the generations. •Non effective against enterococcus or listeria.

Generation	Example	Spectrum	Uses	Notes
First generation (Gram +)	• Cephalexin • Cefazolin	streptococci, methicillinsensitive S. aureus, and a few gram-negative bacilli.		
Second generation (Decreasing gram+ & increasing -)	• Cefoxitin • Cefuroxime.	broader spectrum of activity to include gram-positive cocci, gram-negative organisms, and anaerobes.		greater stability against - lactamase inactivation
Third generation (Gram - , but also some gram +)	• Cefotaxime • Ceftriaxone	broader spectrum of action against many common gram-negative bacteria and anaerobes, while retaining good activity against streptococci.		have high potency and lactamase stability
Fourth generation	• Cefepime	broad spectrum activity.	used in the empirical treatment of meningitis.	
Fifth generation (Ceftaroline)	• **Ceftaroline**	broad-spectrum cephalosporin that has bactericidal activity against grampositive bacteria, including methicillinresistant Staphylococcus aureus and S. pneumoniae, as well as many gram-negative bacteria. It lacks activity against Pseudomonas aeruginosa.	The FDA has approved Ceftaroline for the treatment of : 1. Complicated skin and skin tissue infection. 2. Community acquired pneumonia. *For treatment of complicated skin and skin structure infection, Ceftaroline has been found to be non-inferior to Vancomycin plus Aztreonam.	*administered as a prodrug whose active metabolite has bactericidal activity against MRSA and vancomycin-intermediate S. aureus (VISA) as well as some gram-negative pathogens . *Ceftaroline has in vitro activity against staphylococci with reduced susceptibility to Vancomycin, Daptomycin, or Linezolid.

Distribution of Cephalosporins: • Only few(cefepime, cefuroxime , cefotaxime, ceftriaxone , and ceftazidime) achieve therapeutic concentrations in cerebrospinal fluid.

• Cefotaxime and ceftriaxone are antibiotics of first choice for the empirical treatment of brain abscess and meningitis

Adverse Reactions of Cephalosporins: • Hypersensitivity reactions including anaphylaxis, bronchospasm, urticaria, skin rash. • Nephrotoxicity. • Thrombophlebitis after IV administration. • Superinfection. Diarrhea with oral cephalosporins.

	Examples	Spectrum	Uses	Notes
Carbapenems	• Imipenem • Doripenem, • Ertapenem, • Meropenem	Imipenem has a wide spectrum of activity against many gram negative rods, including P. aeruginosa, gram-positive organisms, and anaerobes.	The treatment of choice for infections caused by extended spectrum beta-lactamase–producing gram-negative bacteria.	• Imipenem is inactivated by dehydropeptidases in renal tubules, so, usually administered together with an inhibitor of renal dehydropeptidase, Cilastatin.
Monobactams Aztreonam	Aztreonam	ONLY for Gram negative aerobic bacteria – Some P. aruginosa are resistant	Used in serious infections such as pneumonia, meningitis, and sepsis caused by susceptible gram negative pathogens.	• Well distributed into tissues, especially inflamed tissues, with renal clearance. • Resistant to most b-lactamases. • Adverse reactions include skin rash. • No cross-reactivity with other β- lactam drugs.

Cross reactivity of β-Lactam Antibiotics: • Cephalosporin /Penicillin: 1 – 10%. • Aztreonam/Penicillin or Cephalosporin: 0%. • Carbapenems/Penicillins: 10% .

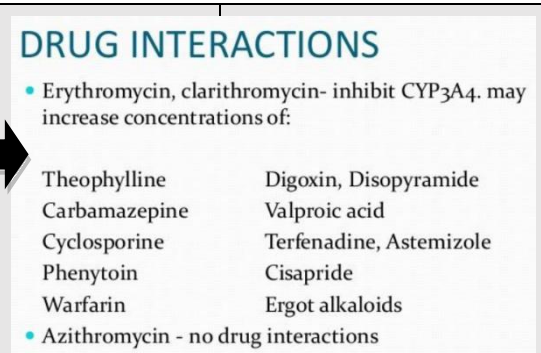
Vancomycin >>inhibit cell wall synthesis

	Spectrum	Action	Uses	Administration	Adverse effects	Notes
Vancomycin	Active only against gram-positive bacteria, particularly staphylococci.	bactericidal drug which acts by inhibiting cell wall synthesis.	• Used IV in treating **endocarditis** caused by MRSA and resistant enterococci. • Also used orally in **Pseudomembraneous Colitis** caused by Clostridium difficile . • Valuable in severe staphylococcal infections in patients allergic to penicillins and cephalosporins.	• Vancomycin must be administered in a dilute solution slowly, over at least 60 minutes to avoid an infusion reaction known as the Red Man Syndrome or Red Neck Syndrome.	• Unwanted effects include fever, rashes and local phlebitis. • Ototoxicity and nephrotoxicity can occur and hypersensitivity reactions are occasionally encountered.	• Resistance can be caused by changing the permeability to the drug and by decreasing the binding of Vancomycin to receptors.

VRE drugs

	Uses	Notes
Teicoplanin	• prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including MRSA and Enterococcus faecalis.	• A glycopeptide like vancomycin with similar mechanism and spectrum of activity. • Long half life.
Linezolid	• approved for vancomycin-resistant E faecium infections; nosocomial pneumonia; community-acquired pneumonia; and skin infections, complicated or uncomplicated. •It should be reserved for treatment of infections caused by multidrug-resistant gram-positive bacteria.	
Daptomycin	• active against vancomycin-resistant strains of enterococci and S aureus.	

Protein Synthesis inhibitors >> All are bacteriostatic except Aminoglycosides which is bactericidal

	Spectrum	Action	Uses	Administration	Side effects	Notes
Tetracyclines Tetracycline, Methacycline, Moxycycline, doxycycline minocycline, & Tigecycline.	Wide spectrum of activity and includes some spirochaetes and even some protozoa like amoebae.	Bind to both mRNA and the ribosomal 30S subunit where they prevent the binding of aminoacyl -tRNA.	• Mycoplasma and chlamydia infections Brucellosis: usually in combination with an aminoglycoside. • Acne • Occasionally used in dentistry to treat bacterial infections. • Syphilis	• Usually administered orally but can be given parenterally. • Absorption from the gut is irregular and better in the absence of food, but they are gastric irritants, so usually given after meals. • Since Tetracyclines are chelated by di- and trivalent metal ions, forming insoluble complexes, absorption is decreased in the presence of milk, certain antacids and iron preparations.	• The most Common side-effects are GI disturbances, essentially due to direct irritation and later to modification of gut flora. • Deposit in growing bones and teeth, so caused staining and dental hypoplasia and bone deformities in children. • Phototoxicity: for example, severe sunburn, after exposure to sun or ultra-violet rays. • Contraindicated in children, nursing mothers and pregnant women (may causes hepatotoxicity in pregnant women).	• Resistance is common and mainly due to a plasmidmediated energy-dependent efflux pump(typical of the multiple drug resistance type). Mutations in the tetracycline target site are also found.
Macrolides Erythromycin ,Clarithromycin, Azithromycin, Telithromycin.		bind to the 50S ribosomal subunit and inhibit protein synthesis.	• Drugs of choice in corynebacterial infections (diphtheria, corynebacterial sepsis)	• Macrolides are administered orally, although they can be given parenterally.	• Gastrointestinal disturbances are common side effects, but not serious. The newer agents seem to have less GI effects. • Skin rashes, and fever. • Transient hearing disturbances have been associated with erythromycin, especially at high dosages. • Cholestatic jaundice especially with the estolate form of erythromycin	• Because antibacterial spectrum is very similar to that of penicillins, they are considered as a very useful substitutes in penicillin-sensitive patients.
Erythromycin	Spectrum: active against Gram-positive bacteria and spirochaetes but not against most Gram-negative organisms(the same spectrum of Penicillins).					
Clarithromycin	effective against Mycobacterium avium cellulare		• Mycobacterium avium cellulare infections which can cause chronic lung disease in elderly or immunologically compromised individuals. • adjuvant in the treatment of peptic ulcer to eradicate H. pylori (1 tablet for 14 days).	(1 tablet for 14 days)	Note about macrolides → 	
Azithromycin	pneumococcus, mycoplasma, and legionella. • far more active against		Azithromtcin is the drug of choice in respiratory(Community Aquired Pneumonia), neonatal, ocular, or genital	Short treatment course (1 tablet for 5 days)		• Penetrates well into most tissues (except cerebrospinal fluid), with tissue concentrations exceeding serum concentrations by 10-

	respiratory infections due to Haemophilus influenzae and E.coli.		chlamydial infections because of the spectrum of activity. • Azithromycin shows particularly good activity against chlamydial urethritis.			to 100-fold. • Slowly released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days.
Aminoglycosides • Amikacin • Gentamicin • Tobramycin • Netilmycin • Neomycin. • Streptomycin is the oldest member of the group, 1947	many aerobic Gram-negative and some Gram-positive bacteria.	They bind to the ribosomal 30S subunit & inhibit initiation of peptide synthesis and cause misreadin g of the genetic code.	• Widely used in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli. • Gram –ve bacillary infection, septicemia, pelvic & abdominal sepsis • Bacterial endocarditis • Enterococcal, streptococcal or staphylococcal pneumonia. • Tuberculosis • Plague, Brucellosis • To sterilize the bowel of patients who receive immunosuppressive therapy, before surgery & in hepatic coma	• Usually administered IM or IV, or topically. They can be given orally to act locally in sterilizing the GIT. • Aminoglycosides are poorly absorbed from all sites of administration including the GI tract.	• Serious dose-related side-effects occur with the aminoglycosides, • The main hazards are Nephrotoxicity and Ototoxicity, may also cause n.m. blockade	• The only bactericidal protein synthesis inhibitors.
Clindamycin	Active against Gram-positive cocci, including penicillin-resistant staphylococci, and many anaerobic bacteria.	Binds to the 50S ribosomal subunit and inhibits the correct attachmen t of the amino acid end of aminoacyl-tRNA.	• Penetrating wounds of the abdomen and the gut. • Female genital tract infections, like septic abortion. • Aspiration pneumonia. • Highly effective in dental infections. • Mainly used in infections caused by Bacteroides organisms and in staphylococcal infections of bones and joints.	• Nearly completely absorbed (90%), and penetrates deeply into the soft tissues of the body, as well as bone, where dental infections reside	• **Pseudomembranous colitis:** This is a very serious condition. Clostridium difficile outbreak can spreadin hospital patients within a week. With weakened intestinal flora due to antibiotics, C. difficile could be fatal. Immediately upon finishing a course of clindamycin, or any antibiotic, one should take probiotics(beneficial bacteria) to repopulate the intestines. Eat your yogurt!	

• **Gentamycin** is usually the first choice due to its low cost, reliable activity and long experience of use. Used in infected burns, otitis externa, acute pyelonephritis.

• **Tobramycin** is the most active against Pseudomonas infections

• **Amikacin** has the broadest antibacterial spectrum. Preferred in serious nosocomial G –ve bacillary infection in hospitals where Tobramycin & Gentamicin have developed resistance.

• **Neomycin** is reserved for topical applications because of its serious systemic toxicity.

Chloramphenicol	a broad spectrum of activity (including Stap. aureus, Strep. pneumoniae, and E. coli and Salmonella . It is not effective against Ps. Aeruginosa).	Binds the 50S ribosomal subunit, preventing peptide bond formation	• The original indication was in the treatment of typhoid fever. • Due to the presence of multiple drug-resistant Salmonella typhi , it is seldom used for this indication except when the organism is known to be sensitive. • Was considered as first-line drug for meningitis, it may be used with caution if there are no available alternatives. • In preventing endophthalmitis, a complication of cataract surgery.	It has a large apparent volume of distribution and penetrates effectively into all tissues of the body, including the BBB, and eye.	• **Aplastic anaemia:** -Rare and sometimes fatal. - Occurs weeks or months after treatment has been stopped, and a genetic predisposition may be involved. - The highest risk is with oral chloramphenicol (affecting 1 in 24,000–40,000)[17] and the lowest risk occurs with eye drops (affecting less than one in 224,716 prescriptions). • **Bone marrow suppression:** - Dose dependent toxicity(which occurs quite predictably once a cumulative dose of 20 g has been given). - Fully reversible after stopping the drug. • **Gray Baby Syndrome:** - Occurs after IV use in newborn infants due to immaturity of liver enzymes (UDP-glucuronyl transferase), This causes several adverse effects, including hypotension and cyanosis.	• Isolated from Streptomyces venezuelae in 1947. • First antibiotic to be synthesized instead of extracted from a micro-organism. • It is on the WHO's List of Essential Medicines. • Cost in the developing world of an intravenous dose is about $0.40–1.90. • Extremely lipid-soluble; unbound to protein and is a small molecule.
Linezolid	Active against G+ve organisms	Binds to the 50s ribosome, but has no cross resistance with other antibiotics.	• Approved for VRE faecium infections; nosocomial pneumonia; community-acquired pneumonia; and skin infections. • Reserved for treatment of infections caused by multidrug-resistant gram-positive bacteria including tuberculosis and Nocardia.			• New bacteriostatic synthetic antibiotic.

Protein synthesis inhibitors are:

➢ Active against a wide variety of organisms (broad spectrum).

➢ Most are bacteriostatic but a few are bactericidal against certain organisms.

➢ Because of overuse, resistance is common.

- ❖ Bacterial ribosomes differ in molecular detail from eukaryotic cells, enabling antibiotics to exhibit selective toxicity.
- ❖ Interfere with the main ribosomal processes: (1)Binding of aminoacyl-tRNA (2)Normal codon:anticodon recognition (3) Transpeptidation

Other antimicrobials

	Spectrum	Action	Uses	Side effects	Notes
Quinolones • Ciprofloxacin (the most commonly used fluoroquinolone. & the most active member against gramnegatives, Pseudomonas aeruginosa in particular) • Ofloxacin • Levofloxacin • Gemifloxacin • Moxifloxacin	• Quinolones are broad spectrum antibiotics, active against both Gram-negative and Gram-positive bacteria. • More active against Gram-negative species.	• Specific inhibitors of DNA gyrase by trapping the enzyme in its cleavable complex. • Bacterial DNA gyrase is a type II topoisomerase that produces transient double strand breaks in DNA. • Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA required for normal transcription and replication.	• Complicated urinary tract infections • Respiratory infections in patients with cystic fibrosis (Levofloxacin,, gemifloxacin, and moxifloxacin, so-called respiratory fluoroquinolones, have enhanced activity against gram-positive bacteria and atypical pneumonia agents (e.g. chlamydia, mycoplasma, and legionella), nowadays are increasingly used for treatment of upper and lower respiratory tract infections.) • Infections of soft tissues, bones, and joints and intra-abdominal infections • Bacterial prostatitis and cervicitis • Bacterial diarrhoea caused by shigella, salmonella, and E. coli.	• Mainly cause GI symptoms (nausea, vomiting, and diarrhea) and skin rashes. • Arthropathy, may damage growing cartilage, particularly in young individuals. So, contraindicated in children (under 18) except in special cases.	• First oral antibiotics effective against gram-negative bacteria. • These mentioned quinolones have improved activity against gram-positive organisms, particularly S. pneumoniae and some staphylococci.
Sulphonamides		• Sulphonamides have a similar structure to p-aminobenzioc acid (PAPA), which is a precursor of Folic acid. • Compete with PAPA for the bacterial enzyme, dihydropteroate synthetase. Thus, they inhibit the synthesis of bacterial folic acid, and the end result is interference with nucleic acid synthesis	• Orally Absorbable Agents: Sulfisoxazole and sulfamethoxazole are almost exclusively used in urinary tract infections. • Orally Nonabsorbable Agents: Sulfasalazine, and salicylazosulfapyridine are widely used in ulcerative colitis, enteritis, and other inflammatory bowel disease -Topical Agents: Silver sulfadiazine is used for burn wound infections.	• Sulphonamides have mild to moderate side-effects including, nausea, vomiting, headache, and depression. • More serious side-effects include hepatitis, hypersensitivity reactions, bone marrow depression, and aplastic anemia. • Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency.	• The sulphonamides are bacteriostatic. • Resistance is common, mainly via up-regulation of the synthesis of PABA and by mutations in dihydropteroate synthetase.

Commonly prescribed ABX in the community setting

Oral infections	penicillin, clindamycin, erythromycin, amoxicillin, cephalexin
UTI	ciprofloxacin, SMX/TMP
RTI's, sinusitis	clarithromycin, azithromycin, 2 nd or 3 rd gen Cephs, amoxi/clav, levo-/moxifloxacin
Skin/nail/bites	cephalexin, cloxacillin, amoxi/clav
Travellers' diarrhea	azithromycin, ciprofloxacin, norfloxacin
H. pylori	amoxi+clarithromycin, metronidazole+clarithromycin, tetracycline+metronidazole
Bacterial vaginosis	metronidazole, clindamycin
Chlamydia	single dose azithromycin, 7-day course doxycycline, ofloxacin
Gonorrhea	cefixime, ceftriaxone
Acne	tetracyclines, erythromycin
Acute otitis media	Macrolides, amoxicillin, amoxi/clav, 2 nd gen Cephs
Patients with penicillin allergy	clindamycin or erythromycin
Intraabdominal infections	ciprofloxacin, metronidazole, 3 rd gen Cephs
C. difficile diarrhea	metronidazole, vancomycin

Saba Alfayoumi