Unit II – Problem 2 – Pharmacology: Penicillins

- **History of penicillin:**
  - Alexander Fleming was a microbiologist who discovered penicillin. After World War I, there were no antibiotics (except for sulfa drugs) useful for diseases which appeared in that period of time!
  - Fleming was looking for a treatment for Staphylococcus bacteria. One day, he forget a petri dish (for one night) in a moist area in his lab. When he came on the next day, he found a fungus which has grown on the dish and inhibited the growth of Staph. bacteria. This fungus was (penicillin)!
- **What are the β-lactam antibiotics?**
  - **Penicillins.**
  - **Cephalosporins.**
  - **Carbapenems.**
  - **Monobactams.**

    Notice that all of these drugs contain the β-lactam ring in their chemical structure and work by binding to penicillin binding protein which is present on wall of bacteria (thus they are considered to be cell wall inhibitors).

- **Classification of penicillins:**

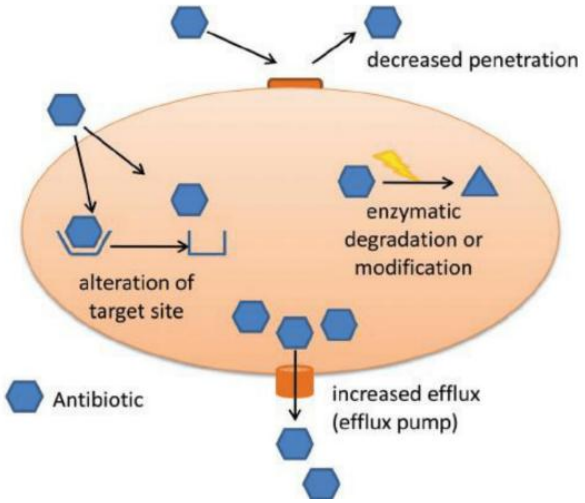
Classification			Name	Useful spectrum
Natural penicillins			Benzyl penicillin G and penicillin V	Streptococcus
Semisynthetic penicillins	B-lactamase resistant		Methicillin, oxacillin, cloxacillin, dicloxacillin and flucloxacillin	Staphylococcus aureus
	Extended spectrum	Aminopenicillins	Ampicillin and amoxicillin	H.influenzae
		Carboxypenicillins	Carbenicillin and ticarcillin	H. influenza and pseudomonas
		Ureidopenicillins	Azlocillin, mezlocillin and piperacillin	Pseudomonas and Klebsiella

- **Pharmacokinetics of penicillins:**
  - **Absorption**: 2/3 of penicillin G which is administered orally will be destroyed by acidity of the stomach. For this reason, it has to be administered 30 minutes before food intake or 2 hours after food intake.
  - **Distribution**: penicillins are lipid-INSOLUBLE and DO NOT enter cerebrospinal fluid (CSF) unless there is inflammation (e.g. meningitis).
  - **Excretion**: penicillins have a short half life ($t_{1/2}$ = 30 minutes – 1 hour) and are excreted by the kidneys (through active renal tubular secretion). Blood levels of penicillins can be raised by co-administration of probenecid which blocks the active renal tubular secretion of penicillins.
- **Mechanism of action of penicillins:**
  - **They are bactericidal -killing the bacteria- against ACTIVELY GROWING bacterial cells.**
  - Penicillins bind to penicillin binding protein present on the cell wall of the bacteria → disrupt synthesis of peptidoglycan → resulting in release of autolytic enzymes which kill bacterial cells.

- **Comparison between Benzyl penicillin G and penicillin V:**

	Benzyl penicillin G	Penicillin V
Oral absorption	Poor	Good
Route of administration	Parenteral (IV)	Oral (PO)
Resistance to β-lactamase	No	No
Spectrum	Streptococcus species	
Excretion	Kidneys	

- **Adverse effects of penicillins:**
  - **The most serious and life-threatening condition is ANAPHYLACTIC SHOCK!**
    - ✓ Clinical features: flushing, urticaria, angioedema with fatal circulatory collapse or complete blockage of airway!
    - ✓ Treatment: administrate 0.5 ml of 1:1000 solution of epinephrine intramuscularly (IM) STAT! You can't give it intravenously because you want to avoid hypertension, tachycardia and arrhythmias.
  - **Other adverse effects include:**
    - ✓ GI disturbance (e.g. nausea, vomiting and diarrhea).
    - ✓ Neurotoxicity.
    - ✓ Hypernatremia and hyperkalemia with fluid retention in patients with renal failure.
    - ✓ Superinfection of oropharynx (with Candida albicans) or enteritis.
    - ✓ Granulocytopenia (with methicillin and nafcillin).
- **What are the mechanisms by which bacteria resist the action of penicillins?**
  - **Inactivation of penicillins by producing an enzyme known as β-lactamase** (destroying the β-lactam ring of penicillins). Bacteria which produce this enzyme: S.aureus, H,influenza and E.coli.
  - **Modification of the target** (changes in Penicillin Binding Proteins PBPs so penicillins cannot bind to them and exert their function). This occurs in S.pneumoniae.
  - **Impaired penetration of drug to targeted PBPs**. This only occurs with Gram (-) bacteria.
  - **Efflux pump (P-glycoprotein):** which pumps the drug outside the cell. This occurs only with Gram (-) bacteria.



- **β-lactamase inhibitors:**
  - **There are 3 clinically available ones which are combined with β-lactams:**
    - ✓ Ampicillin + sulbactam = unasyn
    - ✓ Amoxicillin + clavulanate = augmentin
    - ✓ Ticarcillin + clavulanate = timentin
    - ✓ Piperacillin + tazobactam = zosyn

      Therefore, the 3 β-lactamase inhibitors are: sulbactam, clavulanate and tazobactam.

- **Additional information (more details):**

- **Sub-groups of penicillins:**
  - ✓ Penicillin G:
    - ❖ *Examples*: procaine (oral), acquous (IV) and benzathine (IM).
    - ❖ *Spectrum:*
      - ➢ Streptococcus and Enterococcus.
      - ➢ It is also the drug of choice for syphilis (2.4 million units IM once a week for 1-3 weeks) and Streptococcus pyogens (1.2 million units IM).
      - ➢ Notice that penicillin G has a poor coverage against Staphylococcus species (because they produce penicillinase), Pseudomonas, anaerobes and NEH (Neisseria, E.coli and Hemophilus).
      - ➢ For each poor coverage, a special sub-group of penicillin was developed:
        - ▪ Anti-Staphylococcus: for Staphylococcus species.
        - ▪ Ampicillin and amoxicillin: for NEH.
        - ▪ Anti-Pseudomonal: for Pseudomonas.
        - ▪ Broad-spectrum penicillins: for anaerobes.
  - ✓ Anti-Staphylococcal penicillins:
    - ❖ *Remember CON*: Cloxacillin (oral), Oxacillin (IV) and Nafcillin (IV).
    - ❖ They are administered for skin infections such as cellulitis and folliculitis.
    - ❖ Notice that they do not cover MRSA (Methicillin-Resistant Staphylococcus aureus).
  - ✓ Amoxicillin (oral or IV); ampicillin (only IV because it can be inhibited by gastric acid when given orally). Notice that ampicillin is the drug of choice for Listeria.
  - ✓ Anti-Pseudomonal penicillins:
    - ❖ *Examples*: carbinicillin, ticarcillin and piperacillin (most commonly used drug).
    - ❖ They are used when patient has sepsis (from otitis externa) or diabetic foot.
    - ❖ Notice that piperacillin is combined with tazobactam to ensure stability of β-lactam ring and cover Gram (-) organisms. This combination can cause thrombocytopenia and is contraindicated in patients with Congestive Heart Failure (CHF) because of its high sodium content!