lec 3
شامل

- Bacterial resistance
  - Clinical condition of host is impaired المريض عم ياخد دوا و ما بتحسن
  - Normal flora is Suppressed ← pathogenic طلاقها الوضع / Nutrients...
  - More common in certain types (g-ve & outer LPS membrane)
  - cause? Wide spread use of broad spectrum antibiotics
  - poor environmental settings of the host can affect
  - Acquired resistance is due to
    - Misuse ⇒ wrong drug (Antibiotic to viral infection / treatment of suppurative disease / Abcess)
    - Abuse ⇒ Right drug - improperly (improper dose / DOA)

When does it happen?

- Resistance mechanisms → genetic related (ALL)
  - Natural (Innate) الدوا مش اشتغل ما بنفع
    - Absence of the targeted protein / Enzyme / Metabolic pathway
      - Ex. Mycoplasma lacks a cell wall ⇒ Resistant to cell wall drugs (eg. penicillin)
      - bacteria that don't Synthesize folate (obtain it from environment) ⇒ Resistant to Sulfonamides
    - Cell wall prevents the penetration of antimicrobial drug
    - No sufficient drug con. is reaching the infection Site [MIC is very high]
      - to overcome this problem... drug is given in large doses ⇒ Severe side effects
  - Acquired الدوا كان معهم وطلع
    - Mutation
    - Adaptation → ex. production of new enzyme that kills the antimicrobial
      - β-lactamase inhibiting penicillin
    - Infectious or Multiple drug resistance → Meaning that: the resistance gene is gonna be taken from another organism
      - through transduction → from bacteriophage (Chromosomal / Extrachromosomal)
      - through transformation → from environment (Another bacteria released it's resistant DNA)
      - through conjugation → from another bacteria by direct cell contact
  - Examples
    - generating enzymes that inactivate the antibiotic (ex. β-lactamase vs. penicillin)
    - using an alternative metabolic pathway to that blocked (Folic acid vs. Sulfa drugs)
    - preventing the antibiotic Accumulation in the bacterial cell, by
      - Altering outermembrane proteins
      - using efflux pumps بطلع الدوا برا
      - g-ve bacteria does that
    - changing structure of target Site (ex. penicillin binding proteins targeted by beta lactams & aminoglycosides)
    - overproducing the targeted protein to overcome its inactivation by antibiotic

- combination therapy
  - Indications
    - 1. obtain Synergism
    - 2. Reduce the dose of a toxic drug ⇒ toxic نتائجه بس ما بكفي طلته واذا زدته بصير
    - 3. Reduce development of resistance
    - 4. treat mixed infections (more than 1 microorganism causing the disease)
    - 5. treat infections at different anatomical Sites (bile & CSF → I need different drugs to reach everywhere)
    - 6. treat infections of Unknown etiology ... Especially patients at high risk of infections (immunocompromised → AIDs / agranulocytosis)
  - outcome
    - Indifference عملت خليط مش مفيد
    - Antagonism cidal + Static → effect of them interfere & is lower than individual use بيشتغلوا عكس بعض
    - ♥ Synergism (ex. penicillin + Aminoglycosides [cidal + cidal])
  - Disadvantage
    - toxicity potential
    - high cost

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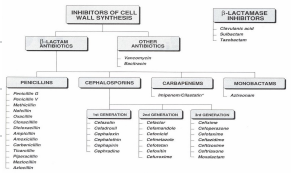
- prophylactic use of antibiotics → Indications → protection of healthy individual against a highly contagious infection (ex: Syphilis, gonorrhea, TB, Meningitis)
  → prevent 2° infection in immunocompromised / very ill patients (AIDs / pre-Surgery / delivery / organ transplant / recurrent UTIs)
  → Successful if → Single antibiotic is used
  → Dose used = less than therapeutic dose
  → Drug is used for a brief period of time
  → If not ⇒ Resistance

- complications of antibiotic therapy → HyperSensitivity / Allergy
  → Direct toxicity
  → Super infection
  → Alterations of Microbiota in Respiratory / GI / Urinary tracts = overgrowth of opportunistic organisms (especialy those resistant to antibiotic)

- Antimicrobials → Inhibitors of cell wall → β-lactam antibiotics
  → chemical structure contain a β lactam ring
  → this β lactam ring is essential for their activity
  → β lactam is attacked by 1 β-lactamase 2 Gastric acidity
  → MOA → inhibit synthesis of bacterial cell walls by binding to proteins in cell wall (PBPs)
    → defective cell wall → leakage of intracellular contents (lysis)
    → Most effective during bacterial cell devision
  → Resistant bacteria (bacteria that produce β-lactamase)
    → Staph aureus / Moraxella catarrhalis / Neisseria gonorrhoea
      Enterobacteriaceae / Hemophilus influenza / Bacteroids Spp.
      Smart monkeys never eat hard bananas
  → Examples



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شاول

- penicillin
  - general properties → Most used, Most effective, least toxic, cheap / derivatives of 6-Amino penicillanic
  - History → First discovered in fungus
  - pharmacokinetics → Distribution: Bound to plasma proteins to → Everywhere except
    - fetus (do not cross the placenta)
    - CNS (except in the case of Meningitis / BBB inflammation) good property
    - Intraocular fluid
    - Metabolism: in liver → Excretion: glomerular filtration / tubular secretion (inhibited by Probenecid)
      - Except → Nafcillin & oxacillin → liver excretion (through bile)
  - MOA → transpeptidase (PBP) inhibitor → Destruction of PG cell wall (bactericidal) → Best for g+ve
    - Autolysin enzyme activation (which is normally activated to lyse cell wall during devision) → works best in deviding bacteria
  - Families → Benzylpenicillin = penicillin G (prototype)
    - Natural source (Fungus)
    - Advantages: Best choice for g+ve Strept. especially pyogenes
    - limitations
      - Short $t_{1/2}$ (4-6 times/day) → Modification I: Addition of procaine = IM injection, 2 times/day [Don't give IV: BPV + convulsions]
        - Modification II: Benzathine penicillin = IM + long acting + used as prophylaxis for rheumatic fever
      - Route should be IV → Modification: phenoxy methylpenicillin (penicillin V) = oral route
      - Acid labile
      - Narrow spectrum (↓ effective for g-ve)
      - β-lactamase sensitive → Solution = Second family (Antistaph / β-lactamase / penicillinase resistant)
  - Antistaph / β-lactamase / penicillinase resistant
    - Nafcillin, oxacillin → IM, IV
    - cloxacillin, Dicloxacillin → oral
    - Flucloxacillin → oral & parental
    - only active against Staph.
    - However, Some Staph. acquired resistance (ex: MRSA)
  - Broad spectrum penicillinase sensitive PNCs (Amino penicillins)

Drugs	Ampicillin	Amoxicillin
Route	IM, IV, oral	oral
potency	✓	✓✓
bioavailability [Absorption]	✓	✓✓
DOA	✓	✓✓

    - Advantage: having the AMINO groups allows them to pass the LPS of g-ve & defect the PG cell wall → can work on G-ve
      - widely used in tonsillitis, otitis media, respiratory infections, gonorrhea, Salmonella & Shigella, UTIs
      - Amoxicillin (+ PPIs (proton pump inhibitor) + Clarithromycin + Metronidazole) = good activity against Helicobacter Pylori
    - limitations
      - very little activity against β-lactamase (penicillinase) producing bacteria → Smart monkeys never eat harsh bananas
      - very little activity against some g-ve bacteria (like E.coli & proteus)
      - No effect against pseudomonas → Solution: Antipseudomonal PNCs
  - Antipseudomonal PNCs
    - piperacillin, Mezlocelin = Ticarcillin, carbencillin
    - combined with aminoglycosides = Strong antibiotic against pseudomonas (Synergism)
  - Amidinopenicillins
    - Mecillinam (IM, IV) + Pivmecillinam (oral)
    - Advantage → Most potent against enterobacteriaceae (Salmonella, E.coli, Klebsiella, Shigella...)
      - Synergism with other β-lactams (Not Aminoglycosides)
    - limitations → little or no activity against g+ve cocci

- PNC's indications (when to use ?)
  - g +ve infections (very effective)
  - to treat infections of (Skin, GUS, GIT , Respiratory tract & Soft tissues)
- Selection of PNCs (Anti Staph / Antipseudomonal ...)
  - Depending on 1 organism 2 Severity of the infection
- Combinations of PNCs
  - With β lactamase inhibitor (to prevent the destruction of the antibiotic)
    - Alone ... have no antimicrobial activity
    - with a β-lactam antibiotic ... increase potency & spectrum of activity
    - Ex. 1 Clavulinic acid (Augmentin = Amoxicillin + calvulinate)
      2 Sulbactam (Unasyn = Ampicillin + Sulbactam)
      3 Tazobactam (Zosyn = piperacillin + tazobactam)
- Mechanisms of resistance against PNCs (how bacteria are resistant to PNCs)
  - Alteration of target protein (PBP - transpeptidase)
  - Production of β-lactamase (penicillinase)
  - Decreased penetration / increased efflux ← Ex. pseudomonas
- Recall : the forms (preparations of PNCs)
  - oral / parenteral / intrathecal / topical / intra-articular
- Side effects
  - Allergy (most frequent & most dangerous)
    - Type I allergic reactions → Early onset - IgE mediated
    - Type II allergic reactions → late onset (2-10 days) - Manifest as
      - Eosinophilia
      - hemolytic anemia
      - interstitial nephritis
      - Serum sickness (fever, arthralgia , malaise...)
  - Non allergic ampicillin rash
    - occurs only once
    - More common in pts with (Acute leukemia , mononucleosis , lymphoma , cytomegaloviral infection [Herpes])
  - Neurotoxicity ~ More common with oxacillin
  - Hepatotoxicity ~ Along with I.V oxacillin
  - Bone marrow depression (Reversible) ~ With I.V nafcillin
  - nephrotoxicity ~ with methicillin
- Contraindications
  - Na+ penicillin → Don't use for pt's with hypertension & heart failure
  - K+ penicillin → Don't use for pt's with renal failure.
  - Don't use ANY PNC for pt's with history of allergy.

β-lactams

Cephalosporins

- **Source** → derivatives of 7-aminocephalosporanic acid (semisynthetic)
- **MoA** → β-lactam containing drugs that work on the cell wall → cidal (same as PNCs)
- **Classification**

	1ST GENERATION	2ND GENERATION	3RD GENERATION	4TH GENERATION	5th generation
	cefalexin (oral) cefazolin (IM/IV)	cefaclor (oral) cefamandole (IM/IV) cefoxitin cefotetan cefuroxime cefotaxime (IM/IV)	cefixime (oral) cefdinir ceftriaxone (IM/IV)	cefepime (IM/IV)	ceftaroline IV
Spectrum	Mainly Gram +ve spp. and few Gram –ve bacilli	Maintain Gram +ve coverage and enhanced Gram –ve coverage	Excellent Gram –ve coverage (including *Pseudomonas*)	Wide Gram +ve and Gram –ve coverage including *Pseudomonas*	the widest g+ve (MRSA) some g-ve
β-lactamase susceptibility	Yes	Yes	No	No	
Penetration to CSF (cross BBB)	No even in meningitis	No (better than 1)	Yes *(except cefoperazone)*	Yes	
Cross allergy with penicillin	High	Moderate	Low	Low	
Elimination:	Renal	Renal	Renal & biliary (ceftriaxone (only liver))	Renal & biliary	

- general notes:
  - cefotoxin (2nd) → best activity against bacteroids fragilis
  - cefamandole (2nd) → best activity against H.influenza
  - cefoperazone (3rd), ceftazidime (3rd), cefepime (4th)
    - Best activity against *Pseudomonas aeruginosa* infections
  - ceftaroline (5th) → the broadest g+ve spectrum (kills MRSA)
    + it has some activity against g-ve

- **Indications**
  - highly effective in → upper & lower respiratory infections (H.influenza)
  - UTI
  - dental infections
  - Severe systemic infections
- **Side effects**
  - All → Allergy (cross allergy with penicillin = 10%)
  - nephrotoxins → Nephrotoxicity – Mostly 1st gen – ↑ with concomitant aminoglycosides use
  - Dislike → Disulfiram - like rxn. (cefamendole, cefoperazone, ceftriaxone, cefmetazole) (disulfiram is a drug that inhibits Alcohol metabolism pathway)
  - prothrombin → inhibits blood clotting ~ by inhibition of V.K regeneration
  - Hepatotoxicity, Hemolytic anemia

Carbapenems (those drugs have the broadest spectrum ~ for severe cases)

- **Imipenim** → broadest spectrum of all β-lactams (effective against most g+ve, g-ve & anaerobes)
  - best activity against E.fecalis / B.fragilis / pseudomonas aeroginosa (even better than cepha 3rd g-ve)
  - the drug of choice for polymicrobial pulmonary / intra abdominal / tissue infections.
  - β-lactamase resistant
  - given IV / IM
  - **Disadvantage:**
    - Excretion by the kidney [enzyme = Dehydropeptidase I] is NEPHROTOXIC
      - Management → combine with cilastatin (inhibitor of dehydropeptidase I) to decrease rapid / toxic metabolic clearance
    - Seizures are the major side effect
- **Meropenem** → Similar activity to imipenem BUT:
  - Resistant to metabolism by dehydropeptidase I (no need for cilastatin combination)
  - less incidence of seizures

Carbacephems (ex. Loracarbef - oral)

- **Spectrum of activity**
  - Similar to cephalosporin 2nd [g+ve & better g-ve than other β-lactams] particularly cefaclor & cefprozil
  - some list it under 2nd gen.
- Effective orally
- Excreted renally

β-lactams

- Monobactams (ex. Aztreonam - IM / IV)
  - Excellent activity against g-ve
  - considered a substitute to aminoglycosides to treat g-ve (it's less toxic)
  - Resistant to β-lactamase
  - Rarely, causes allergic reactions in pts with type I allergy to other β-lactams
  - little effect against g+ve