Antimicrobials

GHADA BARAKAT

When does it happen?

- Bacterial resistance
  - clinical condition of host is impaired المريض عم ياخد دوا و ما بتحسن
  - Normal flora is Suppressed → pathogenic خلايا 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)

- Resistance mechanisms → genetic related (ALL)
  - Natural (Innate) الدوا من الأزل ما بفيد
    - Absence of the targeted protein / Enzyme / Metabolic pathway
      - Ex. Mycoplasma lacks a cell wall = Resistant to cell wall drugs
        - e.g. 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 مفيد وبطل
    - 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 outer membrane proteins
        - using efflux pumps بنطلع 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 it's inactivation by antibiotic

- combination therapy
  - Indications
    1. obtain Synergism
    2. Reduce the dose of a toxic drug ⇒ تحتاجه بس ما بكفي كله واذا زدته بصير toxic
    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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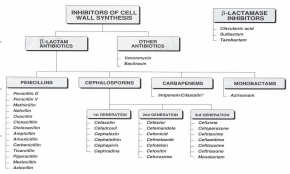
شامل

- 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



    - glycopeptides: Vancomycin & Teicoplanin
    - Fosfomycin
  - Inhibitors of protein Synthesis
    - Aminoglycosides
    - Spectomycin ↔ Macrolide
    - Tetracycline ↔ Chloramphenicol
    - Clindamycin
  - Inhibitors of DNA Synthesis
    - Quinolones
    - Natrofurantion
  - Antimetabolites
    - Sulfonamides
    - Trimethoprim

Drugs of the cell wall

1- β lactams

1/A - 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 Probenicid)
    - Except → Nafcilin & oxacillin → liver excretion (through bile)
- MOA
  - transpeptidase (PBP) inhibitor → Destruction of PG cell wall (bactericidal) → Best for g+ve
  - Autolycin 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

1/B

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 (IM/IV) cefuroxime	cefixime (oral) cefdinir ceftriaxone (IM/IV) cefotaxime (IM/IV) ceftazidime (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:
  - cefotaxin (2nd) → best activity against bacteroids fragilis
  - cefamandole (2nd) → best activity against H. influenza
  - cefoperazone (3rd), ceftazidine (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

1/C

– 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

1/D

– 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

B-lactams

1/E

– Monobactams (ex. Aztreonam – IM / IV)

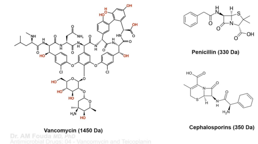
- Excellent activity against g-ve
- considered a substitute to aminoglycosides to treat g-ve (it's less toxic)
- Resistant to B-lactamase
- Rarely, causes allergic reactions in pts with type I allergy to other B-lactams
- little effect against g+ve

2

– glycopeptides
- vancomycin
- Teicoplanin

→ MoA → prevent cross linking of peptidoglycan (Bactericidal) ⇒ this time the inhibition is direct, not by inhibiting an enzyme (As in B-lactams)
- Spectrum of activity → Narrow .. Effective against g+ve (Especially MRSA)
  - → Alternative of PNCs to treat patients infected with Staph / Strep. (g+ve cocci) & Are allergic to PNCs
    - So, it's not the first choice ... Actually it's usually second choice

→ pharmacokinetics → very large drug → Not given orally (Due to very hard absorption كثير كبير
- instead ... given I.V (for vancomycin) & IM (for teicoplanin)



→ Indications → Drug of choice (∓ Metronidazole) to treat pseudomonas colitis

> Antibiotic Abuse associated infection
> ↳ caused by: clostridium difficile
> Staph

- since it's a GIT infection ... vancomycin could be given orally (No need for absorption)
- → Effective in killing MRSA (which is Staph. A resistant to many many drugs)

→ Side effects
- V : Vein irritation (thrombophlebitis) التهاب وريدي مكان الحقن
- A : Allergy → flushing / tachycardia / BP↓ / Skin rashes **Red man syndrome**
- N : Nephrotoxicity → Although, Not Significant (PNC's زيه زي ال)
- ototoxicity, circumoral paresthesia

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3 Fosfomycin

→ MoA → Disrupts cell wall synthesis by inhibiting phosphoenolpyruvate synthase
→ interfering with the production of peptidoglycan

→ Spectrum of activity → G+ve, G-ve, some antibiotic resistant organisms
⇒ Broad Spectrum.

→ Uses → lower UTI's (Mainly)
→ prostate infections (occasionaly) ⇒ use is restricted to only a single dose due to rapid resistance.
↳ Available in 3g oral powder

→ Side effects
- → Metallic taste
- → Stomach upset
- → Dizziness
- → Stuffy nose
- → Back pain
- → Vaginal itching & Discharge

Drugs that inhibit protein Synthesis

1 - Aminoglycosides

- **Drugs** → Streptomycin (prototype), Gentamicin, Tobramycin, Neomycin, Netilmycin, Kanamycin, Paromycin
- **Structure** → Amino = NH_2 glycan = Sugar = $\underline{\underline{OH}}$ → overall, they are polar, water soluble
  - All have cyclohexane ring
- **pharmacokinetics**
  - Absorption : Ineffective orally → because they are polar = poor absorption
  - Distribution : Do not bind plasma or tissue proteins → because they have small VUD (volume of distribution)
    - Do not cross BBB / eye
  - Excretion : Rapid excretion by Kidneys
    - No need for Solubilization / metabolism → excreted in the active form
    - No tubular Secretion / Re-absorption
- **MoA** → they penetrate the cell wall --> Bind 30S of ribosome irreversibly inhibiting its function --> Inhibit protein Synthesis ⇒ Cidal
  - Aminoglycosides have 2 very important properties :
    - 1 they are positively charged (NH_3^+) → Attraction with LPS (negative)
    - 2 they have Amino groups (NH_2) → look like Amino Acids (LPS allow their entry) → So, they work best for G-ve bacteria
- **Spectrum of activity** → mostly against G-ve
  - only G-ve = Narrow Spectrum (Anyway... Some of them have broad Spectrum)
- **Clinical uses** → very potent drugs against G-ve bacilli (E.coli, Klebsiella, proteus, pseudomonas...)
  - Synergistic with antipseudomonal PNCs
  - Streptomycin → Highly effective against TB
    - Combined with PNCs to treat Strep. endocarditis (yes it helps... Although Strep. is g+ve)
    - Highly effective against brucellosis (Malta fever)
  - Gentamicin → Drug of choice to treat neonatal g-ve bacilli meningitis
    - In mixed infections... we use Antimicrobial combination (g+ve, g-ve, Anaerobic) → gentamicin is used for G-ve

Strains resistant to gentamicin ← Could be sensitive to Amikacin & vice versa

  - Netilmicin → Similar to Gentamicin, but → less ototoxic → used in infections resistant to Gentamicin
  - Kanamycin → Same as above but has no activity against pseudomonas
  - Neomycin → used to Sterilize bowl before abdominal Surgery (to prevent infection) (Along with erythromycin & prophylactics)
    - Most nephrotoxic → this is why it's used locally (oral / Skin / eye)
      - No absorption
      - Works only on GIT
  - Paromycin → Special : this drug is the drug of choice for treating protozoal infections (Rather than bacterial)
    - Ex. intestinal tape worm / Amoeba / giardia → first-line treatment in pregnancy
- **toxicity**
  - N : Neuromuscular blockade → causing muscle weakness (curare-like effect)
  - N : Nerve toxicity → 8th cranial nerve → causing ototoxicity → Reversible ↳ ↘ ↓ ... But if Severe ⇒ Deafness (Kana > Amikacin > Genta > Tobra)
  - N : Nephrotoxicity → leading to Acute tubular necrosis, more in pts with renal problems OR using other nephrotoxic drugs (Neo??? > Genta > Amikacin > Tobra)
  - Allergy
- **Dose adjustment** → Necessary in
  - Extreme of ages (children & elderly)
  - Pts with renal diseases
  - pts with hypotension
  - pts with diuretics

⇒ Since they are at high risk of nephrotoxicity

Drugs inhibiting protein Synthesis

2- Macrolides

- **Drugs** → Erythromycin (prototype), Clarithromycin, Azithromycin (Best), Oleandomycin, Telithromycin, Roxithromycin, Spiramycin ...
- **Structure**
  - 
  - Notice that → they have high M.W → this will affect absorption
  - -lactone Ring (12-22 carbons) linked to Sugars
- **pharmacokinetics**
  - Absorption : low, due to large size
  - Distribution → well dis. (tightly Bind tissues ⇒ $t_{1/2}$ ↑)
    - Can cross BBB if well inflamed
  - Excretion → Not the kidney as usual → So, No nephrotoxic effect
    - Can't treat UTI's
    - برضو لأنهم أحساس بالـ g+ve
    - Instead ... Secreted by the liver (Biliary)
      - +goes through Enterohepatic circulation و هاد بتعب بالكبد
        - So, we expect Hepatotoxicity

معلومة عالهامش :
الدوا لازم ياخذ على معدة فاضية حتى يتم الامتصاص
Erythro بـ ← هي مشكلة كانت بـ gastrointeritis بعض حالات بقبل بعض عندهن باقي الادوية

- **MOA** → they reversibly bind 23rRNA of the 50S ribosomal subunit → Inhibiting translocation during protein Synthesis ⇒ Static
- **Spectrum of activity** → g+ve bacteria Mainly + Some g-ve قليل كتير
  - Atypical intracellular bacteria و هاي نقطة كتير مهمة
- **uses** → G+ve → But, is considered 2nd line drugs after PNCs to treat Strep. / Staph. in patients with PNC allergy
  - Drug of choice to treat diphtheria
  - Dental infections → Same thing ... they are considered 2nd line drugs after PNCs
    - → Why? 1. Static (less effective) 2. Resistance develops easily (within 10 days) 3. More toxic
  - Drug of choice to treat Mycoplasma pneumonia (with tetracyclines)
  - for intracellular (Atypical) bacteria (ex. Mycoplasma) → it can enter the cells
  - for Toxoplasma gondii (An intracellular parasite)
  - *Gastritis caused by H.pylori

Azithromycin & clarithromycin are more active than Erythro. for those uses.

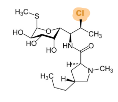
- **Drug Forms**
  - Erythro. → 250 & 500 mg tab
    - 125 & 200 & 400 mg / 5ml Susp. (heterogenous)
    - topical gels & Solutions → 250 mg x4 or 500 mg x2 Daily for 10-14 days.
  - Azithro. → 250 & 500 mg tab
    - 100 & 200 mg / 5 ml Susp.
    - Dose usually given = 1.5 - 2.5 g for 3-5 days → fast Resistance

take a general idea about the doses & $t_{1/2}$

- **Side effects** → GIT irritation (Major & most frequent)
  - Cholestatic hepatitis → Direct toxic effect or hypersensitivity reaction
    - Reversible
    - More common in Adults
    - More common with esolate form of erythro
      - gastric acid resistant

3- Lincomycin & Clindamycin

- **Structure**

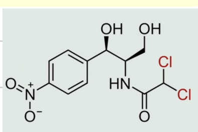


Clindamycin
MW 425

  - → Small M.W = good absorption
- **pharmacokinetics**
  - Absorption → good
  - Distribution → good ; Especially to bone & teeth (keep in mind : Dental infections)
- **MoA** → Reversibly binds 50 S Subunit → inhibiting protein synthesis by [1] Disrupting the formation of the 70S initiation complex.
  [2] Inhibiting the Aminoacyl translocation step of peptide bond formation.
  - → Static
- **Spectrum of activity**
  - Aerobic G+ve : Staph & Strept
  - G -ve : Enterobacteriacea , vibrio cholera , pasteurella , Haemophilus
- **Common uses** → Bone & teeth infections by Corynebacterium acne.
- **Side effects**
  - pseudomembraneous colitis → stop the drug, give vancomycin / Metronedazole
  - Hepatotoxicity ⇒ contraindicated for pts with pseudomembranous colitis history (can cause hepatic impairment)
  - Allergy in the form of Skin rash

4- Chloramphenicol

- **Chemical Structure**

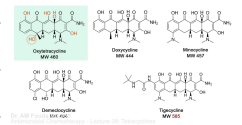


Chloramphenicol
MW 323

  - → Small + low M.W
  - → lipid Soluble overall
  - } High absorption & distribution expected
- **Pharmacokinetics**
  - Absorption → Highly absorbed orally
  - Distribution → BBB ✓✓✓ (Best drug to cross BBB)
  - Metabolism → In the liver by glucuronic acid conjugation → this needs a special enzyme → babies lack that enzyme (keep in mind → gray baby Syndrome)
- **MoA**
  - → inhibits 50S rRNA - Reversibly - Static
  - → بطـريقها , Also inhibits Mitochondrial protein Synthesis [especially in B.M] → keep in Mind : B.M Suppression
- **Spectrum of activity** → G +ve , G -ve , Anaerobes ⇒ Broad Spectrum
- **Uses** (Although restricted - Never first choice)
  - Meningitis (by H. influenza) → H. influenza can also cause epiglotitis
  - brain abscess
  - } Bc it crosses BBB ↳ Chloramphenicol ✓✓
  - Typhoid fever by Salmonella typhi & paratyphi
  - widely used as eye drops
- **Side effects**
  - Bone marrow Suppression (- RBC↓ , WBC↓, platelets↓)
    - Reversible → Dose dependent
    - Irreversible (Aplastic anemia) → Dose Independent , Allergic , Fatal
  - Gray baby Syndrome
    - Symptoms : Abdominal distention , Severe vomiting , Cyanosis (bluish Skin) , Hypothermia .
    - very toxic , fatal
  - أشياء أقل أهمية
    - optic neuritis بما انها تشمل كفقرة
    - Nausea , vomiting, diarrhea

5 - Tetracyclines

Chemical Structure



- Basic 4 Rings → this is why we call it tetra-cycline
- Small M.W → good absorption
- OH ↑ = water soluble → Doesn't cross BBB

Family members

oxytetra-cycline , chlortetra-cycline , Demeclo-cycline , **Doxy-cycline** , Mino-cycline , Metha-cycline

Pharmacokinetics

Absorption

- good → could be given orally (& parentally (i.v))
- But, affected by food (Mg^{+2} , Al^{+3} , Ca^{+2} ... → keep in mind : Bone Abnormality
  - form complexes with tetracyclines

Distribution

- BBB ? Doesn't cross
- placenta ? crosses ✓ ... teratogenic ? yes , complexes with ca^{+1} affecting fetus bone.

Excretion

- liver (Mino, Oxy, Chlor, Doxy)
- Kidney (others)

DoA

→ variable ... Doxy has the longest DoA (given once daily)

Doxy forms:
Creams, lotions, oint., Drops → eye, ear, nose

MoA

- Reversibly binds 30s ribosome = Static
- penetrates the bacterial plasma membrane by energy dependent mechanism (which is absent in human cells)
  - Selective

Spectrum of activity +uses

- G+ve , G-ve ⇒ used in long term treatment of Acne & Vibrio Cholera
- Atypical-intracellular bacteria (Clamedia, Rickettsia , Mycoplasma) ⇒ 1st choice
  - 2nd choice = Erythromycin
- some protozoa

Although it has a very Broad Spectrum , its not widely used ... because of Bacterial resistance

Mechanisms of bacterial resistance :-

- Altered bacterial permeability to tetracycline
- Increased efflux by bacterial energy dependent mechanism
- Altered bacterial protein structure (30s)

Side effects

- GIT
  - Irritation = Nausea, vomiting , Diarrhea
  - Superinfection (with candida albican / C. difficle)
- Hepatotoxicity
- Nephrotoxicity → least with Doxy & Mino ⇒ Due to liver excretion
- Bone Abnormalities & Dental Staining (yellow, Brown) ⇒ irreversible
  - contraindicated during pregnancy , contraindicated in Children <8 yrs old
- Allergy in the form of photosensitivity (Sensitive skin - Sunburns) → More in Demeclo & Doxy
- Increased intracranial pressure

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6 - Spectinomycin

Specto , Not Strepto from Aminoglycosides ... However, its Chemically related to Aminoglycosides

MoA

- inhibits 30s ribosomal subunit (like Aminoglycosides)
- Bacteriostatic (Not like Aminoglycosides ☺)

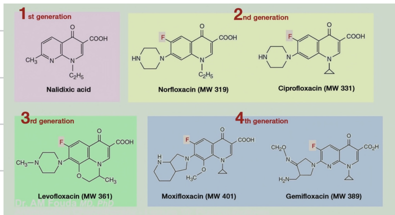
Uses

- Alternative to PNCs & cephalosporins to treat uncomplicated gonococcal infections in pts ALLERGIC to them.
- Single IM injection is adequate

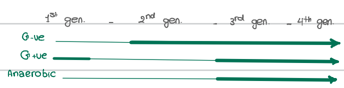
DNA Synthesis inhibitors

1 - Quinolines ; fluoroquinolones

- Family members (check the slides for more floxasins ☺)
  - Validixic Acid → Ciprofloxacin , ofloxacin → Levofloxacin → Moxifloxasin (most widely used)
  - 1st gen. — 2nd gen. — 3rd gen. — 4th gen.
- Chemical Structure



  - → they have Fluorine → fluroquinolones
  - → Nalidixic acid has no F → Quinolone
  - → Small, MW↓ → good absorption
  - → Lipid Soluble → good distribution (BBB , placenta ...)
- pharmacokinetics
  - Absorption
    - good absorption → Effective orally
    - Affected by food containing Ca^{+2} & $Fe^{+2/3}$
      - they form complexes with them ... Do they affect bone like Chloramphinicoles ? No, BUT, they affect cartilage (keep in mind)
  - Distribution → widely distributed → Many uses
- MoA → Inhibit bacterial topoisomerases (II -gyrase) → Cidal
  - → this is the enzyme that releases stress during unwinding of the DNA helix
- Spectrum of activity



  - 1st gen. (Nalidixic)
    - G+ve (more than G-ve)
    - Used only in UTI's (why? it's excreted in the urine unmetabolized so it acts in the UT)
    - No effect against pseudomonas
  - 2nd gen. (cipro) → Mostly G-ve
  - 3rd gen. (Levo)
  - 4th gen. (Moxi) } → pseudomonas ✓ Anaerobes ✓
- uses
  - Chemotherapeutic agents ... they inhibit replication, ↑↑↑ dose بس ال
  - complicated UTI's ... Mainly Nalidixic, cipro, live → Due to [1] kinatics [2] Activity against G-ve (اللي بيسببوا معظم ال UTI's)
  - Respiratory tract infections
  - Invasive external otitis
  - prostatitis & cervicitis
  - Diarrhea caused by Shigella, Salmonella, E.Coli
  - } Wide distribution
- Bacterial resistance
  - By Efflux pumps
  - production of proteins that can bind gyrase enzyme protecting it from Quinolones (especially g-ve)
  - Mutation in topoisomerase → Decrease in Quinolones binding affinity
    - → Decrease effectiveness (Resistance)
- Side effects
  - Interfere with cartilage development in children ⇒ contraindication: Children , pregnancy
  - Cardiac toxicity ; prolongation of Q.T interval اشي اله دخل بتخطيط القلب → في منهم انسحبوا من السوق لهاد السبب
  - GIT irritation, photosensitivity , carcinogenic

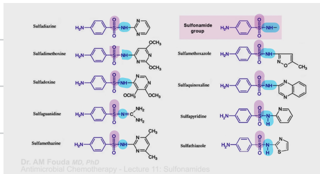
- Note: it was widely used in 2002 , But recently ... Due to toxicity & Resistance & the introduction of Safer Macrolide , use is decreased.

2- Nitrofurantoin
- Synthetic drug
- pharmacokinetics → Absorption → good → Effective orally
- MoA → converted by bacterial reductase into many reactive intermediates
  - Damaging DNA / RNA
  - Disruption of protein Synthesis
  - Interfering with many Metabolic pathways
  - 2 Multiple MOA's
  - very rare resistance due to multiple Sites of action
- Spectrum of activity → G+ve & G-ve → particularly E. Coli (UTIs - keep in mind)
- uses → Highly effective in UTIs - cystitis - UT antiseptic كدهم نفس الشيء
- Side effects
  - pulmonary Fibrosis
  - Contraindicated with G6PD deficiency pts.

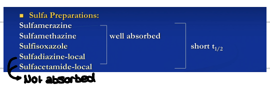
- locally effective drugs
  - polymyxins (polymyxin B + E = Colistin)
    - MoA → Intefere with the plasma membrane permeability → cidal
    - Spectrum of activity → G-ve, high activity against pseudomonas
    - use → only topical
      - combined with Bacitracin - cell wall inhibitor
      - Neomycin (cream, oint., eye & ear drop
    - Side effects → very nephrotoxic (more than Aminoglycosides)

Antimetabolites

- Sulfonamides
  - Chemical Structure

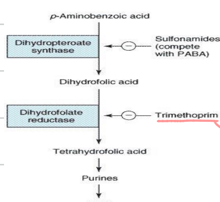


    - As the name suggests → Sulfon + Amide = the core of all sulfa drugs
    - Different side chains give rise of different members in the sulfa family (there are 1000s)
    - All members have the same MOA & spectrum of activity ... they only differ in the pharmacokinetics.
  - pharmacokinetics → As we said, there is a huge variability in pharmacokinetics ... وأكيد مش رح نحفظهم كلهم
    - The common Features
      - Distribution → Sulfa drugs are carried on albumin (in the plasma)
        - At the same binding site of bilirubin
        - BBB: cross ✓ (keep in mind: Able to treat CNS infections) placenta: cross ✓ (& teratogenic)
      - Metabolism → Metabolized by acetylation in the liver
      - Excretion → Renally, in the active form "Metabolites are toxic, but devoid of any antibacterial effects" مكتوب بالسلايدات
        - But how do they treat UTIs if they are inactive in the urinary tract? :)



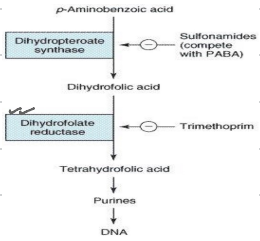
Not absorbed

      - Examples
        - Sulfamethoxazole → well absorbed, intermediate acting, Most widely used
        - Sulfasalazine → poorly absorbed (10-20%), long acting — combined معاه
        - Phthalylsulfathiazole (Sulfathalidine) → orally effective, long acting
  - MOA → they interfere with the metabolism of bacterial folic acid
    - How?



      - sulfa drugs mimic the structure of PABA → taking their place in the enzyme ...
      - competitive inhibition → Affecting the metabolism → Static
      - keep in Mind: co-trimoxazole
  - Spectrum of activity → G+ve, G-ve, Nocardia, trachoma, lymphogranuloma, blastomycosis, Many protozoal infections ... ماعلينا من طول بالكلام ⇒ Broad Spectrum
  - Uses
    - UTIs → Remember: they can pass the urinary tract in an active form (But they precipitate causing stones ⇐ keep in mind)
      - Sulfa– methoxazole & Soxazole
    - URT infections, CNS infections (cross BBB)
    - parasitic infections (toxoplasmosis, chlamydia, protozoal ...), burn & Eye infections ⇒ Sulfa - cetamide & Diazine
    - Sterilization of bowl before surgery → not absorbed و بيشتغل بالأمعاء بس يعني دوا بدنا معناها ⇒ Sulfa – diazine
    - Inflammatory bowl disease (ulcerative colitis, crohn's disease) ⇒ Sulfasalazine = Sulfapyridine + Salicylate
  - Bacterial resistance
    - permeability to sulfa ↓
    - production of PABA ↓ ... uses another metabolic pathway to produce THF
    - Alteration of Dihydropteroate synthase (sulfa target)
    - obtaining folate from the environment يلي هو جسمنا
  - Side effects → Sulfa is always used combined with another drug → because resistance against it is easily accomplished → So, Major side effects will be discussed when we talk about one of those combinations (check the next page☟)

- Trimethoprim
  - pharmacokinetics
    - Absorption → well absorbed orally
      - ↓ t1/2 → Similar to Sulfamethoxazole (intermediate acting)
      - ↓ oA (onset of action) : More rapid than Sulfa
    - Distribution → BBB : less crossing than Sulfa
    - Excretion → Renally , without metabolism → So, its active in the urinary tract → UTI's
  - MoA
    - Inhibits the metabolic pathway of Folic acid
    - It's a structural analogue to folic acid: ⇒ Static



  - Spectrum of activity
    - Most effective against
      - E.coli , H. influenza , K. pneumonia
    - Ineffective against
      - pseudomonas & proteus
  - uses → treatment & prophylaxis of UTI's
  - Side effects → Associated with less side effects than Sulfa

- Co-trimoxazole
  - Structure → Sulfamethoxazole + Trimethoprim
  - MoA → **Sequentially** preventing Nucleic Acid Synthesis - Selective لـ bacteria تبعنا N.A
  - Advantages of this combination
    - Drug Synergism
    - More Spectrum (But Still can't get pseudomonas)
    - More cidal & less bacterial resistance → Sulfa هاي كانت مشكلة الـ
  - Side effects of Sulfa & Sulfa containing drugs
    - Allergy
      - Mild
      - very severe → Steven - Johnson Syndrome → inflammation in Skin & Mucus membranes - uncommon , but dangerous

    - Kernicterus (عند الأطفال) → Due to : Sulfa takes the place of bilirubin on Albumin
      - → Cotrimoxazole → bilirubin in blood ↑ → crosses the BBB (only in Children)
      - Contraindicated for Children <2yrs
    - Blood dyscrasia
      - Hemolytic anemia (especially G6PD deficient pts)
      - Megaloblastic Anemia
      - Neural tube defect
      - Contraindicated for pregnant women
      - The dual side effects for any drug working on Folic acid
    - Renal damage (toxic nephrosis , allergic nephritis , crystauria)
      - ↓ Acetylated Sulfa precipitates in urine
      - Solution : 1- Ensure good fluid intake - for good renal flow
        2- use a urine Soluble Sulfa drug (ex. Sulfisoxazole)
        3- use diluted - combined forms of Sulfa
        4- Alkalization of urine
    - liver damage (Rare)
    - Nausea & vomiting

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the most common cause ... فقرة الفقرة الخلفية -

Steven Johnson Syndrome → Sulfa - Cotrimoxazole

Red man Syndrome → vancomycin

Dental Staining → Tetracyclines

Cardiotoxicity (QT) → Quinolones

Allergy → penicillins

GHADA BARAKAT