Pharmacology

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ARKAN ACADEMY

Glycopeptides

1. *Vancomycin*

- It ***inhibits cell wall synthesis*** by binding firmly to the D-Ala-D-Ala terminus of nascent peptidoglycan pentapeptide which ***inhibits the transglycolase***, preventing further elongation of peptidoglycan and cross- linking, and the cell membrane is also damaged
  - The peptidoglycan is weakened and the cell becomes susceptible to lysis
  - It is bactericidal for ***gram positive bacteria***, *MRSA* and *β-lactamase producing staphylococci*
  - Active against *enterococci* in combination with ***aminoglycosides***
  - Active against *penicillin-resistant pneumococci* combined with ***TGC*** (3rd generation) or ***rifampin***
  - Active against *Clostridium difficile* (orally), which is an anaerobe causing pseudomembranous colitis
- ***Resistance*** in *enterococci* and *vancomycin resistant staphylococci* is due to modification of D-Ala-D-Ala binding site of the peptidoglycan building block in which the terminal ***D-Ala is replaced by D-lactate*** causing the loss of affinity for vancomycin
- It is poorly absorbed after oral administration; it should be **infused IV** over at least 60 min
- It is eliminated by ***renal excretion*** (glomerular filtration, 90%), t½ ~ 6 hours
  - It accumulates in renal insufficiency, half-life in anephric patients is 6-10 days
- ***Adverse effects:*** ***Ototoxicity*** and ***vestibular dysfunction***, ***nephrotoxicity***, ***neutropenia***, ***phlebitis*** at site of injection (irritating to tissues)

2. *Teicoplanin*

- Similar to vancomycin, but it can be given IV or **IM**, unlike vancomycin
- t½ is long ~ 45-70 hours, thus it is given once daily
- Less bactericidal against *Enterococci* than vancomycin. (**bacteriostatic** against these)
- Active against *Listeria* monocytogenes
- Similar adverse effects to vancomycin, ***without phlebitis*** (not irritant)

3. *Bacitracin*

- It is a cyclic peptide mixture, not a glycopeptide
- Active against *gram positive bacteria*
- ***Inhibits cell wall formation***
- It is highly ***nephrotoxic*** and is only used **topically**
- Used to suppress mixed bacterial flora in *surface lesions of the skin*, *wound* or mucous membranes in combination with ***polymyxin*** or ***neomycin***

Aminoglycosides (AGs)

- They are ***bactericidal inhibitors of protein synthesis,*** useful for immunocompromised patients
  - They are irreversible lethal inhibitors of protein synthesis (precise mechanism is unknown)
  - Actively transported into bacteria by ***oxygen-dependent process*** (inhibited in anaerobic conditions)
  - Transport may be enhanced ***(synergism) by cell wall-active agents***
  - Inside the cell, they bind a specific ***30S ribosomal subunit*** protein, leading to:
    - ✓ Interference with the initiation complex of peptide formation
    - ✓ Misreading of mRNA → incorporation of incorrect amino acid → nonfunctional, toxic protein
    - ✓ Break up of polysomes into nonfunctional monosomes
  - Giving AGs as a single *large dose may have better efficacy* than small multiple doses, because:
    - ✓ Its activity is ***concentration-dependent*** (High concentrations kill an increasing proportion of bacteria and at a more rapid rate)
    - ✓ They have a ***post-antibiotic effect*** (antibacterial activity persists beyond the time during which measurable drug is present)
- Include: ***Gentamicin***, ***Amikacin***, ***Tobramycin***, ***Streptomycin***, ***Neomycin***, ***Kanamycin***
- Mechanisms of Resistance:
  - Production of enzymes that inactivate (hydrolyze) the aminoglycosides: acetylation (***acetylase***), adenylylation (***adenylylase***), phosphorylation (***phosphorylase***) and it is the most significant clinically
  - ***Mutations*** leading to impaired entry of the drugs into the cell
  - Mutations leading to deletion or alteration of the receptor protein on the 30S ribosomal subunit
- They are useful mainly against ***aerobic gram negative enteric bacteria***
  - Examples: *Pseudomonas*, *Proteus*, *Enterobacter*, *Acinetobacter*, *Klebsiella*, *Serratia*, *E. coli*
- They have extended spectrum when given in combination with a ***β-lactam*** or ***vancomycin*** include ***gram positive bacteria*** such as *enterococci*, *streptococci* and *staphylococci* in **endocarditis** (synergism)
- **Streptomycin**, **amikacin** are active against ***Mycobacterium tuberculosis***
  - **Streptomycin** in combination with a ***tetracycline*** are active against ***Brucella***
- **Neomycin** has a broader spectrum (active against staphylococci)
  - Used is **topically** due to high nephrotoxicity and ototoxicity when given systematic
- They are water soluble drugs and highly polar compounds, polycations
  - Not absorbed after oral administration, except when gastrointestinal ulcerations are present
  - Largely excluded from the CNS
  - Concentrated in the ***renal cortex*** and endolymph and perilymph of ***inner ear***
- Eliminated by ***glomerular filtration*** and their clearance is directly proportional to ***creatinine clearance***
  - t½ ~ 2-3 hours in normal renal function, increasing to 24 – 48 hours in severe renal impairment
  - Dosage must be reduced in renal dysfunction

- Usually administered ***IV*** as 30-60 minutes infusion and can also be given ***IM***
  - Use should be monitored by measuring peak and trough serum levels
- **Major Adverse Effects:** ***Ototoxicity*** and ***nephrotoxicity*** are more likely to be encountered in:
  - ***More than 5 days*** therapy
  - At higher doses, in the ***elderly*** (should not be given as a single dose)
  - In ***renal failure***
  - Concurrent use of other ototoxic and nephrotoxic ***agents*** (loop diuretics, vancomycin, amphotericin)
  - Contraindicated during ***pregnancy***

Sulfonamides

- Similar chemically to p-aminobenzoic acid (PABA)
- They ***inhibit the enzyme dihydropteroate synthase*** which incorporate ***PABA*** into dihydropteroic acid and thus, ***folate*** production which is essential for production of purines and nucleic acid synthesis
- They inhibit (**bacteriostatic**) both gram positive and gram-negative ***aerobic*** bacteria, *Nocardia*, *Chlamydia* trachomatis, and some *protozoa*
- Some ***enteric bacteria*** such as *E. coli*, *Klebsiella*, *Salmonella*, *Shigella* and *Enterobacter* are inhibited
- Active against, *Pneumocystis jiroveci*, *Toxoplasma*
- Activity is poor against ***anaerobes***
- Mechanism of Resistance:
  - Some bacteria ***lack dihydropteroate synthase*** and are not susceptible to sulfonamides
  - ***Mutations*** that: Cause overproduction of PABA, production of an enzyme with low affinity to sulfonamides or impair bacterial cell permeability to sulfonamides
- Classification:
  - **Oral, absorbable agents:** ***sulfamethoxazole*** and ***sulfadiazine***
  - **Oral, nonabsorbable agents:** ***Sulfasalazine***
  - **Topical agents:** ***Sulfacetamide*** and ***silver sulfadiazine***

- Adverse Reactions:
  - *Exfoliative dermatitis*, *photosensitivity*
  - *Stevens-Johnson syndrome:* a serious (potentially fatal) type of skin and mucous membrane eruption
  - *Stomatitis*, *conjunctivitis*, *arthritis*, *hepatitis*, *polyarteritis nodosa*, *allergic nephritis* and *psychosis*
  - *Crystalluria* which can damage renal tubules
  - *Hemolysis* in patients with G6PD deficiency
  - *Aplastic anemia*, *granulocytopenia*, *thrombocytopenia*
- Contraindicated in pregnancy (***teratogenic***)

Trimethoprim

- It ***inhibits bacterial dihydrofolate reductase*** which converts dihydrofolic acid to tetrahydrofolic acid (the active form of folic acid) which is needed for synthesis of purines and DNA
  - **Pyrimethamine** is similar but inhibit **protozoal** dihydrofolate reductase
    - ✓ Pyrimethamine + ***sulfadiazine*** active against ***Leishmania*** and ***Toxoplasma***
    - ✓ Pyrimethamine + ***sulfadoxine*** active against ***malaria***
- Pyrimethamine & trimethoprim in ***combination with a sulfonamide*** block sequential steps in folate synthesis à synergism of activity of both drugs (The combination is ***bactericidal***)
- **Mechanisms of Resistance:** Reduced cell permeability, overproduction of dihydrofolate reductase and altered dihydrofolate reductase with low binding to drug (most important clinically)
- **Excreted in urine** partially as metabolites (Dose should be reduced in renal failure)
  - It concentrates in prostatic and vaginal fluids, which are more acidic than plasma
- Antibacterial spectrum:
  - *E. coli* (Acute UTI) either alone or in combination with ***sulfamethoxazole*** (**Co-trimoxazole**)
  - *Salmonella*, *Shigella*, *Pneumocystis jiroveci* (IV infusion)
- **Adverse Effects:**
  - ***Megaloplastic anemia***, ***leukopenia***, ***granulocytopenia***
  - ***Diarrhea***, ***hyperkalemia*** (increased risk of cardia arrest) and ***hyponatremia***

Fluoroquinolones

- Block DNA synthesis by ***inhibiting bacterial topoisomerase II*** (***DNA gyrase***) that ***prevents relaxation*** of supercoiled DNA required for transcription and replication and ***topoisomerase IV*** interferes with ***separation of replicated chromosomal DNA*** into daughter cells during cell division
- ***Mechanisms of Resistance***
  - One or more-point ***mutations*** in the quinolone binding region confer high level resistance
  - Change in the ***permeability*** of bacterial cell
  - ***Plasmid-mediated*** resistance:
    - ✓ One *protects DNA gyrase* from fluoroquinolones
    - ✓ Another is a variant of aminoglycoside acetyltransferase which *modifies ciprofloxacin*
    - ✓ Both produce low level resistance but facilitate point mutations
- Resistance to one of these drugs confer resistance to the others (cross-resistance)
- **Ciprofloxacin**, **lovafloxacin**, **ofloxacin**:
  - Have excellent activity against ***gram negative aerobic*** bacteria (*Enterobacter* sp, *Pseudomonas aeruginosa*, *Neisseria meningitidis*, *Haemophilus* sp, and *Campylobacter jejuni*)
  - Moderate to good activity against ***gram positive bacteria***
  - They are active against *staphylococci* (not *MRSA*), and *streptococci* and *enterococci* in less degree
  - ***Ciprofloxacin*** is the most active against ***Pseudomonas*** aeruginosa

- **Gemifloxacin**, **Moxifloxacin**
  - Have improved activity against ***gram positive bacteria***, particularly *Streptococcus pneumoniae* and some *staphylococci*
  - **Levofloxacin** has superior activity against Streptococcus pneumoniae
  - Fluoroquinolones are also active against agents of atypical pneumonia (*Mycoplasma and Chlamydia*) and against intracellular pathogens such as *Legionella* and *Mycobacteria*

- Fluoroquinolones oral absorption is ***impaired by divalent cations*** including those in antacids and dairy product, so administration and intake of dairy products must be gapped by 2 hours at least
- Distributed widely in body fluids and tissues
- Most are eliminated by ***renal mechanisms*** (active tubular secretion or glomerular filtration) so dose reduction is required in renal failure, except for **moxifloxacin** (***hepatic*** elimination)
  - *Renal impairment* reduces creatinine clearance severely but *renal dysfunction* reduces it slightly
  - t½ ~ 3-10 hours

- **Major Adverse Effects:**
  - *Photosensitivity* (improper for patient working in the sunlight)
  - *Arrhythmogenic* (QTc prolongation)
  - *Hyperglycemia*
  - *Damage of growing cartilage* (Should not be used in patients under 18 years of age)
  - *Tendonitis* and tendon rupture in adults
  - Contraindicated in *pregnancy*

- Drugs Used in UTI (urinary tract infection):
  - ***Fluoroquinolones***
  - ***Nitrofurantoin:*** which *damages bacterial DNA* (bacteriostatic)
    - ✓ Active against E. coli and enterococci
    - ✓ Pseudomonas, Proteus, Enterobacter and Klebsiella are resistant
    - ✓ Should not be used in patients with impaired renal function or below 1 month of age
    - ✓ Adverse effects: ***acute pneumonitis***, ***interstitial pulmonary fibrosis*** (with high fatality rate), ***megaloblastic anemia***, ***hemolysis*** in G6PD deficient patients, polyneuropathies, ***colors urine brown***
  - ***Methenamine:*** It is a urinary tract antiseptic because it generates *formaldehyde* in acidic pH
    - ✓ Nearly all bacteria are sensitive to formaldehyde, except *urea-splitting microorganisms* (*Proteus*) which tend to raise urine pH
    - ✓ Contraindicated in ***hepatic failure*** because it also generates ammonia (NH_3)
    - ✓ Used only for chronic suppressive treatment of UTI caused by E. coli
    - ✓ **Antagonize** the action of *sulfonamides* (bind each other causing mutual antagonism)
    - ✓ May cause ***crystalluria***

Macrolide Antibiotics

- ***Inhibition of protein synthesis*** by binding to the 50S ribosomal RNA, leading to prevention of peptide chain elongation (transpeptidation), peptidyl-tRNA is dissociated from the ribosome
- These drugs may be ***bacteriostatic or bactericidal***, particularly at higher concentrations
- Antimicrobial spectrum: ***Aerobic gram-positive cocci and bacilli***, especially *pneumococci*, *streptococci*, *staphylococci*, and *corynebacteria*, *mycoplasma pneumoniae*, *Legionella*, *chlamydia*, *helicobacter pylori* which causes Peptic Ulcer Disease (PUD) and *Listeria*

- Mechanisms of Resistance:
  - ***Reduced permeability*** of the cell membrane or ***active efflux*** (gram positive organisms)
  - ***Modification of the ribosomal binding site*** by chromosomal mutation, macrolide-inducible methylase or constitutive methylase (gram positive organisms)
  - ***Production of esterase*** that hydrolyzes macrolides (Enterobacteriaceae)

- **Erythromycin:** is destroyed by gastric acid and must be administered with enteric coating.
  - Food interferes with absorption
  - Erythromycin estolate is the best absorbed oral preparation
  - t½ is **1.5 hours** (Largely excreted in bile), and it crosses the ***placenta*** (contraindicated for pregnancy)
  - It is taken up by polymorphonuclear leukocytes and macrophages

- **Clarithromycin:** t½ ~ 6 hours, metabolized in the liver to a metabolite with antibacterial activity
  - Similar to erythromycin in except less GIT adverse effects and less frequent dosing (2X)

- **Azithromycin:** Rapidly absorbed and well tolerated, but food and antacids delay absorption
  - Similar to erythromycin in spectrum
  - Penetrates into tissues very well
  - t½ ~ 3 days which allows once daily dosing and shortening of duration of treatment

- **Adverse Effects**
  - ***Acute cholestatic hepatitis*** (erythromycin estolate): intrahepatic obstruction (stasis) to bile flow
    - ✓ Fever, jaundice and impaired hepatic functions, and probably it is a hypersensitivity reaction
  - ***Epigastric distress***, ***anorexia***, ***nausea***, ***vomiting*** and ***diarrhea***
  - ***Increased gastrointestinal motility*** due to stimulation of motilin receptors in colon causing diarrhea
  - Drug interactions: *erythromycin* inhibits ***CYP3A4*** and other cytochrome P450 enzymes, and thus increase concentrations of many drugs, . *Azithromycin* does not
  - Prolongation of the QTc interval (***arrhythmogenic***)

Tetracyclines

- Tetracycline, Doxycycline, Minocycline, Tigecycline
- Broad-spectrum ***bacteriostatic*** antibiotics that ***inhibit protein synthesis***
- Active against many gram positive and gram negative bacteria, including *anaerobes*
- Active against *rickettsiae*, *chlamydiae*, L forms, *mycoplasma*, and *amebae*
- Tetracyclines enter microorganisms by both passive diffusion and active transport, and bind reversibly to the ***30S ribosomal subunit***, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA ribosome complex, preventing addition of amino acids to the growing peptide

- **Mechanisms of resistance**
  - ***Impaired influx or increased efflux*** by an active transport protein pump
    - ✓ The efflux pump of staphylococci does not affect doxycycline, minocycline or tigecycline
    - ✓ Tigecycline is a substrate multidrug efflux pumps of Proteus sp, and Pseudomonas aeruginosa
  - ***Production of protection proteins*** that interfere with tetracycline binding to ribosomes
    - ✓ *Gram positive bacteria* produce resistance to doxycycline and minocycline but not tigecycline, because tigecycline is bulky causing steric hindrance effect to the protection protein

- Active against Mycoplasma pneumonia, Chlamydiae, Rickettsiae and some spirochetes, *Helicobacter pylori*, ***Cutibactrium acnes***, *Borrelia burgdorferi* (***lyme disease***), *Vibrio cholera*, ***Brucella*** (transmitted through drinking **milk**), *Entamoeba histolytica* or *Plasmodium falciparum*
- **Tigecycline** differs in spectrum: *Staphylococcus* aureus including coagulase- negative, methicillin-resistant and vancomycin-resistant strains, *streptococci* including penicillin- resistant strains, *Enterococci* including vancomycin- resistant strains, *Gram positive rods*, *Enterobacteriaceae*, *Acinetobactersp*, *Gram positive and gram-negative anaerobes*, *Atypical agents*, *rickettsiae*, *chlamydia* and *Legionella* and rapidly growing *Mycobacteria*

- Tetracycline is ~65% absorbed while for doxycycline and minocycline are ~95% absorbed, ***tigecycline*** is poorly absorbed orally and must be ***given IV***
  - Absorption is impaired by **food**, **divalent and trivalent cations** (Ca^{2+} , Mg^{2+} , Fe^{2+} and Al^{3+}), **Dairy products** and **antacids**
  - Tetracyclines cross the placenta and are excreted in breast milk
  - They are bound to and damage ***growing bone and teeth***
  - ***Minocycline*** reaches very high concentrations in tears and saliva, which makes it useful in eradication of the meningococcal carrier state (given for individuals going to al haj)
  - *Carbamazepine*, *phenytoin*, *barbiturates*, *chronic alcohol* induce hepatic metabolism of doxycycline

- t½ of elimination of tetracycline (6-8 hrs), doxycycline and minocycline (16-18 hrs), tigecycline (36 hrs)
- **Major Adverse Effects:**
  - ***GIT***: nausea, vomiting and diarrhea
  - ***Superinfections***: Pseudomonas, Proteus, Staphylococcus aureus, Coliforms, Clostridium, Candida
  - ***Photosenstivity***

- Bone & teeth
  - ✓ Fetal teeth: *fluorescence*, *discoloration*, and *enamel dysplasia*
  - ✓ Fetal bone: *deformity* or *growth inhibition*
  - ✓ Similar changes occur in children < 8 years of age
- ***Liver toxicity***: hepatic necrosis and ***Kidney toxicity***: renal tubular acidosis
- ***Thrombophlebitis*** after IV administration, ***Local pain*** after IM administration
- ***Vestibular*** reactions: dizziness, vertigo, nausea, vomiting

Clindamycin (anaerobic antibiotic)

- ***Inhibits microbial protein synthesis***, binding the 50S ribosomal subunit (identical to erythromycin)
- **Mechanisms of Resistance:** Mutation in the ***ribosomal receptor site***, or ***enzymatic inactivation***
  - Resistance to clindamycin generally **confers resistance to macrolides**
- Active against ***anaerobic bacteria*** both gram positive and gram negative, including *Bacteroides* sp (*fragilis*), many ***gram positive cocci*** (*streptococci*, *staphylococci* and *pneumococci*), *Enterococci* and ***aerobic gram negative*** organisms are resistant
  - For infections above the diaphragm, Clindamycin is preferred
  - For infections below the diaphragm, Metronidazole is recommended
- Widely distributed into tissues, including ***bone*** and ***placenta*** and ***breast milk***, **except** brain and CSF
- It penetrates well into abscesses, and actively taken up and concentrated by phagocytic cells
- ***t½ ~ 2.5 hours***, but accumulates in severe hepatic dysfunction
- Major Adverse Effects: GIT irritation (nausea, vomiting, diarrhea), Superinfection (diarrhea & pseudomembranous colitis), Thrombophlebitis, Thrombocytopenia and neutropenia

Chloramphenicol

- Because of potential toxicity, resistance, and the availability of many other safer alternatives, it is now rarely used, it is used ***topically for eye infections***
  - It must not be used for nasal infections

- **Major Adverse Reactions**
  - ***Superinfection:*** Oral or vaginal candidiasis
  - ***Aplastic anemia*** –irreversible and can be fatal
  - ***Toxicity for newborn infants*** (**Gray Baby Syndrome**): vomiting, flaccidity, hypothermia, gray color

Linezolida

- It ***inhibits initiation of protein synthesis*** by inhibiting the formation of ribosome complex, unique binding site, ***23S rRNA of the 50S (large) ribosomal subunit***, results in no cross-resistance
- Resistance is caused by a ***mutation*** of the binding site on 23S rRNA
- Active against ***gram positive organisms***: *Staphylococci*, *streptococci*, *enterococci*, ***gram positive anaerobic cocci***, ***gram positive rods*** (*Corynebacteria*, *Listeria* monocytogenes)
  - It is primarily ***bacteriostatic***, except for streptococci where it is bactericidal
  - It is used as an *alternative to vancomycin* in infections caused by vancomycin-resistant Enterococcus faecium, nosocomial pneumonia, community-acquired pneumonia and skin infection
  - It should be reserved for infections caused by **multi-drug resistant gram-positive bacteria**

- Major Adverse Effects: ***Thrombocytopenia***, ***neutropenia*** and ***MAO inhibition***

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