Chemotherapy

It's not confined to anti cancerous agents only, it includes antibacterial, anti fungal , antiviral and anti parasitic drugs.

Drugs used in treating infectious diseases and cancer

• Infectious diseases are **a major cause** of death worldwide
• The control of the spread of microbes & the protection of people from communicable diseases & infections are carried out on the international, national, community, and individual levels

History:

2500 years ago: anti-infective substances were found:
• Chinese used moldy soya beans for carbuncles & boils
• Greeks (Hippocrates) used wine to treat wounds
• 1900's: Syphilis treated with arsenic
• 1936: Sulfonamides discovered
• 1940's: Penicillin & Streptomycin discovered
• 1950's: Golden age of antimicrobials

Infection related concepts

- Infection: is an invasion of body tissue by microorganisms (MO's) & their growth there
- Such a MO is called:infectious agent
- If the MO produces **no clinical evidence of disease**,the infection is called subclinical or asymptomatic
- If a MO leads to a **detectable alteration in normal tissue function**, it is called an infectious disease
- Pathogenicity: is the ability to **produce disease**;thus a pathogenis a MO that causes disease
- True pathogen causes disease or infection in a **healthy individual**
- Opportunistic pathogen causes disease **only in a susceptible individuals**
- Communicable disease:is the ability of the infectious agent to be **transmitted to an individual by direct or indirect contact or as an airborne infection** E.g.; common cold virus is more readily transmitted than the bacillus that causes leprosy (Hansen's disease)

Types of MOs causing infections

Four major categoriesof MOs cause infections in humans:

1. Bacteria:

the most common, hundred species can attack humans, transferred by air, water, food, soil, body tissues & fluids, and inanimate objects (non-living objects)

2. Viruses:

consist primarily of nucleic acid, therefore must enter living cells in order to reproduce (e.g.; rhinovirus, hepatitis,HIV)

Antiviral drugs **are not highly successful in treating viral infections** and many viruses are self-limiting butthey take time.

3. Fungi:

include yeasts & molds. Candida albicans is a normal flora in human mouth, GIT and vagina

4. Parasites:

live on other living organisms examples: protozoa that causes malaria, helminthes (worms), arthropods (mites, fleas, ticks)

• Community-acquired: e.g. nosocomial = also referred to as **healthcare-associated infections(HAI)** (also known as hospital induced infections)

• Opportunistic infections or overgrowth of a certain fungi or bacteria can occur due to **the constant use or misuse of a certain antiviral or antibiotic** as they don't only affect the pathogenic organisms but also the useful ones(microbiota) which normally exist and have useful functions.

General manifestations of infection:

• Infection caused by bacteria take many forms, ranging from mild local infection to life threatening systemic infection

• Manifestations usually depend on the site of infection, ex: respiratory infections are associated with cough. In general, all infections are associated with fever asbacteria produce toxic substances that lead to fever

- Fever, chills, rigors (more severe than chills) 🥶
- Pain or aches 🤕
- Nausea 🤢
- Vomiting 🤮
- Weakness 🥴

• Many bacterial infections are associated with inflammation, but many **inflammatory conditions are NOT associated with bacterial** infections unless there is a bacterial infection.
• An infection occurs when germs enter the body, increase in number, and cause a reaction of the body
• Inflammation occurs when mediators and inflammatory cells travel to the place of an injury or foreign body like bacteria.It is an essential part of your body's healing process
• Anti-inflammatory drugs have no antibacterial activity e.g. steroids and NSAIDs whereas, certain antibiotics have both antibacterial and anti-inflammatoryeffects e.g. azithromycin (one of the main antibiotics), tetracyclines and co-trimoxazole (one of sulfur drugs).

Azithromycin modulates the function of Phospholipase A2, but we can't say that it acts like steroids because its mechanism differs.It delays its function and interferes with the function of PLA2 thus inhibiting both ways.
Tetracyclins and co-trimoxazole supress the production of TNFs and ILs and cytokines.

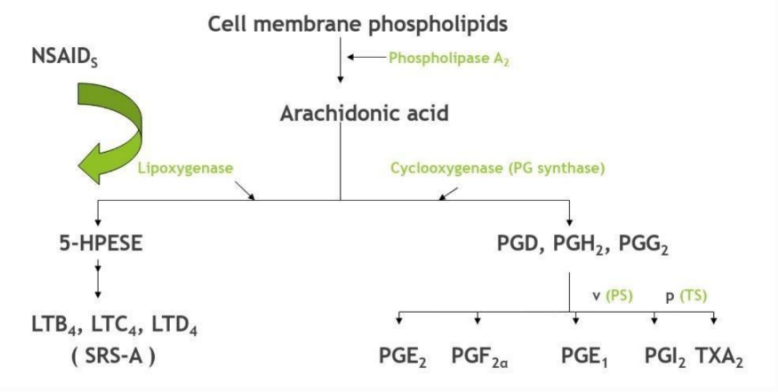
If a patient has an inflammatory disease,there's no need to use antibacterial drugs unlessthe patient has an infection.
And no need to use anti inflammatory drugsin patients with bacterial infections except if they're useful in lowering fever or pain that originatesfrom the inflammatory response to the bacterial infection.

• The mechanism of action for paracetamol is inhibition of prostaglandins synthesis in the CNS only

• Non steroidal anti inflammatory drugs act on cyclooxygenase pathway and inhibit the production of prostaglandins only.
These are less potent comparedto steroidal anti inflammatoryd rugs. In cases of inflammation we start with NSAIDs

• Steroids; cortisone and cortisone derivatives are very potent anti-inflammatory drugs as they inhibit phosphlipaseA2 thus inhibiting both pathways.

• Prostaglandins are Very important and they're the major chemical mediators of inflammation.



• Luekotrienes are also involved in inflammation

Classifications Antimicrobials

1. Antibiotics

Agents or antimicrobials that interfere with the growth or multiplication or kill microorganisms like bacteria, fungi and they are of natural source e.g. Penicillin's

2. Chemotherapeutics

Agents or antimicrobials that interfere with the growth or multiplication or kill microorganisms and they are of synthetic source e.g. Sulfonamides

if the drug is chemotherapeutic then you shouldn't stick to the expiry date written,these drugs can remain viable for years
but if it's an antibiotic then you have to stick to the expiry date because it's accurate .

Semisynthetic drugs, the original substance is taken from a living organism and then it's modified chemically.

Antiseptics

Agents that kill or inhibit growth of microorganisms when applied to tissues (for example:alcohols to **sterilize skin** and during **surgeries** as well as Iodine which has anti fungal, antiviral and anti bacterial effects)

Disinfectants

Agents killing or inhibiting growth of microorganisms when applied to nonliving objects (like Chlorine that is used to **sterilize swimming pools** or detergents that are used to **sterilize floors in hospitals**)

- Alcohol can be used as an antiseptic or disinfectant.

in the therapeutic dose, the drug could be:

1. Cidal (Irreversible inhibition of growth)

An agent that kills microorganisms Bactericidal, fungicidal, viricidal...etc e.g. **Penicillin's**, **Cephalosporin's**, **Aminoglycosides**...etc,

2. Static (Reversible inhibition of growth)

An agent that inhibits growth of microorganism Bacteriostatic, fungistatic, viristatic...etc, e.g.
Sulfonamides, Tetracyclines, Macrolide antibiotics...etc

-Static drugs inhibit the growth and thus allow your immune system to get rid of theinhibited bacteria. So,the static agent will eventually end the infection therefore it'snot only the function of cidal agents.

MIC: (Minimal Inhibitory Concentration)

Lowest concentration of antibiotic that prevents visible microbial growth

MBC (Minimal Bactericidal Concentration)

Lowest concentration of antibiotic that reduces the number of viable cells by at least 1000-fold

The MBC of a truly bactericidal agentis equal to or just slightly above its MIC

AAL (The Attainable Anti-biotic Level)

is the concentration of the drug that can be reached in the target tissues without causing toxic or side-effects

- **Cidal or Static have nothing to do with spectrum of activity nor the mechanism of action.**

A static agent in large doses becomes cidal and cidal agents in low doses become static

- One drug (chloramphenicol) could be bacteriostatic for one organism (gram negative rods), & cidal for another (S. pneumoniae)

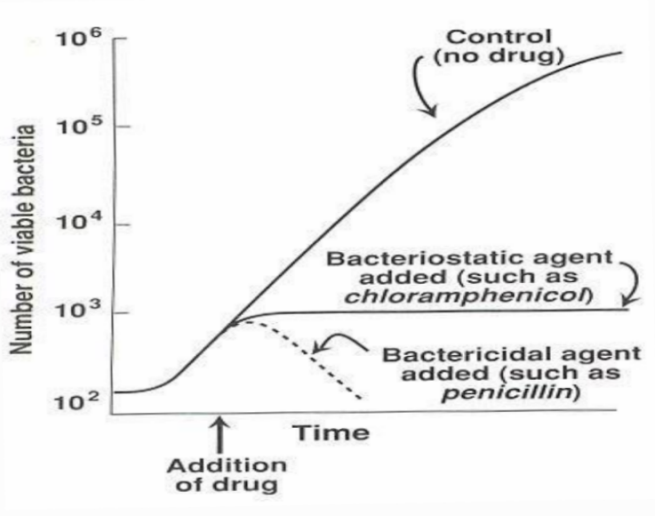
example:

Penicillin that is cidal and Sulfonamidesthat are static and both are in therapeutic doses. If the dose of Penicillin is lowered then it becomes static but you must be aware of not reaching subtherapeutic levels that bacterial resistance may develop. Either cidal or static, they will lead to an end of the infection and the selection differs **according to the state of the patient.** For instance, if a patient is immunocompromised and has a bacterial infection then we have to give him/her bactericidal because his/her immune system cannot get rid of the infection

- If you grow bacteria in a medium and observe the number of viable bacteria without using a drug, their numberis going to increase as they multplicate and reproduce continuously.

- Bacteriostatic is going to decrease the number and bacteriocidal is going to reduce it further.

- **Bacteriostatic can lead to the same effect of bacteriocidal** if the drug is used and along with a good immune system, so it will lead to a complete end of the infection.



Trough Levels:

• Levels of antibiotics reach minimal levels(troughs) at roughly predictable times after administration

• Trough levels in antibiotics are the lowest concentrations in the blood before the next dose, vital for optimal drug efficacy. They help ensure the concentration remains above the (MIC), preventing bacterial growth and minimizing resistance.

• The troughs may be at, or below the MIC

This may or may not be a problem because of two factors:

- Post Antibiotic Effect, a prolonged period before bacteria resume growth
- Synergism between host defenses and subMIC levels of antibiotics

antimicrobial stills effective, even if its level drops below the MIC, due to :

Post-Antibiotic Effect and collaboration between host defenses and sub- MIC levels of antibiotics;where **the host's immune system, when working together with lower antibiotic concentrations, can produce a more effective response than either acting alone.**

• we need our drug concentration to be within therapeutic level.

Exceeding level → toxicity

Lowering level → ineffective & cause resistance to bacteria

Post-antibiotic effect (PAE):

It is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC (continued effect of an antibiotic on bacteria after the drug has been removed from the system.)

- Antimicrobial drugs exhibiting a long PAE (several hours) require only one dose per day (e.g. Aminoglycosides & Fluroquinolones)

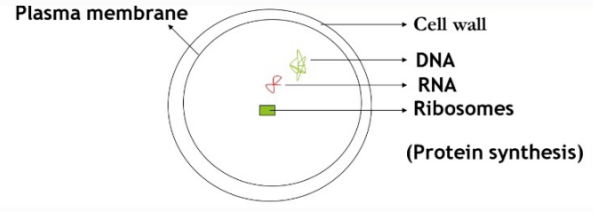
major problem for using antibiotics, it could bear resistance by the bacteria..

• Trough levels may increase the frequency of drug-resistant bacteria

- Frequency of developing resistance is greatly increased at levels below, at or little bit above the MIC
- Development of resistance to ciprofloxacin is 10,000 times more frequent at 2 times the MIC compared to 8 times the MIC

Mechanism of action

bacteria is prokaryotic cell, it has characteristics not found in our cells, which **gives selectivity for the given antibiotic to act on**. Like cell wall of the bacteria. Then, the antibiotics would target these unique structures.



Inhibitors of cell wall synthesis

Penicillins, Cephalosporins, Bacitracin, Vancomycin, Cycloserine...etc

- Most bacteria have **rigid cell walls** that are **not found in host cells** (selective toxicity)
- Cell wall inhibitors work by inhibiting the formation of peptidoglycans that are essential in cell wall formation
- Disruption of the cell wall causes death of the bacterial cell(Bactericidal)

The classification of antibiotics as static (inhibitory) or cidal (killing) is not determined by their mechanism of action.
While some antibiotics acting on the cell wall are static, the distinction between static and cidal antibiotics is based on their overall impact on bacterial growth, not just their mechanism of action

Interference with permeability or function of plasma membrane

Antifungal agents (Colistin, Nystatin, Amphotericin B, Polymyxin B)

Inhibitors of DNA synthesis or replication (DNA disturbers)

Quinolones (Nalidixic acid), Fluoroquinolones, Griseofulvin, Novobiocin... etc

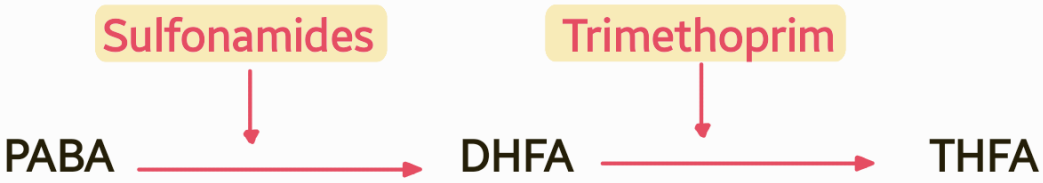
Inhibitors of RNA synthesis

Rifampicin

Inhibitors of protein synthesis

Aminoglycosides (Streptomycin, Gentamicin...), Chloramphenicol, Tetracyclines, Lincomycin, Clindamycin...etc

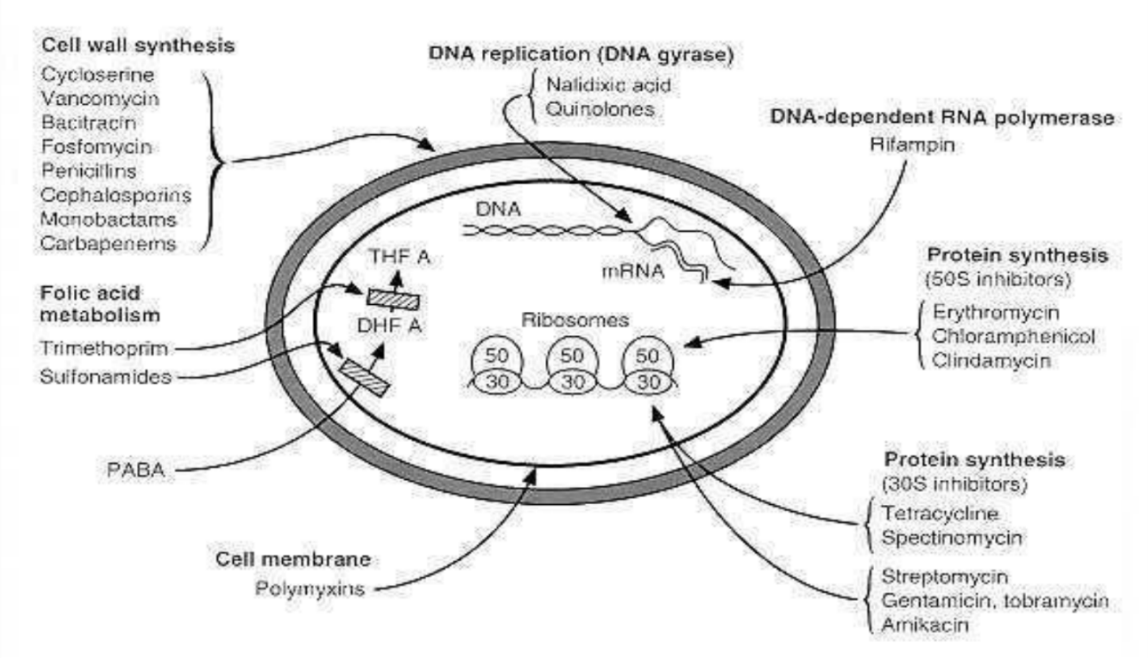
Interference with metabolism of microorganisms



PABA: Para-aminobenzoic acid (PABA) , DHF:dihydrofolate, THF:tetrahydrofolate

• The folic acid pathway in bacteria involves the synthesis of tetrahydrofolate (THF), a crucial coenzyme for nucleotide synthesis.

• **bacteria requires PABA for synthesis folic acid**. Sometimes, we give 2 drugs to clear the bacteria
• Sulfonamides (static) which inhibits the 1st step added with trimethoprim (static) which inhibits the 2nd step, leading to Bactericidal effect with wide spectrum



Classification of antimicrobial

According to:

1. Mechanism of action (eg. cell wall inhibitors)
2. Chemical structure (the best criteria of classification)
3. Antimicrobial activity (spectrum of activity)

spectrum:

the more microorganisms covered by the antibiotic, the higher its spectrum , Always start with low spectrum antibiotics, there are some exceptions for this rule.

A. Narrow spectrum

- effective in G+ve cocci & bacilli
- drugs effective in G-ve bacilli (Aminoglycosides)
- drugs only effective in **specific infections** (Isoniazid is only active against mycobacteria T.B)

The narrower the spectrum the more specific is the antibiotic.

B. Broad spectrum

- effective in G+ve & -ve cocci & bacilli

Affect a wide variety of microbial species (this type could alter the nature of the normal flora & precipitate a superinfection)

C. Extended-spectrum antibiotics

Agents that are effective against G+ve organisms & also against a significant No. of G-ve bacteria or against specific microorganisms e.g. Antipseudomonal penicillin's

General considerations in the usage of antimicrobials:

- Is the antimicrobial agent indicated
- Aim if indicated is to achieve a level of antimicrobial activity at the site of infection that is sufficient enough to inhibit or kill microorganisms without affecting host cells

• Antimicrobials are harmful drugs
• New drugs are **not necessarily better** than old ones.
• Major consideration is identification of the causative microorganism and the use of proper dose for adequate duration, otherwise it will gain resistance to the antibiotic.
• Sometimes there is a **need to combine more than one antimicrobial**

Selection of an antimicrobial agent

Factors affecting selection:

1. Causative microorganism (susceptibility):

the most important factor

The lack of susceptibility guarantees therapeutic failure.

Determined from:

- Clinical picture (Empiric therapy) : the use of an antibiotic **prior to identification of organism** in critically ill patients

clinical picture, which includes the patient's **symptoms, signs, and the likely source of infection**. Identifying the causative microorganism and its susceptibility helps ensure the selection of an appropriate antibiotic.

- Bacteriological examination (culture and sensitivity)
- Serology-measures antibody levels
- Polymerase Chain Reaction (PCR) detects the specific DNA for a specific organism

2. Pharmacokinetic factors:

• important in determination of the drug, like site of infection in the CNS , we need drug can penetrate the BBB(blood brain barrier)

• Renal disease (**poor kidney function causes antibiotics that ordinarily secreted by this route to accumulate** & lead to serious adverse effects e.g. aminoglycosides) do you need to decrease the given does

• Liver disease, antibiotics that are **concentrated or eliminated** by liver are contraindicated in liver diseases (e.g. erythromycin & tetracycline)

• Route of administration

Oral antibiotics are typically avoided for individuals experiencing vomiting because the medications may not be effectively absorbed, reducing their utility in treating the infection.

3. Host factors

- Age (newborn & old pts have **less kidney and liver function** compared to adults)
- Allergic reaction to a given antimicrobial agent
- Host defense mechanisms (alcoholism, DM, HIV, malnutrition, poor hygiene, advanced age, neutropenia, & **the use of immunosuppressive drugs can affect a patient's immuno-competency.** Such patients need higher-than-usual doses or longer courses of treatment), so you should give them a cidal rather than static

4. Genetic factors

Sulfonamides, Chloramphenicol, Nitrofurantoin → severe hemolysis in G6PD deficient individuals (hemolytic anemia) by inducing oxidative stress on red blood cells. In G6PD deficiency, the decreased capacity to handle oxidative stress makes RBCs more susceptible to damage induced by these antibiotics, resulting in hemolysis.

5. Pregnancy

Streptomycin → Deafness 🙉
during pregnancy, the drug can potentially cross the placenta and affect the developing fetus.

6. Lactation

Sulfonamides → hemolysis in G6PD deficient newborn
the passage of sulfonamides into breast milk 🤱

7. Local factors at site of infection

e.g. Abscesses
Systemic antibiotics may have limited penetration into abscesses , so they are treated by drainage, not antibiotics. But can be given to control the spread of bacteria.

8. Toxicity and side effects to antibiotic
9. Interactions with other drugs
10. Cost

Bacterial resistance:

Occurs:

- When clinical condition of host is impaired
- When normal flora have been suppressed
- With interrupted or inadequate Rx (medical prescription)
- More frequently in certain types of bacteria (Gram negatives possess an outer membrane and cytoplasmic membrane preventing passage of antibiotec through pores)
- With widespread use of broad spectrum antibiotics
- In poor environmental setting of host

Mechanisms of bacterial resistance

A. Natural resistance

- Absence of a metabolic process or an enzyme or protein in the bacteria which is required for the action of the antimicrobial
- Absence or hard cell wall making the antimicrobial difficult to penetrate
- The need of antimicrobial drug in large amounts at site of action above its concentration in the plasma

In other words: lower concentration at target tissue as compared to plasma concentration is required or achieved by specific antibiotics this makes the bacteria naturally resistant to the action of the antibiotics

To overcome this type of resistance the drug has to be given in very large doses **which leads to severe side effects**

B. Acquired resistance

Development of resistance in a previously sensitive microorganism. This could occur in the following ways:

1.Mutation or genetic change

2. Adaptation: the bacteria adapts itself against the action of antibiotic by production of enzymes breaking the antimicrobial e.g. **β-lactamases**

3. Infectious or multiple drug resistance

Through:

Transduction by **bacteriophage** which **transfers chromosomal** or extrachromosomal DNA (plasmid) to bacteria

Transformation, **transfer of DNA responsible for resistance** from environment to bacteria

Conjugation Passage of resistant genes from cell to cell **by direct contact**

Most of resistance is acquired due to misuse or abuse of antibiotics e.g. improper dose & DOA, Rx of suppurative diseases, Rx of viral infections with antibacteria agents

Misuse : use the drug in condition which is not indicated

Abuse : the drug is indicated but we use it improperly

Examples on mechanisms of resistance:

- Generating enzymes that inactivate the antibiotic (beta lactamase)
- Changing structure of target site e.g. PBP's (beta lactams and aminoglycosides)
- Preventing cellular accumulation of antibiotic by altering outer membrane proteins or using efflux pumps(the antibiotic enters to the bacteria but it has pumps that will pump it outside the bacteria)e.g. Gve

- Changing the metabolic pathway that is being blocked (sulfa drugs)
- Overproducing the target enzyme or protein to overpower the effects of antibiotics
- Mycoplasma lacks a cell wall making it resistant to penicillins
- Sulfonamides have no impact on bacteria that obtain their folate from environment

Sulfonamides they act by inhibiting the first step in folic acid synthesis by acting on it's synthetaseenzyme Which converts Paraaminobezoic acid (PAPA) to dihydrofolic acid (DHFA)

Combined therapy:

Indications:

- To obtain synergism or reduce the dose of a toxic drug
- To reduce emergence of resistance

if we lower the dose —> no side affects
but the drug become in sub therapeutic dose and this lead to resistance
so the sol is : combined therapy

- Treat mixed infections with microorganisms of different sensitivities
- Treat infections at different anatomical sites (bile, CSF)
- Treat infections of unknown etiology especially in patients at high risk of developing infections e.g. AIDS patients or patients with agranulocytosis

TB is NEVER treated with a single drug, usually we start with three drugs

Outcome of combined chemotherapy:

- Indifference, One drug doesn't have any effect on the second drug

try as much as possible to use drugs with different mechanism of action , use different antibiotics with no over lacking side effects

- Antagonism Cidal + static
- Synergism (Penicillins+aminoglycosides) one drug can enhance the effect of others.

Aminoglycosidesinhibit protein synthesis.
Pencillins interfere with the permeability of the cell wall.
The synerigm occurs in aminoglycosides because when pencillin interfere with the function of the cell wall, they will increase it's permeability, so aminoglycosides will enter one little bit more the bacterial cell increasing it's effect and toxicity.

Disadvantages of combined chemotherapy:

- Toxicity
- ↑ cost

Prophylactic use of antibacterial agents:

Indications:

- Protection of healthy individuals against highly contagious disease or infections e.g.syphilis, gonorrhea, T.B, meningococcalmeningitis

- Prevent second infection in very ill patients

e.g. AIDS, before major surgeries, delivery, organ transplantation, recurrent UTI's...etc

Prophylaxis is successful if:

- A single antibiotic is used
- The dose required for prophylaxis is less than the therapeutic dose
- The drug is needed or used for a brief period

(chronic therapy or prophylaxis is not advised → bacterial resistance)

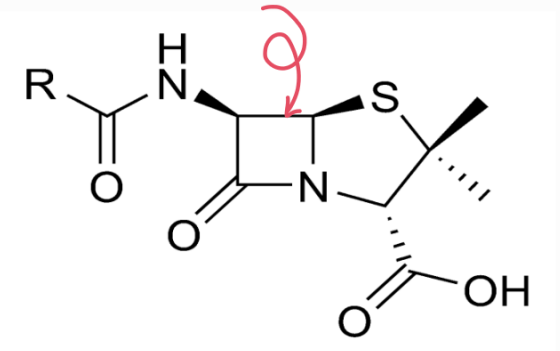
Complications of antibiotic therapy:

1. Hypersensitivity
2. Direct toxicity (toxic to certain site) There are some antibiotics that are toxic to the kidneys
3. Super infection When we use broad spectrum of antibiotic . Alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria

Inhibitors of Microbial Cell Wall

β-lactam antibiotics

- Contain a beta-lactam ring that is part of their chemical structure
- An intact beta-lactam ring is essential for antibacterial activity
- Include: **Penicillins, Cephalosporins, Carbapenems, Carbacephems & Monobactams**

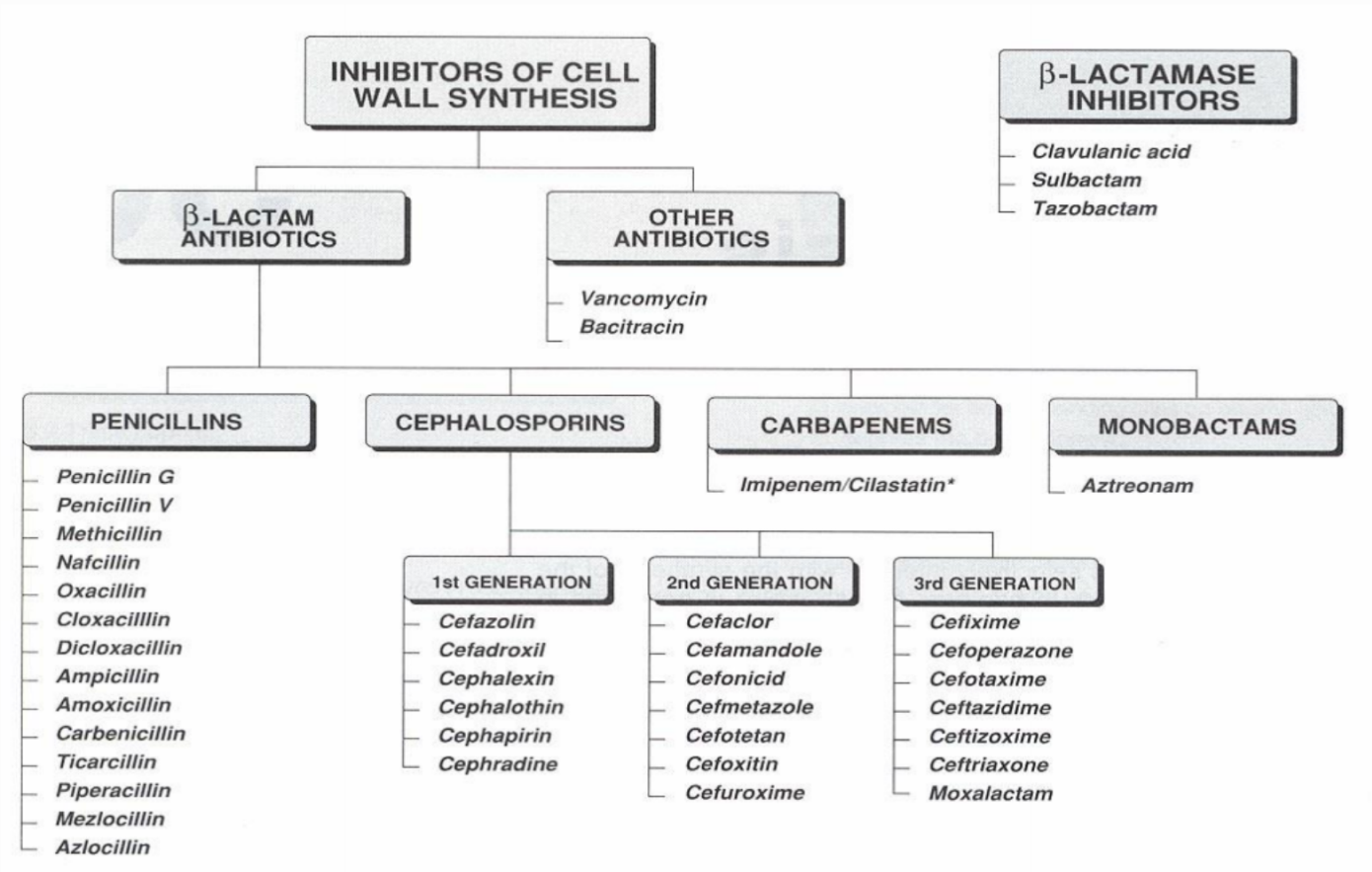


- The R in the structure of β-lactam antibiotic determines the characteristic of antimicrobial agent e.g. narrow or broad spectrum; oral vs parenteral administration; sensitivity vs resistance to β lactamases...
- The β-lactam ring is the site of attack by gastric acidity and lactamases

Beta Lactams Mechanism of Action:

1. Inhibit synthesis of bacterial cell walls by binding to proteins in bacterial cell membranes e.g. PBP's(Pencillin binding proteins)
2. Binding produces a defective cell wall that allows intracellular contents to leak out (lysis of the bacteria and death)
3. Most effective when bacterial cells are dividing

Inhibitors of Cell Wall Synthesis



Bacteria that produce **β-lactamase** (hydrolyze βlactam ring and hence inactivation of antimicrobial activity):

Staph aureus

Moraxella catarrhlis, Neisseria gonorrhoeae, Enterobacteriaceae

Hemophilus influenzae, Bacteroides species (the rest of them is for your information)

1. Penicillins (PNC's)

- Most widely used antibiotics, most effective, least toxic and cheap
- Derivatives of 6-aminopenicillanic acid (**ß-lactam ring is important structure** for antibacterial activity, breaking down such B-lactam inactivate the antibiotic whether by gastric acidity or by specific enzyme lactamase)
- Derived from a fungus
- Prototype is Penicillin G (It's not good for CNS)
- Widely distributed except in CSF (except if inflammation is present) and in intraocular fluid
- Most serious complication is hypersensitivity (most serious side effect are allergic reactions)
- Can cause seizures and nephropathy

Natural penicillins:

Benzylpenicillin = Penicillin G

it should be given **IM, IV**

• Acid labile (the B-lactan will be broken down by the acidity), short acting, given **4-6 times/day**

• Depo IM forms to penicillin G

• Procaine penicillin given IM **twice/day**, IV injection contraindicated (could lead to ↓ BP & convulsions)

• Benzathine penicillin given IM mainly used for **rheumatic fever** prophylaxis

Phenoxy methylpenicillin= Penicillin V

• it should be given Oral

it doesn't work with bacteria produce lactamase

- Natural penicillins are narrow spectrum and penicillinase sensitive
- Considered drugs of choice to treat infections with G+ve Strep. , β-hemolytic type A (most common microbe in tonsillitis)
- Have little effect if any against G-ve bacteria

Narrow spectrum penicillinase resistant penicillins(anti Staph. penicillins)

Nafcillin IM, IV
Oxacillin IM, IV
Cloxacillin Oral
Dicloxacillin Oral
Flucloxacillin Oral & parenteral

Broad spectrum penicillinase sensitive PNC's (amino PNC's):

Ampicillin IM, IV, Oral
Amoxicillin Oral **More potent, has better bioavailability, longer DOA**
(ampicillin is given four times/day , amoxicillin is given three times/day)

- These PNC's have **very little effect**, if any, against PNC ase producing bacteria e.g. H. influenza and against G-ve bacteria e.g. E. coli, Proteus.
- No effect against Pseudomonas
- Amino PNC's are widely used in tonsillitis, otitis media, gonorrhea, respiratory infections, shigella infections, UTI's (urinary tract infections)...etc
- Amoxicillin has good activity against Helicobacter pylori (causes peptic ulcer) (+ PPI's (proton pump inhibitors) + Clarithromycin +Metronidazole)

Antipseudomonal PNC's:

Piperacillin > Mezlocillin = Ticarcillin > Carbenicillin
(the most potent) (the least potent)

- All are synergistic with aminoglycosides against Pseudomonas

Amidinopenicillins:

Mecillinam (IM; IV) Pivmicillinam (oral)

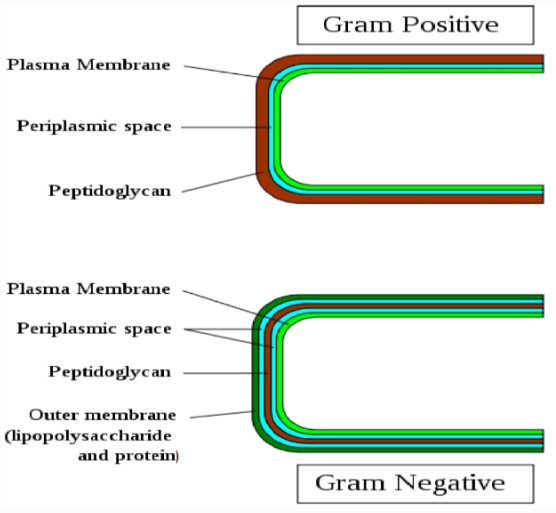
- Most potent PNC's against enterobacteria (Salmonella, E. coli, Klebsiella, Shigella...), have little or no activity against G+ve cocci or pseudomonas; synergistic with other β-lactams but not with aminoglycosides

MOA of Penicillins:

• Most bacteria have rigid cell walls that are not found in host cells (selective toxicity).

• PNC's act by inhibiting transpeptidases, the enzymes that catalyze the **final cross-linking step in the synthesis of peptidoglycan**, thus leading to the lysis of cell wall.

• Disruption of the cell wall causes death of the bacterial cell (Bactericidal effect)



• G-ve is more difficult to be effected by specific antibiotics because in addition of cell wall and plasma membrane, they have an outer membrane (lipopolysaccharide and protein).

Pharmacokinetics of PNC's:

• Bind plasma proteins, widely distributed, their concentrations in ocular fluid, joints and CSF are **poor** (do not cross BBB unless **meninges** are inflamed), do not cross the placenta

• Metabolized by the liver and excreted by glomerular filtration and tubular secretion.

• Probenecid inhibits tubular secretion of PNC's (nafcillin & oxacillin are mainly excreted by the liver)

Indications for Penicillin's:

- More effective in treating G+ve infections
- Used to treat infections of the skin, GUS, GIT, respiratory tract and soft tissues
- Selection depends on the organism and severity of the infection e.g. anti-staph vs. anti-pseudomonal

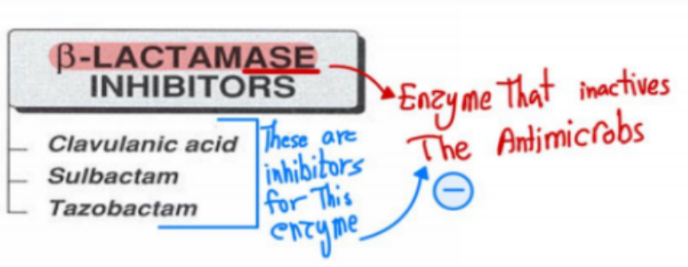
• Combination of PNC's or a cephalosporin with a potent inhibitor of lactamases, make it more resistant to B-Lactamase and some of them make more potentcy and more spectrum antibiotic.

β-lactemase inhibitors:

Have no antibacterial activity, increase potency and spectrum of activity of combined antibiotic

Clavulanic acid, Sulbactam, Tazobactam

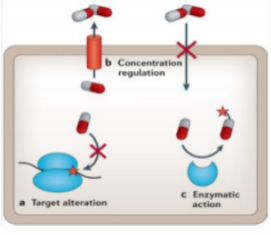
(Augmentin® =amoxicillin/clavulinate)
(Unasyn®=ampicillin/sulbactam)
(Zosyn®=piperacillin/tazobactam)...etc

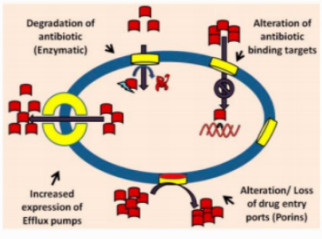


Mechanisms of resistance to PNC's:

- **Altered** penicillin binding proteins (PBPs)
- Production of beta-lactamase (penicillinases)
- Decreased penetration(decrease the permeability /increased efflux pump to flow out the drug)

(pseudomonas is an example of bacteria that use this machanism)





Preparations to PNC's :

Oral, parenteral, intrathecal, topical, intra-articular... 💊💉

Side effects to PNC's:

- Allergy (Most frequent and dangerous)

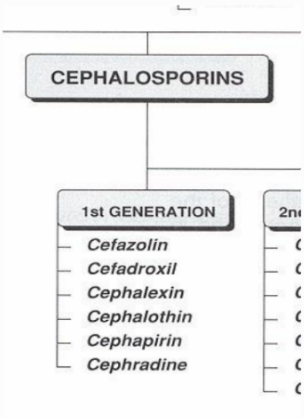
Type I allergic reactions. Early onset (immune IgE mediated)

Type II allergic reactions. Late onset (2-10 days). May manifest as eosinophilia, hemolytic anemia, interstitial nephritis or serum sickness (fever; arthralgia; malaise...)

- Nonallergic ampicillin rash, occurs **only once** (more common in pts with acute leukemias; mononucleosis, lymphomas, cytomegaloviral infections...)
- Neurotoxicity (more common with **oxacillin**)
- Hepatotoxicity (more common with **IV oxacillin**)
- Bone marrow depression (reversible) (more common with **IV nafcillin**)
- Nephrotoxicity (more common with **Methicillin**)

Other restrictions in the use of PNC's:

-Na+ penicillins → restricted use in pts with **hypertension** or **heart failure**
- K+ Penicillins → restricted use in pts with **renal failure** (Hyper or hypokalemia both are dangerous)
- Absolute contraindications to all PNC's in pts with history of allergy



2. Cephalosporins

- Derivatives of 7-aminocephalosporanic acid
- β- lactam antibiotics, Cidal
- Semisynthetic
- Broad spectrum
- Inhibitors of microbial cell wall synthesis
- Differ in pharmacokinetic properties and spectrum of activity
- Classified into 1st, 2nd, 3rd, 4th, and 5th generation

* First generation	*Second generation	* Third generation	* Fourth generation	* Fifth generation
• Cefadroxil • Cefalexin Oral • Cefazolin IM, IV • Cephapirin • Cephradine • Cephaloridine	• Cefaclor Oral • Cephamandole IM, IV • Cephmetazole • Cefonicid • Cefotetan • Cefoxitin • Cefprozil • Cefuroxime • Cefuroxime axetil • Loracarbef *we will talk about it later	• Cefixime Oral • Cefoperazone IM, IV • Cefdinir Cefpodoxime • Cefotaxims Ceftazidime • Ceftriaxone Ceftibuten Ceftizoxime	• Cefepime IM, IV	• Ceftaroline IV *has the widest spectrum of activity.

1st generation cephalosporins

- have the best activity against G+ve microorganisms,
- less resistant to β- lactamases
- and do NOT cross readily the BBB as compared to 2nd, 3rd and 4th generations

• Cephalosporins never considered drugs of choice for any infection, however they are highly effective in upper and lower respiratory infection, H. influenza, UTI's, dental infections, severe systemic infection...

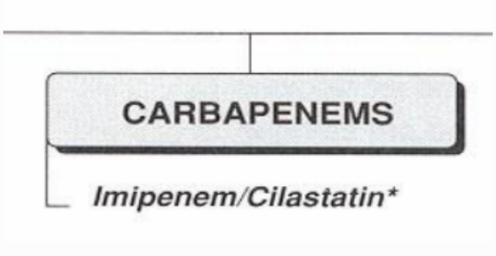
Among cephalosporins:

- Cefoxitin (2nd) has the best activity against Bacteroides fragilis
- Cefamandole (2nd) has the best activity against H. influenza
- Cefoperazone (3rd), Ceftazidine (3rd) and Cefepime (4th) have the best activity against P.aeruginosa infections
- Ceftaroline (5th) has a broader G+ve spectrum of activity than all other cephalosporins due to its activity against MRSA(Methicillin-resistant Staphylococcus aureus); also has some activity against G-ve bacteria

Side effects to cephalosporins:

- Allergy, Cross allergy with penicillins(10%)
- Hepatotoxicity
- Nephrotoxicity, Mostly seen with Cephaloridine (1st)
↑ with concomitant aminoglycosides use
- disulfiram-like reaction (cefamandole, cefoperazone, ceftriaxone, cefmetazole...), disulfiram is a drug used for treating alcoholism
- Hemolytic anemia

All cephalosporins are excreted by the kidney except Ceftriaxone (3rd) which is excreted by the liver



3. Carbapenems

1. Imipenem

• Has the broadest spectrum of activity of all β-lactam antibiotics, effective against most G+ve & -ve bacteria and anaerobes, given IM, IV.
• β- lactamase resistant
• More potent against E. faecalis, B. fragilis and pseudomonas aeroginosa **as compared to 3rd generation cephalosporin**

• Seizures are major side effect to imipenem

• Some consider imipenem the drug of choice in the management of polymicrobial pulmonary, intraabdominal and tissue infections.

• Imipenem is metabolized and excreted by the kidney by the enzyme dehydropeptidase I; so it is combined with Cilastatin (inhibitor to dehydrpeptidase I) to decrease rapid metabolic clearance of imipenem

2. Meropenem

• has similar activity to imipenem; but resistant to metabolism by dehydropeptidase I (no need to combine it with cilastatin) and incidence of seizures is less than imipenem

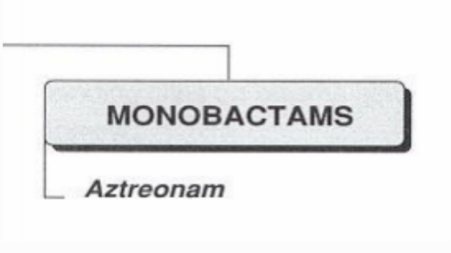
4. Carbacephems

e.g. Loracarbef

• Oral

• Spectrum of activity similar to 2nd generation cephalosporin particularly cefaclor and cefprozil even some list it under 2nd generation cephalosporins; effective orally; excreted renally

5. Monobactams



e.g. Aztreonam IM, IV

• Has excellent activity against G-ve bacteria

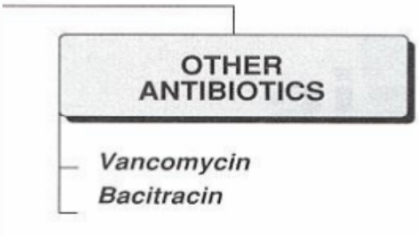
• little if any effect against G+ve MO's

• β-lactamase resistant

• Considered a substitute to aminoglycosides to treat G-ve infections (less toxic compared to aminoglycosides)

• Rarely, causes allergic reactions in pts with type I allergy to other β-lactam antibiotics

Vancomycin & Teicoplanin



• Glycopeptides (Large molecules)

• Prevent crosslinking of peptidoglycans

• Bactericidal in nature but vancomycin has a static action to certain bacteria specially Enterococcus bacteria.

• Narrow spectrum of activity, effective against G+ve bacteria especially methicillin resistant Staph aureus (MRSA)
• Alternatives (Not second line therapy)to PNC's to treat G+ve Strep & Staph infections in pts allergic to PNC's
• Given IV (oral absorption is poor)

• Considered drug of choice + metronidazole to treat pseudomembranous colitis=antibiotic associated colitis (Clostridium difficille colitis; Staph enterocolitis) and in this case vancomycin could be given orally (IV in life threatening cases)
• Teicoplanin is given IM

Side effects:
- Rapid IV → flushing, tachycardia, ↓ BP, skin rashes (Red man syndrome)
- Thrombophlebitis, ototoxicity, circumoral parasthesia...

Inhibitors of Microbial Protein Synthesis

1. Aminoglycosides

• Aminosugars
• Highly toxic
• Polar substances (water soluble=Hydrophilic) never absorbed by intestine .

Include:

Streptomycin	Gentamicin	Netilmicin
Kanamycin	Tobramycin	Amikacin
Neomycin	Paromomycin	

Common properties:
• Have similar structure (group of antibiotics which contain **amino sugars** and a **cyclohexane ring**)
• Differ in pharmacokinetic properties (t ½) Biological half life
• Have similar spectrum of activity; highly effective against G-ve bacteria (some are broad spectrum but mostly used against gram-ve bacteria)

- Bactericidal
- Ineffective orally (because they are polar and the intestines can not absorb them.)
- Interfere with the integrity of bacterial membrane and inhibit bacterial protein synthesis (30S inhibitors) (bind irreversibly to the 30S subunit of ribosome inhibiting protein synthesis and cause misreading of mRNA)
- Do not bind plasma or tissue proteins
- Have small AVD (25% of lean body wt), **do not penetrate the BBB & eye**
- Rapid excretion as free form (unchanged) by the kidney (no secretion or reabsorption)
- Toxic (have narrow therapeutic window)

Ototoxic, Nephrotoxic, Curare-like effect (muscular relaxent effect or muscular weakness), Allergy

- Neomycin the **most nephrotoxic** used only topically and orally (local GIT infection)
- Gentamicin the drug of choice to treat **neonatal G-ve meningitis**
- Streptomycin is effective in **Brucellosis & T.B**

Dose adjustment to aminoglycosides is necessary in:

- Children & old pts 🧓👧
- Pts with renal disease
- Pts with hypotension
- Pts on diuretics

All such conditions could have high incidence of nephrotoxicity

Aminoglycosides clinical uses:

- Gentamicin, netilmicin, tobramycin, amikacin

1. Very potent against G-ve bacilli (E. coli, Klebsiella, Proteus, Pseudomonas)
2. Synergistic with antipseudomonal PNC's
3. Strains resistant to gentamicin could be sensitive to amikacin and vice versa (important sentence)
4. **Gentamicin** is considered the drug of choice to treat neonatal G-ve bacilli meningitis

• Netilmicin
Similar to gentamicin but less ototoxic and could be effective in infections resistant to gentamicin
• Kanamycin
Same as above but has no activity against Pseudomonas
• Neomycin
Most nephrotoxic (not given systemically), used to sterilize bowel before abdominal surgeries (along with erythromycin as prophylactic agents)
Also used locally on skin and eye

• Streptomycin
Highly effective against TB, used with PNC's to treat Strep endocarditis
Highly effective against brucellosis (Malta fever)
• Paromomycin
Effective only to treat tape worm infestation and intestinal amoebiasis.
It is a first-line treatment for amebiasis or giardiasis during pregnancy

Aminoglycosides toxicity:
- Neuromuscular blockade (curare-like effect)
- Ototoxicity (toxic to 8th cranial nerve), reversible but severe toxicity could lead to deafness Kana (most Ottoxin)>Amikacin >> Genta=Tobra
↑ risk with renal failure or concomitant use of other ototoxic drugs
- Nephrotoxicity
Neo (most sever nephrotoxicity)>>> Genta=Amikacin > Tobra
They lead to acute tubular necrosis; more in pts with renal disease or with concomitant use of other nephrotoxic drugs

2. Macrolide antibiotics

• Static, contain lactone ring + sugars (12-22 carbon lactone ring linked to sugars) a unique structure
• differ in their pharmacokinetic properties (t1/2)

Include:

• Erythromycin; has high activity against G+ve bacteria, little effect against G-ve bacteria.

• Clarithromycin and Azithromycin are more active than erythromycin against several G-ve bacteria as well as Mycoplasma pneumonia, Helicobacter pylori, Toxoplasma gondii, cryptosporidia and several atypical mycobacteria
• Oleandomycin; **Telithromycin; Roxithromycin; Spiramycin**...etc

• Erythromycin is available in 250 and 500 mg tab. and 125mg, 200mg, 400mg/5ml susp. and topical gels and solutions.
(dose 250mg x 4 daily or 500mg x 2 for 10-14 days)

• Azithromycin is available in 250 & 500 mg tab. And 100 & 200mg/5ml suspension dosage forms.
Total dose of azithromycin=1.5-2.5g (3days therapy or 5 days therapy)

This is just to give you an idea of how the halflife of the drug affects the dosage

• Macrolides are considered drugs of choice to treat Corynbacteria diphtheria and mycoplasma pneumonia (along with tetracyclines)

Macrolides mechanism of action:

• it interferes with the translocation process.
Reversibly bind 23S rRNA of the 50S subunit of the ribosome inhibiting translocation during protein synthesis

• Considered alternatives to PNC's (particularly erythromycin) (second line drug) to treat Strep. and Staph. infections e.g. **tonsillitis in patients with penicillin allergy**

• Considered 2nd line therapy to PNC's for Rx of **dental infections (never 1st line because they are static;** resistance develops easily to them, less effective than PNC's in orodental infections and more toxic)

• Given orally; distribute well but cross well inflamed meninges

Side effects to macrolide antibiotics:

- GIT irritation (major & most frequent)
- Allergy
- Cholestatic hepatitis (direct toxic effect or hypersensitivy reaction; reversible; more common in adults; more common with estolate form of erythromycin = the gastric acid resistant form of erythromycin)

3. Chloramphenicol

- Bacteriostatic
- Broad spectrum (G+ve & -ve bacteria and anaerobes)
- The drug of choice to treat H. influenza meningitis and epiglotitis, brain abscesses and Salmonella infections (typhoid and paratyphoid fever) (recent restriction due to toxicity)

Chloramphenicol mechanism of action:

- Binds to rRNA of 50S subunit of the ribosome inhibiting transpeptidation during protein synthesis
- Highly lipid soluble, orally effective and widely used locally on eye 👁️💊
- The best antibiotic that crosses BBB 🧠

Metabolized to inactive metabolites by conjugation (glucuronide)

Cholramphenicol side effects:

- Reversible dose-related bone marrow depression (So it will affect the formation of RBC, WBC, and platelets) 🦴
- Aplasic anemia (allergic in nature; fatal; none dose-related)
- Gray-baby syndrome (fatal toxic reaction; abdominal distension, severe vomiting, cyanosis (bluish discoloration of a skin) hypothermia, collapse)
- Optic neuritis, nausea, vomiting, diarrhea 👁️🤢🤮💩

4. Spectinomycin

- Bacteriostatic
- Chemically related to aminoglycoside
- It binds to the 30S subunit of the bacterial ribosome and inhibits protein synthesis
- A single IM injection is adequate

• Alternative to PNC's and cephalosporins to treat uncomplicated gonococcal infection in pts allergic to PNC's and cephalosporins

5. Tetracyclines

• Bacteriostatic
• Broad spectrum (antibacterial, antiparasitic...)
• Have different structure but similar MOA
• Inhibitors of bacterial protein synthesis (bind to the 30S ribosomes)
• Somewhat selective since they penetrate bacterial plasma membrane by **energy dependent mechanism** which is absent in human cells

Tetracyclines include:

Tetracycline Chlortetracycline Oxytetracycline
Demeclocycline Doxycycline Minocycline Methacycline

Mechanisms of bacterial resistance to tetracyclines:

- Altered bacterial permeability to tetracycline
- Increased efflux of tetracyclines by bacterial energy dependent mechanism leading to lower intracellular antibiotic concentration
- Altered bacterial protein structure

Tetracyclines spectrum of activity:

• Effective against G+ve and -ve bacteria
• Considered drugs of choice to treat:
- Rickettsia
- Mycoplasma pneumonia (erythromycin 2nd line)
- Clamydia
• Also effective against certain protozoal infections, long term treatment of **acne** and **vibrio cholera**

Pharmacokinetics of tetracyclines:

- Differ in DOA, Doxycycline has the longest DOA (given **once daily**); available also in topical dosage forms (creams; lotions; oint.; ophthalmic, ear & nasal drops...)

- Could be given orally and parenterally (IV)
- Food, Mg++, AL+++ and Ca++ (milk) form complexes with tetracyclines ↓ absorption of tetracyclines 🍲🥛
- Distribution good but do not cross BBB
- Excretion In feces (Mino-, Oxy- & chlortetracycline) 💩
- In urine (other tetracyclines)

Tetracyclines toxicity & side effects:

- Dental staining; yellowish to brownish (**irreversible**) (incorporate into growing teeth & bones) (contraindicated during pregnancy & in children <8yrs old) 🦷🤰👧
- N, V, D 🤢🤮💩
- Hepatotoxicity
- Photosensitivity; more with Demeclo- and Doxycycline 🌞
- Nephrotoxicity; more in patients with renal disease and with administration of other nephrotoxic antibiotics; least with Doxy- and Minocycline
- Increased intracranial pressure 💀
- Superinfection with Candida albicans and C. difficile

6. Lincomycin & Clindamycin

• Static
• Inhibitors of protein synthesis (bind exclusively to the 50S subunit of bacterial ribosomes, thus suppressing protein synthesis by disrupting the formation of the 70S initiation complex and by inhibiting the aminoacyl translocation step of peptide bond formation)

• Have good activity against G+ve (Strep; Staph), Enterobacteriaceae (Salmonella, Shigella, Escherichia, Klebsiella, Proteus); Vibrioaceae (Vibrio Cholera); Pasteurellaceae (Pasteurella, Haemophilus)...

• Demonstrate good effect against bone and teeth infections and Corynebacteria acne 🦷🦴

Side effects (limit their uses):
- Skin rashes
- Hepatotoxicity
- Pseudomembraneous colitis, Rx: stop drug & give vancomycin + metronidazole

Contraindications:
Hepatic impairment, previous history of pseudomembranous colitis

Locally effective antimicrobials

Polymyxins (Polymyxin B & Polymyxin E = Colistin)
• Cidal
• Interfere with function or permeability of the plasma membrane
• Have good activity against G-ve bacteria & high activity against Pseudomonas
• Very nephrotoxic (more than aminoglycosides)
• Their use is restricted to topical preparations in combination with Bacitracin (cell wall inhibitor) & neomycin (creams, oint's, eye & ear drops...)

Microbial DNA Synthesis Inhibitors

1. Quinolones; Fluoroquinolones

• Inhibitors of microbial DNA synthesis (inhibit bacterial DNA replication by inhibiting bacterial **gyrase enzyme** which is a **type II topoisomerase**)
• Most widely used antibiotics in 2002 but their use has been recently reduced due to toxicity, development of resistance and the introduction of safer new macrolides
• Chemotherapeutic agents
• Cidal
• Broad spectrum (effective against **pseudomonas**)

Quinolones are classified into:

1st generation

Nalidixic acid **Pipemidic acid** **Oxolinic acid**

• **Nalidixic acid** effective more in G+ve infections and only in UTI's (urinary tract antiseptic).
• Has little activity against E. coli; Proteus; Shigella, Enterobacter and klebsiella.
• **No effect against Pseudomonas**

2nd generatipon

Ciprofloxacin Ofloxacin Norfloxacin Enoxacin
Lomefloxcin Nadifloxacin

• exhibit more activity against G-ve bacteria

3rd generation

Levofloxacin Sparfloxacin Gatifloxacin

4th generation

Moxifloxacin Prulifloxacin Gemifloxacin

} have good activity against pseudomonas and anaerobic microorganisms

Most widely used quinolones include:
Ciprofloxacin (2nd); levofloxacin (3rd); moxifloxacin (4th)

• Quinolones are orally effective and well absorbed but affected by food containing Ca++ and iron
• Mainly (particularly Ciprofloxacin & levofloxacin) used in complicated UTI's, respiratory infections, invasive external otitis, bacterial prostatitis and cervicitis, bacterial diarrhoea caused by shigella,salmonella and E.coli

Mechanisms of bacterial resistance to quinolones:
• Some types of bacterial efflux pumps can act to decrease intracellular quinolone concentration
• Production of certain proteins especially by G-ve bacteria that can **bind to DNA gyrase**, protecting it from the action of quinolones

• Mutations in DNA gyrase or topoisomerase which could lead to a **decrease in quinolones binding affinity** and hence decreasing their effectiveness

Quinolones side effects:

• GIT irritation; photosensitivity 🌞
• Cardiac toxicity (many may be associated with prolongation of QT interval) (many were withdrawn because of this side effect) 🫀
• Some are not recommended in children or during pregnancy because they may interfere with cartilage development 🧑🤰
• Some have been reported to be carcinogens 🦀

2. Nitrofurantoin

• Synthetic, bactericidal orally effective antibiotic
• It is effective against G+ve & G-ve bacteria
• Has good activity against G-ve bacteria particularly E. coli
• Highly effective in UTI's (cystitis) (known as UT antiseptic)

Nitrofurantoin MOA (multiple):

It is converted by bacterial **reductases** into many reactive intermediates leading to direct damaging effect of bacterial DNA, disruption of RNA and protein synthesis and also interfering with many metabolic processes in bacteria

This drug is special in its multiple MOA

• **Development of resistance** to nitrofurantoin is rare, due to multiple sites of action(the bacteria that is sensitive to it remain sensitive forever)

• Pulmonary fibrosis is a major **side effect** to nitrofurantoin
• Nitrofurantoin is contraindicated in patients with G-6-PD deficiency

3. Fosfomycin

• It is a broad-spectrum of activity against both gram-positive and gramnegativeorganisms, including many antibiotic-resistant organisms

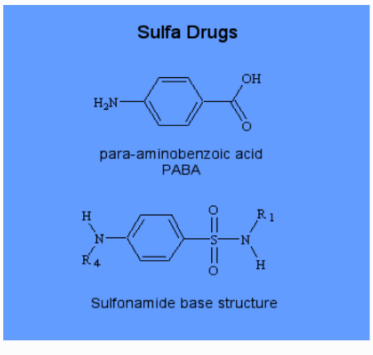
• primarily used to treat lower UTI (cystitis) and occasionally is used for prostate infections
• It disrupts cell wall synthesis by inhibiting phosphoenolpyruvate synthetase and thus **interferes with the production of peptidoglycan**
• It is available in 3g oral powder dosage form for reconstitution
• Use of fosfomycin is commonly restricted to only a single dose because of **rapid microbial resistance**

Fosfomycin is well tolerated but may lead to the following side effects:
- Metallic taste 👅
- Stomach upset
- Dizziness 🥴
- Stuffy nose 🤧
- Back pain
- Vaginal itching or discharge

Antimetabolites

1. Sulfonamides

• Static; broad spectrum chemotherapeutic agents
• Structural analogs of PABA required for synthesis of dihydrofolic acid in bacteria
• Effective against many G+ve & -ve bacteria, nocardia, trachoma, lymphogranuloma, blastomycosis, and many protozoal infections...



Widely used in the management of:

• Upper respiratory tract infections
• UTI's (Sulfamethoxazole; Sulfisoxazole); Toxoplasmosis; Chlamydia infection; protozoal infections; infected burns, eye infection (Sulfacetamide; Sufadiazine)
• Sterilization of bowel before surgery (Sulfadiazine=not absorbed=no systemic effects)
• Sulfasalazine (sulfapyridine - salicylate combination) is used in inflammatory bowel disease (ulcerative colitis, Crohn's disease)

Sulfa Preparations:

- **Sulfamerazine**
- **Sulfamethazine**
- Sulfisoxazole
- Sulfadiazine-local
- Sulfacetamide-local

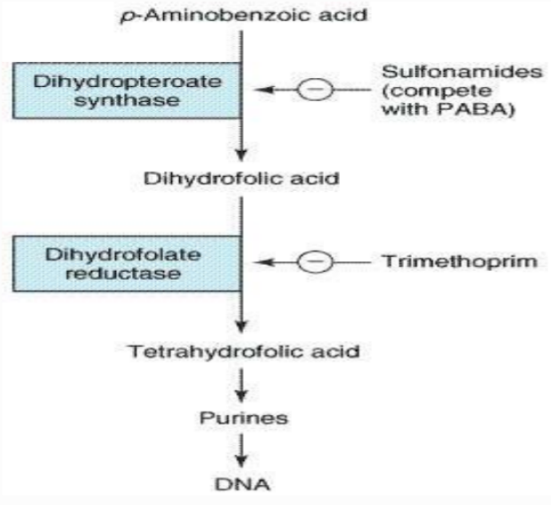
well absorbed

short t1/2

- Sulfamethoxazole (Most widely used sulfa); well absorbed; intermediate-acting
- **Phthalylsulfathiazole** (sulfathalidine) long acting orally effective
- Sulfasalazine; poorly absorbed (10-20%) from the GIT, long acting

Sulfa MOA

Interference with metabolism of MO's



Mechanisms of resistance to sulfa:

- ↓ permeability of bacteria to sulfa
- ↑ production of PABA
- Altered dihydropteroate synthase enzyme

Sulfa drugs inhibit the dihydropteroate synthase enzyme, which is crucial for folate synthesis in bacteria

- Obtained folate by bacteria from environment

Sulfa pharmacokinetics

- Bind plasma proteins (compete with bilirubin binding sites → ↑ bilirubin levels in blood → kernicterus)
- Distribution good including CSF (able to treat CNS infections)
- metabolized by acetylation (metabolites are toxic but devoid of any antibacterial effects) and metabolites are excreted renally

- Sulfa and their metabolites usually precipitate in urine → stones (more common (&most dangerous) with long acting sulfas) 🪨

In order to reduce the risk of renal precipitation:

- Ensure good fluid intake → good renal flow 🚰
- Use sulfa with good urine solubility (Sulfisoxazole)
- Use combined sulfa drugs (synergistic effect, **lower doses → less precipitation)**
- Alkalization of urine (altering the pH)

2. Trimethoprim

-Is a chemotherapeutic agent and is a structural analog to folic acid
- Inhibits dihydrofolate reductase, effective against E. coli; H. influenza; K. pneumonia ineffective against Pseudomonas & Proteus MO's
- Used in Rx and prophylaxis of UTI's
- static and has more rapid OOA as compared to sulfa
- Well absorbed orally like sulfa
- Has similar t1/2life to sulfamethoxazole
- Less crossing to BBB unlike sulfa
- Excreted unchanged (without metabolization) by the kidney
- Associated with less side effects

Sulfamethoxazole + trimethoprim combination:

- is known as Co-trimoxazole
- acts sequentially in preventing nucleic acid synthesis in bacteria (selective)
- is synergistic
- has more spectrum (but still ineffective against Pseudomonal infections)
- more cidal and bacterial resistance is less likely

Sulfa side effects:

- Allergic reactions (frequent)
- Kernicterus 👶
- Renal damage (toxic nephrosis, allergic nephritis, drug crystals)
- Liver damage (rare)
- N & V 🤢🤮
- Blood dyscrasia, hemolysis in G-6PD deficient pts
- Steven-Johnson Syndrome (uncommon); inflammatory condition of skin & mucose membranes

Some Questions that is mentioned by the doctor (characteristic side-effects of drugs)

With what Steven-Johnson syndrome side effect happen? Cotrimoxazole
Red Man Syndrome? Vancomycin
Dental staining? Tetracyclins
Cardiotoxicity? Quinolones
Allergy (Most frequent with) ? PNCs

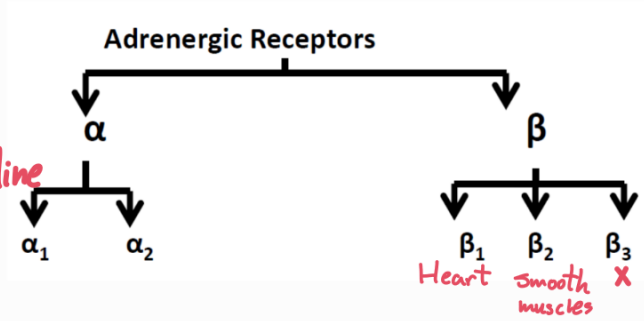
ANS

• Neurotramsmitters: are the chemical mediators released by the neurons to transmit the signals through the synapse
• Sympathomimetic: a drug that **activates sympathetic nervous system**
• Parasympathomimetic: a drug that **activates parasympathetic nervous system**
• Sympatholytic: a drug that **decreases or blocks sympathetic response**
• Parasympatholytic: a drug that **decreases or blocks parasympathetic response**

Sympathetic Nervous system

- fight or flight
- neurotransmitters: Adrenaline/Noradrenaline (the same as epinephrine/norepinephrine) cause **increased dilation and heart - contraction.**
On the other hand, they have **inhibitory effects on GI, secretions, intestines.**
- alpha, beta receptors
In context of asthma, beta agonists are a recommended medication.
In context of hypertension (atherosclerosis), beta blockers are a recommended medication.
But using beta blockers in individuals with **both asthma and hypertension is not recommended** as that will cause more bronchoconstriction.

Adr:	$\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ Adrenaline
NA:	$\alpha_1 + \alpha_2 + \beta_1$ but no β_2 action Nore Adrenaline
Iso:	$\beta_1 + \beta_2$ but no α action



- Adr/Iso: **bronchodilators**
- Beta agonists end with ol eg: **albuterol**
- Beta blockers end with lol eg: **atenolol**
- alpha blockers end with **sin** eg: **prazosin**
- Adr increases heart rate by increasing the automaticity of SA node, cardiac contraction increases.
- Cardioselective beta1 blockers: affect the heart only

Contraindication

- ADR is contraindicated in hypertensive, hyperthyroid, and angina patients
- It should not be given to patients receiving ß blockers (a marked rise in BP can occur)

SNS

Alpha agonist: vasoconstriction (both alpha 1 & 2)
Beta 2 agonist: vasodilation (skeletal muscle, liver, coronaries) Beta 2 stimulants for asthma.

General effects of a blockers

Blockade of vasoconstrictor a1 also a2 receptors peripheral resistance and causes pooling of blood (Hypovolemia) thus decreasing venous return and cardiac output then decreasing BP

• Alpha blockers have no effect on adrenergically induced cardiac stimulation, bronchodilation, or vasodilation because these are predominantly mediated through beta receptors.

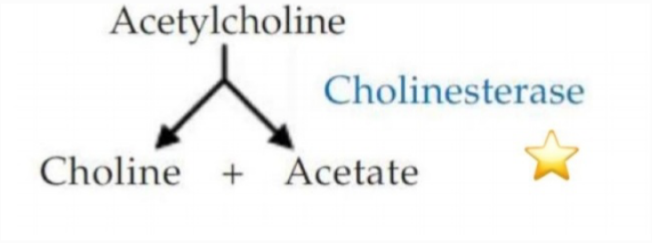
Parasympathetic Nervous System

- rest and digest
- neurotransmitters: Acetylcholine → cholinergic receptors
- Ach has a key role in stimulating GI, secretions, and saliva production.
- cholinergic receptors:

M 1,2,3,4,5 they could be muscarinic or nicotinic (Nn, Nm),
(In GI, muscles & ganglia)

- Nicotinic receptors have no direct therapeutic use
-poisonous gases make irreversible bonds to muscarinic receptors.

Ach structure



• ACh is hydrolyzed by the enzyme cholinesterase, and choline is recycled immediately after release.
• Ach contains ester bond.

Cholinoceptors

Two classes of **cholinoceptors** are **muscarinic** and **nicotinic**

Muscarinic

These receptors are selectively stimulated by muscarine and selectively blocked by atropine

They are located in the heart, blood vessels, eye and glands of the gastrointestinal, respiratory, and urinary tracts, sweat glands, and in the CNS

The muscarinic receptors have been divided into 5 subtypes **M1, M2, M3, M4, and M5**

Muscarinic cholinreceptors

The first 3 have been functionally characterized as following:

M1: has a major role in mediating gastric secretion and relaxation of the lower esophageal sphincter caused by vagal stimulation.

M2: Cardiac muscarinic receptors are predominantly M2 and mediate vagal bradycardia.

M3:Visceral smooth muscle contraction and glandular secretions are elicited through M3 receptors

SNS VS. PSNS effects on Eye muscles

- Sympathetic: mydriasis (**dilation**).
- Parasymp: miosis (**contraction**).

Cholinergic drugs

• They act similarly to ACh, either directly by interacting with cholinergic receptors (**agonists**) or indirectly by increasing the availability of ACh (**anticholinesterases**).

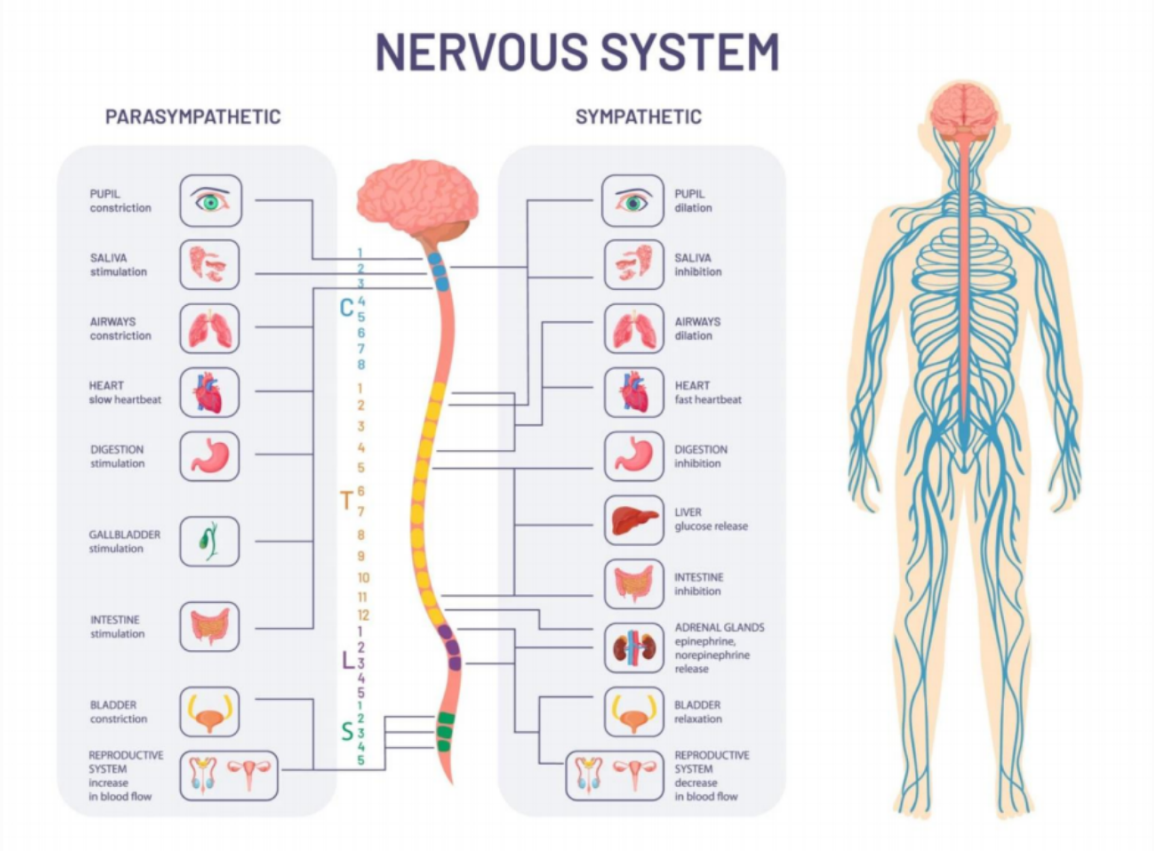
Clinical Uses

1. Parkinson (high Ach, low dopamine).

• It is due to **dopamine deficiency** or **imbalance between Ach and dopamine.**

• The enzyme that degrades dopamine: mono amino oxidase (MAO) catechol-O-methyl transferase (COMT), so if we give a drug to inhibit these enzymes, dopamine increases, Parkinson level decreases.

2. **Cholinergic antidote is atropine** (for example prevents salivation).
3. High doses of Ach will have **minimal effects on sympathetic NS.**



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