# Chemotherapy; Antimicrobials

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# Principles of antimicrobial drugs

- **Objectives**

Know:

- **Principles of antimicrobial therapy**
- **Classes of different antimicrobials**

their spectrum of activity

their pharmacokinetic properties

their mechanism of action

their major side effects…

## Chemotherapy

Drugs used in treating infectious diseases and cancer

- Infectious diseases are a major cause of death worldwide (Kozier, et al. 2008)
- 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 pathogen is 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 categories of 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**
2. ***Viruses:*** **consist primarily of nucleic acid, therefore must enter living cells in order to reproduce (e.g.; rhinovirus, hepatitis, HIV)**

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**

- **General manifestations of infection:**

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

- Fever, chills, rigors
- Pain or aches
- Nausea
- Vomiting
- Weakness

Infection vs inflammation

## Antimicrobials

Classified into 1. antibiotics and

2. chemotherapeutic agents

## 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

## Chemotherapeutics

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

## Antiseptics

Agents that kill or inhibit growth of microorganisms when applied to tissues

## Disinfectants

Agents killing or inhibiting growth of microorganisms when applied to nonliving objects

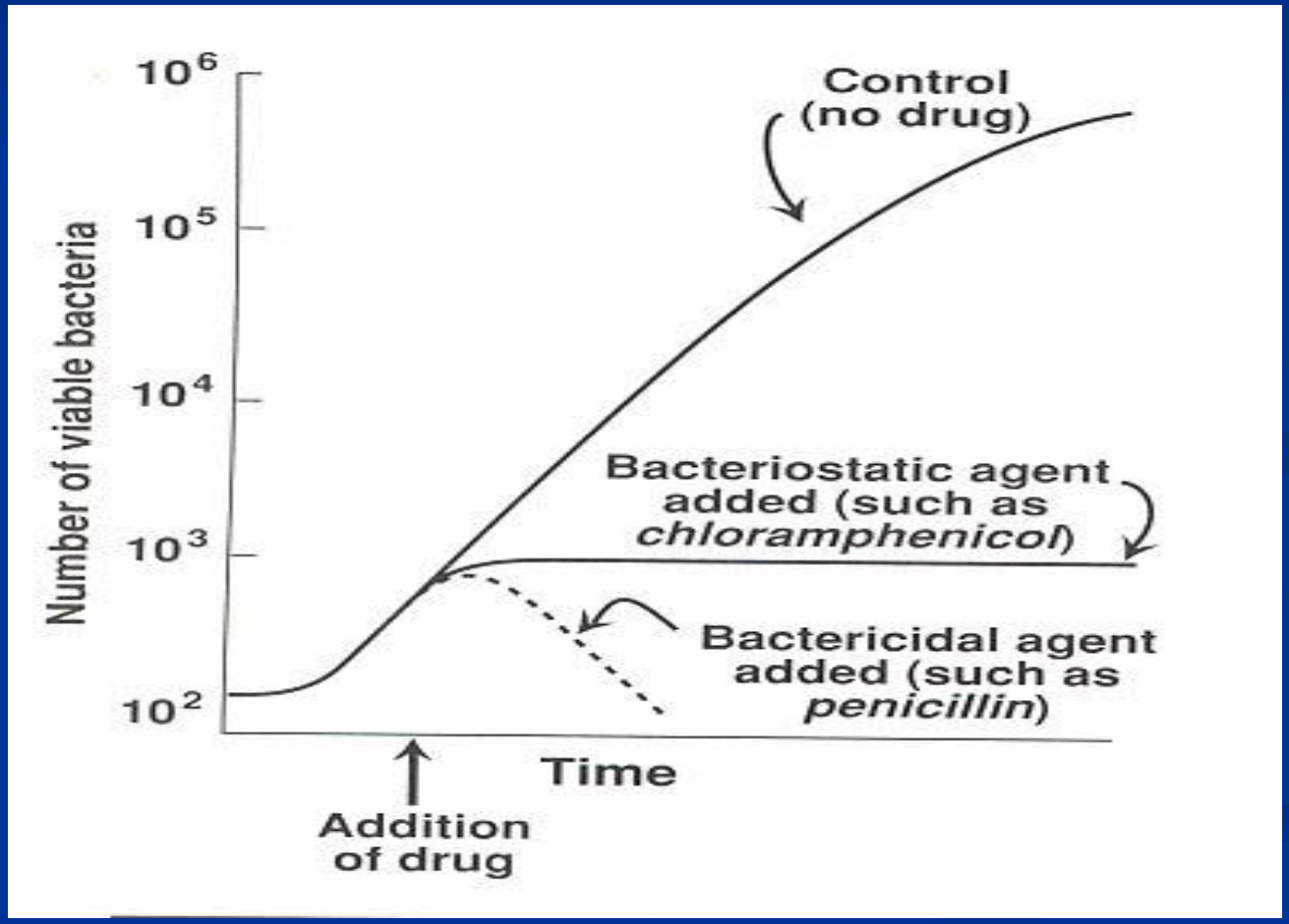
- **Cidal** (Irreversible inhibition of growth)
  An agent that kills microorganisms
  Bactericidal, fungicidal, viricidal…etc
  e.g. Penicillin's, Cephalosporin's, Aminoglycosides…etc
- **Static** (Reversible inhibition of growth)
  An agent that inhibits growth of microorganism
  Bacteriostatic, fungistatic, viristatic…etc
  e.g. Sulfonamides, Tetracyclines, Macrolide antibiotics…etc

- 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)
- **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 agent is 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


$10^6$
$10^5$
$10^4$
$10^3$
$10^2$
Number of viable bacteria
Control
(no drug)
Bacteriostatic agent
added (such as
*chloramphenicol*)
Bactericidal agent
added (such as
*penicillin*)
Time
Addition
of drug

- **Trough Levels:**

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

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 sub-MIC levels of antibiotics

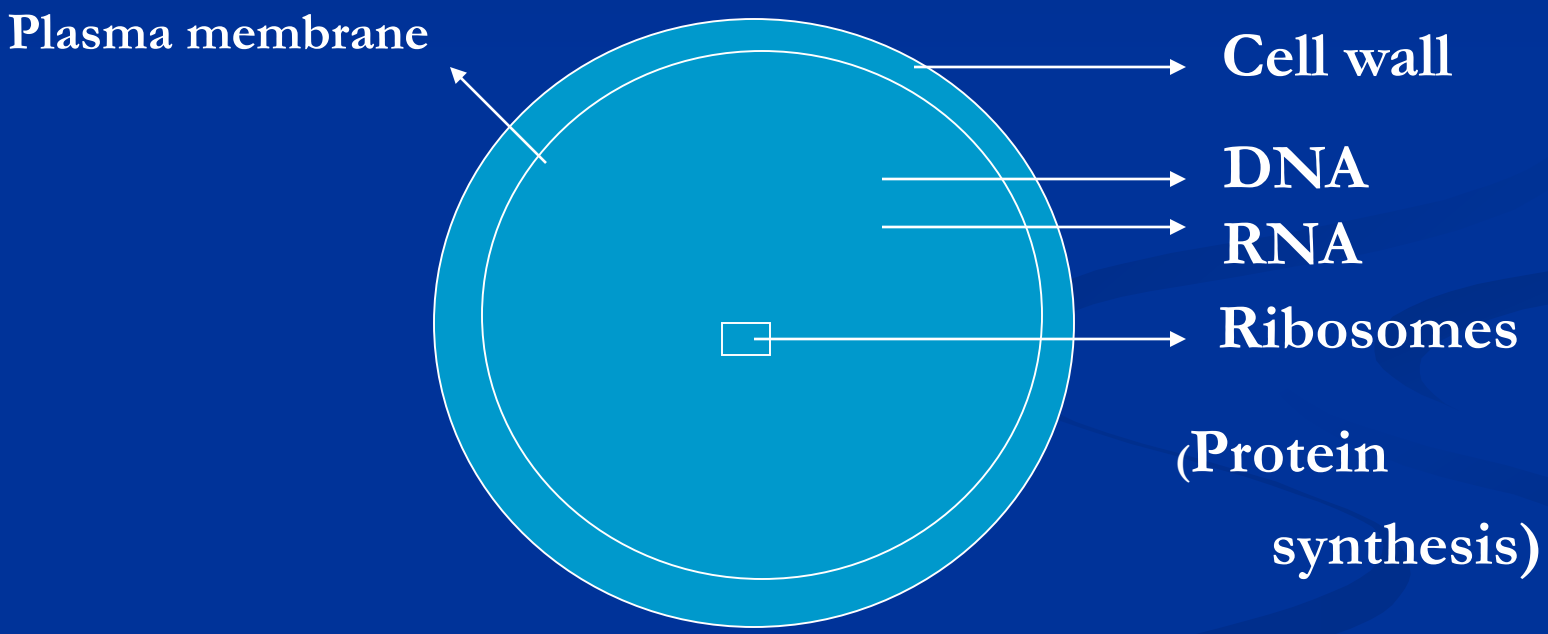
**Post-antibiotic effect (PAE):**

- **PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC**
- **Antimicrobial drugs exhibiting a long PAE (several hours) require only one dose per day (e.g. Aminoglycosides & Fluroquinolones)**

Trough levels may increase the frequency of drug-resistant bacteria

- Frequency of developing resistance is greatly increased at levels just 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:**



- 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)

- 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

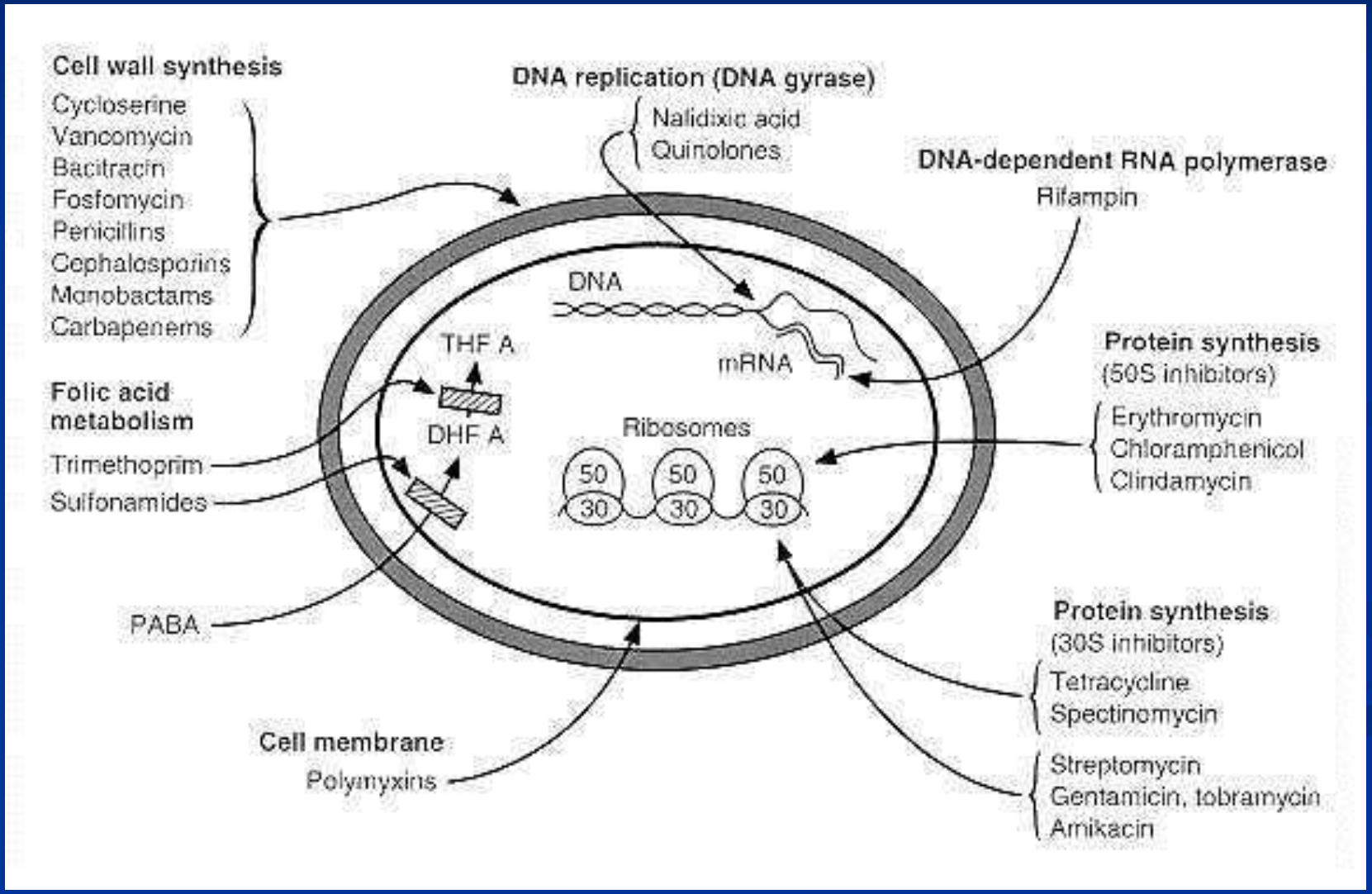
- Inhibitors of RNA

Rifampicin

- Inhibitors of protein synthesis

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

- Interference with metabolism of microorganisms


Cell wall synthesis
Cycloserine
Vancomycin
Bacitracin
Fosfomycin
Penicillins
Cephalosporins
Monobactams
Carbapenems
DNA replication (DNA gyrase)
Nalidixic acid
Quinolones
DNA-dependent RNA polymerase
Rifampin
DNA
mRNA
THF A
DHF A
Folic acid metabolism
Trimethoprim
Sulfonamides
PABA
Ribosomes
50
30
50
30
50
30
Protein synthesis
(50S inhibitors)
Erythromycin
Chloramphenicol
Clindamycin
Protein synthesis
(30S inhibitors)
Tetracycline
Spectinomycin
Streptomycin
Gentamicin, tobramycin
Amikacin
Cell membrane
Polymyxins

- **Classification of antimicrobial:**

According to:

- Mechanism of action
- Chemical structure
- Antimicrobial activity (spectrum of activity)

* 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)

* 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)

* Extended-spectrum antibiotics

Agents that are effective against gram-positive organisms & also against a significant No. of gram-negative 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
- Sometimes there is a need to combine more than one antimicrobial

- **Selection of an antimicrobial agent:**

Factors affecting selection:

1. Causative microorganism (susceptibility): 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)
   - Bacteriological examination (culture and sensitivity)
   - Serology-measures antibody levels
   - Polymerase Chain Reaction (PCR) detects the specific DNA for a specific organism

2. Pharmacokinetic factors:

Site of infection CNS, prostate, vitreous body of the eye…

Renal disease (poor kidney function causes antibiotics that ordinarily secreted by this route to accumulate & lead to serious adverse effects e.g. aminoglycosides)

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

Route of administration

3. Toxicity and side effects to antibiotic
4. Interactions with other drugs
5. Cost

6. 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)

7. Genetic factors

Sulfonamides, Chloramphenicol, Nitrofurantoin → severe hemolysis in G6PD deficient individuals

7. Pregnancy  Streptomycin → Deafness

8. Lactation

Sulfonamides → hemolysis in G6PD deficient newborn

8. Local factors at site of infection e.g. abscesses

- **Bacterial resistance:**

Occurs:

- When clinical condition of host is impaired
- When normal flora have been suppressed
- With interrupted or inadequate Rx
- 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:**

- 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

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

- Acquired resistance

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

- Mutation or genetic change
- Adaptation

Production of enzymes breaking the antimicrobial e.g. β-lactamases

- 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, $R_x$ of suppurative diseases, $R_x$ of viral infections with antibacterial agents

- **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 e.g. G-ve

- 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

- **Combined therapy:**

Indications:

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

- To reduce emergence of resistance

- 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

Outcome of combined chemotherapy:

- Indifference

- Antagonism  Cidal + static

- Synergism (Penicillins + aminoglycosides)

## 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, meningococcal meningitis

- Prevent 2º 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:**

- Hypersensitivity

- Direct toxicity

- Super infection

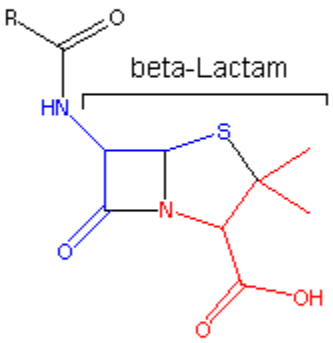
Alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria

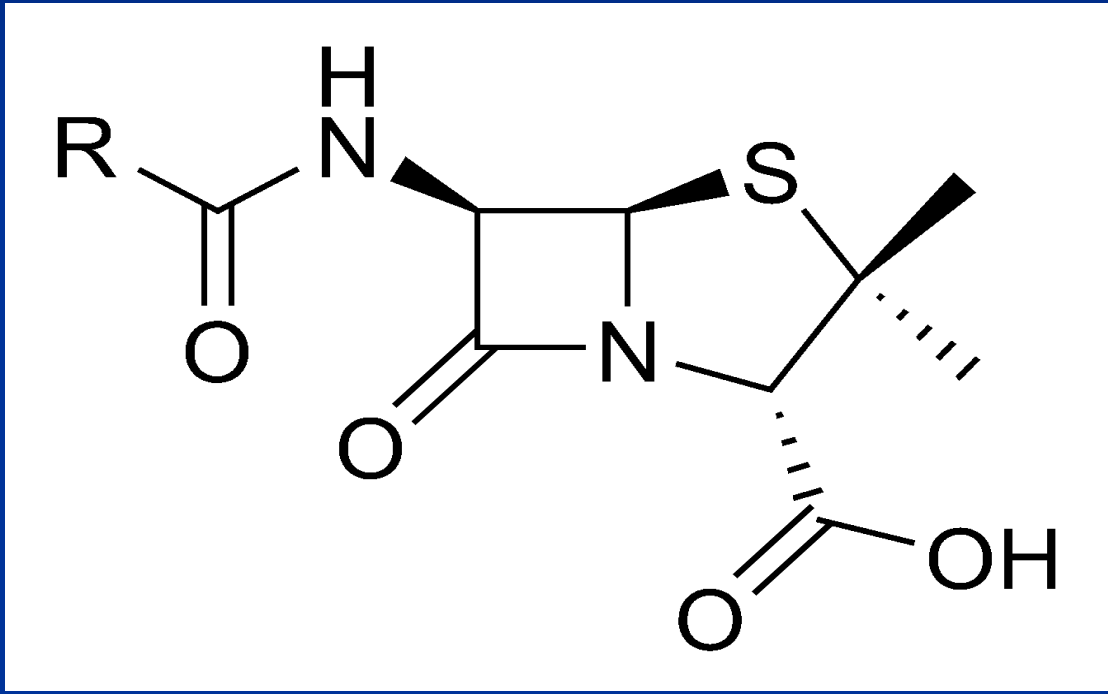
# Inhibitors of Microbial Cell Wall

## 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

## Penicillin - Beta Lactam Structure

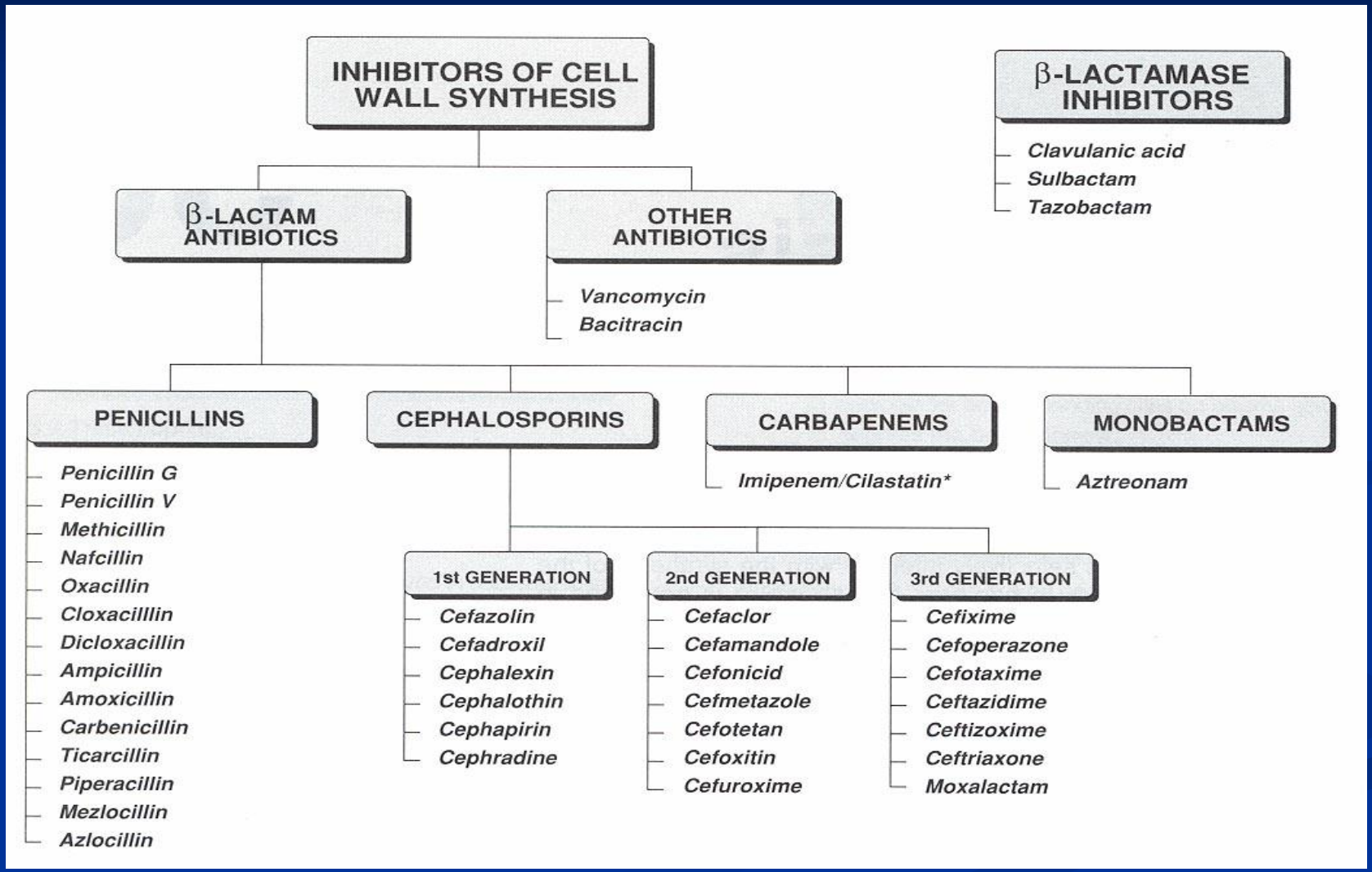



R
H
N
O
S
N
O
O
OH

- 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..etc
- The β-lactam ring is the site of attack by gastric acidity and lactamases

- **Beta Lactams Mechanism of Action:**
- Inhibit synthesis of bacterial cell walls by binding to proteins in bacterial cell membranes e.g. PBP's
- Binding produces a defective cell wall that allows intracellular contents to leak out (lysis)
- Most effective when bacterial cells are dividing

# Inhibitors of Cell Wall Synthesis



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

- Staph aureus
- Moraxella catarrhlis
- Neisseria gonorrhoeae
- Enterobacteriaceae
- Hemophilus influenzae
- Bacteroides species

# Penicillins (PNC's)

- Most widely used antibiotics, most effective, least toxic and cheap
- Derivatives of 6-aminopenicillanic acid (ß-lactam ring is important structure)
- Derived from a fungus
- Prototype is Penicillin G
- Widely distributed except in CSF (except if inflammation is present) and in intraocular fluid
- Most serious complication is hypersensitivity
- Can cause seizures and nephropathy

- Natural penicillins:

Benzylpenicillin=Penicillin G  IM, IV

Acid labile, 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  Oral

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

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…etc
- Amoxicillin has good activity against Helicobacter pylori (+ PPI's ± Clarithromycin ± Metronidazole)

- Antipseudomonal PNC's:

Piperacillin > Mezlocillin=Ticarcillin > Carbenicillin

All are synergistic with aminoglycosides against Pseudomonas

- Amidinopenicillins:

Mecillinam (IM; IV)  Pivmicillinam (oral)

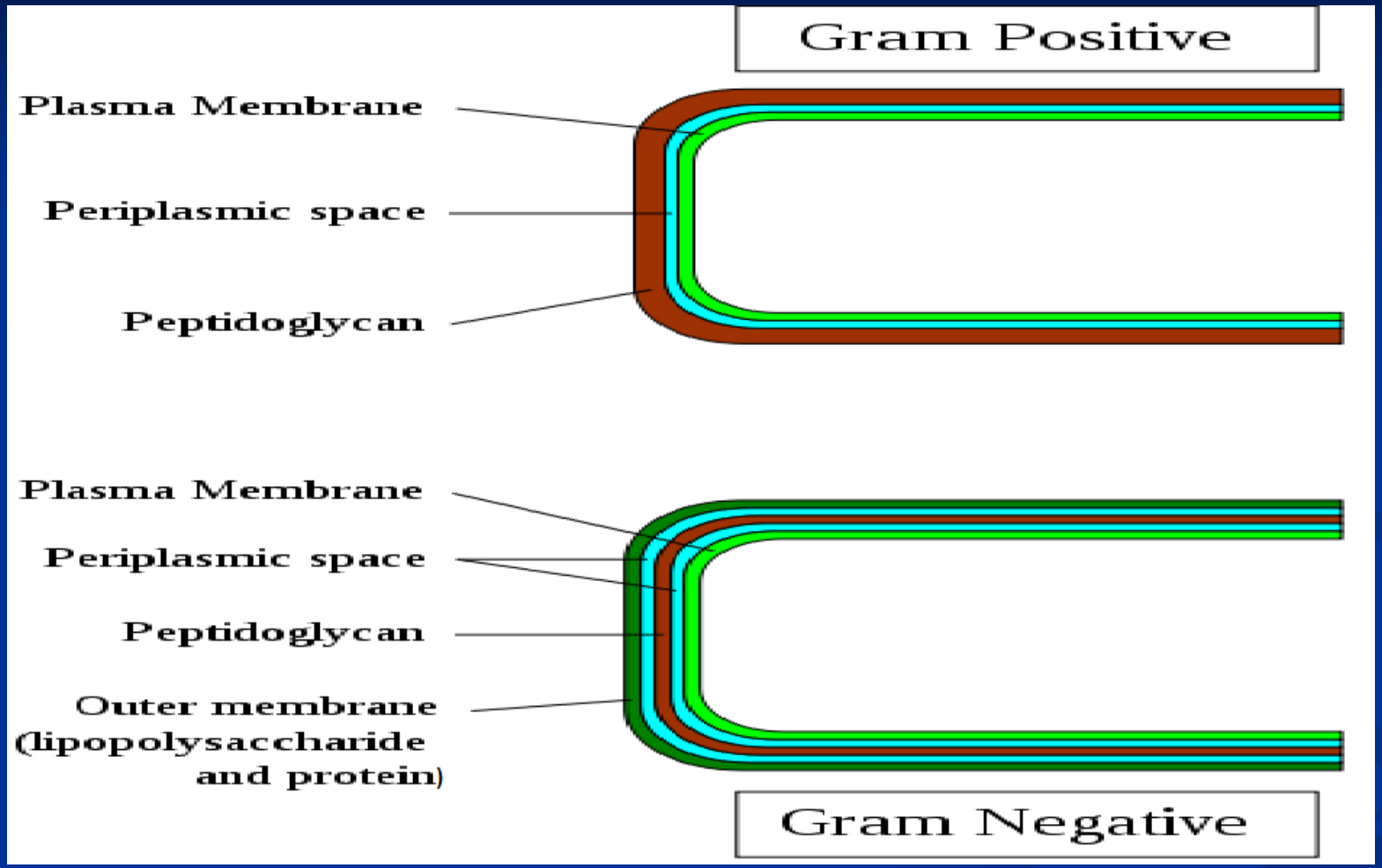
Most potent PNC's against enterobacteria (Salmonella, E. coli, Klebsiella, Shigella…), have little or no activity against G+ve cocci or pseudomonas; synergistic with other β-lactams but not with aminoglycosides

- **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)


Gram Positive
Plasma Membrane
Periplasmic space
Peptidoglycan
Plasma Membrane
Periplasmic space
Peptidoglycan
Outer membrane
(lipopolysaccharide
and protein)
Gram Negative

- **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

- **β-lactemase inhibitors:**

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

Clavulinic 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/increased efflux (pseudomonas)

- **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 (IV oxacillin)
- Bone marrow depression (reversible) (IV nafcillin)
- Nephrotoxicity (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

- Absolute contraindications to all PNC's in pts with history of allergy

# 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 $1^{st}$ $2^{nd}$ $3^{rd}$ $4^{th}$ and $5^{th}$ generations

*** First generation**

Cefadroxil

Cefalexin Oral

Cefazolin IM, IV

Cephapirin

Cephradine

Cephaloridine

*** Second generation**

Cefaclor Oral

Cephamandole IM, IV

Cephmetazole

Cefonicid

Cefotetan

Cefoxitin

Cefprozil

Cefuroxime

Cefuroxime axetil

Loracarbef

*** Third generation**

**Cefixime** Oral

Cefoperazone IM, IV

**Cefdinir** Cefpodoxime

Cefotaxims Ceftazidime

**Ceftriaxone** Ceftibuten Ceftizoxime

*** Fourth generation**

**Cefepime** IM, IV

*** Fifth generation**

**Ceftaroline** IV

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; 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

- Hemolytic anemia

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

- **Other β- lactam antibiotics:**

**- Carbapenems e.g. Imipenem, Meropenem**

*** 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**

- Some consider imipenem the drug of choice in the management of polymicrobial pulmonary, intra-abdominal and tissue infections
- Imipenem is metabolized and excreted by the kidney. It is metabolized in kidney by the enzyme dehydropeptidase I; so it is combined with Cilastatin (inhibitor to dehydrpeptidase I) to decrease rapid metabolic clearance of imipenem
- Seizures are major side effect to imipenem

* **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

- **Carbacephems** e.g. Loracarbef Oral

Spectrum of activity similar to 2nd generation cephalosporin particularly cefaclor and cefprozil; effective orally; excreted renally

- **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)

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
- Narrow spectrum of activity, effective against G+ve bacteria especially methicillin resistant Staph aureus (MRSA)
- Alternatives 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

## Aminoglycosides

Aminosugars

Highly toxic

Polar substances

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 ($t_{1/2}$)
- Have similar spectrum of activity; highly effective against G-ve bacteria (some are broad spectrum but mostly used against gram-ve)

- Bactericidal
- Ineffective orally
- 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 re-absorption)
- Toxic (have narrow therapeutic window)

Ototoxic Nephrotoxic

Curare-like effect 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**

**Very potent against G-ve bacilli (E. coli, Klebsiella, Proteus, Pseudomonas…)**

**Synergistic with antipseudomonal PNC's**

**Strains resistant to gentamicin could be sensitive to amikacin and vice versa**

**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

- **Aminoglycosides toxicity:**

- Neuromuscular blockade (curare-like effect)

- Ototoxicity (toxic to 8th cranial nerve), reversible but severe toxicity could lead to deafness

Kana >Amikacin >> Genta=Tobra

↑ risk with renal failure or concomitant use of other ototoxic drugs

- Nephrotoxicity

Neo >>> Genta=Amikacin > Tobra

They lead to acute tubular necrosis; more in pts with renal disease or with concomitant use of other nephrotoxic drugs

## Macrolide antibiotics

Static, contain lactone ring + sugars (12-22 carbon lactone ring linked to sugars)

Include:

Erythromycin; Clarithromycin; Azithromycin

Oleandomycin; Telithromycin; Roxithromycin; Spiramycin…etc

Erythro. has high activity against G+ve bacteria, little effect against G-ve bacteria

- Clarithromycin and Azithromycin are more active than erythromycin against several gram negative bacteria as well as Mycoplasma pneumonia, Helicobacter pylori, Toxoplasma gondii, cryptosporidia and several atypical mycobacteria
- Macrolides differ in their pharmacokinetic properties ($t_{1/2}$)

- 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 tablet & 100 & 200mg/5ml suspension dosage forms
- Total dose of azithromycin=1.5-2.5g (3days therapy or 5 days therapy)

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

- **Macrolides mechanism of action:**

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 drugs) 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)

# 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
- Aplasic anemia (allergic in nature; fatal; none dose-related)
- Gray-baby syndrome (fatal toxic reaction; abdominal distension, severe vomiting, cyanosis, hypothermia, collapse)
- Optic neuritis, nausea, vomiting, diarrhea

## Spectinomycin

- Bacteriostatic
- Chemically related to aminoglycoside
- It binds to the 30S subunit of the bacterial ribosome and inhibits protein synthesis
- Alternative to PNC's and cephalosporins to treat uncomoplicated gonococcal infection in pts allergic to PNC's and cephalosporins
- A single injection is adequate

# 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

- **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 include:**

Tetracycline

Chlortetracycline

Oxytetracycline

Demeclocycline

Doxycycline

Minocycline

Methacycline

- **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

# 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

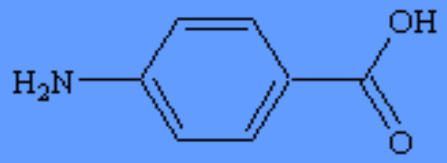
Very nephrotoxic (more than aminoglycosides)

Their use is restricted to topical preparations in combination with Bacitracin (cell wall inhibitor) & neomycin (creams, oint's, eye & ear drops…)

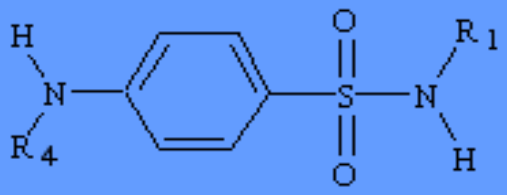
# Antimetabolites (Sulfonamides)

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

# Sulfa Drugs




para-aminobenzoic acid
PABA




Sulfonamide base structure

Widely used in the management of:

Upper respiratory tract infections

UTI's (Sulfamethoxazole; Sulfisoxazole ); Toxoplasmosis; Clamidia 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

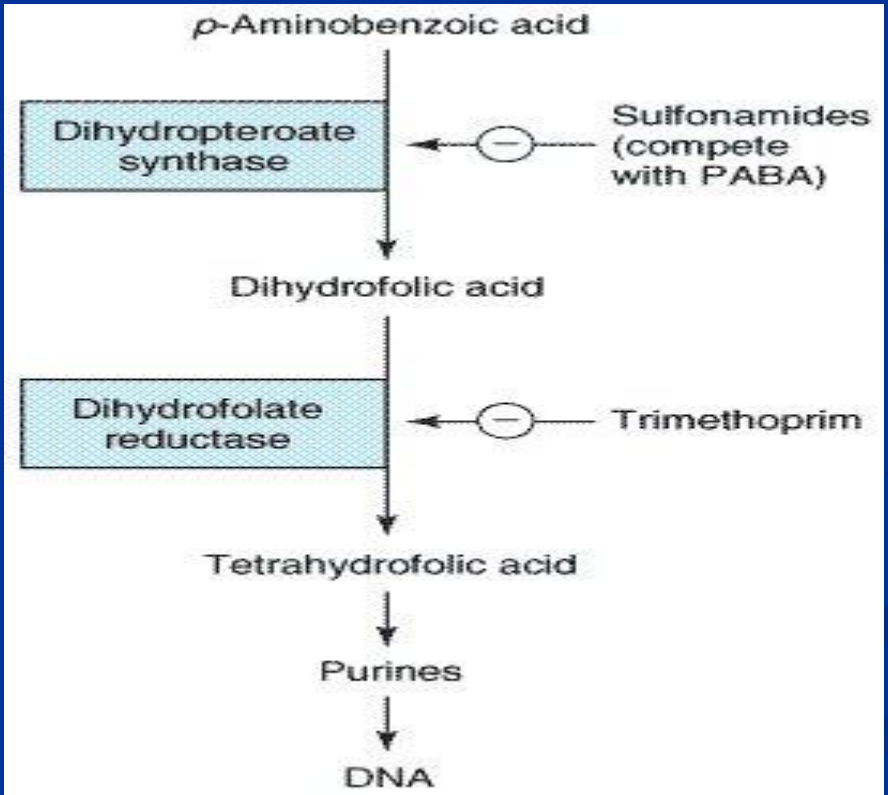
short $t_{1/2}$

Sulfamethoxazole (Most widely used sulfa); well absorbed; intermediate-acting

Sulfasalazine; well absorbed 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
- 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

Sulfa drugs are 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

- Ensure good fluid intake → good renal flow
- Use sulfa with good urine solubility (Sulfisoxazole)
- Use combined sulfa drugs (synergistic effect, lower doses → less precipitation)

- **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

- Trimethoprim is static and has more rapid OOA as compared to sulfa
- Well absorbed orally like sulfa
- Has similar $t_{1/2}$ life to sulfamethoxazole
- Less crossing to BBB unlike sulfa
- Excreted unchanged by the kidney
- Associated with less side effects

- **Sulfamethoxazole + trimethoprim combination:**

- is known as Cotrimoxazole

- 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 & mm's

# Microbial DNA Synthesis Inhibitors

## Quinolones; Fluoroquinolones

- 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)
- Inhibit bacterial gyrase (inhibit bacterial DNA replication by inhibiting topoisomerase)

- **Quinolones are classified into:**

1st generation

Nalidixic acid Pipemidic acid Oxolinic acid

2nd generatipon

Ciprofloxacin Ofloxacin Norfloxacin
Enoxacin Lomefloxcin Nadifloxacin

3rd generation

Levofloxacin Sparfloxacin Gatifloxacin

4th generation

Moxifloxacin Prulifloxacin Gemifloxacin

- 1st generation e.g. 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 generation exhibit more activity against G-ve bacteria
- 3rd & 4th generations 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 Gram-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

## 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

- 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