CHEMOTHERAPY

Chemotherapy
The use of drugs to treat a disease caused by microorganisms & parasitic infections -- bacteria, viruses, protozoa, fungi, worms
By convention the term is used to **include therapy of cancer**
Antimicrobials / Antibiotic
This distinction is no longer used
Antimicrobial --- All chemotherapeutic agents that kills or inhibits the growth of microorganisms
Antibiotic --- The substance **produced by a microorganism** that kills or inhibits the growth of another microorganism
Sulphonamides, INH, quinine are not antibiotics; they are antimicrobials
No antibiotic is effective against all microbes
Spectrum of activity
The spectrum is the group of the bacteria for which a particular class of antibiotic is therapeutically effective
Narrow spectrum
Extended spectrum
Broad spectrum

β-LACTAM ANTIBIOTICS

Bacterial cell wall synthesis inhibitors
Beta-Lactam antibiotics
Glycopeptide antibiotics
Other cell wall or membrane-active agents

BETA-LACTAM ANTIBIOTICS

Penicillins and cephalosporins are the major antibiotics that inhibit bacterial cell wall synthesis. They are called beta-lactams because of the unusual 4-member ring that is common to all their members

PENICILLINS

Discovery of Penicillin

1929 – Alexander Fleming observed antibacterial nature associated with a mold

Fleming published results, but little came from it until 10 years later

Penicillin is the least toxic drug of its kind was the first to be discovered. It was originally obtained from the **fungus *Penicillium notatum,***

The name *Penicillium* comes from penicillus = brush, and this is based on the brush-like appearance of the fruiting structures

Mechanism of action

The penicillins interfere with the last step of **bacterial cell wall synthesis** (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane.
Cell lysis can then occur, either through
osmotic pressure or
through the activation of autolysins.
These drugs are thus **bactericidal**.
Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall.
Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses. |

Penicillin-binding proteins:

Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.

Inhibition of transpeptidase:

Penicillin's inhibit transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity. As a result of this blockade of cell wall synthesis, the "Park nucleotide“ accumulates.

Production of autolysins:

Many bacteria, particularly the gram-positive cocci, produce degradative enzymes (autolysins). In the presence of a penicillin, the

degradative action of the autolysins proceeds in the absence of cell wall synthesis.

PHARMACOKINETICS

ADMINISTRATION:

The route of administration of a B-lactam antibiotic is determined by the stability of the drug to **gastric acid** and by the severity of the infection.

Routes of administration:

Ticarcillin, carbenicillin, piperacillin, and the combinations of *ampicillin* with *sulbactam, ticarcillin* with *clavulanic acid,* and *piperacillin* with *tazobactam* must be administered **intravenously (IV)** or intramuscularly (IM).

Penicillin V, amoxicillin, amoxicillin combined with *clavulanic acid,* and *indanyl carbenicillin* are only available as **oral preparations**.

Others are effective by the oral, IV, or IM routes

Depot forms:

Procaine penicillin G and *benzathine penicillin G* are administered IM and serve as depot forms.

ABSORPTION

Most of the penicillins are **incompletely** absorbed after oral administration,

However, *amoxicillin* is almost completely absorbed.

Absorption of all the penicillinase-resistant penicillins is decreased by food in the stomach, because gastric emptying time is lengthened, and the drugs are destroyed in the acidic environment.

DISTRIBUTION

Distribution of the β-lactam antibiotics throughout the body is good.

All the penicillins cross the placental barrier, but none has been shown to be teratogenic.

However, penetration into certain sites, such as bone or cerebrospinal fluid (CSF), is insufficient for therapy unless these sites are inflamed

Levels in the prostate are insufficient to be effective against infections.

METABOLISM
Most metabolism of the β-lactam antibiotics is usually insignificant
EXCRETION
The primary route of excretion is through the tubular secretory system of the kidney as well as by glomerular filtration.
Naficillin is eliminated primarily through the biliary route.
The penicillins are also excreted into breast milk and into saliva.

ADVERSE REACTIONS

Penicillins are among the safest drugs, and blood levels are not monitored. However, the following adverse reactions may occur.

Hypersensitivity
Diarrhea
Nephritis
Neurotoxicity
Hematologic toxicities.
Cation toxicity

Hypersensitivity
This is the most important adverse effect of the penicillins.
The major antigenic determinant of penicillin hypersensitivity is its metabolite**, penicilloic acid**, which reacts with proteins and serves as a hapten to cause an immune reaction.
Approximately five percent of patients have some kind of reaction, ranging from maculopapular rash to"angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis.

Diarrhea
This effect is a common problem
is caused by a disruption of the **normal balance of intestinal microorganisms**.
It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum.
As with some other antibiotics, **pseudo-membranous colitis** may occur.

All penicillins, but particularly ***methicillin,*** have the potential to cause acute interstitial nephritis.

Hematologic toxicities

Decreased agglutination may be observed with the antipseudomonal penicillins *(carbenicillin* and *ticarcillin)* and, to some extent, with *penicillin G.*

It is generally a concern when treating patients who are predisposed to hemorrhage (for example, uremics) or those receiving anticoagulants.

Additional toxicities include eosinophilia

Cation toxicity

Penicillins are generally administered as the **sodium or potassium salt.**

Toxicities may be caused by the large quantities of sodium or potassium that accompany the penicillin.

Sodium excess may result in hypokalemia.

This can be avoided by using the most potent antibiotic, which permits lower doses of drug and accompanying cations.

RESISTANCE

β -Lactamase activity:

This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity

Decreased permeability to the drug:

Decreased penetration of the antibiotic through the outer cell membrane The presence of an efflux pump can also reduce the amount of intracellular drug.

Altered PBPs:

Modified PBPs have a lower affinity for B-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This mechanism may explain MRSA

PENICILLIN-G (BENZYL PENICILLIN)

Antibacterial spectrum

PnG is a narrow spectrum antibiotic; activity is limited primarily to gram positive bacteria and few others.

Cocci:
Streptococci (except group D or enterococci) are highly sensitive, so are many pneumococci.
Staph, aureus, has acquired resistance
gram negative cocci—*Neisseria gonorrhoeae* and N. *meningitidis*
Bacilli:
Gram positive bacilli—Majority of *B. anthracis, Corynebacterium diphtheriae,* and practically all *Clostridia (tetani* and others), *Listeria* are highly sensitive,
spirochetes *(Treponema pallidum* and others)
Actinomyces israelii is only moderately sensitive. Majority of gram negative bacilli are insensitive to PnG.

Pharmacokinetics
Penicillin G is acid labile—destroyed by gastric acid. As such, less than 1/3 of an oral dose is absorbed in the active form. Absorption of sod. PnG from i.m. site is rapid and complete.
It is distributed mainly extracellularly; reaches most body fluids but penetration in serous cavities and CSF is poor. However, in the presence of inflammation (sinovitis, meningitis, etc.) adequate amounts may reach these sites..
Has very rapid renal excretion; about 10% by glomerular filtration and rest by tubular secretion.
The plasma half life of PnG in healthy adult is 30 min.
Tubular secretion of PnG can be blocked by probenecid
Adverse Effects
Local irritancy and direct toxicity
Pain at i.m. injection site, nausea on oral ingestion and thrombophlebitis of injected vein are dose related expressions of irritancy.
Accidental i.v. injection of procaine penicillin produces CNS stimulation, hallucinations and convulsions due to procaine. Being insoluble, it may also cause microembolism.
Hypersensitivity An incidence of 1-10% is reported. PnG is the most common drug implicated in drug allergy.

Clinical Uses

Streptococcal infections

Like pharyngitis, otitis media, scarlet fever, rheumatic fever respond to ordinary doses of PnG given for 7-10 days. For subacute bacterial endocarditis (SABE) caused by *Strep, viridans* or *faecalis*
Pneumococcal infections
Meningococcal infections
Gonorrhoea PnG has become unreliable for treatment of gonorrhoea
Syphilis T. pallidum
Diphtheria
Tetanus and gas gangrene
Prophylactic uses

The valid prophylactic uses are:

Rheumatic fever: Low concentrations of penicillin prevent colonization by streptococci responsible for rheumatic fever.
Gonorrhoea or syphilis: Procaine penicillin or benzathine penicillin before or within 12 hours of contact affords protection for both these sexually transmitted diseases.
Bacterial endocarditis: can be largely prevented in patients with valvular heart disease by covering by penicillin—dental extractions, endoscopies, catheterization and other surgical procedures, which are likely to cause bacteremia.
Agranulocytosis patients: Penicillin may be used alone or in combination with an aminoglycoside antibiotic.
Surgical infections: can reduce wound infection.

SEMISYNTHETIC PENICILLINS

The aim of producing semisynthetic penicillins has been to overcome the shortcomings of PnG, which are:

Poor oral efficacy.
Susceptibility to penicillinase.
Narrow spectrum of activity.
Hypersensitivity (this has not been overcome in any preparation).
β-lactamase inhibitors have been developed which augment the activity of penicillins against β-lactamase producing organisms
CLASSIFICATION
1. *Acid resistant alternative to penicillin* *G*
Phenoxymethyl penicillin (Penicillin V).

2. Penicillinase resistant penicillins Methicillin, Oxacillin, Cloxacillin.

3.Extended spectrum penicillins

Aminopenicillins: Ampicillin, Bacampicillin, Amoxicillin
Carboxypenicillins: Carbenicillin, Carbenicillin indanyl, Carbenicillin phenyl (Carfecillin), Ticarcillin.
Ureidopenicillins: Piperacillin, Mezlocillin.
Mecillinam (Amdinocillin).
β-lactamase inhibitors Clavulanic acid, Sulbactam.

ACID RESISTANT ALTERNATIVE TO PENICILLIN-G

Phenoxymethyl penicillin (Penicillin V)
It differs from PnG only in that it is acid stable.
The antibacterial spectrum of penicillin V is identical to PnG, but it is about 1/5 as active against *Neisseria,* other gram negative bacteria and anaerobes.
is used only for streptococcal pharyngitis, sinusitis, otitis media, prophylaxis of rheumatic fever, less serious pneumococcal infections and trench mouth

PENICILLINASE RESISTANT PENICILLINS

These congeners have side chains that protect the β-lactam ring from attack by **staphylococcal** penicillinase.

Methicillin must be injected.

Haematuria, albuminuria and reversible interstitial nephritis are the special adverse effects of methicillin. It has been largely replaced by cloxacillin.

Oxacillin, Dicloxacillin, naficillin,cloxacillin are given orally

EXTENDED SPECTRUM PENICILLINS
Aminopenicillins
Ampicillin
many of these have developed resistance

Pharmacokinetics
oral absorption is incomplete but adequate.
Food interferes with absorption.

It is partly excreted in bile. However, primary channel of excretion is kidney,

Uses

Urinary tract infections: Ampicillin has been the drug of choice for most acute infections,.

Respiratory tract infections: including bronchitis, sinusitis, otitis media etc. are usually treated with ampicillin.

Meningitis: It is usually combined with a third generation cephalosporin/chloramphenicol for initial therapy.

Gonorrhoea: It is one of the first line drugs for oral treatment of nonpenicillinase producing gonococcal infections.

Typhoid fever: It is less efficacious than ciprofloxacin in eradicating carrier state.

Cholecystitis: It is a good drug because high concentrations are attained in bile.

Subacute bacterial endocarditis:

Septicaemias and mixed infections: Injected ampicillin may be combined with gentamicin or one of the newer cephalosporins.

Adverse effects

Diarrhoea is frequent after oral administration of ampicillin. It is incompletely absorbed—the unabsorbed drug irritates the lower intestines as well as causes marked alteration of bacterial flora.

high incidence (up to 10%) of rashes,

immediate type of hypersensitivity

Amoxicillin

It is a close congener of ampicillin (but not a prodrug); similar to it in all respects except:

Oral absorption is better; food does not interfere; higher and more sustained blood levels are produced.

Incidence of diarrhoea is less.

It is less active against *Shigella* and *H. influenzae.* Many physicians now prefer it over ampicillin for typhoid, bronchitis, urinary infections, SABE and gonorrhoea.

Carboxy penicillins

Carbenicillin
The special feature of this penicillin congener is its activity against *Pseudomonas aeruginosa* and indole positive *Proteus* which are not inhibited by PnG or aminopenicillins.
It is inactive orally and is excreted rapidly in urine
High doses have also caused bleeding by interferring with platelet function.
The indications for carbenicillin are—serious infections caused by *Pseudomonas* or *Proteus,* e.g. burns, urinary tract infection, septicaemia, but piperacillin is now preferred.
Ticarcillin
It is more potent than carbenicillin against *Pseudomonas,*
but other properties are similar to it.

Ureidopenicillins

Piperacillin
This antipseudomonal penicillin is about 8 times more active than carbenicillin.
It has good activity against *Klebsiella* and is used mainly in neutropenic /immunocompromized patients having serious gram negative infections and in burns.
Elimination *t1/2* is 1 hr. Concurrent use of gentamicin or tobramycin is advised.
Mezlocillin
It has activity similar to ticarcillin against*Pseudomonas* and inhibits *Klebsiella* as well.
It is given parenterally primarily for infections caused by enteric bacilli
CEPHALOSPORINS

Cephalosporins & Cephamycins
Cephalosporins isolated from cephalosporium fungus
Cephamycins are isolated from streptomyces organisms , and are closely related to the cephalosporins
Cephalosporins

Mechanism of action & resistance
Similar to penicillins
Bactericidal
As compares to penicillin are **less susceptible to penicillinases** & therefore has broader spectrum of activity.

Cephalosporins are ineffective against
MRSA,
L. monocytogenes,
Clostridium difficile & **Enterococci**

Classification ---1st to 4th generations
Spectrum of antimicrobial activity
Resistance to beta-lactamases
According to the **order of their introduction into clinical use**
Route of administration

ADVERSE EFFECTS

Cephalosporins – adverse effects
Allergy– skin rashes to anaphylactic shock less frequent than penicillin
Cross reactivity

Complete cross reactivity between different cephalosporins should be assumed
Between penicillin and cephalosporins --- 5 to 10%

Cephalosporins – adverse effects
Patients with history of anaphylaxis to penicillin should not be treated with a cephalosporin

Cephalosporins – adverse effects
I/M --- pain
I/V – phelibitis
↑ nephrotoxicity of aminoglycosides
Hypoprothrombinemia & disulfiram like reaction with ethanol --- drugs containing methythiotetrazole group (**cefamandole, cefoperazone**)
MONOBACTAM & CARBAPENEM

Monobactam & Carbapenem

Monobactam --- **Aztreonam**
Carbapenem -- **Imipenem**, Meropenem, Doripenem, Ertapenem
Imipenem + Cilastatin to protect it from metabolism by renal dehydropeptidase
Monobactam --- **Aztreonam**
No activity against G+Ve bacteria or anaerobes
Narrow spectrum ---enterobacteriaceae, including P aeruginosa
Not used alone in empiric therapy
Monobactam --- **Aztreonam**
Synergistic with aminoglycosides
I/V, elimination by **renal** tubular secretion—t1/2 prolonged in RF
Adverse effects –
GIT upset with possible superinfection, vertigo, headache, & rarely hepatotoxicity, Skin rash may occur
No cross allergenicity with penicillin
Carbapenems --- parenteral
Imipenem, Meropenem, Doripenem, Ertapenem
Low susceptibility to beta-lactamases ---MRSA are resistant
Wide spectrum ---Empiric therapy--- (G (+), G (-), anerobes & pseudomonas)
For pseudomonas often used in combination with aminoglycosides)
Co-drug of choice for infection caused by Enterobacter, Citrobacter, & serratia

Imipenem + cilastatin
Imipenem is rapidly inactivated by **renal dehydropeptidase** and is administered in fixed dose combination with cilastatin, an inhibitor of this enzyme
Cilastatin ↑es the plasma $t_{1/2}$ of imipenem &
inhibits the formation of potentially nephrotoxic metabolite
Imipenem --adverse effects
GIT distress, skin rash, and, at very high plasma levels,
CNS toxicity (confusion, encephalopathy, **seizures**)
There is **partial cross allergenicity with the penicillin**
Imipenem --adverse effects
Meropenem is similar to imipenem except it is not metabolized by renal dehydrogenases, is less likely to cause seizures

Ertapenem has a longer $t_{1/2}$ but is less active against enterococci and pseudomonas, & its I/M injection cause pain and irritation
Glycopeptides

Glycopeptides --- bactericidal
Vancomycin
Teicoplanin
Telavancin
Dalbavancin
Vancomycin **inhibits transglycosylation**
It binds to the D-Ala-D-Ala terminal of nascent peptidoglycan pentapeptide side chain and **inhibit transglycosylation**.
This action **prevents elongation of the peptidoglycan** chain & **interferes with cross-linking**
Mechanism of development of resistance to Vancomycin
Replacement of the terminal D-Ala by **D-lactase** --- ↓ affinity of vancomycin for the binding site --- resistance in strains of
Vacomycin resistant enterococci --- VRE
Vacomycin resistant S.aureus --- VRSA
Vancomycin --- clinical uses
Has **narrow spectrum of activity**
Used for serious infections caused by drug resistant **gram positive organisms**, including **MRSA**
In combination with a 3rd generation cephalosporin such as cefotoxine for treatment of infection due to **penicillin resistant pneumococci (PRSP)**
For clostridium difficile
Vancomycin--pharmakokinetics

Not absorbed from GIT and may be given orally for bacterial enterocolitis
Penetrates most tissue and is eliminated unchanged in the urine
Dose modification is mandatory in RF

Other cell wall
or membrane-active agents

Other cell wall or membrane-active agents

Daptomycin,
Fosfomycin
Bacitracin,

Cycloserine
Daptomycin
Cyclic **lipopeptide**
Spectrum similar to vancomycin but active against vancomycin resistant strains of enterococci and staphylococci
Clinical use --- **endocarditis and sepsis**
Eliminated via kidney
Myopathy – monitor creatine phosphokinase

Fosfomycin --- an **antimetabolite**
An inhibitor of cytosolic **enolpyruvate transferase** ------ prevents the formation of n-acetylmuramic acid, an essential precursor molecule for peptidoglycan chain formation
Resistance develops rapidly ----- ↓ intracellular accumulation of the drug
Synergistic with β-lactam & quinolones
Use – **a single dose treatment of lower UTI in women**. Appears to be safe for use in pregnancy

Bacitracin is a peptide antibiotic
It interferes with a late stage in cell wall synthesis in G +Ve organisms
Nephrotoxic
Use limited to **topical** used
Cycloserine --- **An antimetabolite**
It blocks the incorporation of D-Ala into peptide side chain of peptidoglycan
Neurotoxic ---tremors seizures, psychosis
Second line ATT

BETA-LACTAMASE INHIBITORS

β-lactamases are a family of enzymes produced by many gram positive and gram negative bacteria that inactivate β-lactam antibiotics by opening the β-lactam ring.
Different β-lactamases differ in their substrate affinities.
Two inhibitors of this enzyme are available for clinical use.
clavulanic acid
sulbactam

Clavulanic acid

Obtained from *Streptomyces clavuligerus,*

It inhibits a wide variety **(class II to class V) of β-lactamases** (but not class I cephalosporinase) produced by both gram positive and gram negative bacteria.

Clavulanic acid is a 'progressive' inhibitor : binding with β-lactamase is reversible initially but becomes covalent later—inhibition increasing with time. Called a 'suicide' inhibitor, it gets inactivated after binding to the enzyme.

Pharmacokinetics ---- clavilanic acid

It has rapid oral absorption and a bioavailability of 60%; can also be injected.

Its elimination *t* of 1 hr and tissue distribution matches amoxicillin with which it is used (called co-amoxiclav).

it is eliminated mainly by glomerular filtration

Uses

Addition of clavulanic acid reestablishes the activity of amoxicillin against βlactamase producing resistant *Staph, aureus*, *H. influenzae, N. gonorrhoeae, E. coli, Proteus, Klebsiella, Salmonella, Shigella* and *Bad. fragilis.*

Coamoxiclav is indicated for:

Skin and soft tissue infections,

intraabdominal and gynaecological sepsis

urinary, biliary and respiratory tract infections

Gonorrhoea

Adverse effects

are the same as for a amoxicillin alone;

G.I. tolerance is poorer—specially in children.

Other side effects are Candida stomatitis/vaginitis and rashes.

Some cases of hepatic injury have been reported with the combination

Sulbactam

It is a semisynthetic β-lactamase inhibitor, related chemically as well as in activity to clavulanic acid.
It is also a progressive inhibitor, highly active against class II to V but poorly active against class I (3-lactamase.
On weight basis it is 2-3 times less potent than clavulanic acid
Oral absorption of sulbactam is inconsistent. Therefore, it is preferably given parenterally.
It has been combined with ampicillin

Indications are:

Gonorrhoea.
Mixed aerobic-anaerobic infections,
intra-abdominal, gynaecological,
surgical and skin/ soft tissue infections,

Adverse effects

Pain at site of injection
Thrombophlebitis of injected vein
Rash
diarrhoea