Antimicrobial Agents (Antibiotics)

Website

Videos

Pharmacology 3 | U 3

CHEMOTHERAPY

"Ehrlich" coined the term "Chemotherapy" at the begining of 20th Century to explain the use of Synthetic chemicals to distroy Infective pathogens.

Chemotherapy :- is the use of Synthetic or Natural drugs to distroy or inhibit the growth of patho-gens (bac., virus, Fungi, proto zoa, etc.) & Cancer Cells.

Chemotherapeutic Agents :- Drugs used to treatment of infective dis. & Cancers. → AMA + Antibiotics + Anti cancer

Antimicrobial Agents (AMA) :- Drugs used to treat Infection

Anti-Biotics :- are the substance produced by micro-organism that are used to supress the growth or distroy the other micro-organism at low Concentration (ex- Penicillins etc)

Bacterio statics :- Supress the growth of Bacteria (Sulphonamides)

Bacteriocidals - kill or distroy the Bacteria (Pen., Streptomycin)

$$\text{CHEMOTHERAPEUTIC INDEX} = \frac{\text{Max. Tolarated Dose}}{\text{Min. Curative Dose}} = \frac{LD\ 0.1}{CD\ 99.9}$$

LD 0.1 = Dose which kill all animals except 0.1 %

CD 99.9 = Dose which Cure all animals except 99.9 %

History / Era

Phase I :- Emperical / Pre Ehrlich Phase - befor 1891

↳ Chaulmoogra oil is used by Hindus in Leprosy
↳ Chenopodium by Aztes for intestinal worms
↳ Cinchona bark is used for fever
↳ Mouldy curd by Chinese on boils

Phase II :- Ehrlich Phase (1890 - 1935)

↳ # "Uses of Dyes & Organometalic Compounds"
↳ Arsenical - atoxyl → for Sleeping Sickness
↳ Arsphenamine & Neo-arsphenamine → for Syphilis
↳ "Ehrlich coined the term - Chemotherapy"

Phase III - Modern Era

Domagk (1935) - Prontosil → for Pyogenic Infection. He noticed that p-amino benzene Sulphonamide is an active metabolite. Sulfapyridine, 1st Sulphonamide, marketed in 1938

Antibiotic Phenomeno - by Pasteure (1877) - Anthrax bacilli in urine was inhibited by air born Bacteria.

In 1940s - Waksman research the Actenomycetes as the source of Antibiotics & Discovered Streptomycin

Flemming 1928 - Fungi - ↓ bacterial growth - Penicilline

Domagk, Waksman & Flemming - got NOBEL Prize

Molecular Basis of Chemiotherapy

Target Sites for Chemiotherapy :-

Bacterial Cell :→

1. Cell wall → Peptidoglycan
2. Ribosomes → 70s – Protein Synthesis
3. Chromosome → Single circular DNA

Biochemical Reactions & Drugs :→

Glucose, PO_4^{3-} → [I] → Precursor Molecules, ATP → [II] → Amino ā, Nucleotides, Phospholipids → [III] → Peptidoglycan, Protein, RNA & DNA

Class-I :- Energy Production Pathway, Similar to Human thus, it is not promising Target for Chemotherapy

Class-II :- Utilizatⁿ of Energy & Precursor to make all necessary molecules → Amino ā, Nucleotides, Amino sugar, Phospholipids etc. → Differ From Human, So better promising target site

Synthesis of Folic Acid :- De-Novo Syn.

PABA —DHPS (↑ Sulphonamide (PABA Antagonist))→ DHFA —DHFR (↑ Trimethoprime (Folate Antagonist))→ THFA ~~~ DNA/RNA

Class-III :- Protein, DNA & RNA

\# **Protein Synthesis :-** At 70s Ribosome – 30s & 50s
↳ Protein Syn. Inhibitors – Aminoglycoside, Tetracycline, Erythromycin

\# **Cell wall Syn. – Peptidoglycan Synthesis**
↳ β-lactum Antibiotics – Penicillin, Cephelosporin, Carbepenam
↳ Vancomycin, Bacitracin

\# **Nucleic Acid Synthesis / DNA & RNA**
↳ Bacteria – DNA Gyrase/Toposisomerase IV —✶→ "Quinolones"
↳ Cancer → (A) ↓ Neucleotide → Folate Antagonist & Antimetabolites
(B) DNA —✶→ Alkylating Agents, Nitrosourea
(C) RNA polymerase —✶→ Actinomycin-D
↳ Virus :- (A) DNA polymerase —✶→ Acyclovir, Idoxoridine etc
(B) R.Transcriptase —✶→ Zidovudine
(C) RNA Polymerase —✶→ Foscarnate

Fungi :- (A) Plasma mem. "Ergosterol" —✶→ Azoles

Tubeculosis :- – Mycolic Acid —✶→ Isoniazid
– RNA polymerase —✶→ Rifampicin, Rifamycin

Helminth – Muscle Fibre —✶→ Pyrantel, Avermectins

CLASSIFICATIONS OF CHEMOTHERAPEUTIC AGENTS

I. BASED ON SUSIPTABLE PATHOGENS/cell

1) Antibacterial – β-lactums, Aminoglycoside, etc
2) Antifungal – Amphotericin-B, "Azoles", Griseofulvin
3) Antimalerial – Quinine, Pyrimethamine, Primaquine
4) Anti-T.B. – Isoniazid, Ethambutol, Rifampicin
5) Antileprotic – Dapsone, Ethionamide, Minocycline
6) Antiviral – Acyclovir, Zidovudine, Ritonavir
7) Antihelmintic – Albendazole, Pyrantel
8) Anticancer – Methotrixate, Cyclophosphamide, 5FU

II. Based on Soures: – "AntiBiotics"

1) Fungi – Penicillin, Cephelosporin, Griseofulvin
2) Bacteria → Polymixin B, Bacitracin, Colistin
3) Actinomycetes – Aminoglycoside, Tetracycline, chloramphenicol

III BASED ON ACTION: –

1.) Bactericidal → Penicillin, Streptomycin, Co-trimoxazole, INH, Rifampicin
2.) Bacteriostatic → Sulphonamide, Tetracycline, Chloramphenicol

IV. BASED ON SPECTRUM –

1) Narrow Spectrum – Pen-G, Streptomycin, Erythromycin
2) Broad Spectrum → Tetracycline, chloramphenicol
Ampicillin, Amoxycillin

V BASED ON MODE OF ACTION

1.) Cell wall Synthesis Inhibitors
A) β-Lactums – Pen., Cephelosporin, Carbapenam, Monobactum
B) Others – Vancomycin, Bacitracin

2.) Plasma mem. Functⁿ Inhibitors –
A) Polypeptide – Polymixin, Bacitracin, Colistin
B) Polyenes – Amphoterecin, Nystatin

3.) Protein Synthesis Inhibitors –
A) Aminoglycosides – Streptomycin, Kanamycin, Gentamicin
B) Tetracyclines – Oxytetracycline, Doxycycline
C) Macrolide → Erythromycin, Azithromycin
D) Lincosamides – Lincomycin, Clindomycin
d) others – Chloramphenicol, Linezolide

4) Nucleic Acid Synthesis Inhibitors –
A) Folic Acid Syn. Inhibitor – Sulphonamide, Trimethoprime
B) DNA Gyrase Inhibitors – "Quinolones"
↓
Ciprofloxacin, Ofloxacin, Norfloxacin

General Problem During Chemotherapy & AMAs

1. Toxicity

A) **Local Irritancy** → at the Site of Adm., Gastric irritatn
Abscess formatn at the i.m. injection. Thrombophlebitis of the injected Vein. AmAs – Erythromycin, Tetracyclines, Chloramphenicol, Cephalosporins.

B) **Systemic Toxicity** :– All AMAs produce Dose Related toxicity

High Therap. Index – Pen., Cephalosporins, & Erythromycin

Low Therap. Index –

Aminoglycoside → Ototoxcity, Nephrotoxicity
Tetracyclines → Oto/ Nepro/ Hepato/ Photo - toxicity
Vancomycin → Ototoxicity & Nephrotoxicity
Polymixin-B → Neurotoxicity
Chloramphenicol → BMS, Grey Baby Syndrome
Sulphonamide → "SJS", BMS, Crystalluria, Phototoxicity, Hepatotoxicity

2. Hypersensetivity Reaction :– "Allergic Reactn"

Penicillins – Jarisch - Herxheimer Reaction
Tetracyclines- 〃 —— 〃 —— 〃 ——
Quinolones – Photosensetivity

3. "DRUG RESISTANCE" = Unresponsiveness of a micro-organism to an AMA

"Defense system of Bacteria Against AMA"

4. Super-Infection

↳ Appearance of a new infection as a result of AMA therapy.

Normal Microbial Flora → "Bacteriocins" → Distroy the pathogen

AMAs – Tetracyclines, chloramphenicol, Newer Ceph. Ampicillin, Amoxycillin → Broad Spectrum AmAs

5. Nutritional Deficiency : – "↓ Syn. of Vit. B & K"

Neomycin : alter the morphology of Intestinal mucosa, which can produce Steatorrhoea and malabsorption Syndrome.

6. Masking of an Infection : –

* Syphilis masked by single dose of penicillin, which is Sufficient to cure Gonorrhoea.
# T.B. masked by a short course of Streptomycin given for a minor Respiratory infection

DRUG-RESISTANCE

Drug Resistance :- is the ineffectiveness of an AMA or Antibiotic to the microorganism
AMAs — Pathogen

Super Bugs :- Antibiotic Resistance Bacteria / Fungi
VRSA :→ Vancomycin-R- Staphylococus aureus
MRSA :→ Methicillin-R- 〃 — 〃 —
VRE :→ Vancomycin-R- Enterococci
CRE :- Carbapenam-R-Enterobacteriacege
ESBL-producing K. pneumoniae, 〃 —

Multi-Drug Resistance (MDR) :- Resist to more than one AMA/Antibiotics →"SPACE" Organism.

[Serratia, Pseudomonas, Acinobacter, Citrobacter, Enterobacter]

Cross-Resistance :- Resistance to similar Acting Substance

DRUG RESISTANCE :-

I. **Natural Resistance** :- Due to lack of target site in microbes For particularly drugs.
ex. i) G(-) bac. resist to Pen-G
ii) Anaerobic bac. resist to Aminoglycosite

II **Acquired Resistance** - Developped during chemotherapy
A) Mutation - Genetic Changes
B) Gene Transfer - Spreading gene one to other
↳ Conjugat°, Transduct°, Transformat°

Examples:-
1) Altering Drug binding Site for Entry :- Pen., Aminog., Tetracycline
2) Altering metabolic Enz. - Sulphonamide, Trimethoprime
3) Producing Enz. that distroy the AMAs :-
β-lactamase → β-lactum Antibiotics - Pen., Ceph.
Acetyl transferase - chloramphenicol
Kinase → Aminoglycoside
4) Developing Exporter

PREVENTION :- 1) Inadaquate Dose & Duration
2) Prefer Rapid-acting & Selective (Narrow Spectrum) AMA
3) Rational Combinat° therapy - T.B, AIDS,
4) Select° of Righ Drug For Right pathogen

"Development of Newer Antibiotics/AMA"

① Tigecycline → Tetracycline Derivetive
use :- MRSA, MDR (K. pneumoniae, Pseudomonas, Enterobacteriocceae)
② Eravacycline → "Tetracyclines" - Phase III trial
Use → MDR-G(+)& (-) bac. & Anaerobic bacteria
③ Omadocycline → Tetracycline derv. - Phase III
④ Fluroquindones - Avarofloxacin, NemonoFloxacin, Delafloxacin (P-III), Finfloxain (P-II) ⇒
↳ MRSA, MDR-pseudomonas, G(-) bacteria
⑤ Daptomycin :- Vancomycin derv.
↳ VRE, MRSA

CHOICE OF AN ANTI-MICROBIAL AGENT

PATIENT-RELATED FACTORS :-

1. Age :-
   - # Chloramphenicol – Gray-Baby Syndrom
   - # Sulphomides → Kerinctenus
   - # Quinolones → Cartilage Damage
   - # Tetracyclines → Discoloration & Week-teeth

   } Not used in childrens

   - # Aminoglycoside → Elderly – $\uparrow t_{\frac{1}{2}}$ → Ototoxic Effects
2. Renal & Hepatic Condition :-

"Require ↓ dose in mild-moderate failure"

Aminoglycoside, Vancomycin, Ethambutol, Tetrac., Cotrimoxazole, Meropenem

"↓ Dose or Avoided In Liver Diseases"

- # Erythromycin, Tetrac. Pyrazinamide – ↓ in dose
- # INH, Rifampicin, Chloramphenicol → Avoided

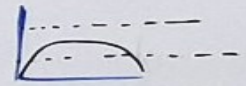
3. Local Factors :-
   - # presence of pus – ↓ efficacy of Sulph. & Aminoglycoside
4. Allergy
5. Pregancy ⇒ Safe ⇒ Cephelosporin

   unsafe/Teratogenic ⇒ Quinolone, Sulph., chloramphenicol
6. Genetic factor → G-6-PD Deficient patient
   - # Haemolysis → Primaquine, Sulph, Chloramphenicol, Nitrofuratn, Fluroquinolones

ORGANISM RELATED FACTOR :- Select AMA After Diagnosis

DRUG-RELATED FACTORS :-

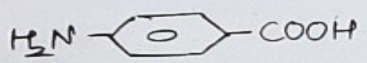
1. Spectrum of Activity :- Narrow Spectrum is Prefered
2. Types of Activity :- Cidal or Statics ~ + Host Defence
3. Sensevity of Org.
   - Trimethoprime → Bacteria
   - Pyrimethamine → Malaria
   - Methotrixate → Cancer
4. P'kinetic profile →



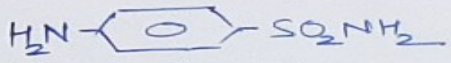
5. Route of Administration :-

   Parenterally :- Pen-G, Aminoglycoside, Vancomycin, Tetracycline can given by inj only
6. Clinical Efficacy =

SULFONAMIDE & COTRIMOXAZOLE



PABA



Sulfanilamide

Sulfonamides were the 1st AMAs, effective against pyogenic bac. infection. Sulf-Chrysoidine (Prontosil dye) was introduced by "Domagk", which is effective against streptococcal infectn in mice.

Prontosil ⟶ "Sulfanilamide" (Active Metabolite)

CLASSIFICATION: - A) Short Acting - Sulfadiazide
B) Intermediate Acting - Sulfamethoxazole
c) Long Acting: - Sulfadoxine, Sulfamethopyrazine
D) For topical use: - "Silver Sulfadiazine", Sulfacetamide

Spectrum & Activity: - "Bacteriostatic" actn on G(+) & G(-) bac.
However, "Bacteriocidal" conc. attained in urine.

MOA: - # Sulfonamide - PABA Antagonist
Trimethoprim → Folate Antagonist

PABA —(DHF Synthetase, ✕ Sulfonamide)→ DHFA —(DHF Reductase, ≀ Trimethoprim)→ "TH Folic Acid" → Nucleic Acid DNA & RNA

Uses: - RTI, UTI → Cotrimoxazole
Inflammatory Dis → Sulfapyridine + Aminosalicylate
Infected Burn → Silver Sulfadiazine
Malaria, Toxoplasmosis - Sulf. + Pyrimethamine
Conjuctivitis → 10-30% Sulfacetamide Sod.

P'kinetic: - Rapid & Complete Absorbed from GIT, 10-90% PB, PCmx - 4-6h, They cross the BBB & placental Barrier.
Metabolised in liver by - "N-Acetylatn & Glucuronide Conjugatn
Exc. through urine," In acidic urine, Acetylated-products are insoluble & produce "Crystalluria" - ADR

ADR: - Allergy → Urticaria, Photosensetivity, "Steven Johnson Synd."
↳ Anaemias → Haemolytic/Aplastic/Megaloblastic Anaemia
↳ Pregnant → Infant - "Kernicterus" - ↑ bilirubin → Liver, Brain
↳ Thrombocytopenia, Granulocytopenia

Resistance - "Gonococci, Meningococci, pneumococci, Shigella, E Coli" - are Resistant to Sulfonamide

Mode of R.: - ↑ productn of PABA
↳ ↓ affinity of DHFS
↳ ↓ permiability & developed Efflux System.

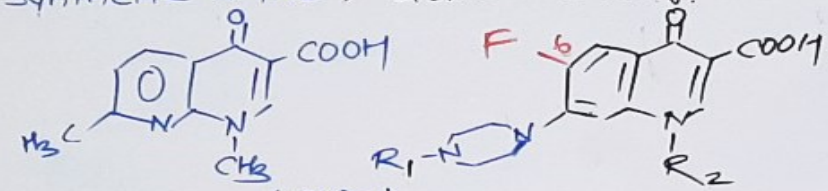
"COTRIMOXAZOLE"

"Sulfamethoxazole + Trimethoprim" = (5:1)
Cotrimazine - Sulfadiazine + Trimethoprim

Trimethoprim = "Diaminopyrimidine derv."
↳ "DHFR & Thymidylate Synthetase"
↳ "More Concentrate in prostatic & Veginal fluids"
↳ Cotrimoxazole → Bacteriocidal Action
↳ Use:- RTI, UTI, GI Infectn

QUINOLONES / FLUROQUINOLONES

→ Synthetic AMAs → QUINOLONE Ring.



I. Quinolone (1960s) - Nalidixic ā, Oxalinic ā, Miloxacin
↳ Active against G(−) bac. only

II Fluoroquinolone — 1980s

A) First Gen. - Norfloxacin, Ciprofloxacin, Ofloxacin
↳ Active against G(−) Bac. > G(+) bac.
↳ 1980s, One fluro Substitutn

B) Second Gen. → Levofloxacin, Moxifloxacin, Lomefloxacin Sparfloxacin, Gemifloxacin → G(−) = G(+) & Anaerobe
↳ 1990s, - add. additional F & other Substitutn

MOA:- They inhibit DNA Gyrase (Topoisomerase IV) Enzyme.

DNA Gyrase / Subunit A :- for nicking of DNA, the Sealing
\ Sub. B. → Introducing Negative Supercoil

FQs → bind with A Subunit & interfere with cutting of DNA

Therapeutic Uses - UTI, RTI, Genital tract infection, TB, Typhoid, Soft tissue infection, chancroid, Gonorrhoea, Conjunctivitis, Anthrax, Maningitis

"Broad Spectrum"

PKinetic (Ciprofloxacin) — BA - 60-80%, PB = 20-35%.
Vd - 3-4L, $t_{1/2}$ = 3-5h, 20% metabolised & Ex.-Urine

"ADR" = Allergy - Urticaria, Photosensetivity, Pruritus.
* Growing Cartilage Damage - Arthopathy. Tendonitis
* CNS - Dizziness, Insomina, anxiety, - Avoid during Driving
* At high dose — "Seizures" due to GABA Antagonising

Interactn - ↓ Abs with food, divelent cations, & Antacids
↳ Cipro → ↑ plasma Conc. of Caffeine, Theophylline & warfarin due to ↓ in metabolism
↳ NSAIDs - ↑ CNS toxicity of Ciprof. — Seizure

Resistance:- Bacteroides, Clostridia, Anaerobic Cocci
↳ Mode → ① Chromosomal mutation on Bac. DNA Gyrase
② Reduce permiability
③ Develop Efflux transport System.

* **Nalidixic acid** - G(−), Bac. cidal, Rapidly resistance developed
↳ CNS toxicity, Haemolysis in G-6PD deficient pat.
↳ Contra indicated in infant, Nitrofuratn Antag. - the effect.
↳ UTI, Coliforms diarrhoea

* **Norfloxacin** - G(−) & G(+) aerobic bac.
Not effective against obligate Anaerobes

ANTI-BIOTICS & β-LACTUMS ANTIBIOTICS

The term "Antibiotic" was introduced by "Waksman" in 1942, → "Streptomycin"

Antibiotics – are the chemical substance produced by micro-organism & they supress the growth or kill other microorganism in low concentration.

Types:– ① Cell wall Syn. Inhibitors – β-Lactums*

② Protein Syn. Inhibitors – Aminoglycoside, Tetracyclines, Macrolide, Chloramphenicol, Lincomycin

A) **Narrow Spectrum:** – Effective against Single or limited group of micro-organism. – Streptomycin, Pen-G, Erythromycin

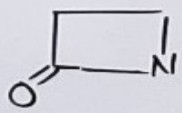
B) **Extended Spectrum** – Effective against g(+) & g(–) Bac.
ex – Ampicillin, Amoxycillin

C) **Broad Spectrum** – Effective against multiple organism.
ex – Tetracycline, chloramphenicol

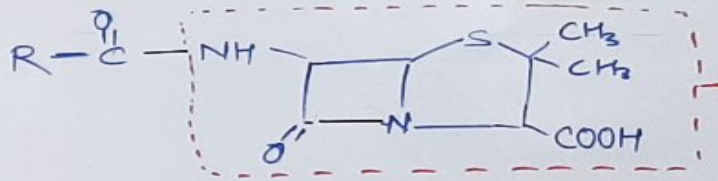
β-Lactum Antibiotics

↳ Penicillins
↳ Cephalosporins
↳ Monobactum
↳ Carbapenam

] – β-lactamase Resistant β-lactum Antibiotic

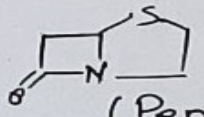


β-lactum Ring (4-membrane cyclic Amide)

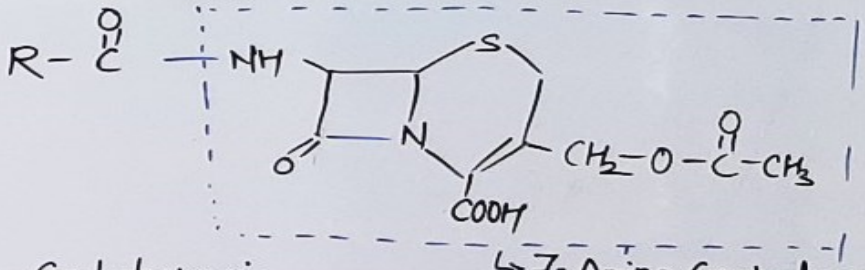


6-Amino Penicillanic ā

Ⓐ Penicillin

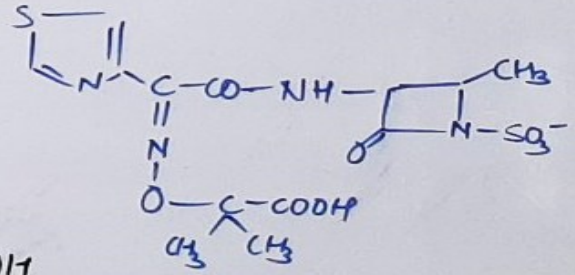


(Penam)

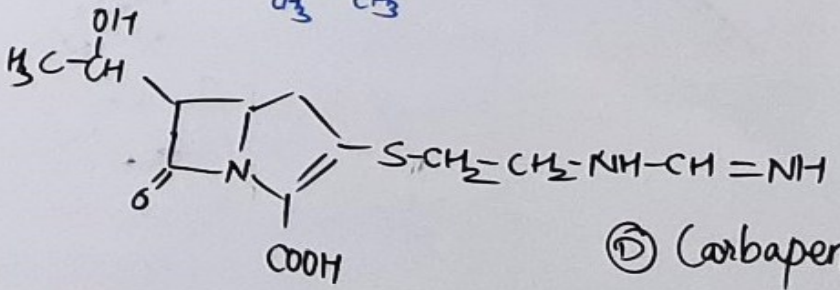


Ⓑ Cephalosporin

↳ 7-Amino Cephalosporanic acid



Ⓒ Monobactum (Aztreonam)
[G(–) aerobic bac.]



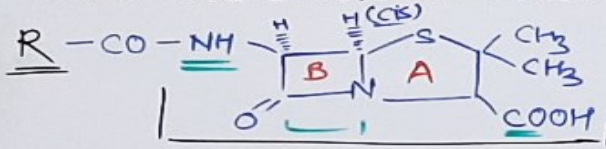
Ⓓ Carbapenam

PENICILLINS

↳ Penicillin was first discovered by A. Flemming in 1928 & first antibiotic to be used clinically in 1941.

Source - Penicillum notatum, P. chrysogenum [Fungi]

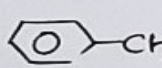
Chemistry :- fused Thiozolidine (A) & β-lactum (B) Ring which side chains are attached through an Amide linkage



"Penicillin Ring"

1 - 6-amino Penicillanic ā

R- Substitutⁿ Alter activity & P'kinetic Profile



→ Benzyl Pen. (Pen-G) - Original Pen. used Clinically

↳ Unstable in GI Acid - used Parenterally

↳ Salts :- Benethamine Pen, Benzathine Pen. & procain Pen. → Slow release preparatn, & administered by deep muscular injection.

↳ Nat or K⁺ Salt of Pen. → more stable than Parent Acid

↳ Highly water Soluble, stable in dry state, Soluth distroyed at room temp, stored at < 4 °C

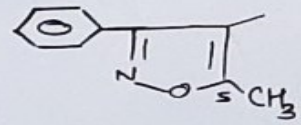
↳ Thermolabile & Acid Labile

↳ Std :- 1U = 0.6g of Sod. Pen. G

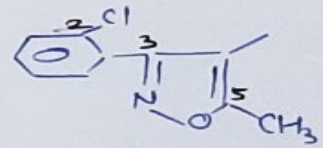
↳ Inactivated by Amidase (Acid Hydrolysis) & Penicillinase (bac-β-lactamase)

Semi-Synthetic

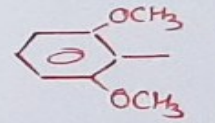
Pen-V = Acid Stable/orally active ⇒ Phenoxy methyl Pen.

Oxacillin = 

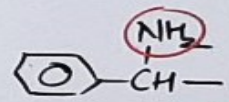
Addⁿ of Isoxazolyl heterocyclic ↓ ↑ Resistance to Acid Hydrolysis

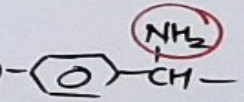
Cloxacillin 

↑ ⊣ —— to Penicillinase

Methicillin – 

- 2,6-dimethoxy phenyl pen.
→ Penicillinase Resistant but Not Acid Resistance

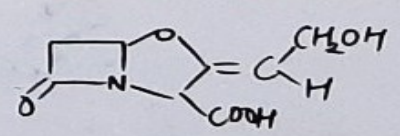
Ampicillin - 

Amoxycillin - 

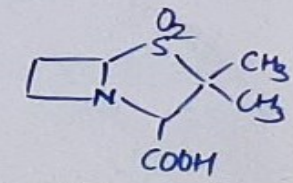
Addⁿ of –NH₂ on α-C positn on benzyl ring ↑ Antibacterial Spectrum – Broad Spectrum

↳ Acid Resistant but not penicillinase Resistance

β-Lactamase Inhibitors -



Clavulanic ā



Sulbactym

PENICILLINS

Classification:- I. Narrow Spectrum –

A) Penicillinase Sensetive – Pen.G (perentarally), Pen-V (orally)

B) Penicillinase Resistant – Oxacillin, cloxacillin, Flyoxacillin Methicillin

II. Broad Spectrum

A) Amino-Pen. – Ampicillin, Amoxycillin, Pivampicillin

B) Urido-Pen. – Azlocillin, Mezlocillin, Piperacillin] Prefered in Pseudomonal Infectn

C) Carboxy-Pen. – Carbenecillin, Ticarcilline]

Mode of Action:- Cell wall synthesis Inhibitor

Pen. ⟶ attached to PBPs ⟶ ↓ Transpeptidase Enzyme

↓

↓ Peptidoglycan Syn ⟵ ↓ Cross linkage b/w NAM & NAG

↓

↓ Cell wall Syn. ⟶ Cell lysis (Bacteriocidal Action)

Spectrum:- G(+) bacteria → streptococci, Pneumococci, B. anthracis, C. diphtheriae, C. tetane

G(-) bac. – N. gonorrhoeae, N. meningitidis,

* majorities of aerobic G(-) bacilli, M. tuberculosis, fungi, Virus, protozoa are insensetive to Pen.G

Therapeutic Uses:-

① streptococci infectn – Scarlet fever, Pharyngitis, Rheumatic Fever, Sub Acute Bacterial Endocarditis (SABE)

② Diphtheria, Tetanus, Meningitis,

③ Prophylactic use for Surgical Infection & Rheymatic fever

④ Pneumonea – Now Not used due to Resistance

⑤ Syphilis (T. palidum)

⑥ Leptospirosis

P'kinetic – variable, depends on the drug

* Penicillins are excreted through Urin by Glomerular filtratn (10·1.) & Tubular Secretion (90·1.)

ADR:- ① Allergy - Rashes, bronchospasm, Fever, Urticaria Anaphylactic Shock, nephritis

② Jarisch-Herxheimer Reactn – on Syphilis pat. due to sudden release of Spirochetelytic product

③ Local Irritancy - during injectim

Resistance:- Styphalococci, Pneumococci, E.Coli, Gonococci, Enterobaderiacae,

① ↑ productn of β-lactamase/Penicillinase Enz. by Bac.

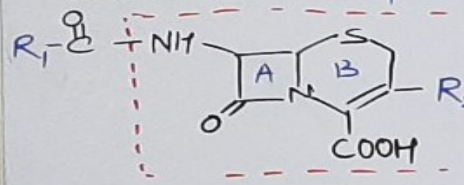
② Alteratn of PBPs & Transpeptidase Enz

③ Development of Efflux transport System.

Drug Interactn:- Probenecid – ↑ the Pc of Pen. by inhibiting its tubular Secretn

CEPHALOSPORINS

↳ Semisynthetic Antibiotics derived from "Cephalosporin-C" obtained from "Cephalosporium"



A = β-Lactam Ring
B = dihydrothiazine
" 7-amino Cephalosporanic ā "
R_2 = $-CH_2OCOCH_3$

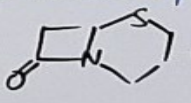
Discovery :- 1945, "G. Brotzn" cultivated "Cephalosporium acremonium" from sea water → Cultured filterate showed therap. activity against staphylococcal inf. & Typhoid fever.

↳ Cephalosporium"- Produced 7 different Antibiotics

5 Antibiotics → Lipid Soluble = One of them "Steroidal" that was known as "Cephalosporin P_1"

2 Antibiotics → Hydrophilic = Cephalosporin C & Cep. N

* Cephalosporin N = Penicillin [(D-4-amino-4-carboxy butyl) penicillanic ā

Cephalosporin-C - has β-Lactam Ring  Cepham

Classificatn :- 1 to 5 Generatn

I. 1st Gen Cep. - 1960s - G(+) > G(−) → E.coli, Proteus, Staphylococci, Streptococci, & Pneumococci | Not effective - Salmonella, Shigella, Anaerobes & Pseudomonas

Oral - Cephalexin, Cefadroxil | Perenteral - Cefazolin

II 2nd Gen - mainly used in G(−) Inf. - H. influenza, Enterobacter
Not effective → Anaerobes & Pseudomonas

oral - Cefaclor, Cefuroxime axetil | Per. - Cefoxitin, Cefuroxime

III. 3rd Gen. - 1980s, G(−) bacilli > G(+) bac.
Oral - Cefixime, Cefdinir | Per - Ceftriaxone, Cefotaxime

IV. 4th Gen - G(−) bac inf., inactive against MR-Staphylococci
Per. - Cefepime, Cefpirome ⇒ More Resistant to β-lactamase

V. 5th Gen. - Per. - Ceftaroline fosamil, Ceftobiprole medocaril

Pharmacology :- Similar to Penicillin

MOA - Inhibit the peptidoglycan Syn. after binding to the β-lactum binding protein

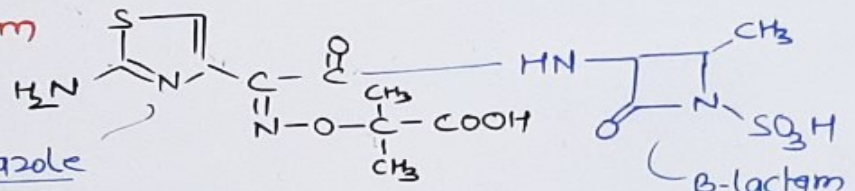
Uses:- RTI, UTI, Soft tissue Inf., Surgical prophylaxis.
Meningitis (H.influenzae) - 2nd/3rd Gen.
Gonorrhoea - Ceftriaxone (3rd)
Typhoid fever

ADR = ① Allergic/Hypersensetive Reactn
② Nephrotoxicity - Cefadinir (3rd), + loop diu./Aminoglycoside
③ Hypoprothrombinemia - bleeding
④ Drug induced Alcohol intolarance

Resistance :- ① ↑ bac. β-lactamase (Cephalosporinase)
② Alteratn on β-lactam Binding protein
③ Develop efflux transport system
= Staphylococci, Gonococci, Pneumococci, E.Coli

MONOBACTAMIS = Monocyclic β-Lactam Ring

Aztreonam (Perenteral)



Source – "Chromobacterium violaceum"

β-Lactamase-Resistant β-lactam antibiotic

Narrow Spectrum → G(−) Aerobic bacteria

MOA :– Binds with PBP-3/ β-lactam binding protein-3 & interfere with the Cell wall Syn. (induce formatn of long fillament bac. structure)

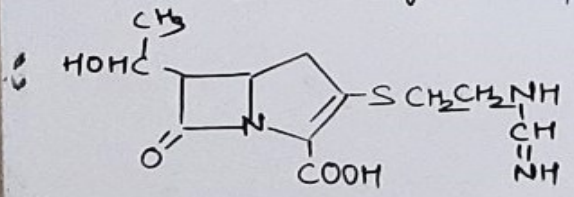
Spectrum – Citrobacter, Enterobacter, H. influenzae, E.coli, Pseudomonas infection

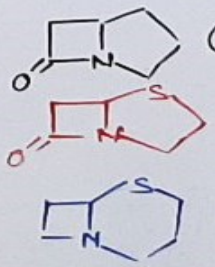
USE = Hospital Acquired inf - UTI, RTI, GITI, Genital tract Inf.

ADR – Hapetotoxicity, Alter taste, ↑ Serum Aminotransferase

CARBAPENEM :- Highly Resistant to β-lactamase

Imipenem → Semisyn. derivative of Thienamycin, whic was obtained from Streptomyces cattleya





Imipenem is given perenterally along with Cilastin (a dehydropeptidase-1 inhibitor, that inhibits the metabolism of Imipenem in the kidney) = "PRIMAXIN"

USES- Broad Spectrum (G(+) & G(−), Aerobes & Anaerobes) including MR-Staphylococci & Ceph.-R-nosocomial bac
↳ Skin, UTI, RTI, Abdominal, GI, Soft tissue inf including neutropenic, cancer & AIDS patient.

ADR – Neurotoxicity & Tinnitis (ear ringing)

Meropenem – Newer Carbapenem that not hydrolysed by Renal dehydropeptidase

---

VANCOMYCIN – Glycopeptide

Bacteriocidal, obtained by "Streptomyces Orientalis"

Effective against – G(+) bac., Staphylococci inf.

MOA = Cell wall Syn. Inhibitor

ADR – Allergy, Thrombophlabitis, Anaphylactoid, Chochleg toxic, Fetal urecemia

---

BACITRACIN – Obtained from bacteria Bacillus subtilis.

Bacteriocidal, Effective against G(+) bacteria

ADR – Nephrotoxcity

Protein Synthesis Inhibitors

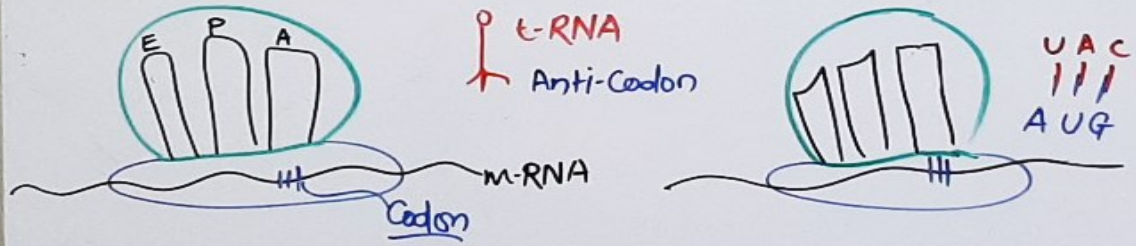
1. **Aminoglycosides** – "Streptomycin"
   ↳ 30s – ↓ Polysome formatn, Disrupt in Codon

2. **Tetracyclines** →
   ↳ 30s – Compete with t-RNA for site A

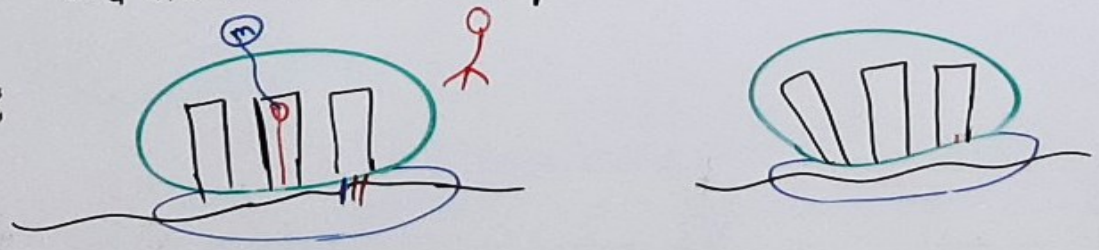
3. **Chloramphenicol** → 50s – ↓ transpeptidatn

4. **Macrolides** – "Erythromycin"
   ↳ 50s – ↓ Translocation

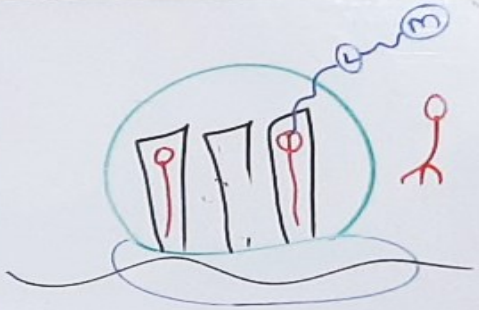
5. **Lincosemide** – 50s – (+) Premature detachment



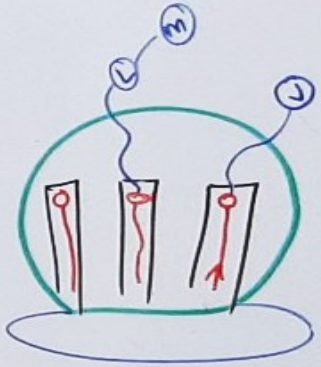
① Binding of t-RNA (Anticodon) to site A (30s, mRNA, Codon) and initiate to amino acid formatn



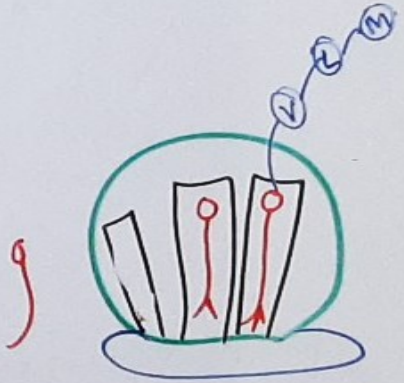
② Transpeptidation



③ Formatn/Elongatn of Amino a chain



④ Maturatn



⑤ Translocation

AMINOGLYCOSIDES / STREPTOMYCIN

Group of Natural & Semisynthetic antibiotics having Polybasic Amino groups linked with Glycosidically to two or more Amino Sugar (Streptidine, 2-deoxy streptidine, garosamine) residues.

"Streptomycin" - was discovered in 1942 by "Waksman" & was isolated from "Streptomyces griseus", & that was active against "Tuberculosis"

Soures - Actinomycetes

Class - ① obtained from "Streptomyces" → "Mycin"

Ⓐ Systemic - Streptomycin, kanamycin, Tobramycin
Ⓑ Topical - Neomycin, Framycin

② obtained from "Micromonospora" → "Micin"
↳ Gentamicin, Sisomicin

MOA - Aminoglycosides → Porin Channel → G(+) Aerobic

Polyamine Oxygen dependent Active transport System (EDP_1 Entry)

act on 30s Ribosomal unit

Streptomycin

Other AminG - 50s or 30-50s

1. mistead the mRNA Codon
2. ↓ Polysome Formation
3. ↑ Wrong monosome / Aminoq formation
4. ↓ t-RNA binding & chain elongatn

"Inhibit Protein synthesis"

Bacteriocidal Actn = Interfere with Bac Cell membrane integrity & enhance the cellular leakage & followed by cell Death.

Spectrum - Narrow Sp. → G(-) Aerobic bacteria
& Some G(+) → S. aureus & S. epidermidis

* Cell wall Syn. Inh. - ↑ penetratn of AmG & Synergism the bac.cidal actn. e.g. - Supraddilive killing on enterococci. endocarditis

PKinetics - Sulfated Salt, Oral inactive due to easily lonizable exc. through urine & directly proportional to creatinine CL through Glomerular filteratn

Uses - TB, SABE, Plague,
Tularemia (1st choice) - Francisella tularensis

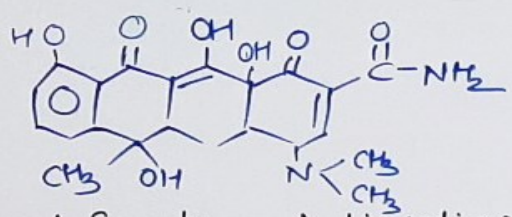
* AmG 20 times more effective in alkalin PH (7-8)

ADR - ① Ototoxic - damage VIII Cranial nerve
② Nephrotoxic → tubular Damage - ↓GFR, Albuminuria, N_2 Retent
3) Neuromuscular Blockade - (-) N-type Ca^{+2} - ↓ Ach release at Motor nerve ending
4) Fetal ototoxic during Pregnancy

Resistance - ① Failure of Penetratn & modify Affinity to Ribosomal
② Degradatn by bac. Enzymes - Phosphorylate / Adenylate or Acetylate the AmG

Drug Interactn - >60Y ⇒ Renal Damage
+NSAIDs / Amphoterecin B / Vancomycin / Cisplatin - ↑Nephrotoxic
+Loop D. / Vanc. / Tetracycline (Minocyclin) → ↑Ototoxic Effect
* Do not mix AmG with any drug in same Syringe / Infusion Bottle

TETRACYCLINES



- Bacteriostatic
→ Protein Syn. Inhibitor

→ Broad Spectrum Antibiotics that consist 4 fused cyclic ring (Octahydronaphthacene)

Source - Actinomycetes - "Streptomyces sps"

→ "Chlortetracycline" was discovered in 1948 under the name "aureomycin" - by S. aureofaciens

Antibac. Spectrum - Broad - G(+), G(-), Rickettsia, Mycoplasma, Chlamydia, Spirochates & protozoa.

Drugs - Tetracycline, Doxycycline, Minocycline, Oxy-Tet.*

Newer - Tigecycline [Glycylcycline]

MOA → Tetracycline → Enters by an Active transport system (energy dependent) "G(+) porin channel" → 30s Ribosomal unit

Inhibits the attachment of Aminoacyl-t-RNA to the Site A on the m-RNA-ribosomal complex

PKinetic - All Tetracyclines are slightly water soluble & HCl Salt are more stable.

↳ Aqueous solut" are unstable

↳ Doxycycline & Minocycline - More lipid Soluble

Oral Abs → depends on lipid solubility

Potency ⇒ Mino > Doxy > Demeclo > Tet/OxyTet

PB ⇒ Mino/Doxy/Demeclo - High

Excretn → Tet/OxyT → Rapid Renal Exc.

Demeclo → Partially metabolised, Slow Renal Ex

Doxy → Exc. in faeces as conjugate

Mino → P° metabolised, Exc. in urin & bile

Microbial Flora Alteratn → Tetra/OxyT > Demeclo > Mino/Doxy

Phototoxic - Tet/OxyT < Doxy < Demeclo

TH Uses - cholera, Gonorrhoea, Syphilis, Rickettsial, Brucellosis, Whippler dis., Leptospirosis, etc

ADR - Nephrotoxicity, Hepatotoxicity, Phototoxicity, - Allergy (J-H. Reactn), Ototoxicity, Discolratn of teeth & Bone, ↓ long bone growth in infant, "Fatty liver in pregnant"

Resistance - ① Alteratn on Entry transport system, ② Syn. of plasmid mediated "protection" protein which ↓ the ribosomal binding. ③ develop Efflux system

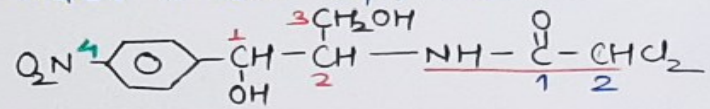
→ E. Coli, Enterobacter

* Pnce of Ca^{+2}, Mg^{+2}, Al^{+3} - ↓ Abs of Tetracyclines
* Tet. excreted throug G. Filteratn
* Tet. are amphoteric Comp. In neutral solution it is exist mainly as Zwitter ion

CHLORAMPHENCOL

It was initially obtained from "Streptomyces venezuelae" in 1947.

Later it was synthesized chemically.



"d-threo"

2,2-dichloro-N[1,3-dihydroxy-1-(4-nitrophenyl)-propane-2-yl] acetamide

Properties – Yellowish-White crystalline Solid,
↳ Aq. solut^n is stable, stands boiling. but it require to protect^n from light.
↳ Nitrobenzene moiety → Antibac. Activity & bitter taste.

MOA – It inhibit the transpeptidation (Cross linking or peptide bond format^n b/w amino acid) process at 50s ribosomal unit → X- protein Synthesis

Antibacterial Spectrum – "Broad Spectrum Backeriostatic Antibiotic", At high conc. it shows bac.cidal action on some bac. – H. influenzae & N. meningitidis

Broad Spectrum – G(+), G(-), Rickettsiae, mycoplasma

highly active against - Salmonella, Influenzae, meningitidis, pertussis, klebsiella.

Ineffective against - Mycobacteria, Pseudomonas, virus & fungi

uses - Enteric fever, Meningitidis, Anaerobic infect^n, Intraocular inf., UTI, Typhoid, Plague

P'Kinetic – Rapidly & Completely abs orally.
PB- 50-60%, Vd = 1L/kg, freely penetrates serous cavity, BBB, Placental barrier. $t_{\frac{1}{2}}$ = 3-5 h

Chloramphenicol conjugated with Glucuronic ā & little fract^n excreted through urine in unchanged form.
= In Cirrhotic & Neonate – dose should be reduce

ADR: – ① BMS – Anaemias
② Gray Baby Syndrome
③ Hypersensetive Reaction
④ Superinfection
⑤ Irritative Effects

Resistance – ① Due to over product^n of bacterial Acetyl-transferase
② ↓ Entry of Chloramphenicol
③ Alterat^n affinity to binding site
④ Developed Efflux system

Bac. – S. typhi

MACROLIDE

Macrolide antibiotics are derived from "Streptomyces" & they are contains –

↳ A macrocyclic lactone ring with attached amino sugar

↳ a ketone group

* All macrolide antibiotics are weak base & slightly soluble in water.

Drugs – "Erythromycin" – discovered in 1950s
Roxithromycin, Clarithromycin, Azithromycin

MOA : – "Protein Synthesis Inhibitors"

They bind to a 23 Sr RNA on 50s ribosomal unit and inhibit the "Translocation" of t-RNA (A site to P site)

Spectrum → Macrolide antibiotics are bacteriostatic in low conc. and Bacteriocidal at high conc. or some highly suseptable organism [G(+) bac.]

* Highly active at alkaline pH

* Narrow Spectrum — mostly G(+) & fewer G(–) bac.

⇒ Str. pyogenes, Str. pneumoniae, N. gonorrhoeae C. diphtheriae & Listeria

⇒ But pen. Resistant Staphylococci & Streptococci are now resistant to Erythromycin

P'Kinetic — Oral active but distroy in Gi acid, So enteric coated tab are used. PB - 70–80 %, Metabolized in liver and excreted through bile mainly

Use – Alternative to penicillin – Diphtheria, Syphilis, Tetanus

First choice – Pneumonia, Whooping Cough, Chancroid

ADR – Gi disturbance, Hearing impairment & Hypersensetive reaction, Hepatotoxicity

* Erythromycin & Clarithromycin – are P450 Enz inhibitors they inhibit the metabolism of other drugs

Resistance – ① by developing Efflux transport System
② producing Erythromycin-Esterase Enz.
③ Alteration in the ribosomal binding site