Antimicrobials - general principles

Drug resistance

Unresponsiveness of a microorg towards an antimicrobial agent

- Natural

  eg. Gram -ve org are normally unaffected by penicillin G

- Acquired

  - Dev of resistance due to the use of AMAs for a long time

    i) Genetic

    - via mutation or gene transfer [transformation, transduction, conjugation]

    ii) Biochemical

    - ↓ entry of bacteria ∴ Aminoglycosides } entry
    - ↑ efflux - eg. Quinolones }
    - Modified target - eg. Altered PBP in MRSA
    - Drug inactivation - eg. β-lactamase

Prevention of resistance

- Avoid indiscriminate use - eg. viral UTI
- Avoid inadequate use
- use narrow spectrum, rapid acting agents whenever possible
- Use combination regimens

Antimicrobial drugs

1) Cell wall synthesis inhibitors

i) β-lactam AB - Penicillin, cephalosporin, monobactam, Carbepenem

ii) Cycloserine

iii) Bacitracin

iv) Glycopeptide group - Vancomycin

v) Fosfomycin

1) PENICILLIN

CLASSIFICATION

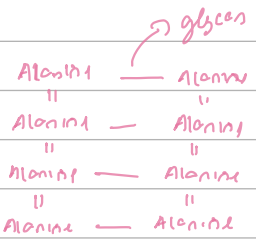
- Natural penicillin
  - Penicillin G
- Semisynthetic penicillins
  - Acid resistant
    - Alternative to penicillin G
    - Penicillin V
  - Penicillinase resistant penicillins
    - Methicillin
    - Cloxacillin
    - Dicloxacillin
  - Extended spectrum
    - Aminopenicillins
      - Amoxicillin
      - Ampicillin
    - Carboxypenicillin
      - Carbenicillin
    - Ureidopenicillin
      - Piperacillin
- β-lactamase inhibitors
  - Clavulanic acid
  - Sulbactam
  - Tazobactam

Spectrum :

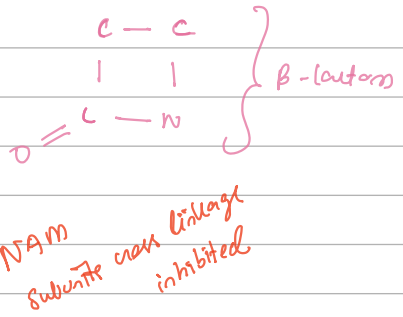
- Narrow spectrum
- Streptococcus, pneumococcus [limited gram +ve cocci activity]
- gram +ve bacilli : Anthracis, C. diphtheriae, Clostridium sp
- Listeria & spirochetes highly sensitive

Mechanism of action :

* Inhibit transpeptidase enzyme
  ↓
  Inhibits cross linking of peptidoglycan layer
  ↓
  inhibit cell wall synthesis



* Penicillin binding protein (PBP) is disrupted as β-lactam binds to PBP
  ↓
  PBP unable to cross link peptidoglycans
  ↓
  no cell wall
  ↓
  cell swells & bursts
  ↓
  lysed



* Inhibits of cell wall synthesis
  - m/c NAM subunits cross links inhibited
  - β-lactam most prominent

RESISTANCE :

* Due to enzymes
  - β-lactamase & penicillinase
    ↓
    opens the β-lactam ring
  eg. Staphylococci, Neisseria gonococcus

* Altered PBP
  - MRSA ; explain mecA gene
  - Alteration due to conjugation & transduction

* Diffused permibility via porin channels
  - gram negative have porin channels on outer membrane
  - Permeability of various β-L differs
  - Ampicillin : active agx gram -ve

Penicillin G - uses

S - Syphilis
M - meningococcus meningitis
A - Actinomycosis
R - Rat bite fever
T - Tetanus

Smart players gayle

Players - Pasteurella

G - Gas gangrene
A - Anthrax
Y - Yaws
L - Leptospirosis
E - Every sp : Streptococcus, Pneumococcus

ADR

* Hypersensitivity reactions
  - Urticaria, fever, rashes, edemas, skin rash
* Serum sickness
* Anaphylactic rare but fatal - Scratch test needed
* Jarisch - Herxheimer reaction - In syphilis
* Hemolytic anemia, pancytopenia.

Ampicillin	Amoxillin
* Pen spectrum + many gram -ve bacilli eg E.coli, H. influenzae, Shigella, Salmonella	* Better oral absorption than Amp * Food does not interrupt absorption * Amo > Amp for bronchitis, UTI * Regimen for H. pylori infection
ADR : Diarrhea & rashes	
Use : Resp TI UTI meningitis H. pylori	Use : same
* Combined with sulbactam (due to its oral inconsistent)	

β-lactamase inhibitors

i) Clavulonic acid
ii) Sulbactam
iii) Tazobactam

1) SULBACTAM

- Semisynthetic
- Related chemically as well as in activity to clavulonic acid
- Oral absorption inconsistent
  ∴ given parenterally, combined with ampicillin to use against β-lactamase producing resistant strains
- Indications :
  - Penicillinase producing Neisseria gonorrhea (PPNG) => inhibits N. gonorrhea
  - Mixed aerobic-anaerobic infections - gynae, surgical & skin/soft tissue infections esp those acq in hospital.
- ADR : Pain @ site of injection, thrombophlebitis, rashes & diarrhea

2) TAZOBACTAM

- Similar to sulbactam
- PK matches with piperacillin ∴ combined
- USES : peritonitis, pelvic/urinary/resp infections, caused by β-lactamase producing bacilli

3) CLAVULONIC ACID

- Obtained from Streptomyces clavuligerus
- Inhibits wide variety of β-lactamases produced by both gram-positive & gram negative bacteria
- eg. Augmentin (clavulonic a 125 mg + Amoxicillin 500mg)
- SPECTRUM : MSSA & upper resp infections & most anaerobes
- ADR : GI intolerance + rashes, candida stomatitis, hepatic injury
- USES : skin & soft tissue infections, intra-abdominal, gynae, urinary biliary, RTI

Cephalosporins

- Structure : β-lactam ring fused to dihydrothiazine ring
- MOA : Same as penicillins, but bind to diff PBP
  - Inhibit bacterial cell wall synthesis
- Resistance : Same as that of penicillin
- classification :

	Parenteral	Oral
1st generation cephalosporins	cephazolin ✓ (surgical prophylaxis)	cephalexin cephadroxil
2nd generation	cefuroxime ✓ cefoxitin	cefaclor cefuroxime axetil cefprozil
3rd generation **	cefotaxime ✓ ceftizoxime ceftriaxone (*) ceftazidime ✓ cefoperazone ✓	cefixime cefpodoxime proxetil cefdinir ceftibuten ceftemet pivoxil
5th generation (anti-MRSA cephalosporins)		ceftaroline fosamil

4th generation : Antipseudomonal

- ANTIMICROBIAL SPECTRUM

1st → gram (+) cocci > gram (-) bacilli

2nd, 3rd } gram (-) microbes > gram (+), anaerobes

4th - Antipseudomonal, gram (-) > gram +ve cocci

5th - Anti-MRSA

- ADR
  - Pain after im injection ✓
  - HS ✓
  - diarrhea : cephalexin
  - Bleeding : ceftriaxone, cefoperazone ✓
  - Neutropenia & thrombocytopenia ✓
  - Disulfiram like reaction - cefoperazone ✓

1st GENERATION CS

- gram (+) cocci
- good activity : streptococci, MSSA
- modest activity : E.coli, Klebsiella
- USES : skin & soft tissue infections
  serious infection due to MSSA
  Perioperative prophylaxis → CEFAZOLIN ✓

2nd GENERATION CS

- gram (-) microbes
  Good activity : E.coli, Klebsiella pneumoniae, H. influenzae
  Anaerobes
- USES : upper resp tract infections (C. diphtheriae)
  gynaecological infection

  Cefuroxime : meningitis
  single dose im therapy → gonorrhea

3rd GENERATION CEPHALOSPORINS

- gram negative microbes + anaerobes
- more activity against E.coli
- Ceftriaxone & Cefotaxime & Antistreptococcal
- Resistance to lactamase

PK

- Oral / parenterally ✓
- Penetrate CSF : ceftriaxone, ceftazidime, cefotaxime
- cefotaxime : deacetylated to a metabolite
- excretion :
  mainly by kidney except cefoperazone (Bile)
  ceftriaxone (mixed)

CEFOTAXIME

gram −ve + CSF

- Uses: meningitis by gram (−) bacilli (penetrate CSF)
  Typhoid
  PPNG urethritis
  Hosp acq. infection (Anti streptococcal)
  Septicaemia

- deacetylated to a metabolite
- excreted kidney

- ADR: Pain @ inj injection site
  HS

CEFTRIAXONE

- DOC for typhoid
- longer dur^n of action
- CSF penetration good
- elimination by urine + bile (equal)

Uses: Bacterial meningitis
multiresistant typhoid
Complicated UTI
Sepsis
PPNG gonorrhea

ADR: Pain @ site
HS
Bleeding

CEFTAZIDIME

- High activity agx Pseudomonas aeruginosa
- Indication: febrile neutropenic patients with haematological malignancies, burn de

CEFOPERAZONE

- High activity: Pseudomonas aeruginosa
  Styphi, B. fragilis

Carbapenems

- Imipenem
- Meropenem
- Faropenem
- Doripenem

Imipenem

- extremely potent, broad spectrum
- Active agx gram +, gram −, anaerobes
- limiting feature: its rapid hydrolysis by the enzyme dehydropeptidase-1 located on the brush border of renal tubular cells
  ∴ combined with cilastin

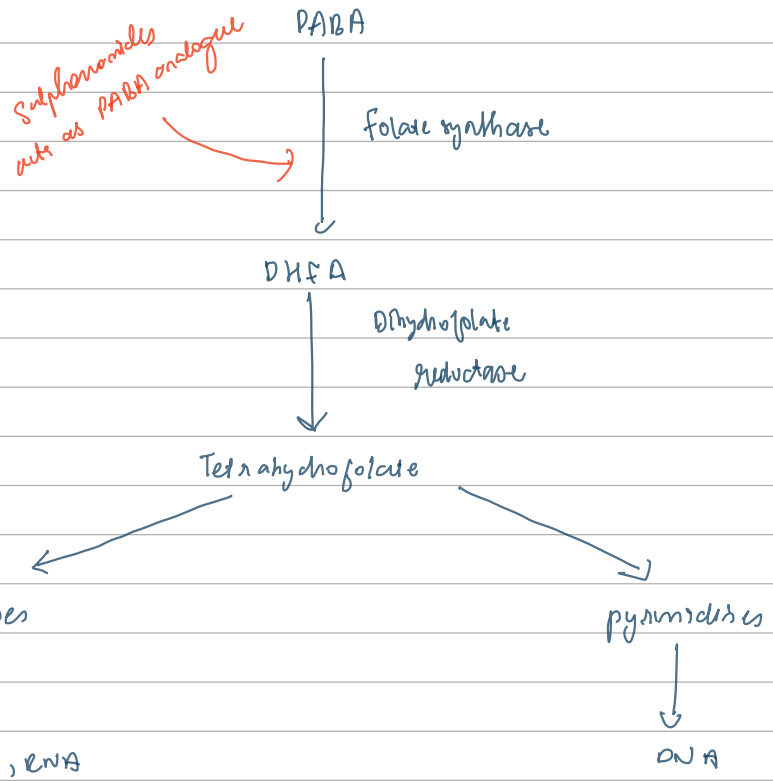
USES: Hosp acq infections, skin & soft tissue infections

ADR: Induce seizures *
diarrhea, vomiting
HS

Sulfonamides

MOA : Bacteriostatic drugs agx gram (-) & (+) bacteria

Inhibition of bacterial folate synthesis



* Bacteria synthesize their own folic acid, PABA is a constituent
* Sulfonamides - structural analogue of PABA
* Inhibit bacterial folate synthesis
  ⇓
  Prevent synthesis of purines & pyrimidines

SPECTRUM :

- gram +ve : S. pyogenes, S. pneumoniae.
  gram -ve : N. influenzae, N. ducreyi
- Poor activity against anaerobes

gram +ve → Staphylococcus
gram -ve → Haemophilus

RESISTANCE :

* ↓ in influx of bacteria
* ↑ efflux of bacteria
* β-lactamase (drug inactivating substances made)
* Alternating pathways for folic acid synthesis
* Altered binding site. eg PBP

CLASSIFICATION

i) Short acting : Sulfadiazine

ii) Intermediate acting : Sulfamethoxazole

iii) long acting : Sulfadoxine

iv) special purpose : sulfasalazine

PK

- Absorbed rapidly from GIT
- wide distribution
- metabolized in liver : N4 acetylation
- Renal excretion

USES

- Silver sulfadiazine : Topical (1% cream) - burns, ulcers

ADR

- Crystalluria : Precipitation of acetylated metabolites in urine
- Nausea, vomiting
- HS
- Hemolysis

Caution :

- Pregnancy
- Infants

Cotrimoxazole

- fixed dose combination of trimethoprim + sulfamethoxazole
- dihydrofolate reductase inhibitor
- Blockade of folate metabolism

Rationale :

- Sulfamethoxazole selected for combining with trimethoprim because of nearly same t1/2
- Optimal synergy
  - → sulfamethoxazole 20 : trimethoprim 1 } conc ratio
    5 : 1 } Dose ratio
  - → Both are bacteriostatic individually → combination bactericidal
- Slow dev to resistance of combined

PK

- Trimethoprim absorbed more rapidly - large Vd, cross BBB & placenta
- Route : IV / oral

Antibacterial spectrum (gram + & -)

- sulfonamide resistant strains
- S. pyogenes, S. aureus, shigella, E. coli, H. influenzae, gonococci, meningococcus
- Additional : Pneumocystis jirovecii
  Klebsiella
  Salmonella

USES

1) UTI
   - Uncomplicated cystitis
   - Complicated pyelonephritis
   - Prostatitis

2) RTI
   - Bronchitis

3) Chancroid

4) Typhoid

5) Bacterial diarrhea & dysentery

6) Pneumocystis jirovecii (severe pneumonia in neutropenia & AIDS)

ADR

- Nausea, vomiting, headache, rash
- Megaloblastic anaemia
- Renal diseases → Uremia

* Contraindicated in pregnancy

AMINOGLYCOSIDES

* Bactericidal antibiotics
* Protein synthesis is interferred

MOA

- Blocking formation of the initiation complex of messenger RNA with ribosomal RNA
- Prevents the formation of polysome & promotes disaggregation of polysomes to monosomes
- Misreading of mRNA code

Mechanism of resistance

- cell membrane bound modifying enzymes which phosphorylate / adenylate or acetylate the antibiotic.
- Mutation decreasing the affinity of ribosomal proteins.
- Decreased efficiency of aminoglycoside transporting mechanism

ADR

- Ototoxicity
- Nephrotoxicity

Gentamicin

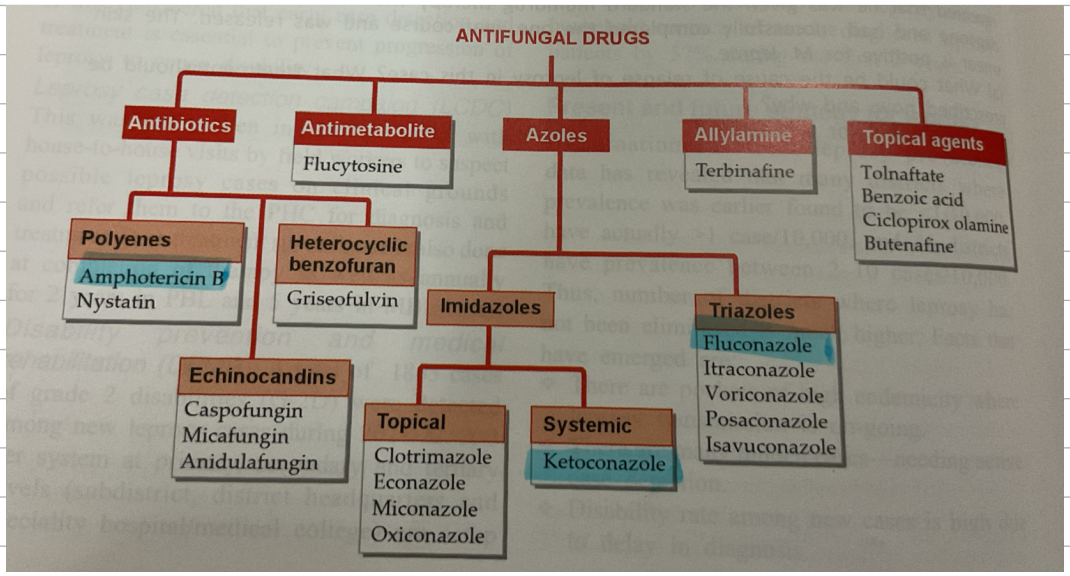
Active against aerobic gram negative bacilli [E.coli, Klebsiella, pseudomonas, Enterobacter, H.influenzae, Proteus]

- Ineffective against mycobacterium

Uses:

- used empirically to treat serious infections by extending the spectrum of coverage to include aerobic gram -ve bacteria.
- Mostly it is added to penicillin / cephalosporin
- Very valuable for preventing & treating respiratory infections
- Pseudomonas, Proteus, Klebsiella infections
- Meningitis caused by gram negative bacilli
- Subacute bacterial endocarditis.

Antifungal drugs



Amphotericin B

- Obtained from Streptomyces nodosus
- Polyene molecule
- Consists of a macrocyclic ring, one side of which has several conjugated double bonds & is highly lipophilic, while the other side is hydrophilic with many OH groups.

MOA

- high affinity for ergosterol present in fungal cell membrane
  ↓
  combines & gets inserted
  ↓
  forms micropores
  ↓
  ions, acid, other substances moves out
  ↓
  fungal permeability is markedly increased

SPECTRUM

- Active against Candida albicans, Histoplasma, Cryptococcus neoformans, Aspergillus.
- fungicidal at high rate & static @ low concentrations

PK

- Administered IV as a suspension made with the help of deoxycholate (DOC)

ADR

- A/c reaction: chills, fever, aches & nausea, vomiting
- long term toxicity: nephrotoxicity

- Anaemia

USES
- Oral, vaginal, cutaneous candidiasis
- fungal corneal ulcer & otomycosis
- systemic mycoses
- Leishmaniasis

Azoles

- Azoles acts by inhibiting fungal cytochrome P450 enzyme 'lanosterol 14-demethylase' & thus impairing ergosterol synthesis.
  => This leads to cascade of membrane abnormalities in the fungus

CLOTRIMAZOLE
- Topical imidazole effective in the treatment of tinea infections like ringworm
  USES: Athletes foot, otomycosis & oral/cutaneous/vaginal candidiasis
  ADR: Well tolerated - local irritation & stinging & burning sensation occurs.

KETOCONAZOLE
- Intro
- MOA

ADR
- Nausea & vomiting
- loss of apetite, headache, paraesthesia, rashes & hairloss
- decrease androgen production from testes - Gynaecomastia, loss of hair, libido & oligospermia

INTERACTIONS
- H_2 blockers, PPI & Antacids decrease oral absorption of KTZ
- Rifampin, carbamazepine & phenytoin induce KTZ metabolism

USE
- Dermatophytosis
- used as a lotion/shampoo - seborrhea of scalp & dandruff

PK
- Oral absorption of KTZ facilitated by gastric acidity

ITRACONAZOLE
- Orally active
- Spectrum: Aspergillus, few moulds, fluconazole resistant candida
- PK
  - Absorption is enhanced by food & gastric acid
  - large VOD
  - largely metabolized & Over by CYP3A4

- ADR
  - Dizziness, pruritis, headache, hypokalemia
- DI
  - reduced by Antacids, H_2 blockers, PPI
- USES
  - systemic mycosis
  - Histoplasmosis, blastomycosis, sporotrichosis
  - DOC for rare fungal infections.
  - Chronic aspergillosis
  - Vaginal candidiasis
  - Dermatophytosis
  - Onchomycosis

Anthelmintic

1) Mebendazole
   - Broad spectrum

MOA

Site of action - β tubulin

* Mebendazole + β tubulin
  ↓
  Inhibits polymerization
  ↓
  microtubules in cells are lost

* Blocks glucose uptake
* Inhibits glycogen stores
* Inhibits mitochondrial enzymes.

USES - Roundworm, Threadworm, trichuris, Enterobius
- Red^n in Eg count
- 100% cure

ADR
- Nausea, diarrhea, abdominal pain
- HS

2) Albendazole
- one dose treatment has produced cure rates

USE: Ascariasis, hookworm, Enterobius, Strongyloides, hydatid disease
- Larva migrans, filariasis

ADR : GI, dizziness, headache, fever, alopecia, neutropenia.

3) praziquantel

Spectrum/use: Schistosomes, trematodes, cestodes
- No nematodes (round worm, trichuris)

mon: leakage of intracellular Ca from the muscle producing contracture & paralysis of the worm.

ADR - GI, headache, dizziness, urticaria, rashes, fever.
use - tapeworm, schistosomiasis & flukes