Anti-microbial clinical pharmacology

By
Mohie Aldien Elsayed (MD)
**Microorganism**: Contain all of the enzymes required for their replication and possess the biologic equipment necessary for production of metabolic energy.

<table>
<thead>
<tr>
<th><strong>1-Prokaryotes</strong></th>
<th><strong>2-Eukaryotes (Protistis)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>DNA (nucleoid) is not physically separated from cytoplasm.</em></td>
<td><em>Contain a membrane bound nucleus.</em></td>
</tr>
<tr>
<td><em>No</em></td>
<td><em>Have a membrane bound specialized organelles (mitochondria, endoplasmic reticulum, microtubules).</em></td>
</tr>
<tr>
<td><em>Have the capacity to exchange small packets of genetic information (DNA) e.g. plasmid.</em></td>
<td><em>Genetic transfer depends upon fusion of haploid gametes.</em></td>
</tr>
<tr>
<td><em>Have cell envelop.</em></td>
<td><em>No (some have cellulose, chitin or silica cell wall).</em></td>
</tr>
<tr>
<td><em>No (except mycoplasm)</em></td>
<td><em>Sterols present in membranes.</em></td>
</tr>
<tr>
<td><em>Smaller size.</em></td>
<td><em>Larger size.</em></td>
</tr>
<tr>
<td><em>Have no interon</em></td>
<td><em>Have interon which is segment of DNA that interrupt exon (Transcription part of DNA).</em></td>
</tr>
<tr>
<td><strong>1) Eubacteria:</strong></td>
<td>e.g. 1) Algae 2) Protozoa 3) Fungi 4) Slim molds</td>
</tr>
<tr>
<td>Have no peptidoglycan in their cell envelop.</td>
<td></td>
</tr>
<tr>
<td><strong>2) Arachaebacteria:</strong></td>
<td></td>
</tr>
<tr>
<td>Have no peptidoglycan.&amp; Live in extreme environment(high salt, high temperature or low pH).</td>
<td></td>
</tr>
</tbody>
</table>

**N.B. Viral particles** depend upon host cells for replication and production of metabolic energy - thus they are from living creature, they can be regarded as a genetic extension of its host.
Eubacteria

*Have no cell wall e.g Mycoplasma

Acid-Fast Stain (retain a basic stain in the presence of acid-alcohol, (Mycobacterium)

Non-acid-fast cells lose the basic stain when rinsed with acid-alcohol.

**Have cell wall**

**GRAM+ve**

* Stained purple blue with gram stain
* Cell wall is composed of:
  1 - Much thicker peptidoglycan layer (pg).
  2 - Have only one cytoplasmic membrane
  3 - No.
  4 - No.
  5 - Hydrolysed by lysozyme (tears, saliva, nasal secretion).
  6 - The antigenic structure is lipotechoic acid in cytoplasmic membrane.

**GRAM-ve**

* Stained red with gram stain
* Cell wall is composed of:
  1 - Less thicker peptidoglycan layer
  2 - Have inner and outer cytoplasmic membrane (OM) with space between them
  3 - Have lipoprotein anchor OM to PG.
  4 - (-ve) charges lipopolysaccharides cross bridged by divalent cations forming barrier to hydrophobic molecules.
  5 - Protected by outer membrane

6 - The antigenic structure is polysaccharide.
## Common pathogenic bacteria for humans

<table>
<thead>
<tr>
<th>Group</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I- Gram-ve bacteria that have cell wall</strong></td>
<td></td>
</tr>
<tr>
<td>a) Spirochetes (Long, slender, helically coiled moved by axial filament)</td>
<td>Treponema, Borrelia, Leptospira</td>
</tr>
</tbody>
</table>
| b) Enterobacteriaceae  
  ● Facultative anaerobic  
  ● Live in intestinal tract of human & animals.  
  ● Short rods | Eschericia, Klebsiella, Proteus  
  Salmonella, Haemophilus,  
  Pateurella, Yersina, Vibrio? |
| c) Aerobic/microaerophilic, motile, helical/ vibroides | Vibrios? Helicobacter, Campylobacter |
| d) Aerobic/ microaerophilic  
  ● Coci  
  ● Obligate aerobe  
  ● Obligate anaerobe | Bordetella, Brucella,  
  Moraxella, Neisseria, Pseudomonas  
  Bacteroides, Legionella |
| e) Anaerobic  
  1) Cocco bacilli  
  2) Pleomorphic rods | Bacteroides  
  Fusobacteria |
| f) Obligate intracellular | Rickettsia, Chlamydia, Coxiella |
| **II- Gram+ve bacteria that have cell wall** | |
| a) Gram+ve cocci | a) Staphylococi, Streptococci, Enterococci, Peptostreptococci |
| b) Endospore forming rods  
  1- Obligatory aerobic  
  2- Obligatory anaerobic | Bacillis  
  Clostridium* |
| d) Non sporulating irregular rods anaerobic, branching filament like | Actinomyces* |
| **III- Mycobacteria** | |
| Acid fast= resist decolourization by acid or alcohol. | M. Lepra  
  M. Bovis |
| **IV- Cell wall-less bacteria** | |
| | Mycoplasma  
  Urea plasma |

Endotoxins is a polysaccharide and lipid which are a part of gram-ve cell wall continuously liberated by a rapidly multiplying organisms or bacterial cell death. It lead to hypo-tension, intra-vascular coagulation and multiple organ failure.
General Principles of antibiotic therapy
The antibacterial activity depends on
♦ Susceptibility of the organisms
♦ Drug penetration to the site of infection
♦ Time of contact Minimal inhibitory concentration (MIC) with the organism
♦ Post antibiotic effect (may prolong the period of antibiotic effect in vivo)

I) Susceptibility of the organisms to Antibiotics by Gram stain of Sensitive Organisms

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Effective Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Penicillins</td>
<td>Many Gram+ cocci, some Gram-</td>
</tr>
<tr>
<td>* Cephalosporins</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; generation: Gram +, some Gram -</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; generation: more Gram -. Less Gram +</td>
</tr>
<tr>
<td></td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; generation: more Gram - lesser gram +</td>
</tr>
<tr>
<td></td>
<td>4&lt;sup&gt;th&lt;/sup&gt; generation: more Gram -ve, some Gram +ve:</td>
</tr>
<tr>
<td>* Carbenem</td>
<td>*Gram + Gram-, anaerobe</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>*Aerobic Gram-bacilli</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Gram-only, MRS</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Aerobic Gram-bacilli</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Aerobic and anaerobic Gram+ and Gram-</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Gram+</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Most Gram + cocci, many anaerobes</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Some Gram + and Gram-</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Some Gram + and most Gram -</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Most gram+ and many gram-, mycobacteria, clamydia and pox virus</td>
</tr>
</tbody>
</table>

* Gram+ = Gram-positive; Gram-=Gram-negative. MRS = Methicilne resistant staph.

II) Ability to penetrate to site of action

Depends on: - Lipid solubility - Protein binding - PH
- Molecular size - Tissue binding affinity - Rate of blood flow
- Ability to penetrate bacterial cell
- Ability to cross blood-brain barrier

Antimicrobials achieve high concentrations at:

2) Bile: carbapenem, Cephalosprins, ciprofloxacim, Erythromycin, Penicillinse, Doxycycline, clindamycin, Rifampicin, Amphotericin B

3) Urine: carbapenem, Cephalosprins, Penicillinse, Aminoglycosides, Quinolones Sulphonamides, Nitrofurantion, Ethambutol, Flucytosine

4) Prostate: Quinolones, Cotrimoxazole, nitrofurantion
1) CSF

<table>
<thead>
<tr>
<th>CSF</th>
<th>Bile</th>
<th>Urine</th>
<th>Prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol, Cotrimoxazole, Isoniazid, Metronidazole, Rifampicin Erythromycin, Pyrazinamide Fluoroquinolones, Flucytosine, Meropenem Cephalosporinos e.g cefotaxim, ceftriaxone, ceftazedime</td>
<td>Penicillins (e.g. nafcillin, piperacillin, mezlocillin) Cephalosporins (ceftriaxone, cefoperazone, cefmetazole), Erythromycin, Meropenem, Doxycycline, clindamycin, Rifampicin, Amphotericin B, ciprofloxacin</td>
<td>Penicillins, Cephalosporins, Carbapenems, Aminoglycosides Sulphonamides, Nitrofurantion, Quinolones, Ethambutol, Flucytosine</td>
<td>Quinolones, Cotrimoxazole, nitrofurantion</td>
</tr>
</tbody>
</table>

III) Time of organism contact to minimal inhibitory concentration (MIC): Antibiotic Activity is:

*Concentration dependent*. E.g. quinolones, aminoglycosides. Thus, optimal dosing regimens for such antibiotics therefore need to maximize serum level.

*Concentration independent*. E.g. B-Lacum. The major determinant of their bacteriological activity is the duration that serum levels exceed the MIC of the infecting pathogen.

NB: % dosage interval of serum level > MIC needed to obtain Max. killing rate are: e.g. *carbapenam(30-40%) *Cephalosporin(60-65%) *Penicillin(50-55%)

IV) Postantibiotic effect (PAE):

*Although it is a feature of nearly all antibiotics except B-lactams, it is observed with carbapenams.

- Mechanism(s) not certain (may be extension of bacterial growth lag phase recovery after reversible nonlethal damage/ persistence of drug at binding site/ need to synthesize new enzymes before growth resumes)
- In vivo PAEs > in vitro PAEs

*Although the clinical significance of PAE remains unclear, the observation that meropenem induce PAE in so many potential pathogens could be a desirable feature when considering dosage interval Post-Antibiotic Effect

- Persistent suppression of bacterial growth after limited exposure to an antimicrobial agent

Antimicrobials for which dose modification is required in Renal failure:

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides, Amphotericin B, Cephalosporins, Ethambutol, Flucytosine, Carbapenem, Vancomycin</td>
<td>Metronidazole, Ticarcillin</td>
<td>Co-trimoxazole, Penicillins, Acyclovir</td>
</tr>
<tr>
<td>Avoid: cephalothin, cephloridine, Nalidixic acid, nitrofurantion, Talampicillin, tetracyclines</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7
Antimicrobials in severe liver disease

<table>
<thead>
<tr>
<th>Dose reduced</th>
<th>Avoided</th>
</tr>
</thead>
</table>

### Antimicrobial Agents to be Avoided During Pregnancy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1) ANTIBACTERIAL</strong></td>
<td></td>
</tr>
<tr>
<td>- Possible VIII nerve damage</td>
<td>- Aminooglycosides</td>
</tr>
<tr>
<td>- Gray baby syndrome</td>
<td>- Chloramphenicol</td>
</tr>
<tr>
<td>- Cholestatic hepatitis</td>
<td>- Erythromycin estolate, clarithromycin</td>
</tr>
<tr>
<td>- Possible teratogenic</td>
<td>- Metronidazol</td>
</tr>
<tr>
<td>- Hemolytic anemia</td>
<td>- Nitrofurantoin</td>
</tr>
<tr>
<td>- Hernolysis in newborn with, G6PD</td>
<td>- Sulfonamides</td>
</tr>
<tr>
<td>- Increased risk of kernicterus</td>
<td>- Tetracyclin</td>
</tr>
<tr>
<td>- Limb abnormalities, dental Staining</td>
<td>- Trimethoprim</td>
</tr>
<tr>
<td>- Altered folate metabolism</td>
<td>- Qunolone</td>
</tr>
<tr>
<td>- Abnormalities of cartilage</td>
<td>- Vancomycin</td>
</tr>
<tr>
<td>- Possible auditory toxicity</td>
<td></td>
</tr>
<tr>
<td><strong>2) ANTIFUNGAL</strong>: Griseofulvin</td>
<td>- Teratogenic in animals</td>
</tr>
<tr>
<td>Ketoconazole, Itraconazol, Fluconozol</td>
<td></td>
</tr>
<tr>
<td><strong>3) Antituberclosis</strong>: Isoniazid, Rifampicin</td>
<td>Use with caution</td>
</tr>
<tr>
<td><strong>4) ANTIVIRAL</strong>: Amantadine, Acyclovir, Gancyclovir, Tratogenic, Lamivodine, Zidovudine, Zalcitabine.</td>
<td>- Tratogenic</td>
</tr>
</tbody>
</table>

- **Bactericidal agents**
  - Aminoglycosides, bacitracin, beta-lactam antibiotics, isoniazid, metronidazole, polymyxins, pyrazinamide, quinolones, quinupristin-dalfopristin, rifampin, vancomycin
- **Bacteriostatic agents**
  - Chloramphenicol, clindamycin, ethambutol, macrolides, nitrofurantoin, novobiocin, oxazolidinones, sulfonamides, tetracyclines, trimethoprim
**Microbial Resistance to Antimicrobial Agents.**

**Acquired resistance:**
1) Natural,
2) Non-genetic: Evasion, bacteria may hide in cells or organelles; L-forms, temporary forms of cell w/o cell walls, removing a target.
3) Mutation: change in transport protein, ribosome, enzyme, etc. Normally harmful mutations are selected FOR in the presence of antibiotic
4) Induced (adaptive)
5) Transferable within Plasmids by:
   * Conjugation (resistance transfer factor)
     → multiple resistance (up to 8 at once)
     → major public health concern.
   * Bacteriophage.
   * Transposition

**1) Non-Chromosomal Microbial Resistance to Antimicrobial Agents:**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| **1-Modification of target enzyme or receptor** | * B-lactams  
* rifampicin.  
* quinolones  
* erythromycin, Clindamycin  
* Trimerhophine  
* amphotericin B |
| *PBP (penicillin binding protein.  
* RNA polymerase.  
* DNA gyrase  
* Methylated 23s RNA  
* Dihydrofolate reductase.  
* Altered sterol synthesis. |  |
| **2↓uptake/↑efflux of drug → inhibit access to target** | *B-lactams, quinolones  
* aminoglycosides  
* tetracyclines  
* 5-flucytosine |
| *Altered porin channels.  
* Membrane energy source lacking  
* Efflux of drug  
* Loss of transport enzyme |  |
| **3-Reduction in importance target** | *B-lactams  
* sulfonamides, trimethoprim |
| *Penicillin binding proteins.  
* Folate pathway |  |
| **4-Incativating enzyme** | *B-lactams  
* chloramphenicol  
* aminoglycosides |
| *B-Lactamases  
* Chloramphenicol transacetylase  
* Phosphorylase, amylase |  |
| **6-Failure to metabolized drug:** | *metronidazole, 5-flucytosine |
| *Anaerobes, Candida |  |

**II) Impermeability (gram-ve organisms)**
The freely penetration of cabapenems depends on:
   1-Low molecular weight.
2-Possess both +ve & -ve regions of charges in solution (zwitter-ionic nature
3-carbabenams enter the cell by different routes (e.g. porines) from other B-lactams as
resistant strains of p.aeroginosa to B-lactams (due to permeability problems) are rarely
resistant to meropenem

Cross resistance: microorganism which is resistant to specific drug may also be resistant
to other drug with the same mechanism of action e.g. erythromycin & oleandomycin or
with unrelated drug e.g. erythromycin & lincomycin.

B-lactamases (* = meropenem is resistant to most of them)

A) Chromosomal B-lactamases:
   a-Inducible: *emerge during B-lactams therapy
      *Reversible derepressed which means removal of repressor protein from
AmPR which is the Part of DNA control transcription of Ampc which is the gene of B
lactamase synthesis e.g. type 1 B lactames, cephalosporinase, cephalosporinase

   AmPC                         Repressor Protein
                             amPR
          Control amPR transcription gene responsible B. lactamase synthesis

b-Constitutively: *organism is originally resistance
   *Caused by mutation in AmPR leading to excessive irreversible
transcription of amPR leading to B.lactamase production (stably derepressed)
e.g. B.lactamase of enterobacteriacea, P.aerogenosa, Carbapenamase of Bacteroids (4 of 7
members synthesis inhibited by meropenem < 4mg/L).

B- Plasmid mediated:
   ♦Produced constitutively by organism which is originally resistant.

<table>
<thead>
<tr>
<th>Types</th>
<th>Penicillinase</th>
<th>E.S.B.L.S.</th>
<th>Cephalosporinase</th>
<th>Carbapenamase</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMI,2...2 6 &amp; SHV1</td>
<td>CAZ1,2...5 &amp;CTX-1&amp;SHV2</td>
<td>MEN-1 &amp; CTX-M1</td>
<td>Cmy1,2 &amp; Fec1 &amp;FPM-1&amp;Mox-1</td>
<td>IMP-1</td>
</tr>
<tr>
<td>Hydrolysis</td>
<td>1-Penicillins 2-1st gener .ceph.</td>
<td>3)monobactam 4-2nd &amp; 3rd gener..ceph.</td>
<td>All ceph. including cephamycines+1,3</td>
<td>All ceph. including cephamycines +1,3</td>
</tr>
<tr>
<td>Dissimination</td>
<td>Widely</td>
<td>Widely</td>
<td>Limited</td>
<td>limited</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Community &amp; hospitals</td>
<td>Hospitals mainly</td>
<td>Hospitals mainly</td>
<td>Hospital mainly</td>
</tr>
<tr>
<td>Common organism</td>
<td>Many</td>
<td>Peneumonia</td>
<td>E.coli</td>
<td>K.pneumonia E.Cili</td>
</tr>
<tr>
<td>Blactama se inhibitor</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>?</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>
Bacterial resistance to carbapenem may be due to:

- Loss of D2 porin, which allow entry of carbapenem
- Over production of carbapenemase e.g. P. aeroginosa

N.B a) Although Meropenem MICs is higher against D2porin-negative mutant than those with the porin but they remain within susceptible range.

b) D2 porin deficient imipenem resistant P.aeroginosa mutant generally remain susceptible to Meropenem. This observations can be explained if we know that meropenem can enter the bacteria through other porines rather than D2 porine

Types of Carbapenemase

a) Zinc dependent (metaloprotinase)
   - Hydrolyze all B-lactam antibiotic
   - Almost all of them are chromosomal (non transferable)
   - e.g. stenotrophomonas (Xanthomonas) maltophilia

b) Zinc independent:
   - Hydrolyse imipenem but not meropenem e.g. S. Marcesenes.

N.B meropenem is a poor (less than imipenem) inducers,

ANTIMICROBIAL COMBINATION:

- **Indications**:
  1. Emergency(empirical) : start treatment before results of sensitivity tests are available
  2. Mixed infections e.g. peritonitis
  3. To prevent or delay the emergence of resistant strains
     - e.g. INH + rifampicin + ethambutol in tuberculosis
  4. To reduce severity or incidence of adverse effects.
  5. To obtain synergism
     a) Blocking successive steps in a metabolic sequence e.g. cotrimoxazole
     b) Blocking enzyme that destroy the active drug(clavulanic acid + amoxicilin)
     c) Promoting entry of the other drug
     e.g. * penicillins (cell wall inhibitors) + aminoglycosides

     * Meropenem + vancomycin or teicoplanin or other B-lactams resistant to B-lactameses against methicillin resistant S.aureus.

- **Combination to be avoided (Antagonism)**
  1. Chloramphenicol & Macroloids compete at the same receptor sites
  2. Minimal doses of bacteriostatic and bactericidal used together
  3. Imipenem (B-lactmase inducers) and piperacillin (B-lactmase) sensitive
  4. Cephalosporines and aminoglycosides (both are nephrotoxic).

**Combinations**

1– Cidal : combinations often synergistic in Immune compromised patients with Severe acute infection (aminoglycosides & beta-lactams)
2– Static: combinations indifferent or additive (tetracyclines, sulfonamides, macrolides)
3– Cidal / Static combinations often antagonistic (Interference with cidal drug especially if cidal drug depends on rapid growth)

* Recommendation – Do not combine group 1 and group 2 drugs
  (Exceptions • Mixed infections • Location)
Antibiotics mechanism/site of action

A) Quinolones:
- Enter through porins (gram-ve) → inhibit gyrase → ↓ DNA rejoining → inhibit DNA [Bactericidal]
- Resistance: - chromosomal gyrase mutation e.g. MRS, Pseudomonas
- Concentrated in: 1) prostatic tissue → used in prostatitis
  2) Macrophage (↓ M. tuberculosis (not M-avium), Mycoplasma, chlamydia & Brucella
- Excreted in P.C.T → ↓ dose in Renal impairment
- Oral/IV
- **Adverse effect:** 1) Cartilage resorption, chondrolytic (not used in pregnancy, & < 18y)
  2) GIT upset  3) rash, photosensitivity  4) crystaluria
  5) sucralfate, antacide, Fe+2 and Zn+2 decrease its absorption
- Classified into:
  - 1st generation (-ve rods)  e.g. Nalidixic acid (U.T.I but not Ps)
  - 2nd generation (-ve rods, +ve cocci, chlamydia, & mycoplasma)
    1) Pass BBB (meningitis), short duration e.g. ofloxacin, pefloxacin & norfloxacin (UTI, not effective in systemic infection)
    2) Not pass BBB & short duration  e.g. ciprofloxacin
3rd generation (-ve rods, +ve cocci, clamidia & mycoplasma)
*Not pass BBB & longer duration (once/day) e.g. sparfloxacin, levofloxacin,
4th generation (-ve rods & bacilli, +ve cocci, anaerobic)
*Longer duration, once/day e.g. trovafloxacin

♦ Uses:
1- gram –ve a) Urogential e.g. gonorrhea b) GIT e.g. Typhoid-
2- Meningococcal carrier
3- Pencillin Res-Staph (e.g. ceprofloxacin)

Methotrexate

Sulfonamides inhibit synthesis of dihydrofolinic acid (DHF) in bacteria. Vertebrates must use preformed DHF. Most bacteria must make their own DHF PABA = Para-aminobenzoic acid; DHPtS = Dihydropteroate synthase; DHF = Dihydrofolic acid; THF = Tetrahydrofolic acid;

B) Antifolate (Mammalian cells take tetrahydrofolate as it is)

I- Sulfonamides:
*Bacteriostatic (+&-ve, chlamydia, nocardia)
♦ Adverse effect:
1-Crystals (acid urine) → ↑fluid, Alkalinize urine
2-Allergy 3- Favism
4- Nausea & vomiting
♦ Classified into:
A- Short acting: 1- Sulphisoxazole (soluble even in acid urine) for treatment of
Toxoplasmosis. & leishmaniasis
2- Sulphadiazine (added to Pyrimethamine for treatment of
Toxoplasmosis. & leishmaniasis
B- Intermediate e.g. sulphamethoxazol added to Trimethoprim to form cotrimoxazol
used for Typhoid, shigella, UTI
C- Long acting e.g. Sulphadoxin (+ pyrimethamine) to treat chloroquin resistant
plasmodium falciparum.
D- Poor absorption (local) Oral e.g. sulphasalazine used for Ulcerative colitis
E- Topical e.g. Sulphacetamide for ocular infection and Mafenide for skin burn
Trimethoprim: ↓ folinic → Megaloblastic anaemia, granulocytopenia
*Trapped in acidic prostatic & vaginal fluids (pH 6.4)
* inhibits excretion of creatinine – so raises serum level.

CO-TRIMOXAZOLE: *trimethoprim(TMP) +sulfamethoxazole→1:5, Similar compounds:* TMP+ Sulfamoxal (Entrim, Supristol), *TMP+ Sulfamoxol (Lidaprim)
*TMP→more lipid soluble→larger volume of distribution

Anti-Bacterial Activity: *1- They produce Sequential block in the synthesis of folinic acid & DNA→Synergism.*2- more potent, wider spectrum & less bacterial resistance that each drug alone.

Therapeutic uses: RTI, UTI, Prostatitis, Gonococcal infection, Shigelle & salmonella enteritis, Systemic salmonella (Typhoid fever & carrier), Prevention & treatment of Toxoplasmosis; Nocardiosis;

Adverse effects: Both Sulfa & TMP.

Antibiotics inhibit Protein synthesis
Protein synthesis

(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S procaryotic ribosome.

(b) In the diagram the black arrows indicate the different points at which chloramphenicol, erythromycin, the tetracyclines, and streptomycin exert their activities.
**1. Bactericidal / narrow spectrum (gram-ve bacilli, gram+ve cocci)**

- **e.g. Aminoglycosides**
  - Large polycationic molecules (hydrophilic) ● Not absorbed from GIT (parentrally)
  - Not pass to CNS ● Excreted in glomerular filtration
  - Concentration in sensitive organism by O2-dependent mechanism (No effect on anaerobes)
  - Bind to 30S irreversibly disturb codon-anticodon interaction leading to misreading and non-functioning proteins
- **can be classified into:**
  - a) Susceptible to destructive bacterial enzymes e.g. phosphorylase e.g. **streptomycin**
    (T.B. plague, RTI, UTI), **gentamicin** (MRSA, Pneumonia, UTI, osteomyelitis, Septicemia, topical), **Neomycin** (topical in skin, gut), **Spectinomycin, Paromomycin**.
  - b) Resistant to most destructive bacterial enzymes e.g. **Amikacin, Netromycin** (Gentamicin – Resistant infections)
- **Toxicity:**

**2. Bacteriostatic, Broad spectrum (gram +ve,-ve)**

- **A) Highly lipophilic** (Pass to CNS freely, taken orally)
  - e.g. **chloramphenicol** (typhoid, paratyphoid, meningitis, mixed aerobic and anaerobic infections e.g. intra-abdominal infections, Rickettsial infections, Vancomycin-resistant enterococci, topically in eye and ear infection)
  - Bind to 50S inhibiting reversibly tranpeptidation
  - **Toxicity:**
    - 1. Bone marrow suppression (reversibly dose dependent inhibition and irreversible or idiosyncrasy which is more dangerous)
    - 2. Gray baby syndrome (shock, Pallor) in neonates due to deficient glucuronidase which metabolize chloramphenicol.
    - 3. Enzyme inhibition leading to ↑ activity of phenytoin, warfarin, oral hypoglycemic.
- **B) Moderate lipophilic** (oral intake but lesser pass to CNS)
  - e.g. 1) **Tetracyclenes** (gram +ve &-ve, RTI, UTI, Venereal diseases, enteritis, skin & eye infection, rickettsia→(typhus, Q-fever, RMSF), Chlamydia, intestinal amebiasis)
  - Bind to 30S and inhibit binding of tRNA to acceptor site A at ribosome.
  - Classified according to excretion route into:
    - a) bile excretion e.g. Doxycyclene (longer duration)
    - b) Renal excretion e.g. tetracycline, oxytetracycline, minocycline
  - **Toxicity:**
    - 1. colitis, chelate Ca²⁺, Fe³⁺, Mg, Al³⁺, milk.
    - 2. discoloration of teeth
    - 3. hepatic, renal toxicity
    - 4. contraindicated in pregnancy, lactation.
    - 2) **Macroloids** (gram +ve &-ve, Chlamydia, H. pylori, atypical T.B)
  - Bind to 50S inhibiting translocation
  - Classified according enzyme inhibition into:–
    - a) Enzyme inhibitors (↑ warfarin, digoxin, theophyline)
      - e.g. **erythromycin** (used in patients allergic to penicillins), **clarithromycin** (erythromycin + H.Influenzae, Chlamydia, H. pylori), **Roxithromycin, Dirithromycin**
    - b) Not enzyme inhibitor e.g. **Azithromycin** (+ Mycobacterium avium)
3) **Lincomycins** (+anaerobes, bone & teeth infections, locally in acne vulgaris)
- Bind to 50S inhibiting translocation
- Toxicity, pseudomembranous colitis
  - e.g. clindamycin, lincomycin

4) **Rifampicin**:
- Lipophilic → pass BBB
- Bactericidal (T.B, gram +ve)
- Inhibit RNA polymerase → ↓ transcription & protein synthesis
- Toxicity 1- immune mediated e.g. flu syndrome, thrombocytopenia
  2- Red urine, saliva.

**Antiobiotics inhibit cell wall synthesis**

**Gram-ve cell wall**
- Lipoteichoic acid
- Peptidoglycan-trichoic acid
- Cytoplasmic membrane
- Cytoplasm

**Gram+ve cell wall**
- Outer membrane (Major permeability barrier)
- Porin
- Lipopolysaccharide
- Braun lipoprotein
- Periplasmic space
- Periplasmic binding protein
- Permease
- Cytoplasm

I) **B-lactam antibiotics**
- Bactericidal: (B-lactam ring is essential): Inhibit cell wall synthesis by inhibiting penicillin binding Protein (PBP) which is the transpeptidase enzyme responsible for final step in peptidoglycan layer synthesis leading to cell lysis.
- *Production of new PBP2 (PBP-2a) → resistance to B-lactam antibiotics.*
- **Pharmacokinetic**:
  - Low plasma protein binding
  - Actively excreted in renal proximal tubules
  - 6-8h duration
- **Can be classified into**:

  I) **Monocyclic (monobactam)** e.g. Azetreonom (mainly aerobic gram-ve including P. aeruginosa, NOT gram+ve or anaerobes, Use in patient allergic to penicillins)
  - Narrow spectrum (gram –ve)
  - Resistant to some B-lactamases.
  - No cross allergy with penicillins
  - May lead to pseudomembranous colitis treated by vancomycin + metronidazol.

  II) **Bicyclic**: A) **Penicillins** (streptococcus, syphilis, gonorrhea)
  - *a-Penicillinase resistant*:
  - Narrow pectrum (gram +ve)
  - Acid resistant (oral)
  - e.g. cloxacillin, Dicloxacillin, flucloxacillin, &naficillin (longer duration due to enterohepatic circulation)
**b-Penicillinase sensitive:**

1-*Acide labile (parenteral), Narrow spectrum*

- *Gram +ve inhibitors:* e.g. benyl penicillin in (I.V or I.M/6h), Procain penicillin (IM/24h), benZathine penicillin (IM/1 month duration)
- *Gram-ve inhibitors:* Micilinam, Pivmicilinam mainly for salmonella, shigella, carbencillin, Indanylcarbencilline (oral), Ticarcillin mainly pseudomonas.

2- *Acid resistant (oral):*

- Narrow spectrum (+Ve) e.g. phenoxypropyl penicillin.
- Wide spectrum (+ve&-ve): *Prodrug*, less colitise (pivampicillin, Bacampicillin) *Active drug*, more colitise (Amoxicillin, Ampicillin)

**Adverse reactions of penicillins 1) Hypersensitivity:**

*Early:* a) Rash (common), urticaria, erythema
   
   b) Anaphylaxis (rare) - circulatory collapse, bronchospasm, laryngeal edema.

*Delayed* by 2-12 days (serum sickness): fever, malaise, arthraglia, angioedema, erythema nodosum, erythema multiforms.

2) *Neurotoxicity* *Encephalopathy* as fits, coma (only in very high doses), impaired renal function and intrathecal injection of over 50000 U

3) *Haemolytic anemia:* only in high doses

4) *Ampicilins* → morbiliform rash (8% of patients, commonly in young woman)

### (B) Cephalosporines

<table>
<thead>
<tr>
<th></th>
<th>1st generation</th>
<th>2nd generation</th>
<th>3rd generation</th>
<th>4th generation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram +ve</strong></td>
<td>++</td>
<td>+++</td>
<td>*+</td>
<td>*+</td>
</tr>
<tr>
<td><strong>Gram-ve</strong></td>
<td><em>++++</em></td>
<td>++&amp;anaerobic</td>
<td>+++</td>
<td>*+++</td>
</tr>
<tr>
<td><strong>B-lactamase</strong></td>
<td>Susceptible to all types</td>
<td>Resistant to penicillinase</td>
<td>Resistant to penicillinase</td>
<td>Susceptible to ESBLs, carbapenemase,</td>
</tr>
<tr>
<td><strong>Omp</strong></td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Pass BBB</strong></td>
<td>No</td>
<td>Unreliable</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td><em>cefalexin, cefradin, cefadroxyl, Cefalothin cefazolin</em></td>
<td><em>Cefaclor, cefprozil, Cefoxitine, Cefamandol, cefuroxime</em></td>
<td><em>Cefixime, cefpodoxime, Cefotaxime, cefoperazone, cefotrixone</em></td>
<td><em>Cefozopran, Cefepim, cefepirox, cefcililin</em></td>
</tr>
<tr>
<td><strong>Parental</strong></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

**Omp:** Outer membrane protein in gram –ve bacteria

**Adverse effects:** 1-Hypersensitivity & cross allergy with penicillins

2-Nephrotoxicity especially older members

3-IM → Local pain & IV → thrombophlebitis

### C) Carbapenam (Ultra- broad Spectrum & IV)

1- *Meropenem:* *higher efficacy in gram –ve (4-64 folds).*

2- *Imipenem-cilastatin:* *higher efficacy in aerobic gram +ve cocci (2-4 folds).*

3- *Ertapenem* (once daily carbapenem), *Not active in pseudomonas & acinetobacter spp.*
used in community acquired infections and not the more serious nosocomial infection

II) Vancomycin:*Bactericidal, narrow spectrum ( +ve including MRS, C.difficil)
*Pass to CNS
*ototoxicity,nephrotoxicity, Histamine release (if rapid IV infusion) → Red man syndrome

III) Bacitracin: Bactericidal (gram +ve) used topically

IV) Polymixin: Bactericidal (gram –ve) used topically

**NB: Combination of Penicillin + B-lactamase inhibitor**
1-Clavulanic acid + amoxicillin = Augmentine (oral)
2-Clavulanic acid + ticarcillin = Timentine (IV)
3-Tazobactam + Pipercillin = Zosyn (IV)
4-Sulbactam + ampicillin = Unasyn (IV, )

**Antituberculosis**
- Resistance develop rapidly → combination & to↑ activity & ↓ toxicity.
  e.g.*INH+Rifampicin(9-12 m) **INH+Ethambutol(12-18m) in pregnancy.
  •1ª line drugs: A)lipophilic (pass BBB,↓ Intracellular & extracellular organisms)
*H.el. → hepatotoxicity. *Bactericidal *oral

<table>
<thead>
<tr>
<th>1-Rifampicin</th>
<th>2-Isoniazide (300m/d)</th>
<th>Pyrazinamide(30mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓TB in caseous pool</td>
<td>-No</td>
<td>-No</td>
</tr>
<tr>
<td>↓RNA polymerase (↓protein)</td>
<td>↓mycolic acid synthesis (↓ cell wall)</td>
<td>?</td>
</tr>
<tr>
<td>Deacytlylated →active Acetylated→inactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-immune(flu syndrome , thrombocytopenia) rapid → hepatotoxicity slow→neurotoxicity (↓vit B₆)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-red urine, tear, saliva polyarthralgia,porphyria, rash, huperuricemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B) hydrophilic (nit pass BBB & ↓ extracellular organisms only, R.el. a-

Bactericidal e.g. Ethambutol (150mg/kg/d oral)
* ↓ cell wall(arabinglycan) *reversal optic neuritis, retinal damage

B) Bacteriostatic: e.g. Streptomycin, amikacin
• 2ª line drugs: fluoroquinolone, macrolids, capreomycin, cycloserine.
• Atypical (M.avium,M.marinum) → ethambutol, rifampicin, maroloids

**Antileprosy: 1ª Dapson:** *lipophylic *↓ folic Acid synthesis
*GIT upset, fever, rash, methaemoglobinemia, favism, rapid Resistance.
2- Acedapson (depot)/3m
3- rifampicin, clofazimine (delay resistance to dapsone)
**Antiviral**

### I) Attachment, penetration, uncoating Is:
- IgG (Hepatitis, measles, rabies, osteomyelitis)
  * parental  * anaphylactoid

- **M₂ Ion Channel Blockers (Flu₄):**
  * Oral  * N, V, embryotoxic, teratogenic (# pregnancy & nursing)

1- **Amantadine:**
- passBBB → insomnia, dizziness, ataxia, hallucination, seizures (# psychiatric & cerebral disorders)

2- **Rilmentadine:** less passBBB

### II) Synthesis of viral components (genome, protein Is:)

A) **RNA polymerase Is:** Ribavirin (Flu₄, B & lassa fever)
  * broadspectrum  * Oral (Fat ↑ absorption) / IV / aerosol
  * R. el  * transient anemia, ↑ bilirubin

B) **DNA polymerase Is:** nucleotide analogue, Renal el. , prodrug

1- **Lamivudin, Adifovir, Entecavir** (HBV): * oral  * headache, dizziness

2- **Acyclovir** (HSV₁,₂, VZV): *↑ by v. thymidylate kinase
  * oral/iv/topical
  * local irritation, headache, Nausea & Vomiting

3- **Famcyclovir → 4- Pencyclovir** * Topical only (toxic)

5-- **Gancyclovir (CMV)**  *↑ Activated by v. kinase
  * neutropenia, embryotoxic, teratogenic#
6- **Cidofovir** *IV, intravitral*  *Renal toxicity*

7- **Foscarnet** *(CMV, Resist. HSV, VZV:)* *IV*
   *Renal toxicity, anemia, N&V, hypo(Ca, Mg, K), arrhythmia, seizure*

8- **Vidarabine** *(HSV<sub>1, 2</sub>, VZV)* *eye ointment in Keratitis immunocompromised patients.*

C) **DNA breakdown:** Iodoxuridine  *only topical*  *Broadspectrum*

### Interferon

Exogenous interferons produced by recombinant DNA techniques
- injected intramuscularly or subcutaneously
- used to treat chronic hepatitis B, chronic hepatitis C, chronic hepatitis D, genital warts from papillomavirus, CMV infection of renal transplant patients, and sometimes, multiple sclerosis and hairy cell leukemia.

A non-antiviral use: Interferon γ is effective against chronic granulomatous disease (a disease of neutrophils and macrophages, where superoxide release is decreased. Interferon γ increases superoxide anion generation by 10% and decreases the number of infections a patient suffers.)

Peak plasma level of IFNs are reached 4-8 hours after administration.

Adverse effects: interferon can cause flu-like symptoms, fatigue, depression, muscle weakness, weight and appetite loss. High dose or chronic therapy can cause bone marrow suppression and neurotoxicity. Also interferon can increase the bone marrow toxicity of myelotoxic drugs such as AZT.

**Variation--Pegylated interferon α-IFNα** with a polyethylene glycol moiety reduces clearance and sustains absorption for an increase in ½ life

### Interferon effects on Viruses
(stimulates synthesis of 2 dozen proteins that contribute to viral resistance)

A. DNA (less sensitive than to interferon than RNA viruses)

B. RNA (B1= orthomyxo- and retro-)  
   (B2= other RNA viruses)

**Functions of interferon induced proteins:**
1. inhibition of penetration or uncoating
2. inhibition of transcription
   - blocks mRNA synthesis
3. **INHIBITION OF TRANSLATION**
   - blocks mRNA cap methylation
   - indirectly activates RNase L which cleaves viral (and cellular) RNA
   - kinase P1 phosphorylates eIF-2 inhibits the initiation of translation
   - phosphodiesterase that cleaves tRNA, preventing peptide elongation
4. inhibition of viral protein processing and maturation
   - blocks glycosylation of viral proteins
   - blocks the maturation of viral glycoproteins
   - causes cell membrane changes that block budding
Neuraminidase is a critical protein on the surface membrane of the influenza virus.
- Enables the replicated virus to bud from the host cell
- Helps the virus to pass through mucous between cells in the entire respiratory tract
- Common to both influenza A & E

Inhibiting the viral neuraminidase prevents newly formed virus from escaping infected cells, thereby interrupting the spread of infection between cells.

**D) Neuroaminidase Is**

* ↓ release & spread of Flu<sub>A,B</sub> & bird Flu

**1. Oseltamvir:**
- prodrug *oral,
- renal el. *GIT upset.

**2. Zanamiver:**
- Inhalation/ intranasal *R.el
- GIT upset,
- R. irritation# asthma, COPD
Current treatments for SARS

Antiviral therapy
(a) Ribavirin— the most frequently administered antiviral agent for SARS. Unproven efficacy and undue side effects
(b) Neuraminidase inhibitor— Oseltamivir phosphate
  was commonly prescribed in Chinese centers. Unproven efficacy.
(c) Protease inhibitors— unproven efficacy
  As in HIV treatment, this is an attempt to block viral RNA replication
(d) Human interferons— Faster recovery was observed in a small number of Canadian patients treated with interferon α. In vitro testing of recombinant interferons against SARS-CoV is now being carried out. Seems to be effective, but needs more investigation
(e) Human immunoglobulins— effectiveness uncertain.
  Used in some hospitals in China and Hong Kong. Also used in Hong Kong was convalescent plasma, collected from recovered patients. Plasma immunoglobulins from convalescent patients seemed to curb increases in viral load. Further evaluation is needed.
(f) Ramantadine

(g) Antibiotic therapy— prophylactic, and this is the FIRST therapy used, since rapid reliable diagnosis of SARS-CoV is not yet widely available. Antibiotic therapy is halted when other pathogens are excluded.

(h) Immunomodulatory therapy— Corticosteroids
  Acute infections can stimulate the release of proinflammatory cytokines, and in SARS, there may be an excessive host response or cytokine dysregulation. Based on the observation that clinical deterioration occurred despite a fall in the SARS-CoV viral load, a model of pathogenesis was proposed comprising 3 phases: viral replication, immune hyperactivation, and pulmonary destruction. This therapy is to target the immune hyperactivation.

Preliminary results suggest that the protease inhibitor, ribavirin and corticosteroids together might reduce intubation and mortality rates, especially when administered early.

E) Reverse transcriptase inhibitors (RTIs):

I) Nucleoside/nucleotide RTIs:
  * prodrug (→ triphosphate) * ↓ mitochondrial DNA polymerase → toxicity
  * cross resistance * used in adults, children
  1) Zidovudine (Azidothymidine): Oral(with food) * pass BBB
  * Renal el. * + in pregnancy (prevent prenatal infection) & prophylaxis
  * nausea, fatigue, headache, anemia, neutropenia, myositis, myalgia, insomnia, restlessness.
  2) Didanosine: * Oral (chewed, buffered tablets / buffered solution).
  * Pancreatitis (monitor Serum amylase) peripheral neuropathy, # Zalcitabine
  3) Zalcitabine: * Oral (food, Mg, Al ↓ absorption) * less pass BBB
  * rash, stomatitis, peripheral neuropathy, # Didanosine...
  4) Stavudin: * oral * pass BBB * peripheral neuropathy.
  5) Lamivudine: * combined with Zidovudine (resistance) & # Zalcitabine.
  6) Abacavir: * GIT upset, headache, dizziness, drug fever, rash (# sensitivity on pre-exposure.
  7) Tenofovir: * oral (with food) GIT upset
  8) Emtricitabine (HIV, HBV): * oral (O/D)
  * diarrhea, headache, dizziness, rash, ↑ pigmentation (palm, soles

II) Non-nucleoside Non-competitive RTIs:
  ● Oral, H. el ● pass BBB
  ● hypersensitivity (rash) ● cross resistance within group
  ● + Zidovudine (Synergistic, No cross resistance & bone marrow depression)
  1) Nevirapine: * block mother to child transmission peri-natal, breast feeding
  (dose at delivery & dose to baby by 72 hours)
  * skin effects (rash, Steven-Jonson syndrome, epidermal necrolysis, hepatotoxicity.
2) **Delavirdin**: *↑* by fluxetene, ketoconazole & *↓* by phenytoin, phenobarbitone) *P450 inhibitor (↑*sqinavir, indenavir) *rash, nausea, headache, dizziness.

3) **Efzvirenz**: *Fat *↓*abs.(OD) *Enzyme inducer *#pregnancy *dizziness, headache, vivid dreams (resolve in weeks)

**F)** V.protease reversible Is: *combined with RTIs

- *↓* cleave viral polypeptide into enzymes (RT, integrase → non-infectious viron)
- H.el (↑ by rifampicin, barbiturate, carbamazepine, nevirapin, efavirenz → suboptimal concentration → *↑* resistance)
- *↑* insulin resistance & lipodystrophy
- enzyme Is (midazolam, triazolam, warfarin, fentanyl). *Not pass BBB

1-**Squinavir**: *Oral, soft-gel capsule (fat *↑*abs. & delavidrin *↓*its metabolism). *headache, fatigue, GIT upset, ↑H aminotransferase in H B,C patients.

2-**Ritonavir**: *Oral with chocalte milk (unpalatable). *GIT upset, *potent enz.Is (*↑*conc. of other Protease Is)

3-**Indenavir**: *Oral (acid *↑* & meal *↓* abs.) *combined with RTIs

- *GIT upset, headache, hyperbilirubinemia, nephrolithesis = R.stone → *↑* fluid intake.

4-**Nelfinavir**: *Oral *diarrhea

5-**Amprenavir**: *oral (BID) *GIT upset, fatigue, parathesia, headache.

6-**Lopinavir**: *oral (tab/solution contain alcoholdisulfiram reaction) with ritonavir in the same formula. *GIT upset

7-**Atazanavir**: *Oral (o/d) *Jaundice

**Anti-fungal agents**

---

### Sites of Action of Antifungal Drugs

- ** Allylamines**: block ergosterol formation in cell membrane via inhibition of squalene epoxidase
- **Polyenes**: bind to and disrupt cell membranes
- **Azoles**: block ergosterol formation in cell membrane via inhibition of cytochrome P450 dependent 14α-demethylase
- **Griseofulvin**: blocks intracellular microtubules
- **Flucytosine**: active uptake via permease blocks DNA/RNA synthesis

---

1) **Amphotericin B (broad-spectrum, toxic)**:

**Mode of action**: *affinity for membranes with high content of ergosterol → forms a channel through the membrane → leak cell content*

- *resistance is rare and slow to develop
- *poorly water soluble (unstable in solution, particularly in normal saline).**
IV infusion (0.1 mg/ml) or (0.3 mg/ml) in 5% dextrose
● Not pass BBB (intrathecally in meningitis)
● renal toxicity: predictable & dose related, usually reversible

II) Flucytosine (narrow spectrum e.g. candida & cryptococcus, less toxic)
● → 5-FU → ↓ thymidylate synthetase → ↓ DNA __● oral __pass BBB
● 1-bone marrow depression leukopenia, anemia, thrombocytopenia
2-GIT upset 3- headache, drowsiness, confusion, vertigo, and hallucinations
* rapid development of resistance during therapy → not used as a single agent

III) Azole derivatives
● broad spectrum, less toxicity, delayed resistance
● oral/parenteral for systemic mycosis & topical for superficial mycosis.
● Mode of action: *↓ CYP450 activity → ↓ conversion of 14-alpha-methylsterols to ergosterol → ↓ ergosterol synthesis → altered membrane permeability → loss of cell contents.
A) Imidazoles:
* Not pass BBB * Enz.Is(↑ phenytoin, oral hypoglycemic)
* ↓ steroid synthesis(libido, gynecomastia)
* e.g. Ketoconazole (oral/parenteral) & miconazole, clotriazole (topical)
B) Triazoles:
* Pass BBB * less ↓ steroid synthesis(libido, gynecomastia)
* e.g. Fluconazole, itraconazole

IV) Griseofulvin: a systemic antifungal used to treat topical ringworm infections, e.g., onychomycosis, Tinea capitis, Tinea pedis, etc.
* poorly water soluble and requires bile salts for solubilization in the gut.
* Mode of Action: disrupts mitotic spindle structure → metaphase arrest.
→ ↓ growth of fungi (drug is static), preventing them from invading. As the skin, hair, or nail is replaced, the fungus is shed.
* Pharmacokinetics: orally (high fat meals ↑ drug solubilizing), unabsorbed drug is eliminated in the feces, small amount is shed in dead skin and hair.
* Adverse effects: 1- hepatomas in mice and thyroid tumors rats
2- include confusion, hypersensitivity (skin rash, hives, or itching), oral thrush (soreness or irritation of mouth or tongue), and photosensitivity.

V) Whitfield's Ointment: * keratolytic (3% salicylic acid + 6% benzoic acid).
* no significant anti-fungal activity, but helps remove keratinous layer to aid penetration of anti-fungals.

VI) Potassium iodide: an old drug that is still the drug of choice for cutaneous-lymphatic sporotrichosis & actinomycosis.
* may cause: hypothyroidism and iodism (Signs include brassy taste, rhinitis, coryza, salivation, lacrimation, sneezing, burning of mouth and throat, ocular irritation, sialadenitis, and dermal lesions).
1-treatment of serious systemic (deep) mycosis Systemic:
- Systemic candidiasis: AmpB and/or 5-FU, Keto, Mic, Flu
- Cryptococcosis (meningitis): AmpB + 5-FU, Mic, Flu better
- Systemic aspergillosis: AmpB and/or 5-FU
- Blastomycosis: AmpB, Keto, Itra
- Histoplasmosis: AmpB, Keto, Flu
- Coccidioidomycosis: AmpB, Keto, Itra
Paracoccidioidomycosis: AmpB, Keto, Itra

2-superficial mycosis involving skin and mucous membranes
*Amphotericin B  *Carbol-Fuchsin  *Ciclopirox  *Clotrimazole
*Terbinafine *Tolnaftate *Undecylenic acid

3-Vaginal drugs: Butoconazole, Clotrimazole, Econazole, Gentian violet
Miconazole, Nystatin, Terconazole, Tioconazole

Antimalarial

I) Blood schizonticidal → clinical cure & prophylaxis except Artemisinin.
A) Chloroquin: *concentrate in RBC, bind to heme → ↓ its polymerization into hemozin → ↑ heme (lethal to parasite)
*oral  *pass BBB  *H&R.el.  *Resistance developed
*at high dose, pruritis, headache, blurring of vision, GIT upset, ECG changes, # pregnancy, porphyria.

B) Mefloquine: *damage parasite membrane. *↓ P.F  *H/el.  *oral  *↓ PF
*High dose → GIT upset, disorientation, hallucination, depression
C) Artemisinin: *free radical → damage parasite  *oral, Rectal, IV
*H/el,  *Short T1/2 (not used in prophylaxis)  *GIT upset
D) Pyrimethamine (+Sporontocidal)  *↓ P.F  *+ sulphonamide → ↓ PM, toxoplasma
*antifolate (plasmodium selective)  *GIT upset, nephrotoxicity
II) Tissue schizontcidal (Mefloquene)
*oral *H.el.
*used for eradication and prophylaxis
*GIT upset, headache,
methaemoglobinemia , favism

**Antiamoebiasis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>drugs</th>
<th>intestine</th>
<th>tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Diloxanide, iodoquine, paromomycin</td>
<td>↓↓</td>
<td>-</td>
</tr>
<tr>
<td>Mild / severe</td>
<td>Metronidazole, 10d. tinidazole, 3d</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Hepatic abscess</td>
<td>Mornidazole + diloxanide → chloroquine</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>

**Pneumoconiosis & toxoplasmosis:**
1-Pentamidine: $T_{1/2}$-4Ws (tissue binding) parenteral/inhaler, ↑ then ↓ CNS & ↓ BP
↓ glucose.
2-Antifolate 3-Atovaquine: oral (food ↑ abs.), GIT upset.

**Warms:**
1) Round warm (Nematode):
1-intestinal e.g ascaris, anklystoma, strongyloid, pinwarm, whipwarm
2-tissue e.g Filaria, toxicariasis.

II) Flat (platyhelminthes)

a-Flukes (trematodes) e.g. Schis. H & M
b-Tapewarm (cystode) e.g. Taenia saginata

**Antihelminthics:**
* warm immobilization → shift (expulsion) & Phagocytosis. (death)
* pregnancy & ≤4 Y * oral
* toxicity (direct & reaction to dead warm)
* Classified according mechanism of action into: 1) Spastic paralysis

A- $\uparrow$ Ca entry into muscle of parasite → contracture
e.g. Praziquental (4mg/kg once) * Trematode & Cystode
* Direct toxicity (headache, weakness, GIT upset) & reaction to warm protein (pruritis, skin rash)

B- $\uparrow$ Nicotinic receptor in warm: 1- Anticholinesterase:
a) Levamisole (intestinal nematode): *150mg/kg once *GIT upset *Immunomodulators.

b) Metriphonate (Sch.H.): *GIT upset, dizziness, vertigo
*7.5mg/kg/2w for 3 doses (living eggs found in urine for several months.

2-Direct NR stimulation (intestinal nematode)
e.g. Pyrethral pamoate: *GIT upset, headache, dizness

II) Flaccid paralysis (↑GABA in parasite):
● Tissue nematodes (filarials): Ivermectine: headache, fever, rash, muscle & joint pain.
  2-Diethylcarbamazebine: *D.T = headache weakness, anorexia.
● For intestinal nematode: e.g. Pipazine: *Git upset, # seizures

III) Impair energy production:
A) Uncoupling oxidative-phosphorylation (cystodes): e.g. Neclosamid:
*Taenia: 4x0,5 gm chewable tab. on empty stomach.
*Hymenolepis Nana: 2 gm/d after breakfast for 7 days
*↓ scoleces & segment but not ova, thus
1-cure is confirmed by absence of ova after 3-4 ws (regeneration time).
2-use purgative at previous night and 2 h prior the drug (confirm scoleces expulsion)

B) ↓ glucose uptake / microtubule formation:
● For nematodes: e.g Albendazole (reversible leucpenia, alopecia)
● For nematodes & cystodes: 1-Mebendazole (GIT upset)
2-Thiabendazole *dizziness, headache, reversible leucpenia *immunosuppressive effect