ANTIBIOTICS
Inhibitors of Bacterial Cell Wall Synthesis

Penicillin (β-Lactam)

I  Penicillin G, Penicillin V
II Methacillin, Nafcilin (Beta-Lactamase resistant)
III Amoxicillin, Ampicillin
IV anti-pseudomonal

- Methacillin resistant: alteration of the a.a. sequences of PBP
- Renal excretion mainly by secretion (inhibited by probenecid)
- Side effects: hypersensitivity due to minor determinants
- Methacillin: interstitial nephritis

USES:
- Gram +ve infections
- Treponema (Syphilis DOC)
- Pseudomonas (Penicillin IV + Aminoglycosides)

Cephalosporins (β-Lactam)

I  Cephazolin
II Cephamandole, Cephotetan
III Ceftriaxone, Cefoperazone (anti-pseudomonal)
IV (good for gram +ve and –ve) penetrates the CSF

- Renal elimination
- Ceftriaxone & Cefoperazone biotransformation in the liver.
• Cephamandole, Cephotetan & cefoperazone all have been noted to have a disulfiram like reaction.
• Thrombocytopenia associated with cefamandole and cefoperazone NOT cefotetan!!
• Pyrogenic (highest rates of drug induced fever)

USES:
• Respiratory Tract Infections
• Prophylaxis: abdominal surgery (Cephazolin)
• Meningitis (gram –ve) and endocarditis is treated with CEFTRIAXONE
• CEFTRIAXONE (IM) as single dose DOC for simple gonorrhea. (painful)

**Not covered by cephalosporins:**
(LAME)

*Listeria Monocytogenes, Atypicals (Chlamydia) MRSA and Enterococci*

Monobactams β-Lactam Aztreonam

• Resistant to betalactamases
• GRAM NEGATIVE ACTIVITY ONLY
• Can be used in patients who are allergic to penicillins or cephalosporins (i.e. no cross sensitivity with other B-lactams)
• Work synergistically with aminoglycosides
Carbapenams β-Lactam:

**Imipenam**

- High Resistant to betalactamases
- no cross sensitivity with other B-lactams
- LARGEST SPECTRUM OF ACTIVITY of any B-lactam
- Septicemia of unknown origin: treat with Imipenam while the test results are coming, then give more narrow spectrum antibiotic
- MAJOR DISADVANTAGE: renal tubular cells metabolize the drug by *renal dipeptidase* and cause decreased urinary concentration, so IMIPENAM + CILASTATIN (inhibitor of enzyme) are given together
- SIDE EFFECTS: SEIZURES, nausea, vomiting, rashes, etc.

**Meropenam**

- Does not need cilastatin
- Less likely to cause seizures
NON β-Lactam ANTIBIOTICS

VANCOMYCIN

- Used for Staph or Strep infections RESISTANT to methicillin (i.e. MRSA and MRSE)
- Inhibits cell wall synthesis by binding to the 2 terminal d-alanine
- Resistance by replacing the terminal d-alanine by d-lactate
- Vancomycin must be given IV, cannot be absorbed in GI tract
- Vancomycin potentiates the nephrotoxicity of aminoglycosides
  - SIDE EFFECTS:
    1. RED-NECK SYNDROME: too rapid infusion...histamine release...slow down infusion
    2. OTOTOXICITY: Irreversible loss of hearing (enhanced toxicity by loop diuretics and aminoglycosides)

FOSFOMYCIN

- Analogue of PEP, inhibits the synthesis of NAM (inhibits cell wall synthesis)
- Gram +ve and –ve spectrum
- SINGLE DOSE ORAL: treatment of uncomplicated UTI ONLY IN FEMALES!!!

***DRUGS THAT ARE CONTRAINDICATED IN PREGNANCY:

1. Aminoglycosides
2. Erythromycin estolate
3. Clarithromycin
4. Tetracyclines
5. Fluoroquinolones
# Inhibitors of Bacterial Protein Synthesis

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<td>Formation of Initiation Complex</td>
<td><strong>30S</strong></td>
<td>Aminoglycosides (bacteriostatic and also distorts reading frame; bacteriocidal)</td>
<td>Inhibits formation</td>
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| 2 | Incorporate next aa | 50S | Quinupristin Dalfopristin  
Tetracyclines | Inhibits insertion into the A-site |
| 3 | Formation of the peptide bond | 50S | Chloramphenicol | Inhibits peptidyl transferase |
| 4 | Translocation | 50S | Macrolides Clindamycin | Inhibits translocase |

- (Buy AT 30, sell when 50)
- all bacteriostatic except aminoglycosides
### Aminoglycosides

**Amikacin, gentamicin, neomycin, tobramycin, streptomycin**

**MOA:**
- bind irreversibly to 30S ribosome and prevent the formation of the initiation complex (BACTERIOSTATIC)
- cause misreading of the genetic code of the mRNA leading to incorrect aa incorporation into proteins (BACTERICIDAL)

**Bacterial resistance:**
- bacterial enzymes that **phosphorylate, acetylate** and **adenylate** the aminoglycoside (plasmid mediated)
- decrease influx (p-glycoprotein)

**Pharmacokinetics:**
- 100% water soluble; can be given by IV only
- Cannot be used for intracellular infections (exception; active T.B.)
- VERY HIGH concentrations found in the kidneys and inner ear.
- Excreted renally

**Side effects:**

1. **OTOTOXICITY:** Vestibular (reversible) and Auditory (Irreversible and additive)
2. NEPHROTOXICITY: Mild renal impairment (reversible) → metabolic acidosis

3. Neuromuscular blockade: Ach cannot be released → resp. paralysis. Treat by Ca++ ion infusion.

Drug interactions:
- B-lactams and aminoglycosides work synergistically. However, do not put in same IV line.

USES:
- GRAM –ve infections
- Streptomycin is first line drug for treating active T.B.

**Tetracyclines**

* tetracycline, demeclocycline, doxycycline, minocycline

MOA:
- bind irreversibly to 30S ribosome and prevent the formation of the initiation complex (BACTERIOSTATIC)
- Demeclocycline has anti-ADH effect.

Resistance: production of an active transport system out of cell

Pharmacokinetics:
- oral absorption is impaired by the presence of ions (calcium, iron, antacids)
- renal excretion (all except doxycycline; hepatic)
- minocycline achieves good levels in tears and saliva (eradicates meningococci when it resides in the tear ducts, but DOC is rifampin)
- good penetration in bone → but get inactivated (useless)
SIDE EFFECTS:
1. Teeth: yellow to brown discoloration in children
2. Outdated tetracyclines produce toxic breakdown products that cause a form of FANCONI SYNDROME. (n/v, polyuria, polydipsia, proteinuria, glycosuria and acidosis)
3. Hepatic: Contraindicated in pregnancy
4. Other: phototoxicity and vestibular ototoxicity (minocycline)

USES:
- DOC for Mycoplasma pneumoniae, Chlamydia and Rickettsial infections.
- Minocycline used for eradicating asymptomatic nasopharyngeal meningococcal carrier state.
- Doxycycline→ gonococcal infections
- Demeclocycline→ treat chronic hyponatremia in SIADH
- Prophylaxis in acne

Chloramphenicol
(Underused antibiotics)
- Binds reversibly with the 50S→ prevents protein synthesis (bacteriostatic)
- Metabolized by hepatic glucoronidation

Side effects:
1. Hematological: (most common) True toxicity is dose dependant→ reticulocytopenia, anemia, with or without
thrombocytopenia. **Aplastic Anemia** may appear weeks or months after stopping the drug

2. GREY BABY SYNDROME: (decreased glucuronidation; glucuronyl transferase is not active in neonates)

3. Irreversibly inhibits cytochrome P450, and may inhibit the metabolism of drugs like phenytoin, sulfonylureas (tolbutamide) and warfarin.

**Macrolide Antibiotics**

*Erythromycin, Clarithromycin* (twins)

*Azithromycin* (cousin)

MOA: binds to 50S and inhibits translocation reactions

**SIDE EFFECTS:**

1. Allergy: fever, rash
2. Cholestatic Jaundice; primarily caused by the estolate form
3. GI tract: stimulate motilin receptors and cause GI distress
4. Erythromycin may cause ototoxicity when given at very high doses (HIV +ve patients)

**DRUG INTERACTIONS:**

- Erythromycin and clarithromycin inhibit CYP3A4, may potentiate the effects carbamazepine, theophylline etc.

**Erythromycin**

- Inactivated by gastric content, so must be enteric coated or in salt form.
- Estolate is the best absorbed oral form
• Wide tissue distribution and is excreted via biliary system

Uses:
• gram +ve cocci (not MRSA) Resp. tract infections
• atypical organisms (chlamydia and mycoplasma pneumoniae)
• Pneumonitis is non AIDS patients
• Legionnaires’ disease

**Clarithromycin**

Uses: Increased activity against **MAC** infections and **H.Pylori**.

**Azithromycin**

• Accumulates in tissues and blood cells and is excreted renally
• **Co-drug of choice for Chlamydia**
• Used for resp. tract, skin and soft tissue infections
• Safe in pregnancy

**Clindamycin**

• Binds to 50S and blocks translocation reactions
• EFFECTIVE AGAINST **GRAM +VE ORGANISMS** (Not MRSA) AND **ANEROBES** (B.fragilis) ONLY!!
• Well distributed in fluids, tissues and BONE.
• RESISTANCE: Plasmid mediated methylation at the binding site.

USES:
• Anaerobic infections
• **CLINDAMYCIN + PYRIMETHAMINE** used for Toxoplasmosis gondii
• Alternative for beta-lactam antibiotics for staph and strep

SIDE EFFECTS:

1. PSEUDOMEMBRANOUS COLITIS: due to a superinfection with *Clostridium difficile* → necrotizing toxin released (Metronidazole is the DOC with Vancomycin as an alternate)
2. Skin rashes
3. NEUROMUSCULAR BLOCKADE: Inhibit neuromuscular transmission

**Quinupristin/Dalfopristin**

- MOA: bind to 50S and prevent the interaction of aminoacyl-tRNA with the A-site
- Must be given parenterally (IV)
- Inhibits CYP 3A4 which may lead to drug-drug interactions
- New drug used for:
  1. Drug resistant Gram +ve cocci
  2. **VRSA and VRE** (S.aureus & enterococci)

**Linezolid**

- 1st member of new group of oxazolidones
- binds to 50S and prevents formation of initiation complex
- USED for: VRSA, VRE and MRSA in people allergic to vancomycin
Daptomycin

- Given IV
- Binds to bacterial membranes causing a rapid decrease of membrane potential → loss of protein and nucleotide synthesis → cell death
- Spectrum is for AEROBIC GRAM +VE bacteria that are methicillin, vancomycin and linezolid resistant strains
- Side effects: superinfections

Metronidazole

MOA: unknown

USES:

1. **Antiprotozoal**: Metronidazole is the DOC for most infections caused by *Entamoeba histolytica*, *Giardia* species, and *Trichomonas vaginalis*.
2. **Antibacterial**: DOC for most anaerobic infections
3. **BMT regimen** (*Bismuth, Metronidazole, Tetracycline*): for *H. Pylori*

Side Effects:

- Metallic taste in mouth
- Brown/black urine
- Neurotoxicity
- **DISULFIRAM-LIKE INTERACTION WITH ETHANOL!!!!!**
- Metronidazole + Disulfiram → PSYCHOSIS
ANTI-METABOLITE ANTIBIOTICS

SULFONAMIDES

- Structural analogues of PABA
- MOA: Sulfonamides are competitive inhibitors of the bacterial enzyme DIHYDROPTEROATE SYNTHETASE
- Bacteriostatic action
- Classified into 4 groups; rapidly absorbed/excreted, poorly absorbed (Sulfasalazine), topically (Ag Sulfadiazine) used and long acting.
- Sulfasalazine is broken down by GI bacteria; mesalamine (DOC for treating ulcerative colitis)

Pharmacokinetics:
- Well distributed in the body including the CSF
- Part of the dose is acetylated in the liver
The acetylated conjugates tend to be less water soluble (unique characteristic) and may crystallize in the kidney → hematuria!!

**Side effects:**
- Crystalluria
- Rashes (Stevens-Johnson syndrome)
- Photosensitivity
- **Contraindicated in neonates** and **last month of pregnancy** because they displace bilirubin from proteins → jaundice and kernicterus
- They bind to plasma proteins → increase drug interactions → increase the effect of methotrexate, warfarin and phenytoin.

**USES:**
1. UTIs (sulfoxazole)
2. **DOC FOR NOCARDIA INFECTIONS**
3. **TOC FOR TOXOPLASMOSIS (SULFADIAZINE + PYRIMETHAMINE)**
4. Ag Sulfadiazine → BURNS
5. Sulfasalazine → Ulcerative colitis

**COTRIMOXAZOLE**

*(Sulfamethoxazole + Trimethoprim)*

- Trimethoprim is an **inhibitor of DIHYDROFOLATE REDUCTASE**
- Side effects: anemia, leucopenia or thrombocytopenia

**DOC FOR SALMONELLA AND PNEUOMOCYSTIS CARINII INFECTIONS.**
Contraindications: Pregnancy and pt. with G6PD deficiencies
QUINOLONES (FQS)
Ciprofloxacin, ofloxacin,
- Inhibit the enzyme DNA gyrase \( \rightarrow \) inhibit DNA synthesis \( \rightarrow \) bactericidal
- Activity against gram +ve and –ve cocci and anaerobes.
- Active when administered orally (inhibited by antacids) and have a wide distribution, including BONE.

Side effects:
- Photosensitivity; lomefloxacin, sparfloxacin
- Increased QT interval; for gatifloxacin, grepafloxacin and sparfloxacin.

Uses:
- UTI, prostatitis, children with cystic fibrosis.
- RTI caused by \( S. \ pneumonias \)
- CIPROFLOXACILIN used for the prophylaxis and treatment of “traveler’s diarrhea”
- Diabetic foot complications: FQ + anaerobic drug
ANTITUBERCULAR DRUGS

\textit{isoniazid (INH), rifampin, ethambutol, pyrazinamide}

- TB caused by \textit{Mycobacterium tuberculosis} (acid fast)
- M. leprae $\rightarrow$ Leprosy $\rightarrow$ DOC DAPSONE
- \textit{M. avium} $\&$ \textit{M. intercellulare} produce a \textbf{pulmonary infection}.
- \textit{Mycobacterium avium complex (MAC)} is a mixture of the 2 bacteria and produce a \textbf{disseminated infection} (GI $\rightarrow$ Lungs $\rightarrow$ Liver $\rightarrow$ Spleen) in AIDS patients.

ISONIAZID (INH)

- Bacteriostatic for resting bacilli, bacteriocidal for dividing bacteria
- PRODRUG $\rightarrow$ Must be activated by catalase/peroxidase $\rightarrow$ penetrate cells $\rightarrow$ \textbf{MOA: inhibits synthesis of mycolic acids} (cell wall component)
- \textbf{Bacterial resistance: mutation of the catK (Kat) gene that codes for catalase}
- Given orally $\rightarrow$ needs catalase for activation
- Biotransformation occurs in the liver via acetylation (you get SLE-like syndrome in slow acetylation while taking any of these drugs; \textit{isoniazid, hydralazine, procainamide})
- Severe hepatic insufficiency $\rightarrow$ dose reduction

SIDE EFFECTS:

- Peripheral neuritis (use B6)
- Age-dependant hepatitis (worsens with age)
- Hemolysis in G6PD deficiency
- SLE-like syndrome in slow acetylators
RIFAMPIN

- Inhibits DNA-dependant RNA polymerase $\rightarrow$ inhibits RNA synthesis $\rightarrow$ bactericidal (for both intra and extra cellular oraganisms)
- RESISTANCE: Change in enzyme!! (never use drug alone)

SIDE EFFECTS:
- Hepatitis
- Flu-like syndrome
- Induction of cytochrome P450
- **Orange-red metabolites (stain contact lens)**

PYRAZINAMIDE

- MOA: unknown
- Used against active TB
- Side effects: hyperuricemia & arthralgia

ETHAMBUTOL

- Inhibits bacterial cell wall component (arabinogalactan)
- Bacteriostatic $\rightarrow$ works for *M.tuberculosis* only
- Side effects: dose dependant **retrobulbar neuritis** $\rightarrow$
  **diminished ability to differentiate red from green**
ANTIVIRAL DRUGS

HAART → Highly Active Anti-Retroviral Therapy → 2 NRTI & PI

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

**ZIDOVUDINE (AZT; Azidothymidine)**
- Incorporated into viral DNA and causes chain termination
- Can inhibit reverse transcriptase
- Orally active, metabolized by liver via glucoronidation
- Drug interactions: don’t use with drugs that interfere with glucoronidation → e.g. aspirin, indomethacin
- Uses: HIV infections, treat HIV +ve pregnant mother to prevent vertical transmission

**DIDANOSINE (DDI)**
- Side effects: peripheral neuropathy, *pancreatitis (fatal)*, liver dysfunction

**ZALCITABINE (DDC)**
- Side effects: *peripheral neuropathy*, pancreatitis (DON’T GIVE WITH DIDANOSINE), GI distress

**LAMIVUDINE (3TC)**
- LEAST TOXIC OF THE NRTIs, *Used to prevent and treat Hepatitis B*

**STAVUDINE (D4T)**
- Side effects: *peripheral neuropathy*, myelosuppression
NON-Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Nevirapine → hepatotoxicity → induces CPY3A

Protease Inhibitors (PIs)
- Inhibits aspartate protease (enzyme that cleaves the poly-protein into functional viral proteins)
- Prevents the spread of the viral infection
- Drugs:
  1. Saquinavir
  2. Ritonavir
  3. Indinavir (nephrolithiasis, Crix belly)

Unacceptable Drug Combinations:
1. Didanosine + Zalcitabine combo has overlapping toxicity.
2. Zalcitabine + Stavudine combo has overlapping toxicities.
3. Zidovudine + Stavudine combo is antagonistic.

Fusion Inhibitors: Enfuvirtide
Inhibits the fusion process by mimicking the peptide sequence of gp41

DNA Polymerase Inhibitors

Acyclovir
- MOA: monophosphorylated by viral thymidine kinase (TK) → further activated by host-cell kinases to the triphosphate.
• Acyclovir- triphosphate is both a substrate for and inhibitor of viral DNA polymerase
• It is a chain terminator (lacks a 3’-hydroxyl group.

DOC: **HSV, VZV and varicella** (not effective in recurrent episodes)
Side effects: Nephropathy

**Ganciclovir**
• No chain termination
• Side effects: neutropenia, leucopenia, thrombocytopenia (dose-limiting hematotoxicity)
• Uses: CMV chorioretinitis, prophylaxis against CMV in AIDS and transplant patients

**Foscarnet**
• Only inhibits DNA polymerase
• Side effects:
  1. dose limiting nephrotoxicity
  2. hypocalcemia → tremors and seizures
  3. **AVOID PENTAMIDINE** IV → increases seizures → **FATAL**

**RNA Polymerase Inhibitors**

**Amantadine**
• MOA: blocks attachment and penetration of Influenza A virus
• SIDE EFFECTS:
  1. Seizures
  2. **LIVEDO RETICULARIS** (Purple ankles)
  3. atropine like effect
  4. orthostatic hypotension
• Uses: Influenza A, anti-parkinsons agent
Ribavarin

**MOA:** inhibits viral RNA polymerase, inhibits capping of mRNA

**Uses:** HEPATITIS C, Respiratory syncytial virus, Influenza A/B

**Side effects:** decreased respiratory function, teratogenic and mutagenic