ANTIMICROBIAL AGENTS

① β-LACTAM ANTIBIOTICS.

CLASSES: BACTERIOSTATIC / BACTERIOCIDAL

β-LACTAM Antibiotic: STOP CELL WALL SYNTHESIS → LYSIS.
- ↳ only work on rapidly growing bacteria w/ PG cell wall. (Not myco, fungi, viruses).
- → Bind to "Penicillin Binding Proteins" which are proteins involved in cross-linking cell wall + inactivate
- → These are PENICILLINS, CEPHALOSPORINS, CARBAPENEMS, COMBINATION THERAPY.

PENICILLINS: Pen. G, Pen. V. — V. is more acid Resistant than G - used for ORAL INFECTIONS
- Bacteria make β-Lactamases (resistant to penicillin) Staph. especially resistant.
  - we make Methicillin, the become resistant (MRSA), we make Vancomycin
  - ↳ these aren't acid-resistant so must be given I.V. but they avoid β-lactamases.

Extended Spectrum Penicillins (used for G -ive bacteria).
- AMPICILLIN (G -ve bacilli + G -ve enteric rods)
- AMOXICILLIN (G -ve enteric rods, G -ve bacilli)

} can be administered orally (* only ones HIGH Fxnal)
- inactivated by β-lactamases.
- Tx Helicobacter pylori.

ANTI-PSEUDOMONAL Penicillins:
- Carbenicillin + PIPERACILLIN: Kill P. Aeruginosa, G -ve bacilli + enteric Rods

PHARMACOKINETICS: given IV, IM, oral - most penicillins have low F oral - poor absorption
so stay in Gut + kill normal flora = stomach ache diarrhea
* Not metabolized, eliminated solely from kidney.
- High concentrations — Neurotoxic, platelet dysfunction, kidney dysfunction.

BACTERIAL RESISTANCE: β-lactamases Hydrolyze antibiotics → we Combat w/ β-lactamase-INHIBITORS:
- CLAVULANIC ACID (this + AMOXicillin = AUGMENTIN)
- TAZOBACTAM (this + Piperacillin = PIPTAZ)
- SULBACTAM

or Modify β-lactam antibiotic: ① CEPHALOSPORINS: kill G+ and G-, resistant to β-lactamases
- used in oral cavity - kills anaerobes

1st Gen Ceph's: Cefiexin, Cephazolin — Substitute for Penicillin
2nd Gen: Cefoxitin - better for G- rods, worse for G+
3rd Gen: Cefixime - Good for H. influenza, N. Gonorrhoeae
4th Gen: Cefepime - resistant to diff. types of β-lactamases

} Allergies ✓ Bleeding ✓ Resistance ✓

② CARBAPENEMS → Broadest spec. β-lactam

③ MonoBactams → Narrow spec (only aerobic G-) but very resistant to lactamases.

④ Vancomycin → Not a β-lactam but acts at cell wall too. Now resistance is emerging so only used for a severe infection or allergic to β-lactams.
- IV, gives fever.

ANTIMICROBIAL AGENTS ② — Gyrase inhibitors, Anti-metabolites, Anti-Mycobacterial.

QUINOLONES = Gyrase Inhibitors. Gyrase helps in DNA replication - block it = bacteriocidal.

1st Gen: Nalidixic Acid: Treat UTI

2nd Gen: (Fluoroquinolone) = ~~CIPROFLOXACIN~~ CIPROFLOXACIN: More Broad Spec (Gram⁻ and pseudomonas)

- Resistance: Mutations of DNA Gyrase, Decreased Drug Accumulation
- Few side effects

Treating UTI's ∴ use Methenamine: Low pH of urine breaks it down to formaldehyde - kills bacteria

NITROFURANTOIN: Bacteria convert drug into Damaging molecule.

ANTI-METABOLITES - Inhibit Folate biosynthesis - Bacteria need Folate to make DNA.

- Drugs: ~~[redacted]~~ ① SULFONAMIDES: Competitive inhibitors of PABA which bacteria use to make their own Folate

② Trimethoprim - inhibit folate pathway further down.

ANTI-MYCOBACTERIAL (tuberculosis): 1st line therapy: Isoniazid + rifampin + pyrazinamide + ethambutol

Isoniazid - inhibit mycolic acid synthesis - Bacteriostatic (lag phase) Bacteriocidal (log phase)

↳ rapid resistance so never used alone

Rifampin - Binds to RNA Polymerase - Blocks transcription.

- Major problem: These induce liver enzymes, ↑ Metabolism of several other drugs.

Ethambutol - inhibits cell wall synthesis (blocks arabinosyl transferase activity).

Pyrazinamide - Similar target as Isoniazid - blocks cell wall synthesis

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③ **PROTEIN SYNTHESIS INHIBITORS** - Tetracycline, Aminoglycosides, Macrolides, Clinda., Chloram.

- all act at translation sites (ribosome blocking)

TETRACYCLINE → Binds to 30s ribosome - blocks access to tRNA to its receptor

- BACTERIOSTATIC
- Better for G⁺
- Widespread Resistance via plasmid transfer. - EFFLUX pumps, Ribosome-protecting proteins, and Enzymes to Inactivate tetracycline.
- Other types: DOXYCYCLINE + MINOCYCLINE - Better G.I. absorption. (95-100%).
- Adverse RXNS: PHOTOSENSITIVITY, Hepatic/Renal toxicity, Tooth discoloration

AMINOGLYCOSIDES (Streptomycin): Binds to 30s, interferes w/ ribosome complex assembly.

↳ ex Streptomycin, Tobramycin, Neomycin.

- Limited Spectrum - only aerobic organisms. often used with β-lactams
- Poor Bioavailability - IV or IM admin
- Adverse RXNS: OTOTOXICITY - irreversible Deafness/balance issues
- Resistance: decrease influx, mutate 30s ribosome, enzymatic inactivation.

MACROLIDES → Irreversibly binds to 50s subunit - inhibits translocation of ribosome
- Bacteriostatic at low concentrations, 'cidal at high concentrations.

- Erythromycin - same spectrum as penicillin, also used for UTI, chlamidia, syphillis,
- Clarithromycin - same spec. as ~~Erythro~~ Erythro. but better for chlamidia
- Azithromycin - less active for strep + staph but better for H. influenzae.

Adverse Rxns: GI problems, ototoxic, cholestatic jaundice
- don't give if pt is on carbamazapine, cyclosporine, Warferin.

- Administered orally, extensively metabolized.
- Resistance: decreased influx, ↓ binding affinity on 50s, plasmid associated esterase.

CHLORAMPHENICOL - Binds to 50s, inhibits peptidyl transferase Rxn
- Broad spec against all bacteria,
- can cross blood - brain barrier
- RARELY USED - LOW THERAPEUTIC INDEX: · Toxicity due to inhibiting human protein synth.
  · Inhibits various P450's - bad drug Rxns.

Resistance: "R" Factor - on plasmid - encodes an enzyme that inactivates the drug.

CLINDAMYCIN: Same mechanism as Erythromycin
- Used extensively to tx anaerobic bacteria.
- Extensively metabolized.