Bacteriostatic Inhibitors of Protein Synthesis

Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, Linezolid, Dalfopristin/Quinipristin, Spectinomycin

Tetracyclines

- Broad spectrum
- All agents similar in terms of action & adverse effects
- Main differences are pharmacokinetic
- Mechanism of Action
  - Bind to 30S ribosomal subunit and inhibit binding of tRNA to mRNA/ribosome unit
  - Result is inability to add amino acids to proteins

Tetracyclines

- Resistance
  - Decreased uptake of drug
  - Inactivation
  - Ribosomal protective proteins
- Treatment of Infectious diseases
  - Rickettsial diseases: Rocky Mountain spotted fever, typhus, Q fever
  - Chlamydia trachomitis
  - Brucellosis, cholera, mycoplasm pneumoniae, anthrax

Tetracyclines

- Other uses
  - Acne (low doses only)
  - PUD (Peptic Ulcer Disease)
  - Periodontal Diseases
- Classification
  - Short acting: tetracycline, oxytetracycline
  - Intermediate: Demeclocycline, Methacycline
  - Long acting: Doxycycline, Minocycline

Tetracyclines

- Absorption: PO, Short acting better on an empty stomach; all are bound by calcium supplements, milk, magnesium, iron supplements, most antacids
- Distribution: widely distributed, low CSF
- Elimination: Short and intermediate through kidneys; long acting by liver

Tetracyclines: Adverse Events

- GI irritation: burning, pain, cramps, NVD
- Bone and Teeth: discolor developing teeth, hypoplasia of enamel; suppress long-bone growth in premature infants
- Suprainfection: pseudomembranous colitis, candida
- Hepatotoxicity: lethargy and jaundice
- Renal toxicity
- Photosensitivity

Macrolides

- Mechanism of action: binds to 50S ribosomal subunit
- Broad spectrum
- All cause GI adverse effects
- Agents
  - Erythromycin
  - Clarithromycin
  - Azithromycin

Erythromycin

- Legionella
- Diphtheria
- Pertussis
- Chlamydia
- Mycoplasm pneumoniae (atypicals)
- Used as alternative to PCN G with allergy
  - Usually for Strep pneumo and pyogenes

Erythromycin: Kinetics

- PO: four forms, varying doses and absorption
- Distribution: most tissues other than CSF
- Elimination: 90% hepatic; 10% renal
- Adverse effects
  - GI: pain, NVD (off-label use)
  - Liver injury: caused only by estolate form
- Interaction:
  - Astemizole and terfenadine: dysrhythmias
  - Inhibits Chloramphenicol and Clindamycin
  - Increases: Theophylline, Carbamazepine, Warfarin

Other Macrolides

- Common: used for CAP and atypicals
  - Clarithromycin: H. pylori; metallic taste; same adverse events and interactions
  - Azithromycin (Z-pack): long half-life; does not inhibit does not inhibit metabolism of other drugs
- Uncommon:
  - Dirithromycin
  - Troleandomycin

Clindamycin

- Binds to 50S subunit of Ribosome
- Broad Spectrum: Most aerobes (+/-), gram + anaerobes
- Adverse events: Pseudomembranous colitis
- Not as widely used today d/t severity of colitis
- PO, IM, IV (Caution: slow IV infusion only)

Linezolid (Zyvox)

- New class of antibiotic
- Used for VRE and MRSA
- Binds to 23S and 50S ribosomal unit
- Spectrum: gram positive
- Adverse events
  - Nausea, diarrhea
  - PKU with oral dosing
  - Myelosuppression
  - Mild MAO inhibition: avoid tyramine and sympathomimetics

Rarer Drugs

- Chloramphenicol
  - Potential for Fatal Aplastic Anemia
  - Used only when no other viable alternative
- Dalfopristin/Quinupristin
  - New class of Drugs (streptogramins)
  - MRSA, VR E. faecium
- Spectinomycin: rarely used d/t resistance
- Telithromycin: new drug class (ketolide)
- Mupirocin: ointment; works on MRSA

Bacteriocidal Inhibitors of Protein Synthesis

Aminoglycosides

General Aminoglycosidology

- Narrow spectrum: primarily aerobic gram negative bacilli
  - Cannot kill anaerobes (oxygen is required for uptake)
- Highly polar:
  - Not absorbed in GI tract
  - Do not enter CSF
  - Rapidly excreted by kidneys

General Aminoglycosidology

- Mechanism: bind to 30S ribosomal subunit
  - Inhibit protein synthesis
  - Production of abnormal proteins
  - Bacteriocidal in high concentrations
    - Postantibiotic effect
- Resistance
  - Production of inactivating enzymes

General Aminoglycosidology

- Parenteral use: serious infections d/t gram (-) aerobes: esp, Pseudomonas, Enterobacters
- PO: used for local effects in stomach, especially as prep for bowel surgeries
- Topical: Neomycin for skin, ears, eyes; gentamicin and tobramycin for conjunctivitis

General Aminoglycoside Kinetics

- Absorption: Highly polar; little to no GI absorption
- Distribution: mainly extracellular fluid, little CSF; binds to renal tissues (50x higher than serum levels); cross into lymph of inner ear
- Elimination: kidney
- Interpatient variation: must monitor levels

General Aminoglycosidology

- Adverse events:
  - Ototoxicity: high trough levels
    - Cochlear: Tinnitus, hearing decline
    - Vestibular damage: headache, nausea, vertigo
  - Nephrotoxicity: ATN (cumulative dose)
  - Neuromuscular blockade
- Interactions
  - PCN mixture
  - Other ototoxic or nephrotoxic drugs.
  - Skeletal muscle relaxants

General Aminoglycosidology

- Dosing schedule
  - Divided doses
  - Single daily dose
  - Levels need to drawn at the appropriate time
    - 30 minutes for peak
    - Trough for divided dosing just before next dose
    - Trough for single daily dosing 2 and 12 hours

Common Aminoglycosides

- Gentamicin
  - Use: Gram negative bacilli: pseudomas and enterobacters
  - Low cost, but resistance is common
- Tobramycin
  - Similar to gentamicin; more active against pseudomas, less against enterobacter
  - Inhaled version for cystic fibrosis
- Amikacin
  - Broadest action and least likely to be inactivated

Less common Aminoglycosides

- Netilimicin
- Neomycin
- Kanamycin
- Streptomycin: 1st discovered; tuberculosis
- Paromomycin

Sulfonamides and Trimethoprim

Sulfonamides

- First systemic antibiotics discovered
- Structurally similar to PABA (a component of folic acid)
- Sulfonamides inhibit bacterial synthesis of folic acid by competing with PABA
- Spectrum: broad
- Resistance: common
  - Increased Synthesis of PABA
  - Alteration of folic acid synthesis enzymes
  - Decreased uptake of drug

Sulfonamides

- Therapeutic use has declined
  - Resistance
  - Toxicity
- UTI is primary indication
- Kinetics
  - Well absorbed PO
  - Distributed in all tissues
  - Metabolized in liver: become more toxic
  - Excreted in liver

Sulfonamides: Adverse events

- Older sulfonamides were bad news
  - Newer sulfonamides are less toxic
  - Severe: Stephen-Johnson's syndrome
    - 25% mortality
    - Systemic epithelial lesions
    - Discontinue if rash appears
    - Avoid in patients with hypersensitivity to thiazides & loop diuretics, and sulfonylureas
- Hemolytic anemia, et al.
- Kernicterus
- Renal damage

Sulfonamides

- Interactions
  - Intensifies Warfarin, Sulfonlyureas, phenytoin (Dilantin)
- Agents
  - Sulfamethoxazole: drink lots of water
  - Silver Sulfadiazine

Trimethoprim

- Not a sulfonamide, but similar action
- Inhibits the step after PABA in folic acid synthesis
- Hardly ever given solo. Almost always with Sulfamethoxazole:
  - TMP-SMZ aka Septra, Bactrim
- Uses
  - UTI
  - Pneumocystis carinii, esp immunocompromise

Fluoroquinolones

- Broad spectrum antibiotics
- Uses: Pneumonia, UTIs, sinusitis, skin infections, bones, everything
- Mechanism of action
  - Inhibition of bacterial DNA gyrase
- Adverse effects
  - GI reactions, dizziness, headache, fatigue, tendon rupture
  - Discontinue if tendon pain

Fluoroquinolones: Interactions

- Cationic substances: aluminum or magnesium antacids, Iron salts, Zinc salts, milk, other dairy products, anything with calcium
  - give quinolone 2 hours before or six hours after
- Theophylline
- Warfarin

Fluoroquinolones

- Common Agents: all PO and IV
  - Ciprofloxacin (Ciprofloxacin)
    - First, most resistance
  - Levofloxacin (Levaquin)
  - Moxifloxacin (Avelox) – most assocated with tendon rupture

Metronidazole (Flagyl)

- Protozoal infections and some bacterial
- Spectrum: anaerobes only
- Mechanism: disrupts DNA
- Uses:
  - Anerobic infections
  - C. diff colitis
  - GI surgery

UTI Drugs

- UTI is most common infection in U.S.
- 25% - 35% of women have one per year
- 30% - 50% in nursing homes have UTI
- Location:
  - Urethritis
  - Cystitis
  - Pyelonephritis
  - Prostatitis
- Complicated vs. Uncomplicated

UTI

- 80% of infections are E. coli
- G(+) cocci account for 10% - 15%
- Nosocomial: E. coli only 50%
- Urinary Tract Antiseptics
  - For uncomplicated lower tract only
  - Nitrofurantin: lung and neuro adverse effects
  - Methenamine
  - Nalidixic acid
  - Cinoxacin

Mycobacterium

- Tuberculosis
  - Multidrug therapy: 1st line
    - Isoniazid
    - Rifampin (Rifapentine long acting)
    - Pyrazinamide
    - Ethambutol
    - Streptomycin
- Leprosy (Hansen's Disease)
- M. avium complex

Antifungals for Systemic

- Opportunists vs. Nonoppurtunists
- Amphotericin B (Amphoterrible)
  - Highly toxic to humans
  - Broad Spectrum
  - DOC for most systemic Mycoses
  - Infusion reactions and Renal toxicity
  - Binds to sterols in fungal membrane and causes leakage
  - May cause hypokalemia
  - Test dose

-azoles

- *Ketoconazole, *Itraconazole, *Miconazole, Clotrimazole, *Fluconazole, *Voriconazole, Econazole
- *Systemic use
- Strong inhibitors of Cytochrome P-450
- Generally safer than Amphotericin B
- Some cause hepatotoxicity

Superficial Mycoses

- Dermatophytes
  - Tinea Capitis – ketoconazole shampoo
  - Tinea corporis – topical azole or terbinafine
  - Tinea Cruris – topical azole
  - Tinea Pedis – topical azole
- Candidiasis
  - Vulvovaginal – local azole or oral fluconazole
  - Oral – nystatin,clotrimazole; severe oral flucon-
- Onychomycosis: nails
  - Oral preferred: terbinafine, itraconazole

Classes for Superficial Mycoses

- Grisefulvin: oral antifungal affects skin only
- Azoles: oral, creams, suppositories
- Polyene Antibiotics: Nystatin and Amphotericin B topical
- Allyamines: terbinafine (Lamisil) most common
- Other
  - Tolnaftate, Haloprogin, Ciclopirox

Antivirals: Purine Nucleoside Inhibitors

- Acyclovir
  - Against Hepes Simplex and Varicella-Zoster
  - Topical, Oral, IV
  - Poorly absorbed PO
  - Resistance is extremely rare in non-immunocompromised patients
- Valacyclovir
  - Pro-drug form of acyclovir
  - Allows IV levels of acyclovir with PO dosing

Purine Nucleoside Inhibitors

- Ganciclovir
  - Used for CMV, only in immunocompromised
    - HIV
    - Prevention of CMV in organ transplant
  - Large doses
  - Potentially severe side effects: granulocytopenia, thrombocytopenia
- Valganciclovir
  - Prodrug form

Purine Nucleoside Inhibitors

- Famciclovir
  - Herpes zoster and genital herpes
  - Well tolerated; PO administration
- Cidofovir
  - Used only for CMV retinitis in HIV patients
- Penciclovir
  - Topical drug for cold sores

Hepatitis B & C drugs

- Hep B: Vaccine Vaccine Vaccine
- Interferon alpha: used for both
  - Family of naturally occuring immunomodulators
  - Flu like symptoms
  - Depression, fatigue, alopecia, blood disorders, thyroid dysfunction, heart damage
- Ribavirin: only in combo with Interferon
- Lamivudine: HIV and HepB
- Adefovir: new for HepB

Influenza

- Vaccine: three strains; reformulated q year
  - Coverage from 2 weeks to 6 months
  - 70% - 90% of young adults become immune
  - Elderly: less efficacy of duration and immunity
  - IM injection or intranasal
- 1st Gen: Amantadine and Rimantidine
  - Low activity, high resistance, Type A action
- 2nd Gen: Neuraminidase inhibitors
  - More activity, less resistance, Type A & B
  - Oseltamivir, Zanamivir