Antiparasitic Drugs
(Other than anti-malarials)

ID Fellows Core Curriculum
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Presented by:
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Benzimidazoles

- Albendazole
- Mebendazole
- Triclabendazole
Albendazole

• Now the drug of choice for intestinal nematodes
  » Better spectrum of activity
  » Better pharmacokinetics

• Treatment for:
  » Ascaris lumbricoides
  » Trichuris trichiura
  » Hookworms
  » Pinworm
  » Cutaneous larva migrans
  » Echinococcus
  » Cystercercosis
  » Certain filarial species
Albendazole

• **Mechanism of Action:**
  » Binds to beta-tubulin
    • Prevents microtubule assembly
      » Beta-tubulin dependent glucose uptake
  » Other potential mechanisms:
    • Inhibits fumarate reductase (parasite specific)
      » Decreases levels of NADH
    • Degradation of endoplasmic reticulum and mitochondria
      » Decreased production of ATP

• **Mechanism of Resistance:**
  » In livestock, loss of affinity to tubulin seen
Albendazole

- **Pharmacokinetics:**
  - Poorly water soluble
    - <5% absorbed
  - Well absorbed with fatty meal
    - Increases absorption by 4-5 times
  - Serum half live: 8-9 hours
  - CSF: 40% penetration
  - Concurrent administration of steroids increase serum levels by 50% (and thus CSF concentration > neurocystercercosis)
  - Metabolized: (1st pass) in liver to albendazole sulfoxide (excellent anti-helminthic activity)
  - Elimination: renal and feces
Albendazole

- **Dosage:** Varies with Indication
  - 10-15 mg/kg/day (max 800mg/day)

- **Adverse Events:**
  - **Pregnancy:** C/D
    - Embryotoxic in animals
    - Accidental exposures
  - **Occasional:**
    - Abdominal pain
    - Migration of worm
    - Reversible alopecia
    - Increased LFTs
  - **Rare:**
    - Leukopenia (reversible)
    - Fever
    - Increased ICP
    - Rash
    - Renal toxicity
Mebendazole

• **Treatment for:**
  » Intestinal helminths
  » Trichinella spiralis

• **Mechanism of Action:**
  » Binds to beta-tubulin
    • Prevents microtubule assembly
      » Beta-tubulin dependent glucose uptake

• **Mechanism of Resistance:**
  » Not report in humans, but not well studied
Mebendazole

• Pharmacokinetics:
  » Minimally water soluble
  » Poorly absorbed in GI tract
    • Limits use for tissue parasites
  » Serum half life: 2.5 to 5 hours
  » Metabolized: liver
  » Excreted: urine
Mebendazole

- **Dosage: Variable with Indication**
  - 100mg to 500mg

- **Adverse Events:**
  - **Pregnancy: C**
    - Accidental exposures
  - **Occasional:**
    - Abdominal pain
    - Diarrhea
    - Migration of worm
    - Reversible alopecia
    - Increased LFTs
  - **Rare:**
    - Leukopenia
    - Agranulocytosis
    - Hypospermia
    - Seizure
Triclabendazole

- **Treatment for:**
  - Fasciola hepatica
  - Paragonimus sp.

- **Mechanism of Action:**
  - Binds to beta-tubulin
    - Prevents microtubule assembly
      - Beta-tubulin dependent glucose uptake

- **Dose:** 10mg/kg

- **Pharmacokinetics:**
  - Bioavailability: unquantified
  - 99% Protein bound
    - Metabolized: liver
    - Excreted: urine

- **Pregnancy:** ?
Avermectins: Macrocyclic lactones

• Ivermectin
Ivermectin

- Macrocyclic lactones are products or chemical derivatives of soil microorganisms belonging to the genus Streptomyces.

- **Treatment for:**
  - Intestinal helminths
    - Dirofilaria immitis
  - Treatment of choice for:
    - Strongyloidiasis
    - Onchocerciasis
  - Ectoparasites
    - Scabies
    - Lice

Has broad spectrum against helminths and is used extensively in livestock.
Ivermectin

• Mechanism of Action:
  » Activates the opening of gated chloride channels
    • Influx of Cl ions paralysis the pharyngeal pumping mechanism of helminths

• Mechanism of Resistance:
  » No known resistance
  » Failures have lead to multi-dose regimens
Ivermectin

• Pharmacokinetics:
  » Well absorbed in GI tract
  » Serum half live: 12 hours
    • Highly protein bound
    • Collects in adipose tissue
  » Subject to enterohepatic recirculation
  » Metabolized: liver
  » Eliminated: stool
Ivermectin

- **Dosage:** Variable with Indication
  - 100-150 mcg/kg dose

- **Adverse Events:**
  - Pregnancy: C
  - Common:
    - Itching
    - Dizziness
  - Occasional:
    - Mazzotti-type reaction in onchocerciasis
      - Fever, pruritis, tender LN, HA, joint pain
    - Seizure
  - Rare:
    - Hypotension
Pyrazinoisoquinolines

Praziquantel
Praziquantel

- **Treatment for:**
  - Cestodes (tapeworms)
    - Taenia sp.
    - Diphyllobothrium latum
    - Echinococcus
  - Trematodes (flukes)
    - Schistosomiasis
    - Chlonorchis sinensis
    - Paragonimus westeramani
    - **Exception:** Fasciola hepatica
  - Cystercercosis (second line)
Praziquantel

• **Mechanism of Action:**
  » **Tapeworms:**
    • Release of Ca from endogenous stores
      » Paralysis and expulsion of worm
  » **Schistosomes**
    • Damage to tegument (covering) resulting in intense vacuolation and increased permeability to Ca.
    • Sequestered Ag exposed to parasite surface allowing for immune recognition

• **Mechanism of Resistance:**
  » Unclear mechanism
  » Has been seen in mice models
Praziquantel

- **Pharmacokinetics:**
  - Well absorbed in GI tract (~80%)
  - Serum half live: 4-6 hours
    - Highly protein bound (80%)
    - Collects in adipose tissue
  - CSF penetration: 15-20%
    - Levels in CSF decreased with steroid co-administration
  - Increased serum levels with: cimetidine, ketoconazole, miconazole
  - Metabolized: liver
    - Extensive 1st pass metabolism to inactive metabolites
  - Eliminated: urine (99% as metabolites)
Praziquantel

- **Dosage:** varies with indication
  - 10-25 mg/kg/dose

- **Adverse Events:**
  - Pregnancy: B
  - Frequent:
    - Abdominal pain
    - Diarrhea
    - Malaise
    - HA
    - Dizziness
  - Occasional:
    - Sedation
    - Fever
    - Sweating
    - Nausea
    - Eosinophilia
  - Rare:
    - Pruritus
    - Rash
    - Edema
    - Hiccups
Novel Anti-protozoal Drugs: Synthetic nitrothiazolyl-salicylamide

Nitazoxanide
Nitazoxanide

• **Treatment for:**
  » Intestinal protozoa
    • Cryptosporidium
    • Giardia

• **Mechanism of Action:**
  » Metabolized rapidly to active form- tizoxanide
  » May be due to interference with the pyruvate:ferredoxin oxidoreductase enzyme-dependent electron transfer reaction essential for anaerobic metabolism

• **Mechanism of Resistance:**
  » None reported
Nitazoxanide

- **Pharmacokinetics:**
  - 70% > absorption with suspension vs. tablet
  - >99% protein bound
  - Metabolism: hepatic
  - Excretion: urine, bile and feces

- **Dose:** variable by indication
  - 100 BID to 500 BID

- **Adverse Events:**
  - Pregnancy: B
  - Common:
    - HA
    - GI complaints (Abdominal pain, diarrhea, nausea, vomiting)
  - Uncommon:
    - Allergy
    - Increased ALT
    - Anemia
    - Anorexia
Other Antimicrobials for Parasites

Atovaquone
Dapsone
Pentamidine
Others
Atovaquone

- **Treatment for:**
  - PCP
  - Malaria
  - Babesia

- **Mechanism of Action:**
  - Unclear
  - May inhibit electron transport in mitochondria thus inhibiting metabolic enzymes

- **Mechanism of Resistance:**
  - Malaria
    - Mutations in cytB associated with *in vivo* and *in vitro* resistance

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Atovaquone

- **Pharmacokinetics:**
  - Poor oral absorption (23% in tablets, 47% suspension)
  - Improved with high fat meals
  - >99% protein bound
  - Metabolism: minimal
    - Undergoes enterohepatic recirculation
  - Excretion: stool (94% as unchanged drug)

- **Dose:** variable by indication
  - 1000-1500mg a day

- **Adverse Events:**
  - Pregnancy: C
  - Common:
    - HA
    - GI complaints
    - Rash
  - Uncommon:
    - Pruritis
    - Hypoglycemia/natremia
    - Anemia, neutropenia
    - Increased LFTS
Dapsone

- **Treatment for:**
  - PCP
  - Possibly malaria

- **Mechanism of Action:**
  - Competitive antagonist of para-aminobenzoic acid (PABA) for folate synthesis

- **Mechanism of Resistance:**
  - Unclear
  - Potential for resistance in dhfr/dhps genes
Dapsone

• **Pharmacokinetics:**
  » Good oral absorption (>75%)
  » 70-80% protein bound
  
  » Metabolism: hepatic
    • CYP3A4: azole antifungals, clarithromycin, INH, rifamycin, phenobarbital
    • CYP2C9: phenytoin, rifampin, carbamazepine
  
  » Excretion: urine (85%)

• **Dose:** variable by indication
  » 50-100mg a day

• **Adverse Events:**
  » Pregnancy: C
  
  » Major:
    • Hemolysis (G-6-PD)
    • Methemoglobinemia
    • Erythema multiforme, TEN
    • Neuropathy
    • Cholestatic jaundice
Pentamidine

• **Treatment for:**
  » Leishmania
  » Trypanosoma brucei

• **Mechanism of Action:**
  » Aromatic diamine synthesized in the late 1930s
  » Inhibits synthesis of parasitic DNA by blocking thymidine synthase
  » Fixation of transfer RNA

• **Mechanism of Resistance:**
  » Unclear
  » Failures reported in literature
Pentamidine

- **Pharmacokinetics:**
  - Poor oral bioavailability so used by aerosol or IV
  - Metabolism:
  - Excretion: urine

- **Dose:** variable by indication
  - 4mg/kg IV every other day for four days

- **Adverse Events:**
  - Pregnancy: C
  - Major:
    - Immediate with IV: hypotension, tachycardia, nausea, vomiting, syncope, etc.
    - Urticaria
    - Pancreatitis
    - New onset DM
    - Altered glucose metabolism
    - Renal failure
    - Cardiac dysrhythmia
    - Leukopenia
    - Thrombocytopenia
# Other Antimicrobials for Parasites

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Drugs for Parasitic Infections

With increasing travel, immigration, use of immunosuppressive drugs and the spread of AIDS, physicians anywhere may see infections caused by parasites. The table below lists first-choice and alternative drugs for most parasitic infections. The table on page 12 summarizes the known prenatal risks of antiparasitic drugs. The brand names and manufacturers of the drugs are listed on page 14.

Treatment Guidelines from The Medical Letter Vol 5 (Suppl). 2007
Other Uncommon Antiparasitic Drugs
Filariasis
DEC
(Diethylcarbamazine)

- **Treatment for:**
  - Filaria infections
    - Wuchereria bancrofti
    - Brugia sp.
    - Loa loa

- **Mechanism of Action:**
  - Effective against adult worms, not microfilaria

- **Pharmacokinetics:**
  - High bioavailability with oral administration
  - Rapid absorption and peak drug levels
  - Metabolism: liver
  - Excretion: >50% unchanged in urine, <10% feces, urine

- **Dose:** variable by indication
  - 25-100mg a day

- **Adverse Events:**
  - Pregnancy: ?
  - Major:
    - Mazzotti reaction
    - Seizure
    - Encephalitis
    - Ocular lesions (due to worm death)
  - Minor:
    - Anorexia
    - Vomiting
Leishmania sp.
Sodium Stibogluconate

- **Treatment for:**
  - Leishmania sp.

- **Mechanism of Action:**
  - Pentavalent antimony (100mg Sb/ml)
  - vs. meglumine antimoniate with 85mg Sb/ml
  - Unclear
  - Inhibition of ATP synthesis

- **Pharmacokinetics:**
  - IV administration (poor oral bioavailability)
  - Metabolism: liver (<10%)
  - Excretion: urine (96%)

- **Dose:** variable by indication
  - 20mg/kg/day for 20-28 days

- **Adverse Events:**
  - Pregnancy:
    - Intolerance: shivers, fever, arthralgias, myalgias, skin rashes, abdominal symptoms, HA
  - Toxicities:
    - Reversible elevation of LFTs
    - Pancreatitis
    - Anemia, lymphocytopenia and thrombocytopenia
    - Prolonged Qt
    - Inversion of T waves
    - Prolonged PR interval
    - Sudden death in excessive doses
    - Rash
    - Increased lipids
    - Proteinuria
    - N/V/Abd pain
Miltefosine

- **Treatment for:**
  - Leishmania sp.

- **Mechanism of Action:**
  - Alkyl phospholipid
    - Oral antineoplastic
  - Phosphocholine analogue
    - Affects cell signaling and membrane synthesis

- **Pharmacokinetics:**
  - Well absorbed in mice
    - No human data
  - Metabolism: liver
  - Excretion: urine

- **Dose:** variable dosing by age
  - 100mg/day over 4 weeks

- **Adverse Events:**
  - Pregnancy: ?
  - Major:
    - Retinal degeneration
    - Hepatitis
    - Renal failure
  - Minor:
    - Itching
    - Rash
    - N/V/D
    - Leukocytosis
Trypanosome sp.
Suramin

- Introduced in the 1920s in Germany

- Treatment for:
  - Trypanosoma brucei spp.
    - 1st stage both subspecies
    - Pentamidine preferred for 1st stage gambiense

- Mechanism of Action:
  - Non-specific enzyme inhibition
  - Differential accumulation in human and trypanosomes

- Pharmacokinetics:
  - IV administration (IM is an irritant)
    - No oral absorption
    - Poor CSF penetration
    - 99.7% protein bound
  - Metabolism: ?
  - Excretion: urine

- Dose:
  - Test dose: 100-200mg (4-5mg/kg)
  - 1gm (20mg/kg) IV qday on day 1,3,7,14, and 21

- Adverse Events:
  - Pregnancy:
    - Major:
      - Renal failure (common, mild and reversible)
      - Allergy
      - Anemia
      - Peripheral neuropathy
      - Agranulocytosis
      - Circulatory collapse/shock
      - Erythema multiforme
      - Adrenal insufficiency
Melarsoprol

- **Developed in 1949**

- **Treatment for:**
  - Trypanosoma brucei spp.
  - 2nd stage both sub species

- **Mechanism of Action:**
  - Unclear
  - Trivalent arsenical compound
  - Highly non-discriminating inhibitor of a large number of enzymes
  - High numbers of treatment failures

- **Pharmacokinetics:**
  - IV administration
  - CSF: <2% of plasma levels
  - Metabolism: liver
  - Excretion: bile

- **Dose:**
  - Complex dosing regimen for 30 day period

- **Adverse Events:**
  - Pregnancy: ?
  - Major:
    - Encephalitis syndrome (10-15% of patients, fatal in 10-70%)
  - Minor:
    - HA
    - Nausea
    - Thrombophlebitis
    - Neuropathy
    - Renal failure
Eflornithine

- Approved by the FDA for HAT in 1990

- **Treatment for:**
  - Trypanosoma brucei spp.
    - 2nd stage only for gambiense

- **Mechanism of Action:**
  - Inhibits ornithine decarboxylase (ODC)
    - Involved in polyamine synthesis and nucleic acid synthesis

- **Pharmacokinetics:**
  - Bioavailability: 10% (oral)
  - CSF:Plasma ratios: 0.13-0.51
  - Metabolism: none
  - Excretion: renal (80-86%)

- **Dose:**
  - 400mg/kg/d IV in 4 doses X 14 days

- **Adverse Events:**
  - Pregnancy: C
  - Major:
    - Bone marrow toxicity (25-50%)
    - Convulsion (7%)
  - Minor
    - GI symptoms (10%)
Nifutimox

- **Treatment for:**
  - Trypanosoma cruzi

- **Mechanism of Action:**
  - Synthetic nitrofuran
  - May act by increasing oxidative stress through production of free radicals

- **Pharmacokinetics:**
  - GI absorption 80% in animal models
    - Lower in humans
  - Metabolism: liver (extensive P-450)
  - Excretion: renal (1% as native drug)

- **Dose: variable dosing by age**
  - 8-10mg/kg divided 3 times a day for 90 days

- **Adverse Events:**
  - Pregnancy: ?
  - Major:
    - Usually hospitalize to monitor for side effects
    - Hemolytic anemia
    - Multiple CNS effects
    - Renal failure
  - Minor:
    - Rash
    - N/V/Abd pain
    - Increased LFTs
    - Leukopenia
Benznidazole

- **Treatment for:**
  - Trypanosoma cruzi
  - Current treatment of choice for acute cases

- **Mechanism of Action:**
  - Nitroimidazole
  - DNA binder

- **Pharmacokinetics:**
  - 92% bioavailability after oral dose
  - 44% protein bound
  - Metabolism: ?
  - Excretion: urine and bile

- **Dose: variable dosing by age**
  - 5-7mg/kg divided 2 times a day for 60 days

- **Adverse Events:**
  - Pregnancy: ?
  - Major:
    - Bone marrow depression
    - Carcinogenesis
  - Minor:
    - Rash
    - Itching
    - Peripheral neuropathy