Parasitology I & II
Protozoa

Mechanisms of Human Disease
Paul O’Keefe, M.D.
January 4, 2019

Parasitology: Introduction

- Human parasites – protozoa or helminths
- Life cycle – understand pathogenesis
  - Transmission: ingestion, sexual, skin penetration, insect vectors
  - Other hosts: insects, animals (domestic and wild), crustaceans, fish
- Diagnosis usually not by culture
  - Morphologic from feces, urine, blood or tissue
  - PCR becoming more common and widely used
**Malaria**

**Plasmodia - Species and Distribution**

<table>
<thead>
<tr>
<th>Species</th>
<th>Disease Cycle</th>
<th>Geographic Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. vivax</td>
<td>44-48 hour</td>
<td>Benign, Worldwide, Temperate</td>
</tr>
<tr>
<td>P. falciparum</td>
<td>36-48 hour</td>
<td>Malignant, Tropical Africa and Asia, Americas</td>
</tr>
<tr>
<td>P. malariae</td>
<td>72 hour</td>
<td>Malignant, Tropics and subtropics</td>
</tr>
<tr>
<td>P. ovale</td>
<td>48 hour</td>
<td>Tropical Africa</td>
</tr>
<tr>
<td>P. knowlesi</td>
<td>24 hour</td>
<td>Malaysia, SE Asia</td>
</tr>
</tbody>
</table>

**Epidemiology of Malaria**

- **Worldwide trend - infections decreasing**
  - 21% 2010-2015; death decreased by 29%
  - Scaled up interventions
  - Increased resistance to chemotherapy
  - Increased resistance of Anophelus to insecticides
  - Ecologic and climate change
- **219 million in 2017 (WHO estimate)**
  - 2 million more than 2016
- **435,000 deaths in 2017**
  - African region: 92% cases, 93% deaths-70% children <5
- **Subsaharan Africa and Oceania**
  - India>Southeast Asia>S. America>C. America
- **Autochthonous, "Airport"**
- **2015 – 1517 US cases reported to CDC (12% decline)**


**Malaria Life Cycle**

- **Sporogony – mosquito (Sexual)**
  - Gametocytes (male and female) → zygote → Oocyst → sporozoite
- **Schizogony – Man (Asexual)**
  - Exoerythrocytic - Liver
    - Sporozoite → Hepatic schizont → merozoite
  - Erythrocytic
    - Merozoite → trophozoite → RBC schizont → merozoite or gametocyte
Malaria – Life Cycle

Malaria - Characteristics

- *P. vivax* and *P. ovale* Schuffner’s dots - caveole-vesicle complexes
- *P. falciparum* - electron dense knobs
  - Facilitate binding to endothelium and uninfected RBCs
- Pigment (hemozoin)-degraded hemoglobin
- Abnormal RBC’s and malaria
  - S hemoglobin impairs falciparum growth
  - Also C, E, thalassemia, G6PD deficiency

Plasmodium - Cell Interactions, Resistance

<table>
<thead>
<tr>
<th>Species</th>
<th>Type of RBC infected</th>
<th>Hepatic Dormancy</th>
<th>Chloroquine Resistance</th>
<th>Other Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. vivax</em></td>
<td>Reticulocyte</td>
<td>Yes (rare)</td>
<td>Yes (becoming more common)</td>
<td>Schuffner’s dots</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>Reticulocyte</td>
<td>Yes</td>
<td>No</td>
<td>Schuffner’s dots</td>
</tr>
<tr>
<td><em>P. falciparum</em></td>
<td>All RBC’s</td>
<td>No</td>
<td>Widespread</td>
<td>Electron dense knobs, heavy parasitemia</td>
</tr>
<tr>
<td><em>P. malariae</em></td>
<td>Senescent RBC’s</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><em>P. knowlesi</em></td>
<td>All</td>
<td>No</td>
<td>No</td>
<td>Heavy parasitemia</td>
</tr>
</tbody>
</table>
Malaria - Pathogenesis

- Fever associated with schizont rupture
- Anemia - hemolysis
  - Renal failure - hemoglobinuria
- Tissue hypoxia - sludging of parasitized RBC's
  - Knobs and up-regulated endothelial adhesion molecules
  - Brain, kidney, lung
- Immunopathologic events
  - Cytokine release
  - Immune complex nephritis

Malaria - Clinical Manifestations

- Prodrome: flu-like illness
- Chills, fever, headache, myalgias, nausea, splenomegaly
- Anemia, thrombocytopenia
- Organ dysfunction with *P. falciparum*
  - Cerebral malaria
  - Renal failure
  - Pulmonary edema

Malaria – Species-Specific Clinical Features – *P. falciparum*

- Very high level of parasitemia
- Microvascular events due to high parasitemia and sludging
- Cerebral malaria
- Pulmonary edema
  - Vascular events
  - Severe anemia
- Renal failure
  - Severe hemolysis ("Blackwater fever")
  - Shock – ischemic insult to kidney
Malaria – Species-Specific Clinical Features

- *P. vivax* and *P. ovale*
  - Moderate parasitemia (reticulocytes)
  - Microvascular events not seen
  - Hypnozoites in liver → RELAPSE – need primaquine

- *P. malariae*
  - Low parasitemia – mild symptoms, prolonged infection

Plasmodium knowlesi

- Malaria parasite of monkeys
- Human cases (relaxed host specificity) in Malaysia
- Unique 24 hour cycle
- No sludging
- 7% severe
- Rings resemble falciparum
- Trophozoites and schizonts like *P. malariae*
- Chloroquine sensitive

Diagnosis of Malaria

- Demonstration of parasite stages in blood
  - Thin smears – standard stained blood smear
  - Differentiate species
  - Thick smears – lyse RBC’s
- PCR done in reference laboratories
- Rapid diagnostic tests
  - Rapid monoclonal antibody – Binax NOW®
    * Utilized in some hospital laboratories
  - Immunochromatographic strips in field
- Serology - epidemiology
**P. vivax - Trophozoites**

[Images of trophozoites from CDC Parasite Image Library]

**P. vivax - Schizonts**

[Images of schizonts from CDC Parasite Image Library]

**P. Vivax – Gametocytes**

[Images of gametocytes from CDC Parasite Image Library]
P. Falciparum – Ring Forms and Gametocyte

P. falciparum - Gametocytes

Treatment of Malaria

- Erythrocytic
  - Chloroquine
    - Effective for all species except falciparum and chloroquine-resistant vivax
    - Resistance in falciparum worldwide
  - Quinine/quinidine
  - Others: Mefloquine, Malarone (atovaquone/ proguanil), antifolates, sulfonamides, tetracycline, clindamycin, Artemether/ arteether, Halofantrine
- Exoerythrocytic (vivax and ovale only)
  - Primaquine
Malaria - Treatment

- Vivax/ovale – Chloroquine + primaquine
  - CQ resistant – quinine + doxy
  - mefloquine
- Falciparum
  - CQ sensitive – same as vivax without primaquine
  - CQ resistant (uncomplicated)
    - Artemether/lumefantrine
    - Atovaquone + proguanil
    - Mefloquine
  - CQ resistant (complicated, severe)
    - IV – Quinidine + doxy or clindamycin
    - Alternative – IV artesunate available from CDC

You need not know specific treatment regimens.

Chemoprophylaxis of Malaria

- Lower doses of antimalarials are given to travelers to endemic areas
  - Risk: Oceania 1:30, Africa 1:250, India 1:250, SE Asia 1:1000, S. America 1:2,500, C. America 1:10,000
- Agents
  - Sensitive
    - Chloroquine
    - Primaquine if prolonged exposure to vivax or ovale
  - Resistant
    - Atovaquone/Proguanil
    - Mefloquine
    - Doxycycline

Prevention of Malaria

- Vector control
  - Insecticide-treated mosquito nets (ITNs)
  - Indoor spraying with residual insecticides
    - 80% of dwellings
    - Effective for 3-6 months
- Intermittent treatment of pregnant women and infants
- Mosquito repellants (DEET), long sleeves and pants, avoid dusk to dawn
- Vaccines – experimental
  - RTS, S/AS01
Malaria – Key Concepts
- Transmitted by mosquitoes
- To liver for one cycle, released to blood
  - vivax and ovale can remain in liver
- Illness – cycles of fever with hemolytic anemia
- Falciparum – severe
  - High level of parasitemia
  - Endothelial adherence and sludging
- Diagnosis blood smear, rapid tests
- Treatment
  - Blood
  - Liver for vivax and ovale
- Chemoprophylaxis for travelers

Babesiosis
- Zoonosis with same distribution as Lyme borreliosis
- Organism: Babesia microti, (B. divergens in Europe)
- Vector: Ixodes scapularis - Tick
- Reservoir: Small rodents

Babesiosis: Life Cycle
Babesiosis: Clinical Features

- Majority asymptomatic
  - Fever
  - Headache
  - Fatigue
  - Hemolytic anemia
- Severe sepsis occurs in immunocompromised or splenectomized
- Co-infection with lyme borreliosis or anaplasmosis occurs

Diagnosis and Treatment of Babesiosis

- Diagnosis
  - Blood smear
    - Small rings to tetrads
  - PCR
  - Serology
- Treatment
  - Atovaquone plus azithromycin OR
  - Clindamycin plus Quinine - severe
Babesiosis – Key Concepts

• Transmitted by ixodes ticks (same as Lyme)
• Majority no symptoms
  – Immunocompromized or splenectomy
• Severe sepsis
• Diagnosis blood smear
  – Characteristic tetrads

Toxoplasma gondii

• Zoonosis - reservoir: CATS, sheep, pigs, cattle, birds
• Mechanism of transmission
  – Ingestion of cat feces containing oocyst
    • food or environment
  – Ingestion of inadequately cooked meat containing cysts
  – Intrauterine transmission
  – Blood transfusion or organ transplant

Toxoplasmosis: Life Cycle
Toxoplasmosis: Clinical

• Asymptomatic with or without lymph node enlargement
• Acute - mononucleosis-like illness
  – fever and generalized lymphadenopathy
• Localized lymphadenopathy
• Intrauterine: multisystem disease including CNS
  – Greatest risk - acquired by mother in 3rd trimester
  – Severe manifestations - 1st trimester
• Chorioretinitis
• Immunocompromised: encephalitis in AIDS or encephalitis, myocarditis, pneumonia in HSCT

Toxoplasmosis – CT Scan

Diagnosis and Treatment of Toxoplasmosis

• Tissue biopsy
  – See cysts or tachyzoites
  – PCR – limited sensitivity
• Serology: IgG or IgM responses
  – Complex profile employed to diagnose infection in pregnancy
• Treatment
  – Pyrimethamine + sulfadiazine
  – Alternatives: clindamycin, dapsone, clarithromycin, azithromycin, atovaquone
  • Spiramycin prevent vertical transmission
• Prevention in HIV/AIDS, immunocompromised
  – Trimethoprim/sulfamethoxazole
**Toxoplasmosis – Key Concepts**

- Transmission by ingestion of oocysts (cat feces) or undercooked meat
- Illness
  - Mononucleosis
  - Chorioretinitis
  - Immunocompromised – encephalitis (AIDS), disseminated
  - Congenital
- Diagnosis biopsy or serology
- Common

**Cryptosporidium**

- Coccidian protozoan which carries out life cycle in intestinal villi of animals and man
- Reservoir: domestic animals, humans
- Mechanism of transmission
  - Fecal-oral: ingestion of cysts
    - Person to person
    - Waterborne outbreaks - 400,000 cases in Milwaukee in 1993
Cryptosporidiosis: Clinical

- Immunocompetent
  - Explosive, watery diarrhea
  - Abdominal pain
  - Lasts one to two weeks
- Immunocompromised
  - Severe, watery diarrhea with malnutrition
  - Biliary disease
  - Continues until immunity restored

Diagnosis and Treatment of Cryptosporidium

- Diagnosis
  - Acid-fast stain of cysts in feces
  - Direct fluorescence
  - PCR
  - Biopsy

- Treatment
  - Nitazoxanide recently released by FDA
    - Effective in immunocompetent including children (not with AIDS)
    - Possibly effective in larger doses in persons with AIDS
  - AIDS – HAART to restore immune function

LUMC PCR results
August-December, 2018
Cryptosporidium Oocysts

Cryptosporidiosis – Key Concepts

- Transmission – fecal oral (water), sexual
- Complete life cycle on surface of host gut
- Illness – Watery diarrhea
  - Self limited in healthy person
  - Relentless in immunocompromised
- Diagnosis – cysts in stool (Acid fast or DFA)

Amebiasis: Epidemiology

Reservoir is infected humans

- 10% of world’s population
- Rare in US: institutionalized, migrant labor, gay men, AIDS
- Fecal-oral transmission
  - Ingest infectious cysts
  - Food or waterborne outbreaks
- Venereal transmission
Amebiasis: Life Cycle

Amebiasis: Pathogenesis and Virulence

- Commensal versus pathogen
  - Markers of pathogenicity: Zymodene (isoenzymes), DNA analysis, monoclonal staining
    - Separate *E. histolytica* (pathogen) from *E. dispar*, *E. moshkovskii*, *E. bangladeshi*
  - Antibody formation - marker of pathogen

- Virulence
  - Endocytic capacity
  - Adherence: galactose-specific lectin
  - Lytic capacity
    - Initiated by the lectin
    - Pore-forming protein
  - Extracellular proteinases → complement, collagen

*E. histolytica*: Pathologic Features

- Pathology
  - Undermined “flask” ulcers
  - Ameboma - mass of granulation tissue
  - Abscess-metastatic spread to liver, pleura, pericardium, lung, brain
Amebiasis

Amebiasis: Clinical

- Intermittent diarrhea, flatulence, pain
- Dysentery-tenesmus, bloody diarrhea, severe pain
  - perforation, abscesses
- Disseminated-abscesses in liver, lung, pericardium, brain
- Asymptomatic

Amebiasis: Diagnosis and Treatment

- Diagnosis
  - Stool exam for trophozoites and cysts
    - Direct fluorescence antibody test
    - Stool antigen test (Gal/Gal-Nac lectin)
  - Serology: IHA, ELISA, gel diffusion
  - PCR available to distinguish pathogenic from nonpathogenic species
    - Included in LUMC multiplex PCR stool test
- Treatment
  - Invasive: metronidazole, tinidazole
  - Cyst: iodoquinol, paromomycin, diloxanide furoate
Morphology: *E. histolytica*

Amebic Trophozoite

Wet mount stained with iodine

*E. histolytica* Trophozoites
Amebiasis – Key Concepts

- Transmitted – cysts ingested (fecal oral), sex
- Illness
  - Asymptomatic
  - Nonspecific diarrhea
  - Dysentery (pain, fever, blood, pus)
  - Spread – liver, pleural (lung), pericardium
- Diagnosis – cysts or trophs in stool, PCR, stool antigen, serology

Free Living Amoebae

- *Naegleria fowleri*
  - Encephalitis in healthy person
  - Acquire by swimming in brackish water
- *Acanthamoeba*
  - Encephalitis in immunocompromised
    - Unknown mechanism of transmission
  - Eye infections with trauma or contact lens
- *Balamuthia*
  - Soil-associated, rare encephalitis
  - Transmitted to organ recipients

Morphology – *Giardia lamblia*

Intestinal flagellate causes food, water and sexually
Transmitted diarrhea

- Trophozoite
  - Two nuclei
  - Four pairs of flagella
  - Sucking disc
- Cyst
  - Clear cyst wall
  - Four nuclei
  - Survives in cold water > 2 months
Epidemiology – *Giardia lamblia*

- Cosmopolitan
  - Contaminated food or water
    - Rural water: wells or municipal water
    - Recreational water
    - Reservoir – beavers, muskrats, sheep, cattle, dog, cat
  - Person to person
    - Day care
    - Sexual transmission

Giardia - Life Cycle

- Trophozoite
- Cysts
- Oral ingestion
- Stomach
- Intestines
- Life cycle begins
Giardia – Pathogenesis

• Attach to villi by sucking disc
• Malabsorption type of diarrhea
  – Fat
  – Carbohydrate
• Virulence mechanisms speculated
• Jejunal biopsy – flattening of microvilli and inflammation

Giardia: Clinical Manifestations

• Asymptomatic – 1/3 to 2/3
• Diarrhea – foul-smelling, bulky, can be watery, no blood
• Crampy abdominal pain
• Fever in about 20%
• May become chronic or relapse

Diagnosis and Treatment of Giardia

• Trophozoites and cysts shed intermittently in stool
  – See in stained or unstained preparations
• Three or more samples may be required
• Direct fluorescence antibody test
• Multiplex PCR
  – 2018 at LUMC – 25 cases in 10 months
• Treatment – tinidazole (2 gram single dose), nitazoxanide
  – Metronidazole now considered alternative
**Giardia lamblia** Direct Fluorescence

Stool specimen  Water specimen

**Giardiasis – Key Concepts**

- Transmitted - Water, food, person-person, sex
- Illness – malabsorption-type diarrhea, pain, fever
- Diagnosis – Cysts and trophs in stool

**Other Intestinal Protozoa**

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Source</th>
<th>Reservoir</th>
<th>Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balantidium coli</td>
<td>Ciliate</td>
<td>Water</td>
<td>Swine, monkeys</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Cystoispora belli</td>
<td>Coccidian</td>
<td>Food, water, person to person</td>
<td>Human</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Cyclospora cayetanensis</td>
<td>Coccidian</td>
<td>Water, food</td>
<td>Reptiles, birds, mammals</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Microsporidiosis</td>
<td>?</td>
<td>Many invertebrate and vertebrate hosts</td>
<td></td>
<td>Diarrhea, encephalitis, Eye infections</td>
</tr>
</tbody>
</table>

Outbreak of Cyclospora in July-August 2018 linked to Salads from fast-food chain in Midwest. 19 by PCR at LUMC
Morphology *Trichomonas vaginalis*

- Oval shaped
- Axostyle
- Four flagella
- Undulating membrane

*Trichomonas vaginalis*

Epidemiology *Trichomonas vaginalis*

- 3.7 million cases annually in the US
- Prevalence in developed countries
  - Up to 13% black women
  - 2-10% men
- Spread by sexual intercourse
- Non-venereal transmission is rare
Trichomonas: Pathogenesis and Clinical Manifestations

• Damages squamous mucosa of female genital tract
  – Neutrophilic inflammatory reaction
  – Petechial hemorrhages
• Virulence not defined
• Associated with preterm births
• Causes persistent vulvovaginitis
  – Frothy discharge, itching, burning, vaginal erythema
  – Associated with pelvic inflammatory disease (PID)
• 75% men asymptomatic but may cause urethritis, epididymitis or prostatitis

Diagnosis and Treatment of Trichomonas

• Diagnosis
  – Wet mount of vaginal discharge
    • See motile organisms (NEJM 2006; 355: 2797)
  – Urinalysis
  – These are being replaced by nucleic acid amplification tests – combined with GC and chlamydia
  – Culture – gold standard
• Treatment
  – Metronidazole
  – Tinidazole
  – Single dose therapy effective

Trichomonas vaginalis
Trichomonas – Key Concepts

- STI – very common
- Profuse vaginal discharge with itching
  - Associated with PID
- Urethritis, epididymitis, prostatitis in men
- Diagnosis
  - See motile protozoa on wet prep of vaginal discharge
  - NAAT
- Male partner infected - TREAT

Blood and Tissue Flagellates
Leishmania and Trypanosoma

- Life cycles
  - Definitive host – man
  - Intermediate host – insect
- Vectors
  - Sand fly (phlebotomus, Lutzomyia) - Leishmania
  - Tsetse fly (Glossina) - African trypanosomiasis
  - Triatomid bug – American trypanosomiasis
Amastigote: Intracellular form found in human

Promastigote: Extracellular form in Insect (Leishmania)

Epimastigote: Extracellular form in Insect (Trypanosoma)
Trypomastigote: Extracellular form in human and insect (Trypanosoma)

Morphology: Leishmania, Trypanosoma
- Amastigote
- Promastigote
- Epimastigote
- Trypomastigote

Introduction
Leishmania, Trypanosoma – Key Concepts
- Insect vector – fly or crawling bug
- Four recognized morphologies
  - Man
    - Intracellular amastigote (all Leishmania, T. cruzi)
    - Macrophages and circulating monocytes
    - Blood trypomastigote (T. brucei, T. cruzi)
  - Insect
    - Promastigote gut and mouth
    - Epimastigote gut and mouth
Leishmaniasis – Types

<table>
<thead>
<tr>
<th>Strain</th>
<th>Manifestation</th>
<th>Reservoir</th>
<th>Unique Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. tropica</td>
<td>Localized cutaneous (LCL)</td>
<td>Rural: rodents</td>
<td>Urban: dog Localized chronic ulcer</td>
</tr>
<tr>
<td>L. braziliensis</td>
<td>Mucocutaneous</td>
<td>Forest rodents</td>
<td>Metastatic to mouth, nose, perineum</td>
</tr>
<tr>
<td>L. donovani</td>
<td>Disseminated visceral Leish.</td>
<td>Africa, rodents Asia, L Am: dog India: human</td>
<td>Blood to liver, spleen, BM, LN, gut, skin</td>
</tr>
</tbody>
</table>

With molecular techniques, there are currently many species of Leishmania. Future taxonomy is uncertain.

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Disease</th>
<th>Geographic Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. donovani</td>
<td>Visceral (cutaneous)</td>
<td>Africa, Asia</td>
</tr>
<tr>
<td>L. infantum (L. chagasi)</td>
<td>Visceral</td>
<td>Africa, Mediterranean, America</td>
</tr>
<tr>
<td>L. tropica</td>
<td>Cutaneous</td>
<td>India, Middle East, Africa</td>
</tr>
<tr>
<td>L. major</td>
<td>Cutaneous</td>
<td>Middle East, Africa</td>
</tr>
<tr>
<td>L. mexicana</td>
<td>Cutaneous (diffuse, mucocutaneous)</td>
<td>Africa, Yemen</td>
</tr>
<tr>
<td>L. amazonensis</td>
<td>Cutaneous, mucocutaneous</td>
<td>Central America</td>
</tr>
<tr>
<td>L. braziliensis</td>
<td>Cutaneous</td>
<td>Cen, S. America</td>
</tr>
<tr>
<td>L. panamensis</td>
<td>Cutaneous</td>
<td>Cen, S. America</td>
</tr>
<tr>
<td>L. venezuelensis</td>
<td>Cutaneous</td>
<td>Venezuela</td>
</tr>
<tr>
<td>L. venezuelensis</td>
<td>Cutaneous</td>
<td>Venezuela</td>
</tr>
<tr>
<td>L. infantum</td>
<td>Cutaneous, mucocutaneous</td>
<td>Venezuela</td>
</tr>
<tr>
<td>L. leonine</td>
<td>Cutaneous</td>
<td>Brazil</td>
</tr>
<tr>
<td>L. amazonensis</td>
<td>Cutaneous (local, diffuse)</td>
<td>Brazil, Venezuela</td>
</tr>
<tr>
<td>L. mexicana</td>
<td>Cutaneous (local, diffuse)</td>
<td>Brazil, Venezuela</td>
</tr>
<tr>
<td>L. naiffi</td>
<td>Cutaneous</td>
<td>Brazil, Caribbean</td>
</tr>
<tr>
<td>L. pifanoi</td>
<td>Cutaneous (local, diffuse)</td>
<td>Brazil, Venezuela</td>
</tr>
<tr>
<td>L. amazoniensis</td>
<td>Cutaneous (local, diffuse)</td>
<td>Brazil, Venezuela</td>
</tr>
<tr>
<td>L. lainsone</td>
<td>Cutaneous</td>
<td>Brazil</td>
</tr>
<tr>
<td>L. venezuelensis</td>
<td>Cutaneous</td>
<td>Brazil, Venezuela</td>
</tr>
<tr>
<td>L. pifanoi</td>
<td>Cutaneous</td>
<td>Brazil, Venezuela</td>
</tr>
</tbody>
</table>

Current drug treatments based on PCR identification of species.

Leishmania – Life Cycle
Leishmaniasis: Pathogenesis

- Injected promastigotes opsonized with complement
- Taken up by macrophages; amastigotes multiply intracellularly
- Released to another cell or fly
- Controlled by CMI OR
- Immune failure - circulation and dissemination

Cutaneous Leishmaniasis: Clinical Manifestations

- Cutaneous
  - Papule - self limited ulcer
- Diffuse cutaneous
  - Multiple lesions
- Mucocutaneous
  - Local lesion enlarges or heals
  - Metastatic destructive lesions of face and perineum
Mucocutaneous Leishmaniasis

Disseminated (Visceral) Leishmaniasis: Clinical Manifestations
- 3 - 12 months after bite – fever
- Disseminates to liver, spleen, bone marrow, lymph nodes
- Diarrhea, lymphadenopathy, massive splenomegaly
- Anemia, leukopenia, thrombocytopenia, elevated IgG
- Progressive weakness, emaciation
- Untreated mortality - 75-90%
- Cutaneous Disseminated Leishmaniasis

Leishmaniasis: Diagnosis and Treatment
- Diagnosis
  - Localized
    - Biopsy, smear
    - Culture
    - Antigen detection
    - PCR accurate speciation
  - Visceral
    - Aspirates: bone marrow, spleen, liver, lymph node
    - PCR
    - Serology
- Treatment
  - Visceral
    - Lipo. amphotericin b
    - Antimony
    - Miltefosine
  - Cutaneous/Mucocutaneous (PCR based)
    - No Rx or topical for mild
    - Paromomycin/methylbenzethionium chloride
    - Pentavalent antimony
    - Ketoconazole
    - Fluconazole
    - Lipo amphotericin b
    - Miltefosine
Leishmaniasis – Key Concepts

- Many species with geographic differences
- Transmitted by flies
  - Promastigote → intracellular amastigote
- Illnesses
  - Chronic sore
  - Mucocutaneous (S. America)
  - Visceral – skin, liver, spleen, bone marrow, lymphnodes, gut.
    - Fever, weight loss, hepatosplenomegaly, ascites, pancytopenia, diarrhea
- Diagnosis – biopsy, culture, PCR, serology

African Trypanosomiasis

<table>
<thead>
<tr>
<th>Species</th>
<th>Geographic area</th>
<th>Reservoir</th>
<th>Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>T. brucei</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gambiense</td>
<td>Saharan W. Africa</td>
<td>Human</td>
<td>Glossina</td>
</tr>
<tr>
<td>(98% of cases)</td>
<td>DRC 90% of cases</td>
<td></td>
<td>(tsetse)</td>
</tr>
<tr>
<td><em>T. brucei</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rhodesiense</td>
<td>Savannas E. Africa</td>
<td>Antelope, domestic</td>
<td>Glossina</td>
</tr>
<tr>
<td>(limited range)</td>
<td></td>
<td>animals</td>
<td>(tsetse)</td>
</tr>
</tbody>
</table>

Species distinguished by biologic and genetic characteristics
African Trypanosomiasis – Life Cycle

- Fly ingests trypomastigotes which develop in midgut
- Migrate to salivary gland and become epimastigotes → infectious trypomastigotes
- Fly (painful bite) inoculates trypomastigotes which multiply locally and invade lymphatics and bloodstream → lymph nodes, heart and CNS
- Fly infected with blood meal

Life Cycle – African Trypanosomiasis

African Trypanosomiasis: Pathogenesis

- Change antigenic structure of surface glycoprotein
  - Mechanism involves switching silent to expressed genes
  - Immune evasion - re-emerge in blood
- Localize in endothelium – vasculitis in heart, CNS
  - Immune mediated?
- Hemorrhage, demyelination
African Trypanosomiasis: Clinical Manifestations

- First stage
  - Local chancre
  - Fever, rash, itching
  - Lymphadenopathy
    - Tbg – Posterior cervical node “Winterbottom sign”
    - Tbr – node depending on location of bite
- Second stage
  - Headache, impaired mentation
    - Tbg – slow progression to coma
    - Tbr – CHF, coma, death ≅ 1 year

African Trypanosomiasis: Diagnosis and Treatment

- Diagnosis
  - See trypomastigotes in smears form fluid expressed from lesions, blood or lymph node aspirate
  - Elevated IgM levels (screen)
  - Serology (Card agglutination test)
- Treatment
  - First stage
    - Tbg – pentamidine
    - Tbr – Suramin
  - Second stage
    - Tbg – Eflornithine with or without nifurtimox
    - Tbr – Melarsoprol

African Trypanosomiasis


CDC: DPDx
African Trypanosomiasis – Key Concepts

- Transmitted by Flies
- Epimastigotes in fly, trypomastigotes in man
- Illness
  - Local lesion (chancre)
  - Acute illness with fever
  - Encephalopathy
    - Rapid East
    - Slow West
- Diagnosis – blood smear, serology, PCR

American Trypanosomiasis

- Organism: Trypanosoma cruzi
- Geographic area: Central and South America
  - Present in Southern US but human disease rare because human habitat not supportive for vector and reservoirs not infected
- Reservoir: rat, cat, dog, opossum, armadillo
- Vector: Reduviid (triatomid) bug
- Epidemiology
  - 15-20 million infected; 50,000 deaths annually
  - Bug-cracks of mud walls and thatch

Trypanosoma Curzi – Life Cycle
Reduviid Bug

American Trypanosomiasis: Pathogenesis
- Chagoma - local inflammation
- Dissemination
  - Heart, muscle, sm. muscle, nerve
  - Adherence: Adhesin-penetrin, host fibronectin
  - Endocytosed, escape, multiplication, rupture, INFLAMMATION
  - Controlled by immune system
- Heart – affect blood vessels, muscle, conduction, nerve
  - Autoimmune mechanisms postulated
- GI tract – affect nerve, smooth muscle

American Trypanosomiasis: Clinical Manifestations
- Chagoma
- Acute - fever, rash, splenomegaly, lymphadenopathy, edema
- Chronic illness
  - Heart – 20-30% chronic infections
  - Megaesophagus
  - Megacolon
- AIDS – disseminated with CNS manifestations
American Trypanosomiasis: Diagnosis and Treatment

- Diagnosis
  - Blood smear – difficult to find after acute illness
  - Xenodiagnosis
  - Serology – sensitive/specific tests not available
    - Recommended by CDC
  - Gene amplification (PCR)

- Treatment
  - Nifurtimox
  - Benznidazole

CDC Parasite Image Library

T. Cruzi – Key Concepts

- Transmitted Reduviid bug feces
- Circulates (trypomastigote) and taken up in heart, muscle and nervous tissue (amastigote)
- Illness
  - Acute febrile
  - Chronic heart failure, arrhythmia
  - Megaesophagus and megacolon
- Diagnosis – blood smear, xenodiagnosis, serology, PCR
**Pneumocystis jiroveci (carinii)**

- Unsettled taxonomic position
  - Ribosomal RNA sequences like fungi
  - Other features like sporozoa
- Probably acquired via respiratory aerosol
  - Sporadic - activation of latent infection
  - Outbreak - possibly represent contagious spread

**Pneumocystis: Morphology**

- **Cysts** - 5-8 microns
  - Contain 2-8 sporozoites
- **Sporozoites** released with cyst rupture, combine and mature to form
- **Trophozoites** which again form cysts

**Life Cycle: Pneumocystis jiroveci**
Pneumocystis: Clinical Manifestations

- Interstitial pneumonia in immunocompromised
  - Fever
  - Dry cough
  - Severe dyspnea
- CXR Diffuse interstitial infiltrates
- Low oxygen level in blood

Pneumocystis carinii Pneumonia

Pneumocystis: Diagnosis and Treatment

- Diagnosis
  - Demonstration of organisms
    - Induced sputum
      - 50% yield
    - Bronchoalveolar lavage
    - Open lung biopsy
    - Silver stain
    - DFA

- Treatment
  - Trimethoprim/sulfamethoxazole
  - Pentamidine
  - Other medications effective and used

- Chemoprophylaxis
  - AIDS, transplant, other immunocompromised
  - Trimethoprim/sulfamethoxazole, others
Pneumocystis DFA

Pneumocystis in Lung

Pneumocystis – Key Concepts
- Fungus but like sporozoan
- Transmission Airborne, reactivates
- Clinical – Immunocompromised (AIDS, Transplant
  - Fever, cough, shortness of breath, hypoxemia
  - Interstitial pneumonia
- Diagnosis – See cysts in lung tissue and secretions
  - Silver stain, DFA
Thank you