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Make Your Own Assessment

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What do you need to learn for this course?

- Recognize the names of pathogens associated with characteristic diseases (Don’t memorize names or spellings)
- Remember the key features of the life cycles (i.e., how do the parasite get from one host to the next?)
- Remember the main mechanisms of disease (i.e., how does damage to the host occur?)
• “zoonosis”
• “enzootic” ~ “endemic”
• “epizootic ~ epidemic”
• “reservoir”
• “vector”
Protozoan (single-celled) parasites

Low branching protozoa (*Entamoeba*)

Kinetoplastids (African trypanosomes, *Leishmania*)

Apicomplexa (*Plasmodium, Toxoplasma*)

Fungus-like protozoa (*Microsporidia*)

Metazoan (multicellular) parasites

Nematode (Onchocerca or hookworm)

Trematode (*Schistosoma*)

Cestode (Tapeworm e.g., *Echinococcus*)
Parasites on the Tree of Life

- Metazoans
- Entamoeba*
- Microsporidia
- Apicomplexan
- Kinetoplastids
- Giardia

*low-branching eukaryote
Global Morbidity and Mortality from Parasitic Diseases

<table>
<thead>
<tr>
<th>Category</th>
<th>Name</th>
<th>Infections* (millions)</th>
<th>Disease* (millions)</th>
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*Annual

West Nile Virus  <0.5   <0.01   <0.3

Source Undetermined
New Trends in Emerging Infectious Diseases

Jones et. al., Nature Feb 2008
Factors influencing the geography of parasitic infections

- Local ecology
  - vectors
  - reservoirs (animal and human)
  - local habitats
- Local socioeconomic conditions
  - sanitation
  - exposure to vectors
  - untreated carriers
Protozoal Infections
Classification of protozoa

- **Entamoebae** (shapeless)
- **Flagellates**
- **Alveolates** (sub-membrane cytoskeleton confers a fixed shape)
- **Apicomplexa** (Sporozoa)
- **(Ciliates)**
Outline of protozoal diseases

- Intestinal protozoal infection
- Systemic protozoal infection
Outline of protozoal diseases

- **Intestinal protozoal infection**
  - Invasive (dysentery/bloodstream invasion)
    * Entamoeba histolytica
  - Non-invasive (watery diarrhea/weight loss)
    * Giardia lamblia (G. intestinalis)
    * Cryptosporidium and Cyclospora
    * microsporidia

- **Systemic protozoal infection**
Amebiasis

- **Entamoeba** - an enteric amoeba, i.e., not free-living.
- **histolytica** - human invasion by the parasite involves tissue lysis (histo-lytica)
E. histolytica - parasitic forms

Trophozoite
- Ingested RBC
- Single nucleus
- Pseudopod
- Purposeful ameboid movement

Mature Cyst
- 4 nuclei
- Thick wall
- 10-15 μm
Trophozoites in Ulcer with Ingested Red Blood Cells
Entamoeba histolytica -- life cycle

- Humans are the only reservoir excreting amoebic cysts
- Cysts resist environmental conditions
- Fecal-oral transmission (food, water)
- In response to gastric acid, ingested cysts release trophozoites in the upper intestine
- Trophozoites invade the large intestine and replicate by fission.
- Trophozoites that reach the lower colon encyst again.
Trophozoite in stool

Cyst in stool
Entamoeba histolytica -- pathogenesis

- Trophozoites disrupt mucus layer
- Key virulence factors:
  - amebic lectin: binds parasite to galactose-containing sugars on host cells
  - amoebapores: adherence-dependent cytolysis
  - cysteine protease: cleaves preIL-1β to IL-1β which triggers NF-kB and pro-inflammatory cytokines; also cleaves antibodies and C3
- Trophozoites ingest human cells
- Colonic ulceration
Risk Factors for Amebiasis in the United States

- Hispanic/Asian/Pacific Islanders - 50% of U.S. cases reported to CDC
- Travelers - 0.3% incidence in one study
- Institutions for mentally retarded
- Men who have sex with men
- Men - 90% amebic liver abscesses in men (male mice also more susceptible, in part because of lower IFNγ and fewer functional NKT cells)
Carbohydrate side-chains terminating in gal - galNAc (□)
1. Adherence
2. Lectin Signal
3. Cell killing
4. Phagocytosis and Invasion

Intestinal Lumen

Ameba
TUNEL Stain Demonstrates Apoptosis at Sites of Amebic Invasion of Mouse Colon
Histopathology of amebiasis

Classic Flask-Shaped Ulcers (side view)

Tissue Destruction in Amebic Colonic Ulcer
Amebiasis - clinical syndromes

- **Intestinal**
  - Ranges from asymptomatic to chronic diarrhea to amebic dysentery

- **Extraintestinal**
  - amebic liver abscess
  - other metastatic foci (e.g., brain)

Dx: identification of trophozoites or cysts in the stool, stool antigen tests, serology
Two microscopically indistinguishable *Entamoeba* sp.

- **E. histolytica**
  - invades tissues
  - should always be treated, even in asx patients

- **E. dispar**
  - is non-pathogenic, even in AIDS
  - should not be treated
The parasites in two locations are treated sequentially with two drugs:

- For invasive forms: metronidazole
- For luminal forms: diiodohydroxyquin, paromomycin, diloxanide furoate

Do not treat asymptomatic intestinal *E. dispar* infection
Giardiasis
• *G. lamblia* is a zoonosis (infected small mammals pass cysts and contaminate surface waters)
• Waterborne transmission is most common, but can also be spread person-to-person by young children (e.g., day-care centers)
• Ingested as cysts
• Excystation of the trophozoite and attachment to the mucosa occurs in the upper small intestine.
Trophozoites in duodenum

Cyst in stool
Giardia pathogenesis

- Parasites elicits localized hypersensitivity
- Intestinal villi become blunted
- Malabsorption develops
Dorsal “Suction Disc”

Ventral
Giardia - clinical features

- Acute, self-limited diarrhea
- Chronic diarrhea with malabsorption, steatorrhea, and weight loss
- Chronic asymptomatic cyst passage

Dx: stool antigen testing, stool examination, duodenal aspirate.
Giardiasis - treatment

- Metronidazole (or nitazoxanide)

Giardiasis - prevention

- Filtration of water
- Heating water to >50°C
- 2% iodine x 30 minutes
Generalizations about other intestinal protozoa (Cryptosporidium, Cyclospora, Microsporidia)

- All acquired by fecal-oral route
- All grow abundantly inside of mucosal cells
- All cause watery diarrhea, cramps, anorexia (not inflammatory) - pathogenesis uncertain
- All require special stains or examinations of stool for dx.
Cryptosporidium in tissue

Organisms attached to an intestinal villus

Intestinal organisms by scanning EM

Source Undetermined
Cryptosporidium parvum

• Associated with-
  – prolonged self-limited diarrhea in immunocompetent individuals
  – traveler’s diarrhea
  – chronic, unrelenting diarrhea in AIDS

• Usual acquired from
  – drinking water (e.g., Milwaukee, 1993)
  – swimming pools

• Relative chlorine resistance
Number of cryptosporidiosis cases, by date of onset, Delaware Co., Ohio, Jun–Sep 2000

- Relative risk of swimming at a private swim club = 42.3 (12.3–144.9)
- At least 5 fecal accidents witnessed
Cryptosporidium

Iodine stain of stool

Acid-fast stain of stool
Treatment of cryptosporidiosis

- Supportive (rehydration, antimotility agents)
- No FDA-approved rx
- Nitazoxanide?
Cyclospora

Source Undetermined
Cyclospora

- Food and waterborne transmission
  - 1996-97 outbreaks associated with Guatemalan raspberries shipped to U.S.
- Also replicates within mucosal cells
- Diarrhea may persist for 1-2 months without treatment
- Trimethoprim/sulfa x 7 days is effective therapy (unlike Cryptosporidium)
Microsporidia

- Primitive fungi that were initially thought to be protozoa
- Long recognized as animal pathogens
  - human cases in AIDS
  - recent human cases also seen in immunocompetent persons
- Hundreds of species identified
Ex, exospore
En, endospore
AD, anchoring disc
PT, polar tube
Sp, sporoplasm
Explosive Discharge of the Invasion Tube

- 4-30 coils depending on spp
- Stimulus varies depending on spp, can be pH shift, dehydration/rehydration, mucin, UV, etc
- Stimulus increases osmotic pressure, water influx
Outline of protozoal diseases

- Intestinal protozoal infection
- Systemic protozoal infection
Outline of protozoal diseases

- **Intestinal protozoal infection**
  - Malaria (*Plasmodium* sp.)
  - Babesiosis (*Babesia* sp.)
  - Toxoplasmosis (*T. gondii*)
  - Leishmaniasis
  - Others:
    - African trypanosomiasis (sleeping sickness)
    - American trypanosomiasis (Chagas’ disease)

- **Systemic protozoal infection**
  - (RBC infection and fever)
  - (Intracellular infections)
Toxoplasmosis
Toxoplasma Features

- Apicomplexan parasite (similar to Cryptosporidium, Cyclospora and Plasmodium)
Gliding Motility of Apicomplexa

Cary Engleberg

DanielCD, wikimedia commons
Entry of Apicomplexa into cells
• Cats infected by predation
• $10^7$ oocysts passed in feces
• Stable in soil/water for months
• Either indirect thru intermediate host or direct via food/water
• Vertical transmission during pregnancy

![Toxoplasmosis](https://www.cdc.gov/parasites/toxoplasmosis/images/pdf/Toxoplasmosis-fig5-2.pdf)

- Ingests cysts in raw or undercooked meat
- Contamination of food/water
- Both oocysts and tissue cysts transform into tachyzoites shortly after ingestion. Tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites. If a pregnant woman becomes infected, tachyzoites can infect the fetus via the bloodstream.
Toxoplasmosis - clinical syndromes

- acute acquired toxoplasmosis
- congenital toxoplasmosis
- ocular toxoplasmosis
- cerebral toxoplasmosis (AIDS)
congenital toxoplasmosis

- 30-40% transplacental if mother is infected during pregnancy
- 60% of infected newborns are asymptomatic (but later show chorioretinitis)
- Affected infants may have hydrocephalus, hepatosplenomegaly, jaundice, fever, anemia, pneumonia
Diagnosis of toxoplasmosis

• **direct identification is difficult**
• **culture is not routinely done**
• **serology**
  – IFA or ELISA
  – single high IgM or very high IgG level
  – seroconversion not reliable in AIDS
• **clinical features and response to rx**
Treatment of toxoplasmosis

When RX is indicated . . .

sulfadiazine + pyrimethamine*

OR

clindamycin + pyrimethamine*

* plus folinic acid
Malaria
Asexual replication

Exoerythrocytic cycle

- Sporozoites released from mosquito salivary glands invade hepatocytes within 30 mins.

- Infected cell releases sporozoites, which migrate to the salivary glands.

Erythrocytic cycle

- Male and female gametocytes
- Sporozoites released from mosquito salivary glands invade hepatocytes within 30 mins.
- Erythrocytic cycle
  - Merozoites released
  - RBC releases merozoites
  - Ruptured RBC releases merozoites
  - Trophozoite
  - Ring form
  - Schizont

Sexual replication

- Fertilization and invasion of mosquito gut
- Infected cell releases sporozoites, which migrate to the salivary glands.
Asexual stages

Exoerythrocytic cycle

Erythrocytic cycle

6-15 days

2-3 days
Sporozoites and hepatic schizont
## Plasmodium species

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>CYCLE</th>
<th>LATENCY</th>
<th>RECURRENCES</th>
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<td>no</td>
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<tr>
<td><em>P. vivax</em></td>
<td>48 hrs</td>
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<td>yes</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>48 hrs</td>
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<td>yes</td>
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<tr>
<td><em>P. malariae</em></td>
<td>72 hrs</td>
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Imported malaria cases, by species and interval between date of arrival and onset of illness — U.S., 1992

- P. falciparum
- P. ovale
- P. malariae
- P. vivax

<table>
<thead>
<tr>
<th>Species</th>
<th>&lt;1</th>
<th>1-2</th>
<th>3-5</th>
<th>6-12</th>
<th>&gt;12</th>
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<tbody>
<tr>
<td>No. of cases</td>
<td>76</td>
<td>226</td>
<td>60</td>
<td>180</td>
<td>140</td>
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Vernon Carruthers
Imported malaria cases, by year, 1973-2000, U.S.

~ 1/2 are imported from Africa

Source Undetermined
## Stable and unstable malaria transmission

<table>
<thead>
<tr>
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<th>“stable” continuous transmission</th>
<th>“unstable” epidemic malaria</th>
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<tbody>
<tr>
<td>Clinical disease</td>
<td>children</td>
<td>all ages</td>
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<tr>
<td>Mortality</td>
<td>children</td>
<td>all ages</td>
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<tr>
<td>Enl. Spleen rate (2-9 yrs)</td>
<td>&gt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Immunity among adults</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>Parasitism rate</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>
Malaria - clinical features

- paroxysms associated with synchronous release of merozoites from RBCs
  - Infected RBCs release substances that stimulate the release of TNF-$\alpha$ and IL-1 from host cells
  - rigorous chills, fever, myalgia, severe headache $\pm$ GI symptoms (5-6 hours)
  - profuse sweating and exhaustion (2-3 hours)
Malaria - clinical features

- immunologically-mediated hematologic changes
  - anemia
  - thrombocytopenia
  - leukopenia
Enhanced virulence of *P. falciparum*

- merozoites can enter RBCs of any age
- parasitemias reach very high levels
- adhesin proteins deployed on infected RBCs (trophozoites and schizonts)
  - attachment to venular endothelial cells (e.g., via ICAM-1)
  - reduced blood flow in small vessels --> microinfarction, hemorrhage
Adherent *P. falciparum* schizonts

Schizonts adhering to retinal blood vessels
Antimalarial treatment

• based on species and location acquired
  – chloroquine-sensitive species
    rx: chloroquine (blocks heme iron detoxification)
  – Chloroquine ® *P. falciparum*
    Rx (quinine + doxycycline) or Malarone®
• Add primaquine for *P. vivax* and *P. ovale*
Hemezoin Formation: Eating the Host From the Inside Out

- Hemoglobin 300 mg/ml inside RBC!

- Parasite digests hemoglobin for nutrients and to create room for growth

- Problem: Free heme is extremely toxic because generates oxygen radicals

- Solution: sequester in hemezoin crystals!

- Most malaria drugs interfere with hemezoin formation
Sequence of the creation of hemozoin in red cell removed
Based on what you have just learned, suggest three simple strategies to prevent the propagation of malaria.

1) _________________
2) _________________
3) _________________
Strategies to prevent malaria

1) mosquito control (insecticides, remove habitats)
2) mosquito protection (nets, screens, repellants)
3) mass treatment
   • vaccines (immunity is species and stage-specific)
   • release of genetically altered mosquitoes
Leishmaniasis
*Leishmania* are intracellular parasites that reside in macrophage phagolysosomes.
Chronic skin ulcerations with raised edges at site of sand fly bite.

(organisms do not survive well at 37°C, therefore, they don’t tend to disseminate)
*L. braziliensis* lasts longer and may recur later with destructive lesions in the nose and throat.
Visceral leishmaniasis - “Kala-azar”

- Infection of macrophages in the liver, spleen and lymph nodes
- Fever, malaise, weight loss, abdominal pain
- **Dx**: aspirate of bone marrow, spleen or liver; serology
- **Outcome**: 75-90% fatal if untreated (death 2º to bacterial pneumonia)
Additional Source Information
for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 7: Sandy Baldauf / Boris Striepen
Slide 8: Vernon Carruthers
Slide 9: Source Undetermined
Slide 10: Jones et. al., Nature Feb 2008
Slide 13: Source Undetermined
Slide 17: Cary Engleberg
Slide 18: William Petri
Slide 20: Source Undetermined
Slide 23: Cary Engleberg
Slide 24: William Petri
Slide 25: William Petri
Slide 26: William Petri
Slide 27: Source Undetermined
Slide 28: Source Undetermined
Slide 33: Vernon Carruthers
Slide 34: Sources Undetermined
Slide 36: Source Undetermined
Slide 40: Sources Undetermined
Slide 42: Center for Disease Control and Prevention, MMWR 2000; 50:406, http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5108a1.htm
Slide 43: Sources Undetermined
Slide 45: Source Undetermined
Slide 48: Louis Weiss
Slide 55: Cary Engleberg
Slide 56: Center for Disease Control and Prevention, Alexander J. da Silva, PhD / Melanie Moser, CDC PHIL #3421, http://www.cdc.gov
Slide 57: McGill University Department of Medicine, http://www.medicine.mcgill.ca/tropmed
Slide 60: Source Undetermined
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Slide 62: Sources Undetermined
Slide 63: Source Undetermined
Slide 67: Source Undetermined
Slide 68: Center for Disease Control and Prevention, James Gathany, CDC PHIL #7950 http://www.cdc.gov
Slide 69: Vernon Carruthers
Slide 70: Vernon Carruthers
Slide 71: McGill University Department of Medicine, http://www.medicine.mcgill.ca/tropmed (Both Images)
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Slide 74: Center for Disease Control and Prevention/ Steven Glenn, CDC PHIL #5941
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Slide 77: Source Undetermined
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Slide 84: Source Undetermined
Slide 86: Source Undetermined; Undetermined; Tulane University, http://www.tulane.edu/~wiser/malaria/B-heme.gif; Madame Curie Bioscience Database, http://www.landesbioscience.com/curie/
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