Chagas Disease, Human African Trypanosomiasis, and Hookworms

Alex Lankowski, Emma Noble, Andreas Pilarinos, John Prensner, and David Watkins

On behalf of the Universities Allied for Essential Medicines (UAEM) Neglected Diseases Working Group

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Learning Objectives

1. Describe basic aspects of the epidemiology, life cycle, and pathogenesis of Chagas disease, human African trypanosomiasis, and hookworm infection
2. Recognize the clinical presentation and natural history of each of these 3 infections
3. Understand the current diagnostics, therapeutics, and preventative measures that exist for each of these 3 infections
4. Discuss the barriers to control and global eradication of these 3 infections
Chagas Disease
(American Trypanosomiasis)
Etiology and Transmission

- Etiologic agent is *Trypanosoma cruzi*, a protozoan parasite in the family Kinetoplastidae
- Transmitted by several species of triatomine insects, primarily *Rhodnius prolixus* (north of the Amazon River), and *Triatoma infestans* (Southern Cone countries)

[Image of triatomine insect]
• Discovered by Dr. Carlos Chagas in 1909
  – While working on an anti-malaria campaign in a railroad camp, Dr. Chagas was introduced to the vector, known as “the Barber,” because it fed on the faces of its victims.
  – Dissection by Dr. Chagas led to the discovery of Trypanosoma cruzi, named after his mentor Oswaldo Cruz, in the hind-gut of the vector.
  – Dr. Chagas was then able to identify the parasite in the blood of a cat, followed by the owner of the cat, and linked it to similar symptoms he recognized in railroad workers.
16 to 18 million infected individuals worldwide

Endemic to most of Latin America and areas of the southern United States, with an infection rate of 1.4%

~ 25% of the Latin American population at risk of infection

*T. cruzi* may be transmitted transplacentally, via contaminated blood products, contaminated food and water as well as infected donor organs.

The contamination of blood products with *T. cruzi* has become an international problem.

Number of individuals infected in non-endemic countries:
USA (300,167), Spain (47,743), Japan (3592), Canada (1789), Australia (1392)

http://www.treatchagas.org/imagens/MapChagasJun09_large.jpg
Blood Donations (USA)

- Blood bank screening for T. cruzi established in January, 2007

- Currently, 75 – 90% of US blood donations screened for T. cruzi, (screening is voluntary)

- Enzyme-linked immunosorbent assay (ELISA) used for detection

- 14 million donations were screened in 16 month period (beginning January, 2007)
  - 1851 samples found repeatedly reactive (ELISA)
  - 519 of 1851 confirmed T. cruzi positive by radioimmunoprecipitation assay (RIPA)
**Life Cycle**

- *T. cruzi* metacyclic trypomastigotes (found in feces of the kissing bug) infect mammalian hosts via mucous membranes and skin lesions.
- Trypomastigotes become amastigotes once they infect cells; intracellular binary fission leads to the formation of pseudocysts.
- Eventually, host cell lyses and parasite is disseminated throughout blood and lymphatics.
- *T. cruzi* amastigotes preferentially infect reticuloendothelial, neural, epithelial, muscle cells (most commonly, cardiac myocytes) and adipocytes.
Acute Clinical Presentation

• The initial or acute stage is usually mild but can present with an array of nonspecific symptoms including:
  – Fever
  – Malaise
  – Generalized lymphadenopathy
  – Mild hepatosplenomegaly
• Abnormal cardiac findings are more prevalent in infected children and are associated with a worse prognosis
• Approximately 2-8% of infected children die from acute Chagas disease
• In most people, the acute symptoms resolve within 2-4 months

Typical appearance of an acute Chagas infection; painless periorbital edema occurs when the parasite enters via the conjunctiva
Intermediate/Chronic Presentation

- An infected individual can remain asymptomatic in the intermediate phase for many years
- 10-30% of people infected with *T. cruzi* develop chronic disease, characterized by heart failure, megaesophagus and/or megacolon
- Heart failure is the most common cause of death from chronic Chagas disease

* Please refer to supplemental notes for more details on clinical presentation
The presence of the *T. cruzi* parasite in the human host elicits both an innate and adaptive immune response. At the site of infection, there is immediate leukocyte infiltration and upregulation of inflammatory cytokines, chemokines, and leukocyte adhesion molecules. *T. cruzi* stimulates the production of extracellular matrix metalloproteases in the heart, which enable immune cells to pass through the extracellular matrix and into the tissue, where they cause inflammation.

Two hypothesis on the mechanism of immune-mediated tissue damage conferred by *T. cruzi*:

1. Chronic myocardial inflammation directly results from the presence of parasites in the tissue
2. *T. cruzi* parasite incites an autoimmune response in host; generation of autoantibodies and cytolytic T-lymphocytes leads to destruction of both infected and healthy host tissue.
1. Blood sample staining and examination
   - 35 – 50% sensitivity
   - Samples collected from presumably infected individuals, stained, and microscopically examined for trypomastigotes

2. Xenodiagnosis
   - >70% sensitivity
   - Healthy vectors are grown and allowed to feed on infected individuals
   - ~6 weeks later, hindgut or feces of vector are examined for presence of trypomastigotes

3. Antibody detection
   - 90% sensitivity
   - High concentrations of antibodies generated against T. cruzi.

4. PCR oligochromatography test
   - Highly sensitive (94%) and specific (100%)
   - Amplifies a satellite trypanosomal DNA sequence that is detected by a single-step molecular dipstick assay
   - Complex technique involved; has restricted use in diagnostic laboratories

Only 2 drugs are currently available for treatment (nifurtimox and benznidazole)

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<thead>
<tr>
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<th>Nifurtimox</th>
<th>Benznidazole</th>
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</table>
| Acute/congenital Infection: | • Reduces severity and duration  
• Decreases mortality with a 70% cure rate in acute infections | • Similar efficacy to Nifurtimox                   |
| Chronic infection:      | • ~20% cure rate                                                           | • ~60% cure rate                                  |
| Common side effects:    | • Nausea and vomiting  
• Abdominal pain  
• Weight loss  
• Paresthesia  
• Insomnia    | • Peripheral neuropathy  
• Rash  
• Granulocytopenia |

The treatment course with these drugs is at least 60 days, which poses significant challenges in terms of compliance and treatment success.

No evidence to support use of either drug for treatment of intermediate/chronic *T. cruzi* infection in adults.

*p*lease see supplementary notes for dosages
Prevention and Control

- Due to lack of treatments for Chagas disease, emphasis has been on vector control, mainly by use of insecticides on houses.
- Insecticide use has proven to be extremely effective; notable spraying initiatives include:

  **Southern Cone Initiative**
  - 1991: participating countries included Argentina, Bolivia, Brazil, Chile, Paraguay, Peru and Uruguay.

  **Andean and Central American Initiative**
  - 1997: participating countries included Columbia, Venezuela, Peru, Andean Ecuador, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, and Panama.

Spraying measures, along with more thorough bloodbank screening and early detection/treatment of congenital Chagas disease, have decreased infection rates.
Barriers and Needs

- Detection of intermediate/chronic Chagas disease
  - More prevalent and more difficult-to-detect stages, since vast majority of patients are asymptomatic
  - Detection of acute Chagas disease is key to effective treatment
  - Better diagnostics are needed to enable earlier detection

- Lag time between acute infection and presentation with chronic disease
  - Can be anywhere from 10-30 years
  - Poses great logistical challenges to developing rigorous clinical trails

- Assessing efficacy of treatments: conventional serological testing for *T. cruzi* can remain positive for >5 years after treatment is complete
Human African Trypanosomiasis (sleeping sickness)
Background

• Etiologic agent is a protozoan parasite in the family Kinetoplastidae:
  – *Trypanosoma brucei gambiense* (West African)
  – *Trypanosoma brucei rhodesiense* (East African)

• Transmitted by the tsetse fly, *Glossina spp.*
• 500,000 currently infected
• 1.5 million DALYs lost annually
• 60 million people at risk in 36 countries
• 50,000 to 70,000 estimated annual mortality (>90% *T. brucei gambiense*; <10% *T. brucei rhodesiense*)
• Localized to Sub-Saharan Africa
  – *gambiense* sub-species in NW
  – *rhodesiense* sub-species in SE

http://www.medecology.org/diseases/print_d_african_tryp.htm
Life Cycle

• In fly vector:
  – Procyclic trypomastigotes in midgut
  – Epimastigotes and metacyclic trypomastigotes in salivary gland

• In human host:
  – Trypomastigotes in blood, lymphatics, and CSF
  – No intracellular phase

• Early hemolymphatic stage → late meningoencephalitic stage
• Most infected individuals do not present to medical care until disease has progressed to meningoencephalitic stage
• Even if cured of the parasite, patients often suffer irreversible long-term neuropsychiatric deficits
• Vertical transmission can occur with either sub-species

http://www.finddiagnostics.org/programs/hat/find_activities

http://pathmicro.med.sc.edu/parasitology/sleep2.jpg
**Immunopathogenesis**

- Antigenic variation and immune evasion – Variable Surface Glycoprotein (VSG)
  - Waves of parasitemia
  - Challenge for vaccine development
- Translocation of trypanosomes across the blood-brain-barrier (BBB)
- CNS histopathology is mainly inflammatory (non-demyelinating), suggesting immune-mediated pathogenesis
  - Parasites rarely detected in brain parenchyma

Vincendeau and Boutteille 2006 (see notes)
Diagnosis

- Establish history of residence or travel within endemic zone, potential exposure to tsetse fly
- Clinical signs and symptoms are relatively non-specific, especially in the early hemolymphatic stage
- Direct light microscopy is current “gold standard”
  - specific but not sensitive
- Serologic: Card Agglutination Trypanosomiasis Test (CATT)
  - adequately sensitive and specific; good for screening
- Molecular methods: up to 96% sensitive
  - mainly experimental; need for field adaptation
- Pressing need for more sensitive and specific diagnostic tests which are feasible in rural settings
Current Treatments

- Treatments for early-stage (hemolymphatic):
  - Pentamidine – IM administration; adverse effects in 50%
  - Suramin – IV administration
  - Nifurtimox – oral administration

- Treatments for late-stage (meningoencephalitic):
  - Eflornithine – requires extensive IV dosing regimen
  - Melarsoprol – IV administration
    - Most effective medicine available for the treatment of meningoencephalitic stage
    - Post-treatment reactive encephalopathy (PTRE) in 10% of patients receiving therapy, half of whom die as a result
    - Emerging resistance (up to 50% resistance in some areas)

- Nifurtimox/Eflornithine Combination Therapy (NECT)
  - Lower toxicity, less frequent dosing, and shorter treatment regimen than eflornithine monotherapy
  - More amenable to delivery in resource-limited settings, although still requires twice daily IV dosing of eflornithine
Prevention and Control

• **Vector control**
  – Active surveillance of infected tsetse fly prevalence to inform vector control efforts
  – Insecticide application (aerial, terrestrial, cattle)
  – Baited fly traps
  – Sterile Insect Technique (SIT) relies on the release of laboratory-raised sterile male flies to compete with existing male fly populations

• **Permethrin-impregnated bed nets**

• **Avoidance of environmental locations of high tsetse fly density**

• **Currently no vaccine**
  – Due to both economic and scientific barriers
  – VSG is the primary immunogen, however there are >1000 different possible antigenic variants, making it a poor vaccine target
Barriers and Needs

- **Stigma and fear**
  - “If they catch you with the disease and you cannot pay for the treatment, they go accusing you by the state…, the state may even come to arrest you.”

- **Significant cost and access barriers to existing medications**
  - “Before they will treat [you], you need to have money, a lot of people die because of the money.”
  - individual interviewed by Robays et al, *ibid*.

- **Improved surveillance methods to minimize cost and labor while maximizing field feasibility and sensitivity**

- **More sensitive and field-adapted diagnostics**

- **Treatments which are more efficacious and less toxic for the treatment of both stages of infection**
  - Ideal drugs will penetrate blood-brain barrier, be orally bioavailable and heat-stable
Areas of Investigation & Progress

• Product Development Partnerships (PDPs) for diagnostics and therapeutics
  – Foundation for Innovative New Diagnostics (FIND): developing new serologic, molecular, and disease staging methods
  – Drugs for Neglected Diseases Initiative (DNDi): NECT added to WHO Essential Medicines List in 2009

• Re-purposing of anti-trypanosommal drug development
  – Synthesis of molecules based on drugs targeting human proteins with known trypanosommal homologues
Hookworms
Background and Epidemiology

- **Native**
  - *Necator americanus* and *Ancylostoma duodenale*

- **Zoonotic**
  - *Ancylostoma braziliense*, *Ancylostoma caninum* and *Uncinaria stenocephala*

- Both native and zoonotic forms enter human hosts through skin penetration
  - But only native species can enter the GI tract
  - Zoonotic species perish in human epidermis, hallmarked by the “creeping” eruption of cutaneous larva migrans

- An estimated 500-750 million native cases globally
- Comparatively few deaths (~65,000)
- 22 million disability-adjusted life years lost annually

Diemert et al. 2008
Humans are the definitive host for *N. americanus* and *A. duodenale*
- Rare cases in other mammals

Third-stage larvae (L3) penetrate human skin from the ground

Larvae enter lymphatic or circulatory system

Exit through the alveolae (lungs), and ascend bronchial tree to epiglottis where they are swallowed

Adult life spent in proximal small intestine

Eggs shed in feces
• Main symptoms occur when parasites access intestinal vessels
  – Iron-deficiency anemia
    • Please see slide 31
  – Malnutrition
    • Hypoalbuminemia → edema
    • May result in secondary cognitive defects in children
  – Wanaka Syndrome
    • Resulting from oral ingestion of worms
      – Cough
      – Esophageal itchiness
      – Hoarseness

• Cutaneous larva migrans is a hallmark of *A. braziliense* but not *A. duodenale* or *N. americanus*
Clinical Presentation: Anemia

- **Iron-deficiency anemia**
  - Hookworm parasites consume blood and iron
  - Insufficient iron results in an inability to deliver enough oxygen to tissues

- **Common symptoms**
  - Pale skin
  - Fatigue
  - Weakness
  - Dizziness/light-headedness
  - Cold extremities
  - Arrhythmia (if extreme anemia)

- **Severity of the anemia is proportional to the burden of infection**
Diagnosis

• Microscopy – definitive
  – Eggs seen in feces
  – Eggs of *N. americanus* and *A. duodenale* are similar morphologically
  – Number of eggs is proportional to the burden of infection

• Complete blood count
  – Microcytic RBCs (MCV < 76)
  – Eosinophilia (suggesting Th2 response)
Treatment and Prevention

- **Therapeutic Intervention**
  - Benzimidazole antihelmintics
    - Albendazole – most efficacious
    - Mebendazole – second-line
  - Pyrantel pamoate is also second-line
  - High single-dose cure rates; cheap (2 cents per dose)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Side Effects</th>
<th>Single-dose cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole</td>
<td>400mg</td>
<td>Prevents microtubule polymerization in worms</td>
<td>Generally well-tolerated, diarrhea and nausea in a small number of patients</td>
<td>72%</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>500mg</td>
<td>Blocks glucose uptake in worms</td>
<td>Well-tolerated, minor abdominal discomfort</td>
<td>15%</td>
</tr>
<tr>
<td>Pyrantel pamoate</td>
<td>10mg/kg</td>
<td>Depolarizing neuromuscular agent causing worm paralysis</td>
<td>Abdominal pain, nausea, dizziness in up to 50% of patients</td>
<td>31%</td>
</tr>
</tbody>
</table>

- **Prevention**
  - Increased sanitation and access to clean water
  - School “deworming”: yearly administration of drugs to children (high risk population for being infected)

Keiser et al. 2008
Treatment Challenges

• Variable cure rates of current therapeutics, especially with single-dose therapy
• High recurrence rate of infection after treatment, several treatments may be required per year
• Concern regarding development of drug resistance
• SANITATION – poor general public health and living conditions are a prime contributor
Goals for therapeutics research:

- Establish efficacy of drugs other than albendazole, mebendazole, pyrantel and levamisole
- Consider drugs and drug combinations that may be useful against multiple parasitic infections
- Monitor resistance in areas where mass drug administration has taken place

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Diseases targeted</th>
<th>Reduction in prevalence cited in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole plus diethylcarbamazine</td>
<td>Elephantiasis</td>
<td>16.7% to 5.3%</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>10.3% to 1.9%</td>
</tr>
<tr>
<td></td>
<td>Roundworm</td>
<td>34.5% to 2.3%</td>
</tr>
<tr>
<td></td>
<td>Whipworm</td>
<td>55.5% to 40.3%</td>
</tr>
<tr>
<td>Albendazole plus ivermectin</td>
<td>Elephantiasis</td>
<td>12.6% to 4.6%</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>7.8% to 0%</td>
</tr>
<tr>
<td></td>
<td>Roundworm</td>
<td>33.5% to 6.1%</td>
</tr>
<tr>
<td></td>
<td>Whipworm</td>
<td>42.7% to 8.9%</td>
</tr>
<tr>
<td>Levamisole plus mebendazole</td>
<td>Hookworm</td>
<td>94% to 71.8%</td>
</tr>
<tr>
<td></td>
<td>Roundworm</td>
<td>62% to 1.4%</td>
</tr>
<tr>
<td></td>
<td>Whipworm</td>
<td>93.1% to 74.5%</td>
</tr>
<tr>
<td>Pyrantel-oxantel</td>
<td>Hookworm</td>
<td>93.4% to 85.2%</td>
</tr>
<tr>
<td></td>
<td>Roundworm</td>
<td>22.8% to 1.4%</td>
</tr>
<tr>
<td></td>
<td>Whipworm</td>
<td>86.8% to 59.5%</td>
</tr>
<tr>
<td>Albendazole alone</td>
<td>Hookworm</td>
<td>8.1% to 1.3%</td>
</tr>
<tr>
<td></td>
<td>Roundworm</td>
<td>28.4% to 0.9%</td>
</tr>
<tr>
<td></td>
<td>Whipworm</td>
<td>51.9% to 31.9%</td>
</tr>
</tbody>
</table>

Reddy et al. 2007
A vaccine is desirable because of concerns about the sustainability of antihelmintic drug therapy.

Successful canine vaccine provides a good model and compelling evidence that a good human vaccine may be possible, despite complex immune evasion mechanisms of the pathogen.

A successful vaccine would:
- Reduce blood loss to a level below which clinical anemia develops.
- Reduce egg output, therefore interrupting transmission.
- Not necessarily induce an immune response that would kill the entire pathogen.
Human Hookworm Vaccine Initiative

- Led by the Sabin Vaccine Institute, HHVI is an international product development partnership with partners in the USA, Brazil, China, UK and Australia

- Two main antigens in hookworm biology have been identified as prime targets:
  - ASP-2, a protein secreted during host invasion
  - APR-1, an enzyme that helps digest hemoglobin

- Plans to combine at least 2 hookworm antigens in the final vaccine - one targeting the larval stage and another targeting the adult worm

http://sabin.org/vaccine-development/vaccines/hookworm
Vaccine Targets and Goals

- **Recombinant ASP-2 and APR-1 proteins**
  - ASP-2 is expressed exclusively by L3 hookworm larvae to facilitate host invasion
  - APR-1 is a hemoglobinase that helps hookworms digest blood

<table>
<thead>
<tr>
<th>Vaccine antigen</th>
<th>Stage of infection</th>
<th>Function</th>
<th>Possible mechanism</th>
<th>Intended effect</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASP-2</td>
<td>Larval</td>
<td>Chemotaxin mimic</td>
<td>Neutralizing Antibody</td>
<td>Attenuates larval migration through tissue</td>
<td>Phase 1</td>
</tr>
<tr>
<td>APR-1</td>
<td>Adult</td>
<td>Aspartic protease-hemoglobinase</td>
<td>Neutralizing Antibody</td>
<td>Blocks hemoglobinases lining parasite digestive tract</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Adapted from Diemer et al. 2008

- **Vaccine goals:**
  - Reduce blood loss to a level below which clinical anemia develops
  - Reduce egg output, therefore interrupting transmission → possibility for eradication

Loukas et al. 2006
Early development and testing of the hookworm vaccine has been possible because of the establishment of a product development partnership (PDP).

Manufacture of vaccine will be carried out in a public sector vaccine manufacturer in Brazil (Instituto Butantan), where the disease is endemic.

Barriers to access include:
- Development of field vaccination programs, possibly in association with mass drug administrations currently in place.
- Identifying mechanisms by which the Global Alliance for Vaccines and Immunization (GAVI) could accommodate these new vaccines.
Zoonotic Hookworms

- *Ancylostoma braziliense, Ancylostoma caninum* and *Uncinaria stenocephala*
  - Endemic in many resource-poor areas
    - Up to 10-15% of the population in Latin American countries
- Native host: dogs and cats
  - Up to 90% of dogs and 33% of cats harbor the parasite in certain urban areas in Latin America
- Frequently contracted by tourists traveling to tropical areas
- Life Cycle: identical to *Necator americanus* and *Ancylostoma duodenale* in dogs and cats
  - In humans third-stage larvae perish in the epidermis after penetrating the skin
    - A “creeping” eruption outlines the path of the hookworm in the skin

Heukelbach and Feldmeier 2008

Cutaneous larva migrans
Clinical presentation

- Itching
  - Begins within hours of a hookworm infection
  - Cutaneous larva migrans
    - Appears 3-7 days after infection

- Superinfections of hookworm lesions
  - 8-24% of infected patients
  - *Staphylococcus aureus* and streptococci most common

- Bullous lesions (10-15%)
  - Co-occur with cutaneous larva migrans
  - Pathophysiology unknown

Infection occurs on the feet (39%), the buttocks (18%), and the abdomen (16%)

- Infections are rarely serious
  - Superinfections may pose greater health consequences

Treatment

- Ivermectin (200ug/kg)
  - Single dose cure rates: 75-100%

- Oral albendazole
  - 400mg daily for 5-7 days
Quiz

• Now we invite you to take the module quiz and test your recent learning.
• This module quiz contains 15 questions covering the epidemiology, clinical presentation, pathogenesis, diagnostics, treatments, and prevention strategies for the infections discussed in the module.
• Note your answers on a separate piece of paper and then check them against the answers given after Question #15.
• After completing your quiz, come back for the summary of this module presentation.
1. High prevalence of Chagas' disease is seen in:

A  North America  
B  Europe  
C  Africa  
D  South America  
E  Southeast Asia

2. Trypanosoma cruzi is primarily transmitted by:

A  Rhodnius prolixus  
B  Triatoma infestans  
C  Anopheles mosquitoes  
D  A and B  
E  All of the above
3. The most serious clinical manifestation of chronic phase Chagas' disease is:

A  Kidney failure  
B  Heart failure  
C  Romana’s sign  
D  Megaesophagus

4. The following diagnostic method involves the inspection of a vector's hind gut after it is allowed to feed on a suspected Chagas' disease patient:

A  Blood sample staining  
B  Xenodiagnosis  
C  Antibody testing  
D  PCR oligochromatography
5. Which of the following statements about the treatment of Chagas disease is true?

A  Benznidizole has significantly greater efficacy than nifurtimox for treating acute Chagas disease
B  Treatment duration is 7-10 days
C  Granulocytosis is a common side effect of benznidazole
D  Nifurtimox is highly effective in treating chronic Chagas disease
E  Conventional serologic testing can remain positive for >5 years after treatment is complete

6. Two sub-species of Trypanosoma brucei are known to cause HAT – gambiense and rhodesiense. Which of the following is true regarding the differences between these two sub-species?

A  Gambiense accounts for a greater number of total annual infections and deaths than rhodesiense
B  Gambiense is localized to Southeast Asia, whereas rhodesiense is localized to Northwest Africa
C  Gambiense is transmitted by the tsetse fly, whereas rhodesiense is transmitted by the kissing bug
D  Gambiense infection causes a more rapid disease progression than rhodesiense, with death usually occurring within weeks to months of infection if untreated
7. Which of the following is a typical clinical manifestation of the meningoencephalitic stage of T.brucei infection?

A  Excessive nocturnal somnolence and daytime hyperactivity
B  Dilated cardiomyopathy
C  Brain hemorrhage
D  Psychiatric symptoms
E  Polyphagia

8. Which of the following is the most commonly used diagnostic test for HAT in routine screening?

A  PCR amplification of trypanosomal DNA from the CSF
B  Identification of tsetse fly DNA from chancre aspirate
C  Card Agglutination Trypanosomiasis Test (CATT)
D  Loop-mediated Isothermal Amplification (LAMP)
9. Which of the following adverse reactions is associated with melarsoprol therapy?

A  Disseminated intravascular coagulation (DIC)
B  Disulfiram-like reaction (DLR)
C  Post-treatment reactive encephalopathy (PTRE)
D  Acute myelogenous leukemia (AML)

10. Which of the following is a significant barrier to treatment for individuals affected by HAT?

A  There are currently no effective treatments
B  Lack of awareness of the disease in endemic areas
C  There is a long period of clinical latency (on average 10 years) between acute presentation and onset of neuropsychiatric symptoms
D  Most treatments have significant side effects and must be administered intravenously
11. Hookworm infections most commonly result from what scenario?

A  Swimming in infested waters  
B  Drinking contaminated water  
C  Infection of an open wound  
D  Contact of skin to infested soil

12. Which patient presentation(s) is/are most consistent with hookworm infection?

A  Hemolytic anemia, thrombocytopenia, purpura, renal failure  
B  Megaloblastic anemia, neurological symptoms  
C  Microcytic anemia, fatigue, weakness, and malnutrition  
D  Anemia accompanied by Howell-Jolly bodies, jaundice, and vaso-occlusive crises  
E  B and C
13. Definitive diagnosis of hookworm is achieved by:

A  Microscopy on patient fecal samples  
B  Blood cultures  
C  CBC with differential  
D  Clinical symptoms

14. The preferred treatment for hookworm infection is:

A  A single dose of triclabendazole  
B  A single dose of albendazole  
C  Vancomycin IV for 10-14 days  
D  Praziquantel
15. The Human Hookworm Vaccine initiative aims to develop antibodies against which of the following hookworm processes?

A  Larval maturation in the gastrointestinal tract
B  Adult hookworm reproduction
C  Larval migration through host tissue
D  Adult digestion of hemoglobin
E  C and D
And now for the answers to the questions
1. High prevalence of Chagas' disease is seen in:

D  South America -- Correct -- 18 million people are infected worldwide, the vast majority of which are located in Latin America; 25% of the Latin American population are believed to be at risk of infection.

2. Trypanosoma cruzi is primarily transmitted by:

A  Rhodnius prolixus
B  Triatoma infestans
C  Anopheles mosquitoes
D  A and B -- Correct -- Only Rhodnius and Triatoma transmit trypanosomes; Anopheles mosquitoes transmit Plasmodium spp. and are responsible for malaria rather than Chagas disease.
E  All of the above
3. The most serious clinical manifestation of chronic phase Chagas' disease is:

A  Kidney failure  Incorrect -- Chagas disease is not associated with kidney failure.
B  Heart failure  Correct -- Chronic Chagasic cardiomyopathy resulting in congestive heart failure is the most serious and life-threatening manifestation of chronic Chagas disease.
C  Romana's sign  Incorrect -- Romana's sign is the name given to the painless periorbital edema typical of acute (not chronic) Chagas infection; this occurs when the parasite enters via the conjunctiva.
D  Megaesophagus  Incorrect -- Although megaesophagus is debilitating and is indeed seen frequently in chronic Chagas disease, it is generally not fatal; heart failure is the most serious life-threatening manifestation.

4. The following diagnostic method involves the inspection of a vector's hind gut after it is allowed to feed on a suspected Chagas' disease patient:

A  Blood sample staining  Incorrect -- Blood sample staining does not require the use of vectors.
B  Xenodiagnosis  Correct -- Xenodiagnosis involves detection of trypomastigotes in the hindgut of a vector; this technique takes up to 6 weeks and is about 70% sensitive.
C  Antibody testing  Incorrect -- Antibody testing involves measuring levels of T. cruzi specific antibodies in the patient’s blood.
D  PCR oligochromatography  Incorrect -- PCR oligochromatography is a molecular diagnostic method and does not require the use of vectors.
5. Which of the following statements about the treatment of Chagas disease is true?

A  Benznidazole has significantly greater efficacy than nifurtimox for treating acute Chagas disease -- Incorrect -- Both drugs are equally effective in treating acute Chagas disease; benznidazole is more effective than nifurtimox (60% vs 20%) in treating chronic Chagas disease.

B  Treatment duration is 7-10 days -- Incorrect -- Treatment duration is >60 days, and associated side effects make it difficult for patients to adhere to Chagas therapy regimens.

C  Granulocytosis is a common side effect of benznidazole -- Incorrect -- Granulocytopenia, not granulocytosis, is a common side effect of benznidazole. Rash and peripheral neuropathy are also common side effects of this medication.

D  Nifurtimox is highly effective in treating chronic Chagas disease -- Incorrect -- Nifurtimox has only a 20% cure rate for chronic Chagas disease; benznidazole is somewhat more effective (60% cure rate).

E  Conventional serologic testing can remain positive for >5 years after treatment is complete -- Correct -- Persistently positive antibody testing makes it difficult to ensure a cure after a standard course of therapy.
6. Two sub-species of Trypanosoma brucei are known to cause HAT – gambiense and rhodesiense. Which of the following is true regarding the differences between these two sub-species?

A  Gambiense accounts for a greater number of total annual infections and deaths than rhodesiense  --  Correct -- Gambiense account for >90% of HAT cases.
B  Gambiense is localized to Southeast Asia, whereas rhodesiense is localized to Northwest Africa  --  Incorrect -- Gambiense is actually localized to NW Africa, and rhodesiense is localized to SE Africa.
C  Gambiense is transmitted by the tsetse fly, whereas rhodesiense is transmitted by the kissing bug  --  Incorrect -- Both sub-species are transmitted by the tsetse fly. The kissing bug is endemic to Central and South America, and is responsible for the transmission of T. cruzi (Chagas disease).
D  Gambiense infection causes a more rapid disease progression than rhodesiense, with death usually occurring within weeks to months of infection if untreated  --  Incorrect -- Rhodesiense is characterized by a more rapid disease progression than gambiense.
7. Which of the following is a typical clinical manifestation of the meningoencephalitic stage of T.brucei infection?

A. Excessive nocturnal somnolence and daytime hyperactivity — Incorrect — Although HAT is associated with disturbances in the normal sleep-wake cycle, the typical pattern is daytime somnolence and nocturnal insomnia.

B. Dilated cardiomyopathy — Incorrect — Although on rare occasions T.brucei infection can cause cardiovascular morbidity, dilated cardiomyopathy is not a typical manifestation (this is, however, a common manifestation of chronic Chagas disease).

C. Brain hemorrhage — Incorrect — Although meningoencephalitic infection affects the brain, hemorrhage is not generally associated with this disease.

D. Psychiatric symptoms — Correct — Psychiatric symptoms are a common manifestation, and contribute to the stigma associated with HAT.

E. Polyphagia — Incorrect — The opposite is true: anorexia, not polyphagia, is a common manifestation of meningoencephalitic disease.
8. Which of the following is the most commonly used diagnostic test for HAT in routine screening?

A  PCR amplification of trypanosomal DNA from the CSF -- Incorrect -- This is not a routine test and is not yet amenable to resource-limited settings.
B  Identification of tsetse fly DNA from chancre aspirate -- Incorrect -- Tsetse flies are only a vector – they do not invade host tissue or play a role in disease pathogenesis.
C  Card Agglutination Trypanosomiasis Test (CATT) -- Correct -- This is a common test which can be done relatively easily in resource-limited settings.
D  Loop-mediated Isothermal Amplification (LAMP) -- Incorrect -- This testing modality, though promising, is still experimental.
9. Which of the following adverse reactions is associated with melarsoprol therapy?

A  Disseminated intravascular coagulation (DIC)  Incorrect -- DIC is not associated with melarsoprol; post-treatment reactive encephalopathy, however, occurs in 10% of treated patients, half of whom die as a result.

B  Disulfiram-like reaction (DLR)  Incorrect -- A disulfiram-like reaction is not associated with melarsoprol; post-treatment reactive encephalopathy, however, occurs in 10% of treated patients, half of whom die as a result.

C  Post-treatment reactive encephalopathy (PTRE)  Correct -- PTRE occurs in 10% of patients treated with melarsoprol, half of whom die as a result.

D  Acute myelogenous leukemia (AML)  Incorrect -- Leukemia is not associated with melarsoprol therapy. Post-treatment reactive encephalopathy, however, occurs in 10% of treated patients, half of whom die as a result.
10. Which of the following is a significant barrier to treatment for individuals affected by HAT?

A  There are currently no effective treatments -- Incorrect -- Although most of the available medications are difficult to administer in resource-limited settings and have significant toxicity, there are several effective medications for the treatment of HAT, including melarsoprol, eflornithine, pentamidine, and suramin.

B  Lack of awareness of the disease in endemic areas -- Incorrect -- Generally, there is a high level of awareness of HAT in populations inhabiting disease endemic areas.

C  There is a long period of clinical latency (on average 10 years) between acute presentation and onset of neuropsychiatric symptoms -- Incorrect -- There is no significant period of clinical latency in HAT.

D  Most treatments have significant side effects and must be administered intravenously -- Correct -- This statement is true; novel therapeutics for HAT are desperately needed.
11. Hookworm infections most commonly result from what scenario?

A  Swimming in infested waters  Incorrect -- One example of a parasitic infection that is transmitted by swimming in infested water is schistosomiasis.
B  Drinking contaminated water  -- Incorrect -- One parasitic infection which is transmitted by drinking contaminated water is ascariasis (roundworm).
C  Infection of an open wound -- Incorrect --
D  Contact of skin to infested soil  -- Correct -- Both native and zoonotic hookworms enter the host through the skin, when the host steps in infested soil. Another parasitic infection that is also transmitted in this manner is strongyloidiasis.

12. Which patient presentation(s) is/are most consistent with hookworm infection?

A  Hemolytic anemia, thrombocytopenia, purpura, renal failure -- Incorrect -- This is the classic presentation of thrombotic thrombocytopenic purpura, not hookworm infection.
B  Megaloblastic anemia, neurological symptoms -- Incorrect -- This is a common presentation of vitamin B12 deficiency secondary to fish tapeworm (Diphyllobothrium latum) infection, not hookworm infection.
C  Microcytic anemia, fatigue, weakness, and malnutrition -- Correct -- Hookworms feed on the blood of infected hosts resulting in iron deficiency which leads to microcytic anemia. Symptoms of fatigue and weakness can be attributed to this anemia and to the general malnutrition caused by hookworm infection.
D  Anemia accompanied by Howell-Jolly bodies, jaundice, and vaso-occlusive crises -- Incorrect -- This is a common presentation of sickle cell crisis, not hookworm infection. Howell-Jolly bodies are found in asplenic patients, including those with sickle cell disease whose spleens have completely infarcted.
E  B and C -- Incorrect -- While C represents the typical presentation of hookworm infection, B is more consistent with vitamin B12 deficiency secondary to fish tapeworm (Diphyllobothrium latum) infection.
13. Definitive diagnosis of hookworm is achieved by

A Microscopy on patient fecal samples -- Correct -- Confirmation of hookworm infection is achieved definitively by inspection of hookworm eggs in the feces.

B Blood cultures -- Incorrect -- Parasitemia is not a part of the hookworm life cycle; blood cultures are therefore of limited diagnostic utility.

C CBC with differential -- Incorrect -- While complete blood count showing anemia and/or eosinophilia is suggestive of hookworm infection, definitive diagnosis is achieved by inspection of hookworm eggs in the feces.

D Clinical symptoms -- Incorrect -- Clinical symptoms of hookworm infection are non-specific; confirmation of parasite infection is achieved definitively by inspection of hookworm eggs in the feces.
14. The preferred treatment for hookworm infection is:

A  A single dose of triclabendazole -- Incorrect -- Albendazole, not triclabendazole, is the first-line benzimidazole for hookworm infection.
B  A single dose of albendazole -- Correct -- Single-dose albendazole is the preferred first-line therapy for hookworm infection.
C  Vancomycin IV for 10-14 days -- Incorrect -- Vancomycin is not appropriate for treatment of parasites; single-dose albendazole is the first-line therapy for hookworm infection.
D  Praziquantel -- Incorrect -- Praziquantel is indicated for parasitic infections such as schistosomiasis, but not for hookworm infection. Single-dose albendazole is the first-line therapy for hookworm infection.
15. The Human Hookworm Vaccine initiative aims to develop antibodies against which of the following hookworm processes?

A  Larval maturation in the gastrointestinal tract -- Incorrect -- ASP-2 is expressed by hookworm larvae and facilitates invasion of the host; APR-1 is a hemoglobinase that enables adult worms to digest of blood. Both are targets of the HHVI.

B  Adult hookworm reproduction -- Incorrect -- APR-1 is a hemoglobinase that enables adult worms to digest of blood; ASP-2 is expressed by hookworm larvae and facilitates invasion of the host. Both are targets of the HHVI.

C  Larval migration through host tissue -- Incorrect -- ASP-2 is expressed by hookworm larvae and facilitates invasion of the host; APR-1 is a hemoglobinase that enables adult worms to digest of blood. Both are targets of the HHVI.

D  Adult digestion of hemoglobin -- Incorrect -- APR-1 is a hemoglobinase that enables adult worms to digest of blood; ASP-2 is expressed by hookworm larvae and facilitates invasion of the host. Both are targets of the HHVI.

E  C and D -- Correct -- APR-1 is a hemoglobinase that enables adult worms to digest of blood; ASP-2 is expressed by hookworm larvae and facilitates invasion of the host. Both are targets of the HHVI.
Neglected Diseases and the Research Innovation Gap

- The “90/10 Gap”: Only an estimated 10% of global annual R+D funding is spent on diseases which constitute 90% of the global disease burden.
- Neglected tropical diseases (NTDs) like Chagas, Hookworm, and HAT suffer from lack of adequate R+D funding.
- Need for rapid increase in funding for NTDs to more equitably address global disease burden.
- Most populations affected by NTDs lack the political power to advocate on their own behalf for enhanced R+D.
What Can We Do?

- Advocate for funding agencies, such as the NIH, to increase grants and other incentives for research on NTDs
- Raise awareness in our communities or academic institutions about NTDs and the disparities that currently exist between funding and global disease burden
- Facilitate interactions and collaboration between/amongst NTD researchers and NGOs such as DNDi, FIND, Global Network for NTDs
Credits

• Alex Lankowski is an MD candidate (c/o 2012) at Boston University School of Medicine
• Emma Noble is an MD candidate (c/o 2012) at the University of British Columbia
• Andreas Pilarinos is a health science student (c/o 2012) at Simon Fraser University
• John Prensner is an MD-PhD candidate (c/o 2014) at the University of Michigan
• David Watkins is an MD candidate (c/o 2010) at Duke University School of Medicine

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