Helminths (Parasitic worms)

Kingdom Animalia

Phylum Platyhelminthes

Trichurida

Ascaridida

Rhabditida

Strongylida

Spirurida

Phylum Nematoda

Trichuris trichuria

- AKA: Whipworm - posterior end
- Definitive Host: Humans, pigs and monkeys
- Intermediate Host: None
- Geographic distribution: Approx 800 million infections/year Cosmopolitan, including southern U.S.
  - Warm Climate
  - High rainfall
  - Unsanitary conditions
  - Use of nightsoil as fertilizer
  - Geophagy

Trichuris trichuria

- Location: large intestine from cecum and appendix to rectum
  - Burrows head into mucosa
- Transmission: Ingestion of embryonated eggs, usually in contaminated food
  - Requires high humidity, warm climate and shade to develop properly.
**Trichuris trichuria Life Cycle**

- Eggs embryonate in soil (~21 days)

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**Pathology and Symptoms:**
- Low-level infections (<100 worms) are asymptomatic.
- Large infections can result in diarrhea, bloody stool, abdominal pain, and rectal prolapse.
- Prolonged infection in children may cause developmental retardation.
- Often associated with *Ascaris lumbricoides* infections.
- Mode of transmission same.

**Treatment:** Mebendazole or albendazole.

**Rectal prolapse**

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**Diagnosis:** Bipolar eggs in feces. Colonoscopy can also uncover worm infections.

- Females may lay 3,000 to 20,000 eggs a day for many years.
- There are 60-70 species in this genus; all live in large intestine.
  - *T. felis* – cats
  - *T. discolor* – cattle
  - *T. leptons* – rabbits
  - *T. mus* – rodents
  - *T. ovis* – sheep
  - *T. vulpis* – canids
  - Occasionally infects humans
  - *T. suis* – pigs
The Hygiene Hypothesis

- There has been a considerable increase in the diagnosis of autoimmune diseases and allergies over the second half of the 20th century.
- Prevalence of allergies in urban areas appears higher than in rural environments.
- Environmental factors like pollution, nutrition etc. can be important for specific allergies but have shown little consistent overall association with allergies and autoimmunity.
- Childhood infections though show strong negative correlation with both autoimmune disease and allergies.

The Hygiene Hypothesis: Treatment by worm infection?

- Several clinical trials using Trichuris suis have been conducted to treat human Crohn’s disease or ulcerative colitis (autoimmune inflammation of the intestine).
- T. suis does not productively infect humans yet modulates the immune response.
- Most studies show clinical improvement for a significant fraction of the patients.

One example (double blind study with 54 patients suffering from acute ulcerative colitis): The patients received either a placebo or 2000 T. suis ova every 2 weeks for 12 weeks.

- 43.3% of the patients given T. suis improved compared with those given placebo (16.7%).
- Also a 12 week crossover limb: patients originally on placebo where switched to T. suis and those on T. suis were switched to placebo.
- In the crossover limb, 56.3% of the patients given T. suis improved compared with 13.3% of patients given placebo.

(See Elliott et al. (2007), International Journal for Parasitology 37: 457-464 for detail)

Don’t try this at home!
**Trichinella spiralis**

- **Hosts:** swine, rats, humans, bear, walrus, and other carnivores.
  - Individual is the D.H. for the adults and I.H. for larvae.
- **Geographic Distribution:** Cosmopolitan. More common in temperate areas than tropics.
  - There are at least seven sibling species and at least 3 strains
  - Different hosts, ribosomal DNA, gene sequences, and allozymes
  - Look identical

**Trichinella spiralis**

- **Location:** Adults in wall of small intestine. Larvae in striated muscles and organs.
  - Favorite are eye, tongue and masticatory muscles
  - Then diaphragm and intercostal
  - Heavy muscles of arms and legs
  - Why they prefer certain muscles is unclear
- **Transmission:** Ingestion of larvae in under cooked meat.

**Trichinella spiralis Life Cycle**

- **Factoid:** more female than male larvae (2:1).
  - Males mate multiple times in the small intestine.
Domestic infection through pigs has become rare in the US and Europe.

Meat control, rat control, prompt removal of dead animals, limit access of wildlife to pigs.

Almost all cases now are sylvatic transmission from game.

You want your bear or walrus inspected before consumption.

And you always want your bear-burger well-done!

Disease is trichinosis

A.K.A. Trichiniasis or trichinellosis

The Great Mimic

Mimics many other conditions

Rarely exhibits a set of symptoms

Symptoms depend on location, number and age of larval worms

Most cases are asymptomatic

Initial phase: flu-like symptom

Caused by females penetrating mucosa

As worms mature, symptoms may include nausea, vomiting, sweating and diarrhea for five to seven days.

Body’s reaction to worm waste
Trichinella spiralis

- Migration of larva causes many symptoms
  - Including pneumonia, pleurisy, encephalitis, meningitis, nephritis, deafness, peritonitis, brain and eye damage, muscle stiffness, weak pulse, difficulty breathing, hallucinations
- Death is rare
  - Usually due to inflammation of heart muscle, respiratory complications or kidney malfunction

Trichinella spiralis

- Diagnosis: Antigenic and serological tests, muscle biopsy plus case history.
- Treatment: No effective treatment.
  - Thiabendazole has worked in experimental animals but results in human mixed
  - Steroids reduce inflammation
  - Bed rest and analgesics help relieve pain and discomfort
- Prevention: Cook meat well,
  - Most U.S. cases are from undercooked pork!
  - Includes processed meats, chops, sausages, ham, etc.
  - Can also occur in bears, walrus, fox, etc.
  - Rarely occurs in cattle and horses
    - How they get it is unknown
  - Can survive freezing down to ~15°C

Trichinella spiralis

- Largest intracellular parasite
- Larvae invade a muscle cell and converts it into a nurse cell
  - Alters the metabolism of the cell to do what it wants
  - Alters gene expression so it doesn’t make contractile proteins
  - Releases Vascular endothelial growth factor (VEGF)
    - Stimulates formation of capillaries around cell
  - Nurse cell secretes collagen coating
  - Don’t understand how worm does it
  - Eventually the body walls off the nurse cell by calcifying the walls
  - Immune system will eventually kill the larvae
    - But they can live over 30 years
Nurse Cells

- Vasculature is similar to liver sinusoids
  - Flattened wider vessels
  - Highly permeable
  - Similar to venules (deoxygenated blood)
- Hormones serum proteins - rapid inflow of nutrients and outflow of rates
- Setting up its own anaerobic niche
- Nurse cell can survive several days after the host has died.

Larval Invasion

1. Larvae possess a sword-like stylet

Nurse Cell Formation

- Major Phase I
  - De-differentiation
    - 2 days of little larval growth
    - Host cell becomes disorganized
    - Actin and myosin filaments become disorganized
    - Host cell mitochondria become vacuolated
    - ATP synthesis diminished
    - Nuclear enlargement
    - Multiple nuclear DNA replication and divisions
    - Correlated with larval secretions

Down regulation of Myogenic Program
Nurse Cell Formation - Early Events

- Muscle cell de-differentiation
- Mitochondrial damage
- Tyvelosylated protein secretion

Tyvelose modification

- Dideoxy sugar usually found in bacterial lipopolysaccharides
- Many of the Trichinella excreted larval proteins are glycosylated with tyvelose
- Immunodominant portion of major larval antigens
- However, tyvelose component alone does not provide protection - much more complicated

Nurse Cell Formation

- Major Phase II
  - Re-differentiation
    - Continued larval growth
    - Continued larval secretions
    - Mononuclear cell invasion
    - Collagen capsule formation
    - Type IV collagen synthesis
    - Type VI collagen synthesis
    - Angiogenesis - formation of circulatory rete
      - Induction of vascular endothelial growth factor
**Nurse Cell Formation - Later Events**

- Collagen synthesis
- Circulatory role
- Angiogenesis

**Helminths (Parasitic worms)**

- Kingdom Animalia
- Phylum Platyhelminthes
- Phylum Nematoda
- Trichurida
- Ascandida
- Rhabditida
- Strongylida
- Spirurida
- Strongyloides
- Many different species (~38)
  - S. stercoralis and S. fuelleborni in humans and primates
  - S. westeri in horses
  - S. ratti in rats
  - S. ransomi in swine
  - Many other species parasitize birds, reptiles, and amphibians
- Little development of head or tail structures
- These organisms bridge a gap between free-living and parasitic life styles

**Strongyloides sp.**

- Small worms: ~2-9 mm

- Many different species (~38)
  - S. stercoralis and S. fuelleborni in humans and primates
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  - Many other species parasitize birds, reptiles, and amphibians
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**Strongyloides stercoralis**

- **AKA:** Threadworm
- **Definitive Host:** HUMANS, mammals
- **Intermediate Host:** None
- **Geographic distribution:**
  - Cosmopolitan, including U.S.
  - Endemic in tropics & subtropics
  - Appalachia and rural southeast U.S.
  - Highest prevalence in warm, moist climates
  - Unsanitary conditions

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**Strongyloides stercoralis**

- Free-living stages mixed with parasitic stages:
  - Random mix
  - Free-living worms are male or female
  - Parasitic worms are all parthenogenic females (no fertilization)
  - No sperm has been found in parasitic forms
  - Free-living stages are important reservoirs for the parasitic stage
- 2 larval forms
  - rhabditiform - non-infective, feeding form
  - filariform - non-feeding, infective form

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**Strongyloides stercoralis**

- Ability to autoinfect and invade nearly any organ (also CNS)
- Worms may live in body for 40 years replicating via parthenogenesis
- 4 major routes of infection - depend on conditions, nutrients
  - A. Skin penetrating L3 filariform larvae
  - B. Autoinfection (only 2 molts)
  - C. Free-living sexual cycle (only 1X)
  - D. Direct host-soil-host cycle (2 molts)
**Strongyloides stercoralis Life Cycle**

- **L3**
- **Non-infective**
  - A: Only parasitic females
  - B: Filariform larva
  - Migrate via circulation to lungs

**Strongyloides stercoralis**

- Rarely penetrate deeper than intestinal mucosa - mainly asymptomatic
- Hyperinfection (disseminated) especially in immunocompromised (steroid treatment, burns, lymphomas)
- Large numbers of filariform larvae in intestine
- Larvae migrate, e.g., heart, liver, CNS
- Causes fulminating, fatal infection
- Death due to respiratory failure