intestinal protozoa

Giardia, Cryptosporidium, Entamoeba histolytica
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2. *Giardia*
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Frequently found intestinal protozoa

- *Giardia lamblia*
- *Cryptosporidium spp*
- *Entamoeba histolytica/dispar*
Clinical presentation *Giardia lamblia*

Intermittent diarrhoea

- Flatulence
- Smelly diarrhoea
- Sticky
  - A toilet brush is needed!
- Bloating
- Fatigue
Clinical presentation *Giardia*:

- Can become chronic

- Malabsorption of fat and fat-soluble vitamins.
  - Frequency?

- Mucosal damage and villous atrophy
  - Frequency?

- Failure to thrive in young children
  - Frequency?

- Extra intestinal symptoms
  - Arthritis
  - Urticaria
  - Eosinophilia
Giardia outbreak Bergen 2004

Hanevik K, Wensaas KA, Rortveit G, Eide GE, Mørch K, Langeland N.

Irritable bowel syndrome and chronic fatigue 6 years after giardia infection: a controlled prospective cohort study.


PMID: 25115874 Free PMC Article

Follow up > 6 years

Association with chronic fatigue and IBS
RR Giardia exposure - persisting CF : 2.13 [95% CI, 1.55–2.64]
Giardia exposure persisting IBS in 2010 (RR, 1.64 [95% CI, 1.29–1.95])
Bruijnesteijn van Coppenraet LE ea

Table 4: Positivity for all targets by age category

<table>
<thead>
<tr>
<th>organism</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 5yr</td>
<td>5-20</td>
</tr>
<tr>
<td>Giardia</td>
<td>14</td>
<td>9.2</td>
</tr>
<tr>
<td>Crypto</td>
<td>12</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Age difference detection *Giardia* in controls:
5-20 yr old cases: 7.7 %; controls 7.2 %
>50 yrs cases: 4.7 %; controls 0.9%
Humans acquire infection through consumption of contaminated water or food, or by the fecal-oral route on or by hands or fomites.

Contamination of water, food, or hands/fomites with infective cysts.

Trophozoites are also passed in stool but they do not survive in the environment.

Excytation occurs in the small intestine. Two trophozoites are released from each cyst.

The trophozoites multiply by longitudinal binary fission. They remain in the lumen of the proximal small bowel where they can be free or attached to the mucosa by a ventral sucking disk.

Encystation occurs as the parasites transit toward the colon. Both cysts and trophozoites can be found in the feces (diagnostic stages). The cyst is the stage found most commonly in non-diarrheal feces. Cysts are resistant forms and are responsible for transmission.
The life-cycle of *Giardia lamblia*

- Person-to-person spread
- Cysts ingested with contaminated food or water
- Cysts excyst; trophozoites adhere to epithelium of small intestine and multiply by binary fission
- Cysts passed in faeces
- Water-associated hosts (if endemic)
- ? Zoonotic disease
Clinical presentation Giardiasis
Spectrum disease

- Asymptomatic

- Mild; intermittent, not comfortable

- Acute diarrhea (travellers)

- Chronic; persistent diarrhea, brush border abnormalities, malabsorption (children: failure to thrive)
“risk factors” chronic giardiasis

• Host related factors
  – Immune status
  – Hypogammaglobunaemia (IgA def)
  – Age
  – Nutritional status

• Parasite related
  – Genotype: Assemblage A or B
GCC study results parasites (the Netherlands)

Giardia % pos per age group

- <5 yr
- 5-20 yr
- 21-50 yr
- >50 yrs

- cases
- controls
Therapy

● When to treat? possible but not always necessary

Drugs of choice: depending on availability of drugs
  ○ Eg Tinidazole is no longer available on the Dutch market- only via Belgium or international farmacy

● Metronidazol 250 mg 3xdd 7 days
  – Alternative drug: albendazole 400 mg 5 days
  – Pregnancy: paromomycine 500mg 3dd 7 days

● Resistance against metrinodazol: increasing?

● See ESCMID library: presentation Hanevik  www.escmid.com
### Giardia drugs and treatment efficacy

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Drug name</th>
<th>Efficacy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-nitroimidazoles</td>
<td>Metronidazole</td>
<td>36-100%</td>
<td>Common first choice</td>
</tr>
<tr>
<td></td>
<td>Tinidazole</td>
<td>74-100%</td>
<td>Single dose possible</td>
</tr>
<tr>
<td></td>
<td>Ornidazole</td>
<td>90-100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secnidazole</td>
<td>79-98%</td>
<td></td>
</tr>
<tr>
<td>Nitrofurane deriv.</td>
<td>Furazolidone</td>
<td>20-92%</td>
<td></td>
</tr>
<tr>
<td>Benzimidazoles</td>
<td>Albendazole</td>
<td>35-96%</td>
<td>Equal to metronidazole?</td>
</tr>
<tr>
<td></td>
<td>Mebendazole</td>
<td>42-86%</td>
<td></td>
</tr>
<tr>
<td>Acridine deriv.</td>
<td>Quinacrine</td>
<td>84-100%</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Paromomycin</td>
<td>40-91%</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>5-nitrothiazolyles</td>
<td>Nitazoxanide</td>
<td>64-94%</td>
<td></td>
</tr>
</tbody>
</table>

*(Escobedo et al. Trends in Parasitology, 2010)*
Suggested management of treatment failure

- *Giardia* eradicated?
- Immunodeficiency?
- Poor compliance?
- Suggested treatment ladder
  - If *Giardia* successfully treated, perform individual workup for other organic causes.
  - If negative consider PI-IBS.
Medical letter:
different treatment preferences in the USA

<table>
<thead>
<tr>
<th>GIARDIASIS (Giardia duodenalis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Drug of choice:</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Alternative:</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>OR</td>
</tr>
</tbody>
</table>

* Availability problems. See table of manufacturers on pages e30-31:
1. A nitroimidazole similar to metronidazole, tinidazole appears to be as effective as metronidazole and better tolerated (Med Lett Drugs Ther 2004; 46:70). It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist can crush the tablets and mix them with cherry syrup (Humco, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use (HB Hing and TL Doan, Clin Ther 2005; 27:1859). Ornidazole, a similar drug, is also sold outside the US.
2. Not FDA approved for this indication.
4. Additional option: albendazole (400 mg/d PO x 5d in adults and 10 mg/kg/d PO x 5d in children) (K Yereli et al, Clin Microbiol Infect 2004; 10:527; O Karabay et al, World J Gastroenterol 2004; 10:1215). Refractory disease; combination therapy with tinidazole or metronidazole plus paromomycin, furazolidone or quinacrine has been successful (TE Nash et al, Clin Infect Dis 2001; 33:22; R Lopez-Velez et al, Am J Trop Med Hyg 2010; 83:171). In one study, nitazoxanide was used successfully in high doses (1.5 g PO bid x 3d) to treat a case of *Giardia* resistant to metronidazole and albendazole (P Abboud et al, Clin Infect Dis 2001; 32:1792).
5. Paromomycin should be taken with a meal.
6. Poorly absorbed; may be useful for treatment of giardiasis in pregnancy.
7. Not available commercially. It may be obtained through compounding pharmacies such as Expert Compounding Pharmacy, 6744 Balboa Blvd, Lake Balboa, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-7064). Other compounding pharmacies may be found through the National Association of Compounding Pharmacies (800-867-7850) or the Professional Compounding Centers of America (800-331-2498, www.pccarx.com).
8. Quinacrine should be taken with liquids after a meal.
Clinical presentation *Cryptosporidium*:

**Non-immunocompromised individuals:**

- Self-limiting diarrhea (watery)
- Vomiting
- Nausea, decreased appetite, weight loss, flatulence
- Abdominal pain and cramps.
- Recurrent gastrointestinal symptoms (30 - 40% of cases).
- Malabsorption: frequency?
Immunocompromised individuals:
CD4 Tcell-count < 200 mm$^3$

- persistent diarrheal infection > 30 days
- severe illness.
**Therapy**

**Non immunocompromised:**
- Selflimiting
- No therapy proven to be effective
- Debate: nitazoxanide (expensive; not on the European market)

**Immunocompromised individuals:**
- The most effective therapy in patients with AIDS is highly active antiretroviral treatment (HAART) of HIV.
- Restore cellular immunity

Role nitazoxanide: very debatable
Clinical presentation & genotyping

- Sporadic cases:
  - 35% at least one nongastro-intestinal symptom
    - joint pain, eye pain, recurrent headaches, dizzy spells, and fatigue
    - 14.5% two or more
  - different clinical symptoms *C. hominis* and *C. parvum*.
    - *C. hominis* infections more non-gastro symptoms: 44.3% and 27.9%
    - *C. parvum* infections 28.0% and 4.0%;
    - controls 15.1 and 5.2%.
  - Duration of symptoms shorter in *C. parvum*
  - Age difference Adults > children.

● Overall there is no indication for different risks for sex
  – Differs per age group

● Protozoa cases are also seen in elderly

● Transmission within families? difficult to tell
  – GPs are hesitant to send in samples for testing; only for YOPIs
  – (Young, Old, Pregnant, Immunocompromised)
  – changes in finances: insurance company only pays after patients pay first 250 euro (or more) ‘eigen bijdrage’

● Transmission within family study (G&G study): not enough cases of Cryptosporidium to tell.
GCC study results parasites

Cryptosporidium % pos per age group

- <5 yr: 8 cases, 5 controls
- 5-20 yr: 3 cases, 1 control
- 21-50 yr: 3 cases, 1 control
- >50 yrs: 1 case, 0 controls
Blood on top of feces: blood contains parasites
Amoebic ulcer in intestine
Severe amoebic colitis with multiple ulcers: mortality is higher than 40%
Typical flask shaped ulcer in amoebiasis of gut (spread laterally in submucosa)
Spread of amebiasis from intestine
Small amoebic abscess
Several liver abscesses

Yellow necrotic tissue

Intact abscess
Complications of amoebic abscesses
Rupture of large amoebic abscess in peritoneal cavity
Amoebic liver disease with cutaneous involvement following spontaneous rupture
Diagnosis

Intestinal

Extra-intestinal
Diagnosis of intestinal protozoa

- *Ascaris*
- *T. trichiura*
- *C. cayetanensis*
- *D. fragilis*
- *S. stercoralis*
- *G. lamblia*
- *E. histolytica/dispar*
- hookworm
With microscope *Entamoeba histolytica* morphological identical *Entamoeba dispar*

But:

*Entamoeba dispar*: non-pathogen!

*Entamoeba histolytica*: pathogen
differentiation *Entamoeba histolytica* and *Entamoeba dispar*: i.e. polymerase chain reaction

E. histolytica

E. dispar
Entamoeba species humans

- *Entamoeba hartmanni*
- *Entamoeba histolytica*
- *Entamoeba dispar*
- *Entamoeba coli*

Rare species
- *E. moshkovski*
- *E. polecki*
- *E. chattoni*
- *E. gingivalis*
Triad: swinging temperature, profuse sweating and leukocytosis
ELISA method for detection of specific antibodies to *Entamoeba histolytica*
Ultrasound scan: amoebic liver abscess
CT scan of amoebic liver abscess (500-1500 ml)
Raised right hemidiaphragm due to amoebic liver abscess
Drainage of an amoebic liver abscess
Filling defect in barium enema due to an amoeboma
tissue phase:

- Metronidazol (750 mg tid x 7-10d)

luminal agents:

- clioquinol 250mg 3dd 10 days
- Paromomycin (500 mg 3dd x 7 days)
- Diloxanide furoate (500 mg tid x 10d)

Always treatment with a luminal agent after treatment for the tissue phase! Otherwise up to 30% will remain infected and may relapse (Irusen et al. 1192)
### AMEBIASIS (Entamoeba histolytica)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dosage</th>
<th>Pediatric dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodoquinol(^1)</td>
<td>650 mg PO tid x 20d</td>
<td>30-40 mg/kg/d (max 2g) PO in 3 doses x 20d</td>
</tr>
<tr>
<td>OR Paromomycin(^2)</td>
<td>25-35 mg/kg/d PO in 3 doses x 7d</td>
<td>25-35 mg/kg/d PO in 3 doses x 7d</td>
</tr>
<tr>
<td>OR Diloxanide furoate(^3)</td>
<td>500 mg PO tid x 10d</td>
<td>20 mg/kg/d PO in 3 doses x 10d</td>
</tr>
<tr>
<td><strong>Mild to moderate intestinal disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500-750 mg PO tid x 7-10d</td>
<td>35-50 mg/kg/d PO in 3 doses x 7-10d</td>
</tr>
<tr>
<td>OR Tinidazol(^5)</td>
<td>2 g once PO daily x 3d</td>
<td>≥3 yrs: 50 mg/kg/d (max 2g) PO in 1 dose x 3d</td>
</tr>
<tr>
<td><strong>either followed by</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodoquinol(^1)</td>
<td>650 mg PO tid x 20d</td>
<td>30-40 mg/kg/d (max 2g) PO in 3 doses x 20d</td>
</tr>
<tr>
<td>OR Paromomycin(^2)</td>
<td>25-35 mg/kg/d PO in 3 doses x 7d</td>
<td>25-35 mg/kg/d PO in 3 doses x 7d</td>
</tr>
<tr>
<td><strong>Severe intestinal and extraintestinal disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>750 mg PO (or IV) tid x 7-10d</td>
<td>35-50 mg/kg/d PO (or IV) in 3 doses x 7-10d</td>
</tr>
<tr>
<td>OR Tinidazol(^5)</td>
<td>2 g once PO daily x 5d</td>
<td>≥3 yrs: 50 mg/kg/d (max 2g) PO in 1 dose x 5d</td>
</tr>
<tr>
<td><strong>either followed by</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodoquinol(^1)</td>
<td>650 mg PO tid x 20d</td>
<td>30-40 mg/kg/d (max 2g) PO in 3 doses x 20d</td>
</tr>
<tr>
<td>OR Paromomycin(^2)</td>
<td>25-35 mg/kg/d PO in 3 doses x 7d</td>
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</tr>
</tbody>
</table>

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**Notes:**
1. Iodoquinol should be taken after meals.
2. Paromomycin should be taken with a meal.
3. Not available commercially. It may be obtained through compounding pharmacies such as Expert Compounding Pharmacy, 6744 Balboa Blvd, Lake Balboa, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-7064). Other compounding pharmacies may be found through the National Association of Compounding Pharmacies (800-687-7850) or the Professional Compounding Centers of America (800-331-2498, www.pccarx.com).
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