Neglected Parasitic Diseases

Professor PL Chiodini
The Hospital for Tropical Diseases (HTD)

- Imported parasitic and infectious diseases
- From any part of the globe
- Tourists, refugees, migrants, business people etc
- A window on the world
- Important in sentinel surveillance
The global importance of parasites

MALARIA IS BY FAR THE GREATEST CHALLENGE

Neglected tropical diseases (WHO)
Apart from soil-transmitted helminthiases (affect >1 billion people):
• Schistosomiasis
• Lymphatic filariasis
• Blinding Trachoma (not a parasite)
• Onchocerciasis
• Chagas’ disease
• Leishmaniasis
Schistosomiasis

- 779 million people at risk
  (Steinmann et al, 2006 Lancet Inf Dis 6: 411-25)
- 200 million people infected
- 80% live in sub-Saharan Africa
- 120 million symptomatic
- 20 million with severe disease
  (Hatz 2005 J Travel Med 12: 1-2)
- Annual mortality 280,000
  (Southgate et al, 2005 J Helminthol 79:181-5)
Global distribution of schistosomiasis

Areas where schistosomiasis is a public health problem
Areas where schistosomiasis is transmitted
Pathogenesis of Schistosomiasis

Mostly due to passage of eggs and the granulomatous reaction to eggs left in tissues

• Cercarial penetration
• Larval migration and maturation
• Early egg deposition
• Late egg deposition
Clinical Features of Schistosomiasis

Common to all:
- Papular dermatitis; Swimmers’ Itch
- Katayama Fever
Katayama Fever

- Fever, myalgia, arthralgia, urticaria
- Abdominal discomfort
- Watery diarrhoea

- Hepatosplenomegaly
- Pneumonitis
- Eosinophilia
Clinical Features of Schistosomiasis

• *S. haematobium*:
  Terminal haematuria, frequency of micturition, bladder pain, pyelonephritis, hydronephrosis, pyonephrosis, haematospermia, vulval papillomata, cervical growths, bladder carcinoma
Clinical Features of Schistosomiasis

• *S. mansoni*: Malaise, abdominal pain, frequent stools with blood and mucus, rectal polyps, hepatomegaly (reversible at first), portal hypertension, haematemesis from bleeding oesophageal varices, ascites
Clinical Features of Schistosomiasis

- *S. japonicum*: Extremely rare in travellers
  - Similar to & more severe than *S. mansoni*
  - Small bowel also affected
  - Hepatic fibrosis with splenic enlargement
  - CNS symptoms in about 5%: convulsions, hemiplegia, paraplegia, blindness
Schistosomiasis at HTD

- 1107 cases over 5 years
- 28% residents of or migrants from an endemic country
- 62% travellers
- Ova seen in only 45% of cases
Schistosomiasis at HTD


• 68% *S*. *haematobium*
• 29% *S*. *mansoni*
• 2% *S*. *haematobium* plus *S*. *mansoni*
• 1% *S*. *intercalatum*
Schistosomiasis at HTD

• *S. mansoni* in:
  45% residents
  22% travellers
• *S. haematobium* in:
  94% of those exposed in Malawi
  60% of those exposed in West Africa
Schistosomiasis at HTD

Katayama Syndrome uncommon
  • *S. mansoni*  5% of cases
  • *S. haematobium* 1.5% of cases
Schistosomiasis at HTD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% cases</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>50</td>
</tr>
<tr>
<td>Tiredness</td>
<td>25</td>
</tr>
<tr>
<td>Itch</td>
<td>8</td>
</tr>
<tr>
<td>Frank haematuria</td>
<td>19</td>
</tr>
<tr>
<td>Haematospermia</td>
<td>1</td>
</tr>
<tr>
<td>Semen changes</td>
<td>4</td>
</tr>
<tr>
<td>Bloody diarrhoea</td>
<td>3</td>
</tr>
</tbody>
</table>
Schistosomiasis of the Nervous System

- Cerebral
  Mainly *S. japonicum*
- Slowly expanding mass lesion
  Headache, fits, speech disturbance, hemiparesis, ataxia, papilloedema
- Diagnosis by CT, MRI, serology, eggs elsewhere, biopsy
Schistosomiasis of the Nervous System

• Spinal
  Mainly *S. mansoni* reported

• Relatively rapid onset
  Lumbar &/or lower limb pain, muscle weakness, sensory impairment, bladder dysfunction

• Diagnosis by CT, CT myelography, MRI, serology, eggs elsewhere
Diagnosis of Schistosomiasis at HTD

- **Microscopy** of:
  Stool, terminal urine, [semen], rectal snips, [bladder biopsies]
  Only 45% of cases egg positive
- **Antigen detection** insufficiently sensitive
- **Serology**
  ELISA for IgG antibodies to *S. mansoni* soluble egg antigen [SEA]
- **Ultrasonography** for complications
HTD SEA ELISA

- Reported sensitivity of 96% for *S. mansoni* & 92% for *S. haematobium*
- 97% specificity
- Takes approx 6 weeks to seroconvert
HTD Treatment of Schistosomiasis

All species:
• Praziquantel (higher dose for *S.japonicum*)
• Katayama syndrome: Steroid cover and re-treat after 6 weeks
• Neuroschistosomiasis: 3 day course under steroid cover

Alternatives:
• Oxamniquine for *S.mansoni*
• Metrifonate for *S.haematobium*
Problems in Practice

• Education of the traveller
• Clinical awareness in a non-endemic area
• Late referral of neuroschistosomiasis
• Misdiagnosis of genital lesions
• We lack a good test for treatment failure
Prevention of Travellers’ Schistosomiasis

- Avoidance of freshwater exposure
  - Easier said than done
- Vigorous towelling after exposure?
  Outwater et al 2005 J Travel Med 12:265-9
- DEET or Dimeticone?
  Cooper et al 2004 J Pharm Pharmacol. 56:957-62
- Partnership with local health teams
- Control in endemic areas
Leishmaniasis

- Infection with genus *Leishmania* - obligate intracellular parasite transmitted by the sandfly
- Identified by Leishman & Donovan in 1903
- Human infection 3 clinical syndromes
  1. Cutaneous Leishmaniasis
  2. Mucosal Leishmaniasis
  3. Visceral Leishmaniasis
Cutaneous Leishmaniasis

• 1.5 million cases/year globally
• Old World
  \(L. \ tropica, \ L. \ major, \ L. \ aethiopica\)
• New World
  \(L. \ mexicana \) complex, \ Viannia \ subgenus}
Old World Cutaneous Leishmaniasis in American troops

- Dec 2003- June 2004
- 360 suspect skin lesions in 200,000 troops returning from one year deployment in Iraq
- 237 diagnosed CL
- 181 laboratory confirmation
- PCR +ve in all 122 smear positive and 34 smear negative cases
HTD Agarose Gel Electrophoresis - Old World Primers

1 - Patient: no amplification
2 - Patient: L.donovani
3 - L.donovani control
4 - L.major control
5 - Negative control

Marker (size in base pairs)
## HTD Investigations

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Patients</th>
<th>+ves</th>
</tr>
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<tbody>
<tr>
<td>Skin Smear: microscopy for amastigotes</td>
<td>32</td>
<td>19 (59%)</td>
</tr>
<tr>
<td>Histology:</td>
<td>37</td>
<td>37 (100%)</td>
</tr>
<tr>
<td>H&amp;E for granulomata</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;E for amastigotes</td>
<td>37</td>
<td>25 (68%)</td>
</tr>
<tr>
<td>NNN culture</td>
<td>31</td>
<td>15 (48%)</td>
</tr>
<tr>
<td>PCR: primers for New &amp; Old World spp.</td>
<td>34</td>
<td>32 (94%)</td>
</tr>
</tbody>
</table>
Indications for local Rx:

- Lack of risk of developing mucosal lesions
- Old World cutaneous leishmaniasis
  *L. mexicana* cutaneous leishmaniasis
- Small, single lesion
- Absence of lymph node metastasis
Indications for systemic Rx:
- Presence of mucosal lesion or lymph node metastasis
- New World CL except *L. mexicana* lesions
- Lesions unresponsive to local Rx
Treatment of Cutaneous Leishmaniasis

Determine whether “simple” or “complex”

Complex:
- >2-3 in number
- >40 mm maximum diameter
- Lymphatic or lymph node involvement
- Could give cosmetic problems (eg face)
- Could give functional problems (eg hand)
- Poor response to Rx as a “simple” lesion
Treatment of Cutaneous Leishmaniasis

• **ALL** *L. Viannia/braziliensis*, or untyped New World lesions, whether “simple” or “complex” require Rx with intravenous sodium stibogluconate (SSG)

• Lesions due to other species:
  “Simple”: intralesional SSG or a physical treatment

  “Complex”: IV SSG
Protection against leishmaniasis

- Insect repellent
- Long sleeves
- Bed nets
- Sleeping undercover
- Vector control programmes
CYSTIC HYDATID DISEASE

*Echinococcus granulosus*
Structure of hydatid cyst

- Laminated membrane
- Germinal membrane
- Cyst fluid
DIAGNOSIS OF HYDATID DISEASE

- Imaging: plain X ray ultrasound CT or MRI
- Serology
- Microscopy protoscoleces, hooks
Hydatid is not one disease

Multiple sites (any organ possible)
Different types of cyst within sites
CE 1
CE 2
CE 4
HTD Hydatid Serology

- ELISA using whole cyst fluid from *Echinococcus granulosus* isolated from horses
- Optical density cut off for a positive 0.250
- Sensitivity 84-93%; Specificity 82-89%
- False positives with larval cestodes; filariases; some advanced neoplasms
Cystic Echinococcosis

Clinical presentation
## Clinical Presentation
### HTD Series

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<thead>
<tr>
<th></th>
<th>No</th>
<th>%</th>
<th></th>
<th>No</th>
<th>%</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
<td>16</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>36</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Abdo distension</td>
<td>6</td>
<td>10</td>
<td></td>
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</tr>
<tr>
<td>Pruritis</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>Anaphylaxis</td>
<td>4</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>10</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>7</td>
<td>12</td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Complicated</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>Rupture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Imminent</td>
<td>5</td>
<td>9</td>
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<tr>
<td>Infected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Secondary</td>
<td>2</td>
<td>3.5</td>
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</table>
## Baseline Characteristics of the Cysts

<table>
<thead>
<tr>
<th>Cyst type</th>
<th>Number</th>
<th>%</th>
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<tbody>
<tr>
<td>CE1</td>
<td>6</td>
<td>10.5</td>
</tr>
<tr>
<td>CE2</td>
<td>34</td>
<td>59.6</td>
</tr>
<tr>
<td>CE3a</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>CE3b</td>
<td>6</td>
<td>10.5</td>
</tr>
<tr>
<td>CE4</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>CE5</td>
<td>5</td>
<td>8.8</td>
</tr>
<tr>
<td>Ruptured/Post op</td>
<td>5</td>
<td>8.8</td>
</tr>
</tbody>
</table>
TREATMENT OF HYDATID DISEASE

Albendazole
Praziquantel
Surgery
Aspiration: “PAIR”
Scolicide (silver nitrate, alcohol)
RCT of Albendazole

18 patients no drug pre-surgery
18 albendazole 10 mg/kg for 1m
19 albendazole 10 mg/kg for 3 months
US and viability studies:
50%; 72%; 94% non-viable respectively
Protoscolex (p=0.039) and cyst viability (p=0.018) lower in Rxd patients
RCT of albendazole in hydatid disease
Keshmiri et al (2001) Iran

Albendazole 400 mg BD for 3 6-week blocks vs placebo

Rx group: 134/172 cysts improved or cured
Placebo: 4/31 cysts improved or cured

P < 0.001

18/22 (82%) Rxd patients cured or improved
vs 1/7 (14%) placebo improved but not
cured
Albendazole vs Mebendazole

448 patients with 929 cysts
3 to 6 month mebendazole or albendazole
Follow-up 1 to 14 years
At end of Rx 74.1% degenerate cysts
(Albendazole 82.2%; mebendazole 56.1%)
25% of cysts relapsed, most often type 2 cysts
78.5% recurred in the first 2 years
Albendazole plus Praziquantel

Albendazole alone
1985-90
22 patients
8 (36.4%) complete cyst disappearance (Rx in 4 was 6-24 m)

Albendazole plus Praziquantel
1990-98
22 patients
Rx was 2-6 m
Follow-up 2m to 3y
9 (47.4%) complete cyst disappearance
5 (36.8%) >50% cyst reduction
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Viable protoscoleces</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABZ + Praziquantel</td>
<td>1/25</td>
</tr>
<tr>
<td>Albendazole</td>
<td>5/8</td>
</tr>
</tbody>
</table>

\[ p = 0.0013 \]
PAIR vs Surgery; Meta-analysis

769 patients with liver hydatid Rxd with PAIR plus albendazole or mebendazole
952 era-matched historical controls Rxd with Surgery plus albendazole or mebendazole
PAIR vs Surgery; Meta-analysis

PAIR showed significantly:
• Greater clinical & parasitological cure rates
• More common fever
• More common minor allergic reactions
• Shorter mean hospital stay (2.4 days)
PAIR vs Surgery; Meta-analysis

Surgery showed significantly more frequent:
• Disease recurrence; major complications
  (anaphylaxis, biliary fistula, cyst infection, liver/abdominal abscess, sepsis);
  minor complications; & death
• Significantly longer mean hospital stay
  (15.0 days)
Current HTD Practice (1)

Lung cyst

- No albendazole (risk of rupture)
- Start praziquantel
- Prepare for surgery
Liver cyst

- Depends on WHO U/S cyst type (see below)
- Praziquantel is given for 2 weeks pre and post surgery or PAIR
<table>
<thead>
<tr>
<th>Liver cyst type</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE1</td>
<td>Albendazole +/- PAIR</td>
</tr>
<tr>
<td>CE2</td>
<td>Albendazole + Surgery</td>
</tr>
<tr>
<td>CE3a</td>
<td>Albendazole +/- PAIR</td>
</tr>
<tr>
<td>CE3b</td>
<td>Albendazole + Surgery</td>
</tr>
<tr>
<td>CE4</td>
<td>Watch and wait</td>
</tr>
<tr>
<td>CE5</td>
<td>Watch and wait</td>
</tr>
</tbody>
</table>
Viability testing of operative material

Eosin exclusion test
HYDATID DISEASE

Follow-up is long-term
Hydatid Follow-up

- Eosinophil count sometimes helpful
- Serology
- Ultrasound or CT
Cystic Echinococcosis

• Clinical trials on CE should assign interventions specific to the WHO CE type
• The outcome of clinical interventions should be reported for each CE type
Hydatid Questions and Problems

• What is the optimum duration of albendazole Rx?
• What is the role of praziquantel?
• The lack of alternative drugs
• Reliably defining cure
ONCE YOU ARE INFECTED, STRONGYLOIDES IS WITH YOU FOR LIFE
1. Eggs are produced by fertilized female worms.
2. Development into free-living adult worms.
3. Rhabditiform larvae hatch from embryonated eggs.
4. New generation of adults
5. The rhabditiform larvae develop into infective filariform.
6. Infective filariform larvae penetrate the intact skin initiating the infection.
7. The filariform larvae enter the circulatory system, are transported to the lungs, and penetrate the alveolar spaces. They are carried to the trachea and pharynx, swallowed, and reach the small intestine where they become adults.
8. Adult female worm in the intestine.
9. Eggs deposited in intestinal mucosa, hatch, and migrate to lumen.
10. Autoinfection: Rhabditiform larvae in large intestine, become filariform larvae, penetrate intestinal mucosa or perianal skin, and follow the normal infective cycle.
STRONGYLOIDES

- Asymptomatic
- Larva currens
- Diarrhoea
- Malabsorption
- Hyperinfestation
Risk factors for hyperinfestation

- Transplant recipients
- Lymphomas
- Corticosteroid Rx
- Malnutrition
- HTLV 1 infection
Strongyloides diagnosis

- Microscopy
- Culture
- String test
- Serology

98% sensitive in migrants
73% sensitive in travellers
HTD *Strongyloides* treatment

- Oral thiabendazole obsolete
- Oral albendazole less effective
- Oral ivermectin

Hyperinfestation may require:
- Subcutaneous ivermectin

NB unlicensed in humans
STRONGYLOIDES

- Think of the diagnosis, before it is too late
- Microscopy
- Serology
- Ivermectin
- Secondary septicaemia in hyperinfestation