Abnormal LFTs in the Returning Traveller

Professor PL Chiodini
Entamoeba histolytica

• 1875 Discovered by Feder Losch in Saint Petersburg

• 1903 Named by Fritz Schaudinn

• 1925 Emile Brumpt postulated it consisted of two morphologically indistinguishable species and was ridiculed

• 1993 Diamond and Clark redescribed
Amoebic liver abscess

- Textbook presentation of fever, tender enlarged liver and tender intercostal space far from universal
- Fever may be the only presentation
- Polymorph leucocytosis
- Raised ESR
Diagnosis of amoebiasis

- **Dysentery**
  - Hot stool microscopy
  - Histology of biopsy
  - Serology (75% positive)

- **Liver abscess**
  - Imaging
  - Serology (95% positive by two weeks)
Amoebic serology

- IFAT positive at a titre of 1 in 320
- CAP positive
- Compatible with active amoebic infection
Treatment of amoebiasis

• Cyst passage
  – Luminal amoebicide
    • Diloxanide furoate
    • OR Paromomycin

• Dysentery or Abscess
  – Metronidazole OR tinidazole
  – Then a luminal amoebicide
When to aspirate?

• At risk of rupture
• In left lobe of liver
• >10 cm diameter
• Slow response to medical treatment
• Where there is genuine doubt about the diagnosis

- Acquired immunity in children to intestinal amoebiasis
  
  - Associated with mucosal IgA response to the carbohydrate recognition domain of the Gal/GalNAc lectin
  
  - Children with this response had 86% fewer new infections over one year

- Gal-lectin based intranasal synthetic peptide vaccine
- Cholera toxin as adjuvant
- 6 vaccinated and 6 control baboons
- 4 immunisations at 7 day intervals
- Challenged with amoebic trophozoites via colonoscopy
90 days follow up

- 6 controls
  - 250/415 (60.24%) stool samples PCR +ve
  - 4/6 inflammatory colitis; 2 with amoebae seen on histology
- 6 vaccinated
  - 36/423 (8.51%) stool samples PCR +ve
  - 0/6 with inflammatory colitis or parasite invasion

Inverse correlation between presence of intestinal anti-peptide IgA antibodies and positive faecal PCR

An alternative adjuvant will be needed (potential neurotoxicity)

- Recombinant LecA protective in mouse model of intestinal amoebiasis
Stanley SL. Vaccines for amoebiasis: barriers and opportunities. Parasitology. 2006; 133: S81-S86

- Little or no market in developed countries
- Amoebiasis vaccine must be highly cost-effective in resource-poor settings
- Multivalent anti-diarrhoeal vaccine may be way forward
  - amoebiasis
  - Cryptosporidiosis
  - Shigellosis
  - pathogenic *E.coli et al.*
Echinococcus granulosus causes hydatid disease.

Life cycle:
- Intermediate host: Sheep, cattle etc. and other herbivores
- Cyst in offal, esp. liver
- Ovum (30–37 μm)
- Definitive host: Dog and other canines
- Adult:
  - 30–36 hooks in two rows
  - 4 suckers
  - Immature
  - Mature
  - Gravid
  - Proglottids
  - Length 3–8 mm
WHO CE staging

Fig. 2. WHO-IWGE standardized classification.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Viability</th>
<th>Image</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE1</td>
<td>Viable</td>
<td></td>
<td>&lt;5cm- albendazole alone &gt;5cm PAIR and albendazole</td>
</tr>
<tr>
<td>CE2</td>
<td>Viable</td>
<td></td>
<td>Surgery or other percutaneous procedure with albendazole</td>
</tr>
<tr>
<td>CE3A</td>
<td>Transitional</td>
<td></td>
<td>&lt;5cm- albendazole alone &gt;5cm- PAIR and albendazole</td>
</tr>
<tr>
<td>CE3B</td>
<td>Transitional</td>
<td></td>
<td>Surgery or other percutaneous procedure with albendazole</td>
</tr>
<tr>
<td>CE4</td>
<td>Inactive</td>
<td></td>
<td>Watch and wait</td>
</tr>
<tr>
<td>CE5</td>
<td>Inactive</td>
<td></td>
<td>Watch and wait</td>
</tr>
</tbody>
</table>

PAIR

PAIR Sequence

The steps of the puncture procedure (cartoon): the critical point is the angle of puncture: normal liver parenchyma must be present between the puncture point and the surface of the cyst to avoid leakage of cyst fluid (prevention of anaphylactic reactions) and protoscoleces spillage (prevention of recurrences). Direct puncture of a cyst close to the abdominal wall must be avoided.
Disseminated disease
HTD

- MDT discussion
- Remove as many cysts as is safely possible
- Indefinite albendazole therapy
  - Regular FBC and LFTs
- Perioperative praziquantel
- Yearly imaging and serological follow up for 10 years minimum
- Engage with patient.
Fasciola hepatica – Life cycle

Image from Carlo Denegri Foundation
Global Burden of Fascioliasis


- 91.1 million people at risk
- Infects 2.5 to 17 million people annually
- Sheep and cattle-rearing communities
  - Bolivia
  - Ecuador
  - Egypt
  - Iran
  - Peru
  - Vietnam
Fasciola issues in Europe

• Increase in livestock infection
• Triclabendazole treatment failure
Fasciola hepatica in Dairy Herds in England and Wales
Fasciola hepatica in Dairy Herds in Germany
Kuerpick et al (2013) Parasitology 140, 1051-1060
Fasciola hepatica in Sheep

See Taylor MA (2012) Vet Parasitol 189, 2-7

• Can infect all grazing animals
• Mainly sheep and cattle
• Most pathogenic in sheep
• More prevalent with high summer rainfall
• If milder winter, acute fluke disease appears much earlier in the year
**Fasciola and UK Climate Change**


- Increased rainfall in Autumn and Winter
- Warmer average temperatures throughout the year
- 4 week extension of herbage growing season over past 40 years
Triclabendazole-resistant *Fasciola* in UK Sheep


- Two female sheep
- Live, undamaged flukes at necropsy 7 days after a 3\(^{rd}\) dose of triclabendazole
Triclabendazole-resistant *Fasciola* in UK Sheep

See Gordon et al (2014) *Veterinary Record* August 11, 159-160

- 6 sheep infected with *F. hepatica* derived from two naturally infected ewes
- Treated with triclabendazole at 12 weeks when infection patent; second dose repeated 3 weeks later
- Post-mortem 14 days after second dose showed between 19 and 70 live adult fluke in each animal
Treatment Failure in Humans (1)

• 70 y old male patient
• Right upper quadrant abdominal pain; 10kg weight loss
• Alk phos 347 (75-140); Eosinophils 3.44
• CT scan suggested liver metastases
• Biopsy: eosinophilic infiltrates; no cancer
Treatment Failure in Humans (2)

- “Lover of wild watercress”
- *Fasciola* eggs in stool
- Fasciola IFAT 1 in 1024 (<1 in 28)
- Two doses of triclabendazole given
Treatment Failure in Humans (3)

- Follow-up one year later
  - Much better
  - Eosinophil count 0.34 (normal)
  - Alkaline phosphatase 103 (normal)
  - Fasciola IFAT 1 in 128 (much improved)
  - **BUT** Fasciola eggs in stool
“water carriers and production beds must be protected from the intrusion of livestock”
Bithionol

- No longer obtainable in England for human use
- Dosage regimen
  - 30 to 50 mg/kg po alt die in 2 divided doses to a total of 10 to 15 doses
Alternative Drugs

- Triclabendazole (TCBZ) acts against mature and immature *F. hepatica*
- Albendazole (ABZ) is active against flukes older than 12 weeks
- Some isolates resistant to TCBZ but sensitive to ABZ
- Some isolates resistant to ABZ but sensitive to TCBZ (ABZ drug pressure in the field)
RCT of Artesunate vs Triclabendazole

- Triclabendazole 10 mg/kg
  2 doses, 12 hours apart
- Artesunate 4 mg/kg/d daily for 10 days
### Artesunate vs Triclabendazole


<table>
<thead>
<tr>
<th>Endpoint at 3m, ITT</th>
<th>Triclabendazole</th>
<th>Artesunate</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>46/50 (92%)</td>
<td>38/50 (76%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Eosinophils &lt;400/μL</td>
<td>21/50 (42%)</td>
<td>8/50 (16%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Improved U/S scan</td>
<td>35/50 (70%)</td>
<td>33/50 (66%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Complete response</td>
<td>18/50 (36%)</td>
<td>5/50 (10%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Nitazoxanide vs Placebo

- 50 Adults (40 active Rx)
  Nitazoxanide 500 mg bd for 7 days
- 50 Children (40 active Rx)
  Age 2-3 y 100 mg bd for 7 days
  Age 4-11 y 200 mg bd for 7 days
  Age >12 y 500 mg bd for 7 days
Nitazoxanide vs Placebo

Cure based on egg counts

<table>
<thead>
<tr>
<th>Age group</th>
<th>Nitazoxanide</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>18/30 (60%)</td>
<td>1/8 (12.5)</td>
<td>0.042</td>
</tr>
<tr>
<td>Children</td>
<td>14/35 (40%)</td>
<td>0/8</td>
<td>0.038</td>
</tr>
</tbody>
</table>
Experimental Chemotherapy for Fascioliasis

- Triclabendazole plus artesunate

- Triclabendazole plus ivermectin

- Triclabendazole plus verapamil

- Triclabendazole plus ketoconazole
Changing Pattern of Acute Hepatitis

68 cases of hepatitis
Alanine transaminase >1000
Serology positive for hepatitis virus
Hepatitis E is the commonest cause for admission with hepatitis to HTD
Travelled to Indian Subcontinent

- Hepatitis A
- Hepatitis E
Hepatitis E

RNA virus  Four Genotypes
Resource-poor settings with poor sanitation

- HEV1 and HEV2
  - Faecal-oral route
  - Usually via contaminated water
  - Sporadic cases
  - Large outbreaks
    - Formerly known as water-borne Non-A, Non-B hepatitis
- Case load
  - Approx 3.4 million/yr; 70,000 deaths; 3,000 stillbirths
Affluent industrialised countries

• HEV3 and HEV4
  – Zoonotic transmission; animal reservoirs (pigs)
  – Sporadic cases
  – Chronic HEV3 infection in immunocompromised patients
    • Chronic hepatitis
    • Cirrhosis
Complications (1)

• Neurological
  – GBS; transverse myelitis; meningoencephalitis

• Kidney injury

• Pancreatitis (HEV1)

• Haematological
  – Thrombocytopenia; aplastic anaemia
Complications (2)

• HEV1 or HEV2 in Pregnancy
  – 20 to 25% mortality
  – Usually third trimester
  – Haemorrhage
  – Eclampsia
  – Fulminant hepatic failure (HEV1)
The UK Blood Supply


- 225,000 donations screened for HEV RNA
  - 79 viraemic with HEV3
  - RNA prevalence 1 in 2848
  - 18/43 (42%) recipients infected
  - Estimated 80,000 to 100,000 acute HEV infections in England in one year
  - HEV3 from pigs
Prevention

- Vaccine only licensed in China
- Good sanitation
- Thorough cooking
http://www.thehtd.org/