Tropical Diseases in Travellers and Migrants Intrigue and Confound Clinicians

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Disclosures

- None to declare
Clinical Case 1

- 47-year-old man immigrated to Canada from the Philippines in 2008
- Noticed a large red patch of inflamed skin on his back in 2010, which resolved spontaneously after a few months without treatment
- 2 years later, he noticed fairly acute onset of increased redness and tenderness of multiple hypopigmented, elevated plaques on the skin of his face, ears, neck, back, arms, abdomen, and legs
Clinical Case 1

- There was no accompanying fever, sweats, weight loss, cough, gastrointestinal symptoms
- He did not report weakness, but complained of the sensation of numbness in the finger tips bilaterally and 3 toes of the right foot
- No current medications or past medical hx
- Family members were all asymptomatic
Clinical Case 1

- On exam, vital signs revealed tachycardia, but were otherwise normal
- Examination revealed abnormalities of the skin and nerves:
  - Peripheral nerves including the greater auricular, radial cutaneous, ulnar, and common peroneal nerves were all thickened
  - Power was 5/5 throughout with normal DTRs
  - Gait was normal
  - Skin exam.......

Audience Poll Question:
The Initial Management of this Patient’s Illness is Likely to Include:

- Isoniazid
- Prednisone
- Thalidomide
- Itraconazole
- Minocycline
A practical approach to common skin problems in returning travellers

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Worldwise Traveller’s Health, 72 Remuera Road, Newmarket, Auckland, New Zealand
Skin problem

Infection/infestation (more common)

Cosmopolitan infection (~75%)
- Scabies
- Bacterial skin infections
- Superficial fungal infections
- Swimmer’s itch
- Herpes simplex
- Herpes zoster

Tropical disease (~25%)
- Cutaneous larva migrans
- Cutaneous leishmaniasis
- Myiasis
- Tungiasis
- Rickettsial infections
- Dengue fever
- Mycobacterium marinum
- Filariasis
- Leprosy

Non infectious disease (less common)

- Arthropod bite
- Allergic reaction
- Sunburn
- Injuries
- Animal bites
- Dermatitis
- Phytophotodermatitis
- Malaria rubra

a From non human schistosomes

Figure 1  Categorisation of skin problems in returning travellers with common examples.
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Diagnosis</th>
<th>Travel and traveller factors</th>
<th>Skin problem characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common</td>
<td>Pityriasis versicolor</td>
<td>Worldwide, especially tropics; hot and humid climates; sweat</td>
<td>Usually asymptomatic well defined flaky brown, white or pink patches; trunk, neck, arms</td>
</tr>
<tr>
<td>Common</td>
<td>Post-inflammatory</td>
<td>Worldwide; following skin trauma or infection</td>
<td>Hyperpigmentation at site of trauma or infection</td>
</tr>
<tr>
<td></td>
<td>Phytophotodermatitis^d</td>
<td>Worldwide; beach holidays; skin exposure to furocoumarin containing compound, e.g. citrus juice, then sun</td>
<td>Painful burning erythema, then vesicles, then hyperpigmentation; mild pruritis; streaky lesions on skin exposed to furocoumarins and sun</td>
</tr>
<tr>
<td>Rare</td>
<td>Other fungal skin infections e.g. tinea nigra</td>
<td>Tropical regions; skin trauma and contact with soil</td>
<td>Hyperpigmentation of palms or soles</td>
</tr>
<tr>
<td></td>
<td>Leprosy</td>
<td>Mostly seen in immigrants or long-term travellers to developing and tropical regions. Africa, Indian subcontinent, Latin America</td>
<td>Hypo or hyperpigmentation; decreased sensation and sweating; peripheral nerve thickening</td>
</tr>
<tr>
<td></td>
<td>Pinta</td>
<td>Latin America, rural; skin contact</td>
<td>Papule, then plaque, then pigmented; lower limbs</td>
</tr>
<tr>
<td></td>
<td>Vitiligo</td>
<td>Worldwide; young adults</td>
<td>Hypopigmented patches; head, hands, feet</td>
</tr>
</tbody>
</table>
Approach to this Patient

- Investigations included chest x-ray, bloodwork, and slit skin smears
- Patient started on oral prednisone, calcium, vitamin D, bisphosphonate, iron, multivitamin, PPI and triple therapy for multibacillary leprosy:
  - Dapsone + Rifampin + Ofloxacin
- Close follow-up arranged
What Happened Next?

- Approximately 7 weeks after initiation of therapy, patient presented to hospital with a 5-day history of fever, productive cough, diffuse confluent pruritic maculopapular rash, jaundice, and biochemical hepatitis requiring hospitalization for 6 days.

- Hb 100 g/L, bilirubin 250 umol/L, AST 749 U/L, ALT 493 U/L
Panel Question:
What could be going on here?
Dapsone Hypersensitivity Syndrome

- DHS is a rare idiosyncratic reaction that can cause irreversible organ damage
- Part of the “DRESS” spectrum of hypersensitivity reactions
- Incidence ranges from 0.5% to 3%, and onset is typically weeks after starting dapsone, but can be out to 6 months
- Metabolites of dapsone are thought to form haptens, with subsequent production of anti-dapsone antibodies
- Rechallenge with dapsone is therefore not recommended
Clinical Case 1

- All medications were stopped in hospital, and the patient was restarted on rifampin and ofloxacin following resolution of hepatitis.
- Patient continued on daily therapy to 1 year, and a steroid taper over several months.
- Remained clinically well thereafter with resolution of his reversal reaction and only mild hyperpigmentation of lepromatous plaques.
- No evidence of relapse or reaction 2 years post-treatment.
5 Key Points – Dapsone and DHS

- Dapsone causes hemolysis and can lead to methemoglobinemia >> close follow-up warranted
- DHS is a rare, dose-independent potentially fatal systemic hypersensitivity syndrome
- DHS usually occurs 6-8 weeks into dapsone therapy
- Diagnosis of DHS based on clinical features: fever, rash, lymphadenopathy, hepatitis, and other end-organ involvement, along with history of antecedent dapsone exposure
- Management of DHS includes withdrawal of dapsone, corticosteroids, and supportive care
Clinical Case 2

- 77 year-old Indian-born resident of India visiting Canada x 2 weeks
- Presented with a 16-day history of fever, anorexia, headache, myalgia, and fatigue
- Co-morbidities include diabetes and hypertension
- Febrile on examination in the ER
- CBC – Hb 97 g/L, WBC 7.3 bil/L, Platelets 81 bil/L
Malaria Diagnostics Workflow

EDTA Blood

Microscopy

Mixed Infection or Unable to Speciate

Neg or Pf, Pv, Pm, Po

Discrepant Results

Resolve by Real Time PCR

Pf, Pv, Pm, Po, Pk

Immuno-Chromatography Test

Neg or Pf or non-Pf

Pm

Po
Audience Poll Question:
The most likely explanation for the malaria microscopy, RDT, and PCR pattern is:

- Expired RDT kit
- Infection with Plasmodium ovale
- Infection with Plasmodium malariae
- Absence of malaria infection
Further History

- For 6 weeks prior to arrival in Canada, he had been staying with other family in Massachusetts near the New Hampshire border
- Wooded area in the backyard, and patient endorsed finding ticks on his person
- Daughter removed a small dark foreign-body from the patient with tweezers upon arrival in Canada
Panel Question:
What could be going on here?
<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Babesia</th>
<th>Plasmodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy</td>
<td>Rings</td>
<td>Rings</td>
</tr>
<tr>
<td></td>
<td>Tetrads (Maltese Cross)</td>
<td>Schizonts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gametocytes</td>
</tr>
<tr>
<td>Malaria Rapid Diagnostic Test</td>
<td>Negative</td>
<td>Positive for Pf</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less sensitive for non-Pf</td>
</tr>
<tr>
<td>PCR</td>
<td>Cross-reactive with standard 18S genus level assays</td>
<td>Logarithmic curve with lower ct value at parasitemia &gt;1%</td>
</tr>
</tbody>
</table>
Clinical Case 3

- 28 year-old previously well, Ghanian-born woman, traveled home to VFR in urban Ghana x 1 month
- Presents 5 days after return home with a day of fever and chills
- Pre-travel advice obtained, Malarone prescribed and filled in Canada
- Patient took Malarone each day 1-hr before breakfast, and began her prophylaxis 1 day prior to departure from Canada
Audience Poll Question:
The most likely explanation for the malaria microscopy and RDT pattern is:

- Infection with P. falciparum malaria
- Inadequate absorption of atovaquone-proguanil
- Drug resistant P. falciparum infection
- All of the above
The most likely explanation for the malaria microscopy and RDT pattern is:

- Infection with *P. falciparum* malaria
- Inadequate absorption of atovaquone-proguanil
- Drug resistant *P. falciparum* infection
- All of the above
### Top Countries of Exposure

**P. falciparum**

N=282

<table>
<thead>
<tr>
<th>Country of Exposure</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigeria</td>
<td>33</td>
</tr>
<tr>
<td>Ghana</td>
<td>29</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>21</td>
</tr>
<tr>
<td>Cameroon</td>
<td>20</td>
</tr>
<tr>
<td>Cote d'Ivoire</td>
<td>20</td>
</tr>
<tr>
<td>Guinea</td>
<td>18</td>
</tr>
<tr>
<td>Uganda</td>
<td>14</td>
</tr>
<tr>
<td>Congo, Democratic Republic Of The</td>
<td>13</td>
</tr>
<tr>
<td>Kenya</td>
<td>12</td>
</tr>
<tr>
<td>Chad</td>
<td>8</td>
</tr>
<tr>
<td>Mozambique</td>
<td>8</td>
</tr>
<tr>
<td>Liberia</td>
<td>8</td>
</tr>
<tr>
<td>Benin</td>
<td>7</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>7</td>
</tr>
<tr>
<td>Tanzania, United Republic of</td>
<td>7</td>
</tr>
<tr>
<td>Togo</td>
<td>6</td>
</tr>
<tr>
<td>Congo</td>
<td>6</td>
</tr>
</tbody>
</table>
The most likely explanation for the malaria microscopy and RDT pattern is:

- Infection with *P. falciparum* malaria
- **Inadequate absorption of atovaquone-proguanil**
- Drug resistant *P. falciparum* infection
- All of the above
Atovaquone is highly lipophilic with low aqueous solubility and is therefore poorly absorbed unless consumed with a fatty meal.

Co-administration of atovaquone and a fatty meal leads to a 5-fold increase in maximum plasma concentration (Cmax) over fasting.
## Serum Drug Concentrations

Table 1  Clinical and parasitologic parameters in a patient with *Plasmodium falciparum* malaria who failed atovaquone-proguanil chemoprophylaxis.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Parasitemia (by thin film microscopy)</th>
<th>Expected plasma drug concentration</th>
<th>Plasma drug concentration&lt;sup&gt;a&lt;/sup&gt;, atovaquone</th>
<th>Plasma drug concentration&lt;sup&gt;a&lt;/sup&gt;, proguanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 of illness</td>
<td>3%</td>
<td>Atovaquone: 11.5 µg/mL; Proguanil: 0.509 µg/mL</td>
<td>2 ng/mL (0.002 µg/mL)</td>
<td>1.3 ng/mL (0.0013 µg/mL)</td>
</tr>
<tr>
<td>Day 3 of illness</td>
<td>&lt;0.1%</td>
<td>Atovaquone&lt;sup&gt;b&lt;/sup&gt;: 9.43 µg/mL; Proguanil&lt;sup&gt;b&lt;/sup&gt;: 0.102 µg/mL (102 ng/mL)</td>
<td>1.3 ng/mL (0.0013 µg/mL)</td>
<td>0.7 ng/mL (0.0007 µg/mL)</td>
</tr>
</tbody>
</table>

<sup>a</sup> By LC-MS/MS; limit of detection for UV-HPLC is 100 ng/mL.

<sup>b</sup> Half-life of atovaquone is 59 h, and that of proguanil is 14.5 h [11].

The most likely explanation for the malaria microscopy and RDT pattern is:

- Infection with P. falciparum malaria
- Inadequate absorption of atovaquone-proguanil
- **Drug resistant P. falciparum infection**
- All of the above
Resistance to atovaquone results from a single point mutation in parasite cytochrome b, which leads to reduced binding affinity for atovaquone.

Resistance to proguanil involves the stepwise development of point mutations in the dhfr gene.
Atovaquone-Proguanil Treatment Failures

TABLE 3
Reported cases of AP failure for treatment of *P. falciparum*

<table>
<thead>
<tr>
<th>Patient age, sex</th>
<th>Immune status</th>
<th>Dose, duration</th>
<th>Country of acquisition</th>
<th>Molecular marker of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>45, M³⁴</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Nigeria</td>
<td>Cyt b Tyr268Asn</td>
</tr>
<tr>
<td>24, F³⁵</td>
<td>Non-immune traveler</td>
<td>Four adult tabs daily, 3 days</td>
<td>Kenya</td>
<td>Cyt b Tyr268Ser</td>
</tr>
<tr>
<td>28, M³⁶</td>
<td>Non-immune traveler</td>
<td>Four adult tabs daily, 3 days</td>
<td>Mali</td>
<td>Cyt b Tyr268Ser</td>
</tr>
<tr>
<td>28, M³⁷</td>
<td>Non-immune traveler</td>
<td>Four adult tabs daily, 3 days</td>
<td>Cameroon</td>
<td>Cyt b Tyr268Ser DHFR triple-codon mutation 51,59,108</td>
</tr>
<tr>
<td>1,5, M³⁸</td>
<td>Non-immune traveler</td>
<td>One adult tab daily, 3 days</td>
<td>Ivory Coast</td>
<td>Wt cyt b and DHFR</td>
</tr>
<tr>
<td>4, M³⁸</td>
<td>Non-immune traveler</td>
<td>One adult tab daily, 3 days</td>
<td>Ivory Coast</td>
<td>Cyt b Tyr268Ser DHFR triple-codon mutation 51,59,108</td>
</tr>
<tr>
<td>Adult, F³⁸</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Ivory Coast</td>
<td>Cyt b Tyr268Ser</td>
</tr>
<tr>
<td>38, F³⁹</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Democratic Republic of Congo</td>
<td>Wt cyt b</td>
</tr>
<tr>
<td>30, M³⁰</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Gambia</td>
<td>Wt cyt b</td>
</tr>
<tr>
<td>33, M³⁰</td>
<td>Non-immune traveler</td>
<td>Four adult tabs daily, 3 days</td>
<td>Kenya, Tanzania</td>
<td>Wt cyt b</td>
</tr>
<tr>
<td>56, M³⁰</td>
<td>Semi-immune</td>
<td>Four adult tabs daily, 3 days</td>
<td>Nigeria</td>
<td>Wt cyt b</td>
</tr>
<tr>
<td>25, F³¹</td>
<td>Non-immune traveler</td>
<td>Two adult tabs twice a day, 3 days</td>
<td>Sierra Leone</td>
<td>Cyt b Tyr268Ser DHFR C59R, S108N</td>
</tr>
</tbody>
</table>

Sequencing results of *Plasmodium falciparum* isolate

- Cytochrome b Y268N/S/C = Y (wild type)
- DHFR C50R = C (wild type)
- DHFR N51I = I (mutant)
- DHFR C59R = R (mutant)
- DHFR S108N = N (mutant)

- Patient did not absorb atovaquone and then was left with proguanil monoprophylaxis in the setting of a triple-mutant *P. falciparum* infection
Clinical Case 4

- 16-year-old male volunteered in Ghana x 3 weeks in June and July, without malaria prophylaxis
- 10 days after return, presented to ER with 4-day history fever, chills, headache, nausea, vomiting
- Past travel history – Kenya 1 year prior

Physical Exam / Labs:
- Hypotensive
- Platelets 19 bil/L
- ALT 134 U/L, AST 106 U/L
Clinical Case 4

- Thick and thin blood film positive for P. falciparum malaria, parasitemia 2.5%
- Malaria RDT positive for HRP-2 antigenemia
- Treated with a 3-day course of IV artesunate + po Malarone
- Clinically improved on day 5 of admission, and discharged home with negative blood smears, though HRP-2 remained detectable
- Follow-up 1 week post-discharge: asymptomatic
Clinical Case 4

- One month later, patient returned to ER with 2-day hx of recurrent HA, nausea, and vomiting without fever
- Laboratory investigations benign
- Repeat malaria testing:
  - Thick and thin blood films positive, parasitemia <0.1%
  - RDT positive for isolated HRP-2 antigenemia
Panel Question:
What could be going on here?
<table>
<thead>
<tr>
<th>Date</th>
<th>Parasite</th>
<th>Stages</th>
<th>Parasitemia (%)</th>
<th>ICT kit</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 28</td>
<td>Pf</td>
<td>Rings</td>
<td>2.5</td>
<td>T1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>July 28</td>
<td>Pf</td>
<td>Rings, Young trophs</td>
<td>1.2</td>
<td>T1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>July 29</td>
<td>Pf</td>
<td>Rings, Young trophs</td>
<td>2.0</td>
<td>T1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>July 29</td>
<td>Pf</td>
<td>Rings</td>
<td>0.1</td>
<td>T1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>July 30</td>
<td>Pf (based on ICT kit)</td>
<td>No parasites found</td>
<td>N/A</td>
<td>T1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>Aug 1</td>
<td>Pf (based on ICT kit)</td>
<td>No parasites found</td>
<td>N/A</td>
<td>T1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>Aug 3</td>
<td>Pf (based on ICT kit)</td>
<td>No parasites found</td>
<td>N/A</td>
<td>T1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>Sep 6</td>
<td>Po only Pf not seen</td>
<td>Growing and Mature Trophs of Po</td>
<td>&lt; 0.1</td>
<td>T1 1+ T2 Neg</td>
<td>Both Pf and Po detected</td>
</tr>
<tr>
<td>Sep 7</td>
<td>Po only Pf not seen</td>
<td>Growing and Mature Trophs of Po</td>
<td>&lt; 0.1</td>
<td>T1 1+ T2 Neg</td>
<td>Not done</td>
</tr>
<tr>
<td>Sep 10</td>
<td>Po only Pf not seen</td>
<td>Growing and Mature Trophs of Po</td>
<td>&lt; 0.1</td>
<td>T1 1+ T2 Neg</td>
<td>Not done</td>
</tr>
</tbody>
</table>
Clinical Case 4

- Patient treated with 3-day course of Malarone and resolved quickly
- Species identification results then obtained, and patient treated with 4 doses of oral chloroquine and 14-day course of primaquine following G6PD testing
- Follow-up 2 weeks post-treatment: asymptomatic, negative blood smears
5 Key Points – Malaria Diagnostics

- Microscopy remains the gold standard diagnostic tool and is the only technique that can reliably distinguish asexual from sexual parasitemia.
- RDTs are designed to detect *P. falciparum* with >95% sensitivity at parasitemia of 0.004% (200 parasites/uL).
- Sensitivity of RDTs for non-falciparum malaria can be as low as 15-30% and is reduced for all species with very low parasitemias.
- Babesiosis can produce false positive results on microscopy and standard genus-level Plasmodium PCR assays.
- Thick and thin smears ± RDT should be performed on all febrile returned travelers from risk areas even in the setting of seemingly appropriate prophylaxis.
Clinical Case 5

- 41-year-old UK-born vegetarian triathlete referred to our unit with a several week history of severe myalgia, fatigue, and high-grade eosinophiliaia (3.5 bil/L)
- Benign travel history
- 6-weeks prior, he consumed a large piece of barbecued pig at his in-laws’ house
- Within a few days, he noted significant, function-limiting diffuse myalgia and fatigue
Panel Question:
What is your differential diagnosis for this patient?
Clinical Case 5

- Patient underwent full rheumatologic work-up, which was negative
- Inflammatory markers including CK, CRP, and ESR were all elevated
- Serology for Toxocara, Strongyloides, Filaria, Schistosoma, and Trichinella were all negative
- By 5 months after onset, myalgia and eosinophilia had almost resolved (0.51 bil/L)
Audience Poll Question: All of the following statements are probably true except:

- In Canada, bear and walrus are more likely associated with human trichinosis than pig
- Antihelminthics therapy is most effective early on in the course of trichinosis
- The diagnosis of trichinosis is excluded in this patient by negative serology
- Eosinophilia and myalgia usually take months to resolve even with antihelminthics treatment
Trichinella Serology

- EIA-based assays
- IgG response is slow and proportional to larvae ingested
- Antibody detectable at 2-4 weeks post-infection; peaks at 3-6 months; declines thereafter

- Performance characteristics of assays:
  - CDC – sensitivity 93%, specificity 91%
  - NRCP – sensitivity 85%, specificity 93% against *T. spiralis* or *T. nativa*
  - Cross-reactivity – *Strongyloides*, filarial helminths
MAJOR TRICHINELLOSION OUTBREAK IN NORTHERN LAOS

304 suspected cases seen at the hospital

134 suspected cases not attending the hospital and interviewed by the team in the villages

138 patients interviewed

133 Trichinella ELISA tests

90 ELISA positive confirmed cases

650 estimated number of cases from May to 21 June after calculation of attack rates in the different foci

68% seropositive

Figure 3. Results of the Trichinella outbreak investigation (15-21 June 2005).
1. Only 55% seropositive despite high probability of disease (compatible symptomatology and epidemiology)

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Gender</th>
<th>Age</th>
<th>WBC (x 10^9/L)</th>
<th>Eosin. (x 10^9/L)</th>
<th>% Eosin.</th>
<th>CPK (U/L)</th>
<th>ELISA*</th>
<th>CF†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>28</td>
<td>16.4</td>
<td>10.82</td>
<td>66</td>
<td>239</td>
<td>NEG (1:32)</td>
<td>NEG</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>31</td>
<td>13.4</td>
<td>6.03</td>
<td>45</td>
<td>500</td>
<td>1:128</td>
<td>NEG</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NEG (1:32)</td>
<td>NEG</td>
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<tr>
<td>4</td>
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<td></td>
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<td></td>
<td></td>
<td>1:512</td>
<td>1:32</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1:128</td>
<td>NEG</td>
</tr>
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<td>6</td>
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<td>NEG</td>
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<tr>
<td>9</td>
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<td></td>
<td>1:256</td>
<td>NEG</td>
</tr>
</tbody>
</table>

* ≥ 1/128 was considered positive
† any titre was considered positive

5 Key Points – Trichinosis

- Trichinosis is a disease caused by parasitic nematode residing in the theoretically edible flesh of many mammals.
- Clinical and laboratory features contribute to the diagnosis of trichinosis.
- High-grade eosinophilia and myopathy are classic clinical features.
- Antihelminthics may play a role early in disease when adults are still in the gut.
- Larvae of *Trichinella* species are best eaten cooked.
Clinical Case 6

- 58 year-old previously well, UK-born woman presents with a 20-year history of pruritic, rapidly migrating, serpiginous, erythematous rash on back, buttocks, and legs once per month lasting 3-5 days
- Rheumatologic, allergic, and dermatologic work-up was negative
- Referred to the Tropical Disease Unit for query cutaneous larva migrans
- Travel history = 2 weeks in each of Thailand and the Gambia in the year prior to onset
Audience Poll Question:
The most likely cause of creeping eruption in this case is:

- Ancylostoma duodenale
- Ancylostoma braziliense
- Gnathostoma spinigerum
- Loa loa
- Strongyloides stercoralis
### Table 8  Differential diagnosis of linear lesions in returning travellers.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Diagnosis</th>
<th>Travel and traveller factors</th>
<th>Skin problem characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common</strong></td>
<td>Cutaneous larva migrans&lt;sup&gt;d&lt;/sup&gt; (nonhuman nematodes)</td>
<td>Tropics, especially Caribbean; beach holidays; walking barefoot or sitting on sandy soil; preponderance in children and teenagers</td>
<td>Migratory. Narrow serpiginous tract that moves a few cm per day; feet &gt; buttocks &gt; trunk</td>
</tr>
<tr>
<td><strong>Less common</strong></td>
<td>Phytophotodermatitis&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Worldwide; beach holidays; skin exposure to furocoumarin containing compound, e.g. citrus juice, then sun</td>
<td>Nonmigratory. Painful burning erythema, then vesicles, then hyperpigmentation; mild puritis; streaky lesions on skin exposed to furocoumarins and sun</td>
</tr>
<tr>
<td></td>
<td>Jelly fish sting</td>
<td>Tropics, subtropics; swimming in ocean</td>
<td>Nonmigratory. Painful, pruritic, linear lesions; may be systemic features</td>
</tr>
<tr>
<td></td>
<td>Blister beetle dermatitis</td>
<td>Wide distribution, especially South America; rural; cantharidin or pederin toxin released when beetle crushed on skin</td>
<td>Nonmigratory. Painful vesicular dermatitis in a linear array; exposed skin</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Human helminth causes of creeping eruption e.g. fasciolaoaisis, Strongylodes stercoralis (larva currens)</td>
<td>Tropics and subtropics; developing regions; various exposures including walking barefoot; ingesting undercooked foods</td>
<td>Migratory. Larva currens occurs on buttocks as broad pruritic serpiginous tract that moves several cm per hour</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis: CHIEF COMPLAINT DERMATOLOGIC (N=865)</th>
<th>Total Number</th>
<th>Top 3 Source Countries for Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>155</td>
<td>Mexico, Cuba, Peru</td>
</tr>
<tr>
<td>Arthropod Bite</td>
<td>135</td>
<td>United States, Cuba, Mexico</td>
</tr>
<tr>
<td>Skin and soft-tissue infection†</td>
<td>107</td>
<td>India, Cuba, Costa Rica</td>
</tr>
<tr>
<td>Cutaneous larva migrans</td>
<td>62</td>
<td>Jamaica, Mexico, Barbados</td>
</tr>
<tr>
<td>Animal Bite**</td>
<td>30</td>
<td>Thailand, India, Honduras</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>21</td>
<td>Syria, Libya, Costa Rica, Belize, Afghanistan</td>
</tr>
<tr>
<td>Marine Envenomation</td>
<td>19</td>
<td>Cuba, United States, Mexico</td>
</tr>
</tbody>
</table>
IPAC Issues to Consider

- Simple intestinal strongyloidiasis or larva currens in a patient NOT shedding larvae >> routine precautions
- Strongyloides hyperinfection / disseminated strongyloidiasis >> contact precautions
  - Why?
    - Filariform larvae are motile and will penetrate intact skin
    - Filariform larvae are found in all bodily effluents and can reside on surfaces and at ambient temperatures
    - Filariform larvae are difficult to disinfect
    - Person-to-person transmission is possible and difficult to document
Clinical Case 6

- Treated for larva currens (simple intestinal strongyloidiasis) with ivermectin 200 mcg/kg x 2 doses
- Initial eosinophil count 0.58 x 10^9/L; 1-month post-treatment 0.37 x 10^9/L
- Initial *Strongyloides* serology 17.51 OD units (negative <1.7); 18-month post-treatment serology 4.4
- Symptoms resolved with therapy
5 Key Points – Larva Currens

- Rapidly migrating serpiginous rash due to *Strongyloides stercoralis*
- Rate of migration differentiates it from other serpiginous rashes which migrate more slowly
- Confirmation of infection by serology + examination of stools for larvae
- Prompt initiation of therapy essential to minimize risk of hyperinfection in setting of immune suppression
- May also occur in patients with hyperinfection or dissemination therefore contact precautions for hospitalized patients with larva currens until stools and sputum deemed negative
Clinical Case 7

- 20-year-old male born in Afghanistan but lived in India from 1992-2001 before immigrating to Canada
- Previously healthy, on no medications
- Suffered 3 witnessed tonic-clonic seizures and was taken to hospital
- Started on anti-seizure medication
- Investigated for the cause of new onset seizures with blood work and imaging........
Panel Question:
What is your differential diagnosis for this patient?
Natural History of Parenchymal Neurocysticercosis

Viable Cyst
-fluid filled
-Scolex
-Immune Evasion

Cysticercal Granuloma
-“Enhancing Lesion”
-Edema

Degenerated Cysticercus
-Punctate Calcified Scar

Asymptomatic
Seizures, Headache

Symptom Resolution; Potential for Seizure Recurrence
Panel Question:
What is your suggested treatment approach for Single-Lesion NCC?
Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial


Summary
Background Neurocysticercosis causes a substantial burden of seizure disorders worldwide. Treatment with either praziquantel or albendazole has suboptimum efficacy. We aimed to establish whether combination of these drugs would increase cysticidal efficacy and whether complete cyst resolution results in fewer seizures. We added an increased dose albendazole group to establish a potential effect of increased albendazole concentrations.

Methods In this double-blind, placebo-controlled, phase 3 trial, patients with viable intraparenchymal neurocysticercosis were randomly assigned to receive 10 days of combined albendazole (15 mg/kg per day) plus praziquantel (50 mg/kg per day), standard albendazole (15 mg/kg per day), or increased dose albendazole (22.5 mg/kg per day). Randomisation was done with a computer generated schedule balanced within four strata based on number of cysts and concomitant antiepileptic drug. Patients and investigators were masked to group assignment. The primary outcome was complete cyst resolution on 6-month MRI. Enrolment was stopped after interim analysis because of parasiticidal superiority of one treatment group. Analysis excluded patients lost to follow-up before the 6-month MRI. This trial is registered with ClinicalTrials.gov, number NCT00441285.

Findings Between March 3, 2010 and Nov 14, 2011, 124 patients were randomly assigned to study groups (41 to receive combined albendazole plus praziquantel [39 analysed], 43 standard albendazole [41 analysed], and 40 increased dose albendazole [35 analysed]).
5 Key Points – NCC

- Human infection with *Taenia solium* can lead to 2 different forms of disease:
  - Taeniasis = ingestion of pig >> adult worm in gut
  - Cysticercosis = ingestion of human stool >> larvae in brain or other tissue tissue

- Human-to-human transmission directly has infection control implications

- Symptoms of NCC begin when host overtakes parasite’s ability to evade immunologic mechanisms of clearance

- Treatment of viable or transitionally viable NCC of low to moderate cyst burden with combination albendazole and praziquantel is standard

- Single lesion NCC from the Indian sub-continent tends to have a benign course
Clinical Case 8

- 25-year-old Canadian born tourist who had traveled to the Manu reserve in 2011
- Returned home with ulcers on the arm (10-cm), lip, and neck, as well as a thickened lymphatic cord
- Diagnosed with cutaneous leishmaniasis and started on a 20-day course of IV sodium stibogluconate
- 11 days into therapy, treatment was interrupted by severe biochemical pancreatitis and thrombocytopenia with bleeding
Audience Poll Question:
What would you choose to do next:

- Switch him to topical paromomycin
- Switch him to parenteral amphotericin B
- Switch him to oral miltefosine
- Switch him to oral fluconazole
- Nothing
Clinical Case 8

- Patient was switched to liposomal amphotericin 3 mg/kg x 5 days, with weekly doses thereafter to 7 weeks
- Recovery was full and uneventful
- 2 years after treatment, he was referred to the TDU for a small new ulcer at the margin of the large scar on the arm
- Confirmed by PCR to be a relapse of *Leishmania Viannia braziliensis* infection
Clinical Case 8

- Treated with an 8-week course of high-dose oral fluconazole and topical paromomycin with wound care
- Counseled patient around potential relapse with trauma to healed ulcers
- ENT examination was normal
- Lesion healed uneventfully
- Patient remains well 2 years after oral treatment
Periodic Table of the Elements

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*Lanthanide Series

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+Actinide Series

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FDA NEWS RELEASE

For Immediate Release: March 19, 2014
Media Inquiries: Stephanie Yao; 301-796-8094, stephanie.yao@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Impavido to treat tropical disease leishmaniasis

The U.S. Food and Drug Administration today approved Impavido (miltefosine) to treat a tropical disease called leishmaniasis.

Leishmaniasis is a disease caused by Leishmania, a parasite which is transmitted to humans through sand fly bites. The disease occurs primarily in people who live in the tropics and subtropics. Most U.S. patients acquire leishmaniasis overseas.

Impavido is an oral medicine approved to treat the three main types of leishmaniasis: visceral leishmaniasis (affects internal organs), cutaneous leishmaniasis (affects the skin) and mucosal leishmaniasis (affects the nose and throat). It is intended for patients 12 years of age and older. Impavido is the first FDA-approved drug to treat cutaneous or mucosal leishmaniasis.

“Today’s approval demonstrates the FDA’s commitment to making available therapeutic options to treat tropical diseases,” said Edward Cox, M.D., director of the Office of Antimicrobial Products in the FDA’s Center for Drug Evaluation and Research.
Practical Treatment of CL?

- Parenteral therapies such as pentavalent antimony and amphotericin formulations are toxic, expensive (liposomal amphotericin), and difficult to access.

- Oral therapies such as miltefosine expensive and difficult to access.

- Local therapies may be inappropriate for metastasizing species like *L. V. braziliensis*.

- Species identification may not be readily available or timely.
High-Dose Oral Fluconazole Therapy Effective for Cutaneous Leishmaniasis Due to *Leishmania (Vianna) braziliensis*

Anastácio Q. Sousa,1 Mércia S. Frutuoso,2,3 Elisabete A. Moraes,4 Richard D. Pearson,5 and Margarida M. L. Pompeu3

1Department of Internal Medicine, School of Medicine, 2Christus School of Medicine, 3Department of Pathology, School of Medicine, 4Department of Physiology and Pharmacology, School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil; and 5Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia School of Medicine, Charlottesville

We report for the first time the successful use of fluconazole to treat cutaneous leishmaniasis due to *Leishmania braziliensis*. We used escalating doses from 5 to 8 mg/kg per day. At a dose of 5 mg/kg per day, 75% patients were cured, and at 8 mg/kg per day, the cure rate was 100%. Fluconazole was well tolerated.

Fluconazole impedes the growth of leishmania in culture by inhibiting cytochrome P-450-mediated 14-α-demethylation of lanosterol, blocking ergosterol synthesis, and causing accumulation of 14-α-4methyl sterols [9]. In this study, we evaluate the use of high-dose oral fluconazole for the treatment of CL due to *L. braziliensis*.

**METHODS**

Fluconazole treatment was used in individuals with contraindications to receive pentavalent antimonial drugs. They included the elderly population, those with diabetes mellitus, and patients receiving immunosuppressants. The success rate was assessed by clinical and histopathological evaluation.
Results - Outcomes

Table 1. Characteristics of the Patients and Results of Treatment According to Fluconazole Dose

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5 mg/kg (n = 8)</th>
<th>6.5 mg/kg (n = 14)</th>
<th>8 mg/kg (n = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>37.5 (8–88)</td>
<td>16.5 (2–64)</td>
<td>40.5 (10–58)</td>
<td>.271</td>
</tr>
<tr>
<td>Female sex, no. (%) of patients</td>
<td>3 (37.5)</td>
<td>7 (50)</td>
<td>5 (83.3)</td>
<td>.219</td>
</tr>
<tr>
<td>Duration of the disease, median weeks (range)</td>
<td>8 (4–64)</td>
<td>12 (2–64)</td>
<td>10 (4–24)</td>
<td>.662</td>
</tr>
<tr>
<td>Duration of treatment, median weeks (range), mean weeks</td>
<td>7.5 (4–12), 7.6</td>
<td>6 (4–10), 6.2</td>
<td>4 (4–5), 4.2</td>
<td>.012</td>
</tr>
<tr>
<td>Cure rate, no. (%) of patients</td>
<td>6 (75)</td>
<td>13 (92.8)</td>
<td>6 (100)</td>
<td>.272</td>
</tr>
</tbody>
</table>

Distributions of continuous variables were described by median values (range) and compared using the Kruskal-Wallis test. Proportions were compared using the χ² test.

Review

Local or systemic treatment for New World cutaneous leishmaniasis? Re-evaluating the evidence for the risk of mucosal leishmaniasis

Johannes Blum, Diana N.J. Lockwood, Leo Visser, Gundel Harms, Mark S. Bailey, Eric Caumes, Jan Clerinx, Pieter P.A.M. van Thiel, Gloria Morizot, Christoph Hatz, Pierre Buffet

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b London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK
c Leiden University Medical Centre, Albinusdreef 2, C5P-41, 2333 ZA Leiden, The Netherlands
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e Royal Centre for Defence Medicine, Vincent Drive, Birmingham B15 2SQ, UK
f Service de Maladies Infectieuses et Tropicales, Hôpital Pitié Salpêtrière, 47 Boulevard de l'hôpital, 75651 Paris Cedex 13, France
Local Therapy for NWCL?

- Exclusion of mucosal involvement by ENT examination
- Exclusion of multiple lesions
- Lesion <4 cm²
- Exclusion of localization to head or neck
- Absence of immunosuppression
- Infection acquired outside Bolivia
- No clinical evidence of lymphatic spread
- Patient will be adherent to treatment and long-term follow-up is feasible

5 Key Points – Tegumentary Leishmaniasis

- TL is on the differential diagnosis of ulcers from the tropics
- Evidence for prevention of mucosal disease following parenteral treatment of NWCL is scant
- Available parenteral therapies are highly toxic and difficult to access in Canada, and require admission to medical day units
- Gentler oral and topical options are becoming increasingly utilized in NWCL
- Species-directed therapy for NWCL from countries with multiple co-endemic species may be difficult
Clinical Case 9

- 59-year-old Philippines-born woman referred for a 10-year history of a pruritic papule on the left second dorsal finger with subsequent involvement of the left MCP area and wrist
- Over time, the lesions took on more a granulomatous appearance with some central ulceration
- Treatment consisted of topical steroids
- There were no complaints of fever, sweats, chills, cough, dyspnea, weight loss, motor weakness, pain in the extremities, paresthesias, or anesthesia
- She denied work in the garden or any antecedent trauma, but had maintained a fish tank since 1992, and cleaned the filter, tank, and rocks approximately every 2 months using mostly her left hand and arm
- She immigrated to Canada 30 years prior, and returned to the Philippines for 1-month 3- and 6-years prior to presentation
Panel Question:
What is your differential diagnosis for this patient?
Clinical Case 9

- HIV negative
- Chest x-ray – spotty opacities in upper lung zones
- Histopathology of skin biopsy:
  - Suppurative microabscesses with non-necrotizing granulomas
  - ZN, PAS, GMS staining negative
  - Fungal and AFB culture negative
  - PCR for TB and NTM negative
Clinical Case 9

- **Summary of Findings:**
  - Recurrent nodulo-ulcerative lesions on the extremity
  - Granulomatous inflammation on histopathology
  - Absence of acid-fast bacilli on histopathology
  - Markedly positive tuberculin skin test
  - Evidence of likely old TB in the lungs
Audience Poll Question: The clinical picture most likely represents:

- Active infection with *Mycobacterium tuberculosis*
- Infection with a rapidly-growing *Mycobacterium*
- Latent infection with *Mycobacterium tuberculosis*
- Infection with *Sporothrix schenckii*
- Sporotrichoid leishmanianiasis
Erythema Induratum of Bazin

- “Tuberculid”
  - Immunologic hypersensitivity reaction to *Mycobacterium tuberculosis* antigens
- Diagnostic Criteria for EI:
  - Nodules with purulent drainage
  - Absence of AFB on histopathology
  - Lobular (granulomatous) panniculitis on histopathology
  - PPD strongly positive
  - Clinical response to anti-tuberculous therapy
Clinical Case 9

- Patient was treated by our TB clinic for active tuberculosis with a combination of rifampin, pyrizinamide, ethambutol, and moxifloxacinc x 6 months
- Recovery was complete and uneventful
5 Key Points – Tuberculids

- Tuberculids are a form of cutaneous TB
- Represent an immunologic hypersensitivity reaction to M. tuberculosis antigens
- History of repeated biopsies for fungal and AFB staining/culture common
- Hallmark features are the absence of AFB on histopathology and markedly positive TST
- Treatment is as for active pulmonary TB
Clinical Case 10

- 77-year-old Sudanese man referred for a 6-month history of a large painless hyperkeratotic plaque on the right arm
- Past medical history notable for type 2 diabetes (40-years), hypertension, CAD
- Immigrated to Canada 12 years ago, and recently returned to VFR for 6 months in rural Sudan, where he was exposed to dry trees and soil on his farm but no trauma
- Systemically completely well
Panel Question: What is your differential diagnosis for this patient?
Clinical Case 10

- Tuberculin skin test negative
- Chest x-ray normal
- HIV and HTLV-1 negative
- Skin biopsy with histopathology:
  - Granulomatous reaction of superficial and deep dermis with central necrosis
  - Absence of foreign body
  - Staining with ZN, GMS, PAS negative
  - TB PCR negative
  - Fungal culture negative
Mycobacterial culture

- Positive for *Mycobacterium gordonae*

- Usually interpreted as an indicator organism or non-pathogen......

- But, in an elderly diabetic vasculopath granulomas on histopathology, this organism may be significant
# Cutaneous *M. gordonae*

**TABLE 1. Characteristics of Patients with Cutaneous *M. gordonae***

<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>Age (y) /Sex</th>
<th>Site(s) of Soft Tissue Involvement</th>
<th>Presentation</th>
<th>Pt. History</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shelley and Folkens¹</td>
<td>70/F</td>
<td>Left hand</td>
<td>Nodules on dorsum</td>
<td>Thorn from rose bush</td>
<td>Eth Rif × 14 days</td>
<td>Nodule reduction</td>
</tr>
<tr>
<td>2</td>
<td>McIntyre et al²</td>
<td>30/F</td>
<td>Right wrist; Left foot (sole)</td>
<td>Serosanguinous wound; fever, vomiting, anorexia, swolleninguinal lymph nodes (left)</td>
<td>Stepped on nail</td>
<td>Wrist aspirations; Cycloserine, Eth, TMP/SMX</td>
<td>Cured</td>
</tr>
<tr>
<td>3</td>
<td>Gengoux et al³</td>
<td>38/F</td>
<td>Right hand</td>
<td>Nodules on dorsum</td>
<td>Rat bite</td>
<td>Rif</td>
<td>Cured</td>
</tr>
<tr>
<td>4</td>
<td>Nakagawa⁴</td>
<td>37/F</td>
<td>Left hand (4th/5th fingers) and left wrist</td>
<td>Small aggregate (palmer side of wrist); Reduction in flexion of fingers</td>
<td>Unknown origin; no trauma</td>
<td>Nodule excision</td>
<td>Died (multiple comorbidities)</td>
</tr>
<tr>
<td>5</td>
<td>Antony</td>
<td>54/F</td>
<td>Right and left upper arms and neck</td>
<td>Small, raised papular lesions</td>
<td>Unknown origin; no trauma</td>
<td>Eth, Rif, Clarith × 90 days</td>
<td>Cured</td>
</tr>
</tbody>
</table>

Clarith indicates Clarithromycin; Eth, Ethambutol; Rif, Rifabutin; Rif, Rifampin; TMP/SMX, Trimethoprim/Sulfamethoxazole.
5 Key Points – *Mycobacterium gordonae*

- *M. gordonae* is a low pathogenicity non-tuberculous mycobacterium
- Usually interpreted as a marker of inoculation with some other environmental organism, so care must be taken to exclude other primary diagnosis
- Most reported cases occur in those with immunocompromise of some sort
- 2-3-drug combinations of standard anti-mycobacterial medications are typically chosen
- Duration of treatment is 3-6 months
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