Fever after a stay in the Tropics

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Outline

• Introduction

• Epidemiology of travel-related fever

• Update in the management of the main imported tropical conditions

World Tourism Organization
Health problems in travelers “to the tropics”

- 15-65% experience some sickness
- 5-15% need to seek medical care
- 5-10% develop fever

Fever and travel: GeoSentinels studies

**1996-2004**
- 30 travel clinics
- 17,353 ill travelers
- 22.6% of consultations

**2007-2011**
- 53 travel clinics
- 42,173 ill travelers
- 23.3% of consultations

Leder K et al. Ann Intern Med 2013

Fever and travel

Differential diagnosis of imported fever

Keystone et al. Travel Medicine
### Main causes of imported fever (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>ITMA, n=2071</th>
<th>GeoSentinel, n=6957</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Bacterial enteritis</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Skin/soft tissue infection</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Genito-urinary infection</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dengue</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

### Top tropical conditions, ITMA 2000-2006

<table>
<thead>
<tr>
<th>Region</th>
<th>Africa (n=1401)</th>
<th>Asia (n=381)</th>
<th>America (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum malaria</td>
<td>(30%)</td>
<td>Dengue (13%)</td>
<td>Non-falc. malaria (9%)</td>
</tr>
<tr>
<td>Non-falc. malaria</td>
<td>(5%)</td>
<td>Non-falc. malaria (9%)</td>
<td>Dengue (9%)</td>
</tr>
<tr>
<td>Rickettsial infection</td>
<td>(4%)</td>
<td>Enteric fever (3%)</td>
<td>Non-falc. malaria (4%)</td>
</tr>
<tr>
<td>Katayama</td>
<td>(2%)</td>
<td>P. falciparum malaria (2%)</td>
<td>Protoz. enteritis (2%)</td>
</tr>
</tbody>
</table>

### Top tropical conditions, GeoSentinel 2007-2011

- Evolving epidemiology
Tropical conditions (n,%) according to “latency”

<table>
<thead>
<tr>
<th></th>
<th>Within 1 month</th>
<th>During 2nd-3rd month</th>
<th>From 4th to 12th month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=1619</td>
<td>n=228</td>
<td>n=224</td>
</tr>
<tr>
<td>P. falciparum malaria</td>
<td>401 (25)</td>
<td>29 (13)</td>
<td>10 (4.5)</td>
</tr>
<tr>
<td>Non-falciparum malaria</td>
<td>34 (2)</td>
<td>41 (18)</td>
<td>38 (17)</td>
</tr>
<tr>
<td>Rickettsial infection</td>
<td>70 (4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dengue</td>
<td>64 (4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Katayama</td>
<td>28 (2)</td>
<td>9 (4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>15 (1)</td>
<td>1 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>Amoebic liver abscess</td>
<td>8 (0.5)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Other tropical diseases</td>
<td>39 (3)</td>
<td>4 (2)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

Main diagnoses (%) according to traveler demography

<table>
<thead>
<tr>
<th></th>
<th>Western travelers</th>
<th>Western Expatriates</th>
<th>VFR travelers</th>
<th>Foreign visitors/migrants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1245)</td>
<td>(n=300)</td>
<td>(n=286)</td>
<td>(n=240)</td>
</tr>
<tr>
<td>P.falciparum malaria</td>
<td>14</td>
<td>37</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>Non-falcip. malaria</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Rickettsial infection</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dengue</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Katayama</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bacterial enteritis</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.25</td>
<td>0</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

Less frequent febrile conditions, ITMA 2000-2006

- Few cases
  - Cyclospora enteritis (7)
  - Histoplasmosis (6)
  - Leptospirosis (6)
  - Hepatitis E (4)
  - Cryptosporidium enteritis (4)
  - Loeﬄer syndrome (3)
  - Strongyloidiasis (3)
  - Human African trypanosomiasis (3)
  - Sarcocystosis (3)

- Single cases
  - Relapsing fever
  - t. belli enteritis
  - Angiostrongyloidiasis
Evolution and outcome, ITMA 2000-2006

- Hospitalization: 27% (n = 564)
- Intensive care: 2% (n = 43)
- Death: 0.5% (n = 9)
  - Tropical conditions = 5 (all P. Falciparum malaria)
  - Cosmopolitan infections = 2
  - Non-infectious diseases = 2
  - Fever of unknown etiology = 0

Severe tropical conditions: GeoSentinel

About 5% of all post-travel consultations

Epidemiology of imported fever: conclusions

- Both tropical and cosmopolitan infections
- Etiological spectrum depending on
  - Travel destination
  - Latency period
  - Traveler demography
- Considerable morbidity
- P. falciparum malaria is the leading life-threatening condition
Fever and travel: diagnostic panorama

- P. falciparum malaria
- Non-falciparum malaria
- Dengue
- Rickettsial infection
- Enteric fever
- Katayama
- Cosmopolitan infections
- Unknown etiology
- Other tropical conditions

Malaria

Gething et al. Malar J 2011

Malaria imported to Belgium: decreasing trend?

- 240 cases in 2011

Website MIF-IOP accessed 20 Oct 2013
Malaria: clinical and laboratory predictors

Does This Patient Have Malaria?

- Splenomegaly: 6.5 (3.9-11.0)
- No localizing symptoms: 4.5
- Hyperbilirubinemia: 7.3 (5.5-9.6)
- Thrombocytopenia: 5.6 (4.1-7.5)

Malaria: progress in diagnosis

- Microscopy: card, dipstick, hybrid
- Rapid diagnostic test (RDT): cassette

Malaria RDTs: multiple combinations

<table>
<thead>
<tr>
<th></th>
<th>HRP-2</th>
<th>pLDH</th>
<th>Aldolase</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum-specific</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pan-specific</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>P. vivax-specific</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two-band tests

Three-band tests

Four-band tests
Malaria RDTs in 2013: which one to choose?

Malaria RDTs: performance in 2013

- Accurate for diagnosis of (uncomplicated) P. falciparum malaria
  - Sensitivity > 95% at parasitemia > 100/µL; specificity > 95%
  - May replace microscopy in ENDEMIC SETTINGS
    ▪ Abba K et al. Cochrane Database Syst Rev 2012
- Less accurate than EXPERT microscopy
- Equivalent to/better than ROUTINE microscopy
  - In endemic settings (Batwala Meika / 2010; Hendriksen Clin Infect Dis 2011)
  - In US hospitals (Palmer / Clin Microbiol 2003; Stauffer Clin Infect Dis 2009)

Malaria RDTs: limitations in accuracy

<table>
<thead>
<tr>
<th>False negative</th>
<th>False positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low P. falciparum parasitemia</td>
<td>Persistence HRP-2</td>
</tr>
<tr>
<td>Plasmodium other than P. falciparum</td>
<td>Delayed reading</td>
</tr>
<tr>
<td>High P. falciparum parasitemia (prozone); only HRP-2</td>
<td>Buffer substitution</td>
</tr>
<tr>
<td>P. falciparum with pfhrp2 or 3 gene deletions; only HRP-2</td>
<td>Cross reactions between species</td>
</tr>
<tr>
<td>Faint test line...</td>
<td>Concomitant conditions</td>
</tr>
</tbody>
</table>
Malaria RDTs in travel medicine

- **ALWAYS perform both RDT AND microscopy**
  - If RDT negative and no malaria predictor, microscopy may be delayed
    - Rossi et al. Malar J 2012
  - If RDT positive, microscopy immediately
    - Parasite load; species differentiation
  - If both tests negative
    - Repeat RDT/microscopy within 12-24h especially if presence of malaria predictors (Botteau. Eur J Clin Microbial Infect Dis 2006)

- **Self/peer testing during travel?**
  - Need of safety studies

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Dengue

Dengue, countries or areas at risk, 2010

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Dengue in Belgium (2005-2012)

Performed tests

Positive results

Courtesy Dr Van Embden M. CLSR, ITM Antwerp 2013
Dengue (n=64): clinical and laboratory predictors

- Leucopenia (< 4000/µL) 3.3
- Skin rash 2.8
- Thrombocytopenia (150,000/µL) 2.0

Adjusted LR+

Dengue: RDTs for diagnosis

- RDT IgM/IgG: 70-80%
- RDT NS1 Ag: 50-75%
- Dengue Duo Rapid Test: > 90%

Dengue: early diagnosis with NS1 Ag in travelers

- Study on 99 early phase serum samples of dengue patients seen at Helsinki
- Evaluated against conventional RT-PCR and virus isolation
Dengue: management

Rickettsial infection in travelers

<table>
<thead>
<tr>
<th>Rickettsial infection</th>
<th>ITMA, n=70 2000-2006</th>
<th>GeoSentinel, n=261 1996-2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spotted fever group</strong> (R. africae, R. conorii,...)</td>
<td>63 (90%)</td>
<td>231 (88%)</td>
</tr>
<tr>
<td><strong>Tick-borne</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Typhus group</strong> (R. typhi)</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td><strong>Flea-borne</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Orientia tsutsugamushi</strong></td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td><strong>Mite-borne</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others/indeterminate</strong></td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

Rickettsial infection: predictors

- Skin ulcers: 11.1
- Skin rash: 3.8
Rickettsial infection (n=70): diagnosis

- Most of the time clinical
- (Paired serology)
- PCR on eschar, (blood)

Acute schistosomiasis (Katayama) and travel

Katayama (n=38): predictor

- Eosinophil count > 500/µL 32 0.06
Katayama: diagnosis

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg detection</td>
<td>69%</td>
<td>25%</td>
</tr>
<tr>
<td>Serology</td>
<td>77%</td>
<td>72%</td>
</tr>
<tr>
<td>Serology AND egg detection</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Serum Schistosoma DNA (PCR)</td>
<td>100%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Kleins I et al. / Food Med 2011; Wichmann D et al. BMC Infect Dis 2013

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Enteric fever (Salmonella Typhi and Paratyphi A).

![Map of World showing incidence of Typhoid Fever](image)

- Enteric fever (n=16): predictors
  - Splenomegaly: Adjusted LR+ 10.0
  - Elevated transaminases (ALT > 70 IU/L): Adjusted LR+ 2.5


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Enteric fever (n=16): predictors

- Splenomegaly: Adjusted LR+ 10.0
- Elevated transaminases (ALT > 70 IU/L): Adjusted LR+ 2.5

Bottieau et al. Medicine 2007
Enteric fever in Belgium (2011)

- S. Typhi (n=25) and S. Paratyphi A (n=6)
- Resistance to nalidixic acid ("decreased cipro susceptibility": MIC>0.064 mg/ml)
  - S. Typhi: 33%
  - S. Paratyphi A: 50%
- Resistance to ciprofloxacin (MIC>1 mg/ml): 3%

Fever and travel: diagnostic panorama

P. falciparum malaria

Fever

- No focal symptom
- Hyperbilirubinemia
- Splenomegaly
- Leucopenia
- Thrombocytopenia
- Skin rash
- Elevated transaminases
- Eosinophilia
- Skin ulcer
- Katayama
- Dengue
- Rickettsial infection
- Other tropical conditions

Website ITG/IMT - NRC/CNR


http://www.itg.be
Thank you for your attention.

Interesting websites/diagnostic aids

- GIDEON at [www.gideononline.com](http://www.gideononline.com)
- FEVERTRAVEL at [www.fevertravel.ch](http://www.fevertravel.ch)
- KABISA TRAVEL at [www.kabisa.be](http://www.kabisa.be)