**The Febrile Pediatric Traveler**

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**Patient 1: Thailand travel₁**

- 16 years-old previously healthy male is admitted to a tertiary-care hospital in Indiana USA on **July 16, 2018**.
- 6 days prior to admission [PTA]: Headaches, myalgias, fever, diffuse rash over trunk and extremities [not involving palms and soles].
- 4 days PTA: Dark urine, nausea, vomiting, sore throat. Evaluated at a clinic: Viral illness.

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**Patient 1: Thailand travel₂**

- Presented to an ER with fevers, meningismus and hypotension. Referred. Admitted to PICU.
- Travel history:
  - **June 14-June 30, 2018**: Chiang Mai, Thailand. Volunteer at elephant sanctuary.
  - **June 30, 2018**: Florida. Deep sea diving, Gulf of Mexico. Lives on a farm. Exposure to horses, cows, rabbits, chickens, pigs, cat [recently died], and emus.

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**Patient 1: Thailand travel₃**

- Came to Indiana on **July 9, 2018** [1 day prior to onset of illness] for engineering summer camp.

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**Patient 1: Thailand travel₄**

- **Relevant lab abnormalities:**
  - Elevated creatinine [1.21], elevated aldolase, transaminitis, thrombocytopenia, coagulopathy, elevated bilirubin and urinary urobilinogen. **CSF pleocytosis** [WBC 297 with 80% neutrophils], elevated CSF protein [140], with CSF glucose 65.
  - Multiplex PCR, CSF: Non-reactive
  - Chest X-ray: Right lower lobe infiltrate with bilateral pleural effusions.
Patient 2: Niger travel₁
- 22 months-old previously healthy female.
- Lives in Indiana USA.
- Back home for ~1 week after spending 2½ months in Niger visiting family.
- Onset of diarrhea on the flight back home.
- >10 diapers/day [with leakage].
- 1 day after onset of diarrhea: Fevers, as high as 105°F [40.5°C].
- 3 years-old sister with similar diarrheal illness.

Patient 2: Niger travel₂
- Evaluated at an urgent care center 2 days prior to admission. IVF; acetaminophen.
- Urinalysis [normal], rapid GAS [negative], urine and stool specimens for culture sent.
- Abdominal pain, truncal rash, no conjunctivitis.
- WBC: 4500, 60% neutrophils. Platelets: 268,000. Normal liver enzymes.

Patient 2: Niger travel₃
**Pre-travel:**
- Visited primary care physician. No travel clinic.
- Prescribed mefloquine as antimalarial prophylaxis.
- No antimicrobial “self-treatment”.
- Has hepatitis A vaccination.
- No typhoid vaccination [based on age].
- 1 dose of measles-mumps-rubella vaccine.

 Differential diagnoses?
- Malaria
- Leptospirosis
- Hepatitis E
- Typhoid fever [enteric fever]
- Dengue fever
- Meningococemia with meningitis
- Japanese encephalitis virus
- Others?
The febrile pediatric traveler: Need to worry?

- Fever is a non-specific clinical feature. Many etiologies. Tropical infection? Cosmopolitan infection?
- Delay in a diagnosis and effective therapy: High risk of morbidity, and potentially mortality.
- Non-targeted investigations: Expensive.

Illness in children after international travel: GeoSentinel

- 1840 pediatric patients. 37,791 adults.
- Only patients with probable or confirmed diagnoses included, ~ 86%.
- Most common reason for travel: Tourism [68%].
- More VFR travel in children [17%].


The febrile pediatric traveler: Determining a cause

- Risk assessment: Country/region traveled.
- Pre-travel vaccines and chemoprophylaxis
- Duration of travel. Determine a likely incubation period for the illness. Onset of disease in relation to travel. Known outbreaks in traveled area?
- History [potential exposures, symptoms] + physical examination [rash, hepatosplenomegaly]

10.0 μm
Illness in children: GeoSentinel®
- Diarrheal: 28%
- Dermatologic: 25%
- Systemic febrile illnesses: 23%
  - Malaria: 38%
  - Viral syndromes: 28%
  - Unspecific febrile illnesses: 11%
    - Dengue fever: 6%
    - Enteric fever: 6%
- Respiratory: 11%


Undifferentiated febrile illness: Definition
- Fever without a focus of infection on initial physical examination or in basic laboratory tests.
- Diagnostic and therapeutic challenge.
- Empiric therapies needed & prescribed?
- Is it viral, bacterial, or parasitic? Other etiologies?
The febrile pediatric traveler: Determining a cause
- Risk assessment: **Country/region traveled.**
- Pre-travel vaccines and chemoprophylaxis
- Duration of travel. Determine a likely incubation period for the illness. Onset of disease in relation to travel.
- History [potential exposures, symptoms] + physical examination [rash, hepatosplenomegaly]
Risk assessment: Exposures, precautions taken
Regional variations of disease

- Dermatologic: Latin America
- Diarrheal disorders: Middle East & North Africa
- Systemic febrile illnesses: Sub-Saharan Africa & Asia

**Asia:**
- Enteric fever: 19%
- Dengue fever: 17%
- Malaria: 9%

**Africa:**
- Malaria: 64% ($P. falciparum$, 56%)

The febrile pediatric traveler: Determining a cause

- Risk assessment: Country/region traveled.
- Pre-travel vaccines and chemoprophylaxis.
- Duration of travel. Determine a likely incubation period for the illness. Onset of disease in relation to travel. Most infections present within ~1 month.
- History (potential exposures, symptoms) + physical examination (rash, hepatosplenomegaly)
Incubation periods, causes of fever: < 14 days
- Malaria [Reminder: If < 7 days, not likely malaria]
- Dengue
- Enteric fever: typhoid, paratyphoid
- Rickettsial infections
- Leptospirosis
- Diarrheal illnesses: shigellosis, salmonellosis, campylobacteriosis
- Viral respiratory infections
- Yellow fever
- Meningococcal sepsis and meningitis

Incubation periods, causes of fever: 2-6 weeks
- Malaria
- Dengue
- Enteric fever: typhoid, paratyphoid
- Rickettsial infections
- Leptospirosis
- Diarrheal illnesses: shigellosis, salmonellosis, campylobacteriosis
- Viral respiratory infections
- Yellow fever
- Meningococcal sepsis and meningitis

Incubation periods, causes of fever: > 6 weeks
- Malaria
- Tuberculosis
- Hepatitis B
- Visceral leishmaniasis
- Schistosomiasis
- Amoebic liver abscess
- Brucellosis
- Visceral larva migrans
- Filariasis
- Endemic mycoses

The febrile pediatric traveler: Determining a cause
- Risk assessment: Country/region traveled.
- Pre-travel vaccines and chemoprophylaxis
- Duration of travel. Determine a likely incubation period for the illness. Onset of disease in relation to travel.
- History [potential exposures, symptoms] + physical examination [rash, hepatosplenomegaly]
- Abnormal labs: Eosinophilia, thrombocytopenia, leukocytosis/leukopenia, Transaminitis, Renal dysfunction.
Fever in returned travelers, Birmingham, UK
- Prospective review, hospital admissions, 2½ years
- Fever >37.5°C, travel to tropics/subtropics past 12 months
- 153 children. Median age: 5 years [0.1-15]
- 133 [85%] visited South Asia
- 18/135 [13%]: Malaria prophylaxis
- Median time to presentation after travel: 4 weeks
- Viral illness [34%], diarrheal illness [27%], malaria [14%]
- Treatable cause of illness: 46%

Types of illness, travel to tropics
- Incidence rates of common illness [episodes/100 person-weeks]: Children [16.9], adults [15.1]
- Diarrhea, abdominal pain, and fever: Most common.
- Similar incidence of morbidity.
- More fever in children. Especially, 0-5 years of age.
- Most episodes: First 10 days of travel.

Diagnostic syndrome groups, hospitalization rates

<table>
<thead>
<tr>
<th>Diagnoses in children</th>
<th>N (%)</th>
<th>Proportion hospitalized, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrheal disorders</td>
<td>449 [28]</td>
<td>7</td>
</tr>
<tr>
<td>Acute diarrhea</td>
<td>357 [22]</td>
<td>8</td>
</tr>
<tr>
<td>Bacterial diarrhea*</td>
<td>104 [7]</td>
<td>12</td>
</tr>
<tr>
<td>Cutaneous larva migrans**</td>
<td>66 [4]</td>
<td>2</td>
</tr>
<tr>
<td>Systemic febrile illnesses</td>
<td>358 [23]</td>
<td>38</td>
</tr>
<tr>
<td>Malaria</td>
<td>124 [8]</td>
<td>69</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>21 [1]</td>
<td>60</td>
</tr>
</tbody>
</table>


*Campylobacter: 25%; Salmonella: 24%; **44% Cebusae

The febrile pediatric traveler: Clues to a diagnosis
- Non-specific fever: Malaria, dengue, typhoid fever, rickettsiae
- Jaundice: Malaria, viral hepatitis, leptospirosis, typhoid, typhus
- Rash: Typhoid fever, rickettsiae, meningococcal disease
- Respiratory: Influenza, histoplasmosis
- Diarrhea: Salmonellosis, amebiasis, shigellosis
- CNS: Malaria, meningococcal disease, viral

Eosinophilia: Schistosomiasis, helminthic infections
- Hepatitis [transaminits]: Hepatitis A and E, Epstein Barr virus, cytomegalovirus, typhoid fever
- Arthritis, arthralgias: Chikungunya, Septic arthritis
- Hemorrhagic findings: Dengue, hemorrhagic viruses
- Lymphadenopathy: EBV, CMV
The febrile pediatric traveler: Diagnosis & treatment
- Comprehensive medical and travel history: Underlying conditions & medications, past history
- Destinations and dates of travel
- Purpose of travel, activities: Visit family & relatives. Exposure to H₂O, etc.
- Living and “eating” conditions
- Prophylaxis: Medications and vaccines

The febrile pediatric traveler: Determining a cause
- Thick and thin blood smears
- CBC and differential. Thrombocytopenia, Eosinophilia?
- Hepatic and renal function tests
- Urinalysis
- Chest radiograph & other imaging
- Microbiology: Cultures, O&P, PCRs
- Serology

Is it a cosmopolitan or tropical disease?
- Tropical infections: Infections acquired in a tropical or sub-tropical region of the world. Examples: Malaria, dengue, typhoid, etc.
- Cosmopolitan infections: Infections fairly distributed throughout the world. Examples: Influenza, Epstein Barr virus, STIs, etc.
Fever in children after international travel, France: Cosmopolitan infections
- Fever occurring within 3 months of stay abroad.
- 43.5% of children seen in ED first.
- 19% evaluated in foreign country before return.
- Cosmopolitan infections: 85% of established diagnoses.
- North Africa, 97.8%. Sub-Saharan Africa, 63.9%

Patient 1: Thailand travel
- Initial empiric antimicrobial therapy: Vancomycin, ceftriaxone, and doxycycline.
- Extensive workup: Thick and thin blood smears [negative], West Nile serology [negative], blood cultures [negative], serologies for dengue, Chikungunya, and tularemia [negative], echocardiogram [negative], EBV & CMV serologies [negative], arboviral panel [negative].

Acute undifferentiated febrile illness, Thailand
- Etiologies of acute undifferentiated fevers: 271 [68.3%]. Most common causes:
  Dengue: 157 [39.6%]
  Murine typhus: 20 [5.0%]
  Leptospirosis: 16 [4.0%]
  Influenza: 14 [3.5%]
  Bacteremia: 6 [1.5%]
  Concurrent infections, ≥2 pathogens: 37 [9.3%]. Mostly dengue plus.

Additional workup:
- Acute and convalescent leptospirosis serologies [negative].
- Acute and convalescent serologies for Rickettsia typhi, 1:64 and 1:512, respectively. Diagnosis: Murine typhus.
- Received 10 days of ceftriaxone and doxycycline.
- Return to Florida. Recovered.

Patient 2: Niger travel
- Urine culture: ESBL-producing Escherichia coli, 30,000 CFU/mL. Contaminant?
- Stool culture: Negative
- Blood culture: Salmonella enterica subsp. enterica serovar Typhi.
- Treated with 10 days of ceftriaxone, followed by 4 days of azithromycin.
- Recovered. No complications.

Acute undifferentiated febrile illnesses in pediatric travelers: A challenge
- Non-specific findings [if any] on exam.
- Delays in receiving "expert" care.
- Delays in laboratory results: Serologies, PCRs, etc. Need of more point-of-care tests.
- Delays in initiation of most effective therapy?
- Need for empiric antimicrobial therapy.
- Empirc therapy: Too broad?
- End result: Increased morbidity?