Evaluation of Fever in the Returning Traveler

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Fever in Travelers

- What is common?
- What is an emergency?
- What do I need to look out for?
- How do I approach work-up (without wasting lots of money and time)
  - Developing the differential
  - Laboratory diagnostic approach
- Specific diseases of importance
- Therapeutic considerations

Moderated by

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Common causes of fever in travelers

Undifferentiated
- Malaria
- Dengue
- Enteric fever (typhoid, paratyphoid)

With focal complaint
- Diarrheal disease
- Respiratory infections
- UTI

GeoSentinel CID 2007

6958 returning travelers with fever as chief c/o (28% of ill travelers)
- Malaria 21%
  - 33% of deaths in febrile pts
- Dengue
- Enteric Fever
- Rickettsioses
- No specific dx in 22%

Other noted causes of fever

"Exotic"
- Other arboviruses (WNV, Chikungunya, Zika)
- Acute schistosomiasis (Katayama fever)
- Leptospirosis
- Hepatitis A and B (less since vaccines)
- African trypanosomiasis
- Histoplasmosis
- Coccidiomycosis

Not so exotic
- Influenza
- STDs including acute HIV
- Tuberculosis
- Measles
- Mononucleosis
What is an emergency?  
i.e. what might kill the patient

Diseases with the potential to be rapidly fatal

<table>
<thead>
<tr>
<th>No specific interventions (other than supportive)</th>
<th>Specific therapies may be lifesaving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever</td>
<td>Malaria</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Rickettsial disease</td>
</tr>
<tr>
<td>Other arboviral encephalitides</td>
<td>Meningococcemia</td>
</tr>
<tr>
<td>Dengue (Shock Syndrome)</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Ebola and most other hemorrhagic fevers</td>
<td>African Trypanosomiasis</td>
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<tr>
<td></td>
<td>Lassa fever</td>
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<tr>
<td></td>
<td>Amoebiasis</td>
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<tr>
<td></td>
<td>Typhoid</td>
</tr>
<tr>
<td></td>
<td>Avian flu</td>
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</tbody>
</table>

What do I need to watch out for?  
i.e. what might kill me???

Diseases which require rapid public health response

- Hemorrhagic fevers
- Meningococcemia
- Measles
- Tuberculosis
- Diseases with potential application for bioterrorism
- Avian flu

Developing the differential

- Evaluate exposure - thorough travel history
  - itinerary
  - mode of travel
  - food and drink
  - accommodations
  - activities
  - exposure to people, animals, insects
  - timing
Food and Water Exposure

| Undercooked meat or fish | Toxoplasmosis  
Hepatitis A 
Trichinella |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsanitary food or water</td>
<td>Enteric fever, Hep A or E, bacterial enteritis, amoebiasis</td>
</tr>
<tr>
<td>Unpasteurized milk products</td>
<td>Brucellosis, Enteric fever, bovine TB, other Salmonella</td>
</tr>
</tbody>
</table>

Arthropod exposure

<table>
<thead>
<tr>
<th>Mosquitoes</th>
<th>Malana, dengue, Chik, Zika, filariasis, loa, YF, other arboviruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticks</td>
<td>Tick typhus, RMSF, CCHF, Lyme, Relapsing fever, tularemia, babesiosis, ehrlichia</td>
</tr>
<tr>
<td>Sandflies</td>
<td>Leishmaniasis, sandfly fever, Oroya fever</td>
</tr>
<tr>
<td>Blackflies</td>
<td>Onchocerciasis</td>
</tr>
<tr>
<td>Tse-tse flies</td>
<td>Afr. trypanosomiasis</td>
</tr>
<tr>
<td>Reduvid bugs</td>
<td>Am. trypanosomiasis</td>
</tr>
<tr>
<td>Chiggers</td>
<td>Scrub typhus</td>
</tr>
</tbody>
</table>
Other exposures

- Caves: Rabies, histoplasmosis
- W. Hemisphere desert: Coccidiomycosis
- Animals: Brucella, rabies, tularemia, Q fever, anthrax, plague, VHF
- Sex: HIV, HBV, STDs
- Bloodborne: HBV, HIV, HCV
- People: Menigococcal, flu, TB, SARS, VHF, Hep A
- Fresh water contact: Schistosomiasis, leptospirosis
- Chickens, feathers: Avian flu
- Camels: MERS

Developing the differential - 2

- Evaluate preventive measures
  - vaccines
  - prophylactic medications
  - behavior

Efficacy of vaccines

- immunizations: efficacy:
  - yellow fever: > 95%
  - hepatitis A: > 95%
  - hepatitis B: 80-95%
  - typhoid fever: 70%
  - meningococcal meningitis: > 90%
  - Japanese encephalitis: > 90%
Medications

Malaria chemoprophylaxis:
• drug
• dose
• compliance
• duration
Other medications

Developing the differential - 3

- Seasonal and Geographic Distribution – use resources!
  • CDC Traveler's Health Web site
  • WHO International Travel and Health site
  • GeoSentinel (ISTM)
  • Wilson’s World Guide to Infections (oldie but goodie!)
  • Several commercial apps

Developing the differential – 4
Incubation period

<table>
<thead>
<tr>
<th>Incubation period</th>
<th>&lt; 10 days</th>
<th>10-21 days</th>
<th>&gt; 21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>Malaria</td>
<td>Typhoid</td>
<td>Typhoid</td>
</tr>
<tr>
<td>Typhus</td>
<td>Typhus</td>
<td>Typhoid (typical)</td>
<td>Q fever</td>
</tr>
<tr>
<td>Typhoid (maybe)</td>
<td>Bacterial TD</td>
<td>East African</td>
<td></td>
</tr>
<tr>
<td>Marburg/Ebola</td>
<td>Typhus</td>
<td>trypanosomiasis</td>
<td>Influenza</td>
</tr>
<tr>
<td>Marburg/Ebola</td>
<td>Brucellosis</td>
<td>Malaria</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>(malaria rarely)</td>
<td>Leptospirosis</td>
<td>Typhoid</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Lassa</td>
<td>Viral hepatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schistosomiasis</td>
<td></td>
</tr>
</tbody>
</table>
Laboratory Diagnostic Approach
- Start with the bad, common things
  - MALARIA
    - thick (to find it) and thin (to speciate it) smears
    - turnaround time
    - lab proficiency
    - rapid dipstick assays

Laboratory Diagnostic Approach
- The basics
  - CBC
    - High WBC with neutrophils
      - pneumonia, uti, leptospirosis, Borrelia, brucella
    - Low WBC with neutrophils
      - typhoid, other Salmonella
    - Low WBC with lymphs
      - viral, rickettsial, malaria
    - Eosinophils
      - helminth, drug rx
      - NOT likely bacterial

Laboratory Diagnostic Approach
- LFTs
  - very high transaminases
    - viral hepatitis, yellow fever, toxin
  - high bili, only moderate transaminases plus renal dysfunction
    - leptospirosis
- U/A
- Stool O&P
- blood, urine, stool, sputum cultures
- CXR
Laboratory Diagnostic Approach - 4

- Some quick, cheap tests
  - Rapid strep
  - Rapid flu test
  - Monospot
  - RPR
  - DFA of ulcerative lesion (HSV, VZV)
  - Gram stain of skin lesion (GC, meningococcemia)
  - Rapid HIV
  - Pneumococcal urinary Ag
  - Rapid malaria test

Laboratory Diagnostic Approach - 5

- Resist the urge to order lots of (exotic) specific stuff with a long turn-around time
  - (at least at first)
  - Many serologic assays
    - know sensitivities and specificities
  - Know what rapid tests are available locally

Specific Diseases of Importance

- MALARIA
- Enteric fever
- Dengue
- Leptospirosis
- Rickettsial infections
- Acute schistosomiasis
- East African trypanosomiasis
- Viral hemorrhagic fevers
- Other Arboviruses
Malaria in travelers

- Up to 30,000 cases/yr
  - Potentially rapidly fatal
- Species varies according to geography
  - P. vivax – India, Central America
  - P. falciparum – Africa, Haiti, New Guinea
  - Both – S. E. Asia, Oceania, S. America
- Geographic risk varies
  - 2% per month in W. Africa without prophylaxis

Malaria in travelers

However, if minimal precautions in a high risk place:

- Summer 2003: American troops in Liberia for 2 weeks
  - Of the 157 troops who spent at least one night ashore, 69 became infected – an attack rate of 44 percent
  - By blood levels, <5% taking prophylaxis correctly

Malaria in travelers - 2

- 1,688 cases of imported malaria in US in 2010 (10% severe, 9 fatal)
- 123 deaths in travelers between 1963-2001
  - most taking no prophylaxis, inappropriate prophylaxis, or taking inappropriately
- Falciparum malaria:
  - MOST COMMON CAUSE of infectious disease death in travelers
  - 90% of imported is from Africa
Malaria in travelers

- Diagnosis frequently missed or delayed
  - New York – dx not considered in majority of cases presenting to community physician
  - Canada – mean time from 1st presentation to community MD to 1st malaria smear = 6.2 days
  - Delay in dx associated with mortality

Why is malaria missed?

- “Not classic fever pattern”
  - Falciparum usually isn’t
  - Others take days – weeks to settle in
- “On prophylaxis”
  - wrong or taken wrong prophylaxis is common
  - No travel hx taken
  - Travel was not recent
    - falciparum usually w/in 1st weeks (but)
    - vivax can be years later

Presentation of traveler’s malaria

- Incubation – usually at least 10 d
  - falciparum as short as 7
  - 98% of falciparum presents w/in 2 mos
- Very nonspecific!!!
- Diarrhea: 17-44%
  - N/V even more often
- Cough, sore throat: 14-16%
- Common: HA, myalgias, abd pain
- Classic rigors – more common w vivax
Malaria: Diagnostic Approach

Most important: LOOK FOR IT!

- Smears: thick (to find it) and thin (to speciate it)
- Know about your lab:
  - turnaround time
  - lab proficiency
  - rapid dipstick assays
    - Great for falciparum, pretty good for vivax

Lab findings in traveler’s malaria

- MAY BE PRETTY NORMAL
- About ½ of patients:
  - mild thrombocytopenia
  - mild anemia
  - minimally decreased WBC
- May see:
  - increased TB and LDH
  - mildly increased transaminases
- Severe malaria – looks like DIC, encephalitis, hemorrhagic fever, etc

NO SYMPTOM, SIGN, OR LAB TEST, OR CONSTELLATION OF ALL 3, IS USEFUL IN PREDICTING MALARIA

- Except a high quality malaria test!
Binax NOW

P. Falciparum HRP II
Pan-malarial aldolase

Tx of malaria

- Check updated recs CDC
  - Artesunate from CDC if severe
  - Coartem now available in US
  - Call CDC if need to!
- Consider empiric tx if lab slow or bad, pt looking bad
  - don’t keep doing it in face of multiple negative smears – look for other etiologies
- HYPOGLYCEMIA
Enteric fever (Typhoid, Paratyphoid)
- Incidence in travelers: $1/10^4$ - $1/10^5$
  - 70% from Indian subcontinent, Mexico, Haiti, Philippines
  - 77% in persons visiting friends and family
- Most cases occur 7-14 days after exposure
  - rarely up to 8 weeks

Initial Presentation of Enteric Fever
- Initially a non-specific fever
  - classically non-remitting, step-wise increase
- Constipation more common than diarrhea
  - initial loose stools fairly common
- Relative bradycardia only in 1st week
- Maybe evanescent rash (rose spots)
Diagnosing enteric fever

- Cultures
  - Blood 1st week
  - Stool, urine, may stay positive longer
  - Bone marrow most reliable

- Serologies in general not sensitive or specific
  - Widal, newer IH, IFA, ELISAs very variable

Dengue

- Epidemic in Latin America and South-east Asia
  - Most cases in travelers come from Asia
- No vaccine, no specific prophylaxis or tx

Full Moon Party, Koh Phangan
Dengue Presentation

- Short incubation: 3-8 days
- Undifferentiated fever
  - sudden onset
  - myalgias ("breakbone fever")
  - headache
- Rash: 30-44% appearing day 2-5
- DHF / DSS: occur 5-7 d into illness after initial improvement
  - severe thrombocytopenia, capillary leak

Dengue rash

(The above photos are courtesy of CDC, Tan Tock Seng Hospital, Singapore)

Leptospirosis

- Wide distribution in tropics and temperate zones
- Risk: exposure to fresh surface water, rodents (urine)
  - Sports events
  - River rafting
  - Rescue efforts after flooding

Leptospirosis presentation

- Incubation: 1-4 wks
- Initial non-specific febrile illness
  - Acute onset
  - Myalgias, especially legs
  - Abd pain, n/v, diarrhea
  - Conjunctival suffusion
- Mild cases resolve and are never recognized
Leptospirosis – more severe

- Biphasic – initial improvement, then return of fever/malaise
  - host immune response
- Weil’s disease
  - hepatic and renal involvement
  - profound jaundice, conjunctival suffusion/hemorrhage on PE
  - Lab – high bilirubin, mod transaminitis, elevated creatinine
  - can be fulminant

Rickettsial Infections

- RMSF, typhus (all types), tick typhus, Q fever
- Travelers – tick typhus
  - Mediterranean – R. conori
  - Africa – R. africae
    - vectors are rapid feeders
    - short exposure can result in infx
    - exposure – walking through brush, cattle areas
Tick typhus - Presentation

- Incubation period: 7-28 d
  - most in 2 wks
- Nonspecific fever initially
- headache, adenopathy, RUQ pain
- Maculopapular rash
  - less common w R. africae
  - R. africae may be vesicular
- Eschars
  - R. conori – single
  - R. africae – multiple (clustered)

Acute Schistosomiasis in travelers

- Katayama fever: acute serum-sickness like illness
  - 2-6 weeks after exposure
  - Starts before eggs are produced!
    - So need serology, not stool/urine exams
- Exposure: fresh still water
  - rafting
  - swimming
  - snorkeling (Lake Malawi)
- In travelers often occurs in clusters
- Severe disease can be fatal
East African Trypanosomiasis

- T. brucei rhodiense
  - acute, rapidly fatal form of “sleeping sickness”
  - vector: Tse-tse fly

- In travelers, exposure is game parks in East Africa
  - increasing cases in travelers recently
  - sentinel for failing disease control locally

Other (than dengue) Arboviruses

- Chikungunya – fever, arthritis, rash
- Zika – rash, maybe fever (80% no sx!)
- West Nile – fever, maybe rash, encephalitis
- O’nyong nyong – fever, arthritis, rash
- Ross River – fever, arthritis
- Murray Valley Fever – fever, encephalitis
- Rift Valley Fever – fever, maybe HF
- Oropouche – fever and rash
- Crimean-Congo hemorrhagic fever – fever, HF

- And many more!
Chikungunya Fever

- Historically Africa and Asia
- Major recent outbreak from Indian Ocean area
  - Comoros, Mauritius, Reunion and Seychelles
  - Affected many travelers
- Recent autochthonous transmission in Italy, Singapore
- Clinical
  - Nonspecific flu-like
    - Frequently mistaken for dengue
  - Severe joint pains
    - May be persistent

Viral hemorrhagic fevers in travelers

- RARE but bad

- Yellow fever is most common
  - Vaccination extremely effective
    - Cases in travelers are due to failure to vaccinate appropriately
  - PH risk only if patient accessible to vectors (Aedes mosquitoes)

VHF Presentation

- Acute febrile illness
- Myalgia, HA, conjunctival suffusion
- Sore throat (esp Lassa, Ebola)
- Severe diarrhea (Ebola)
- Occasional faint rash
- Severe hepatic involvement in YF
- Capillary leak syndrome + shock
- Hemorrhagic complications
  - Most severe in CCHF
Empiric Therapeutic Considerations

- 3rd gen cephalosporins for many bacterial infx
- Consider quinolones, azithromycin (R typhoid)
- Remember the tetracyclines
  - "No one should die in the tropics without doxycycline on board" Ted Kuhn
- Empiric malaria tx if falciparum suspected and lab slow or unreliable

Try to make dx even if they get better

- Empiric tx may suppress but not cure
  - Malaria
  - Brucella
  - Tuberculosis
- May be important to traveler to know
  - Dengue
  - Zika

Conclusions

- Use exposure hx to guide differential
- Remember what can kill them
- Remember what can kill you
- Get the quick easy tests first
- Treat empirically when necessary but don’t give up on making dx
- MALARIA MALARIA MALARIA!