Infections in Returning Travelers
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UCSF, Division of Infectious Diseases

International travel

• ~1 billion travelers cross international boarders annually

• 60 million travel from the US
  – Half to developing countries
Travelers crossing international borders

Why do people travel from the US?

- Leisure: 50%
- Service Work: 15%
- Research/Education: 9%
- Visiting Friends and Relatives: 11%
- Business: 15%

N=13,235

Larocque R. *Clin Infect Dis.* 2011
Travel related morbidity/mortality?

- 20-70% report some illness
  - 1-5% seek medical attention
  - 0.05% evacuation

Top 5 complaints in returning travelers leading to MD visit

- Fever
- Acute diarrhea
- Dermatological disorders
- Chronic diarrhea
- Nondiarrheal gastrointestinal disorders
Top 5 complaints in returning travelers leading to MD visit

- Fever
- **Acute diarrhea**
- Dermatological disorders
- Chronic diarrhea
- Nondiarrheal gastrointestinal disorders

Freedman DO. NEJM. 2006.

Case

29 y/o presents to urgent care with fever and myalgias for 3 days.

He returned 4 days ago from a 3-week trip to Bangladesh. He is working for an NGO creating sustainable housing.
How do you think about determining the cause of fever and rash in a returning traveler?

<table>
<thead>
<tr>
<th>Question</th>
<th>Why you are asking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where?</td>
<td>Geographic disease association</td>
</tr>
<tr>
<td>Vaccination/prophylaxis?</td>
<td>Helps narrow/influence DDx</td>
</tr>
<tr>
<td>Consumption (food/H₂O)</td>
<td>TD, giardia, Hep E/A, flukes, etc.</td>
</tr>
<tr>
<td>Immune status?</td>
<td>Alters risk of infections</td>
</tr>
<tr>
<td>Fresh water?</td>
<td>Leptospirosis, schistosomiasis</td>
</tr>
<tr>
<td>Skin to soil?</td>
<td>Strongyloides, cutaneous larva migarns</td>
</tr>
<tr>
<td>Insect bites?</td>
<td>Malaria, viruses, ATBF, etc…</td>
</tr>
<tr>
<td>Animal exposure/bites?</td>
<td>Rabies, brucella, etc.</td>
</tr>
<tr>
<td>Other ill travelers?</td>
<td>TB, VZV, etc…</td>
</tr>
<tr>
<td>Sex, tattoos, piercing?</td>
<td>HIV, HCV, HBV, syphilis, GC, etc.</td>
</tr>
</tbody>
</table>
Fever in a returning traveler

Febrile returning traveler → Severe illness and/or malaria risk → Higher level of care setting

Assessment based on signs/symptoms:
- +Rash
- +Resp Sx
- +Transaminits
- +Diarrhea
- +Eos

Initial lab testing:
- Check CBC w/diff
- LFTs, Chem 7
- Malaria smear
- Other testing PRN

- • Dengue
- • Zika
- • Chikungunya
- • Rickettsial
- • Acute schisto
- • Measles
- • Influenza
- • Bac PNA
- • TB
- • Histo/Cocci
- • Malaria
- • Typhoid fever
- • Acute EBV, CMV, HIV

- • Dysentery
- • E histolytica
- • Hepatitis A, E > B, C
- • EBV, CMV

- • Acute schisto
- • DRESS
- • EBV, CMV

- • Influenza
- • Bac PNA
- • TB
- • Histo/Cocci

- • Measles

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- • E histolytica
- • Hepatitis A, E > B, C
- • EBV, CMV
Use resources

- CDC travel website
- WHO website
- http://healthmap.org
- GeoSentinel articles

Destination: Etiology of fever according to region traveled

- Unknown
- Malaria
- Dengue/Chikungunya/Zika
- EBV/CMV
- Rickettsia
- Typhoid

Freedman DO. NEJM. 2006.
Causes of fever in traveler by incubation period

<table>
<thead>
<tr>
<th>Incubation</th>
<th>Common causes</th>
</tr>
</thead>
</table>
| **Short**  | Bacterial: Rickettsia  
Viral: Dengue, Chikungunya, Zika, Yellow fever respiratory viruses |
| **Intermediate**  | Bacterial: Lepto, typhoid fever, GC, syphilis  
Fungal: Acute histo or cocci  
Viral: acute HIV, CMV, EBV  
Protozoal: Plasmodium species, E histolytica  
Helminthic: Acute Schisto |
| **Long**  | Bacterial: TB  
Viral: acute HIV, CMV, EBV  
Protozoal: P ovale, P vivax, Leish, Amoebic abscess  
Helminthic: Acute schisto |
Case

29 y/o presents to urgent care with fever and myalgias for 3 days.

He returned 4 days ago from a 3-week trip to Bangladesh. He is working for an NGO creating sustainable housing.

Skin Exam

Labs

- WBC: 2.1
- HCT: 37
- PLT: 67
- Cr: 0.8
- AST: 78
- ALT: 93
- Alk Phos: 88
- Bili: 0.7
DDx and why?

Dengue fever

- 100 million infections/year
- Mosquito vector (daytime)
- Urban and rural
Dengue fever: worldwide distribution


Dengue fever: clinical disease

- **Incubation period**: Short (4-7 days)
- **Clinical Manifestations**:
  - Fever, headache, joint and muscle aches
  - Nausea and vomiting
  - Rash
- **Labs**:
  - leukopenia, thrombocytopenia, transaminitis
- **Dengue Hemorrhagic Fever/Shock**
  - Occurs 3-7 days into illness, often w/ end of fever
Dengue rash

- 1-2 days post onset of symptoms
- 3-5 days

MORBILLIFORM ERUPTION

- w/ petechiae and islands of sparing

Phases of Dengue Infection

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Febrile phase</th>
<th>Critical phase</th>
<th>Recovery phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-10</td>
<td></td>
<td></td>
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</tbody>
</table>

Potential clinical issues:
- Shock
- Bleeding
- Organ impairment

Viraemia
- IgG/ IgM

Inflammatory host response
- Capillary leakage

Dengue treatment/prevention

- Risk for DHF -> high level of care
- Treatment
  - Fluid resuscitation
- Prevention
  - Insect avoidance
  - Vaccine – helpful in seropositive only

Capillary Leak Signs/Sx
- Vomiting
- Abdominal pain
- ↑ hematocrit
- ↓ platelets
- Effusions, ascites, bleeding

Chikungunya fever

- Came to Caribbean in 2013 → C and S America
  - 1.7 million cases
- 116 cases in US in 2018
- Still in Asia/Africa

http://www.cdc.gov/chikungunya/geo/united-states.html
Chikungunya fever

- **Incubation period**: 2-4 days (1-14)
- **Clinical manifestations** (resolved within 7d)
  - Fever + **Polyarthralgias** 2-4 days later
  - Rash: ~ 50%, maculopapular
- **Labs**:
  - Lymphopenia >> thrombocytopenia, transaminitis
- Severe complications/deaths rare

Chikungunya rash
Chikungunya: Diagnosis & Treatment

- Lab diagnosis
  - IgM/IgG
  - PCR available
- Treatment:
  - Supportive

Zika virus

- **Incubation period**: 2-4 days (1-14)
- **Clinical manifestations**:
  - Fever, rash, joint pain, **conjunctivitis**
  - Severe complications rare: Guillian Barre
- **Risk of fetal complications greatest concern**
Zika virus associated microcephaly

• Recommendations to pregnant women
  – Avoid travel to Zika risk areas
  – Testing after travel to risk area

• Considering pregnancy
  – Avoid for 2 months if woman visited
  – Avoid for 3 months if man visited


Zika vs. Dengue vs. Chikungunya

<table>
<thead>
<tr>
<th>Features</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Case

63 year-old male with no PMH returned from a 10 day vacation to South Africa with complaints of fever, myalgias, and rash.

Case continued

To South Africa

In South Africa

Fevers (Tm-101), myalgias, fatigue

To US

UCSF ED
Physical Exam

- VS: 38.5, 76, 128/70, 16, 99% RA
- Lymph:
  - 1 cm R inguinal LAD, mild tenderness
- Skin:
  - right waistband region, 1.5 x 1 cm ulcer
  - 20 x small papulo-vesicular lesions
### Labs and Microbiology

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8 -------- 214</td>
<td>Chem 7 - wnl</td>
</tr>
<tr>
<td>/ 47 \</td>
<td>LFTS – wnl; UA - wnl</td>
</tr>
</tbody>
</table>

**Micro**

- 7/18 - Bld Cx X 2 – NGTD
- 7/18 – thin/thick smear - neg

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### African Tick Bite Fever

- *Rickettsia africae*
- Aggressive Bont ticks live on undulates and in grassy areas

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*Mediannikov. Emerging Infectious Diseases 2010*
Clinical Presentation

- Fever
- Headache
- Muscle aches
- Inoculation eschar, often multiple
- Regional lymph node swelling
- Rash – papular


African tick-bite fever: skin findings
Treatment

• Doxycycline 100 mg BID x 7 days or until 48h after defervescence

• Symptoms often improve 24-48h after initiation of treatment


Case

• 28 y/o male returned 3 weeks ago from a 3-month trip to Kenya

• Last week developed
  – fever (up to 103)
  – urticaria
  – cough/wheezing
Skin exam

Now 5 weeks ago

Absolute eosinophil count 6.0 (<0.4 wnl)

Eosinophilia?
Eosinophilia in returning travelers

Case continued

- Schisto IgG – positive
- Swam in Lake Victoria during stay
Schistosomiasis

Weerakoon. Clin Micro Rev. 2015

Schistosoma worldwide distribution

“Swimmer’s itch” (12-24 hrs)

“Katayama Fever” 3-8 weeks

Chronic Disease (bladder/iver)
Diagnosis

• Micro
  – Stool O&P
  – Urine O&P
• Serology
• Histology

Gryseels B. Lancet ‘06

Treatment

• Praziquantil is the treatment of choice
  – Not active against immature forms
  – Katayama fever, repeat 6-8 weeks later (+/- steroids)
Top 5 complaints in returning travelers leading to MD visit

• Fever
• Diarrheal disease
• Dermatological disorders
• Nondiarrheal gastrointestinal disorders

Freedman DO. NEJM. 2006.
Diarrheal diseases

• Most likely travelers’ diarrhea
• Consider empiric treatment

Self-treatment of TD

• Ciprofloxacin:
  – 500 mg PO BID for 1-3 days
• Azithromycin: SE Asia, children, pregnancy
  – 500 mg PO QD x 3 days or 1000 mg PO x 1
• Rifaximin: not for invasive infections
  – 200 mg PO TID x 3 days
• Loperamide: not for invasive infections
  – Added benefit, use in “emergency”
Chronic diarrhea

• Protozoal infections
  – Giardia
  – Cryptosporidium
  – Entamoeba histolytica
  – Other: Cyclospora, isospora, etc…

• Other infections
  – C. difficile colitis

• Non-infectious etiologies
Evaluation of chronic diarrhea

- Bacterial culture
- Stool O&P x 3
- Other tests
  - Giardia antigen
  - Stool AFB stain (cryptosporidium, isospora, etc.)
  - Stool Cryptosporidium antigen
  - Stool Entamoeba histolytica antigen

Case

- 29 y/o present with enlarging lesion on his left foot & bilateral thighs
- Denies constitutional symptoms
- Returned 2 weeks ago from a 4-month trip through Central and South America
Top 5 complaints in returning travelers leading to MD visit

• Fever
• Acute diarrhea
• Dermatological disorders
• Chronic diarrhea
• Nondiarrheal gastrointestinal disorders

Freedman DO. NEJM. 2006.

other cases of the same disease
Returning traveler from Costa Rica

Returning traveler from Portugal
Your diagnosis?

Cutaneous leishmaniasis
Leishmaniasis: Clinical disease

Distribution of species by clinical disease

Visceral
- L. infantum
- L. donovani

Cutaneous
- L. major
- L. aethiopica
- L. tropica
- L. braziliensis
- L. panamensis
- L. mexicana

Mucosal
“Old World”

Aronson Clin Infect Dis 2016

“New World”

Aronson Clin Infect Dis 2016
How do you get it?

Clinical manifestations

- Incubation period: **1-4 weeks**
- Morphology:
  - Small raised bump → ulcer (months)
  - May grow as large as 5 cm
- Not painful in most cases
- Often self-resolves within 6-12 months
Mucocutaneous disease

• Caused by a few species
  – *L. braziliensis*
  – *L. panamensis*
• Weeks to years
• Ulcerations that eventuate in mutilating destruction of the oropharynx


Diagnosis

• Coordinate with reference lab for testing
• CDC is excellent resource to provide
  – Microscopic evaluation
  – Culture
  – PCR
  – Speciation
• CDC lab at 404-718-4175 or DPDx@cdc.gov

Diagnosis

• What types of samples can you send?
  – Biopsy: place in sterile culture media
  – “Touch prep”
  – Needle aspirates
  – Derm scrapings


Treatment of Cutaneous Leish

Key factors:
1. Species (mucosal vs. non-mucosal risk)
2. Extent of disease (lesion size, number of lesion, location)
3. Comorbidities (e.g. IS state)

Options:
1. No treatment
2. Cryotherapy and thermotherapy
3. Topical: Paromomycin (available via compounding pharmacy)
4. Intraleisional injections: Antimony (not in US)
5. Systemic: Miltefosine; Ampho B; Antimony (CDC only); Azoles
Treatment of Cutaneous Leish

• Is treatment always needed?
  – If non mucosal-causing species and small and healing - ok not to treat

• When to treat with local therapy?
  – Few and small, non mucosal causing species -- topical or intralesional OK

• When to treat with systemic therapy?
  – Mucosal disease, > 4 lesions, > 5 cm lesion, IS patient

L guyanensis- Ambisome

Aronson Clin Infect Dis 2016
L. panamensis – miltefosine
*L. infantum* – posaconazole then topical amphotericin (study)
L major – topical paromomycin
10 top derm conditions in returning travelers

- Insect bite – w/ or w/o infection
- Cutaneous larva migrans
- Allergic rash
- Skin abscess
- Rash of unknown cause
- Superficial mycosis
- Animal bite
- Leishmaniasis
- Myiasis
- Swimmer’s itch

Freeman D. NJEM. 2008
Cutaneous larva migrans

Life Cycle of Animal Hookworms:
1. Eggs in feces
2. Rhabditiform larva hatches
3. Rhabditiform larva develops into filariform larva in the environment
4. Cutaneous Larva Migrans
5. Adults in small intestine

www.parasitesinhumans.org
Cutaneous larva migrans

• Treatment:
  – Albendazole 400 BID x 3-7d
    OR
  – Ivermectin 200 mcg/kg QD
    x 1-2d

• Prevention: wear shoes

Returning traveler from Amazon

Botfly

Returning researcher from Ethiopia
Tungiasis

Top 5 complaints in returning travelers leading to MD visit

- Fever
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Freedman DO. NEJM. 2006.
Nondiarrheal gastrointestinal disorders

- Intestinal nematode infection
  - Strongyloides, schistosomiasis, ascaris
- Gastritis/PUD
- Acute hepatitis
  - Hepatitis A, E, B
- Constipation

Evaluation of nondiarrheal gastrointestinal disorders

- Check LFTs
- CBC w/ differential (eos?)
- Stool O&P x 3
- Serology: Strongyloides and schistosoma IgG
- GI referral for other diagnoses
Post-infectious irritable bowel syndrome

• 3-10% of travelers after episode of TD
• Diagnosis of exclusion
• Last months - years

Connor BA. Clin Inf Dis. 2005

Summary

• **Fever and rash in returning traveler:** Consider geography, incubation period, exposures, etc.
• Use **resources** to help with DDx
• Recognize the varied presentation and long latency of **cutaneous leishmaniasis**
• Partner with local **infectious diseases provider**