Infections in Travelers

Lisa Winston, MD
University of California, San Francisco / San Francisco General Hospital

Outline – Part 1

Before getting sick
- Risk assessment
- Personal precautions
- Immunizations
- Prophylactic medications
- Immunocompromised patients

Outline – Part 2

After getting sick
- Fever in the returned traveler
  - Review common / important infections

Risk Assessment

- Itinerary
  - Where generally (e.g. Africa – malaria risk)
  - Where and what specifically
    - Urban vs. rural
    - Type of accommodations
    - Activities
      - Hiking
      - Fresh water exposure
      - Visiting friends and relatives
    - Medical conditions

“Cook it, boil it, peel it, or forget it”

- In order to prevent travelers’ diarrhea
  - Avoid uncooked food
    - Except fruits and vegetables you peel
  - Hot food hot; cold food cold
  - Bottled water only – avoid ice cubes
How well does it work?

*Hillel et al, J Travel Med 2005;12:243-7*

- Interviewed 114 travelers in India
- None adhered strictly to WHO guidelines
- 83% had diarrhea
- Degree of adherence did not correlate with diarrhea
- Conclusion: "Dietary restraint of travelers as proposed by the WHO is both difficult to comply with and lacks a proven value for long-term travelers to a developing country."

Arthropod-borne Infections

- Use repellents
  - Skin – DEET-containing products recommended
  - Those with picaridin ("Bayrepel" outside of U.S.) are an alternative
  - Oil of lemon eucalyptus (p-menthane 3,8 diol or PMD) have some activity
- Clothes – can treat with permethrin products
- Long sleeves, long pants
- Minimize outdoor activity dusk to dawn (malaria)
- Mosquito bed nets
- Check for ticks with rural outdoor activity

Other

- Avoid non-chlorinated fresh water
- Avoid acupuncture, piercing, tattooing
- Do not pet or feed animals

Sexually Transmitted Infections

- Abstain from sex
- Use safe sex precautions
  - Condoms

Websites

- www.cdc.gov
- www.who.int/topics/travel/en
- www.fas.org/promed
- www.astmh.org

Guidelines

*Hill et al, Clin Infect Dis 2006;43:1499-1539*

Available at www.idsociety.org
Travel Vaccines

- Review childhood vaccine series and indicated boosters, including:
  - Measles (those born in or after 1957 may need second dose)
  - Tetanus-diphtheria (+/- pertussis)
  - Polio
- Hepatitis A almost always if not immune
- Typhoid commonly:
  - Typhim Vi, single dose injectable; lasts 2 yrs
  - Vivovif, oral Ty21a strain; 4 capsules – one taken every other day; lasts 5 yrs

- Yellow fever: certain areas of sub-Saharan Africa and tropical South America
  - Designated provider
- Japanese encephalitis: rural Southeast Asia
- Polio booster: parts of Africa and Asia
- Meningococcus: parts of Africa, seasonal
- Consider rabies – exposure risk
- Consider hepatitis B – exposure risk

Travelers’ Diarrhea

- Most common illness affecting travelers
  - 25 – 50% of international travelers (~10 million people)
- Most common cause enterotoxigenic Escherichia coli (ETEC)
- Prophylaxis rarely required
- Okay to give short course therapy to take if symptoms develop:
  - Usually fluoroquinolone x 3 days: ciprofloxacin 500 mg bid or norfloxacin 400 mg bid
  - Consider single dose azithromycin (1 g), especially in Southeast Asia and India
  - Consider rifaximin 200 mg TID x 3 days, especially for ETEC

Malaria Prophylaxis

- Started before travel, take during travel, continued after leaving malaria-endemic area
- Most areas have chloroquine resistance
Malaria Prophylaxis

- Chloroquine or hydroxychloroquine
  - Selected areas only
- Mefloquine (Lariam)
- Doxycycline
  - Used mefloquine resistance/intolerance
- Atovaquone/proguanil (Malarone)
  - Used mefloquine resistance/intolerance
- Primaquine for terminal prophylaxis *P. vivax* and *P. ovale* – high risk only
  - Check G6PD level

Malaria Prophylaxis Regimens

- Mefloquine 250 mg q week starting 2 weeks before travel, during travel, and 4 weeks after travel
- Doxycycline 100 mg daily starting 1-2 days before travel, during travel, and 4 weeks after travel
- Atovaquone/proguanil (Malarone) 250/100 mg (1 tab) daily starting 1-2 days before travel, during travel, and 1 week after travel
- Chloroquine 500 mg (300 mg base) q week starting 1-2 weeks before travel, during travel, and 4 weeks after travel

Immunocompromise

- Most persons in stable health can travel safely
- Review drug interactions
  - Especially protease inhibitors, cyclosporine, tacrolimus, sirolimus
- Usually avoid live virus vaccines
  - Yellow fever, *S. typhi* Ty21a, MMR
  - Also oral polio vaccine and BCG – not routine U.S.

Returned travelers - hospitalization

- Febrile illnesses > 75% admissions
- In Israeli study, most common diagnoses malaria, “febrile illness,” and dengue fever
- Travel to Africa highest risk of hospitalization


It Matters Where You Went

*Freedman et al, NEJM, Jan 2006*:

- Surveyed travel and tropical medicine clinics on 6 continents (GeoSentinel Surveillance Network)
- Data on 17,353 ill returned travelers
- Disproportionate illnesses:
  - Systemic febrile illness: sub-Saharan Africa and Southeast Asia
  - Diarrhea: south central Asia
  - Dermatologic: Caribbean, Central, South America

*Freedman et al, NEJM, Jan 2006 cont*:

- Malaria in top 3 of systemic febrile illness from all regions
- But, dengue more common than malaria in every region except sub-Saharan Africa and Central America
- Sub-Saharan Africa: rickettsial infection particularly common – more common than typhoid or dengue
Fever Is Important


- Reviewed data from 24,920 returned travelers seen at GeoSentinel clinics 1997 – 2006
- 28% with chief complaint fever
- Of patients with fever, 26% hospitalized (compared with 3% without fever)
- Malaria most common diagnosis (21%) in febrile patients in this survey
- Visiting friends and relatives risk factor for fever

Traveler with a Fever

- Short incubation period (< 14 days): Big 3
  - Malaria (especially falciparum)
  - Dengue
  - Typhoid fever
- Also, non-tropical diseases

Traveler with a Fever

- Incubation period > 14 days
  - Malaria: falciparum (~ 1 month) and non-falciparum
  - Typhoid fever (3 weeks; rarely up to 60 days)
  - Hepatitis, especially A and E

More Complete List

- Fewer than 21 days
  - East African trypanosomiasis
  - Dengue fever
  - Japanese encephalitis
  - Leptospirosis
  - Malaria
  - Meningococemia
  - Nontyphoidal salmonellosis
  - Typhoid fever
  - Typhus
  - Viral hemorrhagic fevers
  - Yellow fever

- More than 21 days
  - Acute HIV
  - Acute schistosomiasis (Katayama fever)
  - Amoebic liver abscess
  - Brucellosis
  - Leishmaniasis
  - Malaria
  - Rabies
  - Tuberculosis
  - Viral hepatitis
  - West African trypanosomiasis

Traveler with a Fever

- Work up for fever
  - Right away
    - Malaria smears
    - Blood cultures (typhoid, meningococcus)
    - Other, directed appropriate evaluation: e.g. CXR for respiratory symptoms

Other tests to consider
- Eosinophil count
- Stool studies (diarrhea or elevated eosinophils)
- Serologies (hepatitis, dengue, leptospirosis, helminthic infections)
- HIV
**Traveler with a Fever**

- Initial therapy
  - Ideally, etiology directed
  - Supportive
  - If very ill, antibiotics (e.g. ceftriaxone, fluoroquinolone) pending diagnosis
  - Consider empirical therapy if characteristic syndrome, e.g.
    - Rickettsial disease
    - Leptospirosis

**Malaria**

- Most important diagnosis to consider upfront
  - Fever, malaise, headache, myalgias
  - Also, abdominal pain and diarrhea
  - Anemia, thrombocytopenia, leukopenia, elevated bilirubin
  - Elevated AST and ALT common

**Artesunate**

- Eligible if parenteral therapy required because
  - Can’t take oral medication or
  - High density parasitemia (> 5%) or
  - Severe malaria – e.g. ARDS, severe anemia
  - AND
  - Artesunate more rapidly available than quinidine (if equally available, discuss with CDC) or
  - Quinidine failure or intolerance or
  - Quinidine contraindicated

- Class: artemisinins, from sweet wormwood plant (*Artemisia annua*)
- Administered in 4 equal doses of 2.4 mg/kg over 3 day period
- Short half-life, follow with oral drug

- Call to obtain artesunate
  - Mon – Fri 8 am – 4:30 pm Eastern time 770-488-7788
  - Other times 770-488-7100, ask to speak with Malaria Branch clinician

- Hypoglycemia, renal failure, altered mental status in severe disease
- Diagnose by blood smear
  - 3 smears collected every 8-12 hours
  - *P. falciparum* usually treated in U.S. with oral quinine plus doxycycline
    - When IV therapy required
      - IV quinidine – traditional rx
      - IV artesunate is available under an Investigational New Drug Application (IND)
**Coartem: Artemether + Lumefantrine**
- FDA approved 4/09 for treatment of uncomplicated falciparum malaria in patients ≥ 5 kg
- Not used for severe malaria or prophylaxis
- Lumefantrine has longer half life but slower onset of action
- Careful with drug interactions, potential QT prolongation
- Given in 6 doses based on body weight

**Dengue**
- *Flavivirus*, 4 distinct subtypes
  - Can get up to 4 times
- Transmitted by *Aedes* mosquitoes
  - *Ae. aegypti* day biting, urban areas
- Increasing transmission past 20 years
- Incubation 3 – 10 days

**World Distribution of Dengue - 2005**

**Typhoid Fever**
- Enteric fever caused by *Salmonella enterica* serotype typhi (or *S. paratyphi*)
- Fecal-oral spread or contaminated food or water – humans only reservoir
- Incubation usually 5 – 21 days
- Fever, anorexia, malaise, abdominal pain
  - Diarrhea not typical
  - Rose spots – fleeting macules

**Dengue**
- Fever, headache, myalgias, arthralgias, may have rash
  - “break bone fever”
- Leukopenia and thrombocytopenia
- In minority, progresses to dengue hemorrhagic fever or dengue shock syndrome
- Diagnosis usually by serology
- Treatment is supportive
Typhoid Fever
- Diagnosed by blood or stool culture (also bone marrow)
- Concerns re emerging antibiotic resistance, including fluoroquinolones, which have been drugs of choice
  - Ceftriaxone and cefotaxime can be used

Rickettsial Infections
- Intracellular bacteria transmitted by ticks, lice, fleas, mites
- Cause many diseases, e.g. Rocky Mountain Spotted Fever
- Major rickettsiae in travelers
  - R. conorii – Mediterranean spotted fever
    - Usually an eschar – tache noir
  - R. africae – African tick typhus
    - Often more than one eschar

Rickettsial Infections
- Usually 5 - 7 day incubation
- Fever, headache, myalgias, rash beginning on trunk
- Diagnosed by convalescent serology
  - Immunohistology or PCR (if available) from skin biopsy
- Treated with doxycycline

Schistosomiasis
- Three main Schistosoma trematodes: S. mansoni, S. haematobium, S. japonicum
- Contact with fresh water - cercariae penetrate intact skin
- Prevalence increasing sub-Saharan Africa; other areas risk mostly decreasing
- Interesting recent article about multi-faceted approach to reduction
  A strategy to control Schistosoma japonicum in China, Wang et al, NEJM, 2009;360(2):121-8

Schistosomiasis
- Acute syndrome: Katayama fever
  - 2 – 12 weeks incubation
  - Fever, weight loss, abdominal pain, eosinophilia; may have hematuria
- Dx: schistosome eggs urine or stool, minimum 6-8 weeks or serology
- Treatment - praziquantel
Leptospirosis
- Caused by *Leptospira* spirochete
- Excreted in urine of carrier animals
- Highest incidence in U.S in Hawaii
- Transmission through contact with contaminated water or soil
- Incubation 7-12 days

Leptospirosis
- May have biphasic illness
- Fever, headaches, myalgias; sometimes conjunctival suffusion, rash
  - Minority develop Weil’s syndrome – jaundice, renal failure
- Diagnosis: serology
- Treatment: doxycycline or penicillin

This syndrome is most commonly caused by

- A. Human hookworm (*Necator americanus*)
- B. Dog or cat hookworm
- C. *Strongyloides* species
- D. Fish tapeworm (*Diphyllobothrium* species)
- E. Pork tapeworm (*Taenia solium*)

Case:
- A 40 year-old woman returned 2 days ago after a 3-week trip to east Africa. She had been prescribed mefloquine (Lariam) for malaria prophylaxis but stopped taking it due to insomnia. She developed a fever during the flight home. Other symptoms include chills, diaphoresis, myalgia, and headache. She has had no diarrhea. Activities included frequent hikes and swimming in fresh water 1 week before her departure.

You are concerned about all of the following EXCEPT

Case:
- A. Malaria
- B. Typhoid
- C. Rickettsial infection
- D. Acute schistosomiasis (Katayama fever)