Travel Medicine: Helping Patients Prepare for Trips Abroad and Return Safely

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Background
- More people are traveling around the world
- Travel medicine is increasingly important
- One third experience a travel-related illness
  - 1-5% seek medical care
  - 1 in 100,000 die of illness or injury
- Most travel-related illnesses are preventable

Goals of travel medicine
- To assess risk of illness or injury
- To educate patients about region-specific health risks
- To advise travelers regarding prevention of accidents, disease, and death
- To minimize impact of illness abroad
  - self-therapy, immunizations against vaccine preventable infections, treatment of travelers’ diarrhea, vector-borne diseases
  - food and water precautions, and mosquito avoidance

Leading causes of mortality among travelers
- Cardiovascular diseases
- Trauma/Traffic Accidents
- Infectious diseases

Pre-travel Evaluation

• Perform at least 4 weeks before travel
• Assess traveler’s medical conditions
• Obtain details of trip
  • Length of stay in each area
  • Potential exposures
  • Urban vs. rural
  • Business vs. backpacking
  • Level of accommodation
  • Expected activities
• Traveler’s insurance

High-risk travelers

• Persons with known cardiovascular disease or complex chronic diseases
• Traveling off the usual tourist routes
• Backpackers
• Long-term travelers
• Foreign-born persons (“Visiting Friends and Relatives”)

Relative risk of travelers contracting infectious diseases in developing countries

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diarrhea</td>
<td>Campylobacteriosis</td>
</tr>
<tr>
<td>ETEC (10%)</td>
<td>Dengue</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>Giardiasis</td>
</tr>
<tr>
<td>Dermatologic disorders</td>
<td>Hepatitis A</td>
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<tr>
<td></td>
<td>Malaria</td>
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<td>Salmonellosis</td>
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<td>Shigellosis</td>
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Motor vehicles accidents

• Most common cause of death in travelers

• Prevention advice
  • hire local driver
  • rent vehicles with seat belts
  • avoid nighttime driving in rural areas
  • look both ways before crossing street
  • avoid use of motorcycles and mopeds
Routine Vaccines for Travelers

- All travelers should be up to date with routine immunizations
  - Influenza
  - Pneumococcal
  - Tdap
  - MMR
  - Polio
  - Varicella

Traveler’s diarrhea

- Most common illness of travelers
  - 30-80% of travelers to developing nations
  - 20% become bedridden
  - 40% change their itinerary

- Causative pathogen identified in 50-75% of cases

Pathogens associated with traveler’s diarrhea

- Watery diarrhea
  - Enterotoxigenic E. coli (ETEC) 10%
  - Salmonella species
  - Shigella species
  - Campylobacter species
  - Vibrio species

- Dysentery
  - Shigella species
  - Salmonella species
  - Campylobacter species
  - E. coli O157:H7 and other shiga-toxin producing E. coli
  - Entamoeba histolytica

Epidemiology of traveler’s diarrhea

- Bacterial enteric pathogens (80%)
- Viral causes less commonly identified (15%)
- Parasitic infections are rare (<5%)

- Mean duration of untreated illness of 4 days
  - Typical range: 3-7 days
Sequelae of food borne diseases

- Kidney failure
- *E. coli* O157:H7
- Arthritis
- *Salmonella, Shigella, Yersinia*
- Paralysis
- *Clostridium botulinum, Campylobacter*
- Miscarriage
- *Listeria*

Examples of U.S. outbreaks traced to foods from other countries

- Coconut milk from Thailand
- Canned mushrooms from China
- Snack food from Israel
- Cantaloupe traced to Mexico & central America
- Green onions traced to farms in Mexico
- Frozen strawberries picked in Mexico

Causes of chronic diarrhea in travelers

- Pathogen
  - *Giardia lamblia* (most common)
  - *Entamoeba histolytica*
  - *Cryptosporidium parvum*
  - *Cyclospora cayetanensis*

Treatment of traveler’s diarrhea

- Treatment
  - Antibiotics
    - Fluoroquinolone or azithromycin x 3 days
  - Increased resistance to ciprofloxacin and levofloxacin in certain countries, such as Thailand, Nepal and Spain, where azithromycin is now the preferred drug
  - Antimotility agents
    - Avoid if bloody diarrhea or fever
  - Vaccines
    - ETEC vaccine under development
Safe food for travelers

• Food thoroughly cooked; hot when served
• Avoid uncooked food, particularly fruits and vegetables that cannot be peeled
• Avoid eating food from street vendors
• Remember the dictum: “Boil it, cook it, peel it or leave it”

Safe water for travelers

• Avoid tap water
• Brush teeth with bottled water
• Safe drinks
  • Bottled water
  • Boiled water
  • Carbonated beverages
• Avoid ice
• Cruise ships outbreaks associated with consumption of water and ice cubes
• Learn how to self-treat water (REI has a number of methods)

Case History—Audience Response

• 30 year-old couple returns to SF after 2 week trip to Bali for their honeymoon. They return with 10 days of watery diarrhea, abdominal cramps, anorexia and 10 lb weight loss. In spite of treatment with 3 days of Ciprofloxacin their diarrhea persists.

Management—Audience Response

1. I would assume that travelers associated diarrhea was resistant to Cipro, and empirically treat with azithromycin
2. I would assume that this may be a parasitic infection, and I would empirically treat with metronidazole
3. I would order stool studies and screen for enteric bacteria and parasites, and treat based on culture results
Answer to Case

- **Diagnosis:**
  - Cyclospora

- **Treatment:**
  - TMP-SMX DS tab po bid x 7 days

Prophylaxis for travel: Cholera

- No vaccine licensed in the U.S.
- Vaccines available in Europe and Canada
- No country requires cholera vaccine
- Vaccination not currently recommended
- Recent outbreaks in Haiti, Cuba, and Dominican Republic

Prophylaxis for travel: Typhoid

- Spread via contaminated food and water
- Two typhoid vaccines in United States
  - Live-attenuated, oral Ty21a vaccine
  - Polysaccharide vaccine (Vi CPS) q 2-3 years
  - Both about 70% effective
- Oral vaccine q 5 years
  - Four enteric-coated capsules taken every other day over week
  - Should not be taken with antibiotics 3 days before or 3 days after administration
  - Can be taken with malarone, mefloquine, and chloroquine (though not recommended)
  - Contraindicated in immunocompromised hosts
  - Immunization recommended before travel

Hepatitis A

- Risk of infection
  - Most common travel-related, vaccine-preventable illness
  - 5 to 7 times higher risk for backpackers
  - Endemic in Asia, Africa, and S. America
- Vaccine underutilized
  - Recommended for ALL travelers to countries with high or intermediate risk
Prophylaxis for travel: Hepatitis A

- Two highly immunogenic, inactivated vaccines (Havrix & Vaqta)
  - Single dose administered 2 to 4 weeks before travel
  - Confers >95% protection for 1 year
  - Two doses provide long-term immunity, 6-12 mo apart
- Combined Hepatitis A and B vaccine (Twinrix)
  - Three doses, given on 0-, 1-, and 6-mo schedule; same schedule used for hep B
  - Vaccine effective if given 1 day before trip

Hepatitis E (HEV)

- Major cause of acute viral hepatitis in many developing countries—especially Nepal and South America
- Transmission
  - Shellfish: bioaccumulate human enteric viruses, often act as vectors in foodborne spread
  - Studies have shown that HEV transmission occurs predominantly by ingestion of contaminated water
- Acute, self-limited disease
  - Low mortality rate
  - However, during pregnancy 20% mortality rate reported

Global Distribution of Hepatitis E

Mosquito-borne illnesses

- Worldwide, approximately 1 in 50 deaths caused by mosquito-borne illness
- Malaria and dengue are the two most common mosquito-borne diseases
- Mosquitoes and transmission
  - Dengue: daytime and urban
  - Malaria: night-biting and usually rural
Malaria

- Malaria is a global health problem
- 500 million symptomatic infections
- 1-3 million deaths/year, mostly in Africa
- No vaccine, research continues
- *Plasmodium falciparum*
  - Most malignant form and responsible for deaths
- Prophylaxis not 100% effective
- Resistance to chloroquine widespread
- Prompt diagnosis and treatment essential

Malaria: Public Health Importance United States

- US travelers
  - 20 million travel annually to endemic countries
  - Approx. 5-7 million have significant exposure
  - Approx. 1700 cases of imported malaria/year
  - Average: 6 deaths annually among US travelers due to malaria

Plasmodium falciparum Infection in U.S. Travelers

- Most acquired in sub-Saharan Africa
- Less than 2% of travel
- 90% of infections from sub-Saharan Africa
- All countries with chloroquine resistance

Diagnosis of Malaria

- Fever or flu-like symptoms
- Detailed travel history
- Chemoprophylaxis use
- Peripheral blood smear examination
- Species identification
- Quantification of parasite density
Thick vs. Thin Smears

• Thick smears:
  • More concentrated—easier detection
  • Species identification difficult

• Thin smears:
  • Most used in US laboratories
  • Optimal for species identification
  • Less sensitive for detection

Clinical presentation of malaria

• Infections caused by:
  + P. vivax & P. ovale may relapse and remain latent
  + Secondary to persistent liver stages
  + May emerge months to years later

• Most cases of P. falciparum (90%) in travelers present within 1 month of exposure, almost 100% < 2 months

Chemoprophylaxis of malaria

• Areas with chloroquine-resistant P. falciparum
  + Malarone
  + Mefloquine
  + Doxycycline

• Areas without chloroquine-resistant P. falciparum
  + Chloroquine

MMWR: July 20, 2001 / 50(28);597-9

• Malaria Deaths Following Inappropriate Malaria Chemoprophylaxis — United States

  • During January–March 2001, two U.S. citizens died from malaria after taking chloroquine alone or with proguanil for malaria chemoprophylaxis in countries with known chloroquine-resistant Plasmodium falciparum malaria.
Prevention of malaria including cerebral malaria caused by *Plasmodium falciparum*.

- 98% effective in prevention of malaria
- As effective as mefloquine or doxycycline

Adult dosing regimen for prophylaxis:
- One adult tablet daily
  - Start 1 to 2 days before travel, taken daily during travel, and continuing daily for 7 days after leaving the malarious area
  - >10 days elapsed since last dose of oral typhoid vaccine

**Indications**
- Prophylaxis of *P. falciparum* malaria
- Treatment of acute, uncomplicated *P. falciparum* malaria

**Side Effects** (versus placebo)
- Headache (5% vs. 7%)
- GI upset (3% vs. 5%)
Mefloquine

- Prophylactic efficacy 91%
- Side effects: Sleep disturbances, nausea, dizziness, neuropsychiatric adverse effects
- Administer weekly beginning two weeks prior to exposure, during exposure, and for 4 weeks following exposure

Lobel HO, et al. Lancet

Treatment of malaria

- Chloroquine-sensitive malaria
  - Chloroquine
  - Primaquine
  - Eradicate *P. vivax* & *P. ovale* residual malaria in liver
- Chloroquine-resistant malaria
  - Artemether/lumefantrine (Coartem), 95% cure rates in RCTs for *P. falciparum* for children and adults
  - Quinine plus doxycycline
  - Mefloquine
  - Malarone

Dengue fever

Mosquito-borne worldwide pandemic: outbreaks in Rio de Janeiro, Singapore, India, Vietnam, Mexico, Puerto Rico, Caribbean, Hawaii, Pacific Islands

Known as “break-bone” fever; severe muscle, joint pains, headache, rash

WHO estimates:
- 50-100 million infections/year
- 12,000 deaths annually

Dengue Global Map
Dengue Risk Map

Dengue Hemorrhagic Fever

- **CLINICAL FEATURES**
  - Incubation period of 4-7 days
  - More aggressive form of disease occurs with a second infection
  - Sudden onset of fever, severe headache, myalgias and arthralgias, leukopenia, thrombocytopenia and hemorrhagic manifestations
  - Occasionally produces shock and hemorrhage, leading to death
  - Average case fatality rate of DHF is about 5%

- **ETIOLOGIC AGENT**
  - Dengue viruses (DEN-1, DEN-2, DEN-3, DEN-4)

Dengue Vaccine Trial

- Live-attenuated tetravalent vaccine
- Efficacy estimates against DENV 1, 3, 4 were approximately 70%
- One of the dengue virus serotype 2 eluded the vaccine, reasons unclear
  - Analyses ongoing to understand the lack of protection for serotype 2
  - Ongoing studies will provide additional efficacy data

Diagnosis and management of dengue infections

- Consider dengue in patients with fever and a history of travel to tropical areas within 2 weeks
- Use acetaminophen for pain & fever management
- Avoid aspirin and other NSAIDs because of risk of bleeding
- Serological and molecular diagnostic tests for viral isolation and diagnosis
Yellow fever

- Mosquito-borne, multisystem hemorrhagic fever
- Nearly 30% case-fatality rate
- Occurs in parts of South America & Africa
  - Recent outbreaks in Brazil, Guinea, Ivory Coast, Peru, Senegal, and Sudan
- Live, attenuated vaccine highly efficacious q 10 yrs

Yellow fever and vaccine safety in elderly

- Elderly travelers at increased risk for adverse events to vaccine
- Persons >65 years at least:
  - 6 times greater risk for adverse events
  - 3.5 times greater risk for adverse events resulting in death or hospitalization
- Adverse events must be balanced against risk of yellow fever infection

Altitude Illness Prevention

- High-altitude destinations include:
  - Cuzco (11,000 ft)
  - La Paz (12,000 ft)
  - Lhasa (12,100 ft)
  - Everest Base Camp (17,700 ft)
  - Kilimanjaro (19,341 ft)
- Ascend gradually, if possible. Try not to go directly from low altitude to >9,000 feet
- Consider using acetazolamide to speed acclimatization if abrupt ascent unavoidable

Prevention and Treatment of Altitude Illness

- Acetazolamide
  - AMS and HACE Prevention: 125 mg bid
  - Treatment: 250 mg twice a day
- Dexamethasone
  - AMS, HACE Prevention: 2 mg every 6 h
  - or 4 mg q 12 h
  - AMS, HACE treatment 4 mg every 6 h
- Nifedipine
  - HAPE Prevention Oral 30 mg SR bid, or 20 mg SR version every 8 h
Rabies

- Rare, but potentially fatal viral infection
- Dog rabies endemic in developing countries
  - U.S. soldier recently back from Afghanistan died from canine rabies.
  - At least 50,000 rabies deaths, primarily due to dog and cat bites are reported annually to WHO
  - In Thailand, 8% of all street dogs infected

Rabies pre-exposure vaccination

- Risk of animal bite may exceed 1-2%/yr for travelers
- RabAvert Vaccine recommended for long-term travelers
  - Inactivated rabies vaccine-3 doses on days 0,7, and 21 or 28
  - No booster doses required once immunized
  - Preexposure immunization does not eliminate need for Post-exposure treatment with two booster doses spaced by 3 days

Meningococcal infections

- Neisseria meningitidis
  - cause meningococcemia and/or meningitis
  - case-fatality rate of 15%
  - endemic and frequent cause of epidemics in sub-Saharan Africa ("meningitis belt"-type A and W-135)
  - increased risk during dry months (Dec-June)
  - quadrivalent vaccine q 5 years
  - covering serogroups A/C/Y/W-135
  - Two types available in United States

Primary differential diagnosis of febrile illness in a returning traveler

- Common Febrile Illnesses
- Malaria
- Typhoid
- Acute Hepatitis prodrome
- Dengue
Case History

- 38 year-old man presents for a pre-travel appointment. He is going to Kenya and Tanzania on safari.
  - What vaccines are indicated?

Case Vaccinations

1. Hepatitis A
2. Typhoid
3. Yellow Fever
4. Influenza
5. All routine immunizations
6. Meningitis vaccine?

Appropriate evaluation of returning traveler

- Fever
  - Peripheral blood smears for malaria
  - Blood cultures for typhoid fever
  - UA, LFTs, CXR
- Diarrhea
  - Stool cultures for bacterial pathogens
  - Stool ova and parasites
- Eosinophilia
  - Stool ova and parasites

Travelers’ Medical Kit

- Loperamide
- Anti-diarrheal antibiotic
- Antimalarial
- Mosquito repellent
- Antifungal
- Analgesic
- Decongestant
- Topical steroids
- High Altitude Illness medication
Key Points

- Food and waterborne diseases
  - basic precautions necessary
  - diarrhea responds to quinolone or macrolide
- Malaria and mosquito-borne diseases
  - avoid contact with mosquitoes, use DEET-containing mosquito-repellent, wear long sleeves and pants, light colored clothing
  - take malarone, mefloquine, or doxycycline
- Trauma
  - avoid motorcycles and mopeds
  - rent vehicles with seat belts and use them
- Vaccinations
  - routine vaccines; vaccination against hepatitis A and typhoid

Conclusions

- Primary care doctors can provide effective travel advice to reduce risk for low risk patients
- Prevention based global epidemiology of diseases and country specific resource data
- High-risk travelers with moderate to complex travel plans should be referred to specialist or travel clinics

Web sites with health advice for travelers

- CDC Yellow Book
  - http://cdc.gov/travel
- World Health Organization
  - http://www.who.int/ith
- U.S. State Department
  - http://www.state.gov
- ProMed
  - http://www.promedmail.org/
- Malaria Treatment Hotline  770-488-7760
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