Fever in the Tropics
A Few Easy Pieces

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Fever Cases: Goals

• Review some high-yield cases of fever

• Reinforce your general approach to febrile patients

• Interactive Please!
Fever Cases: Resources

• Case Summaries
• Post-Travel Fever Workup Guide
I have fever
For curing cold,
it is important to rest with warming.
Fever: *Significance*

- Fever may be the patient’s *only* presenting complaint
- Workup seems daunting
- What could this be?
  - What should I ask?
  - What should I look for?
  - What tests should I order?
- *Will this patient die?*
You can do it

• Febrile patients rarely die acutely… big exception is *falciparum malaria*

• Many of the diagnoses are the *same ones* you already know

• Your skills with *history and physical* will serve you well

• Many diagnoses require only *standard* lab tests
Fever: *First Question*

- **Careful H&P**
- Localizing Symptoms or Signs?
Fever: First Question

Localizing Symptoms or Signs?

Yes → Careful H&P

No →
Fever w/o Localization

1) Grab malaria smears, BCx’s, CBC with diff.

2) Is fever acute or chronic?
Fever w/o Localization

**Acute**

↑ Neutrophils
- Bacterial sepsis
- Leptospirosis
- TBRF
- LBRF

↑ Lymphocytes
- Viral syndrome
- Mononucleosis
- Rickettsia
- Typhoid
Fever w/o Localization

Chronic

Is this TB or HIV?
Fever w/o Localization

**Chronic**

↑ **Neutrophils**
- Occult abscess
- Cholangitis
- ALA
- ENL
- Relapsing Fever

↓ **Leukocytes**
- Malaria
- Brucellosis
- Extrapulm. TB
- Kala-Azar

↑ **Eosinophils**
- Schistosomiasis or other invasive Helminth
Fever w/o Localization

Chronic

Normal WBC
- TB
- Brucellosis
- \(2^{nd}\) Syphilis
- Trypanosomiasis
- Toxoplasmosis
- SBE
- SLE
- Meningococcemia

\(\uparrow\downarrow\) WBC
- Malignancy
- Drug Reaction
- Connective tissue disease
## Typical Incubation Periods for Selected Tropical Infections

<table>
<thead>
<tr>
<th>Short  (&lt;10 Days)</th>
<th>Medium (10-21 Days)</th>
<th>Long (&gt;21 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbovirus (Dengue)</td>
<td>Malaria Brucellosis Leptospirosis Q fever</td>
<td>Malaria Amebic abscess Filariasis HIV</td>
</tr>
<tr>
<td>Enteric Fever</td>
<td>Scrub typhus</td>
<td>Leishmaniasis</td>
</tr>
<tr>
<td>Influenza</td>
<td>Spotted fevers</td>
<td>Viral hepatitis</td>
</tr>
<tr>
<td>Plague</td>
<td>Trypanosoma Typhoid</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Rickettsiae</td>
<td></td>
<td>TB</td>
</tr>
<tr>
<td>Typhoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VHF (Lassa, Ebola, Marburg)</td>
<td>Trypanosoma Typhoid</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Strickland
CHANGED PRIORITIES AHEAD
Fever & Rash

- 22 y/o F (G₁P₀ 25 wks) with acute fever, malaise, and pruritic skin lesions x 7 days.
- Lesions began on abdomen → spread to chest, face, then extremities. Several mouth lesions have now resolved. Fresh lesions are still appearing.
- No previous medical problems. No cough, dyspnea, or shortness of breath.
- Lifelong resident of Iquitos, Peru. Three younger siblings living at home developed a similar febrile rash 2 weeks prior.
Fever & Rash

• Afebrile now. Chest clear. No LAN or HSM. OP clear.
• Hct 40%. WBC 7.0. Malaria smear neg.

DDX?
Fever & Rash

In this pt:
• VZV
• VZV
• VZV
• HSV
• Monkeypox
• Variola

Variola: Synchronous Pustules
Fever & Rash

In general:
- Acute HIV
- Poxviruses
- Arboviruses
- 2\textsuperscript{nd} Syphilis
- Measles
- Typhoid & Paratyphoid
- Rickettsiae
- Bartonellosis
- Connective tissue dz
A 20 y/o college student returned from spring break in Cancun 2 weeks ago where he "partied on the beach." Now has 3 days of fever, fatigue, myalgias, sore throat. Oral ulcers. This rash appeared on trunk, arms, face yesterday.
Viral exanthem?

- HIV
- HIV
- HIV
- Dengue actually *low risk* in Cancun
- Measles (should have gotten MMR)
- R/O other STD’s (2° syphilis)
Fever & Rash

- A 32 y/o M sheep rancher in rural Venezuela with fever, 4 days painful left arm, painful warm 5x10 cm mass in the axilla, and these painless ulcers on the left forearm.
Yup, it’s cutaneous anthrax

• Key words: bullae, painless eschar, raised / indurated border, livestock exposure
• Pneumonic form: wide mediastinum, shock, hemorrhagic meningitis, US Mail
• Dx: Culture (warn lab!)
• Rx: Isolation, PCN or doxy or cipro
• 44 y/o M game warden in Kruger National Park with fevers = 39C

• Close inspection revealed this lesion on posterior calf

*Rickettsia africaines* (African tick typhus)
Fever & Rash

- 22 y/o M Yemeni goat herder with acute fever, b/l leg pain, and rapidly spreading rash

Disseminated meningococcemia
An Urgent Care pt...

• A 21 year-old woman complaining of malaise, fevers, rigors, and a rash.

• She returned from a trip to Haiti four days ago.
• Spent ten days in January in a small jungle village on western coast of Haiti, building low-income housing.

• Lived in canvas tent. Some windows screened. Sometimes used bed net. Lots of insect bites.

• Ate “camp food” with everyone else.

• Denies sexual activity.
• Had mild diarrhea starting on third day of trip… getting better.

• Awoke with shaking chills on eighth day… bunkmate said she was “burning up.” Had this twice a day until stopped yesterday.

• Terrible headache. Muscle aches all over. “Even moving my eyes hurts.”

• Saw sunburn on trunk yesterday.
• PMH: none
• Vaccinations: childhood series up to date
• Meds: chloroquine, immodium
• Habits: none
• FH: none
Exam

- 37.8° / 72 / 110/62 / 16 / 120 lbs
- Appears tired but not in extremis
- Diffuse, crimson, macular rash on trunk and a bit on upper arms/thighs. + Handprint sign. Many bug bites, no eschars.
- Marble-sized LAD in inguinal and axillary chains b/l.
- Neck slightly stiff… so are all other muscles. O/P clear.
- No murmur, lungs clear, abdomen benign, GU normal
Labs in Clinic

• WBC 6.2 (nl diff), HCT 45, Plt 220
• First thick & thin smears negative
• CMP pending
• Extra red top tube frozen in lab (in case acute serologies need to be sent later)
Quick Differential

Incubation < 2 weeks, Haiti, insect bites, fever, M-P Rash, LAD, nl CBC, first smears negative, normal host

- Dengue “breakbone” fever
- Acute HIV seroconversion
- Other viral exanthem (measles, rubella?)
- Bacterial infection (lepto, typhoid, 2° syphilis)
- Malaria less likely but rule it out anyway
Dengue Hemorrhagic Fever?

- Occurs in patients previously infected with a different serotype of Dengue virus.
- Pathogenesis: Ab-mediated enhancement of virus uptake into macrophages.
- High fever, lethargy, increased vascular permeability (hypovolemic shock).
- Abnormal hemostasis, profound thrombocytopenia, hemorrhagic manifestations on day 3 of illness on average + Tourniquet sign
  Bleeding at venipuncture sites

Adapted from Bill Petri
1. Inflate BP cuff ½ between SBP & DBP
2. Wait 5 minutes, then deflate cuff.
3. Tourniquet Sign if > 20 petechiae / sq. inch
Plan

Discuss with ID, consider admission to finish ruling out malaria & follow clinically… could do this as outpt, vs. brief “obs” admission.

- Acetaminophen (“avoid NSAIDs to minimize bleeding risk”)
- oral nutrition and hydration
- Send HIV / RPR / blood cultures / acute serologies for Dengue and whatever other viruses ID suggests
Beware of dengue fever

ACT NOW
Fever & Jaundice

- 54 y/o woman from rural Peru, previously healthy, on no meds
- 3 weeks of fatigue, malaise, intermittent fever, and epigastric pain
- Pain radiated to the back and into chest
- Mild dry cough
- Presented in June when she awoke jaundiced
Fever & Jaundice

- 38.4°C, HR 100, BP 110/65, RR 18
- Uncomfortable, no acute distress
- Scleral icterus OU
- Moderate RUQ TTP, no HSM, normal BS

DDX?
**Fever & Jaundice**

**Hepatic Source**
- Acute Hep A/B/C/…
- Cholangitis
- Herpes (HSV, CMV, EBV)
- Arbovirus (Dengue, YF)
- Borrelia
- Coxiella
- 2\textsuperscript{nd} Syphilis
- Leptospirosis

**Hemolytic Source**
- Malaria
- Drug-induced
- Malignancy
**Fever & Jaundice**

- Direct bili 15, indirect modestly elevated, Normal AST & ALT
- Alk phos elevated to 460
- WBC 10 K with 12% eos
- Abdominal U/S: Gallstones seen and noted to have CBD dilated to 14mm…
- She sells “berros” for a living…

**DDX now?**
“A Diagnostic Procedure was Performed”

Adult fluke:
*Fasciola hepatica*
Fasciola Egg in Stool

- Measure 130-150 microns in length
- Unembryonated
- Operculate
- Similar to Fasciolopsis buski in size & appearance
- Roughened abopercular end
Rx: Triclabendazole (not PZQ)

Don’t tell JCAHO!
Fever & Jaundice

21 y/o rancher from the Pampas

- Fever
- Jaundice
- Abdominal pain
- Oliguria
- Hematuria
- Mucosal bleeding

Think YF!

- 15% are seriously ill
- Not all die of gastric bleed
Fever & Diarrhea

• 19 y/o M from Delhi visits relatives in Sri Lanka
• Develops fever, diffuse abdominal pain, bloody diarrhea
  Trichrome:
  • Moderate Few Cysts of *Entameba histolytica/dispar*,
  • Few *Entameba hartmanni* Trophozoites and Cysts,
  • Few *Endolimax nana* Trophozoites and Cysts,
  • Few *Blastocystis hominis*

Your Thoughts?
Fever & Diarrhea

Quick DDX

• Campylobacter
• Salmonella enteritidis
• Shigella
• Clostridium difficile
• E. coli (EPEC & EHEC)
• Yersinia enterocolitica
• Aeromonas, plesiomonas
• Entamoeba histolytica
• Balantidium coli
• Schistosoma mansoni

• Malaria can cause diarrhea, but almost never dysentery
Amebic Dysentery

• *Entameba histolyctica* ("tissue-destroying blob within")
  - Fecal-Oral route
  - Proliferative form: trophozoite (RBC phagocytosis)
  - Passage form: Cyst (non-invasive)

• *Entameba dispar* ("different blob")
  - Does not eat host flesh, but cysts have same appearance
Amebic Dysentery

- **Gold Standard:** Microscopy of phagocytosed red cells… stool steaming hot, on a warmed saline stage

- **Backup:** Stool antigen (specific for histolytica species) by ELISA, RIA, or IF

- **Also suggestive:** Flask-shaped ulcers on fixed tissue specimen

- Consider empiric metronidazole if these assays not available!
Non-Hist/Dispar Protozoans

• Stool may contain numerous other species
• Most considered non-pathogenic commensals
• Controversy: Blastocystis hominis a true pathogen?
  ✓ Patients usually Rx’d for B. hominis with metronidazole, but weak evidence for cause & effect
Blastocystis hominis

Entameba hartmanni

Endolimax nana

Entameba coli
A 9 y/o Sudanese girl is brought to your refugee hospital with fever, prostration, and productive cough

- Wheezes, ronchi, and decreased breath sounds at left base

Your plan?
Fever & Cough

Pneumonia

• Clinical impression has high PPV
• Empiric abx may be life-saving
• Old drugs are fine
  • TMP/SMX & Chloro excellent
• Caveats:
  • MTB & pertussis more prevalent in tropics
  • Eyes open for epidemics
  • IMCI guidelines a great start
A previously healthy 48 y/o M from Hong Kong c/o fever, CP, cough, SOB 2 days after returning from business trip to Guangzhou

SARS v. HPAI until proven otherwise
Did I mention... *HIV*?
Gary Larson: The Far Side

"What a day! ... I must have spread malaria across half the country."
Fever: Summary

• The diagnostic workup of acute illness acquired in the tropics is not impossible

• Your detailed H&P, basic lab work, and imaging will often lead to the diagnosis

• *Please oh please don’t miss* malaria or HIV
Common Dermatologic Lesions in Travelers Returning from Developing Countries
**Studies**

**Labs**

- Blood

  - Multiple thick & thin blood films for malaria

  CBC with manual diff, chem-7, LFT's, coags, HIV, Hepatitis serologies, other serologies if indicated

  Eosinophilia can represent reaction to parasites, and is helpful if present (*absolute count* >500/mcL)

  Eosinophilia is *not* present with viral or bacterial pathogens, and is therefore *useless* if absent

  Freeze a red top or two for later antibody detection
Case 2

• A 45 year-old man complains of bloody diarrhea.

• Returned from a trip to Costa Rica yesterday.
History

- Spent a week in capital city of San Jose on business (manufacturing).
- Dined with clients at restaurants and in their homes.
- Stayed in a high rise hotel. No excursions out of town.
- Denies sexual activity while there.
• Stools turned “runny” on the third day there. Used immodium with some improvement for two days, then no benefit.

• Stool now foul-smelling, gelatinous, brown with some bright red blood on paper.

• Severe abdominal cramps with bm’s.

• Subjective fevers for last few days.
• PMH: untreated HTN, elevated lipids
• Vaccinations: childhood series unclear
• Meds: imodium, APAP
• Habits: 20 pk/yr tobacco
• FH: none
Exam

• 38.1° / 92 / 130/90 / 20 / 196 lbs
• Appears exhausted, pale
• HEENT clear.
• No murmur, lungs clear, GU normal
• Hyperactive bowel sounds, diffusely tender to firm palpation, voluntary guarding, no HSM, engorged external hemorrhoids, minor rectal tenderness, small amount of maroon blood on glove
Labs in Clinic

- WBC 12.4 (nl diff), Hct 39, Plt 300
- First thick & thin smears negative
- Others pending
Algorithm for the Evaluation of Acute Diarrhea

1. Acute diarrhea (acquired outside of hospital)
   - Symptomatic therapy (hydration, alteration of diet)
     - Severe illness (dehydration, blood, fever, duration >48 hours, severe abdominal pain in patient >age 50, elderly [≥70 years], or immunocompromised)
       - Illness resolves
       - Illness continues
     - Examine stool for inflammatory cells
       - Noninflammatory (e.g., Norwalk, Rotavirus, C. perfringens, S. aureus, B. cereus, Giardia, drugs, occasionally IBD)
         - Continue symptomatic therapy
         - Further evaluation if symptoms persist
       - Inflammatory (e.g., Campylobacter, Shigella, Salmonella, Enterohemorrhagic E. coli, C. difficile)
         - Routine stool culture
         - Consider nonroutine stool culture or ova and parasites in select situations (see text)
         - Consider C. difficile if recent antibiotic therapy
         - Consider empiric therapy while awaiting culture results in the following groups: patients with fever or bloody diarrhea; patients with >8 stools per day, dehydration, symptoms >one week, immunocompromised, if hospitalization considered.
         - Consider specific therapy once pathogen identified (see text for indications, type of treatment)
Algorithm for the Evaluation of Acute Diarrhea

Acute diarrhea (acquired outside of hospital)

Symptomatic therapy (hydration, alteration of diet)

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Specificity ~ 50%
Algorithm for the Evaluation of Acute Diarrhea

Acute diarrhea (acquired outside of hospital)

Symptomatic therapy (hydration, alteration of diet)

Severe illness (dehydration, blood, fever, duration >48 hours, severe abdominal pain in patient > age 50, elderly [≥70 years], or immunocompromised)

Illness resolves

Illness continues

Examine stool for inflammatory cells

No

Yes

Noninflammatory
(eg, Norwalk, Rotavirus, C. perfringens, S. aureus, B. cereus, Giardia, drugs, occasionally IBD)

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Inflammatory
(eg, Campylobacter, Shigella, Salmonella, Entero-hemorrhagic E. coli, C. difficile)

Yes

Routine stool culture
Consider nonroutine stool culture or ova and parasites in select situations (see text)
Consider C. difficile if recent antibiotic therapy

No

Consider empiric therapy while awaiting culture results in the following groups: patients with fever or bloody diarrhea; patients with >8 stools per day, dehydration, symptoms > one week, immunocompromised, if hospitalization considered.

Consider specific therapy once pathogen identified (see text for indications, type of treatment)

Further evaluation if symptoms persist
One Routine Stool Culture...
$161.50

Knowing your patient’s pathogen... priceless?
Dysentery Stool Culture / O&P: Indications

- Severe illness beyond several days
- HIV infection
- Significant comorbidity
- IBD
- Food handlers
- Children
When to Treat?

Algorithm for the Evaluation of Acute Diarrhea

- Acute diarrhea (acquired outside of hospital)
  - Symptomatic therapy (hydration, alteration of diet)
    - Severe illness (dehydration, blood, fever, duration >48 hours, severe abdominal pain in patient > age 50, elderly [≥ 70 years], or immunocompromised)
      - No: Illness resolves
      - Yes: Examine stool for inflammatory cells
        - Noninflammatory (eg, Norwalk, Rotavirus, C. perfringens, S. aureus, B. cereus, Giardia, drugs, occasionally IBD)
          - Continue symptomatic therapy
          - Further evaluation if symptoms persist
        - Inflammatory (eg, Campylobacter, Shigella, Salmonella, Enterohemorrhagic E. coli, C. difficile)
          - Routine stool culture
            - Consider nonroutine stool culture or ova and parasites in select situations (see text)
            - Consider C. difficile if recent antibiotic therapy
          - Consider empiric therapy while awaiting culture results in the following groups: patients with fever or bloody diarrhea; patients with >8 stools per day, dehydration, symptoms >one week, immunocompromised, if hospitalization considered.
            - Consider specific therapy once pathogen identified (see text for indications, type of treatment)
Dysentery: Treatment?

598 Adult Swedes with acute diarrhea randomized to norfloxacin 400 PO BID v. placebo

- 51% had pathogens on stool cx (29% campy, 16% salmonella, etc.)
  - Overall time to “cure” with abx 1.7 days v. 2.8 days
  - Among “severely ill,” time to cure 1.5 v. 3.4 days
  - Salmonella clearance less likely with abx at 2 weeks (18% v. 49%)
  - No kids included, no O157:H7
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>First choice</th>
<th>Second choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>Not required</td>
<td>Not required</td>
<td>Due to food poisoning and resolve with hydration only. TMP/SMX* can be used if susceptible; antibiotic therapy required only in severe cases (see text)</td>
</tr>
<tr>
<td>B. cereus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>Usually not required (see text)</td>
<td>Oral quinolone† BID for 3 to 5 days</td>
<td>Same as above</td>
</tr>
<tr>
<td>Shigella</td>
<td>Oral quinolone† BID for 5 days</td>
<td>TMP/SMX* or ampicillin</td>
<td>Many strains now resistant to TMP/SMX* and ampicillin</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Oral quinolone† BID for 5 days</td>
<td>Macrolides¶ or doxycycline</td>
<td>Antibiotics only in severe cases (see text). Quinolone resistance has been reported</td>
</tr>
<tr>
<td>Yersinia</td>
<td>Oral quinolone† BID for 7 to 10 days</td>
<td>TMP/SMX or doxycycline</td>
<td>Antibiotic therapy only in severe (systemic) cases</td>
</tr>
<tr>
<td>C. difficile</td>
<td>Metronidazole 250 mg PO QID</td>
<td>Vancomycin 125 mg PO QID</td>
<td>Duration of therapy 10 days; stop antibiotics, if possible; IV metronidazole if unable to tolerate oral therapy; IV metronidazole ± vancomycin fecal enemas for severe cases</td>
</tr>
<tr>
<td>ETEC</td>
<td>Oral quinolone† BID for 1 to 3 days</td>
<td>TMP/SMX*, doxycycline, furazolidone</td>
<td></td>
</tr>
<tr>
<td>EIEC</td>
<td>Same as for Shigellosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHEC</td>
<td>Not recommended at this time</td>
<td>? oral quinolone†</td>
<td></td>
</tr>
<tr>
<td>V. cholerae</td>
<td>Oral quinolone</td>
<td>Doxycycline</td>
<td></td>
</tr>
</tbody>
</table>

*Trimeprin/sulfamethoxazole 160/800 mg (DS tab) PO q 12 h
† Norfloxacin 400 mg PO, ofloxacin 400 mg PO, ciprofloxacin 500 mg PO
¶ Erythromycin, clarithromycin, azithromycin
Dysentery: Pearls

- Antimotility agents should be avoided: “let it flow.” If you gotta use them, titrate to several stools / day.

- Probiotics *Lactobacillus* and *Saccharomyces* won’t hurt (unless neutropenic), and may help. “BRAT” diet of questionable value.

- For travelers, prophylaxis with bismuth subsalicylate 2 tabs PO QID leads to ~60% reduction in diarrhea.
A Randomized, Double-Blind, Placebo-Controlled Trial of Rifaximin To Prevent Travelers’ Diarrhea

Herbert L. DuPont, MD; Zhi-Dong Jiang, PhD; Pablo C. Okhuysen, MD; Charles D. Ericsson, MD; Francisco Javier de la Cabada, MD; Shi Ke, MD; Margaret W. DuPont, MA; and Francisco Martinez-Sandoval, MD, PhD

Background: Travelers’ diarrhea causes substantial morbidity and postinfectious irritable bowel syndrome.

Objective: To evaluate nonabsorbable rifaximin for prevention of travelers’ diarrhea.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: Guadalajara, Mexico.

Participants: U.S. students.

Intervention: On arrival in Guadalajara, Mexico, 210 U.S. adults received rifaximin (200 mg/d, 200 mg twice daily, or 200 mg 3 times daily) or placebo for 2 weeks.

Measurements: Participants were followed daily for 3 weeks for enteric disease and symptoms and daily for 5 weeks for drug side effects. Changes in intestinal coliform flora were studied.

Results: Travelers’ diarrhea developed in 14.74% of participants taking rifaximin and 53.70% of those taking placebo (rate ratio, 0.27 [95% CI, 0.17 to 0.43]). Rifaximin provided 72% and 77% protection against travelers’ diarrhea and antibiotic-treated travelers’ diarrhea, respectively (P < 0.001 for both), and all rifaximin doses were superior to placebo. In the groups that did not report travelers’ diarrhea, rifaximin significantly reduced the occurrence of mild diarrhea (P = 0.02) and moderate and severe intestinal problems (P = 0.009 for pain or cramps; P = 0.02 for excessive gas). Rates of adverse events were comparable in the rifaximin and placebo groups. Minimal changes in coliform flora were found during rifaximin therapy.

Limitations: Rifaximin safely prevented travelers’ diarrhea in Mexico, where most cases are caused by diarrhea-producing Escherichia coli. A study is needed in Asia to determine whether rifaximin can prevent diarrhea caused by invasive bacterial pathogens.

Conclusions: Rifaximin prevents travelers’ diarrhea with minimal changes in fecal flora, and more liberal chemoprophylaxis against this disease should be considered. Future studies should evaluate whether rifaximin is effective in preventing postinfectious irritable bowel syndrome.

For author affiliations, see end of text.
Trial NCT0098384.
Plan

Several valid approaches

• Emphasize supportive care / hydration
• No admission or abx mandatory unless he becomes more “toxic” or symptoms > 1 week
• Many MD’s will send a culture / O&P, though usually will not change approach
Follow up

Stool cultures come back: *S. typhi*

Three major scenarios with this bug

- Asymptomatic carriage
- Enteric fever
- Typhoid fever
Salmonella typhi and Typhoid Fever

- World-wide incidence ~ 12.5 million cases / yr
- Hospital-based mortality in developing world 1-30%
- Outpt mortality in developed world ~1%
- Most cases imported from travelers to Mexico and Indian subcontinent
- 382 U.S. cases reported to CDC in 1998
Salmonella typhi and Typhoid Fever

- Incubation generally 7-14 d (range 3-60 d)
- Fever 99%
- Headache 85%
- Hepatomegaly 50%
- Abdominal pain 45%
- Diarrhea 45%
- Rose spots 0-50%
- Splenomegaly 35%
- Disorientation 15%, Delirium 10%, Stupor 2%
- Relative bradycardia 15%
Complications of Typhoid Fever

- Intestinal perforation & hemorrhage
- Renal failure
- Pneumonia & ARDS
- Myocarditis & CHF
- Shock
- Meningitis
- Abscesses
- Arthritis
- Osteomyelitis
- Hemolytic anemia
- Cholecystitis
Salmonella typhi and Typhoid Fever

- Bone marrow aspiration most sensitive (95%), but rarely performed
- Culture of blood (40-80%) duodenal secretions (60-80%) and stool (30-50%)
  - Together ~85% sensitive
- Widal’s test (poor PPV and NPV)
Salmonella typhi and Typhoid Fever

Therapy

- Quinolones (14 days)
- Chloramphenicol, TMP/SMZ, ampicillin, 3rd generation cephalosporins (7-10 days after defervescence)
- Multi-drug resistant S. typhi increasingly widespread
- Patients with severe typhoid fever (delerious, obtunded, stuporous, comatose, in shock) should receive steroids
The Next pt…

• A 52 year-old man with fever, malaise, and jaundice

• Returned from a two-month trip to Ghana last week… went home to visit family after living in US for eight years

• Started taking Aralen two weeks ago when he developed symptoms
Quick Differential and Plan

- Malaria
- Malaria
- Malaria
- Typhoid fever
- Dengue fever
- Viral hepatitis
- HIV
- Leptospirosis
When Falciparum Malaria is Likely

- Thorough H&P… fever pattern chaotic during early infection
- Get the first smears done in clinic
- Contact ID
- Arrange admission to begin Rx
- If the patient walked in on his own power, survival almost certain with prompt care
Therapy of Malaria

• Generally: CQ for non-falciparum (not Fansidar or Malarone for vivax)
• Quinine (or IV quinidine) plus doxycycline for drug-resistant-falciparum
• Alternatives
  – Mefloquine (Lariam), Atovaquone / proguanil (Malarone), Sulfadoxine / pyrimethamine (Fansidar), Artemisinin derivatives [not in US, but lumefantrine / artemether soon from Novartis]
• Consider exchange transfusion for parasitemia > 10% or cerebral malaria
• Follow smears for assessment of cure
A Few Quickies...
A previously healthy 45 y/o man c/o fever, chills, HA, myalgias, and thumb / wrist lesions 3 days after returning from a week-long hunting trip in Arkansas.
**Ulceroglandular tularemia**

- Painful ulcer +/- eschar, erythematous border (not “flesh-colored and raised” like anthrax)
- May also be pneumonic, oculoglandular, typhoidal, glandular
- Huntin’ & Fishin’
- May be vector-borne (ticks, flies, mosquitoes)
- “Francisella: Not just in Arkansas anymore!”
- Dx: Serology or cx (warn the lab!)
- Rx: Strep, gent, doxy
21 y/o student
– 6 weeks of enlarging facial lesion
  • No pain or pruritus
  • *No fever*
– Worked for a year in the rainforest in Belize studying the ecology of deforestation
Localized cutaneous leishmaniasis
Viral exanthem?

- HIV
- HIV
- HIV
- Dengue actually *low risk* in Cancun
- Measles (should have gotten MMR)
- R/O other STD’s (2° syphilis)
22 y/o woman c/o fever and rash over entire body 10 days after returning from Nigeria, where she works in US consulate.
Smallpox (Variola major)

- Synchronous pustular vesicles (unlike asynchronous varicella lesions)
- Dx: Vesicle fluid sent to CDC
- Rx: Isolation, support, vaccinate contacts
A previously healthy 48 y/o man c/o fever, CP, cough, SOB 2 days after returning from business trip to Hong Kong.

SARS v. HPAI until proven otherwise
Summary: Coming Home Sick

• The diagnostic workup of acute illness acquired in the tropics is not impossible

• Your detailed H&P, basic lab work, and imaging will often lead to the diagnosis

• If not, the specialists will thank you for getting things started

• Please oh please don’t miss malaria or HIV
**Remember:**

Travel Medicine ≠ Tropical Medicine!
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- > 20 million Americans go overseas each year
- Exotic destinations increasingly common
- Patients rarely return with diseases new to you
- Lucrative for docs
**Remember:**

Travel Medicine ≠ Tropical Medicine!

- > 20 million Americans go overseas each year
- Exotic destinations increasingly common
- Patients rarely return with diseases you have not seen before
- Lucrative for docs

Tropical Medicine:

- Half of all humans live in tropics
- Poverty still the rule… risk for many diseases is rising
- “Exotic” illnesses are common
- Rewards other than $
Travel Medicine: Will it be on the Boards?

- Probably NOT. Very few questions on past Internal Medicine Board exams.
Travel Medicine: Scope of the Problem

For every 100,000 travelers to developing world > 1 month:

- 50,000 get sick
- 8,000 seek medical help
- 5,000 bedridden
- 300 admitted
- 1 dies
Pre-Travel Counseling

Causes of Death While Traveling

- Cardiovascular disease (35-69%)
- Trauma (21-26%)
- Infectious diseases (only 1-4%)
Pre-Travel Counseling

- *Discuss* detailed itinerary
- *Rx* extra supplies and meds
- *Document* medical issues
- *Warn* to maintain judgment
- *Remind* about avoid insect bites
- *Teach* about food & water safety
- *Malaria* “ABCD’s”
- *Offer* vaccinations
Pre-Travel Counseling

A. Awareness of the risk, incubation period, and symptoms
B. Bite of the mosquito should be avoided
C. Chemoprophylaxis must be taken as directed
D. Diagnosis and treatment immediately for

• Malaria “ABCD” ping > 1 week after entering or < 6 months after returning from endemic areas
DEET (30% max)
PICARIDIN (only 8%)
LEMON EUCALYPTUS
PERMETHRIN
(Clothes & Bednets)
Pre-Travel Counseling

Malaria Prophylaxis

✓ Determine risk: www.cdc.gov/travel
Outbreak Notice Lifted

Update: Malaria, Dominican Republic: Outbreak Notice Lifted for La Altagracia Province (Punta Cana area)

The Centers for Disease Control and Prevention (CDC) has lifted the outbreak notice for travel to La Altagracia Province, Dominican Republic, including the resorts at Punta Cana. No new malaria cases in travelers have been reported from the area since January 2005; the numbers of malaria cases in the Dominican Republic have returned to what is normal for this province. The outbreak notice for Duarte Province was lifted on February 23, 2005.

Twenty cases of malaria were reported in persons who had traveled to resort areas in La Altagracia Province from November 3, 2004 to January 10, 2005, and a single case in a traveler to Duarte Province, who returned in early November. Five of the travelers were from the, U.S, 6 from Canada, and 16 from Europe (see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5351a1.htm). These resort areas had previously been malaria-free.

In response to the outbreak, CDC recommended taking an antimalarial drug for all travelers to the two provinces, including resort areas. The Ministry of Health of the Dominican Republic increased surveillance for possible cases, increased mosquito spraying and elimination of breeding sites, and ensured that any malaria cases found were promptly treated. The Pan American Health Organization and CDC provided assistance and advice to the Ministry.

Since malaria continues to be a risk in rural areas of the Dominican Republic (but not in cities or resort areas), travelers to these rural areas should take an antimalarial drug. Chloroquine is the recommended drug for the Dominican Republic. Malaria can usually be prevented by taking an antimalarial drug and by using anti-mosquito measures.

Chloroquine has a long history of use and safety and has been found to be well tolerated by most people, including children. People with an allergy to chloroquine should discuss an alternative antimalarial drug with their health-care provider. To learn more about chloroquine, see this website: http://www.cdc.gov/travel/malaria/drugs.htm.

Because antimalarial drugs are not 100% protective, other measures to prevent mosquito bites should also be used, such as insect repellents that contain the ingredients DEET (N,N-diethyl-m-toluamide) or Picaridin (KBR 3023). To learn more about preventing mosquito bites and the appropriate use of insect repellents, visit these websites: http://www.cdc.gov/travel/bugs.htm and http://www.cdc.gov/ncidod/dvbid/westnile/mosquitorepellent.htm.

Travelers who become ill with a fever or flu-like illness while traveling in the Dominican Republic or after returning home (up to 1 year) should immediately seek medical care. Tell your health care provider that you have been in the Dominican Republic and that you may have been exposed to malaria.
Pre-Travel Counseling

Malaria Prophylaxis

✓ Determine risk: www.cdc.gov/travel
✓ If endemic:
  • Mosquito avoidance
  • If CQ sensitive: Rx CQ!
  • If CQ resistant:
    ➢ MQ (cheap; $ effects)
    ➢ Doxy (cheap; sunburn / esophagitis)
    ➢ Atovaquone / proguanil ($$)
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Dosage regimen</th>
<th>Duration of prophylaxis</th>
<th>Breastfeeding</th>
<th>Children</th>
<th>Main contraindications*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone-proguanil combination tablet</td>
<td>One dose daily. 11-20 kg: 62.5 mg atovaquone plus 25 mg proguanil (1 paediatric tablet) daily 21-30 kg: 2 paediatric tablets daily 31-40 kg: 3 paediatric tablets daily &gt; 40 kg: 1 adult tablet (250 mg atovaquone plus 100 mg proguanil) daily</td>
<td>Start 1 day before departure and continue for 7 days after return</td>
<td>No data, not recommended</td>
<td>No data, not recommended</td>
<td>Hypersensitivity to atovaquone and/or proguanil; severe renal insufficiency (creatinine clearance &lt;30 ml/min). Experience with this drug for prophylaxis in non-immune travellers is still limited. It is registered in European countries for chemoprophylactic use with a restriction on body weight (&gt; 40 kg) and duration of use (varying from 28 days to 3 months). In the USA these restrictions do not apply. Plasma concentrations of atovaquone are reduced when it is co-administered with rifampicin, rifabutin, metoclopramide or tetracycline.</td>
<td></td>
</tr>
<tr>
<td>Choroquine</td>
<td>5 mg base/kg weekly, or 10 mg base/kg weekly divided in 6 daily doses adult dose: 300 mg chloroquine base weekly in one dose or 600 mg chloroquine base weekly divided over 6 daily doses of 100 mg base (with one drug-free day per week)</td>
<td>Start 1 week before departure and continue for 4 weeks after return. If daily doses: start 1 day before departure.</td>
<td>Safe</td>
<td>Safe</td>
<td>Hypersensitivity to chloroquine; history of epilepsy; psoriasis. Concurrent use of chloroquine can reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.</td>
<td></td>
</tr>
<tr>
<td>Chloroquine-proguanil combination tablet</td>
<td>&gt; 50 kg: 100 mg chloroquine plus 200 mg proguanil (1 tablet) daily</td>
<td>Start 1 day before departure and continue for 4 weeks after return</td>
<td>Safe</td>
<td>Safe</td>
<td>Tablet size not suitable for persons of &lt; 50 kg body weight Hypersensitivity to chloroquine and/or proguanil; liver or kidney insufficiency; history of epilepsy; psoriasis. Concurrent use of chloroquine can reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.</td>
<td></td>
</tr>
</tbody>
</table>
Pre-Travel Counseling

Vaccinations

• Guidelines for “routine adult series” at www.cdc.gov/travel/vaccinat.htm

• Consider indications for:
  ✓ Hepatitis A & B
  ✓ Japanese Encephalitis
  ✓ Meningocococcus
  ✓ Rabies
  ✓ Typhoid
  ✓ Yellow Fever
HONOLULU, Hawaii (AP) -- Contaminated carrots served on several flights out of Honolulu likely caused 45 people to suffer food poisoning across 22 states, Japan, Australia and American Samoa, a state epidemiologist said Thursday.
HONOLULU, Hawaii (AP) -- Contaminated carrots served on several flights out of Honolulu likely caused 45 people to suffer food poisoning across 22 states, Japan, Australia and American Samoa, a state epidemiologist said Thursday.

The outbreak has sparked one lawsuit, filed Thursday, against airline caterer Gate Gourmet Inc., which included the carrots in meals served last August 22-24. The company, based in Virginia and Switzerland, was sent a warning letter by the federal FDA on April 21 citing violations found in a February inspection of its Honolulu facility -- such as a "pink slimy substance" dripping onto the conveyor of the pot washing machine, live cockroaches and flies, and mold growing on the windows of a refrigerator. Gate Gourmet provides meals for Northwest, Delta, United, Hawaiian and Aloha airlines.
### Causes of Acute Fever Among Travelers Returning from the Tropics

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>% (n=587)</th>
<th>% (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory Infection</td>
<td>11</td>
<td>2.5</td>
</tr>
<tr>
<td>UTI</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Dengue Fever</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Enteric Fever</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diarrheal Illness</td>
<td>4.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Epstein-Barr Virus</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rickettsiae</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Amoebic Liver Abscess</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Acute HIV</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>25</td>
<td>24.5</td>
</tr>
</tbody>
</table>

The top 22 specific diagnoses for all ill returned travelers within each of the regions. STD denotes sexually transmitted specific etiologic diagnoses could not be assigned.
Discussion: Acute Varicella Zoster Virus (VZV) infection is a clinical diagnosis with a characteristic (see Images A-C) vesicular rash of the superficial dermis involving the trunk, face, and oropharynx. Notably, several crops of fresh vesicles may erupt every few days, becoming crusted and lasting for a total of 6-10 days. In contrast, the lesions of smallpox [Image D] begin on the extremities with all lesions occurring at the same time and appearing and evolving in a similar manner. The incubation period of varicella is 10-21 days, most commonly about 14 days. One of our patient’s siblings had been exposed, while visiting a neighbor, to a young child with varicella. In the tropics, including in developing countries, the age distribution of acute varicella differs markedly from that in temperate climates. Only the minority of individuals acquire varicella in childhood, so that many adults remain non-immune and clinical varicella in adults is common. In temperate climates only 2% of varicella cases occur in those over 20 years of age. In the US and Europe, varicella outbreaks in immigrant and refugee communities are increasingly frequent events. The reasons for the altered behavior of VZV virus in the tropics have not been elucidated.

Complications of varicella are more common in adults, especially varicella pneumonia, which occurs in up to 20% of adult cases. Pneumonia in pregnant women is more severe though perhaps not more frequent than in other adults. Pneumonia usually develops in the first week of rash onset and pregnant women should be followed closely for the onset of respiratory symptoms.

The risk of congenital varicella infection is relatively low ranging from 0.4% in the first trimester to about 2.0% in babies of mothers infected at 13-20 weeks and negligible risk after that. Manifestations of congenital varicella are usually relatively mild with chorioretinitis, optic atrophy, pigmented patches of skin but may include hypoplastic limbs, club feet, cataracts, microphthalmos and early death.

Neonatal varicella is a serious illness with a 25% mortality rate due to disseminated infection and visceral involvement. Women who become clinically ill with varicella from 4 days before delivery until 2 days after delivery may transmit VZV during delivery. Babies of such women should receive Varicella zoster immune globulin (VZIG) intramuscularly immediately after birth.

While the use of acyclovir for acute varicella infection in immunocompetent women has not been rigorously evaluated, most clinicians would use it (safe in pregnancy) to hasten the healing of skin lesions, decrease the severity of maternal disease and reduce the chance of complications which may be more severe during pregnancy. Seronegative pregnant women who are exposed to varicella zoster should receive VZIG for up to 96 hours after exposure, but VZIG is not indicated in an active case.