Travel Medicine
Things to know before you go!

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Disclosures

- None
Objectives

After this presentation you will be able to:

• Discuss current guidelines regarding the management of travelers’ diarrhea
• Identify travelers who will benefit from certain pre-travel vaccinations
• Differentiate between medications available for malaria prophylaxis
• Discuss Yellow fever vaccine use, indications
Case 1

A 36 yo male business traveler to Pakistan develops sudden watery diarrhea with 3 loose stools in first 2 hours with abdominal cramping pain and a fever to 38.5 C (101.3 F). The best course of action at this time is

A. Oral rehydration solution
B. Azithromycin
C. Metronidazole
D. Bismuth subsalicylate
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Travelers’ diarrhea (TD)

- Most predictable travel-related illness
  - rates of 30-70% described
- Travel destination – major determinant, 3 risk grades
  low, intermediate, high
- Poor hygiene practices in local restaurants – large contributor,
  lack of safe water/plumbing, unsafe food storage etc.
- Clinical syndrome – range from mild cramps/loose stools to
  severe abdominal pain, fever, vomiting, bloody diarrhea
- Untreated TD – can last 2-7 days, rarely weeks

TD – causes

• bacteria predominate (80-90%)
  - ETEC, *C. jejuni, Shigella* spp, *Salmonella* spp - common
  - other *E.coli* types (EAEC, EIEC, EHEC)

• intestinal viruses (5-8%)
  - norovirus, rotavirus, astrovirus

• protozoa (~10%)
  - *Giardia, Entamoeba, Cyclospora, D. fragilis*

Original Article

Guidelines for the prevention and treatment of travelers’ diarrhea: a graded expert panel report

Mark S. Riddle¹*, Bradley A. Connor²*, Nicholas J. Beeching³, Herbert L. DuPont⁴, Davidson H. Hamer⁵, Phyllis Kozarsky⁶, Michael Libman⁷, Robert Steffen⁸, David Taylor⁹, David R. Tribble¹⁰, Jordi Vila¹¹, Philipp Zanger¹², and Charles D. Ericsson¹³

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TD – prevention is key

• Pre-travel counseling – reduces risk
• Careful food/beverage selection
• Handwashing or alcohol based sanitizer
• Vaccination
  - none for most common causes of TD
  - Hepatitis A, Typhoid, Cholera vaccines
• Use of prophylactic agents in some situations
Travel and risk of MDRO

• ESBL-Enterobacteriaceae acquisition among travelers to Indian subcontinent
  • 23% who stayed healthy
  • 47% who developed TD, no antibiotics
  • 80% with TD and took antibiotics
• Vast majority – asymptomatic
• Colonization disappears fairly quickly – only 5 - 35% still colonized 6 months later

TD prevention

- antibiotics *not advised* routinely for prevention of TD
- consider in select traveler at high risk for complications (h/o reactive arthritis, serious chronic illness, transplant recipient)
- if used, rifaximin preferred, not absorbed, less side effects but *Campylobacter* spp are R
- non-antimicrobial drugs – bismuth subsalicylate (BSS) in 4 divided doses with meals/bedtime proven in RCTs (>60%)
- side effects – black tongue/stool, tinnitus, constipation, interfere with other meds, avoid in CKD/pregnancy


### Figure 1 Travelers’ diarrhea management algorithm

**Providers should consider the following in counseling the traveler:**

1. Definitions of travelers’ diarrhea and severity classification
2. Importance of oral rehydration through fluid and salt intake for all travelers’ diarrhea
3. Information on effectiveness of treatments for travelers’ diarrhea and the risk of travel, travelers’ diarrhea, and antibiotic use with the acquisition of multi-drug resistance bacteria.
4. Provision of empiric treatment medications as indicated by itinerary and provider-traveler determination
5. Intra- and post-travel illness follow-up recommendations

**Self-determination of Illness Severity**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea that is tolerable, is not distressing, and does not interfere with planned activities</td>
<td>Diarrhea that is distressing or interferes with planned activities</td>
<td>Diarrhea that is incapacitating or prevents planned activities</td>
</tr>
</tbody>
</table>

**During Travel**

- **Mild**
  - *May* use loperamide or bismuth subsalicylates

- **Moderate**
  - *May* use loperamide alone or as an adjunct to antibiotics
  - *May* use antibiotic (Table 2)

- **Severe**
  - *May* use loperamide as adjunct to antibiotics
  - *Should* use antibiotic (Table 2)

**Post-travel**

- Acute travelers’ diarrhea should be treated empirically as above.
- Microbiologic testing is recommended in returning travelers with severe or persistent symptoms or in those who fail empiric therapy.
- Multiplex molecular diagnostics are preferred in patients with persistent or chronic symptoms.
### Table 2

Acute diarrhea antibiotic treatment recommendations

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>1000 mg by mouth or 500 mg by mouth</td>
<td>Single or 1-day divided (^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 day course</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg by mouth</td>
<td>Single dose (^b) or 3 day course</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750 mg by mouth or 500 mg by mouth</td>
<td>Single dose (^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 day course</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg by mouth</td>
<td>Single dose (^b) or 3 day course</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>200 mg by mouth three times daily</td>
<td>3 days</td>
</tr>
</tbody>
</table>

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\(^a\) Antibiotic regimens may be combined with loperamide, 4 mg first dose, then 2 mg dose after each loose stool, not to exceed 16 mg in a 24 hour period.

\(^b\) If symptoms are not resolved after 24 hours, continue daily dosing for up to 3 days.
Pre-travel vaccination
Vaccines - routine

- Important to ensure that traveler is up to date on routine vaccines depending on age/health such as influenza, tetanus
- **Measles outbreaks** – important to discuss
- Acceptable presumptive evidence of immunity to measles:
  - written documentation of 2 doses MMR
  - lab evidence of immunity
  - lab confirmation of disease
  - birth before 1957
- If not, and no CI, give 2 doses of MMR separated by $\geq 28$ d

www.cdc.gov/measles
Hepatitis A

- Common vaccine preventable infection acquired during travel
- Fecal-oral transmission - direct person-person contact
  - contaminated food/drink
- Highly endemic areas (parts of Africa and Asia)
- Low endemic areas - US and Western Europe
  - recent outbreaks in US related to homelessness, drug use
- Vaccination or immune globulin (IG) use are important tools to prevent infection


https://www.cdc.gov/hepatitis/outbreaks/
# Hepatitis A vaccine dosing schedule

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Trade name (Manufacturer)</th>
<th>Age</th>
<th>Route</th>
<th>Schedule</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A vaccine, inactivated</td>
<td>Havrix® (GlaxoSmithKline)</td>
<td>≥ 1 yr</td>
<td>IM</td>
<td>0, 6-12 mo</td>
<td>no</td>
</tr>
<tr>
<td>Hepatitis A vaccine, inactivated</td>
<td>Vaqta® (Merck)</td>
<td>≥ 1 yr</td>
<td>IM</td>
<td>0, 6-18 mo</td>
<td>no</td>
</tr>
<tr>
<td>Combined hepatitis A and B vaccine</td>
<td>Twinrix® (GlaxoSmithKline)</td>
<td>≥ 18 yr</td>
<td>IM</td>
<td>Primary - 0, 1, 6 mo</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Accelerated - 0, 7,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21-30 days</td>
<td>12 mo</td>
</tr>
</tbody>
</table>
Hepatitis A vaccine indications, use

- All susceptible travelers for any purpose, or duration to countries with high or intermediate HAV endemicity
- One dose monovalent vaccine protects most healthy travelers, beginning ~ 2 weeks after dose
- Long-term protection – complete series
- Consider vaccine + IG (0.02 ml/kg) for optimal protection - immunocompromised persons
  - adults >40 yr, chronic medical conditions
  - travel within 2 weeks
Hepatitis A vaccine - things to know

- Interrupted series – do not need to restart
- Monovalent vaccines – similar immunogenicity so can complete series with another brand of monovalent vaccine
- Contraindication – hypersensitivity to vaccine component including neomycin
- Considered safe for pregnant women

Update: Recommendations of the Advisory Committee on Immunization Practices for use of Hepatitis A vaccine for postexposure prophylaxis and for preexposure prophylaxis for international travel
www.cdc.gov/mmwr/volumes/67/wr/mm6743a5.htm?s_cid=mm6743a5_w
Typhoid and paratyphoid fever

- Humans are only reservoir – *Salmonella enterica* serotypes Typhi and Paratyphi A, B, C
- Transmission – fecal-oral through contaminated food and water, rarely via sex in MSM
- Majority of US cases are among international travelers
- Visiting friends and relatives (VFR), longer stay – highest risk, prone to adventurous eating
- Highly endemic – south Asia (India, Pakistan, Bangladesh), also Africa, southeast Asia

Typhoid vaccine

• Two typhoid vaccines available
  - Injectable for IM use, give $\geq 2$ weeks before travel
  - Oral live attenuated, complete doses $\geq 1$ week before exposure
• Protection – varies 50-80%, still follow food and water precautions
• Use of antibiotics within 3-4 weeks of oral vaccine further limits efficacy
• No protection for paratyphoid fever, follow food/water precautions
# Typhoid vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age  (yr)</th>
<th>Dose</th>
<th>Dose number</th>
<th>Booster</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral, live attenuated Ty21a vaccine</td>
<td>≥ 6</td>
<td>1 capsule every 48 hrs</td>
<td>4</td>
<td>Every 5 yrs</td>
<td>CI in pregnancy, immunocompromised or HIV</td>
</tr>
<tr>
<td>(Vivotif®, Paxvax)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Vi capsular polysaccharide vaccine       | ≥ 2       | 0.5 ml IM                     | 1           | Every 2 yrs   | Severe local or systemic reaction after prior dose | (Typhim Vi®, Sanofi Pasteur)
Cholera vaccine - Vaxchora®

- FDA approved (2016) for adults 18-64 yrs traveling to area of active cholera transmission
- live attenuated single dose oral vaccine
- only effective against *V. cholerae* serogroup O1, not O139 (SE Asia)
- efficacy 90% at 10 days, 79.5% at 90 days
- avoid antibiotic use within 14 days prior
- minimal side effects (HA, nausea/vomiting, fever)
- not evaluated in immunocompromised patients

Cholera vaccine

Not recommended for most regular travelers from the US
Case 2

A 48 yo man is admitted to the hospital for unexplained high fever and diarrhea over 1 week. He returned 3 months ago from a 1-month trip to India to visit family. He took mefloquine weekly as advised before, during and after his trip and did not miss any doses. Most appropriate first diagnostic test is

A. a stool O&P exam
B. a blood culture to rule out typhoid
C. a blood smear for malaria parasites
D. an amoebic serology
Case 2 - answer

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Malaria chemoprophylaxis

- Recommendations for prophylaxis differ by country of travel and within countries also

- [www.cdc.gov/travel](http://www.cdc.gov/travel) - enter destination

- No drug is 100% protective, hence still always consider malaria in differential of fever in returning traveler

- take pills before, during and after travel

- Combine with personal protective measures (insect repellant, clothing, bed nets, etc)

- Drug-drug interactions, PMH, side effects, cost determine choice
# Malaria chemoprophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason to use</th>
<th>Reason to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone-proguanil</td>
<td>Daily, <strong>short trips</strong>, well tolerated</td>
<td>Daily, pregnant, nursing, GFR&lt;30 ml/min</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Weekly, <strong>ok for pregnant</strong></td>
<td>Psychiatric, cardiac, seizure, prolonged course</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Weekly, <strong>ok for pregnant</strong>, hydroxychloroquine</td>
<td>Resistance, worsen psoriasis, prolonged course</td>
</tr>
<tr>
<td>Doxycycline</td>
<td><strong>Cheap</strong>, daily, last minute travel, prevent leptospirosis</td>
<td>Prolonged course, pregnant, yeast infection, sunburn</td>
</tr>
<tr>
<td>Primaquine</td>
<td><strong>Great for <em>P.vivax</em></strong>, daily, short course</td>
<td>G6PD, pregnant, nursing</td>
</tr>
</tbody>
</table>
Tafenoquine

- Newest malaria drug, approved in 2018
- 8-aminoquinoline derivative
- active against all stages of *P. vivax* lifecycle, including liver stages and *P. falciparum*
- Must r/o G6PD deficiency before use
- Avoid pregnant, nursing mom - infant G6PD unknown, psychosis
- Adverse reactions – HA, dizziness, back pain, GI, insomnia, depression, abnormal dreams, anxiety, ALT rise
- Methemoglobinemia - asymptomatic
Tafenoquine – prevent and treat malaria

- **Arakoda™** (US Army and 60 Degrees Pharma)
  - discovered by Walter Reed Army Institute of Research in 1978
  - prevention in adults >18 yrs
  - loading dose daily x 3 days before travel, then po weekly and for 1 week after return
- **Krintafel™** (GlaxoSmithKline)
  - treatment, for radical cure of P. vivax with use of other appropriate antimalarial agent (like Primaquine)
  - adults >16 yrs
  - 300 mg single dose po
Case 3

An unvaccinated traveler is at risk of acquiring yellow fever in which of the following countries?

A. Nicaragua
B. South Africa
C. Brazil
D. Indonesia
Case 3 - answer

An unvaccinated traveler is at risk of acquiring yellow fever in which of the following countries?

A. Nicaragua
B. South Africa
C. Brazil
D. Indonesia
Yellow fever

- YFV – RNA virus, genus *Flavivirus*
- bite of *Aedes* or *Haemagogus* spp mosquito
- Sub-Saharan Africa and tropical South America
- Risk of acquisition of YF for 2 week stay –
  - West Africa 50 per 100,000 (death 10 per 100,000)
  - South America 5 per 100,000 (death 1 per 100,000)
- Vary depending on season, location, duration of travel, outdoor exposure etc
- Large ongoing outbreak in Brazil since 2017 - travelers contracted disease in 2018, some died, island of Ilha Grande (Rio de Janeiro state)

Yellow fever vaccine recommendations in the Americas

- Vaccination recommended
- Vaccination recommended since 2017 due to yellow fever outbreaks
- Vaccination generally not recommended
- Vaccination not recommended

(Updated May 5, 2018)
Yellow fever

- Most infection – asymptomatic
- IP 3-6 days, ‘flu-like – fever, chills, HA, myalgias, N/V
- 15% progress to jaundice, hemorrhagic, shock, organ failure
- Diagnosis – via CDC Arboviral Diseases Branch
  - virus isolation or NAAT (early)
  - serology with PRNT (more reliable, eliminates cross reactivity with other Flaviviruses)
- No specific treatment, symptomatic care
Yellow fever vaccine

- Recommended persons ≥ 9 months, going to endemic area
- Required by some countries before entry
- Also transit >12 hrs in airport located in country with risk
- Proof of vaccination required for entry to some countries – International Health Regulation of WHO (yellow card)
- Until recently, booster doses required every 10 yrs, hence signed card of vaccination was only valid for 10 yrs
**International Certificate of Vaccination or Prophylaxis (ICVP)**

![ICVP Form](image-url)
YF vaccine - update

- In 2014, WHO concluded that single dose provided sustained immunity/lifelong protection for most people
- In 2016, completed yellow card – lifetime validity
- Certain high risk groups – revaccinate:
  - pregnant at prior dose
  - BMT recipient after prior dose
  - HIV infection
  - prolonged period in endemic area or rural West Africa in peak season
  - active outbreaks

YF vaccine

- **YF-Vax®** – live attenuated vaccine (Sanofi Pasteur) - only one licensed in US
- Healthy individuals – 80% have neutralizing Ab 10 days after, 99% by day 28
- Long-term protection – Ab present >90% of recipients 16-19 yrs later or longer
- **Contraindicated** - immunosuppressed medical
  - infant <6 months waiver use
- **Cautious use** – older >60 yrs, pregnant, infant 6-9 months

YF vaccine – adverse effects

- Older travelers – higher risk of adverse events – vaccine associated neurologic and viscerotropic disease

<table>
<thead>
<tr>
<th></th>
<th>&gt;60 yrs</th>
<th>&lt;60 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>YEL-AND risk</td>
<td>2.2</td>
<td>0.8 per 100,000 doses</td>
</tr>
<tr>
<td>YEL-AVD risk</td>
<td>1.2</td>
<td>0.3 per 100,000 doses</td>
</tr>
</tbody>
</table>

YF vaccine - update

• Shortage of YF-Vax since 2018, ongoing
• Stamaril® – live, attenuated vaccine, (Sanofi Pasteur) licensed in Europe, other countries
• Use in US currently under IND from FDA
• available only at select licensed centers – map of centers in each state available at cdc.gov
• No resolution for supply shortage known at this time
Thank you for listening

Questions?