Travellers’ Diarrhea Update:
From Prevention to Self-Treatment

Michael Payne
November 4th, 2016
Outline

1. Epidemiology of travellers’ diarrhea
2. Prevention
   – Behavioral
   – Vaccination
   – Medications
3. Self-treatment
4. Outcomes
Illness Course

• TD usually presents within 3 to 4 days of travel

• Symptoms typically last 3-4 days
  – Incapacitating symptoms typically only last up to 1 day (12-50% of patients)

• A health care visit occurs for 10-20% of travellers
  – 30-60% take medication

CATMAT Statement on Travellers’ Diarrhea, 2015.
Most patients have resolution in 3-4 days.

If last longer than 2 weeks is categorized as chronic diarrhea (2-10%).

Duration of Symptoms

- Travelers' Diarrhea, Tropics
- Loose Motions, Tropics
- Travelers' Diarrhea, Subtropics
- Travelers' Diarrhea, North America

Risk of Travellers’ Diarrhea

"We’re interested in a no-diarrhea itinerary."
TABLE 3. Number* and percentage of diagnoses† within syndrome/system groupings in travelers observed after travel — GeoSentinel Surveillance System, United States, 1997–2011

<table>
<thead>
<tr>
<th>Syndrome/System grouping</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute diarrhea</strong></td>
<td>2,811</td>
<td>(22)</td>
</tr>
<tr>
<td>Diarrhea, acute unspecified</td>
<td>1,023</td>
<td>(36)</td>
</tr>
<tr>
<td>Diarrhea, acute bacterial</td>
<td>639</td>
<td>(23)</td>
</tr>
<tr>
<td>Giardiasis</td>
<td>376</td>
<td>(13)</td>
</tr>
<tr>
<td>Amebas, other (Escherichia hartmani, E. nana, E. coli, E. polecki)</td>
<td>122</td>
<td>(4)</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>122</td>
<td>(4)</td>
</tr>
<tr>
<td><strong>Gastrointestinal other</strong></td>
<td>1,908</td>
<td>(15)</td>
</tr>
<tr>
<td>Strongyloides, simple intestinal</td>
<td>292</td>
<td>(15)</td>
</tr>
<tr>
<td>Blastocystis Sp.</td>
<td>289</td>
<td>(15)</td>
</tr>
<tr>
<td>Pain, abdominal</td>
<td>123</td>
<td>(6)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>114</td>
<td>(60)</td>
</tr>
<tr>
<td>Gastritis, <em>Helicobacter pylori</em> positive</td>
<td>114</td>
<td>(6)</td>
</tr>
<tr>
<td><strong>Febrile/Systemic Illness</strong></td>
<td>1,802</td>
<td>(14)</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em> malaria</td>
<td>350</td>
<td>(19)</td>
</tr>
<tr>
<td>Viral syndrome (no rash)</td>
<td>308</td>
<td>(17)</td>
</tr>
<tr>
<td>Dengue, uncomplicated</td>
<td>200</td>
<td>(11)</td>
</tr>
<tr>
<td>Febrile illness unspecified (&lt;3 weeks)</td>
<td>147</td>
<td>(8)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>79</td>
<td>(4)</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td>1,596</td>
<td>(12)</td>
</tr>
<tr>
<td>Insect bite/sting</td>
<td>237</td>
<td>(15)</td>
</tr>
<tr>
<td>Nonfebrile rash of unknown etiology</td>
<td>166</td>
<td>(10)</td>
</tr>
<tr>
<td>Fungal infection (superficial/cutaneous mycosis)</td>
<td>105</td>
<td>(7)</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>100</td>
<td>(6)</td>
</tr>
<tr>
<td>Skin and soft tissue infection</td>
<td>94</td>
<td>(6)</td>
</tr>
<tr>
<td><strong>Chronic diarrhea</strong></td>
<td>1,100</td>
<td>(8)</td>
</tr>
<tr>
<td>Irritable bowel syndrome, post-infectious</td>
<td>605</td>
<td>(55)</td>
</tr>
<tr>
<td>Chronic unknown diarrhea</td>
<td>351</td>
<td>(32)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>44</td>
<td>(4)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>31</td>
<td>(3)</td>
</tr>
<tr>
<td>Postinfectious lactose intolerance</td>
<td>15</td>
<td>(1)</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>1,002</td>
<td>(8)</td>
</tr>
</tbody>
</table>

- GI illness was the diagnosis in **45%** of returning ill travelers!
## Risk by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Travelers* (10⁶)</th>
<th>Travelers to only one region</th>
<th>Cases†</th>
<th>Rate/10⁷</th>
<th>RRR</th>
<th>95% CI</th>
<th>Strata</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western and northern Europe</td>
<td>1,104.8</td>
<td></td>
<td>40</td>
<td>0.4</td>
<td>1.0</td>
<td>Reference</td>
<td>Low</td>
</tr>
<tr>
<td>North America†</td>
<td>393.0</td>
<td></td>
<td>28</td>
<td>0.7</td>
<td>2.0</td>
<td>1.2–3.2</td>
<td>Low</td>
</tr>
<tr>
<td>Central/East Europe</td>
<td>485.0</td>
<td></td>
<td>69</td>
<td>1.4</td>
<td>3.9</td>
<td>2.7–5.8</td>
<td>Low</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>888.2</td>
<td></td>
<td>212</td>
<td>2.4</td>
<td>6.6</td>
<td>4.7–9.2</td>
<td>Low</td>
</tr>
<tr>
<td>Northeast Asia</td>
<td>416.1</td>
<td></td>
<td>155</td>
<td>3.7</td>
<td>10.3</td>
<td>7.3–14.6</td>
<td>Low</td>
</tr>
<tr>
<td>Australasia</td>
<td>40.2</td>
<td></td>
<td>25</td>
<td>6.2</td>
<td>17.2</td>
<td>10.4–28.3</td>
<td>Low</td>
</tr>
<tr>
<td>Oceania</td>
<td>17.0</td>
<td></td>
<td>25</td>
<td>14.7</td>
<td>40.6</td>
<td>24.6–66.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Middle East</td>
<td>183.7</td>
<td></td>
<td>399</td>
<td>21.7</td>
<td>60.0</td>
<td>43.3–88.0</td>
<td>Moderate</td>
</tr>
<tr>
<td>North Africa</td>
<td>68.0</td>
<td></td>
<td>187</td>
<td>27.5</td>
<td>76.0</td>
<td>54.0–106.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Central America</td>
<td>151.6</td>
<td></td>
<td>475</td>
<td>31.3</td>
<td>86.5</td>
<td>62.7–119.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>Caribbean</td>
<td>104.3</td>
<td></td>
<td>356</td>
<td>34.1</td>
<td>94.3</td>
<td>68.0–130.7</td>
<td>Moderate</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>256.8</td>
<td></td>
<td>967</td>
<td>37.7</td>
<td>104.0</td>
<td>75.8–142.7</td>
<td>Moderate</td>
</tr>
<tr>
<td>South America</td>
<td>90.2</td>
<td></td>
<td>663</td>
<td>73.5</td>
<td>203.0</td>
<td>147.6–279.3</td>
<td>High</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>118.5</td>
<td></td>
<td>1209</td>
<td>102.0</td>
<td>281.8</td>
<td>205.7–386.1</td>
<td>High</td>
</tr>
<tr>
<td>South Asia</td>
<td>39.6</td>
<td></td>
<td>1276</td>
<td>322.2</td>
<td>890.0</td>
<td>649.7–1219.2</td>
<td>Very high</td>
</tr>
</tbody>
</table>

J Travel Med 2008; 15: 221–228
Risk by Duration of Travel

- Highest risk for TD occurs in the first 2 weeks of travel, particularly first 2-5 days

---


Figure 2  Daily cumulative incidence of TD infection in East Africa with 95% CI.
Risk by Types of Travel

• Highest risk travellers are those on vacation
  – Business travel is less risky
  – Luxury accommodations are not necessarily protective

• Backpackers and adventure travelling has been associated with higher rates of TD

• Summer travel and high rainfall increase risk

• Cruise ship passengers have lower risk of TD
  – However, are at greater risk of large gastro-enteritis outbreaks
Age Differences

Older patients (>60 years old) are less likely to suffer from acute TD

J Travel Med 2012; 19: 169–177
Higher risk of disease than adults

More likely to require treatment
Gender Differences

Table 2. Comparison of Diagnoses in Ill Female and Male Travelers Who Presented to GeoSentinel Clinics Worldwide

<table>
<thead>
<tr>
<th>Diagnoses in travelers</th>
<th>No. (%) of patients, by sex</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n = 29,643)</td>
<td>Male (n = 29,265)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute diarrhea</td>
<td>7290 (24.6)</td>
<td>6322 (21.6)</td>
</tr>
<tr>
<td>Acute bacterial diarrhea</td>
<td>3681 (12.4)</td>
<td>3257 (11.1)</td>
</tr>
<tr>
<td>Acute parasitic diarrhea</td>
<td>1712 (5.8)</td>
<td>1485 (5.1)</td>
</tr>
<tr>
<td>Acute unspecific diarrhea</td>
<td>2039 (6.9)</td>
<td>1713 (5.9)</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>1922 (6.5)</td>
<td>1543 (5.3)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>679 (2.3)</td>
<td>502 (1.7)</td>
</tr>
</tbody>
</table>

- Women are more likely to present post-travel with GI symptoms, as well as the associated chronic complications

Gender, Sex, and Travel-Associated Disease, CID 2010:50 (15 March)
Host Factors Increasing Risk

• Patients who are infected with HIV, particularly with lower CD4 counts

• Patients with inflammatory bowel disease
  • Also have longer duration of symptoms

• Patients taking protein pump inhibitors (PPI) and histamine 2 antagonists
Changes in Risk Over Time

• Overall, risk is decreasing 😊
  – Attributed to improvements in sanitation/hygiene in developing countries

• Recent studies show risk, worldwide, at 26.2%

• Past studies in 1980’s and 1990’s showed rates of 40-65% in high risk locations

BMC Infectious Diseases 2010, 10:231
# Common Pathogens

## Table 2

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>L. America and Caribbean</th>
<th>Africa</th>
<th>South Asia</th>
<th>Southeast Asia</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies</td>
<td>No. of subjects</td>
<td>No. of positive</td>
<td>Percent</td>
<td>No. of studies</td>
</tr>
<tr>
<td>ETEC</td>
<td>26</td>
<td>3,302</td>
<td>1,109</td>
<td>33.6</td>
<td>10</td>
</tr>
<tr>
<td>EAEC</td>
<td>6</td>
<td>689</td>
<td>166</td>
<td>24.1</td>
<td>2</td>
</tr>
<tr>
<td>EPEC</td>
<td>1</td>
<td>91</td>
<td>13</td>
<td>14.3</td>
<td>3</td>
</tr>
<tr>
<td>EIEC</td>
<td>1</td>
<td>112</td>
<td>3</td>
<td>2.7</td>
<td>4</td>
</tr>
<tr>
<td>EHEC</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>DAEC</td>
<td>2</td>
<td>193</td>
<td>12</td>
<td>6.2</td>
<td>1</td>
</tr>
<tr>
<td>Campy</td>
<td>15</td>
<td>2,031</td>
<td>51</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>Shigella</td>
<td>24</td>
<td>3,302</td>
<td>218</td>
<td>6.6</td>
<td>10</td>
</tr>
<tr>
<td>Salmonella</td>
<td>21</td>
<td>2,537</td>
<td>111</td>
<td>4.4</td>
<td>10</td>
</tr>
<tr>
<td>Aeromonas</td>
<td>12</td>
<td>2,135</td>
<td>16</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>Plesiomonas</td>
<td>9</td>
<td>1,601</td>
<td>21</td>
<td>1.3</td>
<td>4</td>
</tr>
<tr>
<td>Total Vibrios</td>
<td>7</td>
<td>1,048</td>
<td>1</td>
<td>0.1</td>
<td>4</td>
</tr>
<tr>
<td>Non-cholera</td>
<td>7</td>
<td>1,048</td>
<td>1</td>
<td>0.1</td>
<td>4</td>
</tr>
<tr>
<td>Vibrios</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. cholera</td>
<td>7</td>
<td>1,380</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>6</td>
<td>584</td>
<td>42</td>
<td>7.2</td>
<td>5</td>
</tr>
<tr>
<td>Norovirus</td>
<td>1</td>
<td>124</td>
<td>21</td>
<td>16.9</td>
<td>1</td>
</tr>
<tr>
<td>Giardia</td>
<td>13</td>
<td>1,750</td>
<td>23</td>
<td>1.3</td>
<td>6</td>
</tr>
<tr>
<td>Crypto</td>
<td>9</td>
<td>1,007</td>
<td>20</td>
<td>2.0</td>
<td>4</td>
</tr>
<tr>
<td>E. histolytica</td>
<td>11</td>
<td>1,293</td>
<td>14</td>
<td>1.1</td>
<td>3</td>
</tr>
<tr>
<td>No pathogen identified</td>
<td>20</td>
<td>2,130</td>
<td>NA</td>
<td>48.8</td>
<td>6</td>
</tr>
</tbody>
</table>

*Comparisons of the different rates of identification of the specific pathogen between various geographic regions.

ETEC = enterotoxigenic E. coli; EAEC = enteroaggregative E. coli; EPEC = enteropathogenic E. coli; EIEC = enteroinvasive E. coli; EHEC = enterohemorrhagic E. coli; DAEC = diffusely adherent E. coli; Campy = Campylobacter; Crypto = Cryptosporidium; NA = organism was not sought in the studies.

Epidemiology Summary

• Traveler’s diarrhea is the most common travel related illness
  – Young children and young adults at highest risk

• Rates vary greatly by country of exposure
  – Decreasing over time, due to improved hygiene

• Causative pathogens are also highly variable between countries
  – In ~50% of patients no pathogen identified

• Need to know local epidemiology in order to help counsel patient on preventive methods
TD Prevention

Option A

Option B
Behavioral Prevention

• “boil it, cook it, peel it, or forget it” makes biological sense but little data supports its use
  – Review in 2005 examined 8 studies, of which 7 showed no correlation between types of food selected and risk of TD

• Very few travellers actually adhere to these recommendations

• Preparing your own food is protective

Prevention of Traveler’s Diarrhea, CID 2005:41 (Suppl 8).
Hand Washing

• Community based studies in low/middle income countries have shown that hand hygiene promotion decreases diarrheal episodes by ~30%
  – Could be extrapolated to help with travellers

• Would not protect against food/water already contaminated

Cochrane Database Syst Rev. 2015 Sep 3; (9): 1–95.
Water Purification

1. The preferred method is boiling water for 1 minute

2. Filters that trap particles of at least 0.2μm in size are effective against most bacteria and parasites, not reliable for removal of viruses
   - Need to follow with chemical disinfection

3. Iodine is effective, but is cannot be given to pregnant women or those with thyroid disease
   - Only use for up to 1 month

4. Chlorine is an option, but has a bad taste, and its activity depends on temperature and organic material content

5. UV pen lights are a new technology and have been shown to be effective, but may be dependent on agitation technique

Vaccination
Oral Cholera Vaccine
(Killed whole cells plus recombinant B-subunit (WC-rBS))

• There is only 1 licensed vaccine in Canada for prevention of Cholera and TD, Dukoral®

• It is composed of:
  – Heat inactivated \textit{V. cholerae} O1 Inaba classic strain
  – Formalin inactivated \textit{V. cholerae} O1 Inaba El Tor strain
  – Heat and formalin inactivated \textit{V. cholerae} O1 Ogawa classic strain
  – Recombinant non-toxic cholera toxin B subunit

• Efficacy is about 86% for epidemic cholera and approximately 25% for overall travellers' diarrhea
  – Protection for Enterotoxigenic \textit{Escherichia coli} (ETEC) lasts 3 months
Mechanism of Protection

• ETEC is typically the most common cause of TD, depending on region (7-34%)
  – Causes secretory diarrhea by the action of heat labile toxin (LT) and/or heat stabile toxin (ST)
  – LT resembles cholera toxin B

• A Lancet review (2006) found that in TD a median of 21% of patients were positive for ETEC
  – With LT and LT+/-ST constituting a median of 6% and 10% of isolates, respectively (~ 29% and 48% of ETEC)

Vaccine Protection

- Range of protection from TD, given uncertainty in ETEC prevalence and protective efficacy, ranges from 1.2-6.6% (5-10% in other reviews)

Guideline Recommendations

• CATMAT (2015) pooled results of 3 RCTs and a Cochrane review and found no significant decrease in TD, compared to placebo (35% vs 37%, RR=0.94, CI 0.82-1.09)

• They recommend against routine use, can consider for:
  – those for whom a brief illness cannot be tolerated (i.e., elite athletes, some business or political travellers)
  – those with increased susceptibility to TD (e.g. achlorhydia, young children)
  – those who are immunosuppressed due to HIV infection with depressed CD4 count or other immunodeficiency states
  – those with chronic illnesses for whom there is an increased risk of serious consequences from TD (e.g., chronic renal failure, congestive heart failure, inflammatory bowel disease)
Other Considerations

• While assessing a traveller, knowing the prevalence of ETEC can impact the potential benefit of the WC-rBS

• Protection against cholera is also a benefit and may be helpful for:
  – health care/relief workers and in the setting of outbreaks

• The oral cholera vaccine has proven to be very safe, with the main concern being mild, abdominal pain, nausea and vomiting
  – Patient preference therefore should be considered
Medications For Prevention

Probiotics for TD Prevention

• There have been several meta-analyses of studies using probiotics for TD

• These show conflicting results, and there is a lot of heterogeneity due to various products being used
  – *Saccharomyces boulardii* and *Lactobacillus rhamnosus* most promising

• Insufficient data to recommend their use at this time
  – However, probiotics are very safe, and can be used based on patient preference

CATMAT, Travellers’ Diarrhea, 2015.
Bismuth subsalicylate (BSS)

- Can be used for prevention of TD, 3 RCTs were included in CATMAT guidelines

- Showed benefit of BSS with up to a 65% reduction in TD (RR = 0.55 (95% CI: 0.44 – 0.67))
  - Dosing is 2 tablets 4 times a day (2.1/day)
  - Only studied up to 3-4 weeks

- BSS can result in some side effects:
  - Can turn tongue and stool black due to harmless harmless bismuth sulfide salt metabolite
  - Caution in children (Theoretical risk of Reye’s)
  - Caution for those on anti-coagulation medications
  - Avoid if allergy to ASA and in pregnancy
  - Potential risk of salicylate intoxication and bismuth encephalopathy

CATMAT, Travellers’ Diarrhea, 2015.
Prophylactic Antibiotics

• No studies evaluating azithromycin for prevention

• 4 studies evaluated fluoroquinolones (Ciprofloxacin and norfloxacin) for the prevention of TD
  - Found an 88% reduction in TD, over a 5-21 day period
    - Studies conducted from 1986-1994

• Rifaximin has also been shown to reduce TD by 58%
Prophylactic Antibiotics

• Known harms of fluoroquinolones
  – Tendonitis and tendon rupture
  – *Clostridium difficile* infection
  – Prolonged QTc/arrhythmia
  – Retinal detachment
  – Not safe in pregnancy
  – Not recommended for children <18 years old
FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together

The FDA has issued new information about this safety issue, see the FDA Drug Safety Communication issued July 26, 2016

Safety Announcement

[ 05-12-2016 ] The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

An FDA safety review has shown that fluoroquinolones when used systemically (i.e. tablets, capsules, and injectable) are associated with disabling and potentially permanent serious side effects that can occur together. These side effects can involve the tendons, muscles, joints, nerves, and central nervous system.

As a result, we are requiring the drug labels and Medication Guides for all fluoroquinolone antibacterial drugs to be updated to reflect this new safety information. We are continuing to investigate safety issues with fluoroquinolones and will update the public with additional information if it becomes available.
Recommendations

Can consider prophylactic antibiotics in:

1. Those for whom a brief illness cannot be tolerated (i.e., elite athletes, some business or political travellers)

1. Increased susceptibility to TD (e.g., due to achlorhydia, gastrectomy, history of repeated severe TD)

2. Immunosuppressed due to HIV infection with depressed CD4 count or other immunodeficiency states

3. Chronic illnesses for whom there is an increased risk of serious consequences from TD (e.g., chronic renal failure, congestive heart failure, insulin dependent diabetes mellitus, inflammatory bowel disease)
Key Messages for Prevention

• Behavioral prevention, is intuitive, but little data to support

• BSS is a low cost prevention option, with proven effectiveness
  – Caution in certain populations

• Vaccination may reduce TD by 5-25%, can be considered based on:
  • ETEC epidemiology
  • Patient risk factors
  • Patient preference

• Prophylactic antibiotics should be avoided, unless there are special circumstances
Treatment of Travellers’ Diarrhea

• Key references:

Treatment of Travellers’ Diarrhea

• Goals of therapy:
  – Avoid dehydration
  – Reduce severity and duration of symptoms
  – Allow vacation/travel to continue

• Mild/moderate disease does not typically require antibiotic therapy (90% of cases)
  – 1-3 loose stools per day
  – Mild enteric symptoms (Abdominal pain, nausea, vomiting)
  – No bloody stools
  – No high fever (>38.5°C)
Treatment of Travellers’ Diarrhea: Non-antibiotic

Oral Rehydration Therapy (ORS)

• Not recommended routinely for healthy adults
  – Replace loses with water, saltine crackers, soup, sport drinks and fruit juices

• Useful for young children and the elderly

• Can buy commercial packets to mix with boiled/bottled water
Treatment of Travellers’ Diarrhea: Non-antibiotic

**Loperamide**

- Is an anti-motility and anti-secretory agent, that can be used for treatment of TD

- A meta-analysis in 2008 found that antibiotics plus loperamide were more effective than antibiotics alone
  - Increased OR (2.58) of cure at 24h

Loperamide for Traveler’s Diarrhea, CID 2008:47 (15 October).
Loperamide

• A recent systematic review could find no clear evidence that antibiotics were superior to loperamide

• Given the known potential harms of antibiotic treatment, in mild/moderate TD, loperamide alone is the treatment of choice

• This corresponds well with the current recommendations from CATMAT (2015)
Probiotics for Treatment of TD

- Little literature to support use routinely in the treatment of TD

- Recent study in 2015, evaluated Saccharomyces boulardii compared to loperamide for the treatment of adult TD in travellers to Mexico and India

- Probiotic treatment was found to be inferior, compared to loperamide, for symptom resolution
Probiotics for Treatment of TD

• Probiotics for acute gastroenteritis (AGE) of any type has been extensively studied, mainly in children.

• A Cochrane review in 2010 found probiotics:
  • Reduced duration of diarrhea by 1 day
  • Reduced risk of diarrhea lasting 4 days or more
  • Probiotics were found to be safe
  • 57/63 studies were in children

• This finding was supported in another review in 2014, recommending to consider use in children.

JPEN 2014;58: 531–539
Probiotics for Treatment of TD

Key Messages

• In adults, there is a lack of evidence to recommend probiotics routinely for treatment of TD
  • Is likely less effective than loperamide, but unclear of its effect versus placebo

• Extrapolating data from AGE, probiotics can be consider as an adjunct to rehydration therapy for children to treat TD

• Probiotics have been found to be safe, particularly commercial preparations of *Lactobacillus* and *Saccharomyces* species

Gastroenterol 2016; 111:602–622.
Antibiotic Therapy

Fluoroquinolones (Ciprofloxacin)
• Has been the self-treatment drug of choice for many years

• Multiple RCTs and a cochrane review showed significantly increased odds of cure at 72 hours, compared to placebo
  – Shortens illness by 1-2 days
  – Also increased side-effects, compared to placebo

Fluoroquinolones (Ciprofloxacin)

• Increasing resistance is a major problem

• Campylobacter resistance is 71-84% for locations in south and south-east Asia

• ETEC and EAEC were previously quoted to have 1-10% resistance, but this is now increasing to 20-35%

AAC, Feb. 2011, p. 874–878
CATMAT (2015)
Azithromycin

• No studies performed versus placebo, but has been compared to ciprofloxacin in 4 RCTs

• Is non-inferior to ciprofloxacin:
  – Associated with less rapid resolution of symptoms
  – Improved cure after 48 hours

• Improved activity for *Campylobacter*, but may be less efficacious for ETEC/EAEC and *Salmonella/Shigella*

• Preferred agent in south and south-east Asia, due to high resistance rates of *Campylobacter* to ciprofloxacin
Azithromycin

• Can cause significant nausea, particularly the 1g dose

• Has been associated with increased risk of cardiac death

Colonization with Multi-drug resistant (MDR) Bacteria

- MDR *Enterobacteriaceae* are resistant to 3rd generation cephalosporins (ESBL) +/- carbapenems (CRE)

- Limited options are available for their treatment

- Previously, a major risk factor was receiving health care overseas
  - Now have evidence that any travel to developing countries may place patients at higher risk of acquisition
Risk of Acquisition of MDR Bacteria

Antimicrobials Predispose to ESBL-PE, CID 2015:60 (15 March).
Risk of Acquisition of MDR Bacteria

Table 2. Multivariable analysis of acquisition of extended-spectrum β-lactamase-producing *Enterobacteriaceae* by 288 travelers on the basis of administration of treatments for travelers’ diarrhea†

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total, no. (%)</th>
<th>ESBL neg, no. (%)</th>
<th>ESBL pos, no. (%)</th>
<th>Univariate analysis</th>
<th>Multivariable analysis with imputation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>288 (100)</td>
<td>213 (74)</td>
<td>75 (26)</td>
<td>NA</td>
</tr>
<tr>
<td>Study groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LO–AMD–</td>
<td>139 (48)</td>
<td>110 (79)</td>
<td>29 (21)</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>LO+AMD–</td>
<td>90 (31)</td>
<td>72 (80)</td>
<td>18 (20)</td>
<td>0.874</td>
<td>0.9 (0.5–1.8)</td>
</tr>
<tr>
<td>LO–AMD+†</td>
<td>45 (16)</td>
<td>27 (60)</td>
<td>18 (40)</td>
<td>0.012</td>
<td>2.5 (1.2–5.2)</td>
</tr>
<tr>
<td>LO+AMD+</td>
<td>14 (5)</td>
<td>4 (29)</td>
<td>10 (71)</td>
<td>&lt;0.001</td>
<td>9.5 (2.8–32.4)</td>
</tr>
</tbody>
</table>

• Loperamide alone not associated with increased risk
• Highest risk loperamide plus an antibiotic
## Carriage Over Time

### Table 2. Follow-up of Travelers After Their Return

<table>
<thead>
<tr>
<th>Time After Return, mo</th>
<th>Proportion of MRE Carriers Among Carriers at Return (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Proportion of MRE Carriers Among All Travelers (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>0</td>
<td>292/292 (100)</td>
<td>93/93 (100)</td>
</tr>
<tr>
<td>1</td>
<td>83/245 (33.9)</td>
<td>9/72 (12.5)</td>
</tr>
<tr>
<td>2</td>
<td>45/236 (19.1)</td>
<td>5/72 (6.9)</td>
</tr>
<tr>
<td>3</td>
<td>24/233 (10.3)</td>
<td>3/72 (4.2)</td>
</tr>
<tr>
<td>6</td>
<td>11/230 (4.8)</td>
<td>0/72 (0)</td>
</tr>
<tr>
<td>12</td>
<td>5/227 (2.2)</td>
<td>0/72 (0)</td>
</tr>
</tbody>
</table>

Abbreviation: MRE, multidrug-resistant Enterobacteriaceae.

Antibiotic Resistance After Travel, CID 2015:61 (15 August).
Key Messages MDR

• Antibiotic use for TD is associated with increased colonization with MDR bacteria

• Loperamide alone, does not increase risk

• MDR bacteria should be suspected in ill travellers’ returning from developing countries
  • Particularly in the first 3 months after return
Outcomes of Travellers’ Diarrhea

• TD is associated with important secondary illnesses:
  • Guilliane Barré syndrome
  • Reactive arthritis
  • Post infectious irritable bowel syndrome (IBS)
  • Chronic diarrhea

Aliment Pharmacol Ther 2015; 41: 1029–1037.
Conclusions

• TD is a common condition in travellers’ with important health, financial and social consequences.

• Many options are available for prevention:
  – Good evidence for bismuth subsalicylate
  – Use of TD vaccine is controversial
  – Behavioral modification likely has little impact
Conclusions

• For treatment:
  – Most mild/moderate cases should be treated with loperamide alone
  – Antibiotics show clear treatment benefits, but come at a cost of significant side-effects
    • Patients should be counseled on these

• Long-lasting complications can result from TD (eg. IBS)
The End

- Thanks!
Guidelines and Resources
STATEMENT ON TRAVELLERS’ DIARRHEA
AN ADVISORY COMMITTEE STATEMENT (ACS)
COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

TABLE OF CONTENTS

PREAMBLE ......................................................... 1
Key points/Messages ........................................ 1
GRADE Recommendations ..................................... 2
Box 1: Frequently-asked questions on how to interpret GRADE results ....... 6
INTRODUCTION .................................................. 7
BACKGROUND .................................................. 7
Clinical and epidemiological features ......................... 7
Etiological agents ............................................... 7
Epidemiology .................................................... 8
METHODS ....................................................... 9
RESULTS .......................................................... 11
Risk factors ..................................................... 11
Prevention—Best practices .................................... 13
Prevention—Interventions .................................... 16
Prevention—Vaccination and Cholera prophylaxis ............. 16
Treatment ....................................................... 22
Managing TD symptoms—Hydration ......................... 28
Treatment of TD upon return from travel ..................... 29
Values and Preferences ........................................ 29
CONCLUSIONS AND RESEARCH NEEDS ................. 29
ACKNOWLEDGEMENTS ....................................... 30
TABLES .......................................................... 31
Table 1: List of studies considered for inclusion in analysis of efficacy of TD prevention and treatment . 31
Table 2: Dosages for various agents to prevent and treat travellers’ diarrhoea .................. 44
Table 3: Preparing oral rehydration solutions at home ........... 47
REFERENCES .................................................... 48
APPENDICES .................................................... 60
Appendix 1: Literature review search strategy example ............ 60
Appendix 2: GRADE tables for each TD intervention ............ 62

CATMAT (2015)
Traveler's Diarrhea
A Clinical Review

Robert Steffen, MD; David R. Hill, MD, DTM&H; Herbert L. DuPont, MD

IMPORTANCE Acute diarrhea is the most common illness that affects travelers to low-income regions of the world. Although improved hygiene has reduced the risk of traveler's diarrhea in many destinations, the risk remains high in others.

OBJECTIVE To review the current state of knowledge on the etiology, risk factors, prevention, and management of traveler's diarrhea.

EVIDENCE REVIEW A search of the PubMed, Google Scholar, and Cochrane Library databases for the period 2012-April 2014 was performed for articles on traveler's diarrhea. The database search yielded 2976 articles, of which 37 were included in this review. These were added to 85 articles previously identified by the authors.

FINDINGS Improved hygiene has reduced the risk of traveler's diarrhea from 20% or more (for a 2-week stay) to between 8% and 20% in some parts of the world. Acquiring traveler's diarrhea causes 12% to 46% of travelers to change their travel plans. Returning travelers seeking medical care have a diagnosis of gastrointestinal disturbance in approximately one-third of all cases. Postinfectious irritable bowel syndrome may occur in 3% to 17% of patients who have had traveler's diarrhea. Prevention of traveler's diarrhea by dietary avoidance measures is often not successful. Chemoprophylaxis should be restricted to travelers who are at risk of severe complications of diarrhea. Ciprofloxacin is the standard treatment in self-therapy of traveler's diarrhea except when patients are in South or Southeast Asia, where azithromycin is preferred.

CONCLUSIONS AND RELEVANCE Diarrhea remains a common problem for international travelers. Persons intending to travel to at-risk countries should be counseled regarding prevention measures and may be given a travel pack that includes medications for self-treatment should they become ill.

ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults

Mark S. Riddle, MD, DrPH\(^1\), Herbert L. DuPont, MD\(^2\) and Bradley A. Connor, MD\(^3\)

Acute diarrheal infections are a common health problem globally and among both individuals in the United States and traveling to developing world countries. Multiple modalities including antibiotic and non-antibiotic therapies have been used to address these common infections. Information on treatment, prevention, diagnostics, and the consequences of acute diarrhea infection has emerged and helps to inform clinical management. In this ACG Clinical Guideline, the authors present an evidence-based approach to diagnosis, prevention, and treatment of acute diarrhea infection in both US-based and travel settings.

Am J Gastroenterol 2016; 111:602–622; doi:10.1038/aig.2016.126; published online 12 April 2016
BC Diarrhea Guidelines

Infectious Diarrhea – Guideline for Ordering Stool Specimens

Effective Date: March 16, 2009
For full Guideline please go to website: www.BCGuidelines.ca

Scope: This algorithm applies to patients > 3 years-of-age presenting with suspected infectious diarrhea. It does not apply to the investigation of diarrhea in immunocompromised patients or in an outbreak situation.

DIARRHEA

Mild to Moderate
Earlier stool testing is warranted for:
- patients ≥ 70 years-of-age
- severe abdominal pain
- if C. difficile-associated disease is suspected

Severe (one or more of):
- fever ≥ 38.5°C
- bloody stools
- profound systemic illness/toxicity
- hemodynamic instability
- greater than 6 diarrheal episodes per day for greater than 5 days