Diarrhea

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted in an AAALACi accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.
Outline

- Take Home Lessons
- Epidemiology of Infectious Diarrhea in the Military
- Causative Agents
- Clinical Presentation and Differential Diagnosis
- Diagnostic Considerations
- Treatment and Control
Take Home Lessons

- Acute diarrhea/dysentery in deployed military personnel (like travelers’ diarrhea) is predominantly caused by bacterial enteropathogens

- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)

- The U.S. military does not send its forces on overseas vacation

- Population-wide morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae
I expect that our imaginations cannot fathom the problems attendant from the absolute urgency for relief from explosive vomiting and diarrhea when experienced within an armored vehicle under fire and at ambient temperature of >104°F.

David O. Matson, MD, *Clin Infect Diseases* Editorial, 2005
Infectious Diseases Section, Center for Pediatric Research, Norfolk, Virginia
Definition of Travelers’ Diarrhea

- Three or more unformed bowel movements occurring within a 24-hour period
- Often accompanied by other symptoms
  - cramps
  - nausea, vomiting
  - fever
  - blood in stools
- Typically acquired within first few weeks of travel/deployment
- Ingestion of contaminated foods or less often drinks
Impact of Diarrheal Diseases in Modern Military Campaigns

- **World War II**: ‘A few months of the year, malaria would cause more man-days lost, but on the calendar-year average, gastrointestinal infections were well ahead.’¹

- **Vietnam War**: Diarrhea/dysentery largest single disease threat, leading to 4 times more hospitalizations than malaria²

- **OIF**: Acute enteric illness was leading cause of hospital admission among British forces during first 12 months of operations in Iraq³
OEF/OIF, 2001-2007
Disease Burden ‘By the Numbers’

Cumulative deployments and disease burden

- 2,134,578 No. deployments (x, 183 d)
- 145,871 No. deployments (x, 19 d)
- 3,857,002 Cases of diarrhea
- 11,478,270 Diarrhea days
- 850,444 Ambulatory Medical Visits
- 17,356 Hospitalizations
- 1,114,208 Duty days lost
- 162,279 Liters of IV fluids infused
Force Health Impacts

**Clinical Presentations**

- Diarrhea with fever: 9-25%
- Dysentery: 2-8%
- Severe diarrhea:
  - Iraq: 21-27%
  - Afghanistan: 13-14%
- Vomiting only: 5-15%

**Operational Impact**

- Job performance: 45%
- Confined to bedrest: 13%
- Hospitalized: 2%
- IV fluids: 15-17%
- Missed patrol: 9-13%
- Back-fill needed: 12%
- Grounded: 6-12%
- Fecal incontinence: 32%

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**Anonymous Soldier’s Blog**

- Missed patrol
- IV fluids
- Hospitalized
- Confined to bedrest
- Grounded
- Fecal incontinence

It’s sad that you actually have to ask people to do these things.
Incidence of Illness based on Self-Reporting vs. DNBI

Incidence of Health Event (per 100 person-months)

- Diarrhea
- Respiratory
- Non-combat injury

Bar chart showing incidence rates for different periods and health events.
Worldwide: Bacterial Diarrhea Risk to U.S. Forces

This assessment assumes an absence of countermeasures for personnel who consume non-approved local food, water, or ice.

NOTE: This map is based on analyst judgment using FICM risk assessment methodology. The assessment is supported by surveillance and reporting data, outbreak data, case reports, hospital studies, sanitation level, and applicable regional data. Boundaries of risk areas are approximate and should not be interpreted as strict demarcations.
Stressors in Extreme Conditions Amplify Diarrhea Morbidity

- Fluid/Electrolyte Losses
  - 25°C: not ill
  - 30°C: mild
  - 35°C: moderate
  - 40°C: severe

- Insensible water loss
  - 0%
  - 5%
  - 10%
  - 15%

- Illness severity
  - not ill
  - mild
  - moderate
  - severe

- % dehydration
  - 0%
  - 5%
  - 10%
  - 15%

- Symptoms:
  - death
  - circulatory collapse
  - delirium
  - confusion
  - dizziness
  - increasing heart rate
  - diminished G tolerance
  - decline in psychomotor performance
  - decreased exercise endurance
Causative Agents

- **Bacterial agents (80-90%)**
  - **Common**
    - Enterotoxigenic *E. coli* (ETEC)
    - Enteroaggregative *E. coli* (EAEC)
    - *Campylobacter*
    - *Shigella*
    - *Salmonella*
  - **Less common**
    - Enteroinvasive *E. coli* (EIEC)
    - *Aeromonas*
    - *Plesiomonas*
    - *Vibrio cholerae*

- **Viral agents (5-10%)**
  - Norovirus
  - Rotavirus
  - Astrovirus

- **Parasites (uncommon)**
  - *Giardia lamblia*
  - *Cryptosporidium* spp.
  - *Cyclospora cayatanensis*
  - *Entamoeba histolytica*
Etiology of Diarrheal Diseases: U.S. Military on Deployment

- **Rotavirus**: 4%
- **Salmonella**: 5%
- **Shigella**: 7%
- **Norovirus**: 8%
- **C. jejuni**: 10%
- **ETEC**: 22%
- **EAEC**: 13%
- **Other/no pathogen**: 31%

**Latin America, Caribbean**
- **Rotavirus**: 6%
- **Salmonella**: 9%
- **Shigella**: 4%
- **Norovirus**: 3%
- **C. jejuni**: 23%
- **ETEC**: 29%
- **EAEC**: 6%
- **Other/no pathogen**: 6%

**Middle East**
- **Rotavirus**: 7%
- **Salmonella**: 11%
- **Shigella**: 1%
- **Norovirus**: 2%
- **C. jejuni**: 17%
- **ETEC**: 37%
- **EAEC**: 28%
- **Other/no pathogen**: 2%

**Southeast Asia**
- **Rotavirus**: 4%
- **Salmonella**: 9%
- **Shigella**: 13%
- **Norovirus**: 25%
- **C. jejuni**: 12%
- **ETEC**: 23%
- **EAEC**: 3%
- **Other/no pathogen**: 11%
# Common Etiological Agents of Diarrhea in Iraq and Afghanistan

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Area</th>
<th>Pathogens (top 3)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Thornton *et al* CID 2005 | 2003 | Diwaniyah (South of Baghdad) | Norovirus 23%
Shigella spp. 20%
Campylobacter 4% | Sampling favored epidemics, diarrheagenic *E. coli* not assessed |
| Monteville *et al* AJTMH 2006 | 2004 | Kuwait, Qatar, Iraq, Afghanistan | ETEC 32%
EAEC 12%
Salmonella spp. 6% | Case series out of TMC in Doha, Qatar |
| Sanders (unpublished)     | 2004 | Anbar Province, Iraq  | ETEC 23%
EAEC 12%
EIEC 7%            | Systematic cross-sectional study |
| Faix (unpublished)        | 2005 | Anbar Province, Iraq  | Salmonella spp. 38%
Cryptosporidium 38%
ETEC 15%            | Outbreak in food vendors run by FSNs |
Clinical Presentations

- Watery diarrhea (80%)
  - ± Abdominal cramps
  - ± Nausea
  - ± Vomiting
  - ± Fecal urgency
  - ± Low-grade fever

- Dysentery (1-5%)
  - Fever
  - Tenesmus
  - Mucoid stools
  - Grossly bloody stools

- Acute gastroenteritis (≤10%)
  - Recurrent vomiting
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Location</th>
<th>Usual Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-inflammatory (enterotoxin)</td>
<td>Proximal small bowel</td>
<td>All causative pathogens; most commonly ETEC, EAEC</td>
</tr>
<tr>
<td>Inflammatory (invasion or cytotoxin)</td>
<td>Colon or distal small bowel</td>
<td>C. jejuni, Shigella spp., Salmonella (non-typhi) EIEC</td>
</tr>
<tr>
<td>Villus blunting (delayed gastric emptying)</td>
<td>Small bowel</td>
<td>Norovirus Rotavirus</td>
</tr>
</tbody>
</table>
Persistent Travelers’ Diarrhea

- Travelers’ diarrhea is often self-limited, resolving in the majority of cases after several days

- Illness lasting >1 week: 10% of cases
- Illness lasting >1 month: 2% of cases

- Etiological considerations with persistent diarrhea
  - EAEC (occasionally, Campylobacter, Salmonella)
  - Parasitic diarrhea
    - *Giardia lamblia*
    - *Cryptosporidium parvum*
    - *Cyclospora cayatanensis*
**Enterotoxigenic E. coli (ETEC): Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transmission</strong></td>
<td>foodborne (food, water)</td>
</tr>
<tr>
<td><strong>Inoculum size</strong></td>
<td>High ($\geq 5 \times 10^6$ organisms)</td>
</tr>
<tr>
<td><strong>Populations at risk</strong></td>
<td>infants, LDC; travelers to endemic regions</td>
</tr>
<tr>
<td><strong>Estimated no. cases annually</strong></td>
<td>200 million worldwide; $&gt; 500,000$ under five death per year</td>
</tr>
<tr>
<td><strong>Typical clinical syndrome</strong></td>
<td>watery diarrhea; dehydration in moderate-severe disease</td>
</tr>
<tr>
<td><strong>Phenotypic diversity</strong></td>
<td>2 enterotoxins; $&gt; 20$ fimbrial types</td>
</tr>
<tr>
<td><strong>Sequelae</strong></td>
<td>physical and cognitive retardation; malnutrition</td>
</tr>
</tbody>
</table>
# Campylobacter jejuni: Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transmission</strong></td>
<td>foodborne (food, water)</td>
</tr>
<tr>
<td><strong>inoculum size</strong></td>
<td>low ($\geq 5 \times 10^2$ organisms)</td>
</tr>
<tr>
<td><strong>populations at risk</strong></td>
<td>infants, LDC; travelers to hyperendemic regions; young people, HDC</td>
</tr>
<tr>
<td><strong>geographic ‘hotspots’</strong></td>
<td>SE Asia, North Africa (Morocco)</td>
</tr>
<tr>
<td><strong>typical clinical syndrome</strong></td>
<td>acute inflammatory enteritis</td>
</tr>
<tr>
<td><strong>serotypic diversity</strong></td>
<td>multiple (108 Lior, 47 Penner serotypes)</td>
</tr>
<tr>
<td><strong>sequelae</strong></td>
<td>reactive arthritis; Guillain-Barré syndrome; irritable bowel syndrome</td>
</tr>
<tr>
<td>Feature</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td>person-to-person; foodborne (food, water)</td>
</tr>
<tr>
<td><strong>Inoculum size</strong></td>
<td>low (10-200 organisms)</td>
</tr>
<tr>
<td><strong>Reservoirs</strong></td>
<td>humans only</td>
</tr>
<tr>
<td><strong>Populations at high risk</strong></td>
<td>toddlers living in and travelers to LDC; crowding, poor sanitation (e.g., day care, institutions)</td>
</tr>
<tr>
<td><strong>Serotypic diversity</strong></td>
<td>Over 50 different serotypes (determinant, LPS)</td>
</tr>
<tr>
<td><strong>Key pathogenic processes</strong></td>
<td>invasion, spread, inflammatory response; cytotoxicity (<em>S. dysenteriae</em> type 1, Shiga toxin)</td>
</tr>
<tr>
<td><strong>Typical clinical syndrome</strong></td>
<td><strong>Dysentery</strong> (most commonly, acute watery diarrhea)</td>
</tr>
<tr>
<td><strong>Natural immunity</strong></td>
<td>Medium-term, serotype-specific immunity</td>
</tr>
<tr>
<td><strong>Sequelae</strong></td>
<td>Reiter’s syndrome; reactive arthropathy; hemolytic uremic syndrome</td>
</tr>
</tbody>
</table>

LDC, less developed countries
### Differential Morbidity Associated with Major Bacterial Pathogens of Travelers’ Diarrhea

<table>
<thead>
<tr>
<th>Pathogen profile</th>
<th>ETEC</th>
<th>C jejuni</th>
<th>Shigella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global prevalence(%)</td>
<td>22 (17-28)</td>
<td>10 (5-15)</td>
<td>7 (3-10)</td>
</tr>
<tr>
<td>Illness duration w/o treatment (mean, d)</td>
<td>3.6</td>
<td>8.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Probability of causing incapacitation (%)</td>
<td>21-27</td>
<td>47</td>
<td>56-92</td>
</tr>
<tr>
<td>Illness duration after treatment (mean, d)</td>
<td>1.0</td>
<td>2.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Protect Yourself from Norovirus!

- Wash your hands often
- Rinse fruits & vegetables
- Cook shellfish thoroughly
- Clean surfaces & wash laundry
- When you're sick, don't prepare food or care for others

Share this widget | More info
www.cdc.gov/Norovirus
## Noroviruses: Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>transmission</strong></td>
<td>foodborne (food, water); person-to-person</td>
</tr>
<tr>
<td><strong>inoculum size</strong></td>
<td>low (as few as 10 viral particles)</td>
</tr>
<tr>
<td><strong>reservoirs</strong></td>
<td><strong>humans</strong> only; hardy virus, persists on fomites</td>
</tr>
<tr>
<td><strong>populations at high risk</strong></td>
<td>All age groups; outbreak potential in semi-closed populations – military populations, including ships</td>
</tr>
<tr>
<td><strong>genotypic diversity</strong></td>
<td>3 genogroups, and ≥ 25 genotypes</td>
</tr>
<tr>
<td><strong>key pathogenic processes</strong></td>
<td>Limited to small intestine, broadening/blunting of proximal intestinal villi; transient malabsorption</td>
</tr>
<tr>
<td><strong>natural immunity</strong></td>
<td>Short-term homologous immunity; possible long-term immunity with repeated exposure</td>
</tr>
<tr>
<td><strong>sequelae</strong></td>
<td>No evidence of serious long-term sequelae</td>
</tr>
</tbody>
</table>
Giardiasis: Life Cycle

Ingestion of dormant cysts

Cyst can survive for weeks to months in cold water

Only cysts can survive outside of the host.

Cysts and trophozoites expelled in the feces

Encystation during transit toward the colon.

Excystation trophozoite emerge to an active state

Trophozoite undergo asexual replication

Not Everyone exhibit symptoms.
## Giardiasis: Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td>contaminated water; infected food handlers</td>
</tr>
<tr>
<td>Inoculum size</td>
<td>low (as few as 10-25 cysts)</td>
</tr>
<tr>
<td>Reservoirs</td>
<td>Humans and other mammals</td>
</tr>
<tr>
<td>Populations at high risk</td>
<td>backpackers; young children LDC; higher risk with travel to Russia, Mexico, SE Asia, South America</td>
</tr>
<tr>
<td>Antigenic variation</td>
<td>on-off switch of variant specific surface proteins (VSP)</td>
</tr>
<tr>
<td>Key pathogenic processes</td>
<td>Attachment to intestinal epithelium via ventral disc; flagellar motility; VSP switching evades IgA</td>
</tr>
<tr>
<td>Typical clinical syndrome</td>
<td>watery diarrhea; epigastric abdominal pain, bloating, malabsorption, nausea, vomiting, weight loss</td>
</tr>
<tr>
<td>Natural immunity</td>
<td>both humoral and cell mediated immunity play a role in clearance; specific mechanisms poorly understood</td>
</tr>
<tr>
<td>Sequelae</td>
<td>Functional gastrointestinal disorders (IBS)</td>
</tr>
</tbody>
</table>
Cryptosporidium: Life Cycle

Cryptosporidiosis
(Cryptosporidium)

1. Thick-walled oocyst (sporulated) exits host
2. Contamination of water and food with oocysts.
3. Thick-walled oocyst ingested by host

Recreational water
Drinking water

Auto-infection
Asexual Cycle
Type I Meront
Type II Meront
Sexual Cycle

Zygote
Macrogamont
Undifferentiated Ciliates
Merozoites
Microgametes
Microgamont
Trophozoite
Sporozoite
Oocyst

WRAIR
## Cryptosporidium: Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transmission</strong></td>
<td>Contaminated water and food; person-to-person</td>
</tr>
<tr>
<td><strong>Inoculum size</strong></td>
<td>Low (as few as 10 oocysts)</td>
</tr>
<tr>
<td><strong>Reservoirs</strong></td>
<td>Humans and other mammals (including livestock)</td>
</tr>
<tr>
<td><strong>Populations at high risk</strong></td>
<td>HIV/AIDS; urban populations, municipal water contamination; children in LDC; travelers</td>
</tr>
<tr>
<td><strong>Species diversity</strong></td>
<td>Majority of human cases due to <em>C. hominis, C. parvum</em></td>
</tr>
<tr>
<td><strong>Key pathogenic processes</strong></td>
<td>Localizes in parasitophorous vacuoles in intestinal epithelium; distal small intestine; villous atrophy</td>
</tr>
<tr>
<td><strong>Typical clinical syndrome</strong></td>
<td>Watery diarrhea, abdominal cramps, vomiting, mild fever, and loss of appetite</td>
</tr>
<tr>
<td><strong>Natural immunity</strong></td>
<td>Acquisition of natural immunity inferred from human challenge studies and age-related incidence in LDC</td>
</tr>
<tr>
<td><strong>Sequelae</strong></td>
<td>Intractable diarrhea in immunocompromised patients</td>
</tr>
</tbody>
</table>
Cyclosporiasis: Life Cycle

[Diagram showing the life cycle of Cyclospora, including stages such as unsporulated oocyst, sporulated oocyst, zygote, macrogametocyte, microgametocyte, and different types of meronts with annotations for sexual and asexual multiplication.]
<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>transmission</strong></td>
<td>contaminated food and water; no person-to-person</td>
</tr>
<tr>
<td><strong>inoculum size</strong></td>
<td>undefined</td>
</tr>
<tr>
<td><strong>reservoirs</strong></td>
<td>environmental; may be host species-specific types</td>
</tr>
<tr>
<td><strong>populations at high risk</strong></td>
<td>young children in LDC; travelers (especially Peru, Nepal, Haiti, Guatemala (*); immunocompromised</td>
</tr>
<tr>
<td><strong>species diversity</strong></td>
<td><em>C. cayatanensis</em> found only in humans</td>
</tr>
<tr>
<td><strong>key pathogenic processes</strong></td>
<td>not well understood; localizes to small intestinal epithelium, partial villous atrophy, crypt hyperplasia</td>
</tr>
<tr>
<td><strong>typical clinical syndrome</strong></td>
<td>persistent diarrhea, anorexia, nausea/vomiting, abd cramps, flatulence, low grade fever, weight loss</td>
</tr>
<tr>
<td><strong>natural immunity</strong></td>
<td>decreased incidence with increasing age in high endemic areas of LDC;</td>
</tr>
<tr>
<td><strong>sequelae</strong></td>
<td>Chronic diarrhea in immunocompromised patients</td>
</tr>
</tbody>
</table>
Clinical and Diagnostic Evaluation

- Assess for dehydration
  - Mild (3-5%): dry mouth, decreased sweat and urine output
  - Moderate (6-9%): orthostasis, skin tenting, sunken eyes
  - Severe (>10%): hypotension, tachycardia, confusion, shock

- Consider setting of illness
  - Host factors
  - Environment, geographic region
  - Pathogen

- Define the clinical syndrome
  - Watery diarrhea
  - Dysentery
  - Gastroenteritis with recurrent vomiting
  - Persistent diarrhea
Considerations for Laboratory Work-up

- Assess for dehydration
  - Mild (3-5%): dry mouth, decreased sweat and urine output
  - Moderate (6-9%): orthostasis, skin tenting, sunken eyes
  - Severe (>10%): hypotension, tachycardia, confusion, shock

- Consider setting of illness
  - Host factors
  - Environment, geographic region
  - Pathogen

- Define the clinical syndrome
  - Watery diarrhea
  - Dysentery
  - Gastroenteritis with recurrent vomiting
  - Persistent diarrhea
Considerations for Laboratory Work-up

- With military deployments, available laboratory capabilities may be austere

- Several common pathogens are not detectable with routine laboratory diagnostic tests
  - Diarrheagenic *E. coli* (ETEC, EAEC, EIEC)
  - Norovirus

- Differentiate inflammatory vs. non-inflammatory diarrhea
  - Clinical indicators of inflammatory disease include fever, tenesmus, visible blood in stool
  - Gross and microscopic examination of stool for blood and fecal leucocytes
Considerations for Laboratory Work-up

- **Stool culture: clinical indications**
  - Severe diarrhea (≥ 6 loose/liquid stools/24 hrs, incapacitating illness)
  - Febrile enteritis and/or dysentery
  - Persistent diarrhea (≥ 14 days duration)
  - Bloody diarrhea (at risk for Shigella, STEC)
  - Inflammatory enteritis (by stool diagnostics)

- **Stool parasitology: clinical indications**
  - Persistent diarrhea (≥ 14 days duration)
  - Diarrhea in traveler returning from known high risk region
# Stool O&P Testing

<table>
<thead>
<tr>
<th></th>
<th>Isospora</th>
<th>Cyclospora</th>
<th>Cryptosporidium</th>
<th>Giardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (μm)</td>
<td>20-30</td>
<td>8-10</td>
<td>4-6</td>
<td>12-15</td>
</tr>
<tr>
<td>Modified AFB</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Treatment</td>
<td>tmp-smx¹</td>
<td>tmp-smx</td>
<td>HAART³</td>
<td>Flagyl</td>
</tr>
<tr>
<td></td>
<td>Cipro</td>
<td>Cipro</td>
<td>paramomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pyrimeth.²</td>
<td></td>
<td>nitazoxinide</td>
<td></td>
</tr>
<tr>
<td>Antigen detection test</td>
<td>not available</td>
<td>not available</td>
<td>available</td>
<td>available</td>
</tr>
</tbody>
</table>

¹tmp-smx, trimethoprim-sulfamethoxazole. ²Pyrimethamine. ³HAART, for patients with HIV infection/AIDS.
Therapeutics: Water and Electrolyte Replacement

- Cornerstone of diarrhea treatment
- Military settings, insensible fluid losses increased with high ambient temperature, intense physical activity
- Oral rehydration
  - Physiological principle: Integrity of coupled transport of Na+ (plus H$_2$O and other electrolytes) with glucose or amino acids
  - Effective in majority of patients
- Intravenous rehydration
  - Severe dehydration
  - Altered sensorium
  - Intractable vomiting
Oral Rehydration Therapy

- **Mild dehydration**
  - Potable water or appropriate ORS

- **Moderate-severe disease**
  - ORS

<table>
<thead>
<tr>
<th>Rehydration Formulas</th>
<th>CHO g/L</th>
<th>Na mmol/L</th>
<th>CHO:Na</th>
<th>K mmol/L</th>
<th>OSM mOsm/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO ORS</strong></td>
<td>13.5</td>
<td>75</td>
<td>1.2</td>
<td>20</td>
<td>245</td>
</tr>
<tr>
<td>Pedialyte</td>
<td>25</td>
<td>45</td>
<td>3.1</td>
<td>20</td>
<td>250</td>
</tr>
<tr>
<td><strong>Sports Drinks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gatorade</td>
<td>45</td>
<td>20</td>
<td>~6</td>
<td>~3</td>
<td>330</td>
</tr>
<tr>
<td>Powerade</td>
<td>60-80</td>
<td>~10</td>
<td>~6</td>
<td>~3</td>
<td>346-391</td>
</tr>
<tr>
<td><strong>Other fluids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red Bull</td>
<td>108</td>
<td>35</td>
<td>~3</td>
<td>0</td>
<td>601</td>
</tr>
<tr>
<td>Apple Juice</td>
<td>690</td>
<td>3</td>
<td>230</td>
<td>32</td>
<td>694-773</td>
</tr>
<tr>
<td>Chicken Broth</td>
<td>0</td>
<td>250</td>
<td>-</td>
<td>8</td>
<td>500</td>
</tr>
</tbody>
</table>
Non-Antibiotic Therapy

- Consider with mild diarrhea for symptomatic relief

- **Loperamide**: antimotility agent of choice
  - Slows down peristalsis, intestinal transit
  - Increased fluid and salt absorption
  - 4 mg by mouth, then 2 mg after each liquid movement (up to 16 mg per day)

- **Bismuth subsalicylate (Pepto Bismol)**
  - Reduces number of passes stools
  - Does not limit duration of disease
  - 525 mg (2 tabs) every 30 min for 8 doses
  - Contraindicated in persons on salicylates, warfarin
  - Can interfere with doxycycline absorption (malaria prophylaxis)
Effectiveness of Antibiotics, and Additive Effect of Loperamide

Placebo vs antibiotics alone (outcome: cure at 72 hours)
Bruyn G et al Cochrane Collab 2004

<table>
<thead>
<tr>
<th>Favors Placebo</th>
<th>Favors Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>DuPont, 1982</td>
<td>13.96 [5.47,35.65]</td>
</tr>
<tr>
<td>Ericsson, 1983</td>
<td>10.52 [3.43,32.28]</td>
</tr>
<tr>
<td>Mattila, 1993</td>
<td>3.34 [149,7.48]</td>
</tr>
<tr>
<td>Salam, 1994</td>
<td>5.73 [1.14,28.92]</td>
</tr>
<tr>
<td>Steffen, 1993</td>
<td>4.63 [2.20,9.75]</td>
</tr>
<tr>
<td>Wistrom, 1989</td>
<td>4.72 [1.96,11.39]</td>
</tr>
<tr>
<td>Total</td>
<td>5.90 [4.06,8.57]</td>
</tr>
</tbody>
</table>

TLUS = 24 – 36 hours

Antibiotics alone or plus loperamide
(outcome: cure at 24 hours)
Riddle MS et al, CID 2008

<table>
<thead>
<tr>
<th>Study Regimen</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX 800/160mg, b.i.d x 3d [7]</td>
<td>2.74 (1.07, 7.03)</td>
</tr>
<tr>
<td>CIP 500mg, b.i.d x 3d [3]</td>
<td>2.28 (0.91, 5.70)</td>
</tr>
<tr>
<td>CIP 750mg, single dose [8]</td>
<td>1.01 (0.44, 2.31)</td>
</tr>
<tr>
<td>OFL 400mg, single dose[6]</td>
<td>5.88 (2.02, 17.10)</td>
</tr>
<tr>
<td>RIF 200mg, t.i.d. x 3d [5]</td>
<td>2.78 (1.48, 5.20)</td>
</tr>
<tr>
<td>AZTH 500mg, single dose [4]</td>
<td>3.64 (1.49, 8.86)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.58 (1.84, 3.61)</td>
</tr>
</tbody>
</table>

TLUS ~ 12 hours
## Complications of Bacterial Diarrhea

<table>
<thead>
<tr>
<th>Complication</th>
<th>Associated Bacterial Agents</th>
<th>Clinical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>Any bacterial pathogen</td>
<td>Most important complication of watery diarrhea</td>
</tr>
<tr>
<td>Bacteremia</td>
<td><em>Salmonella</em> spp., <em>C. fetus</em></td>
<td>Certain conditions predispose to systemic <em>Salmonella</em> infection</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome (HUS)</td>
<td>STEC, <em>S. dysenteriae</em> type 1</td>
<td>Pathogenesis due to shiga toxin absorption and damage</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td><em>Campylobacter jejuni</em></td>
<td>40% cases of GBS caused by <em>C. jejuni</em>; molecular mimicry LOS</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td><em>C. jejuni, Salmonella, S. flexneri</em></td>
<td>Occurs in 2.1 per 100 000 <em>Campylobacter</em> infections</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Most bacterial pathogens</td>
<td>≤ 10% incidence following bacterial enteric infection</td>
</tr>
</tbody>
</table>
Postinfectious Irritable Bowel Syndrome (PI-IBS)

- Approx. 1 in 12 people develop PI-IBS after infectious diarrhea
- Higher risk associated with prolonged illness and invasive pathogens
- Onset usually occurs within 6 months after infection
- Can persist 5-6 years in 60 - 70% of people

Rifaximin and Chemoprophylaxis of Travelers’ Diarrhea

**PROS**
- Poorly adsorbed oral antibiotic
  - Absent side effects
- Low levels of rifaximin resistance among enteric pathogens
- Prophylaxis against travelers’ diarrhea for short-term travelers
  - ETEC predominant regions
  - ≥70% protection conferred

**Cons**
- Limited studies to date
  - Geographically delimited
  - Predominance of ETEC/EAEC
  - Short duration travel
- Impact of widespread usage for prophylaxis unknown
Take Home Lessons

- Acute diarrhea/dysentery in deployed military personnel (like travelers’ diarrhea) is predominantly caused by bacterial enteropathogens
- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)
- The U.S. military does not send its forces on overseas vacation
- Population-wide morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae
Back-Up Slides
Comparison of Civilian Travelers vs. Deployed Military

<table>
<thead>
<tr>
<th>CIVILIAN TRAVELERS</th>
<th>Deployed Military</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short-term trip (days-wks)</td>
<td>• Long deployment (wks-mos)</td>
</tr>
<tr>
<td>• Less crowding (cruise ship)</td>
<td>• Crowded housing is norm</td>
</tr>
<tr>
<td>• Leisure trips</td>
<td>• Intensive work demand</td>
</tr>
<tr>
<td>• Eating on economy</td>
<td>• Availability of MREs</td>
</tr>
<tr>
<td>• Varied exertion level</td>
<td>• Typically high exertion</td>
</tr>
<tr>
<td>• Typically poor access to medical facilities</td>
<td>• Embedded medical assets</td>
</tr>
<tr>
<td>• Self-treatment of diarrhea</td>
<td>• Encourage early care seeking</td>
</tr>
</tbody>
</table>
Diarrheagenic Escherichia coli
Common in Travelers: Pathogenesis

- Fimbrial colonization factors mediate enterocyte adherence
- Elaboration of secretory heat-labile (LT), heat-stable (ST) enterotoxins

ETEC

- Enterocyte adherence and biofilm formation
- Elaboration of secretory enterotoxins and cytotoxins

EAEC

EIEC

- Colonic epithelial cell invasion
- Lysis of phagosome
- Cell-to-cell spread via actin microfilament nucleation

adapted from Kaper JB et al Nat Rev Microbiol 2004