Traveller’s Diarrhoea

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Diarrhoea in Travellers

Infectious causes
– More common in younger travellers
– Most predictable infection in travellers

Non-infectious causes
– Ciguatera
– Emotional Stress
– Diet (spices, alcohol, caffeine etc.)

GIT Upset in Returned Travellers

- **E.coli** - ETEC, EAEC, EHEC, EPEC
- Other bacterial
  – *Shigella, Salmonella, Campylobacter, AAD/C.difficile*
  – “Tropical enteropathy”
  – “Post-infective tropical malabsorption”
- *Giardia, Entamoeba histolytica*
- *Cryptosporidium, Cyclospora, Isospora*

Diarrhoea in Travellers – More Common

- **E.coli** (ETEC, EAEC, EHEC, EPEC) - 30-60%
- *Campylobacter* - 15%
- *Shigella* - 10%
- *Salmonella* (non-typhoid) - 10%
- *Giardia* - < 3%
- *Cryptosporidium & Amoebic* - < 3%
- Unidentified causes - up to 40%
  – Includes viruses - astro, noro, rotaviruses, more..
Diarrhoea in Travellers – Less Common

Viruses
- Probably more common – PCR enables detection
  - PCR/molecular tests may become the standard for all/most pathogens

- Worms
  - Usually not diarrhoea

- Other protozoa – commonly found (?causative)
  - Dientamoeba fragilis (can be pathogenic, may treat)
  - Blastocystis hominis (can be pathogenic, usually do not treat)

- Systemic infections
  - Malaria
  - Sepsis

Travel & Diarrhoea - VFRs

Compared with Immigrant VFRs:
- Tourist Travellers & Traveller VFRs have:
  - 2 x the odds of acute diarrhoea

In addition:
- Tourist travellers have:
  - 3 x the odds of chronic diarrhoea

VFR = Visiting Friends & Relatives
- Immigrant VFRs – born OS, VFR
- Traveller VFRs – born ANZ, VFR
- Tourist Travellers – born ANZ, tourist travel only, no VFR

1. Leder K et al. Clin Infect Diseases 2006;43:1185-93

Diarrhoea & Travel

What Places
What Bugs
What Risk

Greatest Risk Rate

- Sub-Saharan Africa
- South Asia
- South America

<table>
<thead>
<tr>
<th>Region</th>
<th>N (%)</th>
<th>Case (%)</th>
<th>Rate/1000</th>
<th>HRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western and Eastern Europe</td>
<td>111444</td>
<td>40</td>
<td>0.4</td>
<td>3.1</td>
<td>Reference</td>
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<tr>
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Gastrointestinal infections in International Travelers

Table 1: Gastrointestinal infection reporting rates and HRRs by region of travel, Gastrointestinal 2000 to 2005

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<th>Region</th>
<th>Travelers' (N)</th>
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Greatest Risk by Pathogen
- Sub-Saharan Africa
- South Asia
- South America
A prospective study of travellers' diarrhoea: analysis of pathogen findings by destination in various (sub)tropical regions
J. Lääveri 1, K. Vilkmann 2, S.H. Palkkanen 1, J. Räveskari 1, A. Kantele 1,2,5,6

(Finnish) Travellers with Traveller's Diarrhea

Asymptomatic (Finnish) Travelers

Enterotoxigenic E.coli (ETEC)
- ETEC is the “classic” cause of Traveller’s Diarrhoea (TD)
- Transmission feco-oral (Food > Water)
  — Children G/E in developing countries
  — Turista, Bali Belly, Montezuma’s Revenge, Inca QuickStep etc...
- Some destinations notorious
  Nile Cruises, Mexico City & Resorts
- But...TD can occur in any destination
  > 90% of cases occur in first 2 weeks

ETEC TD Rates in Travellers

Low (< 7%) - ANZ, USA/Can, Western Europe

Intermediate (8-20%) - Mediterranean & Eastern Europe, USSR (parts), Korea, Japan, Israel, South Africa, some Caribbean Islands, Chile, Argentina

High (20-90%) - Most other locations
TD Prophylaxis

Antimicrobial prophylaxis should not be used routinely in travellers [R-S] [E-L/VL].

Antimicrobial prophylaxis should be considered for travellers at high risk of health-related complications of [R-S] [E-L/VL].

Bismuth subsalicylate (BSS) may be considered for any traveller to prevent TD [R-S], [E-H] – Not available in Australia.

When antibiotic prophylaxis for TD is indicated:
- Rifaximin is recommended [R-S], [E-M] – Not used much.
- Fluoroquinolones are not recommended [R-S] [E-L/VL].


Enterotoxigenic E.coli (ETEC)

- Commonest Cause of Traveller’s Diarrhoea
  - Toxins (LT “labile” &/or ST “stable”)
  - “Non-invasive” or Toxigenic TD
- LT: similar to cholera toxin
  - Immunologically, structurally & functionally
  - Active “A” subunit with 5 surrounding “B” subunits

Cholera & ETEC

ETEC & cholera produce a similar toxin

- Toxin from V.cholerae
  - Outer units (white) bind toxin to intestinal cells.
- Toxin from heat labile ETEC (LT)
  - Closely related to cholera toxin
  - Neutralised by antibodies to cholera toxin B-subunit.
  - Majority of ETEC strains produce this toxin.

First ..... TD - Definitions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
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<tbody>
<tr>
<td>Mild (acute)</td>
<td>(a) tolerable, (b) not distressing, (c) does not interfere with planned activities</td>
</tr>
<tr>
<td>Moderate (acute)</td>
<td>(a) distressing, (b) interferes with planned activities</td>
</tr>
<tr>
<td>Severe (acute)</td>
<td>(a) incapacitating, (b) completely prevents planned activities</td>
</tr>
<tr>
<td>Persistent</td>
<td>Diarrhea lasting 2 or more weeks</td>
</tr>
</tbody>
</table>

*All dysentery (grossly bloody stools) is considered severe.

Dukoral contains many artificial B sub-units
- Generates antibodies - prevent LT attach to Gut Cells

Prevention of Traveller’s Diarrhoea
- Ensure strict food & water hygiene
  - Boil it, cook it, peel it, or forget it
- Antimicrobial chemoprophylaxis (not favoured)
  - Rifaximin (200mg – 600mg/day) – non-absorbable, less harmful microbial flora change, not for campylobacter (R), not for invasive pathogens, poor S.Asia, SE.Asia!
    - Norfloxacin 400mg daily or Ciprofloxacin 500mg daily
- Non-antibiotic chemoprophylaxis (OK? efficacy)
  - Travelan (Bovine Colostrum anti-ETEC)
    - Prebiotics, Probiotics (Lactobacilli, Saccharomyces)
  - There is no overall TD vaccine - yet...
    ……But Dukoral fits the bill for ETEC!

Travelan
- Hyperimmune bovine colostrum powder (BCP or HBC)
  - antibodies against 14 different ETEC strains
  - Table 1. Summary of studies 1: prophylactic efficacy of hyperimmune bovine colostrum powder (400 units/dose) and plaques against infection with ampicillin-resistant E. coli strains, 10/0077.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placenta</th>
<th>Colostrum p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of volunteers</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Number of volunteers with diarrhea</td>
<td>11 (73%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Number of diarrhoea stool/ volunteer (mean ± SEM)</td>
<td>4.6 ± 0.9</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Mean number of diarrhoea stools per volunteer with diarrhea (mean and range)</td>
<td>6 (2-8)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ETEC 10/0077 stool</td>
<td>15 (100%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>From face after challenge</td>
<td>But there’s more!!</td>
<td></td>
</tr>
</tbody>
</table>

Anti-ETEC antibodies may have broader protection
BCP/HBC may have other beneficial effects
  - Protection against: campylobacter, shigella, salmonella, others
  - Reduce inflammation
  - (+) Tregs (regulatory T cells)

Travelan (BCP) Effects
- Targeting Virulence Factors
  - Spores
  - Lipo polysaccharide Endotoxins
  - Exotoxins
  - Fimbriae & Molecules which facilitate adhesion
  - Surface Layer Proteins which contribute to Colonisation
  - Flagella (Flagellin)

Antigens Important For
  - Outer Membrane Stability
  - Host Immune Evasion
  - Motility
  - Host Cell Adherence
  - Colonisation
  - Cellular Invasion

Travelan (BCP) Mode of Action
- Direct Protective MOA
  - Suppression of Germination
  - Suppression of Adhesion
  - Suppression of Motility
  - Suppression of Colonisation
  - Toxin Neutralisation

- Indirect Protective MOA
  - Anti-Inflammatory Effect via Stimulation of the Innate Immune Response
  - Enhancement of Gut Barrier Function
  - Inhibition of Epithelial Cell Apoptosis
  - Inhibition of Toxin Induced Inflammatory Signal Cascades

Bioactive Immune Components of Anti-Diarrheagenic Enterotoxigenic Escherichia coli Hyperimmune Bovine Colostrum Products

**Abstract**
Diarrhea is a common disease among tourists to resource-limited count- ries. The most common enteric agent among diarrheagenic E. coli and ETEC. In this study, we have evaluated the efficacy of anti-infective properties of hyperimmune bovine colostrum powder. The powder was promoted in the treatment of diarrhea caused by E. coli, with the goal of reducing the spread of this disease. We observed that the powder was effective in reducing the duration of diarrhea in patients, as well as in reducing the number of stools. The powder also showed promise in reducing the incidence of diarrhea in non-infected patients. In addition, the powder was shown to have a positive effect on the immune system, as evidenced by an increase in the levels of antibodies against E. coli and ETEC. The results of this study suggest that hyperimmune bovine colostrum powder has a potential role in the prevention and treatment of diarrhea caused by E. coli and ETEC. Further studies are needed to confirm these findings and to determine the optimal dosage and administration schedule for the powder.
Travelan (HBC)

In summary, HBC used for prevention of ETEC-induced diarrhea contains cytokines, growth factors, and lactoferrin that provide innate immune defenses and promote intestinal tissue growth and repair. In addition, HBC contains high levels of ETEC-specific antibodies, primarily IgG, including antibodies to key virulence factors. These antibodies have the capacity to inhibit ETEC activity and promote complement-mediated killing in vitro. These findings provide insights into HBC innate immune components and antibody-mediated antimicrobial activities that help prevent TD. The functional antibody assays developed will be useful in monitoring immunity following infection and vaccination. These assays can also be tools to ensure quality of HBC and antibody-based immunotherapeutics. Because of their safety profile, demonstrated biological activity and clinical efficacy, anti-ETEC HBC represents a unique, natural, and efficacious product to prevent TD.

Dukoral – Cholera & ETEC TD

- Licensed for cholera protective efficacy (PE)
  - 85% cholera classic (Bangladesh)
- Licensed (2003) Canada, NZ for ETEC protection
  - PE 67% ETEC TD (LT-ETEC)
  - PE 86% severe ETEC illness
- For regular TD sufferers
- For those who previously may have qualified for antibiotic prophylaxis

Who should get Dukoral for ETEC TD?

Not all TD is due to ETEC but consider Dukoral ....

- For high risk destinations
- For traveller to developing countries with:
  - Past history of severe TD
  - Past history of frequent TD (e.g., on most previous trips to a developing country)
  - History (present or past) of Inflammatory Bowel Disease
  - On medications that reduce gastric acid production
  - Immunesuppressed patients
  - IF TD extremely inconvenient e.g., persons participating in sporting events or business travellers

Cholera

Acute diarrhoeal disease
- Enterotoxin-producing *Vibrio cholerae*
- Serogroups O1 & O139
- In food or water contaminated with *Vibrio cholerae*

Not everyone is sick
- ~75% asymptomatic / ~25% symptomatic

But .... if symptomatic
- ~20% > profuse watery diarrhoea > severe dehydration
- Severe cholera can be rapidly fatal if left untreated
- Focus of treatment is rehydration

Cholera: Endemic in Africa, Asia, South America & Central America

Cholera: Endemic in Africa, Asia, South America & Central America

- Excreted – Vibrio Cholerae
- Serogroups: O1, O139
- In food or water

Cholera: Who to Vaccinate?

- If considerable risk of exposure to/of acquiring cholera
  - e.g. Humanitarian disaster workers
- If at risk of severe or complicated diarrhoeal disease
  - e.g. Poorly controlled diabetes, inflammatory bowel disease
- If at risk of acquiring diarrhoeal disease
  - e.g. Patients with achlorhydria

Dukoral – For Cholera

- Oral inactivated vaccine
  - For immunisation against cholera caused by serogroup O1 Vibrio cholerae
- For adults & children ≥2 years of age
  - Demonstrated 85% protective efficacy against cholera at 6 months after primary course
- Administer doses at an interval of 1-6 weeks:
  - Children 2 – 6 years: 3 doses
  - Adults > 6 years: 2 doses
  - If >6 weeks elapse between doses primary course must start again
- Generally well tolerated
  - Occasional GI symptoms

Dukoral - Boosters

- Protection from ~1 week after primary immunisation completed
  - Ensure 2nd dose is taken at least 1 week before departure
- Protection lasts 2 years but booster doses may be required every 3-6 months for persons at continuous high risk of contracting cholera
  - Booster (for Cholera protection): 1 dose every 3 months if at continuous significant risk
- Booster Doses for ETEC TD protection:
  - After primary course of 2 doses, a follow-up booster (1 dose) given at any time within 5 years from completion of the primary course (or within 5 years after any booster doses eg for cholera protection) should be sufficient for renewed protection against ETEC
  - If >5 years has passed since the primary course or last booster dose, the full primary course (2 doses at least 1 week apart) should be given

TD Treatment

Guidelines for the prevention and treatment of travellers’ diarrhoea: a graded expert panel report

Table 2. Acute diarrhoea antimicrobial treatment recommendations

*Disclaimer: A range of antibiotic regimens have been found to be efficacious and safe. Healthcare professionals should take into account local antimicrobial resistance patterns and individual patient factors before initiating antimicrobial therapy. Inappropriate or unnecessary use of antibiotics can contribute to the development of antimicrobial resistance.
Treatment of Traveller’s Diarrhoea

Mild disease
• Self limiting; oral rehydration ± loperamide

Moderate to severe disease (see definitions) (> 3 stools/24 hours, severe or disabling symptoms - eTG)
• Oral rehydration
• Azithromycin 1 g orally, as a single dose
• Norfloxacin 800 mg orally, as a single dose
• ± Loperamide (avoid if fever or bloody diarrhoea is present)

Children:
• Oral rehydration most important, avoid antimotility drugs

Lessons from practice

The growing burden of multidrug-resistant infections among returned Australian travellers

MJA 202 (2) - 3 February 2014
doi: 10.5694/mja13.0592

Antimicrobials Increase Travelers’ Risk of Colonization by Extended-Spectrum Betalactamase-Producing Enterobacteriaceae

Keywords: ESB, colonization, antimicrobials, travelers’ diarrhea.
What You Eat You Are

Post-Infectious Irritable Bowel Syndrome (PI-IBS)

- What affects our gut microbial flora?
  - Travel
  - Antibiotics
  - Diet

- Persistent GIT upset post-travel tests
  - Stool specimens – standard, PCR, C. difficile (doxycycline)
  - Upper & Lower GI endoscopy
  - Small bowel biopsy
  - Metagenomics, Transcriptomics, Proteomics

Metagenomics

- Probiotics – surge in interest – must be matched with scientific study
Durable Alteration of the Colonic Microbiota by the Administration of Donor Fecal Flora

Marise J. Greco, MBBS, PhD,* Thomas Julius Borody, MD, PhD,† Sharyn M. Lei, RN,† Jordana Campbell, BSc; Hazel Mitchell, PhD‡ and Antony Wettstein, MBBS‡

Results: At intervals of 4, 8, and 24 weeks after the procedure, the bacterial populations in the patient's fecal samples consisted predominantly of bacteria derived from the healthy donor samples. Comparisons of similarity at 4, 8, and 24 week samples to the corresponding baseline samples were performed with a Friedman test. The donor sample was statistically significant with Friedman test.

Conclusions: This study demonstrates a durable beneficial change in the patients' fecal bacterial population that is maintained over time. The donor sample was statistically significant with Friedman test.

Key Words: implantation, fecal bacteriotherapy, probiotic, Clos-tridium

(J Clin Gastroenterol 2008;44:551-561)

Metagenomics

FIGURE 1. A. Dotplot diagram of the 16S rRNA 149 OTUs obtained from fecal matter from the patient and the donor before and after fecal transplantation. B. Dotplot diagram of bacterial species in feces of the donor and the recipient before and after fecal transplantation.

This work was supported by funds from the NCI, the National Institutes of Health.