An approach to the patient with chronic post travel diarrhea

Travelers’ diarrhea

–Self-limited bacterial infection

–Affecting approximately 40% of travelers to developing countries

–Some travelers do not recover completely but, instead, develop chronic diarrhea or a persistent change in gastrointestinal function

• Connor BA. Persistent Travelers' Diarrhea. In: Centers for Disease Control and Prevention (CDC) Health Information for International Travel 2014; 505-507
DIARRHEA IN THE RETURNED TRAVELER

Not always diarrhea:

- May be constipation
- Alternating diarrhea and constipation
- Abdominal pain, bloating and cramping
- Rectal urgency

DIARRHEA IN THE RETURNED TRAVELER

Persistent Travelers’ Diarrhea

- How common?
- How problematic?
- What are the etiologies?
- How to treat or manage?
An approach to the returned traveler with persistent diarrhea

- Three broad pathogenetic categories
  - Persistent and ongoing infection or co-infection
  - An unmasking of a previously undiagnosed gastrointestinal disease or syndrome by the bout of travelers’ diarrhea
  - A post-infectious sequela of the enteric infection

An approach to the patient with chronic post travel diarrhea

- Concurrent with this observation is the recognition that in many patients with long-standing irritable bowel syndrome, an episode of traveler’s diarrhea or gastroenteritis preceded the onset of symptoms
- Before a diagnosis of PI-IBS is considered, other diagnostic considerations must be excluded
Persistent diarrhea in returned travelers

Different scenarios:

• Some travelers develop diarrhea that seems to persist beyond the usual 3–5 days

• These may be consecutive or successive bouts of diarrhea from new pathogens, rather than a prolonged course of diarrhea from the initial microbial agent

Persistent diarrhea in returned travelers

• In some patients who return from travel, their bout of diarrhea persists, sometimes less intense and often with a waxing and waning course

• In others, their symptoms resolve initially, but after a variable period of time, they begin to have diarrhea again
Persistent diarrhea in returned travelers

• In other patients, the diarrhea has resolved, but ongoing symptoms of bloating, gas, and abdominal distention persist, sometimes for variable and prolonged periods of time

• In yet other patients, a considerable gap occurs between the bout of diarrhea and the onset of altered bowel habits and gastrointestinal function.

Persistent diarrhea in returned travelers

• All of these patients fall within the rubric of post-travel chronic diarrhea, but the clinical manifestations differ, as well as the diagnostic approach and management
Persistent diarrhea in returned travelers

Duration of symptoms relative to the index episode of travelers’ diarrhea.

Travelers who are seen shortly after:

4–6 weeks post-travel—may present with diarrhea of different etiology than patients who present 3–6 months later or 1–3 years or more later

Persistent diarrhea in returned travelers

Persistent Infection or Co-infection:

• Parasitic Infection
  • Bacterial pathogens are most common cause of acute travelers’ diarrhea,
  • As a group, parasites as pathogens are most likely to be isolated from patients with persistent travelers’ diarrhea

CHRONIC DIARRHEA IN THE RETURNED TRAVELER

Parasites

- Their probability relative to bacterial infection increasing with increasing duration of symptoms
  - Travelers to Nepal, protozoans detected in 10% with symptoms <14 days vs. 27% with symptoms >14 days

Hoge CW, Shlim DR, Echevarria P. Epidemiology of diarrhea among expatriate residents living in a highly endemic environment. JAMA 1996;29:533-538

PROTOZOAN ETIOLOGIES

- *Giardia lamblia*
- *Cyclospora cayetanensis*
- *Cryptosporidium*
- *Entamoeba histolytica*
- *Dientamoeba fragilis*
- Microsporidia
Persistent diarrhea in returned travelers

Co-infection:

• New molecular diagnostics: mixed infections common
• For example:
  – patient with a treated bacterial infection with a relapse of symptoms, only to be found to have a *Giardia* co-infection perhaps acquired through the same contaminated meal

Persistent diarrhea in returned travelers

Underlying Gastrointestinal Disease:

• In some cases, a bout of travelers’ diarrhea unMASKs an underlying gastrointestinal disease in a person who may be genetically predisposed

• idiopathic inflammatory bowel disease (IBD)
• celiac sprue
• lactose intolerance
• colorectal neoplasia (rarely)
UNMASK PREVIOUSLY ASYMPTOMATIC GASTROINTESTINAL DISORDER

- Inflammatory Bowel Disease
  - Ulcerative Colitis
    - May be indistinguishable from amebic colitis
    - Unmasking of previously asymptomatic UC vs. true consequences of acute intestinal infection
  - Before steroid rx must rule out infection

Persistent diarrhea in returned travelers

Inflammatory Bowel Disease

• Idiopathic IBD diagnosed in 25% of patients in a retrospective British review of 129 cases of bloody diarrhea acquired during or within 2 weeks of return from the tropics
• These patients denied preexisting gastrointestinal symptoms prior to their travels
• Prevailing hypothesis of IBD pathogenesis is an infectious trigger.
• Whether a genetically determined individual can develop IBD as an accelerated course of TD is unknown.

Harries AD, Myers B, Cook GC. Inflammatory bowel disease: a common cause of bloody diarrhea in visitors to the tropics. BMJ 1985;291:1686-1687
Persistent diarrhea in returned travelers

- IBD may result from alterations in normal bowel flora, such as occur in travelers
- Most common form of IBD uncovered in the post-travel setting is ulcerative colitis but Crohn’s disease and microscopic colitis, including collagenous and lymphocytic colitis, have also been described.

Persistent diarrhea in returned travelers

Colorectal Neoplasia
- Colorectal cancer must be considered in patients with persistent travelers’ diarrhea, particularly in those who are found to have fecal occult blood or new iron deficiency anemia
- Especially true if these findings persist after the diarrhea has resolved
- In many such patients, and especially those over the age of 50, a colonoscopy should be performed even if the symptoms seem consistent with infectious colitis
Persistent diarrhea in returned travelers

• In the cases of celiac sprue and colonic adenocarcinoma, it seems clear that the acute infection acquired in travel is not causative, but it allows the underlying pathology to become clinically apparent, bringing the patient to medical attention.

Persistent TD: Evaluation

• Thorough and directed history
  – Travel history
  – Nature of initial symptoms
  – Onset (sudden or gradual)
  – Duration
  – Frequency and characteristics of bowel movements
  – Stool volume
  – Tenesmus
  – Association with particular foods
  – Use of antibiotics
  – Associated symptoms (nausea, vomiting, abdominal pain, bloating and gas, fever, chills)
  – Weight loss
TD and the Gut Microbiome

- Initial evaluation:
  - CBC (anemia, eosinophilia)
  - Stool analysis (PCR preferred)
  - *C. difficile* assay
  - Celiac serologies

Persistent diarrhea in returned travelers

Diagnostic possibilities by duration of symptoms or time from initial episode to medical provider visit

- First 3 to 4 weeks:
  - Persistent infection or co-infection
    - Work-up: stool O & P X 3 or multiplex PCR
    - *C. difficile* stool toxin assay
  - Temporary post-infectious malabsorption
    - Trial lactose free diet
  - Unmasked GI disease
    - Anti-gliadin, endomysial, tissue transglutaminase antibodies
    - ASCA, ANCA serologies for IBD
Persistent diarrhea in returned travelers

1 month to 3 months:
- Co-infection:
  - Stool O & P or multiplex PCR
  - *C. difficile* stool toxin assay
- Unmasked GI disease
  - Anti-gladin, endomysial, tissue transglutaminase antibodies
  - ASCA, ANCA serologies for IBD
- Nonceliac gluten sensitivity
  - Trial gluten-free diet
- Empiric treatment for *Giardia*
- Endoscopy?

Endoscopy in the Evaluation

- In patients with chronic symptoms
  - upper GI endoscopy and/or colonoscopy may contribute to the evaluation:
    - for sustained or progressive weight loss, EGD may be considered especially if empiric therapy or symptomatic measures have not helped
  - Infectious etiologies (*Giardia, Cystoisospora, Cyclospora, Microsporidia*)
  - Non-infectious etiologies (celiac disease, Crohn’s, microscopic colitis, eosinophilic gastroenteritis)
Endoscopy in the Evaluation

Colonoscopy

For chronic diarrhea (>30 days)
Diagnostic yield ranges from 7 to 32%
IBD and microscopic colitis most common diagnoses
Yields a non infectious diagnosis more often than EGD
Review of 18 primary studies looked at diagnostic value of colonoscopy in patients with chronic diarrhea
Review of 9 published guidelines: findings range from 15 to 70%
most common were microscopic, collagenous, lymphocytic colitis

Shah RJ, Fenoglio-Preiser C, Bleau BL et al. Usefulness of colonoscopy with biopsy in the evaluation of patients with chronic diarrhea. Am J. Gastro 2001;96:1091-1095
Persistent diarrhea in returned travelers

Greater than 3 months:

- Co-infection:
  - Stool O & P or multiplex PCR
  - *C. difficile* stool toxin assay
- Unmasked GI disease
  - Anti-gliadin, endomysial, tissue transglutaminase antibodies
  - ASCA, ANCA serologies for IBD
- Non-celiac gluten sensitivity
  - Trial gluten-free diet
- Empiric treatment for *Giardia*
- Endoscopy?

Persistent diarrhea in returned travelers

Greater than 3 months:

- PI-IBS: treatment for SIBO, ± GI dysmotility
- O & P, multiplex PCR
- ASCA (anti-saccharomyces cerevisiae) antibodies, ANCA (perinuclear antineutrophil cytoplasmic) antibodies for IBD
- Endoscopy?
CHRONIC TRAVELERS’ DIARRHEA

- The longer the symptoms persist, the less likely a pathogen will be found
- If no pathogen is found, what can you offer the patient?

Persistent diarrhea in returned travelers

Post-infectious Irritable Bowel Syndrome (PI-IBS)
- In the majority of patients with persistent travelers’ diarrhea, as more time passes from the initial bout of diarrhea, no specific etiology will be found
- Concurrent with the recognition of the importance of persistent diarrhea as a presenting complaint in travelers has been the observation that in certain patients with irritable bowel syndrome (IBS), the onset of symptoms can be traced to an acute episode of gastroenteritis

Persistent diarrhea in returned travelers

PI-IBS

• Irritable bowel syndrome which develops after acute gastroenteritis originally called Post-Infectious Enteropathy
• Now known as Post-Infectious IBS (PI-IBS)
• PI-IBS is now a topic of considerable clinical and investigative interest as evidence validating it as a diagnosis and elucidating its pathophysiology has accumulated
• PI-IBS may be a cause of symptoms in a large number of patients with persistent travelers’ diarrhea in whom no specific etiology is found


Persistent diarrhea in returned travelers

PI-IBS as a specific diagnosis requires a paradigm shift:

a peripheral event—in this case, an infection—leads to prolonged and permanent changes in gastrointestinal function.
Post Infectious Irritable Bowel Syndrome (PI-IBS)

• Rome III Criteria (?)
  – ≥3 months, with onset ≥6 months previously, of recurrent abdominal pain or discomfort associated with ≥2 of the following:
    • Improvement with defecation and/or
    • Onset associated with change in frequency of stool and/or
    • Onset associated with change in form (appearance) of stool
• Following an episode of gastroenteritis or TD
• Work-up for microbial pathogens and underlying GI disease is negative

Persistent diarrhea in returned travelers

• Adherence to rigid Rome III criteria (e.g., symptoms present for 6 months)
  – may not apply to the post-travel IBS population—hence, a modification in duration of symptoms to conform to the usual travel clinic scenario.
• GeoSentinel definition
• PI-IBS may be characterized by diarrhea as predominant symptom, but constipation and mixed IBS occur
• In many patients, it is bloating, gas, and generalized abdominal discomfort that cause the most distress.
Persistent diarrhea in returned travelers

- The incidence of IBS after enteric infection has been reported to range from 4% to 32%
- This wide range may be related to:
  - differences across studies in the definition of PI-IBS, and time to follow-up between infections
- Many of the studies were retrospective and subject to bias
- In addition, most of the studies did not include a control group to define the incidence of new IBS in the absence of preceding infection.

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-Up</th>
<th>PI-IBS, No.</th>
<th>PI-IBS, %</th>
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<tr>
<td>McKendrick et al, 1994</td>
<td>12 mo</td>
<td>12/38</td>
<td>32</td>
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<tr>
<td>Gwee et al, 1999</td>
<td>3 mo</td>
<td>22/100</td>
<td>22</td>
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<td>Okhuysen et al, 2004</td>
<td>6 mo</td>
<td>6/60</td>
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<td>Neal et al, 1997 &amp; 2003</td>
<td>6 mo</td>
<td>23/357</td>
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<td>6 yr</td>
<td>14/192</td>
<td>7</td>
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<td>Thornley et al, 2000</td>
<td>6 mo</td>
<td>9/93</td>
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</table>
Persistent diarrhea in returned travelers

- Alternative explanations for persistent bowel symptoms were often not assessed
- Especially true for patients labeled PI-IBS in the first 3 months after travel
- When other causes such as *C. difficile*, protozoan pathogens, and temporary post-infective phenomena may be found

The limitations of these studies notwithstanding
- Data suggest that PI-IBS may be relatively common sequela of acute gastroenteritis.
- Studies comparing individuals having an acute episode of gastroenteritis with matched controls consistently show an elevated incidence of IBS among those with a preceding episode of gastroenteritis
- Those with acute gastroenteritis 2.5–12 times more likely to develop IBS over follow-up periods of up to 1 year

Persistent diarrhea in returned travelers

Incidence of PI-IBS specifically associated with TD

Recent studies:
• 121 U.S. military travelers returning from routine deployment (>6-month follow-up) to the Middle East
• More than a 5-fold increase in IBS among those who experienced an episode of travelers’ diarrhea compared with those who did not (17.2% vs. 3.7%, p=0.12)


Travelers from Israel:
• Significantly more people (14%) who had travelers’ diarrhea developed IBS after 6 to 7 months, as compared with only 2% of those who did not have diarrhea

American students in Mexico:
PI-IBS of 10% in patients who acquired travelers’ diarrhea

Mucosal Abnormalities in PI-IBS

• **Hypothesis**
  - Patients destined to develop PI-IBS are somehow unable to down-regulate intestinal inflammation after clearance of the microorganism


Diagnostics: What’s New

• Diagnostics to determine specific microbial etiologies have advanced in the past number of years
• High throughput multiplex DNA extraction PCR for evaluation of infectious causes of Travelers’ Diarrhea, both acute and chronic
• This multiplex approach well suited for the syndromic nature of TD
Limitations of Conventional Methods of Enteric Pathogen Detection

• Diagnosis of a variety of bacterial, viral and parasitic enteric pathogens:

• Patchwork of modalities
  – Culture
  – Microscopy
  – Antigen based tests

Limitations of Conventional Methods of Enteric Pathogen Detection

• Current methods:
  – Time consuming: culture 48 to 72 hours
  – Operator dependent: microscopy
  – Incomplete: miss >50% of pathogens (bacteria, viruses)
  – Lead to:
    • Delay in diagnosis
    • Inaccurate diagnosis
    • Wrong treatment (e.g antibiotics for viral pathogens) or no treatment
    • ? increase incidence of post infectious sequelae
Limitations of Conventional Methods of Enteric Pathogen Detection

Bacterial Culture

- Often low yield for enteropathogens, particularly in setting of antibiotic use or for certain pathogens
- Campylobacter difficult to isolate in presence of normal stool flora, thus selective techniques employed which may limit detection of other pathogens
- Time consuming (48 to 72 hours)

Limitations of Conventional Methods of Enteric Pathogen Detection

Microscopy

- Insensitive
- Operator (technician) dependent
- Under-reading
- Over-reading
New Diagnostics

Qualitative high throughput multiplex nucleic acid-based in vitro diagnostic tests

• Capable of simultaneous detection and identification of nucleic acids from multiple bacteria, viruses and parasites
• Directly from stool samples collected in Cary-Blair transport media

New Diagnostics

• Several well designed studies have shown:
• Molecular diagnostic tests can provide a more comprehensive assessment of disease etiology
  – Increase diagnostic yield
  – Faster, provide results in hours not days

### Commercial PCR-based culture-independent systems

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Test System</th>
<th>Platform</th>
<th>Pathogens Detected</th>
<th>Detection time (h)</th>
<th>FDA Approved</th>
<th>Date Approved</th>
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<tbody>
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<td>Luminex</td>
<td>GPP</td>
<td>xTAG</td>
<td>B, V, P</td>
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<td>Hologic/Gen-Probe</td>
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<td>BD Diagnostics Inc.</td>
<td>EBP</td>
<td>BD MAX</td>
<td>B</td>
<td>4</td>
<td>3-4</td>
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<td>Bioline Diagnostics Inc.</td>
<td>GI Panel</td>
<td>FilmArray</td>
<td>B, V, P</td>
<td>22</td>
<td>1-2</td>
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<td>Nanosphere</td>
<td>EP</td>
<td>Verigene</td>
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<td>Fast-Track Diagnostics Inc.</td>
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<td>FTD Viral GE</td>
<td>-</td>
<td>V(2)</td>
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<td>&lt;6</td>
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<td>Seegene, Inc.</td>
<td>Diarrhea ACE B-1</td>
<td>Seeplex</td>
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<td>Serosep Ltd</td>
<td>Gastro Panel III</td>
<td>EntericBio</td>
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### High Throughput Multiplex DNA Extraction Technology

- **Sample Prep** + **Amplification** + **Detection**
Gastrointestinal (GI) Panel

Bacteria
- Campylobacter (jejuni, coli, and upsaliensis)
- Clostridium difficile (Toxin A/B)
- Plesiomonas shigelloides
- Salmonella
- Vibrio (parahaemolyticus, vulnificus, and cholerae)
- Vibrio cholerae
- Yersinia enterocolitica

Diarreagenic E. coli/Shigella
- Enteroaggregative E. coli (EAEC)
- Enteropathogenic E. coli (EPEC)
- Enterotoxigenic E. coli (ETEC)
- Shiga-like toxin-producing E. coli (STEC)
- E. coli O157
- Shigella/Enteroinvasive E. coli (EIEC)

Parasites
- Cryptosporidium
- Cyclospora cayetanensis
- Entamoeba histolytica
- Giardia lamblia

Viruses
- Adenovirus F 40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)
Persistent Travelers’ Diarrhea

Co-infection

• New molecular diagnostics: mixed infections common
• For example:
  – patient with a treated bacterial infection with a relapse of symptoms, only to be found to have a *Giardia* co-infection perhaps acquired through the same contaminated meal

Patient Case

• A 59-year-old Norwegian man traveling through South America. He visits Chile, Argentina, Uruguay, Brazil and Peru until his arrival in Bogota, Colombia
• On the 2nd night awakens with nausea and vomiting and vomits for about 3 hours. He feels tired but otherwise well the next day, eats gingerly. He was well until 4th day in Bogota when he has watery diarrhea, lasting 8 hours
• Treated with one dose ciprofloxacin, no better, switches to azithromycin, better with formed stool in 24 hours.
Patient Case

- He then travels to Mexico City and the 2nd day after arrival feels nausea, intermittent soft stool and frank watery diarrhea begins
- On the 3rd day symptoms resolve
- Travels to Guatemala. On arrival intermittent watery, semi formed diarrhea, nausea, belching and burping

Patient Case

- Stool sample sent in Cary Blair medium to New York
New diagnostics in Travelers’ Diarrhea

- Traditionally enteric infection is conceptualized as a binary state—the pathogen is either present in the gut or not.
- Point of care molecular diagnostics might provide a more nuanced picture of infection and understanding of the concept of pathogenesis.
- May require reconsideration of basic concepts of colonization, infection, and disease.
PERSISTENT DIARRHEA
IN THE RETURNING TRAVELER

Summary

- Many people with acute travelers’ diarrhea do not recover completely but develop one of several gastrointestinal syndromes.
- In some patients an episode of travelers’ diarrhea seems to unmask a pre-existing underlying gastrointestinal disorder.
- In others enteric infection leads to persistent or permanent changes in GI motility.

Summary

- Potential consequences of TD extend beyond the acute illness.
- Increasing recognition of serious, disabling, and permanent sequelae of TD.
- Need to reconsider strategies for treatment and prophylaxis of TD.
Persistent diarrhea in returned travelers

Conclusions
Although most cases of travelers’ diarrhea are acute and self-limited

Some patients will develop persistent gastrointestinal symptoms

• The pathogenesis of persistent travelers’ diarrhea generally falls into one of three broad categories:
  • Persistent infection or co-infection
  • Post-infectious processes or
  • Chronic gastrointestinal illnesses unmasked by an enteric infection