Chronic Diarrhea: is it infectious?

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Overview

Infectious diarrhea
  Acute
  Chronic
  Diagnosis
  SIBO
### Characteristics of Diarrhea

<table>
<thead>
<tr>
<th>Small intestinal</th>
<th>Ileocolonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Usually not inflammatory</td>
<td>• May be inflammatory (invasive)</td>
</tr>
<tr>
<td>• Watery, large volume</td>
<td>• Smaller volume, may be bloody</td>
</tr>
<tr>
<td>• May be malabsorptive</td>
<td>• No malabsorption</td>
</tr>
<tr>
<td></td>
<td>• Tenesmus if rectum involved</td>
</tr>
</tbody>
</table>

### Diarrhea- definitions

- Acute
  - 1-2 wks
- Persistent
  - 2-4 wks
- Chronic
  - Longer than a month
### Infectious Diarrhea

#### Non-invasive—Small Intestine

<table>
<thead>
<tr>
<th>Viruses **</th>
<th>Parasites</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td><em>Giardia lamblia</em></td>
<td>Toxigenic <em>E. coli</em> (ETEC)</td>
</tr>
<tr>
<td>Norovirus</td>
<td><em>Cryptosporidium</em></td>
<td>Enteroagg <em>E. coli</em></td>
</tr>
<tr>
<td>Adenovirus (enteric)</td>
<td><em>Cystoisospora belli</em></td>
<td><em>Vibrio cholera</em></td>
</tr>
<tr>
<td>Astrovirus</td>
<td><em>Cyclospora</em></td>
<td><em>Salmonella</em> (colon also)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Strongyloides</em></td>
</tr>
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</table>

#### Invasive—Ileocolonic

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<tr>
<th>Bacteria **</th>
<th>Parasites</th>
<th>Virus</th>
</tr>
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<tr>
<td><em>Campylobacter</em></td>
<td><em>Entamoeba histolytica</em></td>
<td>CMV (rare)</td>
</tr>
<tr>
<td><em>Salmonella</em> (SI also)</td>
<td><em>Trichuris</em> (whipworm)</td>
<td></td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td><em>Schistosomiasis</em></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em> 0157:H7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Yersinia</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Aeromonas</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Plesiomonas</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Noncholera Vibrio</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evaluate and treat acute diarrhea- watery

- Mild: ORS and loperamide
- Moderate to severe:
  - If travel associated: antibiotics
  - If no travel stratify by fever and duration:
    - No or low grade fever, loperamide
  - If fever 101 and less than 72 hrs., loperamide
  - If fever 101 and longer than 72 hrs., stool culture
- Persistent diarrhea (2 wks.): stool culture

Riddle et al, ACG guideline Am J Gastroenterol, May 2016

Evaluate and treat acute diarrhea- dysentery (bloody)

- Afebrile or low grade fever: stool culture and treat with antibiotics (not STEC)
- Severe symptoms and fever
  - No travel: same as above
  - Travel: empiric antibiotics (one dose azithromycin 1 gram or 500 mg for 3 days).
When is chronic infection likely?

- Travel to developing countries
- Immigrants from developing countries
- Recent antibiotics (CDI)
- Contaminated water or unpasteurized milk/dairy products
- HIV and other immune compromised states

Chronic diarrhea- infectious

- Immune competent - stool studies usually adequate for Dx
  - Parasites
    - Protozoa and amoeba
  - Bacteria
    - Recurrent C. difficile
    - Yersinia, Aeromonas, Salmonella, noncholera Vibrio
- Immune deficient - a separate topic
  - More extensive workup with blood cultures, endoscopy/colonoscopy and biopsy
  - Can be viral (CMV) or opportunistic infections
**Bacterial causes uncommon**

- Campy/Shig/ STEC uncommon chronic unless immune compromised
- *Plesiomonas / Aeromonas*:
  - Case reports of chronic colitis but may be PI-IBD
- *Salmonella* (nontyphoidal) may be recurrent
  - Hematogenous (2-4%)
  - Can infect grafts, artificial joints etc
  - Blood culture if febrile

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**Salmonella—Risks**

- Reptiles
  - 50-90% carry it
  - They are not sick
  - **CAUTION**: Children and immunosuppressed
- Eggs, peanut butter, spinach, raw almonds, aquatic frogs, Italian salami, hydrolyzed vegetable protein, mangos, cantaloupes
**Yersinia enterocolitica & Y. pseudotuberculosis**

- Ileitis, Mesenteric adenitis
- Granulomatous appendicitis
  - DDx Crohn’s, sarcoid, foreign body
- Chitterlings
- Cold enrichment medium—delay
- Reactive arthritis 2-3 weeks later—classic: middle-aged man with diarrhea and arthritis (also for Whipple’s)

**Stool tests – Bacteria**

- Overall yield in diarrhea w/u 1-5%
- Fecal leukocytes nonspecific
- Fecal calprotectin and lactoferrin not helpful in this setting
- Expensive
- Enteric pathogens (*Salmonella, Shigella, Campylobacter, STEC*)
  - Expanded enteric – *Yersinia, Aeromonas, Plesiomonas*
- *C. difficile* PCR for gene for toxin B
- PCR panels- role uncertain
PCR multiplex panels

• 2 available currently
  • One for 14 pathogens
  • One for 22 pathogens
  • Do not distinguish between active infection or carriers (false positives)

Case

2 gastroenterologists attended DDW in Chicago
4 and 7 days (home in Germany) after a shared meal at a fancy hotel both developed
  - Watery diarrhea
  - Bloating
  - Abdominal pain
  - Low grade fever
Sought care 12 and 14 days after onset of symptoms
**Labs**

- Normal CBC, CRP
- Liver enzymes, lipase
- Stool test was diagnostic
- Likely pathogen?

**Persistent Diarrhea**

- they had
  - *Cyclospora cayatenensis*
    - (Shared “exotic” fruit plate)
    - possibly imported raspberries –
    - Similar symptoms -
      - *Cryptosporidium*
      - *Giardia*
      - *Cytoisosporiasis*
Course

Both treated with 1 week TMP – Sx
Responded - 48 hours
Resolved - 1 week
Wrote it up for publication

Brand et al, Am J Gastroenterol letter 2012

Cyclospora
(Cyanobacter/Blue-Green Algae)

Epidemic diarrhea - traveler’s diarrhea, explosive / raspberries from Guatemala

Incubation 1 week (1-23 days)

Prolonged diarrhea (43 d mean)

Treatment: TMP – SX: 7 days

“Big crypto” “Crypto grande”
**Cryptosporidia (C. parvum)**

- Waterborne
- Watery diarrhea—often voluminous
- Nitazoxanide Rx (14 days)
  
  FDA approval for *C. parvum* and *G. lamblia*

**Cryptosporidia - Cyclospora**

Big Crypto, Crypto grande, Twice as large
Cystoisospora belli
(Isospora belli)

Giardia lamblia

• Small bowel biopsy usually not needed

• *Giardia* antigen detects 30% more than microscopy
  (Sensitivity 95-100%; specificity 100%)

• Hypogammaglobulinemia—predisposes to *Giardia* infection
**Giardia- Rx options**

- Metronidazole 250 mg tid x 7 days
- Nitazoxanide 500 mg bid x 3 d
- Tinidazole 2 gm single dose

- Recurrence common, re treat

**Small Intestine—Protozoa**

- Generally noninvasive
  - *Giardia*
  - *Cryptosporidia*
  - *Cyclospora*
  - *Cystoisosporiasis (Isospora belli)*

- Best tests: Stool giardia antigen and acid fast stains
- Stool O&P: expertise needed, 3 samples optimum yield, picks up other organisms
Other parasites

E. histolytica

Cysts — Infectious

Trophs — Invade (phagocytozed rbc = pathogenic)

• 90% are asxic carriers—do treat
• 10% colitis/dysentery
Diagnosis

• Stool O + P—cysts or trophs
  – Limited use
• Stool antigen—specific serology
  – Best
• Colonoscopy + Bx
  – (Ileum, asc colon)—can help

Cecal ulcer

Amoeba

Courtesy of Melissa Upton
Nonpathogenic Amoeba

- *Entamoeba coli, hartmanii, dispar*
- *Endolimax nana*
- *Iodamoeba buetschlii*
Treatment Options

A. No treatment needed  
B. Albendazole  
C. Metronidazole  
D. Trimethoprim sulfasoxazole

Answer: B

This is *Trichuris trichuria*—treatment is albendazole
Trichuriasis (Whipworm Infection)

- Tropics, US
- Colon
- ASXIC
  - Chronic diarrhea
  - Colitis
  - Dysentery

Question

A primary care doctor calls you for advice. Her 34-year-old patient with chronic diarrhea has numerous Blastocystis hominis in the stool sent for O&P.

What do you tell her?

A. This is not a pathogen so she can ignore the test result
B. She should test the patient for immune deficiency
C. These are not pathogens but can be treated
Answer: C

There is debate if *B. hominis* is a pathogen or not; most studies suggest it is not in immune-competent patients, but treatment might get rid of diarrhea. Follow-up is indicated to evaluate the diarrhea if there is no response to therapy.

### Blastocystis hominis

- Pathogenicity debated
- Look for other pathogens first
- If none, Rx nitazoxanide or metronidazole or TMP-SX
- Level I evidence – RCT of nitazoxanide
  - 600 mg b i d x 3d
- 86% resolved vs. 38% on placebo
  
  Rossignol, Clin Gastro & Hep 2005
Candida causes chronic diarrhea?

- Case series in “elderly” with response to nystatin
- Can see yeast in stools from normal individuals
- Decide on a case by case basis?

What stool tests to order- Parasites

- O&P exam x 3 is standard
- Giardia antigen
- Acid fast stain for protozoa
Role of antibiotic or antiparasitic therapy for chronic diarrhea?

- Treat organisms identified
- Travelers - high risk areas
  - Antibiotic - azithro
  - Antiparasitic - metronidazole or nitazoxanide
  - Loperamide safe as adjunct

- No role for other groups

A few other things to consider....

- TB
- *Strongyloides*
- Brainerd diarrhea
- SIBO
- Colorectal biopsy: infection vs IBD
GI tract TB

- Abdominal pain more common than diarrhea
- Predilection for ileocecal area
- Only half will have pulmonary TB on chest xray
- PPD can be negative
- Colonoscopy and biopsy, with PCR, often needed

TB

- Can mimic Crohn’s- granulomas
- Ulcers more likely circumferential vs longitudinal in Crohn’s
- Predictors for TB in Korean population:
  - Ring shaped ulcers
  - Suspicion of pulmonary TB
- For Crohn’s: diarrhea, sigmoid involvement
- Jung et al Am J Gastroenterol 2016:111:1156
Death After Heart Transplant

- 62-year-old man admitted a few months after heart transplant, emigrated from Ethiopia 29 years prior
- Acute dyspnea, abdominal pain, white out on lungs, rapid decline
- All cultures negative
- BAL negative for bacteria, fungi, parasites
- Stress dose steroids, Abx, continued decline

Day 5

- Sputum O & P showed
  *Strongyloides stercoralis*, filariform larvae
(Seen retrospectively on Day 1 sputum)
Day 6

- Therapy
  - Ivermectin tablets per NG tube
- Patient died
- Diagnosis:
  - Disseminated strongyloidiasis, hyperinfection syndrome
- No pre-transplant screening done (serology)

Any clues?
- Transient eosinophilia pre-transplant
- Emigrated from high-risk area

Strongyloides Hyperinfection Syndrome

- Any clues pre-op?
  - Had normal colonoscopy
- Transient eosinophilia pre-op
- High-risk groups now screened with serology pre-op

**Strongyloides stercoralis**

**Acute**
- Itching/cough
- N/V/D

**Chronic**
- Vague abd pain
- Alternating diarrhea/constipation
- Occult blood
- Malabsorption

**Strongyloides—Diagnosis**

- ↑ Eosinophils—75% (mild)
- Serology—85-100% positive
- ELISA—98% negative predictive value
- Stool and serology—98% positive
Finding *Strongyloides*

**SCREEN**
Serology best

**DIAGNOSE**
Serology and stool

*Strongyloides* Auto-Infection

- Non-infective (rhabditiform) larvae $\rightarrow$ infective (filariform) larvae
- Millions of them go to skin
- Increased risk
  - High-dose steroids
  - HTLV—1 infection
  - HIV
  - Solid organ transplant
Brainerd diarrhea

- Probably post infectious (Brainerd, Minnesota 1st epidemic)
- Unpasteurized milk or untreated water
- May last up to 2-3 yrs
- May have microscopic colitis
- Resolves spontaneously

Small Intestinal Bacterial Overgrowth

- May present with diarrhea, but bloating more common, flatulence
- Nonspecific
- Associations: blind loop, strictures, dysmotility, diabetes, IBS
**SIBO diagnosis**

- Jejunal culture - not realistic
  - Gr than 10x3 cfu colonic flora/ml
- Breath tests - not reliable, sensy 70-90%; specy 40-100%
  - Measure products of fermentation
  - Glucose - better but only for proximal SIBO
  - Lactulose
  - Interpretation variable
- Empiric therapy
  - Antibiotics

**Rx for SIBO**

- Rifaximin 1200 mg/day w and w/ guar gum x 10 days
  - Eradication by glucose breath test
    - Rifax 62%
    - Rifax and guar gum 85%

- Rifaximin 1200 mg/day vs metronidazole 750 mg/day
  - Eradication
    - Rifax 63%
    - Mzd 44%

(Fumari et al APT 2010; Lauritano Eur Rev Med Pharm 2009)
SIBO

- Diagnostic tests not perfect and interpretation requires expertise
- Recurrences common after therapy- often need retreatment
- Rifaximin expensive and may not be covered
- Risks of antibiotics

Colon Biopsy—Colitis

<table>
<thead>
<tr>
<th>IBD</th>
<th>Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distorted</td>
<td>Architecture NL</td>
</tr>
<tr>
<td>Acute + Chronic</td>
<td>Acute inflammation</td>
</tr>
<tr>
<td>Basilar inflammation</td>
<td>No basal inflammation</td>
</tr>
</tbody>
</table>
Normal Colon Biopsy
### Infectious diarrhea

<table>
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<tr>
<th>Small Intestine (noninvasive)</th>
<th>Ileocolonic (invasive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Viral GE—most common</td>
<td>• Bacteria- most common</td>
</tr>
<tr>
<td>‒ Rotavirus, Norovirus</td>
<td>Campylobacter, Salmonella,</td>
</tr>
<tr>
<td>• Bacteria</td>
<td>Shigella, STEC, C. difficile,</td>
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<tr>
<td>‒ Enterotoxigenic <em>E. coli</em> common</td>
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<tr>
<td>• Parasites –</td>
<td>• Parasites</td>
</tr>
<tr>
<td>• Protozoa</td>
<td>Amoeba, <em>Trichuris</em>,</td>
</tr>
<tr>
<td>‒ <em>Giardia</em></td>
<td><em>Schistosoma</em> (endemic)</td>
</tr>
<tr>
<td>‒ <em>Cryptosporidia</em></td>
<td>• Viral rare</td>
</tr>
<tr>
<td>‒ <em>Cyclospora</em></td>
<td></td>
</tr>
<tr>
<td>‒ <em>Cystoisospora Strongyloides</em></td>
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Chronic Diarrhea—Infectious

- Giardia
- Cryptosporidia
- Cyclospora
- Amoeba
- Yersinia
- Aeromonas/Plesiomonas
- C. difficile (recurrent)
- Tuberculosis
- Candida (?)
- Epidemic chronic syndromes (Brainerd)
- Tropical sprue
- Post-infectious IBS
- SIBO

Summary

- Infectious diarrhea uncommonly chronic
- Parasites
  - Stool O&P x 3
  - Giardia antigen
  - Acid fast stain for protozoa

- Sometimes endoscopy/ colonoscopy and biopsy
THANK YOU