Acute and Chronic Diarrhea: A distillation

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Goals
• Acute and Chronic Diarrhea
• Focus on essentials
• New developments

Topics Covered
• Definitions
• Approach to acute diarrhea
  – Differential diagnosis
  – Diagnostic approach
    • When to watch
    • When to test
    • When to treat
• Approach to chronic diarrhea
  – Mechanisms
  – Diagnostic evaluation
    • Initial testing
    • Follow-up testing

Diarrhea: Definitions
• Objective definition
  – Excessive stool weight: >200gm/day
• Subjective definition
  – Excessive frequency of defecation (≥3 stools)
  – Less-than-normal form and consistency
• Acute diarrhea: < 4 weeks duration
• Chronic diarrhea: > 4 weeks duration
• Persistent diarrhea: 2-4 weeks duration

Normal Intestinal Physiology
• 10 L of fluid enters the jejunum daily
  – 2 L: Food and drink
  – 8L: Salivary, gastric, biliary, pancreatic secretions
• 1L enters the colon
• 80-100 mL excreted daily
### Abnormal Intestinal Physiology

- Loosening of stools: 50-60mL increase daily fecal water
- Diarrhea: 100mL (1-2%) increase in fecal water
- Many disorders disrupt intestinal fluid and electrolyte absorption by at least this amount
  - Frequent event
  - Extensive differential diagnosis

### Acute Diarrhea: Major Causes

- **Infectious:** Most common
  - Viral: Noroviruses, Rotavirus
  - Bacterial: Food poisoning, C. difficile
  - Parasitic/protozoal
- **Noninfectious**
  - Medications
  - Consumption of poorly absorbed sugars (e.g. sorbitol)
  - Enteral feeding
  - Ischemic colitis
  - Fecal impaction: “paradoxical diarrhea”

### Diagnostic Evaluation

- Majority of cases are mild and self-limited
- 90% of cases need no diagnostic evaluation

### Situations Requiring Additional Testing

- Bloody diarrhea
- Profuse diarrhea leading to dehydration
- Duration >48 hrs or > 6 unformed stools/24 hrs
- Severe abdominal pain: Over age 50
- Temperature > 38.5°C (101.3°F)
- Immunocompromised or elderly (>70 yrs)

### Initial Diagnostic Evaluation

- Stool assessment:
  - Fecal leukocytes
  - Occult blood
  - Presence of both: Dysentery
    - Supports a bacterial etiology for acute diarrhea
    - Campylobacter, Salmonella > E.Coli 0157:H7, Shigella
  - Exception: Nosocomial diarrhea
    - Testing for C. difficile toxin higher yield than fecal leukocytes
- **Wright’s stain**
- **Fecal lactoferrin assay**

### Stools Negative for FOBT and Leukocytes

- Not severely ill
- Treat symptomatically for several days
- Likely etiologies:
  - Viral (>75%)
    - Noroviruses, Rotavirus,
  - Bacteria elaborating preformed toxin
    - S. aureus, B. cereus, C. perfringens
- **Stool culture positive:** 1.5-5.6%
Further Testing: Stool Culture

- Sick/bloody diarrhea
  - Stool culture positive: 40-60%
- Food handlers
- Patients with IBD
- Routine culture:
  - Campylobacter, Salmonella, Shigella
- Notify lab:
  - E. Coli O157:H7, Yersinia, Aeromonas
- Single specimen: Bacteria shed continuously
  - Antibiotic/Chemotherapy within preceding 2 weeks
  - Hospital-acquired diarrhea

Stool For Ova and Parasites

- Cost-effective in high risk groups
  - Persistent diarrhea (>14 days)
  - Community waterborne outbreak
  - Exposure to untreated water (e.g. streams)
  - Daycare center exposure
  - Travel to Russia, Nepal
    - Giardia, Cryptosporidia
    - Homosexual men (Giardia, E.histolytica)
    - Patients with AIDS (Giardia, E.histolytica and others)
  - Intermittent shedding
    - 3 specimens on consecutive days

Who needs Endoscopic Evaluation?

- Bloody diarrhea
  - IBD versus infectious diarrhea
  - Suspected ischemic colitis
- Pseudomembranous colitis
- Immunocompromised or other high-risk patients: Look for CMV
- Flexible sigmoidoscopy versus colonoscopy

Supportive Therapy

- Rehydration: Glucose-Na+ co transporter
  - WHO oral rehydration solution (per liter of water)
    - 20gm glucose, NaCl, NaHCO3, KCL
  - Alternative rehydration solution (per liter of water)
    - 4 tablespoon sugar
    - ½ teaspoon salt
    - ½ teaspoon baking soda
  - Rice-based oral rehydration solution (e.g. Cera-lyte)
  - Fluids for sweat replacement (e.g. Gatorade)
    - Not equivalent to ORS. Sufficient for mild cases
    - Diluted fruit juice plus saltine crackers
  - Dietary modification
    - Lactose free diet for several weeks
    - Boiled starches or cereals with salt
    - BRAT diet: Bananas, rice, apple sauce, toast

Supportive Therapy: Other Measures

- Stools nonbloody and fever low-grade
- Antimotility agents: Decrease peristalsis
  - Loperamide (Imodium)
    - 4mg initially, then 2mg after each loose movement
    - Maximum: 16mg/day for 2 days
  - Diphenoxylate atropine (Lomotil)
    - Central opiate and anti-cholinergic side-effects (atropine)
    - 1-2 tabs t.i.d/qid
- Other agents
  - Pepto-Bismol: 2 tabs every 30 minutes; Can also help vomiting
  - Kapectate
### Empiric Antibiotic Therapy

- Severely ill immunocompetent individuals
  - Fever, bloody diarrhea
  - Dehydration
  - >8 stools/day or symptoms for > 1 week
- Immunocompromised patients
  - AIDS, malignancy, transplant recipients
- Drugs of choice
  - Quinolone: Ciprofloxacin, levofloxacin, norfloxacin (3-5 days)
  - Alternatives: Azithromycin (3 days) and erythromycin (5 days)
- Suspect fluoroquinolone resistance
  - Metronidazole: C. difficile suspected

### Probiotics: Mixed Results

- Prevention of travelers diarrhea
  - Supportive studies/meta-analysis
  - Lactobacillus GG and acidophilus
  - Saccaromyces boulardii: N. Africa, Turkey
- Infectious diarrhea
  - Mixed data: Lactobacillus species
  - Reduce duration of diarrhea: about 24 hours
  - 10 billion CFU within first 48 hours
- Antibiotic associated diarrhea: Preliminary data
  - Supportive meta-analysis: JAMA May 8, 2012; Hempel S)
  - 11,811 participants in 63 RCTs (Many flawed)
  - 42% reduced risk for diarrhea; NNT: 13
  - Many unknowns: Which probiotic? How much?

### Acute Diarrhea

**Select Infectious Causes**

<table>
<thead>
<tr>
<th>Campylobacter jejuni</th>
<th>Enterohemorrhagic E. coli (EHEC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leading cause of bacterial diarrhea: 4-11%</td>
<td>May elaborate 2 proteins:</td>
</tr>
<tr>
<td>Source - Contaminated poultry: 50-70%</td>
<td>- Shiga toxin = verotoxine</td>
</tr>
<tr>
<td>Relapsing course: 15-20%</td>
<td>- Coded by genes Stx1/Stx2</td>
</tr>
<tr>
<td>Drug of choice: Erythromycin</td>
<td>- Adhesine protein= Intimin</td>
</tr>
<tr>
<td>500mg BID or 250mg QID for 5 days</td>
<td>- Coded by Eae gene</td>
</tr>
</tbody>
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### Campylobacter: Complications

- Reactive arthritis/Reiter’s Syndrome: 1%
  - 1-2 weeks after diarrhea onset
  - Self-limited: several months
- Guillain-Barré Syndrome
  - Responsible for 25% cases
  - Symptoms within 3 months of diarrhea onset
  - May be Culture negative but serology positive
- Antibiotics do not prevent these complications

### Enterohemorrhagic E. coli (EHEC)

- Acute renal failure
- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Selective culture required
- Avoid Antibiotics: Increased risk of HUS
**EHEC Infections**

- Most prevalent in U.S.: E. coli 0157: H7
  - Undercooked meat ingestion
  - Predisposing factors: Age < 10 or > 50
  - Watery diarrhea → bloody diarrhea
  - Often afebrile
- STEC 0104:H4
  - New strain: Germany
  - Contaminated vegetables or salad
  - June 23rd 2011:
    - Almost 4000 sick; >12 European nations
    - 862 cases HUS; 43 dead
  - Highlights risk of a global food supply

**C. Difficile: New Therapies**

- Fidaxomicin (Dificid): Macrolide antibiotic
  - FDA approved for CDAD May 2011
  - 200mg BID for 10 days
  - 629 patients with acute C. Difficile infection*
    - Fidaxomyin 200 BID vs. Vancomycin 125 QID X 10 days
    - Cure rate similar: 88.2% vs 85.6%
    - Relapse rate: 15.4% vs 25.3%; P = .005
    - Adverse events: 4.7% vs 1.2%; P = .01 (lab abnormalities)
  - Side effects: Nausea, vomiting, headache, abdominal pain, and diarrhea.
  - Promise: Rifaximin chaser; Fecal bacteriotherapy; Probiotics: Saccharomyces boulardii, Lactobacillus GG


**Chronic Diarrhea:**

**A Systematic Approach**

- Myriad of disorders
- Order of prevalence varies
  - Practice setting
- Optimum evaluation strategy
  - Not established
  - Expert opinion

**MAJOR CAUSES IN DEVELOPED COUNTRIES**

- Irritable bowel syndrome
- Inflammatory bowel disease
  - Ulcerative colitis, Crohn’s disease
  - Microscopic colitis
- Malabsorption syndromes
  - Lactose intolerance
  - Celiac disease
- Medications
- Chronic infections
  - Immunocompromised
  - Bacterial, parasitic

**Categorization of Diarrhea**

- Watery
- Secretory
- Osmotic
- Inflammatory
- Fatty
- Several mechanisms may coexist
Osmotic Diarrhea

- **Hallmarks**
  - Diarrhea stops with fasting
  - Large osmotic gap: > 125 mOsm/kg

- **Mechanism**
  - Ingestion of osmotically active solutes
  - Retention of water in intestinal lumen
  - Electrolyte absorption (Na<sup>+</sup>, K<sup>+</sup>) is normal
  - Large osmotic gap between expected and calculated

- **Stool osmotic gap = 290 – 2([Na<sup>+</sup>] + [K<sup>+</sup>])**

Osmotic or Malabsorptive Diarrhea

- **Exogenous Causes:**
  - Antacids: Mg<sup>2+</sup>
  - Laxatives:
    - Polyethylene glycol (PEG)
    - Poorly absorbed anion (PO₄<sup>3-</sup>, SO₄<sup>2-</sup> , citrate)
  - Sugar substitutes: Sugar-free candy/gum or medication elixirs:
    - Sorbitol, mannitol, Splenda, lactulose
  - Nonabsorbable fats: Olestra

- **Endogenous Causes:**
  - Congenital: Disaccharide deficiencies: Lactose intolerance
  - Acquired
    - Post-enteritis: Lactose intolerance
    - Pancreatic insufficiency
    - Celiac disease

Secretory Diarrhea

- **Hallmarks**
  - Persists with fasting
  - Large volume, watery
  - Small stool osmolar gap < 50 mOsm/kg

- **Exogenous:**
  - Stimulant laxatives: Bisacodyl, senna
  - Prostaglandins, theophylline, colchicine
  - Dietary secretagogues: Ethanol, caffeine, colas

- **Endogenous:**
  - Bile acid malabsorption:
    - Crohn’s ileitis, SB resection, bacterial overgrowth
  - Hormone-producing tumors: VIPoma, gastrinoma

Inflammatory Diarrhea

- **Hallmarks**
  - Mucoid, bloody stool
  - Tenesmus, abdominal pain, fever
  - FOBT positive
  - Fecal leukocytes: Low sensitivity (70%) /specificity (50%)

- **Fecal calprotectin: Zn/Ca binding protein**
  - Derived from neutrophils & monocytes
  - Levels increased in intestinal inflammation
  - Distinguish inflammatory from noninflammatory causes of chronic diarrhea

- **Chronic infections**
  - C. difficile, amebiasis, TB, parasitic pathogens
- **IBD:** Crohn’s, ulcerative colitis
- **Radiation or chemo-induced mucositis**
- **Colonic ischemia**
**Fatty Diarrhea**

- Oil droplets in stool, floating stool
- Diagnosis
  - Positive Sudan III stain: Qualitative
  - 72 hour stool collection
    - Abnormal: > 7gm fat/day
    - Rarely done (limited reproducibility)
  - Stool acid steatocrit
    - Acidify stool
    - Separate fecal homogenate into lipid, water, solid phases; Measure lipid
    - Good correlation with quantitative fecal fat
  - NIRA: Near infrared reflectance analysis
    - Simultaneous measurement of fecal fat, carbohydrates, nitrogen
    - Expanding use in Europe, starting in U.S.

**Fatty Diarrhea: Causes**

- Pancreatic insufficiency
- Crohn’s disease
- Short bowel syndrome
- Bacterial overgrowth

**History**

- Stool characteristics: Watery, bloody, oily
- Epidemiological factors: Travel, sick contacts
- Aggravating/mitigating factors: Diet, stress
- Presence or absence:
  - Fecal incontinence, abdominal pain, weight loss
- Past history:
  - Diabetes, Hyperthyroidism, surgery, XRT, CAD
- Medication history
- Sexual history: Risk factors for AIDS
- Family history: IBD, neoplasm, celiac disease
- Markers of eating disorder, malingering

**PHYSICAL EXAM**

- Extent of fluid and nutritional depletion
- Skin rashes or flushing
- Mouth ulcers
- Thyroid masses
- Arthritis
- Hepatomegaly or abdominal masses
- Anorectal exam: sphincter tone, perianal fistula/abscess
- Scars (suggesting prior abdominal surgery)

**Initial Laboratory Testing**

- Minimum
  - CBC with differential
  - Electrolyte panel
  - Total protein & albumin
  - Thyroid function tests
  - ESR

- Strongly consider
  - Iron studies, vitamin B12, Folate, Prothrombin time
  - Sprue serology

**Initial Stool Testing**

- Fecal occult blood testing
- Fecal leukocytes
- C. difficile toxin: Antibiotic history
- Stool culture
- Stool examination for O & P: Three samples
- ELISA for Giardia antigen
### Endoscopic Evaluation
- Required for evaluation of many patients
- Flexible Sigmoidoscopy
  - Reasonable exam for some patients
- Colonoscopy
  - Patients with iron deficiency anemia
  - Older patients: ≥50 yrs
  - Patients with suspected Crohn’s disease
  - Biopsy normal-appearing mucosa
    - Collagenous/lymphocytic colitis
    - 10% right-sided only
- Upper Endoscopy
  - May be useful to rule-out sprue or Whipple’s

### Difficult to Diagnose Cases
- Common problems overlooked
  - Lactose intolerance
  - Fecal incontinence
  - Review medications again
- Stool culture: Aeromonas and pleisiomonas
- O&P: Cryptosporidium, Microsporidia
- Calculate the osmotic gap

### Difficult Cases: Osmotic
- Laxative screen
  - Inadvertent or surreptitious laxative use
- Stool pH < 5.3
  - Carbohydrate malabsorption (e.g. lactulose, sorbitol)

### Difficult Cases: Secretory
- Plasma peptides:
  - VIP, gastrin, glucagon, calcitonin
- 24 hour urine collection: 5-HIAA
- Imaging: CT scan:
  - Pancreatic neoplasm, intestinal lymphoma, TB
- Imaging: Mesenteric angiography (CT/MRA)
  - Small intestinal ischemia

### Difficult Cases: Inflammatory and Fatty
- Fecal fat assessment
  - Stool sudan stain
- Suspect pancreatic insufficiency
  - Pancreatic imaging: Chronic pancreatitis
  - MRI/MRCP
  - Stool: Fecal elastase, chymotrypsin
    - Reliable only in moderate to severe insufficiency
  - Urine collection: Pancreolauryl test
  - Trial of pancreatic enzymes
- Small bowel follow through
  - Rule-out IBD
- Small bowel biopsies for sprue, Whipple’s
- Trial of antibiotics for bacterial overgrowth

### SYMPTOMATIC THERAPY
- Therapeutic Options:
  - Opiates: most effective
  - Empiric trial of antimicrobial therapy
  - Cholestyramine
  - Octreotide
Summary: Acute Diarrhea

- Infections: Most common cause of acute diarrhea
  - Viral more common than bacterial etiology
  - 90% self-limited, require no further evaluation
- Further evaluation: Sick, bloody diarrhea
  - Sick: Stool for Fecal leukocytes, occult blood
  - Bloody diarrhea: Stool culture
  - Exception: Antibiotic exposure, hospitalized → C. Diff. Toxin
- Empiric Antibiotics: Severely ill, immunocompromised
  - Quinolone
  - Second line: Azithromycin or erythromycin
  - Metronidazole: C. difficile suspected
- Avoid antibiotics: E. coli 0157:H7

Summary (2): Chronic Diarrhea

- Broad differential diagnosis
- Evaluation assisted by:
  - Careful history and physical
  - Categorize the diarrhea:
    - Watery, Inflammatory or Fatty
- Keep in mind possibility of fecal incontinence
- Many patients with chronic diarrhea require endoscopic evaluation
- Acute and chronic diarrhea:
  - Supportive measures: Rehydration, antidiarrheal agents

Question 1:
All of the following pathogens are identified causes of chronic diarrhea except:

a. Aeromonas
b. Plesiomonas
c. Clostridia perfringens
d. Campylobacter
e. Cryptosporidia

Question 2:
In patients with acute diarrhea, empiric antibiotic therapy should be considered in all but one of the following contexts:

a. Fever and bloody diarrhea
b. Moderate to severe travelers diarrhea
c. Known or suspected E. coli 0157: H7
d. Elderly and immunocompromised
e. Hospitalization under consideration

References

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4. Bonis PA, LaMont JT. Approach to the patient with chronic diarrhea. In: UpToDate, Rose, BD (Ed), UpToDate, Waltham, MA, 2011.