Diarrhea

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Objectives

• Review pathophysiology and classification of diarrhea
• Review approaches to evaluation of acute and chronic diarrhea
Diarrhea: Global Perspective

• Globally, there are about two billion cases of diarrheal disease every year.
• In developing countries children < 3 yo have average of 3 episodes of diarrhea every year
• Diarrheal disease is the second leading cause of death in children under 5 yo.
• Diarrheal disease kills 1.5 million children every year.


How do we Define Diarrhea?

• Altered stool frequency
  • Normal range- 3 BMs/day to 3 BMs/week

• Altered stool consistency

• Altered stool weight
  • Normal < 200 grams
### Volume of Fluid in the GI Tract

<table>
<thead>
<tr>
<th>Litters into lumen/24 hours</th>
<th>Litters reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>2</td>
</tr>
<tr>
<td>Saliva</td>
<td>1</td>
</tr>
<tr>
<td>Gastric juice</td>
<td>1-2</td>
</tr>
<tr>
<td>Bile</td>
<td>1-2</td>
</tr>
<tr>
<td>Pancreatic secretions</td>
<td>2</td>
</tr>
<tr>
<td>SB secretions</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>9-10 liters</strong></td>
<td><strong>8-10 liters</strong></td>
</tr>
</tbody>
</table>

The colon can increase absorption to 4-6 liters

Water is absorbed following osmotic forces

### General Mechanisms of Diarrhea:

- Increased fluid volumes:
  - Secretory
  - Osmotic
- Maldigestion
- Malabsorption
Classification

Duration
- Acute
- Persistent
- Chronic

Volume
- Small volume
- Large volume

Pathophysiology- stool characteristics
- Watery
- Fatty
- Inflammatory
Acute, Persistent, Chronic

• Acute diarrhea:
  – Lasts less than 2 weeks
  – Most commonly caused by infectious agents

• Persistent diarrhea:
  – Lasts > 2 but < 4 weeks

• Chronic diarrhea:
  – Lasts more than 4-6 weeks
  – Many causes

ARS Question 1

A newlywed couple travels to Los Angeles and they have dinner at an oyster bar. The following day they board a cruise ship. A day later both develop severe watery diarrhea, abdominal pain and nausea…
What is the most likely cause of their symptoms?

A. *Shigella sonnei*
B. Enterotoxigenic *Escherichia coli*
C. Norovirus
D. Rotavirus
E. *Clostridium perfringens*

Acute diarrhea- Different settings

- Community-acquired (infant, childhood, and adult settings)
- Hospital-acquired
- Traveler’s diarrhea
Acute diarrhea – Community acquired

Infections are the leading cause of acute diarrhea

- Viral- 50% to 70%
  - Begins 1-3 days after exposure
  - Causes changes in small intestinal cell morphology
    - Villous shortening and an increase in the number of crypt cells
- Bacterial-15% to 20%
  - Develop 6–24 hours after ingestion of infected food
- Protozoal infections – 10% to 15%
  - Cause of prolonged diarrhea

Norovirus

- In the United States > 23 million cases of acute gastroenteritis each year are due to norovirus
- Infection develops by swallowing stool-contaminated food or water.
- Outbreaks in the US are often linked to raw oysters.
- Other sources of outbreaks:
  - Ships- naval ships and cruise ships
  - Natural disasters- Hurricane Katrina
Acute diarrhea: Bacterial

- *Campylobacter*
- Nontyphoidal *Salmonella*
- *Shigella*
- *Yersinia*
- EHEC
- EAEC
- C. difficile – 22-44% of cases are community acquired

Question

Nausea and vomiting 12 hours after ingesting fried rice:

A. *Escherichia coli* 0157:H7
B. *Yersinia enterocolitica*
C. *Campylobacter jejuni*
D. *Bacillus cereus*
Answer

*D. Bacillus cereus*

- Produces a heat stable toxin that results in nausea and vomiting
- Diarrhea 12 hours after ingestion of contaminated food

Question

- Diarrhea, vomiting, mesenteric adenitis
- Occasionally mistaken for acute appendicitis

_A. Escherichia coli 0157:H7_
_B. Yersinia enterocolitica_
_C. Campylobacter jejuni_
_D. Bacillus cereus_
Answer

B. *Yersinia enterocolitica*

- Usually transmitted by ingestion of incompletely cooked pork or contaminated dairy products
- Can lead to extraintestinal symptoms of arthritis, erythema nodosum, and aphthous stomatitis

Question

Febrile prodrome, followed by abdominal pain and diarrhea

A. *Escherichia coli* 0157:H7
B. *Yersinia enterocolitica*
C. *Campylobacter jejuni*
D. *Bacillus cereus*
C. Campylobacter jejuni

- Transmitted by eating incompletely cooked poultry or drinking raw milk.
- Febrile prodrome with headache and vomiting
- Abdominal pain, bloody diarrhea
Acute diarrhea pathophysiology

• Secretory
  – Increased chloride secretion, decreased sodium absorption, or increased mucosal permeability

• Inflammatory
  – Cellular invasion or toxins produced by the organism elicit an inflammatory response from the host, causing chemokine secretion and recruitment of immune cells in the intestinal tissue


Traveler’s Diarrhea

• Bacterial infections 50-80% of cases
  – *Escherichia coli* leading cause- ETEC
    • More cases than all other infectious causes combined
  – *Campylobacter*

• Virus
  – In some areas second commonest cause

• Protozoa < 12% of cases

• Most common organisms in persistent diarrhea
  – Cryptosporidium and Giardia
ARS Question 2

A family goes on a one week camping trip. There is a swimming pool on the park grounds, and they go water rafting and fishing. One week later 5 of the 8 develop diarrhea, abdominal cramps, bloating, greasy stools and flatulence.

ARS Question 2

Which is the most likely causative organism?

A. Enteroaggregative E. coli
B. Ameba histolytica
C. Giardia
D. Isospora
Parasitic Infections

- Cryptosporidium and Giardia are the most common parasitic infections in the United States
- **Giardia**
  - Time from infection to symptom onset- 7-14 days
  - The acute phase lasts 2-4 weeks
  - Drinking water from lakes or streams
- **Cryptosporidium**- outbreaks have been linked to:
  - Drinking from contaminated public water supplies
  - Drinking unpasteurized cider
  - Swimming in contaminated pools and lakes

Chronic Diarrhea
Chronic diarrhea

- Prevalence:
  - 3-20% of children worldwide
  - US- ~ 5%
- Approximately 20% of patients with “chronic diarrhea” have normal stool weight
- A specific diagnosis can be reached in ~90% of patients

Chronic Diarrhea – Etiology

<table>
<thead>
<tr>
<th>Developed countries</th>
<th>Developing countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td>Chronic infections</td>
</tr>
<tr>
<td></td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td>Parasitic</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium</td>
</tr>
<tr>
<td>IBD</td>
<td>IBS</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Malabsorption</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>Lactose intolerance</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Celiac disease</td>
</tr>
</tbody>
</table>

Chronic infections | IBD
Classification

Duration
- Acute
- Persistent
- Chronic

Volume
- Small volume
- Large volume

Pathophysiology - stool characteristics
- Watery
- Fatty
- Inflammatory

Chronic Diarrhea: General Approach

Inflammatory
- Watery
- Fatty

Pathophysiology:
- Osmotic
- Secretory

Inflammatory Diarrhea

- Symptoms/signs of inflammatory process:
  - Rectal bleeding
  - Abdominal pain
  - Fever/leukocytosis
  - Fecal leukocytes
- Causes of inflammatory diarrhea:
  - Invasive infections
  - Inflammatory bowel disease
  - Ischemia
  - Radiation

Fatty Diarrhea

- Maldigestion:
  - Pancreatic insufficiency
  - Inadequate luminal bile acids
- Malabsorption:
  - Small bowel mucosal disease
  - Short bowel syndrome
  - Small bowel bacterial overgrowth
ARS Question 3

A 22 year old secretary consults you because of bloating, gas and diarrhea:

- Phone operator in a large corporation
- Stressful job, dry environment. Has dry mouth- drinks soda and chews gum.
- Her weight has increased 3 Kg

ARS Question 3

What is the most likely cause for her symptoms?

A. Small intestinal bacterial overgrowth
B. Fructose and sorbitol ingestion
C. Laxative use
D. Irritable bowel syndrome
Causes of Osmotic Diarrhea

- Maldigestion
  - Lactase deficiency
  - Fructose malabsorption
- Carbohydrate malabsorption - low fecal pH
- Ingestion of non-absorbable solutes resulting in excessive water output
  - Lactulose
  - Sorbitol - chewing gum
  - Magnesium - laxatives, antacids
  - PEG solutions

Fructose malabsorption

Fructose \{\begin{align*}
  & \text{free hexose} \\
  & \text{dissacharide - sucrose} \\
  & \text{polymerized - fructans, inulins, fructo-oligosaccharides}
\end{align*}\}

- Free fructose has limited absorption
  - 50% can not absorb a load of 25 g
  - Average daily intake of fructose ~ 11 to 54 g
- Fructans are not hydrolyzed or absorbed in the small intestine

US Department of Agriculture Food Consumption Survey 1977–1978
Monosaccharide Absorption

- Glucose
- Galactose
- Fructose

SGLT1

GLUT15

Na+

Glucose
Galactose
Fructose

GLUT2

K+

Fructose malabsorption

- The majority of fructose ingested is from high fructose corn syrup added to foods
  - HFCS consumption has risen >1000% between 1970 and 1990
- Increased osmotic load
- Substrate for rapid bacterial fermentation
  - Alterations in gastrointestinal motility
  - Promotes mucosal biota
  - Alters bacterial profile

Secretory Diarrhea

- Abnormal ion transport by the enterocyte:
  - Interference with absorption
  - Active ion secretion
- Stool weight of >1 kg/day (volume >1 L/day) generally indicates secretory diarrhea
Causes of Secretory Diarrhea

- Infections:
  - Vibrio cholera
- Stimulant laxatives
  - Phenolphthalein
  - Senna
  - Sodium docusate
- Bile malabsorption
- Microscopic colitis

Causes of Secretory Diarrhea

- Endocrine
  - Hyperthyroidism
  - Addison’s disease
- Neuroendocrine
  - Carcinoid syndrome
  - Gastrinoma
  - Glucagonoma
  - VIPoma
  - Medullary thyroid cancer
Neuroendocrine tumors

- Vasoactive intestinal polypeptide
  - > 1 liter stool/day, hypokalemia, volume depletion
- Calcitonin
  - Medullary carcinoma of the thyroid, lymph nodes
- Glucagonoma
  - Migratory necrotizing erythema
- Gastrinoma
  - Refractory ulcer disease, reflux, extensive ulceration
- Carcinoid syndrome
  - Hepatomegaly, right-sided heart murmurs, flushing

Diarrhea in Zollinger-Ellison Syndrome

- ZES- triad of upper GI ulcers, acid hypersecretion, and non-beta islet cell tumors of the pancreas.
- Frequency of diarrhea in ZES- as high as 73% but wide variation in different reports.
- Pathogenesis of diarrhea in ZES is multifactorial:
  - Increased volume related to acid hypersecretion
  - Inactivation of pancreatic enzymes by acidic pH
  - Decreased solubility of bile acids in an acid milieu
  - Decreased absorption of sodium and water by the small intestine due to high serum gastrin concentrations and hyperacidity
Chronic Diarrhea: General Approach

- Inflammatory
- Watery
- Fatty

- Osmotic
- Secretory


Stool Testing in Chronic Diarrhea
Fecal Weight

- Normal < 200 g per day

- General rules:
  - >500 g/day → NOT functional
  - >1000 g/day → secretory

Fecal Fat

- Collect after consuming 80-100 g fat diet
- Normal ~ 7 g/day BUT diarrhea can cause mild steatorrhea even when digestion & absorption mechanisms are normal:
  - Fecal fat of 7-14 g/day has low specificity
  - Cutoff of > 14 g/day more specific
Osmotic Gap

Osmotic gap = 290 mOsm – [(Na + K) x 2]

– Gap > 50 → osmotic component likely
– Gap > 125 → pure osmotic diarrhea

Why NOT measure stool osmolality?

• Stool osmolality is accounted mostly by stool electrolytes. Can estimate by 2 X (stool Na + K)
• High MEASURED stool osmolality:
  – Bacterial metabolism of carbohydrates during storage (up to 600 mOsm/kg)
  – Contamination by concentrated urine
  – Ingestion of poorly absorbed carbs or fiber
• Low MEASURED stool osmolality:
  – Contamination by hypotonic urine
  – Addition of water
Other Fecal Tests

• Fecal leukocytes- accuracy depends on reader
• Fecal lactoferrin or calprotectin
• Fecal pH < 5.3 \( \rightarrow \) carbohydrate malabsorption
• Fecal alpha1-antritrypsin:
  – Protein losing enteropathy
  – Different ways to measure
• Laxative screen

ARS Question 4

• A 42 year old man with Crohn’s disease of the terminal ileum undergoes surgery- 25 cm of terminal ileum and the cecum were resected. Two weeks after discharge he goes to the ER because of severe diarrhea and dehydration.

  What is the most likely cause of diarrhea?
ARS Question 4

A. Increased secretion of sodium and water in the colon
B. Recurrent Crohn’s disease
C. Small intestinal bacterial overgrowth
D. Shigella infection

Bile salt induced diarrhea
About 95% of bile salts are reabsorbed in the SB

<table>
<thead>
<tr>
<th>Category</th>
<th>Related conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Ileal dysfunction</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease, resection, bypass</td>
</tr>
<tr>
<td>Type 2</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Possible transporter defect or decreased fibroblast growth factor</td>
</tr>
<tr>
<td>Type 3</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td>Cholecystectomy, diabetes mellitus, celiac disease, pancreatitis</td>
</tr>
</tbody>
</table>
Bile salt induced diarrhea

• Bile acids are synthesized from cholesterol in the liver → transported into bile ducts → stored in the gall bladder → released into the duodenum
• 95% reabsorbed by distal ileum and returned to the liver
• After ileal resection:
  – Bile acids spill into the colon → stimulate water and electrolyte secretion
  – Treatment is bile acid binders

ARS Question 5

• A patient with newly diagnosed microscopic colitis responds promptly to budesonide. The diarrhea recurs when the budesonide is stopped, so she remains on budesonide 3 mg/d long term.
• 2 years later she sees you because she has recurrent diarrhea, feels fatigued and has developed a vertebral fracture.
• Laboratory studies are notable for new iron deficiency anemia.
ARS Question 5

What is the most likely cause for her symptoms?

A. Non-compliance with budesonide
B. C. difficile infection
C. Celiac disease
D. Collagenous sprue

Microscopic Colitis

<table>
<thead>
<tr>
<th>Association with other diseases</th>
<th>Collagenous colitis</th>
<th>Lymphocytic colitis</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td>2% to 9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>21%</td>
<td>19%</td>
<td>16-20%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14%</td>
<td>8-15%</td>
<td>5-10%</td>
</tr>
<tr>
<td>RA</td>
<td>7%</td>
<td>4%</td>
<td>2-3%</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>3.5%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Reynaud's/CREST</td>
<td>2.9%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td></td>
<td>23%</td>
<td>13%</td>
</tr>
</tbody>
</table>
Frequency of associated diseases in celiac disease

- Dermatitis herpetiformis 12-24%
- Hashimoto’s 3-13%
- Diabetes mellitus I 2-8%
- Down syndrome 5-12%
- IgA deficiency 2-3%
- Microscopic colitis 4-5%
- Autoimmune diseases
  - RA, thyroiditis, Sjögren’s
- 13% of celiac disease patients have at least one autoimmune disease

Celiac Symptoms

- “Classic symptoms” (62%)
  - Large volume diarrhea, flatulence, stunted growth, weight loss, anemia, neurological symptoms, metabolic bone disease
- Sub-clinical disease (38%)
  - Fatigue, iron deficiency, abnormal liver tests, miscarriages, depression, anemia, osteoporosis
- 50% of adults do not have diarrhea
SUMMARY

General Mechanisms of Diarrhea:

- Increased fluid volumes:
  - Secretory
  - Osmotic
- Maldigestion
- Malabsorption
<table>
<thead>
<tr>
<th>Classification</th>
<th>Duration</th>
<th>Volume</th>
<th>Pathophysiology- stool characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Small volume</td>
<td>Watery</td>
</tr>
<tr>
<td></td>
<td>Persistent</td>
<td>Large volume</td>
<td>Fatty</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td></td>
<td>Inflammatory</td>
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</table>