1. Pathophysiology of Diarrhea

Pathophysiology of Diarrhea

Laurence S. Bailen, MD
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Division of Gastroenterology
Newton-Wellesley Hospital
2007

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2. Case Presentation

Case Presentation

- 55 yo male alcoholic referred to GI with persistent (>4 weeks) loose non-bloody stool
- Diarrhea often wakes him from sleep
- 6 months earlier: surgical resection of 50cm of ileum due to carcinoid tumor of the ileum
- Reports no fever or abdominal pain
- He has lost approximately 10 lbs

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3. “Diarrhea is the too rapid evacuation of too fluid stoo...

“Diarrhea is the too rapid evacuation of too fluid stools”

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4. The Amazing Intestines

The Amazing Intestines

- 10 liters of ingested fluid and secretions enter the intestine daily
- 90% absorbed in small intestine
- 90% of remaining fluid (~800-1000ml) absorbed in colon
- 80-100ml fluid in stool daily
- Normal stool output: 200 grams/24 hours
- Loose stool: increase of 50-60ml

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5. Diarrhea and Malabsorption: Slide 5

6. Diarrhea

Diarrhea

- Acute Diarrhea
  - Diarrhea lasts less than 4 weeks
- Chronic Diarrhea
  - Diarrhea lasts longer than 4 weeks
- Excess water, electrolytes, fat, other substances in intestinal lumen
- More than 200 grams stool in 24 hours

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7. Is it Diarrhea?

Is it Diarrhea?

- Pseudodiarrhea - more frequent bowel movements but \(< 200g/24\) hrs
- Incontinence - involuntary loss of stool
  -- Anal sphincter dysfunction
  -- Neurologic impairment

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8. Pathophysiology of Diarrhea

Pathophysiology of Diarrhea

- Osmotic
- Malabsorption/Maldigestion/Fatty
- Inflammatory
- Secretory
- Altered Motility

Certain causes of diarrhea have several pathophysiologic mechanisms

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9. Case Presentation

Case Presentation

- 28 year old man complains of abdominal bloating and foul smelling gas. He has intermittent diarrhea after eating ice cream. He has always been able to eat ice cream before.

  - What is the most likely explanation for the patient's symptoms?
  - How would you treat his symptoms?

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10. Osmotic Diarrhea

Osmotic Diarrhea

- Excess amounts of poorly absorbed substances that remain in intestinal lumen
- Substances exert osmotic effect
- Obligate water retention in intestinal lumen
- Lactose, lactulose, magnesium, polyethylene glycol (PEG)

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11. Diarrhea and Malabsorption: Slide 11

**Fecal Osmolar Output**

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12. Lactose Intolerance

**Lactose Intolerance**

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13. Fecal Osmotic Gap

Fecal Osmotic Gap

290 mosm/kg H₂O - 2 ([Na⁺] + [K⁺])

Osmotic diarrhea: > 125

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14. Case Presentation

Case Presentation

- 28 year old man complains of abdominal bloating and foul smelling gas. He has intermittent diarrhea after eating ice cream. He has always been able to eat ice cream before.

  - What is the most likely explanation for the patient's symptoms?
    - Lactose intolerance
  - How would you treat his symptoms?
    - Lactose free diet
    - Lactase enzyme tablets

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15. Pathophysiology of Diarrhea

**Pathophysiology of Diarrhea**

- Osmotic
- Malabsorption/Maldigestion/Fatty
- Inflammatory
- Secretory
- Altered Motility

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16. Case Presentation

**Case Presentation**

- 62 year old woman complains of floating stool with oil droplets around stool. She has lost 10 lbs unintentionally. She also notices that she bruises very easily. She often feels bloated and distended. She had surgery 10 years ago to remove several areas of small intestine after an episode of ischemic bowel.

- What is the most likely cause of her symptoms?
- What tests would you order to help confirm the diagnosis?
- How would you treat her?

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17. Malabsorption

Malabsorption

- Luminal phase
  - Intraluminal maldigestion
- Mucosal phase
  - Mucosal loss (i.e. surgical resection)
  - Mucosal disease
- Transport phase

18. Diarrhea and Malabsorption: Slide 18

I. Luminal Phase
- Reduced nutrient availability
  - Nutrient deficiency (genetic or acquired)
  - Nutrient absorption (malabsorption)
- Impaired fat solubilization
  - Reduced bile salt synthesis
  - Impaired bile salt secretion
  - Bile salt metabolism
  - Increased bile salt synthesis
II. Mucosal Phase
- Extensive mucosal loss (infection, inflammation)
- Diffuse mucosal disease (HIV, tropical sprue, Crohn’s disease, radiation, denudation)
- Enterocyte defects
  - Micronutrient absorption
  - Brush border hydrolase deficiency
  - Transport defects (Herxheimer’s cystitis, SB2 and bile salt esterases)
  - Apoptotic processing (A- or A-like apoproteins)
III. Transport Phase
- Vascular (vascular, ischemic)
- Lymphatic (lymphatic obstruction, radiation, renal failure, enteric fistulas)

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19. **Fat Malabsorption**

**Fat Malabsorption**

- Steatorrhea - “oily” stool
- Possible deficiencies of fat soluble vitamins: A, D, E, K
- Causes:
  - Bacterial overgrowth
  - Pancreatic insufficiency
  - Mucosal diseases
- Diagnosis:
  - Sudan stain of stool; 72 hour stool collection and measurement of fecal fat

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20. **Bile Salt Inactivation**

**Bile Salt Inactivation: Small Intestinal Bacterial Overgrowth Syndrome**

- Normal concentration of bacteria in proximal small intestine: $< 10^4$ organisms
- Conditions that predispose to bacterial overgrowth cause:
  - Intestinal stasis
  - Abnormal connections between proximal and distal bowel

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21. Conditions Predisposing to Bacterial Overgrowth

Conditions Predisposing to Bacterial Overgrowth

Intestinal Stasis
- Anatomic
  - Intestinal strictures
  - Small intestinal diverticulosis
  - Surgical procedures
- Motility disorders
  - Scleroderma
  - Diabetes mellitus

Abnormal connections between proximal and distal bowel
- Resection of ileocecal valve
- Fistulas

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22. Diarrhea and Malabsorption: Slide 22

Small Intestinal Diverticulosis

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23. Pathophysiology of Malabsorption in Bacterial Overgrowth

Pathophysiology of Malabsorption in Bacterial Overgrowth

- Reduced nutrient availability
  - Bacteria consume nutrients
- Bile salt inactivation
  - Excess bacteria deconjugate bile salts
  - Unconjugated bile salts unable to solubilize micelles → fat malabsorption

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24. Diagnosis of Small Intestinal Bacterial Overgrowth Syndrome...

Diagnosis of Small Intestinal Bacterial Overgrowth Syndrome

- Direct aspiration of jejunal contents
- Breath tests
  - $^{14}$C glycocholate
    - Conjugated bile acid – deconjugated by bacteria – $^{14}$C metabolized to $^{14}$CO$_2$
    - Low sensitivity and specificity
    - Not widely used in US
  - $^{14}$C xylose – not widely available
  - Glucose or lactulose
    - Measure expired H$_2$ (breakdown product of bacterial fermentation)

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25. Treatment of Small Intestinal Bacterial Overgrowth Syndrome...

Treatment of Small Intestinal Bacterial Overgrowth Syndrome

- Correct predisposing condition
- Correct nutritional deficiencies
- Antibiotics

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26. Increased Bile Salt Losses

Increased Bile Salt Losses

- Mucosal disease in terminal ileum: Crohn’s disease
- Surgical resection or bypass of ileum
- Mechanism of diarrhea: (cholerrheic diarrhea, bile acid diarrhea)
  - Bile acids that reach colon cause colonic secretion of electrolytes and water
  - Fat malabsorption

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27. Case Presentation

Case Presentation

- 62 year old woman complains of floating stool with oil droplets around stool. She has lost 10 lbs unintentionally. She also notices that she bruises very easily. She often feels bloated and distended. She had surgery 10 years ago to remove several areas of small intestine after an episode of ischemic bowel
  - What is the most likely cause of her symptoms?
    - Fat malabsorption – steatorrhea
    - Small intestinal bacterial overgrowth
  - What tests would you order to help confirm the diagnosis?
    - Lactulose H2 breath test
    - Trial of antibiotics
  - How would you treat her?
    - Correct nutrient deficiency
    - Antibiotics

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28. Defective Nutrient Hydrolysis

Defective Nutrient Hydrolysis

- Lipase inactivation by excess HCl (Zollinger-Ellison syndrome)
- Pancreatic enzyme deficiency
  - Chronic pancreatitis
  - Pancreatic cancer - obstruction of pancreatic duct
- Improper mixing or rapid transit of nutrients

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## Tests for Pancreatic Insufficiency

### Invasive:
- Secretin Stimulation Test
  - Inject secretin IV
  - Aspirated pancreatic juice from duodenum
  - Bicarbonate and amylase levels
  - Low levels consistent with pancreatic exocrine insufficiency

### Non-invasive:
- Fecal Chymotrypsin level
  - Low with pancreatic exocrine insufficiency
- Fecal Elastase level
  - Low in pancreatic exocrine insufficiency
  - Most sensitive/specific fecal test
- Serum trypsinogen level

---

## Diarrhea and Malabsorption: Slide 30

### I. Luminal Phase
- Reduced Nutrient Availability
  - Secretory diarrhea (gastroenteritis, gastritis, cholestasis, enteritis, tumors, malignancy)
  - Nutrient consumption (bacterial overgrowth)

### II. Mucosal Phase
- Extensive mucosal loss (infection, infarction)
- Diffuse mucosal disease (celiac disease, Crohn's disease, gluten enteropathy, inflammatory bowel disease)
- Enterocyte defects
  - Microvillus inclusion disease
  - Brush border hydrolase deficiency
  - Transport defects (Hereditary fructose intolerance, cystic fibrosis, inborn errors of metabolism)
  - Epithelial processing (e.g., glycoprotein synthesis)

### III. Transport Phase
- Nonspecific transport disorders
  - Lipase insensitivity (ZI syndrome)
  - Enzyme deficiency (cystic fibrosis, congenital disorder of glycosylation)
  - Inborn errors of metabolism (congenital disorder of glycosylation, inborn errors of metabolism)

---

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31. Malabsorption: Mucosal Loss

Malabsorption: Mucosal Loss

- Extensive surgical resection
  - Short bowel syndrome
- Extensive infarction

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32. Malabsorption: Mucosal Disease

Malabsorption: Mucosal Disease

- Complication of radiation treatments
- Infections
- Vascular insufficiency (ischemia)
- Inflammatory conditions
  - Crohn’s disease
  - Celiac Sprue

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33. Mucosal Disease: Crohn’s Disease

Mucosal Disease: Crohn’s Disease

Source: L. Bailen

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34. Celiac Sprue

Celiac Sprue

• Gluten sensitive enteropathy
• Reaction against gluten in diet
• Epidemiology: whites (highest in Northern European descent)

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Celiac Sprue: Pathogenesis

- Genetic
- Environmental
- Autoimmune

Celiac Sprue: Pathogenesis

- Ingestion of gliadins, hordeins, and secalins: proteins found in wheat, barley, and rye
  - infiltration of intestinal mucosa with intraepithelial CD8+ lymphocytes and CD4+
    lymphocytes in lamina propria → villous atrophy
- CD4+ T cells mediate disease process
- Genetic: very close association with HLA-DQ2
  (presents peptides to and binds CD4)
  - Lesser association with HLA-DQ8
37. Pathogenesis of Celiac Disease

Pathogenesis of Celiac Disease

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38. Celiac Sprue: Pathology

Celiac Sprue: Pathology

- Villous atrophy: flattening of mucosa, loss of villi
- Increased lamina propria lymphocytes

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39. Celiac Sprue: Clinical Presentation

Celiac Sprue: Clinical Presentation

- Varied - depends on extent of mucosal disease
- Typical: crampy abdominal pain, chronic diarrhea, bloating, weight loss, steatorrhea
- Iron deficiency
- Osteoporosis (vitamin D, Ca^{2+})
- Easy bruising (vitamin K)
- Peripheral neuropathy (vitamin B_{12})

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40. Celiac Sprue: Associated Diseases

Celiac Sprue: Associated Diseases

- Dermatitis herpetiformis
  - IgA deposits in skin
  - Pruritic, blistering

- Small intestinal lymphoma
  - Risk may be less with adherence to gluten-free diet

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41. Celiac Sprue: Diagnosis

Celiac Sprue: Diagnosis

- Biopsy of small intestine during endoscopy
- Blood tests:
  - Anti-gliadin antibodies (IgA and IgG)
  - Anti-endomysial antibodies (IgA)
  - Tissue transglutaminase antibodies

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42. Celiac Disease: Treatment

Celiac Disease: Treatment

- Gluten free diet
- Nutritional supplementation:
  - Iron
  - vitamin D, Calcium
  - vitamin B_{12} (intramuscularly)
- The future: ingesting substances that will breakdown gluten

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43. Drugs Causing Malabsorption

### Drugs Causing Malabsorption

<table>
<thead>
<tr>
<th>Luminal effect</th>
<th>Enterocyte damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin</td>
<td>Direct toxicity</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Brush border enzyme effect</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal effect</td>
<td>Intracellular effect</td>
</tr>
<tr>
<td>Villous Flattening</td>
<td>Neomycin</td>
</tr>
<tr>
<td>Colehicine</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
</tr>
</tbody>
</table>

#### Stricture
- Non-steroidal anti-inflammatory

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44. D-Xylose Test: General Test for Malabsorption

### D-Xylose Test: General Test for Malabsorption

- **Xylose:**
  - Sugar absorbed in duodenum and jejunum
  - Not completely metabolized
  - Excreted in urine in intact form
- **Xylose administered orally and urine collected**
- **Abnormal:** <4g xylose in urine after 25g dose
- **Caveats:**
  - Renal function
  - Bacterial overgrowth
  - Very rapid intestinal transit

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45. Pathophysiology of Diarrhea

**Pathophysiology of Diarrhea**

- Osmotic
- Malabsorption/Maldigestion/Fatty
- Inflammatory
- Secretory
- Altered Motility

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46. Case Presentation

**Case Presentation**

- A 44 year-old man is admitted to the hospital with an acute upper GI bleed due to several gastric and duodenal ulcers seen on an urgent upper endoscopy. One of the duodenal ulcers is in the 3rd portion of the duodenum. The patient also complains of a 1 year history of frequent non-bloody diarrhea. A fecal osmotic gap is very low.

  - What type of chronic diarrhea does this patient have?
  - What is the most likely cause?
  - What is the mechanism to explain the diarrhea?
  - What blood test can you check to make the diagnosis?

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47. Secretory Diarrhea

Secretory Diarrhea

- Abnormal ion transport in intestinal epithelial cells
- Decreased absorption of electrolytes
- Electrolytes: major solutes in intestinal lumen
- Electrolytes account for most of luminal osmolality

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48. Fecal Osmotic Gap

Fecal Osmotic Gap

290 mosm/kg H₂O - 2 ([Na⁺] + [K⁺])

Osmotic diarrhea: > 125
Secretory diarrhea: < 50

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49. Secretory Diarrhea

Secretory Diarrhea

- Congenital defects in ion absorption
- Intestinal resection
- Diffuse mucosal disease
- Abnormal mediators

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50. Abnormal Mediators

Abnormal Mediators

- Changes in cAMP, cGMP, intracellular Ca^{2+}, protein kinases
  - Bacterial toxins
    - E.Coli (cAMP)
    - Cholera (cAMP)
- Endogenous secretagogues
- Non-osmotic laxatives: senna, anthraquinones

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### Abnormal Mediators

- Fatty acids: stimulate colon secretion
- Bile acids: stimulate fluid and electrolyte secretion in colon
- Circulating agents released by neuroendocrine tumors

### Table: Diarrhea and Malabsorption: Slide 52

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mediator</th>
<th>Mechanism of Diarrhea</th>
<th>Other Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zollinger-Ellison syndrome</td>
<td>Gastrin</td>
<td>1 Acid inactivation of pancreatic enzymes and bile salts 2 Intestinal fluid and electrolyte secretion 3 Acid induced damage to intestinal mucosa 4 Increased motility</td>
<td>1 Severe peptic ulcer disease 2 Enzyme deficiencies 3 Tumor in pancreas or duodenum</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Serotonin, substance P, Bradenstock, Melanin, Prostaglandins</td>
<td>1 Increased motility 2 Intestinal fluid and electrolyte secretion</td>
<td>1 Throwing 2 Vomiting 3 Right sided heart failure 4 Hypertension</td>
</tr>
<tr>
<td>Medullary Carcinoma of the thyroid</td>
<td>Calcitonin, Prostaglandins</td>
<td>1 Intestinal fluid and electrolyte secretion 2 Increased motility</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cholera</td>
<td>VIP (vasoactive intestinal peptide)</td>
<td>1 Intestinal fluid and electrolyte secretion</td>
<td>1 Hypokalemia 2 Acute pancreatitis 3 Throwing 4 Hypertension</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>1 Intestinal fluid and electrolyte secretion</td>
<td>1 Necrotic islet cell syndrome (with 2 Diabetes 3 Ameliorates 4 Tumor in pancreas)</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Somatostatin</td>
<td>1 Decreased intestinal nutrient absorption 2 Stricture due to decreased pancreatic secretion</td>
<td>1 Diabetes 2 Toxoplasmosis 3 Cholestasis 4 Pancreatic tumor</td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
<td>Histamine</td>
<td>1 Intestinal fluid and electrolyte secretion, 2 Diabetic hyperviscosity 3 Digital ulcers</td>
<td>1 Throwing 2 Nasal swelling 3 Abdominal pain 4 Epinephrine</td>
</tr>
</tbody>
</table>

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53. **Case Presentation**

**Case Presentation**

- A 44 year-old man is admitted to the hospital with an acute upper GI bleed due to several gastric and duodenal ulcers seen on an urgent upper endoscopy. One of the duodenal ulcers is in the 3rd portion of the duodenum. The patient also complains of a 1 year history of frequent non-bloody diarrhea. A fecal osmotic gap is very low.

- What type of chronic diarrhea does this patient have?
  - Secretory
- What is the most likely cause?
  - Zollinger-Ellison syndrome due to a gastrinoma
- What is the mechanism to explain the diarrhea?
  - Acid inactivation of pancreatic enzymes and bile salts
  - Excess intestinal fluid
- What blood test can you check to make the diagnosis?
  - Gastrin level

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54. **Pathophysiology of Diarrhea**

**Pathophysiology of Diarrhea**

- Osmotic
- Malabsorption/Maldigestion/Fatty
- Inflammatory
- Secretory
- Altered Motility

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55. Altered Intestinal Motility

Altered Intestinal Motility

- Autonomic diabetic neuropathy - "diabetic diarrhea"
- Hyperthyroidism
- After vagotomy (peptic ulcer surgery)
- Irritable bowel syndrome (IBS)

56. Irritable Bowel Syndrome

Irritable Bowel Syndrome

- Chronic or Recurrent
  - Lower abdominal pain
  - Disturbed defecation
  - Bloating
- Not explained by structural or unknown biochemical abnormalities
57. IBS: Symptoms

**IBS: Symptoms**

- Abdominal pain with constipation or diarrhea
- Bloating, gas
- Abdominal distention


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58. IBS: Epidemiology

**IBS: Epidemiology**

- Prevalence in North America is 10%-20%
  - Equally divided between IBS with diarrhea, IBS with constipation, and IBS alternating between diarrhea and constipation
  - Prevalence of each subtype is ~ 5%
- 2:1 female predominance in North American population-based studies


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59. Extent and Impact of IBS

![Extent and Impact of IBS Diagram]

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60. IBS: Pathophysiology

**IBS: Pathophysiology**

- IBS is a condition associated with altered brain-gut communication resulting in:
  - Disturbed gut function and sensation
  - Disturbed CNS function
- IBS patients display:
  - Altered CNS responsiveness to visceral stimuli
  - Visceral hyperresponsiveness to environmental and luminal events (gut)

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61. Diarrhea and Malabsorption: Slide 61

IBS Physiology

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62. Diarrhea and Malabsorption: Slide 62

IBS – Post Rectal Stimulation Activation (PET) in Normals and IBS

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63. Role of the Enteric Nervous System

Role of the Enteric Nervous System

- ENS contains many neurotransmitters, including 5-HT, substance P, VIP, and CGRP
- ENS controls motility and secretory functions of the intestine
- ENS functions autonomously, but may be modified by the parasympathetic and sympathetic nervous systems

VIP = vasoactive intestinal peptide.
CGRP = calcitonin gene-related peptide.

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64. Evolution of Hypotheses in IBS

Evolution of Hypotheses in IBS

2003 And Beyond
- Abnormal Motility
- Visceral Hypersensitivity
- Brain-Gut Interaction
- 5-HT-Mediated Visceral Sensitivity and Gut Motility


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65. Selected Mediators of Motility and Visceral Hypersensitivity...

Selected Mediators of Motility and Visceral Hypersensitivity

- Motility:
  - Serotonin
  - ACh
  - ATP
  - Motilin
  - Nitric oxide
  - Somatostatin
  - Substance P
  - Vasoactive intestinal polypeptide (VIP)

- Visceral hypersensitivity:
  - Serotonin
  - Bradykinin
  - Tachykinins
  - Calcitonin gene-related peptide (CGRP)
  - Neurotropins

66. Serotonin and Enterochromaffin (EC) Cells in Altered GI Motility...

Serotonin and Enterochromaffin (EC) Cells in Altered GI Motility

Diarrhea

Increased Circulating 5-HT*

Increased Number of EC Cells in Postinfectious IBS**

Increased Number of EC Cells in Postinfectious IBS**

Decreased Number of EC Cells in Constipation

Increased Number of EC Cells in Constipation

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Rome Criteria

- At least 12 weeks of continuous or recurrent symptoms:
  - Abdominal pain or discomfort
    - Relieved with defecation, or
    - Associated with a change in frequency of stool, or
    - Associated with a change in consistency of stool
- 2 or more of the following, at least on 1/4 of occasions or days:
  - Altered stool frequency
  - Altered stool form
  - Altered stool passage
  - Passage of mucus
  - Bloating or feeling of abdominal distention

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IBS Diagnosis

**Physical:**
- Abnormal exam
- Fever
- Positive occult stool

**Historical:**
- Weight loss
- Onset in older patients
- Nocturnal awakening
- Family Hx CA/IBD

**Initial Labs:**
- Hgb ↓
- WBC ↑
- ESR ↑
- Abnormal chemistry

**Red Flags**

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69. Therapeutic Options for Patients with IBS

**Therapeutic Options for Patients with IBS**

- Antispasmodics: hyoscyamine and dicyclomine
- Bulking agents
- Antidiarrheals
- Antidepressants
- Alosetron
- Tegaserod
- Behavioral therapy


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70. Case Presentation

**Case Presentation**

- 55 yo man referred to GI clinic with persistent (>4 weeks) loose non-bloody stool
- Diarrhea often wakes him from sleep
- 6 months earlier: surgical resection of 50cm of ileum due to carcinoid tumor of the ileum
- Reports no fever or abdominal pain
- He has lost approximately 10 lbs

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Case Presentation

- Stool specimens are negative
- Stool specimen for fecal fat negative
- Blood tests:
  - Hct 42%
  - Normal electrolytes
  - Normal albumin
- Normal upper endoscopy and colonoscopy

Explanations for Diarrhea

- Bile salt malabsorption
  - Cholerrheic diarrhea
- Bacterial Overgrowth syndrome
- Secretagogue
- Pancreatic insufficiency – chronic pancreatitis
- Alcohol
- Possible nutrient deficiencies:
  - vitamin A, D, E, K
  - vitamin B₁₂

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