Diarrhea: Managing exocrine pancreatic insufficiency (EPI), irritable bowel syndrome (IBS) and small bowel bacterial overgrowth (SIBO)

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Case Report

- 60-year-old diabetic man with loose stools for 6 months
- Stools never fully formed, greasy, no blood
- No abdominal pain, some bloating, weight loss of 15 pounds
- Blood sugar control variable, HbA1c=8%
- Mild peripheral neuropathy
- Physical examination: normal except for mild abdominal distention, tympany, reduced basal sphincter tone
Evaluation of Diarrhea

- History
- Physical examination, including digital rectal examination
- Questions:
  - Acute or chronic?
  - Watery, fatty or inflammatory?
  - Painful or not painful?
  - Associated diseases?
  - Associated findings?
  - Scenario?
- Basic laboratory evaluation (if diarrhea severe or prolonged)
Basic Laboratory Evaluation

• Acute diarrhea (<4 weeks)
  – Blood tests: CBC, CMP, CRP
  – Stool tests
    • Occult blood
    • Calprotectin or lactoferrin
    • Culture, O&P, protozoal antigens, *Clostridium difficile* test
      -or-
      Multiplex PCR assay
Multiplex PCR Assays

• Bacteria
  – Campylobacter
  – Clostridium difficile
  – E. coli
  – Salmonella
  – Shigella
  – Vibrio cholerae

• Viruses
  – Adenovirus
  – Norovirus
  – Rotavirus A

• Parasites
  – Cryptosporidium
  – Entamoeba histolytica
  – Giardia
Basic Laboratory Evaluation

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    - Calprotectin or lactoferrin
    - Culture, O&P, protozoal antigens, *Clostridium difficile* test
      - or-
      Multiplex PCR assay

- Chronic diarrhea (>4 weeks)
  - Blood tests: CBC, CMP, CRP, anti-tissue transglutaminase
  - Stool tests
    - Occult blood
    - Calprotectin or lactoferrin
    - Culture, O&P, protozoal antigens, *Clostridium difficile* test
      - or-
      Multiplex PCR assay
    - Qualitative or quantitative stool fat
Case Report

• Questions:
  – Acute or chronic?
  – Watery, fatty or inflammatory?
  – Painful or not painful?
  – Associated diseases? diabetes
  – Associated findings? sphincter weakness
  – Scenario? chronic diarrhea in a diabetic, possible steatorrhea

• Basic laboratory evaluation:
  – CBC, CMP, CRP normal, except for ↑blood sugar of 120 mg/dL
  – IgA tTG: normal
  – Stool occult blood (-)
  – Fecal calprotectin: WNL
  – Multiplex PCR assay (-)
  – Sudan stain (+) for ↑ fat
Steatorrhea in Diabetes Mellitus

• Could be of any etiology

• Diabetics more likely than non-diabetics to have:
  – Pancreatic exocrine insufficiency
  – Small bowel bacterial overgrowth
  – Celiac disease
Diagnosis of Exocrine Pancreatic Insufficiency

• Steatorrhea
  – Confirm with **quantitative** stool collection
• Look for evidence of panmalabsorption
  – ↓ stool pH suggestive of carbohydrate malabsorption
• Look for evidence of pancreatic disease
  – CT or MRI imaging (MRCP preferred), endoscopic ultrasound
• Exclude other causes of malabsorption
  – Small bowel biopsy, test for small bowel bacterial overgrowth
• Stool elastase or chymotrypsin only suggestive
Diagnosis of Exocrine Pancreatic Insufficiency

- Secretin—CCK test
  - Gold standard
  - Technically challenging
  - Rarely done

- Therapeutic trial
  - Frequently done
  - Rarely done correctly
    - Need large dose of enzymes
    - Need to document improvement in steatorrhea with enzymes
Treatment of Exocrine Pancreatic Insufficiency

• Pancreatic enzyme replacement therapy
  – Products had been grandfathered by FDA
  – Restudied using modern placebo-controlled study designs
  – Larger doses used: more effective in reducing steatorrhea
    • 30,000 – 80,000 lipase units per meal in adults
  – Dosing with food to promote mixing
  – Use with snacks as well as full meals
  – No need to limit fat intake if adequate enzyme replacement is given
Dosing Pancreatic Enzymes Appropriately

- Most products are enteric-coated to avoid denaturing of enzymes by gastric acid; gastric acid suppression not needed
- Normal pancreas produces 750,000 units lipase activity with each meal
- Output has to be reduced by 90% to produce steatorrhea
- Replacing ~75,000 units per meal seems to be optimal, but does not completely reverse steatorrhea
- Residual secretion + gastric lipase may reduce dose needed
### Pancreatic Enzyme Replacement Products

*All products of porcine origin*

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Manufacturer</th>
<th>Lipase content (USP units/pill or tablet)</th>
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<tbody>
<tr>
<td>EC microspheres</td>
<td>AbbVie</td>
<td>3000—36000</td>
</tr>
<tr>
<td>EC microtablets</td>
<td>Janssen</td>
<td>2600—21000</td>
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<tr>
<td>EC microspheres + bicarbonate</td>
<td>Digestive Care</td>
<td>4000—16000</td>
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<tr>
<td>EC beads</td>
<td>Aptalis (Allergan)</td>
<td>3000—40000</td>
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<tr>
<td>Non-enteric coated tablet</td>
<td>Aptalis (Allergan)</td>
<td>10440—20880</td>
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Small Intestinal Bacterial Overgrowth

• Traditional variety: a cause of steatorrhea
  – Occurs when mechanisms that reduce overgrowth are compromised
    • Achlorhydria or hypochlorhydria, PPI use
    • Immune deficiencies (e.g., IgA deficiency)
    • Motility disorders of small bowel, narcotic use
    • Anatomic alterations
  – Fat malabsorption due to bile deconjugation
  – Diagnosis with quantitative culture of SB aspirate, breath tests

• “New” variety: a cause of ‘functional’ symptoms
Diagnosis of SIBO

• **Gold standard: quantitative culture of jejunal aspirate**
  – Technical challenges
    • Specimen collection: luminal aspirate
    • Aerobic/anaerobic culture
    • Dilution/quantitation
  – >$10^5$ CFU/mL considered abnormal

• **Breath hydrogen test**
  – Technical challenges
    • Substrate: glucose, xylose, lactulose
    • Time course
    • Definition of an abnormal result
Problems with Breath Testing for SIBO

- Rapid transit
- Absorbability of carbohydrate substrate in small bowel
  - Glucose fully absorbed in initial 100 cm of small bowel
  - Lactulose unabsorbed in small bowel – all gets to colon flora
- 10—20% of people lack H₂ producing flora (measuring CH₄ output may help)
- Threshold for positive tests not standardized (10 or 20 ppm)
- Sensitivity ~70%

Proposed Solutions

- Xylose as substrate – best dose undefined
- Use of scintigraphy with lactulose testing
- Use of isotopically-labeled bile acid
Current Recommendations for SIBO Diagnosis

• For **proximal** small bowel overgrowth
  – Aspirate for quantitative culture
  – Isotopically-labeled 1 g d-xylose breath test
  – Glucose breath hydrogen test

• For **distal** small bowel overgrowth
  – Ideal test not devised
  – Isotopically-labeled bile acid breath test
  – ? Aspiration via double-balloon enteroscopy
Treatment of SIBO

• Effective antibiotic therapy is key
• Few controlled studies
• Choose agents that kill gram-negative aerobic enteric flora and/or anaerobes
  – Trimethoprim-sulfamethoxazole
  – Amoxicillin
  – Fluoroquinolones
  – Tetracyclines
  – Metronidazole
Rifaximin

- Poorly absorbable antibiotic, rifaximin, has been much studied lately
- Currently FDA-approved for treatment of travelers’ diarrhea (200 mg TID X 3 days), hepatic encephalopathy (550 mg BID), IBS-D (550 mg BID X 14 days)
- Doses used in studies: 400—550 mg TID X 7—14 days, more is better
- Did better than chlortetracycline for relief of symptoms and breath hydrogen excretion

Treatment of SIBO

- Initial course of treatment → assess response
- Relapse likely because fundamental process (e.g., stasis, immune problem) not addressed by antibiotics, but time to relapse uncertain
- Rotation of antibiotics to avoid resistance advised, but unproven
- Continuous therapy should be avoided
Irritable Bowel Syndrome with Diarrhea

• Diagnosis
  – Rome IV criteria
    • Discomfort downgraded
  – Serology testing
    • Anti-cytolethal distending toxin B antibody
    • Anti-vinculin antibody

• Treatment
  – Rifaximin
  – Eluxadoline
Rome IV Criteria for IBS

• Removal of “discomfort” from criteria – has to be “pain”

• Introduction of concept of “spectrum” of symptoms
  – IBS-D – chronic diarrhea
  – IBS-C – chronic constipation

• Redefinition of subtypes (D, C, M, U) from proportion of all stools with specified abnormal stool form to proportion of stools while having symptoms (i.e., pain) with specified abnormal stool form
Many cases of IBS-D develop in wake of bacterial diarrhea
  – “Post-infectious IBS”
Bacterial diarrhea often is mediated by enterotoxins
In some patients antibodies to cytolethal distending toxin B develop (CdtB); these can cross-react with vinculin, a normal protein found in intestinal epithelium and enteric nerves
  – IBS as an autoimmune disease?
Abnormal titers of anti-CdtB or anti-vinculin are found in 50% of IBS-D patients

Treatment of IBS-D with Rifaximin

- Treatment with 550 mg TID for 14 days → followed up for 4wks
- Adequate relief of symptoms for 2 of 4 weeks after treatment in 41% (vs 32% with placebo)
- Composite responder rate 47% (vs 38% with placebo)
- 36% had no recurrence for up to 18 weeks after open-label treatment; of those who responded initially, then relapsed 38% responded to retreatment (vs 31% with placebo)
- FDA-approved for up to 3-two week courses of therapy
- Seems to be very safe; no evidence for bacterial resistance
Treatment of IBS-D with Eluxadoline

- Eluxadoline is a μ-opiate agonist/δ-opiate antagonist
- After 26 weeks of treatment with 100 mg BID, 31% of IBS-D patients met composite endpoint (vs 19.5% with placebo)
- Stool frequency, urgency, and bloating improved significantly
- Main side-effects: constipation (8%), nausea (7%)
- Discontinuation due to constipation: 2%
- Other side-effects: “sphincter of Oddi dysfunction,” pancreatitis in <1%; avoid use of alcohol, do not use if previous cholecystectomy
• Quantitative stool collection: 500 g/24h, fat output 60 g/24h, pH 5.5
• CT scan: normal
• Had upper endoscopy to investigate steatorrhea
  – Normal small bowel biopsy
  – Quantitative culture of duodenal aspirate – no growth
• Tried on pancreatic enzyme therapy
  – Symptoms improved
  – Qualitative stool fat (Sudan stain) reverted to negative
Additional Reading


Post-Test Questions