Evaluation and Management of Irritable Bowel Syndrome with Diarrhea

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Learning Objectives

- Describe the role of Rome-IV criteria and other tests in diagnosis
- Differentiate subtypes of IBS
- Review the benefits and limitations of IBS prescription medications
- Individualize treatment for IBS based on current evidence-based guidelines
Case Study

- A 32-year-old science teacher is referred for further management of abdominal symptoms which started after a trip to Mexico one year ago where he and his wife both developed severe food poisoning.

- Since then he has had daily loose, watery, non-bloody, urgent bowel movements and feels somewhat bloated and distended.

- He reports daily pain in his lower abdomen that worsens just before a bowel movement and improves after having urgent diarrhea.

- His wife’s symptoms have completely resolved.
His weight has remained stable. He does not report fevers, chills, rashes, oral ulcers, myalgias or arthralgias.

He does not take any medications or use alternative therapies. Past medical and surgical history are unremarkable.

He does not have a family history of irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), celiac disease, or colorectal cancer.
He went to an urgent care clinic 3 months after the onset of symptoms.

A complete blood count, complete metabolic panel, and stool studies were all normal.

A 2-week trial of a lactose-free diet did not help.

Loperamide taken as needed has not helped his abdominal pain, bloating, or diarrhea.

The patient has done some research and brings several questions to the visit.

The discussion in response to his questions serves as the basis for this presentation.
IBS Overview

- IBS is a common functional bowel disorder characterized by recurrent abdominal pain associated with altered bowel habits\(^1\)
- Abdominal bloating and distension are also often present, but neither is required to make the diagnosis of IBS\(^1\)

<table>
<thead>
<tr>
<th>IBS Classification(^1)</th>
<th>Type of bowel habit alteration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-D(^†)</td>
<td>Diarrhea-predominant</td>
</tr>
<tr>
<td>IBS-C</td>
<td>Constipation-predominant</td>
</tr>
<tr>
<td>IBS-M</td>
<td>Mixed-type has alternating periods of diarrhea and constipation</td>
</tr>
</tbody>
</table>

*Based on stool form only on days with at least one abnormal bowel movement  
*Most common subtype, affecting approximately 40% of patients\(^2\)

Rome IV Criteria for IBS

- Recurrent abdominal pain at least 1 day/week (on average) in the last 3 months associated with ≥ 2 of the following:
  - Related to defecation
  - Associated with a change in frequency of stool
  - Associated with a change in form of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

- Intended to facilitate making a positive diagnosis of IBS as opposed to a diagnosis of exclusion
- A key difference from Rome III: classifies IBS subtypes by the proportion of days per month with symptomatic bowel movements rather than measuring all days

According to Rome IV criteria, IBS is NOT a diagnosis of exclusion.
Role of Diagnostic Testing

- Diagnosis is based on a thoughtful history and limited physical examination to assess the presence of the distinguishing symptom of IBS
- New to Rome IV criteria is the use of limited testing to consider in patients without alarm symptoms\(^1\)
  - Complete blood count to ensure the absence of anemia
  - C-reactive protein or fecal calprotectin to lower suspicion for IBD and prevent indiscriminate use of colonoscopy
  - Celiac serologic testing

Conditions That Mimic IBS

- Lactose intolerance
- Fructose intolerance
- Small intestine bacterial overgrowth (SIBO)
- Celiac disease
- Inflammatory bowel disease
- Microscopic colitis
- Functional diarrhea
- Functional constipation

Alarm Signs & Symptoms Warranting Further Investigation

- Age over 50 years without prior colon cancer screening
- Presence of overt GI bleeding
- Nocturnal passage of stool
- Unintentional weight loss
- Family history of inflammatory bowel disease or colorectal cancer
- Recent changes in bowel habits
- Presence of a palpable abdominal mass or lymphadenopathy

IBS may be a brain-gut disorder

Brain-Gut Pathway

- Genetic predisposition and environmental factors (including modeling, reward behavior, and cultural factors)
- CNS alterations (stress pathway activation, anxiety, depression)
- Alterations in gut epithelium and microbiome, increased risk of intestinal infection
- Changes in tight junction and intestinal permeability
- Localized inflammation, edema, or both; infiltration of inflammatory cells (e.g., mast cells, eosinophils); release of cytokines
- Changes in visceral neuromuscular function
- Development of IBS symptoms

...and a gut-brain disorder

- Infection, inflammation, food antigens, and medications
- Changes in tight junction and intestinal permeability
- Alterations in gut microbiome
- Infiltration of inflammatory cells, changes in immunocyte function, cytokine release
- Development or exacerbation of IBS symptoms
- Changes in CNS function (new-onset anxiety, depression, somatization)

**IBS as a gut-brain disorder**

- Increasing evidence implicates the GI microbiota in the pathogenesis of IBS\(^1\)
- The intestinal microbiota in patients with IBS is altered compared with healthy controls\(^2-4\):
  - General decrease in diversity
  - Decreases in *Bifidobacterium* and *Lactobacillus* species
  - Increase in *Gammaproteobacterium* species
- Infectious gastroenteritis is the strongest risk factor for IBS-D\(^5,6\)
  - Up to one third of individuals who have had IGE develop IBS-D (post-infectious IBS) with symptoms lasting months to years

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Natural History of IBS

- ~50% of patients have persistent symptoms 3-5 years following diagnosis
- No therapy has been proven to alter the natural history of IBS in the long term
- Uncertain if newer medications have altered natural history

Treatment Overview

- Treatment of IBS-D is directed at decreasing symptoms of abdominal pain, bloating, and diarrhea

- Treatment should be individualized in a stepwise manner according to symptoms and severity\(^1,2\)

- Moderate symptoms affecting home, social, and work life will likely require scheduled pharmacologic treatment with one or more of a range of options

- For patients with severe symptoms, consider referral to a gastroenterologist for specialty care, combination therapy, and possibly psychological or behavioral intervention (eg, cognitive behavioral therapy, hypnosis, and various relaxation methods).\(^1,3-4\)

Severity-based Treatment

- **Mild**
  - Education, reassurance
  - Diet, lifestyle advice
  - Loperamide as needed

- **Moderate**
  - Manage stress
  - Pharmacologic therapy

- **Severe**
  - Pharmacologic therapy
  - Psychological treatment
  - Goal is improved function vs. complete resolution of symptoms
### Therapies for IBS-D by Symptom

<table>
<thead>
<tr>
<th>Abdominal pain/Discomfort</th>
<th>Bloating/Distension</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Alosetron (Lotronex)</td>
<td>▪ Rifaximin</td>
<td>▪ Alosetron</td>
</tr>
<tr>
<td>▪ Rifaximin (Xifaxan)</td>
<td>▪ Probiotics*</td>
<td>▪ Eluxadoline (Viberzi)</td>
</tr>
<tr>
<td>▪ Antidepressants* (TCA, SSRI)</td>
<td>▪ Diet*</td>
<td>▪ Rifaximin</td>
</tr>
<tr>
<td>▪ Smooth muscle antispasmodics (dicyclomine, hyoscyamine*)</td>
<td></td>
<td>▪ Cholestyramine*</td>
</tr>
<tr>
<td>▪ Low FODMAP diet*</td>
<td></td>
<td>▪ Diphenoxylate-atropine*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Loperamide*</td>
</tr>
</tbody>
</table>

*Not approved for IBS-D by the US FDA

SSRI, serotonin selective reuptake inhibitor; TCA, tricyclic antidepressant
First-line lifestyle and dietary modifications may provide adequate symptom relief

- Exercise²,³
- Stress reduction (eg, meditation, counseling)⁴
- Attention to impaired sleep⁴
- Limit intake of potential dietary triggers (eg, alcohol, caffeine, spicy foods, fat, gas-producing foods)¹
- Soluble fibers with a low rate of fermentation (eg, psyllium) may have some benefit in addressing diarrhea¹
- Gluten-free diet may help reduce symptoms, but data do not support additive effect over a low-FODMAP diet alone⁵

Low FODMAP Diet

- Restricts short-chain carbohydrates known collectively as fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)
  - Found in such foods as wheat, broccoli, legumes, dairy, apples, and stone fruits\(^1\)-\(^5\)
- Approximately 70% response rate in reducing abdominal pain, bloating, diarrhea, abdominal distention, and flatulence\(^1\)-\(^5\)
- Should be guided by a dietician due to complexity and potential risks for inadequate nutritional intake\(^3\)
- May have durable efficacy even with reintroduction of FODMAPs\(^3\)

ACG 2014 Guidelines concluded¹:

- “Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS”
  - Recommendation: weak
  - Quality of evidence: low

The most convincing data for efficacy are derived from multi-strain probiotics containing both *Lactobacillus* and *Bifidobacteria* with a concentration of 10 billion CFU/day or less²,³

Antibiotics

- Neomycin
  - Symptom improvement but rapid bacterial resistance

- Rifaximin
  - Oral, non-systemic antibiotic associated with a low bacterial resistance profile and a favorable side-effect profile\(^1,2\)
  - FDA-approved for the treatment of adults with non-constipation IBS, including IBS-D

Rifaximin TARGET 1 and TARGET 2 Trials

- Two phase 3 randomized controlled trials; N=1260\(^1\)
- Rifaximin 550 mg TID vs placebo for 14 days
- 40.7% vs. 31.7% with adequate relief of global symptoms at 4 weeks after treatment (P<0.001)
- Incidence of adverse effects (headache, upper respiratory infection, nausea, and diarrhea) was comparable to placebo

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Adequate relief was defined as self-reported relief from symptoms for at least 1 week of every 2-week period.¹

Eluxadoline for IBS-D

- Mixed mu (μ) and kappa (κ) opioid receptor agonist / delta (δ) opioid receptor antagonist
- Low systemic absorption and bioavailability
  - Low potential for drug–drug interactions

Eluxadoline Primary Endpoint: composite responders – pooled data

**Responders (%)**

<table>
<thead>
<tr>
<th></th>
<th>Weeks 1–12</th>
<th></th>
<th>Weeks 1–26</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=808</td>
<td>N=806</td>
<td>N=809</td>
<td>N=808</td>
</tr>
<tr>
<td>PBO</td>
<td>16.7</td>
<td>26.2</td>
<td>27.0</td>
<td>19.5</td>
</tr>
<tr>
<td>75 mg ELX</td>
<td>Δ 9.5*</td>
<td></td>
<td>Δ 7.2*</td>
<td></td>
</tr>
<tr>
<td>100 mg ELX</td>
<td>Δ 10.3*</td>
<td></td>
<td>Δ 11.5*</td>
<td></td>
</tr>
</tbody>
</table>

- **IBS-D - Rome III**
- 1-week baseline
  - BSS ≥5.5 (scale 1–7)
  - WAP >3.0 (scale 0–10)
  - GSS ≥2.0 (scale 0–4³)

*P<0.001 vs placebo; Study 3001 – N=1281; Study 3002: N=1146; mean age = 45 y; 66% women; Rome III

Safety of Eluxadoline in Patients with IBS with Diarrhea

- 2,814 IBS-D patients (Rome III criteria)
  - 1 phase 2 study (12 wks)
  - 2 phase 3 studies (26 and 52 wks)
- Placebo vs. eluxadoline (75 or 100 mg BID)
- Most frequent AEs:
  - Constipation (2.5% vs. 7.4% vs. 8.1%)
  - Nausea (5.0% vs. 8.1% vs. 7.1%)
- 10 Patients had Sphincter of Oddi Spasm (0.5%); all with prior cholecystectomy

Alosetron for IBS-D

- A 5-HT₃ antagonist
- Reduces stool frequency and abdominal pain; improves urgency
- Treatment population
  - Women with chronic, severe IBS-D who have failed other treatments
  - Dose: 0.5-1.0 mg QD to BID
- Patient education regarding possible serious adverse effects of severe constipation or ischemic colitis
  - 0.95 cases of ischemic colitis/1000 patient-years
  - 0.36 cases of severe constipation/1000 patient-years
- If ischemic colitis occurs, it is usually within the first month of therapy

Quality of evidence: moderate.
## Alosetron: Therapeutic Gain for IBS-D

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Female, %</th>
<th>Response: Alosetron, %</th>
<th>Response: Placebo, %</th>
<th>Therapeutic Gain, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camilleri¹</td>
<td>370</td>
<td>53</td>
<td>60</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Camilleri²</td>
<td>647</td>
<td>100</td>
<td>41</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Camilleri³</td>
<td>626</td>
<td>100</td>
<td>43</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Lembo⁴</td>
<td>801</td>
<td>100</td>
<td>73</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td>Jones⁵*</td>
<td>623</td>
<td>100</td>
<td>58</td>
<td>48</td>
<td>10</td>
</tr>
</tbody>
</table>

*Comparison mebeverine† instead of placebo.
†Mebeverine not available in the US.

Selected Pharmacologic Therapies for IBS-D That Do Not Affect the Gut Microbiome*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Efficacy by Symptom</th>
<th>Dose Regimen</th>
<th>Side effects/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide* 1-6</td>
<td>[µ-opioid agonist; decreases peristalsis, prolongs GI transit time, reduces fluid secretion in intestinal lumen]</td>
<td>Improves stool frequency, consistency, and urgency, but not bloating or in abdominal pain3-6</td>
<td>2 to 8 mg/day in divided doses</td>
<td>Abdominal cramps, constipation, bloating, nausea</td>
</tr>
<tr>
<td>Tricyclic Antidepressants* 7-11</td>
<td>[Effects on pain perception, mood, and GI motility]</td>
<td>May improve abdominal pain and diarrhea</td>
<td>10 to 25 mg at bedtime, then titrate up gradually based on symptom response and tolerability to 50-75 mg once daily</td>
<td>Drowsiness, dry mouth, dry eyes, orthostatic hypotension</td>
</tr>
</tbody>
</table>

*Not approved for IBS-D in the United States

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<th>Therapy, Mechanism of Action</th>
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</table>
| Bile Acid Sequestrants* ¹⁻⁴  
[Bind bile acids in the intestine to prevent free bile acid from stimulating electrolyte and water secretion in the colon] | Diarrhea - may be considered after other therapies targeting diarrhea have been unsuccessful | Cholestyramine 9 grams 2 to 3 times daily, colestipol 2 g once or twice daily, or colesevelam 625 mg once or twice daily | Constipation, nausea |

*Not approved for IBS-D in the United States

Summary

- An individualized approach to the management of patients with IBS-D begins with reassurance, explanation, and a positive diagnosis that includes limited testing to rule out disorders that may mimic IBS-D (e.g., IBD or celiac disease).
- Treatment options should be considered in the context of symptoms, possible etiologic factors, and benefits vs risks.
- Treatment typically begins with dietary modifications, increased exercise, and stress reduction.
Summary (cont)

- A probiotic may be considered, particularly for bloating, and a tricyclic antidepressant for pain
- Diarrhea may be ameliorated with loperamide or a bile acid sequestrant
- For persistent and/or more severe symptoms, rifaximin, eluxadoline, or alosetron may be considered, with the specific choice guided by patient-specific factors