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

Case Study (cont.)

- 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
Case Study (cont.)

- 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\(^2\)

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Rome IV Criteria for IBS

Recurrence 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:\n  - 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

...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
- The intestinal microbiota in patients with IBS is altered compared with healthy controls:
  - General decrease in diversity
  - Decreases in *Bifidobacterium* and *Lactobacillus* species
  - Increase in *Gammaproteobacterium* species
- Infectious gastroenteritis is the strongest risk factor for IBS-D:
  - Up to one third of individuals who have had IGE develop IBS-D (post-infectious IBS) with symptoms lasting months to years

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\(^1,2\)
- 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>
</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**

- Exercise\(^2,3\)
- Stress reduction (eg, meditation, counseling)\(^4\)
- Attention to impaired sleep\(^4\)
- 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 diarrhea\(^1\)
- Gluten-free diet may help reduce symptoms, but data do not support additive effect over a low-FODMAP diet alone\(^5\)


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**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\(^3\)

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**Probiotics**

- ACG 2014 Guidelines concluded:\(^1\):
  - “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 less\(^2,3\)


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**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
- 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


Rifaximin: Durability of Effect

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

*Figure 4. Percentage of Patients with Adequate Relief of Global IBS Symptoms in the TARGET 1 and TARGET 2 Studies Combined.*
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

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.
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## 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>

¹Comparison mebeverine⁴ instead of placebo.
⁴Mebeverine not available in the US.


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

<table>
<thead>
<tr>
<th>Therapy, 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 ⁴⁻⁶</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>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

Selected Pharmacologic Therapies for IBS-D that Do Not Affect the Gut Microbiome* (cont.)

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</thead>
<tbody>
<tr>
<td>Bile Acid Sequestrants* 1-4</td>
<td>Diarrhea - may be considered after other therapies targeting diarrhea have been unsuccessful</td>
<td>Cholestyramine 9 grams 2 to 3 times daily, colestipol 2 g once or twice daily, or colesevelam 625 mg once or twice daily</td>
<td>Constipation, nausea</td>
</tr>
</tbody>
</table>

*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 (eg, 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