A 45-Year-Old Man With Recurrent Abdominal Pain, Bloating, Flatulence, and Intermittent Loose Stools

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Case Study: Alan

Alan is a 45-year-old man with a 3-year history of recurrent, right lower-quadrant abdominal cramping, bloating, flatulence, and intermittent loose stools.

• His symptoms began after an acute gastrointestinal illness he developed while vacationing. His stools are loose and non-bloody, without mucous.

• His weight has been stable. Alan has no fecal incontinence but has had several “close calls.”

• He limits his social engagements, and when he does go out, he always looks for the nearest bathroom.

• Alan has tried loperamide and bismuth intermittently, with only limited success.

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History and Physical Exam

• Family history is negative

• Affect is normal

• Physical exam is unremarkable except for mild LLQ tenderness with deep palpation
  ▪ Rectal exam reveals soft brown guaiac negative stool in the vault
  ▪ Tone and squeeze pressures as well as relaxation of the anal sphincter appear normal

LLQ = left lower quadrant.
IBS: Epidemiology, High Burden

• Estimated prevalence: 11% worldwide,\(^1\) 12% in US\(^2\)
• Most common between ~30–50 years of age; affects women > men\(^1,3\)
• IBS is common following an enteric infection
• Decreased work productivity\(^3\)
• IBS patients have HRQoL similar to patients with chronic depression and renal failure
• IBS is second only to GERD for burden of GI illness\(^4\)
  ▪ $1.6 billion – direct costs\(^5\)
  ▪ $19.2 billion – indirect costs\(^5\)

IBS = irritable bowel syndrome; HRQoL = health-related quality of life; GERD = gastroesophageal reflux disease; GI = gastrointestinal.

### Overview of IBS Pathophysiology

<table>
<thead>
<tr>
<th>Host Factors</th>
<th>Environmental Factors</th>
<th>Luminal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI motility</td>
<td>Psychosocial distress</td>
<td>Dysbiosis</td>
</tr>
<tr>
<td>Visceral hypersensitivity</td>
<td>Food</td>
<td>Neuroendocrine mediators</td>
</tr>
<tr>
<td>Intestinal permeability</td>
<td>Antibiotics</td>
<td>Bile acids</td>
</tr>
<tr>
<td>Brain-gut interactions</td>
<td>Enteric infection</td>
<td></td>
</tr>
<tr>
<td>Immune activation</td>
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</tbody>
</table>

Rome IV Criteria*: Irritable Bowel Syndrome

Recurrent abdominal pain at least 1 day/week in the last 3 months associated with 2 or more:

- Related to defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

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

### IBS Subtypes (Rome IV) Are Based on Stool Consistency During Days With Abnormal BMs

#### Bristol Stool Form Scale\(^1,2\)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separate hard lumps, like nuts (hard to pass)</td>
<td>IBS-C(^2)</td>
</tr>
<tr>
<td>Type 2</td>
<td>Sausage-shaped but lumpy</td>
<td>Hard/lumpy stools ≥25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loose/watery stools &lt;25%</td>
</tr>
<tr>
<td>Type 3</td>
<td>Like a sausage but with cracks on its surface</td>
<td>IBS-M(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hard/lumpy stools ≥25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loose/watery stools ≥25%</td>
</tr>
<tr>
<td>Type 4</td>
<td>Like a sausage or snake, smooth and soft</td>
<td>IBS-D(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hard/lumpy stools &lt;25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loose/watery stools ≥25%</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
<td></td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges; a mushy stool</td>
<td></td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces; entirely liquid</td>
<td></td>
</tr>
</tbody>
</table>

BM = bowel movement; IBS-C = IBS with constipation; IBS-M = IBS mixed; IBS-D = IBS with diarrhea.


Other Associated Conditions

- **GI motility disorders**
  - Dyspepsia, GERD, cyclic vomiting, gastroparesis, etc.

- **Psychiatric disorders**
  - Anxiety, depression, somatoform disorders, PTSD

- **Chronic back pain**

- **Fibromyalgia, chronic fatigue syndrome**

- **Chronic headaches, “migraines”**

- **Chronic pelvic pain – men and women**

- **Functional urinary symptoms (e.g., interstitial cystitis)**

- **Dysmenorrhea**

GERD = gastroesophageal reflux disease; PTSD = post-traumatic stress disorder.
Diagnosis of IBS-D: Detailed History and Physical Examination

**History**
- Presenting symptoms
- Establish history timeline
- Presence of alarm features
- Family history: IBS, organic GI disorder
- Prior tests and treatments
- Review current medications

**Examination**
- Signs of systemic and local diseases
- Carnett’s test: somatic vs visceral pain
- Assess the anorectum and pelvic floor muscles
- Other relevant abnormalities

GI = gastrointestinal.

Patients With Alarm Features Require More Detailed Investigation

- **Common Alarm Features (i.e., red flags)**
  - Onset of symptoms after age 50 years
  - GI bleeding or iron-deficiency anemia
  - Nocturnal diarrhea
  - Weight loss
  - Family history of organic GI disease (colorectal cancer, IBD, celiac disease)

Which of the following is a consideration in the diagnosis of IBS-D?

1. C-reactive protein (CRP) and fecal calprotectin can aid in excluding IBD in patients with IBS symptoms

2. It is not recommended that a tissue transglutaminase (tTg) IgA antibody be checked in patients with IBS-D

3. Colonoscopy has a high yield in detecting IBD in patients with IBS symptoms who do not have alarm features
Differential Diagnosis: Excluding IBD
Role of CRP and Fecal Calprotectin in Excluding IBD in Patients With IBS Symptoms

CRP = C-reactive protein;
ESR = erythrocyte sedimentation rate.

• ESR is of no value
• CRP of <0.5 mg/dL confers a <1% risk of IBD
• Fecal calprotectin of <40 mg/g confers a <1% risk of IBD

Differential Diagnosis: Patients With IBS-D Symptoms Should Undergo Celiac Antibody Testing

Odds Ratio Meta-Analysis Plot [Random Effects]

- Sanders 2001: 7.29 (1.65-66.52)
- Shahbazkhani 2003: 4.49 (0.97-17.03)
- Sanders 2003: 28.23 (1.90-578.67)
- Chey 2007: 1.52 (0.22-16.93)
- Qzdil 2008: 0.67 (0.00-26.11)
- Combined [Random]: 4.34 (1.78-10.58)

Differential Diagnosis: Role of Colonoscopy
Patients with IBS Symptoms Without Alarm Features Are Unlikely to Have IBD or Microscopic Colitis

Prospective, multicenter US study in nonconstipated IBS patients and controls undergoing colon cancer screening.

Prevalence of structural abnormalities

Microscopic colitis was more common in IBS-D patients aged ≥45 years

Which patients should be evaluated for microscopic colitis?

1. Younger women or those who have intermittent symptoms
2. Those with stress-associated symptoms or meal-related diarrhea
3. Those with unrelenting symptoms or nocturnal diarrhea
Differential Diagnosis: Microscopic Colitis
Who Should Be Evaluated?

<table>
<thead>
<tr>
<th>Favors IBS</th>
<th>Favors Microscopic Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meal-related diarrhea</td>
<td>Nocturnal diarrhea</td>
</tr>
<tr>
<td>Intermittent symptoms</td>
<td>Unrelenting symptoms</td>
</tr>
<tr>
<td>Longstanding symptoms</td>
<td>Short symptom duration</td>
</tr>
<tr>
<td>Symptoms with stress</td>
<td>New drug in last 1-3 months</td>
</tr>
<tr>
<td>Family history of IBS</td>
<td>Other autoimmune disorders</td>
</tr>
<tr>
<td>Younger women</td>
<td>Older women</td>
</tr>
</tbody>
</table>

- Majority of cases will be diagnosed with left-colon biopsies alone

Co-morbid Condition: SIBO
Role of Breath Testing

• Breath tests are not validated to accurately detect SIBO
• There is insufficient evidence to recommend lactulose or glucose breath tests to identify SIBO in patients with IBS

SIBO = Small intestinal bacterial overgrowth.

Co-Morbid Condition: Role of Bile Acid Diarrhea in IBS-D

- Up to 40% of patients with IBS-D may have bile acid diarrhea
- Bile acids are normally completely absorbed in terminal ileum; in the colon bile acids cause diarrhea
- Serum 7 α-hydroxy-4-cholesten-3-one (C4) (not complement) now available in US
- Bile acid malabsorption results in greater fat malabsorption and increased colon transit

Post-infectious Antibody Titers May Differentiate IBS-D from IBD, Celiac Disease

Antibody Titers in IBS Compared With Healthy Subjects and IBD

<table>
<thead>
<tr>
<th></th>
<th>Anti-CdtB</th>
<th></th>
<th>Anti-Vinculin</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Healthy Control</td>
<td></td>
<td></td>
<td>Healthy Control</td>
<td></td>
</tr>
<tr>
<td>n = 43</td>
<td></td>
<td></td>
<td>n = 43</td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td></td>
<td></td>
<td>IBS</td>
<td></td>
</tr>
<tr>
<td>n = 2,375</td>
<td></td>
<td></td>
<td>n = 2,375</td>
<td></td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td></td>
<td></td>
<td>Crohn’s Disease</td>
<td></td>
</tr>
<tr>
<td>n = 73</td>
<td></td>
<td></td>
<td>n = 73</td>
<td></td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td></td>
<td></td>
<td>Ulcerative Colitis</td>
<td></td>
</tr>
<tr>
<td>n = 29</td>
<td></td>
<td></td>
<td>n = 29</td>
<td></td>
</tr>
<tr>
<td>Celiac Disease</td>
<td></td>
<td></td>
<td>Celiac Disease</td>
<td></td>
</tr>
<tr>
<td>n = 121</td>
<td></td>
<td></td>
<td>n = 121</td>
<td></td>
</tr>
</tbody>
</table>

IBS-D vs IBD

<table>
<thead>
<tr>
<th></th>
<th>Optical Density</th>
<th>Specificity %</th>
<th>Sensitivity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CdtB (cutoff ≥2.80)</td>
<td>91.6</td>
<td>43.7</td>
<td></td>
</tr>
<tr>
<td>Vinculin (cutoff ≥1.68)</td>
<td>83.8</td>
<td>32.6</td>
<td></td>
</tr>
</tbody>
</table>

P < .001 for titers in IBS subjects vs other groups.

Work-Up of Patients With Suspected IBS-D

Typical IBS-D Symptoms

No

- IBS-D
  - CBC
  - CRP or fecal calprotectin
  - tTg (IgA and IgG)
  - SeHCAT or C₄ if available
  - Age-appropriate colorectal cancer screening
  - When colonoscopy or sigmoidoscopy performed, obtain random biopsies

Yes

- Alarm Features
  - Onset of symptoms after age 50 years
  - GI bleeding or iron-deficiency anemia
  - Nocturnal diarrhea
  - Weight loss
  - Family history of organic GI disease (colorectal cancer, IBD, celiac disease)

More detailed evaluation dictated by symptoms

CBC = complete blood count; CRP = C-reactive protein; tTg = tissue transglutaminase.

Based on Alan’s symptoms, history, and physical exam, the following tests are performed:

- tTg IgA antibody, CBC, CRP, stool calprotectin

After evaluation of the results (all negative), a diagnosis of IBS-D is made, allowing the physician to recommend appropriate and effective treatment.

tTg = tissue transglutaminase; CBC = complete blood count; CRP = C-reactive protein.
Summary

• IBS-D can be diagnosed using symptom-based criteria, a detailed physical exam, and select tests to exclude organic diseases.

• Tests to consider include: CBC, CRP/stool calprotectin, tTg (IgA and IgG), and stool analysis.

• Assessment for bile acid malabsorption should be considered where available.

• Role of breath testing remains unclear.

CBC = complete blood count; CRP = C-reactive protein; tTg = tissue transglutaminase.