Diagnostic Approach to IBS
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The Functional Bowel Disorders (FBDs)

- Irritable bowel syndrome
- Functional bloating
- Functional diarrhea
- Functional constipation
- Unspecified FBD

Recognition Challenges

• Irritable bowel syndrome (IBS) remains undiagnosed, even among patients being seen for other medical conditions
  – 25% eventually diagnosed with IBS seen for GI complaints at least 5 times before diagnosis¹
  – Many never seek care or diagnosis
    • Self-treat (OTC agents, CAM) or simply accept
    • Approximately 1 out of 4 people with IBS diagnosed

Pathophysiology of Functional GI Disorders

CNS: Stress, psychosocial factors

? Bacteria / inflammation

Motility

Sensitivity
The Brain Gut Axis and the Control of GI Function

<table>
<thead>
<tr>
<th>Brain-gut axis:</th>
<th>Changes in brain-gut axis in IBS / CC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central factors</td>
<td>Brain activation pattern</td>
</tr>
<tr>
<td>Autonomic factors</td>
<td>Parasympathetic &amp; sympathetic nervous systems (PNS &amp; SNS)</td>
</tr>
</tbody>
</table>
| Peripheral factors | Enteric nervous system (ENS)  
| | Serotonin signaling 
| | Activation of mast cells 
| | Altered cytokine levels |

Changes in GI motility  
Changes in GI secretion  
Visceral hypersensitivity

Cong et al, Gastroenterology 2007; 133: 445–53.
What are the symptoms of IBS?
Irritable Bowel Syndrome: Diagnostic Criteria\textsuperscript{a} (Rome Committee)

Recurrent abdominal pain or discomfort at least 3 days/month associated with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in the frequency of stool
- Onset associated with a change in the form of stool

\textsuperscript{a}Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Longstreth GF et al. \textit{i.} 2006; 130:1480.
Irritable Bowel Syndrome: Diagnostic Criteria

Abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least 3 months

- All criteria lack reference standard test
- No symptom-based criteria have perfect accuracy
- Rome criteria have been inadequately evaluated

What are the diagnostic criteria and subtypes?
IBS Subtypes: Stool Form Is the Differentiating Factor

25% of BM is the threshold for classification

% BM hard or lumpy

% BM loose or watery

IBS-C: Bristol types 1 and 2
IBS-M: Bristol types 1 and 6
IBS-U: Bristol type 6
IBS-D: Bristol type 6

IBS-UIBS-U
IBS-CIBS-C
IBS-MIBS-M
IBS-DIBS-D
What other conditions can mimic IBS?
Differential Diagnosis for IBS

- Chronic constipation
- Celiac disease
- IBD
- Microscopic colitis
- Infectious colitis
- Colon cancer
- Small intestinal bacterial overgrowth
- Functional dyspepsia
- Gallstones

- Gynecologic conditions
  - endometriosis
  - ovarian cancer
  - other chronic pelvic pain conditions

- Musculoskeletal pain
- Renal colic

### Overlapping IBS Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overlapping IBS symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic constipation</td>
<td>Straining, hard and lumpy stools</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Abdominal pain, bloating, diarrhea, constipation, flatulence, depression</td>
</tr>
<tr>
<td>IBD</td>
<td>Diarrhea, abdominal pain</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Chronic pelvic pain</td>
<td>Pelvic pain with defecation or altered bowel habit with chronic pelvic pain</td>
</tr>
<tr>
<td>Chronic functional abdominal pain</td>
<td>Constant or frequent abdominal pain, anxiety, depression</td>
</tr>
</tbody>
</table>

What Brings Patients to Your Office?

• Abdominal pain – 29% state this is the predominant symptom\(^1\)

• Misinformation
  – 15% believe IBS will turn into cancer\(^2\)
  – 30% believe IBS increases risk of IBD\(^3\)
  – 17% believe IBS will lead to malnutrition\(^4\)

• Lack of information
  – etiology thought due to anxiety (80.5%) or depression (63.2%)\(^2\)
  – only 2/3 of patients recognize that IBS does not shorten a patient’s life expectancy\(^3\)

Bridging the Physician-Patient Disconnect

Listen to complaints
- Acknowledge concerns
- Legitimize symptoms
- Provide convincing explanation about nature of symptoms

Ask about stress / distress
- Patients volunteer this information infrequently
- An open approach to inquiring about stress-related factors is validating

Proactively inquire about beliefs; address misconceptions
- Eliciting thoughts / feelings is palliative to anxiety
- Providing reassurance to patients leads to a better response

Educate patients on IBS
- Patients interested in causes of IBS, role of diet in IBS, coping strategies, medications
- Can reduce healthcare costs and primary care consultations

History and Physical Examination for Lower GI Symptoms

**History**
- Presenting symptoms
- Establish history timeline
- Presence of alarm signals
- Family history: IBS, organic GI disorders
- Review diet and current medications

**Examination**
- Signs of systemic and local diseases that might cause constipation or diarrhea
- Assess the anorectum and pelvic floor muscles
- Other relevant abnormalities
What tests are helpful in discriminating IBS from other conditions?
## Utility of Tests in Diagnosing IBS

<table>
<thead>
<tr>
<th>Organic disease</th>
<th>IBS patients (n=366) (%)</th>
<th>Control / population (n=276) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis / IBD</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.4</td>
<td>4–6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>5.5</td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lactose malabsorption²</td>
<td>22.3</td>
<td>26.6/25</td>
</tr>
</tbody>
</table>

<sup>a</sup>Prevalence in the US population.

<sup>2</sup>Cash et al, *Gastroenterology* 2006; 130(4. suppl. 2): A111.
IBS Experts Use Fewer Tests Than Nonexperts

<table>
<thead>
<tr>
<th></th>
<th>PCPs, nurse practitioners and gastroenterologists (n=281)</th>
<th>IBS experts (n=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS is diagnosis of exclusion? (% yes)</td>
<td>72</td>
<td>8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IBS-C</td>
<td>Diagnostic tests (n)</td>
<td>2.2</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Cost of testing ($)</td>
<td>550</td>
<td>288</td>
</tr>
<tr>
<td>IBS-D</td>
<td>Diagnostic tests (n)</td>
<td>4.1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cost of testing ($)</td>
<td>658</td>
<td>297</td>
</tr>
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</table>

Investigation in Patients With No Alarm Features (Rome)

- Flexible sigmoidoscopy
- Colonoscopy
- Rectal biopsy
- Barium enema
- Abdominal ultrasound
- Routine laboratory investigations
- Fecal occult blood test

Insufficient evidence to recommend routine testing

Results based on a literature review.

Serological tests for celiac disease

Should be considered

Routine use of colonoscopy for CRC screening is recommended for all patients ≥50 years old

Longstreth GF et al. *Gastroenterology*. 2006; 130:1480
Investigation in Patients With No Alarm Features (ACG)

- Flexible sigmoidoscopy
- Barium enema
- Abdominal ultrasound
- Routine laboratory investigations
- Fecal occult blood test

Insufficient evidence to recommend routine testing

Routine with IBS-M and IBS-D

Serological tests for celiac disease

Colonoscopy with random biopsies

Breath testing for lactose intolerance

When no response to diet & still suspicious

Routine use of colonoscopy for CRC screening is recommended for all patients ≥50 years old or those with alarm features

What are the red flags and how useful are they?
Alarm Features for Organic Disorders (Rome Committee)

• Age \( \geq 50 \) years old
• Blood in stools
• Nocturnal symptoms
• Weight loss (unintentional)
• Change in symptoms
• Recent antibiotics
• Family history of organic GI disease

If alarm features are present, investigate and treat appropriately
Alarm Features
(ACG Task Force)

• Anemia

• Weight loss (unintentional)

• Family history of organic GI disease
  • CRC
  • IBD
  • Celiac disease

If symptom-based criteria are met and alarm features are absent, the clinician should be reassured that the diagnosis of IBS is correct.
Excluding any patient with a red flag improved agreement between Rome II criteria and clinical diagnosis by 5% but left 84% of patients diagnosed with IBS by their physicians without a diagnosis.

The fact that 84% of patients with functional GI symptoms endorse ≥1 red flag symptoms significantly reduces utility of these symptoms as screening questions.

Multiple Contributing Factors for IBS

- Visceral hypersensitivity
- GI dysmotility
- Post-infectious inflammation
- Brain-gut dysfunction
- Genetic predisposition
- Food sensitivity
- Abnormal central processing
- Environmental factors
- Psychological abuse history
- Inflammation
- Food sensitivity
- GI dysmotility
- Post-infectious
- Visceral hypersensitivity
- IBS Symptom Complex
- Multiple Contributing Factors for IBS
Factors Activating Mucosal Immune System

- Food antigens
- Bacteria
- Plasma cells
- Dendritic cells
- Activated T cells
- Blood
- HPA
- STRESS

= antigen / bacteria
PP = Peyer’s patches
MLN = mesenteric lymph node
Evidence of Mucosal Inflammation in IBS

Fold difference vs controls

- Weston, 1993 D-IBS
- O'Sullivan, 2000 D-IBS
- Gwee, 1999 PI-IBS
- Spiller, 2000 PI-IBS
- Chadwick, 2003 D-IBS
- Dunlop, 2003 D-IBS (not PI-IBS)
- Dunlop, 2003 PI-IBS
- Wang, 2004 PI-IBS & D-IBS
- Barbara, 2004 IBS
Mast Cells in Descending Colon IBS vs Controls

Controls (n=22)  IBS (n=44)

Mast cells area
% mucosa  3.32 ± 10.8%  9.2 ± 2.5%

Enterochromaffin (EC) Cell Hyperplasia in Post-infective IBS

5-HT immunoreactivity
Plasma 5-HT Following a 520 kcal Test Meal in Patients With IBS and Healthy Controls

Selection of Biomarkers to Distinguish IBS From Non-IBS

- Identified pathways affected in IBS: 600–700 pathways, 60,000–70,000 markers
- Identified markers common across multiple pathways: 2000–3000 markers
- Selected potential serum-based IBS markers: 250 markers
- Identified biomarkers measurable with commercially available assays: 140 markers
- Tested assay values in cohorts of IBS and non-IBS samples: 16 markers
- Selected IBS-specific markers: 16 markers
Interleukin 1b (IL-1b)<sup>a</sup>
Anti-neutrophil cytoplasmic antibody (ANCA)
Growth-related oncogene a (GROa)
Brain-derived neurotrophic factor (BDNF)
Anti-*Saccharomyces cerevisiae* antibody IgA (ASCA IgA)
Anti-human tissue transglutaminase (tTG)
TNF-like weak inducer of apoptosis (TWEAK)
Antibody against CBir1 (anti-CBir1)<sup>b</sup>
Tissue inhibitor of metalloproteinase-1 (TIMP-1)
Neutrophil gelatinase-associated lipocalin (NGAL)
**Natural History of IBS**

- 6 months to 6 years after original IBS diagnosis

<table>
<thead>
<tr>
<th>Patients with IBS diagnosis (%)</th>
<th></th>
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<tbody>
<tr>
<td>Alternative diagnosis</td>
<td>2–5</td>
</tr>
<tr>
<td>Worsened IBS symptoms</td>
<td>2–18</td>
</tr>
<tr>
<td>Symptom-free</td>
<td>12–38</td>
</tr>
<tr>
<td>Unchanged IBS symptoms</td>
<td>30–50</td>
</tr>
</tbody>
</table>

Total n=1099; 14 studies included

- IBS is a stable diagnosis

- <5% IBS patients are diagnosed with an alternative organic GI disorder; repeated diagnostic evaluation is not warranted

Pragmatic Issues in IBS

- Patient expectations
- Effect on clinical outcomes
- Reassurance value / Impact on symptoms
- Legal implications of delayed diagnosis of organic GI disease
Diagnosis of IBS: Summary

• IBS patients often remain undiagnosed, even after medical attention
  – Differential diagnosis of IBS comprises other conditions, eg, IBD, which have several overlapping symptoms with IBS

• In IBS patients without alarm features, the prevalence of organic disease is similar to the general population and exclusionary tests have a low pre-test probability of being positive
  – Caveat: Routine celiac disease screening in IBS-D and IBS-M and consider random colonic biopsies to exclude microscopic colitis in IBS-D¹

• Patients with alarm features must be investigated and treated appropriately but the relevance of alarm features remains unknown

Brandt et al, *Am J Gastroenterol* 2009; 104 (suppl1).