Management of Functional Bowel Disorders

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Objectives

• Review epidemiology and pathophysiology of IBS
• Explore workup and importance of lean diagnostic evaluation
• Learn newer treatments and management strategies
What is a Functional Disorder?

- Identified only by symptoms
- Absence of a structural or biochemical disorder
- Symptoms are attributable to the upper (e.g., functional dyspepsia) or lower abdomen
- Research supports multiple etiologies
What are the functional disorders?

- Irritable Bowel Syndrome
- Functional constipation
- Functional diarrhea
- Functional dyspepsia
- Functional heartburn
- Functional bloating
- Functional biliary pain
- Chronic functional abdominal pain
What are the functional bowel disorders?

- Irritable Bowel Syndrome
  - Functional constipation
  - Functional diarrhea
  - Functional dyspepsia
  - Functional heartburn
  - Functional bloating
  - Functional biliary pain
  - Chronic functional abdominal pain
IBS

Defined as

- Lower abdominal pain or discomfort that is associated with a change in bowel habit and features of disordered defecation, with two of three of the following symptoms:
  - Symptoms improve with defecation
  - Onset associated with a change in stool frequency
  - Onset is associated with change in stool form

Longstreth GF et al. Gastroenterology. 2006;130:1480-1491.
IBS epidemiology

• Most common functional bowel disorder
• Affects up to 25% adults and adolescents
• 3:1 female predominance
• Symptoms
  • Significantly impair quality of life
  • Frequent overlap with other functional disorders
  • Result in high health care costs
  • Anxiety and depression have been linked to functional abdominal pain

Longstreth GF et al. Gastroenterology 2006;130:1480.
IBS is classified into subtypes based on stool form.

Longstreth GF et al. Gastroenterology 2006;130:1480.

IBS-M: Hard and loose stools

IBS-U: Unsubtyped IBS
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separate hard lumps</td>
</tr>
<tr>
<td>Type 2</td>
<td>Sausage-like but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
<td>Sausage-like but with cracks in the surface</td>
</tr>
<tr>
<td>Type 4</td>
<td>Smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges</td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces</td>
</tr>
</tbody>
</table>
# ACG task force recommendations for the diagnosis of IBS in patients without alarm symptoms

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Chemistries</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Thyroid function studies</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Stool for ova and parasites</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Abdominal imaging</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Serologic screening for celiac sprue</strong></td>
<td>Pursue in patients with IBS-D or IBS-M</td>
</tr>
<tr>
<td><strong>Lactose breath testing</strong></td>
<td>Consider if symptoms persist after dietary modification</td>
</tr>
<tr>
<td>Breath testing for SIBO</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Perform in patients with alarm features and in those aged &gt;50</td>
</tr>
</tbody>
</table>


ACG: American College of Gastroenterology
 Colonoscopy and/or Abdominal Imaging is Not Recommended in IBS without Alarm Features *Because*

The prevalence of structural abnormalities is not higher in IBS

<table>
<thead>
<tr>
<th>Lesions</th>
<th>IBS Patients (n=466) N (%)</th>
<th>Controls (n=451) N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomas</td>
<td>36 (7.7)</td>
<td>118 (26.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hyperplastic polyps</td>
<td>39 (8.4)</td>
<td>52 (11.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>7 (1.5)</td>
<td>NA</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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

Alarm Features

- Onset of symptoms after age 50
- GI bleeding or iron-deficiency anemia
- Nocturnal diarrhea
- Unintended weight loss
- Family history of organic GI disease (colorectal cancer, IBD, celiac disease)
# IBS Pathophysiology: An Interaction Between Biological and Psychosocial Factors

**Physiologic features**
- Altered motility
- Visceral hyperalgesia
- Disturbance of brain gut interaction
- Abnormal central processing
- Autonomic and hormonal events
- Genetic/Environmental factors
- Post-infectious events

**Psychosocial features**
- Sleep disturbance
- Dysfunctional coping
- Generalized anxiety disorder
- Mood disorder
- Post traumatic stress disorder
- Panic disorder
- Psychiatric disorders
- History of childhood abuse is common

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Rome Foundation Functional GI Specialty Modules
Abdominal Pain is Associated with Anxiety and Depression Scores in the General Adult Population without Organic GI Disease

- N=272
- Colonoscopy, lab, GI questionnaire x 1 week, Rome II criteria met, anxiety and depression q’nairres
- 12% fulfilled Rome II criteria for IBS
- Anxiety and Depression scores *higher* in subjects who reported abdominal pain vs those who did not (*p*< 0.0005 and *p*< 0.0005)
- QOL scores were *lower* in patients with abdominal pain

Patient with recurrent abdominal pain/discomfort associated with disordered bowel habit

- medical and psychosocial history, physical examination
  - alarm features?
    - yes: investigations as indicated: eg, colonoscopy, blood & stool tests, duodenal biopsy
    - no: consider limited screening tests
  - any abnormality identified?
    - yes: any abnormality identified?
      - yes: celiac disease, giardiasis, inflammatory bowel disease, microscopic colitis, small intestinal bacterial overgrowth, colorectal neoplasia
      - no: evaluation of stool consistency (using Bristol Stool Form Scale)
    - no: IBS

- any abnormality identified?
  - yes: IBS-C
  - no: IBS-M
  - no: IBS-D
Diagnosis and Pathophysiology Summary

• Make a positive diagnosis
• Limit the diagnostic workup in patients without alarm symptoms
• Physiological and Psychological factors contribute to pathophysiology
• Abdominal pain correlates with psychological scores
Treatment

• Management will depend on
  • A confident diagnosis
  • Explanation why symptoms occur
  • Suggestions for coping with symptoms

• Education about healthy lifestyle behaviors, reassurance that symptoms are due to a non-life threatening illness, establishing a therapeutic relationship, lifestyle modification, and counseling impact change.

Longstreth GF et al. Gastroenterology 2006;130:1480.
Diets and IBS

- Patients often indicate a link between diet and IBS symptoms

- Food elimination diets may be effective in some patients
  - Lactose free
  - Gluten free
  - Fructose free
  - Low-FODMAP

FODMAP

Fermentable oligo-, di-, monosaccharides and polyols

Excess Fructose
- Honey, apples, pears, peaches, mangos, fruit juice, dried fruit

Fructans
- Wheat (large amounts), rye (large amounts), onions, leeks, zucchini

Sorbitol
- Apricots, peaches, artificial sweeteners, artificially sweetened gums

Raffinose
- Lentils, cabbage, brussel sprouts, asparagus, green beans, legumes
Fructose and Fructans as Dietary Triggers for IBS Symptoms

25 IBS patients with fructose malabsorption who improved with a FODMAP diet

Not controlled (%)

- Glucose
- Fructose
- Fructans
- F&F

* * * *

P≤.002 vs glucose

Psychological Therapy is Effective in Many Patients With IBS

- 20 studies (various psychological therapies), 1278 patients

<table>
<thead>
<tr>
<th>Improvement: Psychological therapy (%)</th>
<th>Improvement: “Usual management” or control therapy (%)</th>
<th>RR symptoms remain (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.1</td>
<td>27.5</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.57-0.79)</td>
</tr>
</tbody>
</table>

Psychological factors may alter symptom perception. Patients' reaction to a symptom may be more important than the symptom itself. Most patients respond to psychological support, strong physician-patient relationship, and multicomponent treatments.

Exercise Has a Positive Impact on IBS Symptoms

- Subjects (N=75) randomized to physical activity* or to maintain their lifestyle
- Physical activity improved IBS symptom scores ($P=.003$)
- Patients in the control group had significantly higher IBS symptom scores than patients in physical activity group

*Intervention: 20-60 minutes moderate to vigorous exercise 3-5 times weekly

More studies needed. Further work on mechanisms and ideal ‘dose’

Truth about Dyssynergy, Biofeedback and IBS-C

• N=50 patients with dyssynergic defecation
• 29/50 met Rome II IBS-C criteria
• Both groups had similar response to biofeedback (16 of 29 vs 14 of 21, p>0.05)
• IBS symptoms disappeared in 12/29 patients who had IBS symptoms before treatment
• Disappearance of IBS symptoms was observed more frequently in those who responded to biofeedback than to those who did not (p<0.05)

More trials needed to clarify the role for biofeedback

Patcharatrakul T et al. J Clin Gastroenterol 2011;45:593
Non-Pharmacologic Treatment Summary:

- Confident diagnosis
- Nurturing physician/patient relationship
- Teach coping strategies
- Lifestyle changes play an important role in treatment
Pharmacologic Management of IBS

**IBS-D**
- Adsorbents
- Rifaximin
- Bile-acid modulators
- 5HT3 antagonists

**IBS-C**
- Fiber
- PEG
- Cl channel activator
- Osmotic laxatives
- Guanylate cyclase C
- 5HT4 agonists

**Drugs targeting pain & hypersensitivity**
- Probiotics
- SSRI
- TCA
- Peripheral opioid antagonists
- Antispasmodics
- SSRI
- TCA
- Gabapentin

**Bloating and distension**
**Abdominal pain and discomfort**
**Altered bowel function**
Is Psyllium Beneficial for IBS-C?

Proportion of Patients With Adequate Relief of Symptoms Each Week

- Psyllium, 10 g (n=85)
- Bran, 10 g (n=97)
- Placebo (rice flour), 10 g (n=93)

Responders, %

*P<0.05.

Polyethylene Glycol (PEG) for IBS-C

- Laxatives have not been studied in RCTs in IBS
- PEG improved frequency of bowel movements but not pain in adolescents with IBS-C (n=27)

Efficacy of the Selective Cl Channel Activator Lubiprostone in IBS-C


10.1% difference

Lubiprostone 8 µg BID

Placebo

Combined analysis in Rome II IBS-C patients using intent-to-treat, last observation carried forward analysis

P = .001
The Guanylate Cyclase C Agonist, Linaclotide in IBS-C

Study week

End of treatment

Mean change in CSBM rate

Mean change in abdominal pain

## Efficacy of TCAs in Relieving IBS Symptoms

<table>
<thead>
<tr>
<th>Study (Year, Drug, Dose)</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heefner (1978, desipramine 150 qd)</td>
<td>10/22</td>
<td>12/22</td>
<td></td>
</tr>
<tr>
<td>Myren (1982, trimipramine 50 qd)</td>
<td>5/30</td>
<td>10/31</td>
<td></td>
</tr>
<tr>
<td>Nigam (1984, amitriptyline 12.5 qd)</td>
<td>14/21</td>
<td>21/21</td>
<td></td>
</tr>
<tr>
<td>Boerner (1988, doxepin 50 qd)</td>
<td>16/42</td>
<td>19/41</td>
<td></td>
</tr>
<tr>
<td>Bergmann (1991, trimipramine 50 qd)</td>
<td>5/19</td>
<td>14/16</td>
<td></td>
</tr>
<tr>
<td>Vij (1991, doxepin 75 qd)</td>
<td>14/25</td>
<td>20/25</td>
<td></td>
</tr>
<tr>
<td>Drossman (2003, desipramine 50-150 qd)</td>
<td>60/115</td>
<td>36/57</td>
<td></td>
</tr>
<tr>
<td>Talley (2008, imipramine 50 qd)</td>
<td>0/18</td>
<td>5/16</td>
<td></td>
</tr>
<tr>
<td>Vahedi (2008, amitriptyline 10 qd)</td>
<td>8/27</td>
<td>16/27</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>319</strong></td>
<td><strong>256</strong></td>
<td><strong>RR=0.68 (95% CI=0.56-0.83)</strong></td>
</tr>
</tbody>
</table>

TCA=tricyclic antidepressant

Efficacy of SSRI’s in Relieving Symptoms of IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>(Year, Drug, Dose)</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuiken (2003, fluoxetine 20 qd)</td>
<td>9/19</td>
<td>12/21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tabas (2004, paroxetine 10-40 qd)</td>
<td>25/44</td>
<td>36/46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vahedi (2005, fluoxetine 20 qd)</td>
<td>6/22</td>
<td>19/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talley (2008, citalopram 40 qd)</td>
<td>5/17</td>
<td>5/16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>113</td>
<td>117</td>
<td></td>
<td>RR=0.62 (95% CI=0.45-0.87)</td>
</tr>
</tbody>
</table>

### Evidence-based summary of Medical Treatments for IBS-D Symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvements in Symptoms</th>
<th>Grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alosetron</td>
<td>+</td>
<td>2A/ 1B</td>
</tr>
<tr>
<td>Antibiotics (rifaximin)</td>
<td>+</td>
<td>1B</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>+</td>
<td>1B</td>
</tr>
<tr>
<td>Loperamide</td>
<td>+</td>
<td>2C</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>±</td>
<td>2C</td>
</tr>
<tr>
<td>Probiotics (Bifidobacteria/some combos)</td>
<td>+</td>
<td>2C</td>
</tr>
</tbody>
</table>

* Global Symptoms | Pain | Bloating | Stool Frequency | Stool Consistency |

ACG Task Forces on IBS. Am J Gastroenterol 2009;104:S1.
Antidiarrheals for IBS

- Loperamide is effective for treatment of diarrhea, reducing stool frequency and improving consistency
- No impact on bloating, abdominal discomfort, or global IBS symptoms
- Low doses (2 mg QD or BID) can be effective
- No other antidiarrheal has been studied in clinical trials

Mayer EA. NEJM 2008;358:1692.
Antispasmodics for IBS

22 RCTs compared 12 different antispasmodics with placebo (n=1778)

Most data available for otilonium, trimebutine, cimetropium, hyoscine, and pinaverium

Symptoms persisted in 39% of patients treated with antispasmodics vs 56% of placebo-treated patients (relative risk 0.68; 95% CI=0.57-0.81)

• Significant heterogeneity among studies
• Most agents are not available in US
• Appear most useful for abdominal pain

Ford AC et al. BMJ 2008;337:a2313
# Efficacy of Alosetron in IBS

## Global IBS Symptoms or Abdominal Pain
Unimproved or Persistent After Therapy

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (Random) 95% CI</th>
<th>RR (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camilleri (1999)</td>
<td>179/290</td>
<td>54/80</td>
<td>0.91 [0.77, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Bardhan (2000)</td>
<td>166/345</td>
<td>57/117</td>
<td>0.99 [0.80, 1.23]</td>
<td></td>
</tr>
<tr>
<td>Camilleri (2000)</td>
<td>191/324</td>
<td>229/323</td>
<td>0.83 [0.74, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Camilleri (2001)</td>
<td>182/309</td>
<td>235/317</td>
<td>0.79 [0.71, 0.89]</td>
<td></td>
</tr>
<tr>
<td>Lembo (2001)</td>
<td>144/532</td>
<td>156/269</td>
<td>0.47 [0.39, 0.55]</td>
<td></td>
</tr>
<tr>
<td>Chey (2004)</td>
<td>167/351</td>
<td>197/363</td>
<td>0.88 [0.76, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Chang (2005)</td>
<td>268/534</td>
<td>77/128</td>
<td>0.83 [0.71, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Krause (2007)</td>
<td>279/529</td>
<td>122/176</td>
<td>0.76 [0.67, 0.86]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>3,214</strong></td>
<td><strong>1,773</strong></td>
<td><strong>0.79 [0.69, 0.90]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Favors Treatment: 0.2 Favors Control: 0.1 0.5 1 2 5 10

RR=0.79
(95% CI=0.69-0.90)

Rifaximin for IBS symptoms and IBS-related bloating

**Global IBS Symptoms During First 4 Weeks**

- **Target 1:** Placebo 40.8, Rifaximin 550 mg TID 31.2, *P = 0.01*
- **Target 2:** Placebo 40.6, Rifaximin 550 mg TID 32.2, *P = 0.03*
- **Combined analysis:** Placebo 40.7, Rifaximin 550 mg TID 31.7, *P < 0.001*

**IBS-Related Bloating During First 4 Weeks**

- **Target 1:** Placebo 39.5, Rifaximin 550 mg TID 28.7, *P = 0.005*
- **Target 2:** Placebo 41, Rifaximin 550 mg TID 31.9, *P = 0.02*
- **Combined analysis:** Placebo 40.2, Rifaximin 550 mg TID 30.3, *P < 0.001*

Pimental M et al. NEJM 2011;364:22.
Probiotics for IBS

4648 probiotics in IBS citations retrieved

21 probiotic studies assessed

included 16 RCTs

**RCTs**

- Adults with IBS defined by Manning or Rome II criteria
- Single or combination probiotic vs placebo
- Improvement in IBS symptoms, and/or decrease in frequency of AEs reported

B. infantis 35624 demonstrated efficacy in 2 appropriately designed RCTs

No other probiotic showed significant improvement in IBS symptoms in appropriately designed RCTs

Management Algorithm

IBS

Lifestyle Modifications: Diet, Coping Skills, Counseling, Exercise, Biofeedback, Better Understanding, Less Medication

Constipation
- Psyllium
- PEG
- Lubiprostone
- Linaclotide

Diarhea (exclude FI)
- Absorbents
- Loperamide
- Alosetron
- Lubiprostone
- Rifaximin

Pain
- Coping skills
- Antispasmodics
- Antidepressants
- Alosetron
- Lubiprostone
- Gabapentin
- Hypnotherapy
- CBT
- Psychotherapy

Gas/Bloating
- Rifaximin
- Probiotics
- Lubiprostone
Summary Management Strategies for IBS

**Centrally acting therapies**
- SSRI
- TCA
- SNRI
- Gabapentin?

**IBS-D**
- Loperamide
- Alosetron
- Probiotics
- FODMAP
- Rifaximin

**IBS-C**
- Fiber
- Cl - Ch activators
- 5-HT4 agonists
- Guanylate cyclase C agonist
- Osmotic laxatives?

**Physician-patient relationship**
- Hypnotherapy
- CBT & mindfulness
- Psychotherapy
- Psychiatry

**Biofeedback**
- Exercise

**Diet**
- ? Fecal microbiota transplant

Thank You!