Optimizing the Diagnosis, Treatment, and Management of Irritable Bowel Syndrome

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Educational Partner
Miller Medical Communications, LLC.
Session 4: Optimizing the Diagnosis, Treatment, and Management of Irritable Bowel Syndrome

Learning Objectives
1. Diagnose IBS and differentiate from other bowel disorders using established clinical guidelines.
2. Summarize the efficacy and safety of pharmacologic and nonpharmacologic treatment options for IBS.

Faculty

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Mobile, Alabama

Dr Brooks Cash is a professor of medicine at the University of South Alabama (USA), Mobile, Alabama; where he has held a faculty position since 2013. He was previously a professor of medicine at the Uniformed Services University of the Health Sciences, Bethesda, Maryland. He currently serves as the director of the motility and physiology service at the USA Digestive Health Center. Prior to his relocation to USA, Dr Cash served in the United States Navy for 24 years, retiring in 2013 at the rank of captain, as the deputy commander for medicine at Walter Reed National Military Medical Center, Bethesda, Maryland.

Spencer Dorn, MD, MPH, MHA
Vice Chief Gastroenterology
Assistant Professor of Medicine
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Dr Spencer Dorn works to improve quality of care, operational efficiency, and patient experiences as vice chief of the University of North Carolina (UNC) division of gastroenterology and hepatology. As assistant professor of medicine, he conducts clinical trials for functional GI disorders, performs health services research, and examines the impact of health policy and regulations on gastroenterology. His clinical practice focuses on functional GI and motility disorders.

Dr Dorn graduated with highest distinction from the University of Michigan, Ann Arbor and summa cum laude from the State University of New York at Brooklyn College of Medicine. He earned a master of public health (epidemiology) degree and later a master of healthcare administration (health policy and management) from UNC. Dr Dorn completed his internal medicine training at Brigham and Women’s Hospital, Boston, Massachusetts; where he was a clinical fellow at Harvard Medical School. He subsequently trained at UNC as a National Institutes of Health postdoctoral research fellow in digestive diseases epidemiology and functional GI disorders, and later as a clinical fellow in gastroenterology and hepatology.
**Faculty Financial Disclosure Statements**
The presenting faculty reports the following:
Dr Cash receives Consulting fees from Zx Pharma; Medical Advisory Board fees from Forest, Ironwood, Paion, Salix, and Takeda; Speakers Bureau honorarium from Forest, Ironwood, Salix, and Takeda.

Dr Dorn is an ad hoc consultant to investors and marketers.

**Education Partner Financial Disclosure Statement**
The content collaborators at Miller Medical Communications, LLC have no financial relationships to disclose.

**Suggested Reading List**


Learning Objectives

After participating in this educational activity the participant should be able to:

- Diagnose IBS and differentiate from other bowel disorders using established clinical guidelines
- Summarize the efficacy and safety of pharmacologic and nonpharmacologic treatment options for IBS
- Implement patient-specific methods for managing IBS symptoms and improving function and quality of life

Drug List

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>Alosetron</td>
<td>Lotronex</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Elavil, Endep, Vanatrip</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Cholestyramine Light, Prevalite, Questran, Questran Light</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>Bentyl</td>
</tr>
<tr>
<td>Diphenoxylate-‐atropine</td>
<td>Lomotil</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Adapin, Silenor, Sinequan</td>
</tr>
<tr>
<td>Elobixibat</td>
<td>Elobixibat</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>Eluxadoline</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac, Sarafem</td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>Anaspaz, Cystospaz, Donnamar, Levsin</td>
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<tr>
<td>Imipramine</td>
<td>Tofranil, Tofranil-‐PM</td>
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<tr>
<td>Ispaghula</td>
<td>Fybogel, Ispagel</td>
</tr>
<tr>
<td>Linaclotide</td>
<td>Linzess</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Imodium, Imodium A-‐D, Kaopectate II, Maalox Anti-‐Diarrheal Caplets, Pepto Diarrhea Control</td>
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<tr>
<td>Lubiprostone</td>
<td>Amitiza</td>
</tr>
<tr>
<td>Mesalamine/Mesalazine</td>
<td>Apriso, Asacol, Lialda, Pentasa</td>
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<td>PEG 3350+E</td>
<td>Colyte, GaviLyte, Golytely, GlycoLax, MiraLax</td>
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<tr>
<td>Paroxetine</td>
<td>Paxil, Paxil CR, Pexeva</td>
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<tr>
<td>Plecanatide</td>
<td>Plecanatide</td>
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<tr>
<td>Prucalopride</td>
<td>Resolor</td>
</tr>
<tr>
<td>Psyllium</td>
<td>Konsyl, Metamucil, Reguloid</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Xifaxan</td>
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</tbody>
</table>

Prevalence and Impact of IBS

- Worldwide prevalence: 7% to 10%
- 1.5 times more prevalent in women
- More commonly diagnosed in patients <50 years of age
- More common in lower socioeconomic groups
- Patients with IBS have more physician visits, hospitalizations, missed workdays, prescriptions, and diagnostic tests than those without

IBS=irritable bowel syndrome.
Rome III Criteria for IBS

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

- Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with symptom onset at least 6 months prior to diagnosis
- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form of stool

Additional IBS "testing," including routine laboratory tests and colonoscopy, unnecessary unless alarm features present

IBS Subtypes

- IBS-C: Constipation-predominant IBS
- IBS-D: Diarrhea-predominant IBS
- IBS-M: Mixed IBS (hard and loose stools, over periods of weeks and months)
- IBS-U: Unsubtyped IBS

What brings patients to your office?

- Abdominal pain – 29% state this is the predominant symptom
- Misinformation
  - 15% believe IBS will turn into cancer
  - 30% believe IBS increases risk for IBD
  - 27% believe IBS will lead to malnutrition
  - Lack of information
  - Prevalent physician belief IBS due to anxiety (80.5%) or depression (63.3%)
  - Only 2/3 of patients recognize that IBS does not shorten life expectancy

Proposed Pathophysiology of IBS

- Enteric nervous system dysfunction
- Gastrointestinal dysmotility
- Visceral hypersensitivity
- Disordered CNS pain processing
- Post-infectious
- Small intestinal bacterial overgrowth
- Dysbiosis
- Food intolerance
- Genetics
- Mast cell dysfunction
- Somatization

Differential Diagnosis of IBS With Constipation

- Gastrointestinal
  - Colorectal cancer
  - Diverticular disease
  - Gynecologic
    - Ovarian cancer
    - Endometriosis
  - Drugs
    - Opiates
    - Anticholinergics
    - Antidepressants
  - Metabolic/Endocrine
    - Hypothyroidism
    - Diabetes
  - Neurologic
    - Parkinson disease
    - Multiple sclerosis
    - Autonomic neuropathy
  - Other
    - Amyloidosis
    - Scleroderma

Differential Diagnosis of IBS With Diarrhea

- Dietary factors
  - Lactose
  - Gluten
  - Other FODMAPs
- Drugs
- Infection
  - Giardiasis
  - Amebiasis
  - C. difficile
- Malabsorption
  - Celiac disease
- Inflammatory bowel disease
  - Crohn's disease
  - Ulcerative colitis
  - Microscopic colitis
- Psychological
  - Panic disorder
  - Somatization
  - Depression

FODMAPs = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.
**Diagnostic Paradigm for IBS**

- IBS is a syndrome—a collection of symptoms
- Diagnosis possible via a thorough history of symptoms and physical examination
  - Because symptoms are non-specific, must consider alternative organic diagnoses
  - Serious organic illnesses typically produce alarm symptoms (e.g., bleeding, weight loss, etc)

**Is a Positive Diagnosis Really Possible?**

- 302 Danish patients aged 18-50 years referred from primary care. No alarm features.
  - Randomized to:
    - Exclusionary strategy: Blood work, stool samples, lower endoscopy with biopsy
    - Positive strategy: CBC and CRP only
  - Followed for 1 year
  - No difference in any outcome measure (symptoms, HRQL, use of health care resources, etc)
  - No cases of IBD, CRC, or celiac disease identified
  - Exclusionary strategy more expensive
    - Direct costs: $863 greater
    - Mean total costs: $1915 greater

**Positive IBS Diagnosis May Reduce Diagnostic Testing and Resource Utilization**

- Clinicians who believed IBS was a diagnosis of exclusion ordered 1.6 times more tests and spent $364 more on diagnostic tests per patient (P<.0001)

**Yield of Colonoscopy in IBS**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>IBS Patients (n=466) (%)</th>
<th>Controls (n=451) (%)</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>Cloacal adenocarcinoma</td>
<td>0 (0.0)</td>
<td>5 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>IBD</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>7 (1.5)</td>
<td>N/A</td>
<td>NA</td>
</tr>
</tbody>
</table>

Microscopic colitis was more common in a subset of patients with IBS-D who were ≥45 years (2.3%).

**Radiological Imaging in IBS**

A Systematic Review

- There is a paucity of evidence guiding radiologic imaging in IBS
  - Imaging study should be influenced by predominant symptoms
  - Data suggest very low yield of CT and Ultrasound
- Definitive recommendations must await further research

**What Can You Miss?**
Chronic Abdominal Wall Pain Syndrome

- Up to 50% of chronic idiopathic abdominal pain
- Entrapment of anterior cutaneous branch of thoracic intercostal nerve
- Sharply localized pain and superficial tenderness
- Carmed sign: accentuated localized tenderness with abdominal wall tensing
- Reassurance and avoidance of precipitating causes often sufficient
- Anesthetic/corticosteroid injection effective in ~75%
- Also serves as diagnostic confirmation

Primary Bile Acid Diarrhea (PBAD)

- 2% of the adult population; 25% of those diagnosed with IBS-D
- Tests that directly assess bile acid malabsorption (SeHCAT, 14C-glycocholate breath tests, serum C₄, fecal bile acids) either not available in United States or not validated
- Therapeutic trial only option
  - Bile acid sequestrants

IBD

- Crohn's disease, ulcerative colitis, undifferentiated IBD
- IBS symptoms ARE common in IBD patients in "remission"
- ~5% overall, higher in Crohn's disease
- Opinion divided as to what they mean
  - Unrecognized (latent) IBD
  - Real or coincident IBS, linked to psychosocial issues

Celiac Disease

- General Practice Research Database in the United Kingdom
  - Celiac patients were 5 times more likely to have a prior diagnosis of IBS, even for 10 years previously
- 8% of celiac disease patients have IBS symptoms; especially if non-adherent with gluten free diet
- Should you screen for celiac disease?
  - YES
  - NO

IBS and Celiac Disease: US Data

- Case-Control Study
  - IBS patients (physician diagnosis) Positive for SUDD and TAMA Celiac disease not biopsy-proven

- Prospective Study
  - Non-convered IBS patients (Rome II) Biopsy-proven celiac disease

Diverticular Disease

- "Post-diverticulitis IBS"
  - 2,204 subjects at Los Angeles Veterans Administration medical center who had an episode of diverticulitis and followed for 6.3 years
  - Almost 5 times more likely to be diagnosed with IBS later
- Symptomatic uncomplicated diverticular disease (SUDD)
  - 229 treated with mesalamine vs L casei alone vs placebo for 10 days per month for 2 months
  - Higher remission rates in treatment groups
  - Symptomatic diverticulitis in 6 vs placebo and 2 vs probiotic group
  - 345 patients with uncomplicated diverticulitis
    - Mesalazine 3 g daily vs placebo for 48 weeks
    - % recurrence-free at 48 weeks: 68% mesalamine, 74% placebo
Between Celiac Disease and IBS: The “No Man’s Land” of Gluten Sensitivity

Is it IBS, Celiac Disease or Something in Between?

IBS symptoms

Spectrum of CD

Motility / visceral sensation

Brain – gut interactions

Immune activation

Altered gut microbe

Non-celiac gluten or wheat sensitivity

Potential / asymptomatic CD

Symptomatic CD

ACG Recommendations: Evaluation of IBS With No Alarm Features

- Routine laboratory tests: CBC, CMP, TSH, stool O&P, abdominal imaging → not recommended
- Serologic testing for celiac disease (IBS-D/M) → strongly consider
- Lactose breath testing → selected cases
- Colonoscopy → recommended if ≥25 years of age, with biopsies in refractory IBS-D (to exclude microscopic colitis)

ACG-American College of Gastroenterology; CMP-Comprehensive Metabolic Panel; TSH-thyroid-stimulating hormone.

Alarm Features in IBS

- Refractory or worsening abdominal symptoms
- Older patient (≥50 years of age; ≥45 years of age if black) at onset
- Blood in stools (hematochezia)
- Anemia
- Weight loss (unintentional)
- Anorexia
- Family history of organic GI disease

Further investigation warranted

Natural History of IBS Meta-analysis

- Only 1% to 9% with IBS diagnosed with an alternative organic GI disorder after 30 years of follow-up
- Long-term follow-up: 2% to 18% worse, 30% to 50% of patients unchanged
- Prior surgery (1 study), higher somatic scores (1 study), higher baseline anxiety (2 studies), depression (1 study) predicted worse symptoms during long-term follow-up
- Short duration and constipation: better outcome

Management of IBS: Symptom-Based Approach

Identify IBS symptoms, presence of alarm features

Meets criteria, no alarm features → make diagnosis of IBS

Does not meet criteria, has alarm features → look for alternative diagnosis

Symptomatic treatment for predominant symptoms

Assess response to treatment

Good response → continue Rx

Poor response → reassess

Irritable Bowel Syndrome Management

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University of North Carolina School of Medicine
Chapel Hill, North Carolina
Overview of Treatment

- Patient-Provider relationship
- Lifestyle changes
- Diet, fiber, and probiotics
- CAM therapies
- Antispasmodics
- Antidepressants
- Psychological therapies
- Gut-specific
  - IBS-D: Alosetron
  - IBS-C: PEG, Lubiprostone, Linaclotide

CAM, complementary and alternative medicine; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; PEG, polyethylene glycol.

Patient-Provider Relationship

- “Cornerstone of treatment”
  - Listen actively
  - Determine reasons for visit
  - Identify and respond to concerns and expectations
  - Educate thoroughly
  - Set realistic expectations
  - Involve the patient in the treatment
- Positive physician-patient interaction reduces health care utilization and increases patient satisfaction

Lifestyle Changes Can Improve IBS Symptoms

- Diary card symptom tracking can help identify exacerbating and alleviating factors and increase sense of control
- Moderate exercise for 20 to 60 minutes x 3 to 5 days/week improves IBS symptoms

IBS and Diet: General Principles

- Among patients with IBS, diet is the #1 topic of interest
- 60% of subjects report that symptoms worsen after meals
- The act of eating as well as the specific foods consumed may be one of many factors that influences IBS
- Studying diet is quite challenging
- True food allergies are very rare
- General recommendations are possible, but diet should be tailored to the individual

What Are FODMAPs?

Fermentable Oligo-, Di-, Monosaccharides And Polyols

<table>
<thead>
<tr>
<th>Excess Fructose</th>
<th>Lactose</th>
<th>Fructans</th>
<th>Sorbitol</th>
<th>Raffinose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honey, apples, pears, peaches, mangos, fruit juice, dried fruit</td>
<td>Milk, ice cream, cheese, whey, curd</td>
<td>Wheat (large amounts), rye (large amounts), onions, leeks, zucchini</td>
<td>Apricots, peaches, artificial sweeteners and gums</td>
<td>Lentils, cabbage, Brussels sprouts, asparagus, green beans, legumes</td>
</tr>
</tbody>
</table>

Soluble Fiber Improves IBS-C, Insoluble Fiber Does Not

<table>
<thead>
<tr>
<th>RCTs</th>
<th>N</th>
<th>Response*</th>
<th>RR of Unimproved Symptoms (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12</td>
<td>591</td>
<td>4.8%</td>
<td>43%</td>
</tr>
<tr>
<td>Soluble</td>
<td>6</td>
<td>321</td>
<td>4.8%</td>
<td>36%</td>
</tr>
<tr>
<td>Insoluble</td>
<td>5</td>
<td>221</td>
<td>4.6%</td>
<td>46%</td>
</tr>
</tbody>
</table>

*Improved or resolved symptoms.

CI, confidence interval; NNT, number needed to treat; RCTs, randomized, controlled trials; RR, relative risk.
Probiotics and IBS

- **Probiotics**: live or attenuated microorganisms that have beneficial effects in humans
- **Meta-analysis of 35 RCTs (n=3452) determined**: “Probiotics are effective therapies for IBS” (global symptoms, pain, bloating, and gas) (NNT=7)
- “We found evidence to support the use of combinations of probiotics as a group, although not for any of the different combinations studied individually.”

Antispasmodic Medications

- **Smooth muscle relaxants with other anticholinergic effects**
  - Examples: dicyclomine, hyoscine
- **Meta-analysis of 22 RCTs comparing 52 different antispasmodics vs placebo (n=1778 patients)**
  - Significant heterogeneity among studies
  - Symptoms persist in 39% of patients receiving antispasmodics vs 56% of placebo-treated patients (RR: 0.68, 95% CI: 0.57-0.81)
  - **Appear most useful for abdominal pain**
- **Overall, these agents are cheap, widely available, and moderately efficacious for treating pain and bloating (and, possibly, urgency)**

Select Antidepressants Are Moderately Efficacious

- **Tricyclic Antidepressants (TCAs)**: 9 studies (N=319 drug vs 256 control)
  - Imipramine*, desipramine*, amitriptyline*, doxepin*, doses 25-150 mg
  - **Meta-analysis favors treatment**
- **Selective Serotonin Reuptake Inhibitors (SSRIs)**: 5 studies (N=113 drug vs 117 control)
  - Fluoxetine*, paroxetine*, citalopram*: dose 10-40 mg
  - **Meta-analysis favors treatment**
- **Putative mechanisms include**: Central effects (antinociception, +/- anxiolysis and antidepressive) Peripheral effects (SSRIs reduce gut transit, TCAs are modestly anticholinergic)

Probiotics: live or attenuated microorganisms that have beneficial effects in humans

Psychologically Based Therapies

<table>
<thead>
<tr>
<th></th>
<th>RR 95% CI</th>
<th>NNT 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Cognitive behavioral therapy</td>
<td>0.60</td>
<td>2-7</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>0.82</td>
<td>6-12</td>
</tr>
<tr>
<td>Dynamic psychotherapy</td>
<td>0.56</td>
<td>2.5</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>0.54</td>
<td>1.5-2</td>
</tr>
</tbody>
</table>

Anecdotal, it is critical to (a) identify appropriate candidates and (b) explain the rationale for psychological therapy

Alosetron for IBS-D

**Study**

- **Camilleri**
  - N: 370
  - Female %: 53
  - Response: Aloeotran, %: 66
  - Response: Placebo, %: 33
  - Therapeutic Gain, %: 32

- **Camilleri**
  - N: 647
  - Female %: 100
  - Response: Aloeotran, %: 44
  - Response: Placebo, %: 29
  - Therapeutic Gain, %: 15

- **Camilleri**
  - N: 616
  - Female %: 100
  - Response: Aloeotran, %: 43
  - Response: Placebo, %: 26
  - Therapeutic Gain, %: 17

- **Lembo**
  - N: 801
  - Female %: 100
  - Response: Aloeotran, %: 73
  - Response: Placebo, %: 57
  - Therapeutic Gain, %: 16

- **Jones**
  - N: 623
  - Female %: 100
  - Response: Aloeotran, %: 58
  - Response: Placebo, %: 48
  - Therapeutic Gain, %: 10

**Notes:**

- The above data are not currently US Food and Drug Administration approved for IBS.
- The use of CAM therapies may have significant side effects. It is important to discuss the potential benefits and risks with a healthcare provider before starting any CAM therapy. Always consult with a professional before making any changes to your medical regimen.
Female patients with chronic, severe IBS-D who failed other treatments

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

Prescribing program mandated by US Food and Drug Administration

Requires patient to sign attestation form

PEG is an alcohol that is not absorbed through the gut lumen. It creates an osmotic gradient that drives water into the lumen

139 adults with IBS-C were randomized to placebo or PEG 3350 plus electrolytes (PEG 3350+E)

During week 4 of treatment, PEG improved number of SBMs (P < .0001), but not pain in IBS-C patients

SBMs, spontaneous bowel movements.

Most common AE diarrhea (19.7% vs 2.5%)


Overview of Treatment

- Patient-Provider relationship
- Lifestyle changes
- Diet, fiber, and probiotics
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- Antidepressants
- Psychological therapies
- Gut-specific
  - IBS-D: Alosetron
  - IBS-C: PEG, Lubiprostone, Linaclootide