Case Studies in the Practical Evaluation and Management of Irritable Bowel Syndrome with Diarrhea

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Disclosures

Stephen Brunton, MD, has disclosed that he is on the advisory board for Abbott Diabetes, Salix, Astra Zeneca, Boehringer Ingelheim, Jansen, Lilly, Novo Nordisk, Teva, and Esperion; as well as on the speaker's bureau for Astra Zeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk.

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Learning Objectives

- Identify patients who are appropriately diagnosed based on history and symptoms
- Describe the role of Rome-IV criteria, colonoscopy, and other tests in diagnosis
- Differentiate subtypes of IBS
- Characterize the benefits and limitations of currently available prescription medications for IBS
- 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.

What is my diagnosis?

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]

IBS Classification[1]	Type of bowel habit alteration*
IBS-D†	Diarrhea-predominant
IBS-C	Constipation-predominant
IBS-M	Mixed-type has alternating periods of diarrhea and constipation

*Based on stool form only on days with at least one abnormal bowel movement
†Most common subtype, affecting approximately 40% of patients[2]

1. Lacy BE, et al. *Gastroenterology*. 2016;150:1393-1407.
2. Lovell RM, et al. *Clin Gastroenterol Hepatol*. 2012;10(7):712-721.e714.

Rome IV Criteria for IBS

Recurrent 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

Lacy BE, et al. *Gastroenterology*. 2016;150:1393-1407.

According to Rome IV criteria,

IBS is NOT a diagnosis of exclusion.

Is there anything worrisome in my history?

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[1]
  - 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

1. Ford AC, et al. *N Engl J Med*. 2017;376(26):2566-2578.

Conditions That Mimic IBS

- Lactose intolerance
- Fructose intolerance
- Small intestine bacterial overgrowth (SIBO)
- Celiac disease
- Inflammatory bowel disease
- Microscopic colitis
- Functional diarrhea
- Functional constipation

1. Lacy BE, et al. *J Clin Med*. 2017;6(11).
2. Lacy BE. *Int J Gen Med*. 2016;9:7-17.

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

1. Lacy BE, et al. *J Clin Med*. 2017;6(11).
2. Begtrup LM, et al. *Clin Gastroenterol Hepatol*. 2013;11(8):956-962.e951.

Reality Check

Which one of the following is true regarding the diagnosis of diarrhea-predominant irritable bowel syndrome?

1. The history and physical examination and colonoscopy are essential
2. A C reactive protein or fecal calprotectin level is recommended for patients without alarm symptoms
3. It is a diagnosis of exclusion
4. According to Rome IV, IBS-D is recurrent abdominal pain at least 1 day/week for a minimum of 30 days

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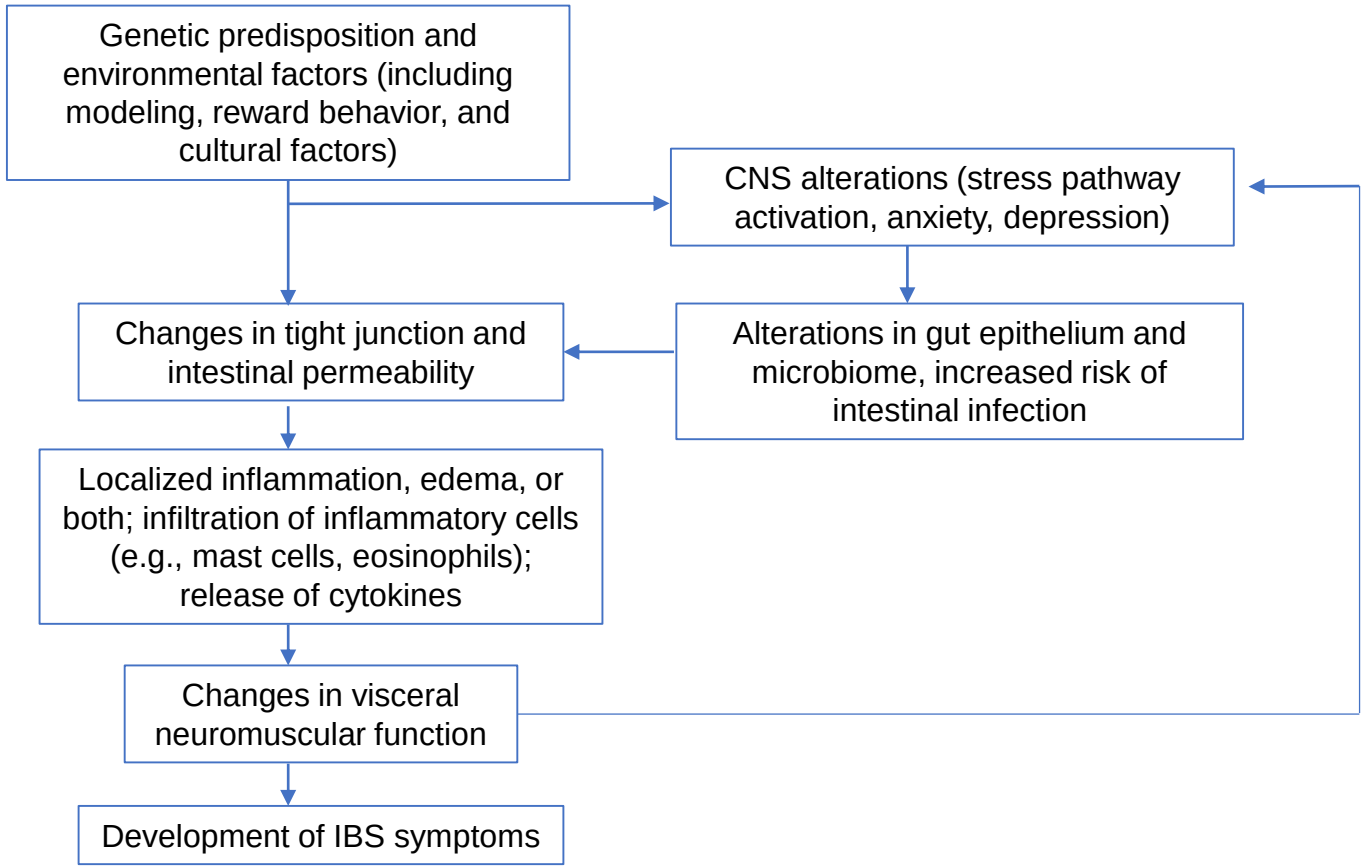
3. It is not a diagnosis of exclusion
4. According to Rome IV, IBS-D is recurrent abdominal pain at least 1 day/week for a minimum of ~~30 days~~ 3 months with associated features

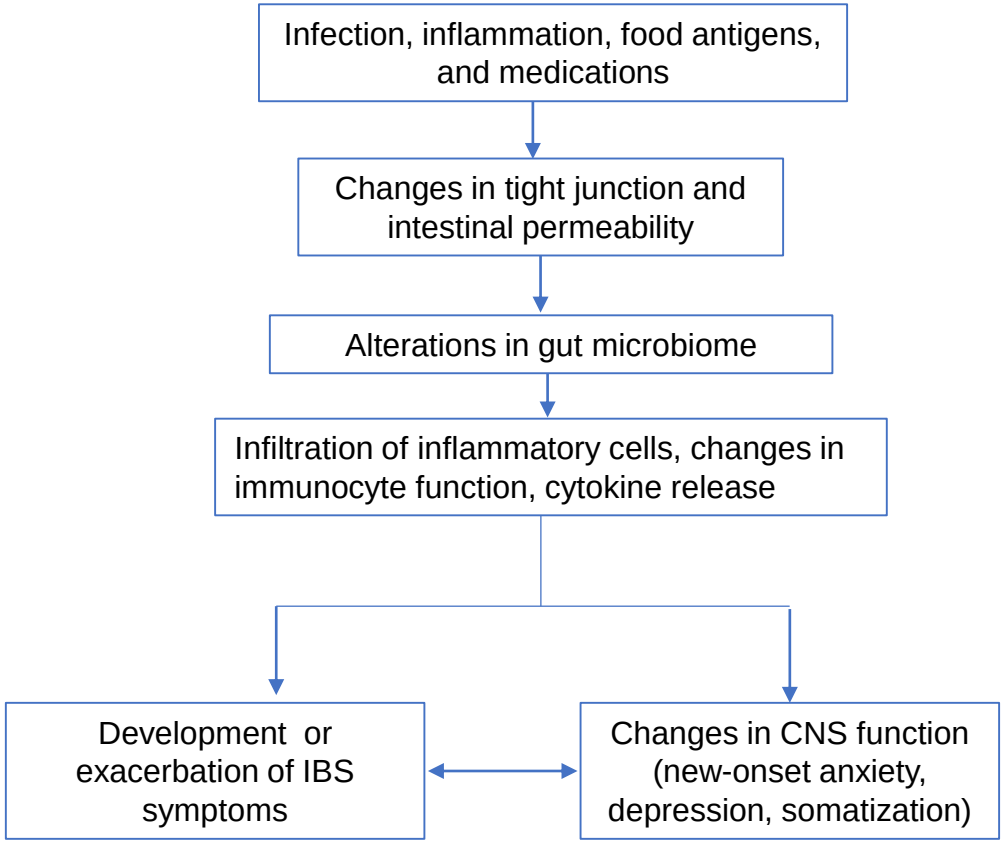
Why did my symptoms develop?

IBS may be a brain-gut disorder

Brain-Gut Pathway



…and a gut-brain disorder



IBS as a gut-brain disorder

- Increasing evidence implicates the GI microbiota in the pathogenesis of IBS[1]
- The intestinal microbiota in patients with IBS is altered compared with healthy controls[2-4]:
  - General decrease in diversity
  - Decreases in *Bifidobacterium* and *Lactobacillus* species
  - Increase in *Gammaproteobacterium* species
- Infectious gastroenteritis is the strongest risk factor for IBS-D[5,6]
  - Up to one third of individuals who have had IGE develop IBS-D (post-infectious IBS) with symptoms lasting months to years

1. Ford AC, et al. *N Engl J Med*. 2017;376(26):2566-2578.
2. Liu HN, et al. *Dig Liver Dis*. 2017;49(4):331-337.
3. Tap J, et al. *Gastroenterology*. 2017;152(1):111-123.e118.
4. Harper A, et al. *Foods*. 2018;7(2).
5. Downs IA, et al. *J Clin Gastroenterol*. 2017;51(10):869-877.
6. Iacob T, et al. *Clujul Med*. 2017;90(2):133-138.

Reality Check

Which one of the following is true about irritable bowel syndrome?

1. It appears to be a brain-gut disorder but not a gut-brain disorder
2. Approximately two-thirds of patients with infectious gastroenteritis develop IBS-D
3. The intestinal microbiota in patients with IBS is altered compared with healthy controls
4. Environmental factors seem to play only a minor role in pathogenesis

Reality Check

Which one of the following is true about irritable bowel syndrome?

1. It appears to be a brain-gut disorder ~~but not~~ and a gut-brain disorder
2. Up to one third ~~Approximately two-thirds~~ of patients with infectious gastroenteritis develop IBS-D
3. The intestinal microbiota in patients with IBS is altered compared with healthy controls
4. Environmental factors seem to play ~~only a minor~~ an important role in pathogenesis

Will my symptoms go away?

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

1. Ford AC, et al. *Gastroenterology*. 2014;109:1547-1561.
2. Pimentel M. *Am J Manag Care*. 2018;24:S35-S46.

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]

1. Lacy BE, et al. Gastroenterology. 2016;150:1393-1407.
2. Pimentel M. Am J Manag Care. 2018;24(3 Suppl):S35-s46.
3. Laird KT, et al. Clin Gastroenterol Hepatol. 2016;14(7):937-947.e934.
4. Moayyedi P, et al. European Gastroenterol J. 2017;5(6):773-788.

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

Abdominal pain/Discomfort	Bloating/Distension	Diarrhea
• Alosetron • Rifaximin • Antidepressants* (TCA, SSRI) • Smooth muscle antispasmodics (dicyclomine, hyoscyamine*) • Low FODMAP diet*	• Rifaximin • Probiotics* • Diet*	• Alosetron • Eluxadoline • Rifaximin • Cholestyramine* • Diphenoxylate-atropine* • Loperamide*

*Not approved for IBS-D by the US FDA
SSRI, serotonin selective reuptake inhibitor; TCA, tricyclic antidepressant

Do diet interventions or exercise help?

First-line lifestyle and dietary modifications may provide adequate symptom relief[1]

- 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]

1. Moayyedi P, et al. *Eur Gastroenterol J*. 2017;5(6):773-788.
2. Hajizadeh Maleki B, et al. *Cytokine*. 2018;102:18-25.
3. Johannesson E, et al. *World J Gastroenterol*. 2015;21(2):600-608.
4. Pimentel M. *Am J Manag Care*. 2018;24(3 Suppl):S35-s46.
5. Ford AC, et al. *N Engl J Med*. 2017;376(26):2566-2578.

Low FODMAP Diet

- Restricts short-chain carbohydrates known collectively as **f**ermentable **o**ligosaccharides, **d**isaccharides, **m**onosaccharides **a**nd **p**olyols (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]

1. Altobelli E, et al. Nutrients. 2017;9(9).
2. Cozma-Petrut A, et al. World J Gastroenterol. 2017;23(21):3771-3783.
3. Gibson PR. J Gastroenterol Hepatol. 2017;32 Suppl 1:32-35.
4. Schumann D, et al. Nutrition. 2018;45:24-31.
5. Varju P, et al. PLoS One. 2017;12(8):e0182942.

Will probiotics help?

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]

1. Ford AC, et al. *Am J Gastroenterol*. 2014;109(Suppl 1):S2-26.
2. Harper A, ,et al. *Foods*. 2018;7(2):1-20.
3. Raskov H, et al. *Gut Microbes*. 2016;7(5):365-383.

Will an antibiotic help?

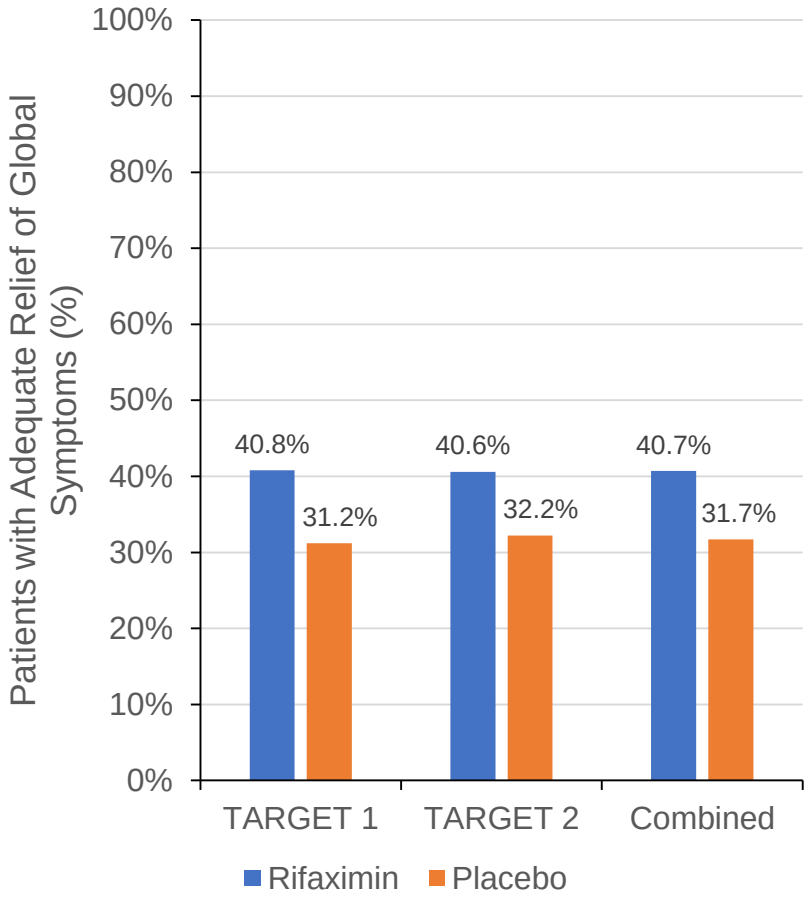
Antibiotics

- 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

1. Pimentel M, et al. *Dig Dis Sci*. 2017;62(9):2455-2463.
2. Pimentel M, et al. *N Engl J Med*. 2011;364(1):22-32.

Rifaximin TARGET 1 and TARGET 2 Trials

- Two phase 3 randomized controlled trials; N=1260[1]
- 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



Pimentel M, et al. *N Engl J Med*. 2011;364(1):22-32.

Rifaximin: Durability of Effect

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

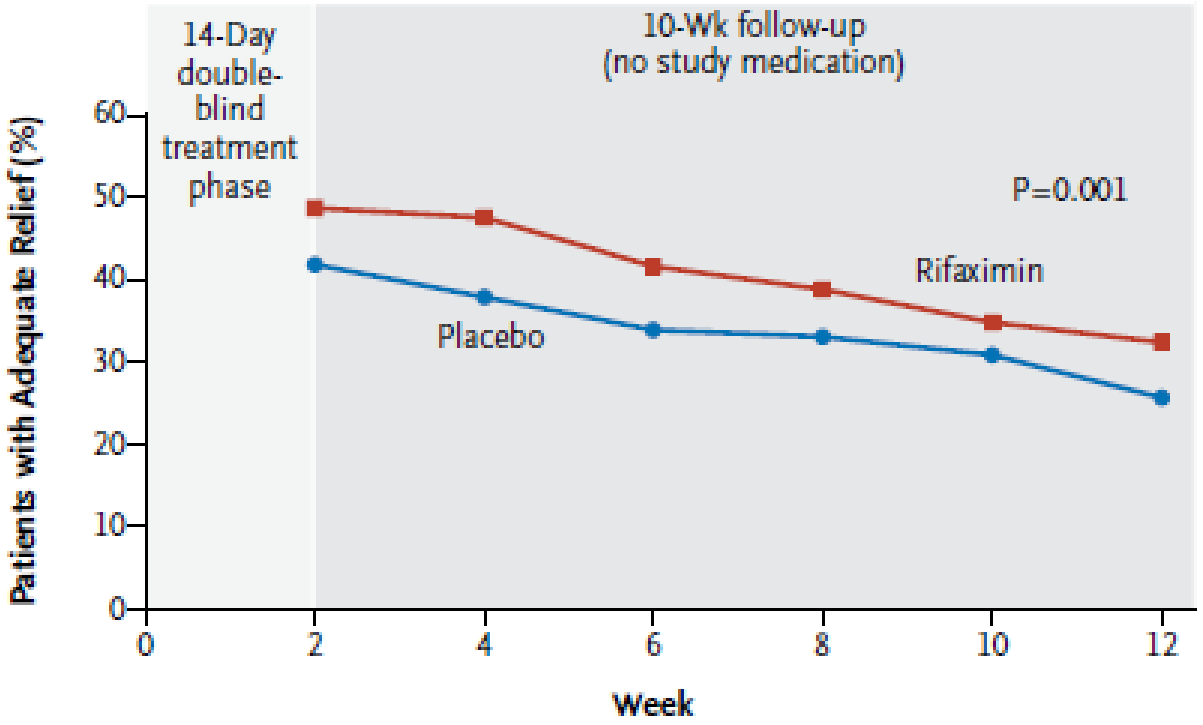


Figure 4. Percentage of Patients with Adequate Relief of Global IBS Symptoms in the TARGET 1 and TARGET 2 Studies Combined.

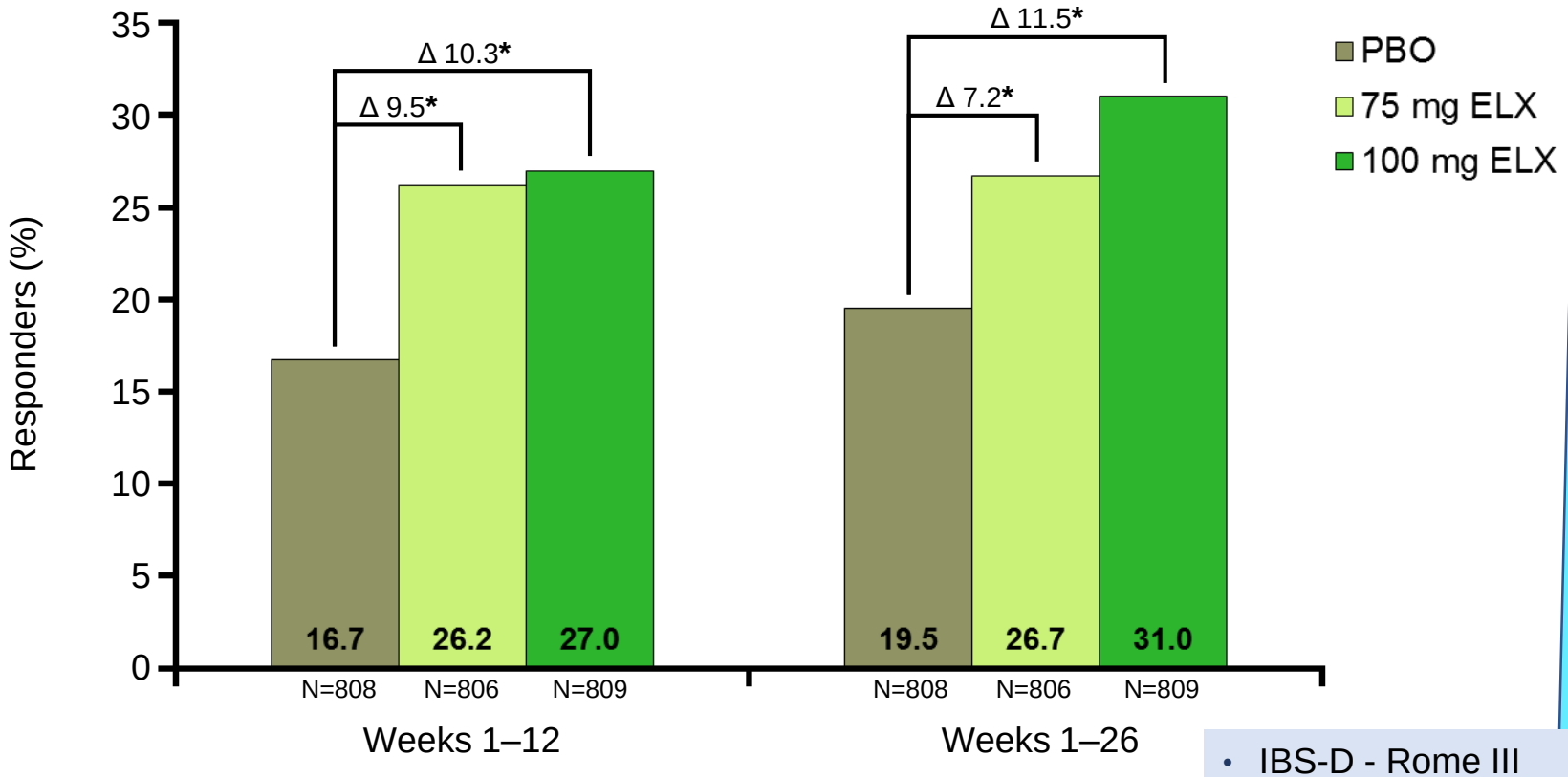
What if none of this works? Are there any other options?

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

Lembo A, Lacy BE, et al. NEJM, 2016

Eluxadoline primary endpoint: composite responders– pooled data



- IBS-D - Rome III
- 1-week baseline
  - BSS ≥5.5 (scale 1–7)
  - WAP >3.0 (scale 0–10)
  - GSS ≥2.0 (scale 0–4[a])

*P<0.001 vs placebo; Study 3001 – N=1281; Study 3002: N=1146; mean age = 45 y; 66% women; Rome III

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

Cash BD, et al. *Am J Gastroenterol.* 2017;112:365-374.

Alosetron for IBS-D

- A 5-HT_3 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.

Ford AC et al. *Am J Gastroenterol*. 2014;109 (Suppl 1):S2-S26.
FDA. Alosetron REMS.
http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM227960.pdf

Alosetron: Therapeutic Gain for IBS-D

Study	N	Female, %	Response: Alosetron, %	Response: Placebo, %	Therapeutic Gain, %
Camilleri[1]	370	53	60	33	27
Camilleri[2]	647	100	41	29	12
Camilleri[3]	626	100	43	26	17
Lembo[4]	801	100	73	57	16
Jones[5]*	623	100	58	48	10

*Comparison mebeverine† instead of placebo.
†Mebeverine not available in the US.

1. Camilleri M et al. *Aliment Pharmacol Ther.* 1999;13:1149-1159. 2. Camilleri M et al. *Lancet*. 2000;355:1035-1040. 3. Camilleri M et al. *Arch Intern Med*. 2001;161:1733-1740. 4. Lembo T et al. *Am J Gastroenterol*. 2001;96:2662-2670. 5. Jones R et al. *Aliment Pharmacol Ther.* 1999;13:1419-1427.

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

Therapy, Mechanism of Action	Efficacy by Symptom	Dose Regimen	Side effects/ Comments
Loperamide* [1-6] [μ-opioid agonist; decreases peristalsis, prolongs GI transit time, reduces fluid secretion in intestinal lumen]	Improves stool frequency, consistency, and urgency, but not bloating or in abdominal pain[3-6]	2 to 8 mg/day in divided doses	Abdominal cramps, constipation, bloating, nausea
Tricyclic Antidepressants* [7-11] [Effects on pain perception, mood, and GI motility]	May improve abdominal pain and diarrhea	10 to 25 mg at bedtime, then titrate up gradually based on symptom response and tolerability to 50-75 mg once daily	Drowsiness, dry mouth, dry eyes, orthostatic hypotension

*Not approved for IBS-D in the United States

1. Lacy BE, et al. *Int J Gen Med*. 2016;9:7-17. 2. Moayyedi P, et al. *United Eur Gastroenterol J*. 2017;5(6):773-788. 3. Cann PA, et al. *Dig Dis Sci*. 1984;29(3):239-247. 4. Efskind PS, et al. *Scand J Gastroenterol*. 1996;31(5):463-468. 5. Hovdenak N. *Scand J Gastroenterol Suppl*. 1987;130:81-84. 6. Lavo B, et al. *Scand J Gastroenterol Suppl*. 1987;130:77-80. 7. Ford AC, et al. *N Engl J Med*. 2017;376(26):2566-2578. 8. Pimentel M. *Am J Manag Care*. 2018;24(3 Suppl):S35-s46. 9. Camilleri M, et al. *J Clin Med*. 2017;6(11). 10. Chey WD, et al. *JAMA*. 2015;313(9):949-958. 11. Ford AC, et al. *Am J Gastroenterol*. 2014;109(9):1350-1365; quiz 1366.

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

Therapy, Mechanism of Action	Efficacy by Symptom	Dose Regimen	Side effects/ Comments
Bile Acid Sequestrants* [1-4] [Bind bile acids in the intestine to prevent free bile acid from stimulating electrolyte and water secretion in the colon]	Diarrhea - may be considered after other therapies targeting diarrhea have been unsuccessful	Cholestyramine 9 grams 2 to 3 times daily, colestipol 2 g once or twice daily, or colesevelam 625 mg once or twice daily	Constipation, nausea

*Not approved for IBS-D in the United States

1. Lacy BE, et al. *Gastroenterology*. 2016;150:1393-1407.
2. Lucak S, et al. *Therap Adv Gastroenterol*. 2017;10(2):253-275.
3. Moayyedi P, et al. *United Eur Gastroenterol J*. 2017;5(6):773-788.
4. Bajor A, et al. *Gut*. 2015;64(1):84-92.

Reality Check

Which one of the following is true regarding the treatment of diarrhea-predominant irritable bowel syndrome?

1. Initial treatment typically consists of lifestyle modification that includes increased exercise, a gluten-free diet, and stress reduction
2. A low FODMAP diet is of little benefit in reducing symptoms such as bloating and abdominal pain
3. Significant improvement in symptoms typically takes 6-8 weeks following initiation of rifaximin
4. Alosetron reduces stool frequency and abdominal pain, but is indicated only for women with IBS-D who have failed other treatments

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1. Initial treatment typically consists of lifestyle modification that includes increased exercise~~, a gluten-free diet,~~ and stress reduction
2. A low FODMAP diet ~~is of little benefit~~ has a 70% response rate in reducing symptoms such as bloating and abdominal pain
3. Significant improvement in symptoms typically takes ~~6-8~~ 4 weeks following initiation of rifaximin
4. Alosetron reduces stool frequency and abdominal pain, but is indicated only for women with chronic, severe IBS-D who have failed other treatments

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.

Questions?

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Thank you!