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# A Practical Approach to Managing IBS: Understanding and Applying the Evidence for Optimal Care

This activity is supported by independent educational grants from Allergan, Ironwood Pharmaceuticals and Salix.

## OVERVIEW

**William Chey, MD**, and **Amy Foxx-Orenstein, DO**, offer their expert insights into the diagnosis and management of irritable bowel syndrome (IBS). These experts discuss several cases that illustrate issues you might encounter when caring for patients with IBS, and will help you navigate the diagnosis and treatment of this common complaint, including making the IBS diagnosis without unnecessary diagnostic testing, recognizing signs that suggest an organic cause for symptoms, and selecting treatments that will address patients' most troubling symptoms.

## CONTENT AREAS

- Diarrhea-predominant IBS
- Constipation-predominant IBS

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# A Practical Approach to Managing IBS: Understanding and Applying the Evidence for Optimal Care

## Target Audience

This activity was developed for primary care physicians, gastroenterologists, physician assistants, nurse practitioners, nurses and other health care professionals who have an interest in IBS treatment.

## Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Establish a timely diagnosis of IBS based upon diagnostic criteria
- Incorporate shared decision-making and individualized patient education into clinical encounter
- Individualize treatment plans for patients with IBS-C based upon clinical data, guidelines, and recommendations
- Tailor treatment plans for patients with IBS-D based upon best available evidence on current therapies, clinical guidelines, and recommendations

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- Read the learning objectives and faculty disclosures.
- Participate in the activity.
- Complete the post-test and activity evaluation.
- Participants who successfully complete the evaluation and the post-test (scoring 70% or higher in a maximum of 3 attempts) will receive Category 1.5 Category 1-B CME credit.

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## **Introduction**

Hello . I'm Dr. Amy Foxx-Orenstein, professor of medicine at the Mayo Clinic College of Medicine. Dr. William Chey of the University of Michigan Health System and I will be presenting three cases of patients with irritable bowel syndrome and discussing issues in diagnosis and management for each.

While some patients will switch between IBS sub-types, the cases we focus on here are for patients with diarrhea or constipation predominant irritable bowel syndrome. We also consider a case where a patient developed IBS following a

gastrointestinal infection. Although we recommend referral to a gastroenterologist for patients who do not respond to dietary modification and over-the-counter treatment, many patients are treated for IBS in the primary care setting. We approached these cases keeping in mind that not all patients are going to be able to see a gastroenterologist and provide guidance for both the initial management and for recognizing cases where the patient does not respond to these approaches. Thank you for joining us for this activity.



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### **Case 1 (part 1):** *A patient with persistent diarrhea after a giardia infection*

#### **History of Current Complaint**

Collin is a 27-year-old Caucasian male in his second year of graduate school. His symptoms of intermittent diarrhea, flatulence, and mild lower abdominal pain began over 18 months ago, several days after returning from a 5-day backpacking trip. Within several days of returning from this trip, he felt feverish and run down, and developed nausea, vomiting, and frequent watery diarrhea that he describes as the worst he has ever had. He was seen at a university health clinic where they collected a stool sample (he never called to confirm the results) and treated him with a 5-day course of metronidazole and as-needed loperamide. By the end of treatment, he felt better overall, but still had gas and loose stools. Although he infrequently has weeks where he feels “normal,” most weeks he will have days where he has diarrhea 3 or more times a day, gas, and mild lower abdominal cramping (pain severity 3 or 4 on a scale of 10). He has tried over-the-counter probiotics (mainly yogurt and kefir). On days where he cannot miss class or a meeting, he uses bismuth subsalicylate preventively, but his symptoms have been a source of anxiety because they frequently interfere with his daily study routine, social activities, and exercise. He does not have watery diarrhea and does not experience nocturnal symptoms, has maintained his weight within its normal range, and denies hematochezia. None of his friends on the trip developed similar symptoms, and he has no family history of irritable bowel disease, inflammatory bowel disease, or a gastrointestinal cancer.

#### **Which of the following is true about the long-term prognosis for post-infectious irritable bowel syndrome?**

- A. The majority of patients will have spontaneous improvement and resolution of symptoms over time
- B. Up to half of patients will have stable or worsening symptoms without treatment
- C. Patients with diarrhea as the primary symptom will often transition to constipation-predominant IBS
- D. The prognosis and disease course are similar to typical IBS

#### **Discussion Points**

This patient likely has post-infectious irritable bowel syndrome (PI-IBS), which occurs in a subset of patients (3%-36%) following a gastrointestinal infection.<sup>1</sup> Any type of infectious gastroenteritis—bacterial, viral, or parasitic—can lead to the development of post-infection IBS (PI-IBS), though bacterial gastroenteritis is most commonly associated with this condition. In this patient, giardiasis may have been the trigger for his symptoms. Risk factors for PI-IBS include severity of the index infection, psychological comorbidity, anxiety or stress at the time of the index infection, and female gender. Establishing a post-infectious etiology can be reassuring to the patient since these patients typically have a better prognosis—two-thirds of these patients will have improvement and resolution of symptoms within 6-8 years.<sup>2</sup> His symptoms of frequent loose stools, abdominal cramping and pain, and variable stool pattern are typical of IBS-D (Table 1), while he has no alarm features that would suggest organic disease (Table 2). Although his stool frequency is consistent with moderate diarrhea when he is experiencing symptoms, Rome IV diagnostic criteria focus on stool consistency rather than stool frequency.<sup>3</sup> In the absence of concerning features, additional diagnostic testing would help rule out organic disease. A complete blood count, fecal calprotectin, and celiac disease screening would be appropriate in this case, as well as giardia antigen testing and a parasite screen to address the patient’s concern that he has an ongoing infection. In the absence of weight loss, GI bleeding, iron deficiency, or a family history of celiac disease, colorectal cancer, or inflammatory bowel disease, diagnostic imaging is not routinely indicated.<sup>4</sup>





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### Case 1 (part 2): Post-infectious IBS-D, work-up and treatment

#### Additional Investigation

The physical exam is unremarkable and the patient is in good health overall. In addition, the blood and CRP values are within normal ranges, and celiac screening is negative, as are the giardia antigen and parasite screens. The patient describes being under considerable pressure at school and is anxious about completing his qualifying exams. You discuss with him the possibility that he developed IBS following gastroenteritis acquired during his backpacking trip, and that this type of IBS typically improves and resolves with time. You discuss the possibility that stress and diet could be contributing to his symptoms and encourage him to maintain his exercise routine.

**Which one of the following would be the most appropriate additional therapy for this patient at this time?**

- A. Loperamide titrated to effect
- B. A FODMAP elimination diet
- C. Alosetron
- D. Eluxadoline

#### Discussion Points

A conservative approach that focuses on over-the-counter medications, dietary modification, and education is appropriate for the patient with mild, post-infectious IBS symptoms. Loperamide can be used when symptoms arise, or as a means of preventing symptoms, as might be the case when a patient goes to work, travels on a plane, or goes out to a restaurant. IBS-D patients should be instructed to start loperamide once or twice per day, and can titrate the dose up to 6 tablets per day. Although it may not improve abdominal pain or discomfort, or other IBS symptoms, loperamide can reduce stool frequency and improve stool consistency.<sup>5</sup> Some patients with mild symptoms will find that a full tablet of loperamide will cause constipation; for these patients, using a pediatric liquid formulation is an easy way for them to lower their dose. If a patient with IBS-D does not improve despite dose escalation of loperamide, other medical

options include a low dose TCA, 5-HT<sub>3</sub> receptor antagonist (alosectron or ondansetron), or the mixed opioid receptor agonist/antagonist eluxadoline. Recently-published data suggests that eluxadoline can provide benefits to IBS-D patients who have not adequately responded to loperamide.<sup>6</sup>

Although this patient's abdominal pain is mild, an antispasmodic (eg, hyoscyamine or dicyclomine) could be used when he anticipates situations that might provoke symptoms. As a class, antispasmodics have been shown to provide symptomatic relief, but may be limited by anticholinergic adverse effects.<sup>5</sup> Peppermint oil can relax smooth muscle and may have an effect on pain sensitivity.<sup>5</sup> In this case, peppermint oil taken up to 3 times per day on an as-needed basis could be considered.<sup>7</sup>

Several lifestyle modifications may also be helpful for this patient. Probiotics can improve global IBS symptoms, but the most effective formulation or dose has not been identified.<sup>8</sup> Regular exercise has been shown to improve overall IBS symptoms, and in this young, healthy patient, maintaining his exercise routine may also be helpful.<sup>9</sup> A diet low in fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs), fat, insoluble fiber, and caffeine, and regular, small meals can reduce symptom severity.<sup>10</sup> The patient should understand that addressing his or her symptoms with a low-FODMAP diet is a 3-step process of Elimination, Sensitivity identification, and Personalization of their diet. During the first 4-6 weeks, FODMAPs should be eliminated to determine if this approach will benefit them. For patients who experience an improvement during the elimination period, individual FODMAPs can be reintroduced to determine what foods they are sensitive to. Based on the results of the previous steps, a personalized maintenance diet can be developed. This 3-step process is best accomplished with the assistance of a registered dietician, and patient education resources, such as [www.MyGINutrition.com](http://www.MyGINutrition.com), can also be helpful.



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### **William Chey, MD, Summary**

This patient exhibits classic features of post infectious IBS. Post infectious IBS occurs in up to a third of patients who will seek treatment for IBS. In these cases, patients associate the onset of their symptoms with an acute bacterial, viral, or parasitic GI infection.

It's important to identify these patients since they're likely to follow a different clinical course than the typical patient with IBS.

Unlike garden variety IBS, remember that two thirds of post infectious IBS patients will experience spontaneous symptom resolution within a period of five to six years. So, the traditional message that we give IBS patients—and, I might add not a very hopeful message, that we really don't know why they have IBS and that it tends to be a chronic, lifelong condition really doesn't hold for patients that have post infectious IBS. For these patients, a much more hopeful message can be relayed to the patient.

You can tell them that their illness is clearly related to changes in function and sensation of the GI tract that occur as a consequence of their acute GI illness, and that most patients get better over time. So, what we need to do in the short term is find solutions for their ongoing symptoms while their body heals itself. This patient has fairly mild IBS symptoms and, as such, providers should focus on establishing a confident diagnosis and doing exactly what we just said: explaining to the patient that they have... that the patient has post infectious IBS.

Educating them on what that means both in terms of why they have the symptoms they do and what to expect going forward, that hopeful natural history oftentimes, in and of itself, often is therapeutic for the patient. I can't tell you how many times

patients who've come in... we've gone [to] take a careful history, identified that they have post infectious IBS... I've explained that to them and they've actually become tearful because they feel like they finally have an explanation for why they have this problem, and they're hopeful because most of the time their gonna get better on their own.

It's also important to talk about the role of diet and lifestyle in all patients with IBS, not just patients with post infectious IBS, but all patients with IBS. The low FODMAP diet is an evidence-based, dietary intervention with IBS. Gluten free diets have also been utilized, less evidence-based but some patients certainly get benefit from this strategy. Remember that if you use a low FODMAP diet for IBS, a 2 to 6-week exclusion period is more than adequate. They should not be placed on long periods of a highly restrictive diet.

If a patient doesn't respond, you can abandon the diet strategy and move on something else. If the patient responds, remember that the low FODMAP diet is a 3-phase process that includes not only exclusion, but also reintroduction of foods that contain individual FODMAPs to identify a patient's individual food sensitivities, and then using that information to fashion a more liberal diet that the patient can take forward.

So thinking about ESP: excluding FODMAPs to determine if someone is FODMAP-sensitive, determining their sensitivities, and then personalizing a diet for them to take forward over the long term.

In addition, over-the-counter medications can be very helpful for patients with mild and frequent symptoms, so, for example, an antidiarrheal either to treat symptoms acutely or, perhaps even more helpful in many patients, using prophylactically to prevent symptoms where one anticipates that they might have problems. Like, for example, if they were



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going to give an important business presentation or travel, using an antidiarrheal to prevent them from having problems with diarrhea can be life changing. Also, using things... supplements, like for example, peppermint oil, can be very helpful for abdominal pain and bloating, and some of the more recently released and enteric-coated formulations can mitigate the risk of developing heartburn as a consequence of using peppermint oil.

And then, finally, probiotics can be very helpful for gas and bloating. If you go to the prescription medication space, drugs like tricyclic antidepressants can be very helpful, particularly for pain. Rifaximin, the nonabsorbable antibiotic, which is

FDA-approved for IBS-D, can be very helpful for some of these patients.

Drugs like 5-HT<sub>3</sub> receptor antagonist... so drugs like ondansetron or what you're probably more familiar with is Zofran or alosetron can also be very, very helpful.

Finally, a recent entry into the IBS-D treatment armamentarium is eluxadoline or Viberzi, which can be very useful in terms of helping patients with their IBS-D symptoms. Remember that if you're going to use eluxadoline you shouldn't use this drug in individuals who have undergone a previous cholecystectomy or consume more than 3 alcoholic beverages per day.

### **Case 2 (part 1):** *A patient with frequent episodes of postprandial urgency and diarrhea, abdominal pain, and bloating*

#### **History of Current Complaint**

Anita is a 32-year-old African American woman with a history of waxing and waning gastrointestinal symptoms, including abdominal cramps and pain, flatulence, and diarrhea. She has had symptoms since high school, but in the past year her symptoms have become more frequent and bothersome. Sometimes her symptoms are provoked by an emotionally stressful event or a "rich, unhealthy meal," and she develops severe cramping and urgency within a half hour, that is relieved by defecation. Otherwise, she frequently feels bloated, distended, has diffuse abdominal pain, and often feels urgency before a bowel movement. Her typical bowel movement is loose and poorly formed (Bristol Stool Scale 5-6), but she has at least one episode a week where her stool is watery and unformed (Bristol Stool Scale 7). Occasionally she wakes early with abdominal pain, but denies nighttime symptoms.

When she has been able to maintain a gluten- and dairy-free diet, she feels like her symptoms have been better, though never completely resolved; currently she is limiting her intake to dairy-free foods and a predominantly vegetarian

diet. She has tried daily peppermint oil to relieve bloating, and currently uses loperamide as needed and a daily Lactobacillus/Bifidobacterium probiotic supplement. During the past 2 years, she has gained 3-5 pounds despite intermittent dieting and regular light exercise. Her IBS Severity Scoring System (Table 3) score places her at the lower end of the range for moderate IBS, with the greatest contributions coming from pain severity ("severe"), satisfaction with bowel habits ("very unhappy"), and interference with activities ("quite a lot").

The patient's physical exam is unremarkable, her CBC, fecal calprotectin, and C-reactive protein results are within the normal range, and a celiac test is negative. She was tested and treated for H pylori infection 6 years ago, and although follow-up showed that antibiotic treatment was successful, it did not alleviate her symptoms. As you discuss her treatment expectations, she explains that while she feels she can at least reduce the frequency of the postprandial diarrhea and cramping through diet, the constant gastrointestinal symptoms are causing her to feel fatigued and unmotivated.



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**Which one of the following therapies would be most appropriate for this patient at this time?**

- A. Eluxadoline 100 mg BID
- B. A tricyclic antidepressant at a starting dose of 10 mg/day and up to a maximum dose of 20 mg/day
- C. A tricyclic antidepressant at a starting dose of 75 mg/day and up to a maximum dose of 150 mg/day
- D. A bile acid sequestrant (eg, colesevelam 1.875 g BID)

### Discussion Points

Because her symptoms improve with defecation and are associated with a change in stool form, she meets the diagnostic criteria for IBS-D (Table 1). She also lacks any of the alarm features that would indicate organic disease (Table 2). Unlike nocturnal diarrhea, the nocturnal pain described by this patient is not discriminative for organic disease. Routine screening for celiac disease can be cost-effective and avoids the risk of long-term consequences from missing this diagnosis, and would be appropriate in a patient with IBS-D.<sup>11</sup> Patients with a normal C-reactive protein (<0.5 mg/dL) or fecal calprotectin (<40 µg/g) are unlikely to have inflammatory bowel disease, and colonoscopy to investigate this possibility is not indicated.<sup>12</sup>

Patients who have tried and not responded to over-the-counter treatments should be considered for either referral to a gastroenterologist for a more integrated approach, or are candidates for adjunctive prescription therapies. For this patient,

an antidepressant, bile acid sequestrant, or eluxadoline could all be considered at this stage. The specific treatment selected should be individualized based on the patient's expectations and concerns, prior treatments, and the symptoms each class or compound is most effective against.

Antidepressants can be useful for both patients with IBS-D or IBS-C. The overlap of IBS symptoms with depression or anxiety initially led to the investigation of antidepressants for IBS, but at sub-psychoactive doses this class can relieve visceral pain.<sup>5</sup> In general, antidepressants are started at a low dose, and then adjusted after several weeks of treatment. A TCA (amitriptyline, nortriptyline, and imipramine are commonly used) could help with the patient's pain and overall symptoms, and the anticholinergic effect on gastrointestinal smooth muscle may slow transit time, making this class useful for patients with diarrhea-predominant IBS.<sup>13</sup> Bile acid sequestrants (eg, cholestyramine, colestipol, or colesevelam) are used empirically since some patients with IBS-D will have bile acid malabsorption, leading to increased colonic motility; however, this class can exacerbate bloating, flatulence, abdominal discomfort, and constipation.<sup>14,15</sup> Eluxadoline is an opioid receptor agonist that has been approved for patients with IBS-D. In phase 3 trials (N=2427) that followed patients at least 26 weeks, eluxadoline improved abdominal pain and stool consistency within 4 weeks of starting treatment.<sup>16</sup>

### Case 2 (part 2): Moderate IBS-D, follow-up and second-line treatment

#### Treatment Plan

You reassure Anita that her symptoms are consistent with IBS-D, and that you would recommend treating this diagnosis without additional testing. You talk to her about some of the triggers and exacerbating factors for her symptoms, and direct her to resources that will help her adhere to a low FODMAP diet. She also decides to try amitriptyline, and you prescribe an initial dose of 10 mg/day taken in the evening, with instructions

to increase the dose to 20 mg after 2-4 weeks if she does not feel that her symptoms have improved. She asks about continuing loperamide, and you recommend that she use it as needed, and may consider reducing the dose. To help assess her response to treatment, you provide her with a symptom diary, and ask her to at least track her symptoms for several weeks right after starting treatment, and for several more weeks right before returning for her follow-up appointment.





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After 3 months, Anita returns for a follow-up appointment. She has been on a low FODMAP diet and increased her dose of amitriptyline to 20 mg; while her symptoms have improved somewhat, she continues to feel bloated and has episodes of cramping and diarrhea still. A referral to the gastroenterology clinic has at least a 4-week wait for an appointment, and she asks what additional treatments could be tried in the meantime.

**Which one of the following would be the most appropriate next step in the treatment of this patient?**

- A. Continue amitriptyline at the current dose and increase the dose of loperamide
- B. Discontinue amitriptyline and switch to eluxadoline 100 mg BID
- C. Discontinue amitriptyline and try a 2-week trial of rifaximin 550 mg TID
- D. Discontinue amitriptyline and switch to alosetron 0.5 mg BID

### **Discussion Points**

Even after an adequate trial of amitriptyline, this patient's symptoms have not been satisfactorily resolved. Either eluxadoline or rifaximin would be acceptable choices for the next step in treatment, since both could address her abdominal pain. Recently published data for eluxadoline suggests that it can provide benefits to IBS-D patients who have not adequately responded to loperamide.<sup>6</sup> Patients should start at the 100 mg dose level, and can decrease the dose to 75 mg if adverse effects (nausea, constipation, and abdominal pain) become problematic. Those with a history of biliary disorders or alcohol use may be at risk for pancreatitis. Rifaximin is a broad-spectrum antibiotic that is poorly absorbed, which largely limits its effect to the gastrointestinal tract.<sup>17</sup> A 2-week trial of rifaximin is recommended, and in randomized trials, this regimen improved diarrhea, global IBS symptoms, and bloating.<sup>17</sup> These benefits persisted through a 10-week follow-up period, and rifaximin is generally well tolerated. Patients can be retreated with rifaximin twice, and treatment did not appear to affect antibiotic sensitivity of the intestinal flora.<sup>18,19</sup>

Selective 5-HT<sub>3</sub> antagonists can reduce visceral pain and slow intestinal transit time. In this class, alosetron has been approved for women with severe IBS-D symptoms despite treatment with other conventional therapies, but the risk of serious adverse events has led to a greater scrutiny of its use. Prescription of alosetron is under a risk evaluation and mitigation program because of an increased risk of ischemic colitis and severe constipation.<sup>20</sup> In clinical trials, 10% of alosetron-treated patients discontinued because of constipation, although the risk of serious complications from constipation does not appear to be significantly increased.<sup>20</sup> Ischemic colitis has an incidence of 0.15%, and is usually transient and without long-term sequelae. When discussing alosetron use with patients, an important finding is that the majority of adverse events have an onset within 30 days of starting treatment

### **Amy Foxx-Orenstein, DO, Summary**

In this case we have a patient with more moderate symptoms than the first and she doesn't respond well to the initial treatment. Although it's appropriate to refer this patient to a gastroenterologist who can coordinate multidisciplinary treatment, we want to consider how this patient could be approached, either after an initial consultation with gastroenterology or, as in this case, entirely in the primary care setting, since waiting for a referral would delay her treatment.

As a GI consultation is not immediately available, she has already escalated amitriptyline without satisfactory improvement, and symptoms of bloating, pain, and diarrhea persist. A reasonable next step would be to switch to a different agent. In this case, eluxadoline 100 mg BID should reduce these symptoms, but be sure to ask about any history of pancreatitis, biliary disorders, and quantify alcohol intake. Or a 14-day course of rifaximin is another effective treatment for reducing bloating and IBS symptoms. I'd continue FODMAP. If she hasn't seen a dietician yet, I would encourage her to. Higher doses of loperamide or the addition of bile acid binding



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agents may aggravate bloating and other symptoms. So neither would be on my first choice at this time.

So, how do you decide that the patient hasn't responded to treatment and when should you consider changing your approach?

I rely on patient's input as to whether or not the plan has worked. To help with that, I invite all patients to keep a simple Bristol Stool Scale and GI symptom diary for a few weeks after any therapy change, and again a few weeks before they return to clinic. Symptom data is better than recall and can be a useful guide to making therapy decisions.

There are instances where every effort should be made to have a patient evaluated and, at least initially, treated by a specialist. If the patient has alarm symptoms, see Table 2, symptoms are not improving with stepwise care, or are worsening, I'd recommend calling the gastroenterologist's office and requesting an early appointment, or asking their advice until the patient could be seen.

### **Case 3 (part 1):** *A patient with constipation, pain during defecation, and occasional blood in her stool*

#### **History of Current Complaint**

Mariabella is a 46-year-old advertising executive and mother of 2 who has a history of infrequent, difficult, and painful bowel movements with hard stool. She has had intermittent constipation since her first pregnancy, but now most of her bowel movements she describes as difficult and painful, and producing hard stools (Bristol Stool Scale 1-2); she does not feel completely evacuated after passing these stools. She does not have regular bowel movements, often attempts to defecate without success, and typically moves her bowels twice per week. Between bowel movements she feels bloated most of the time and experiences abdominal discomfort and cramping. Sometimes she has seen bright red blood in her stools. When her symptoms are at their worst, she has no interest in exercise, sex, or social activities, and has difficulty concentrating at work.

She has tried to increase her fruit and vegetable intake, eats dried fruits daily, and has a high-fiber cereal or bran muffins for breakfast daily; in addition, she is currently using a psyllium-based fiber supplement. She drinks coffee daily and

has 2 to 3 alcoholic beverages a week. While she does not have a family history of inflammatory bowel disease, colorectal cancer, or celiac disease, her mother has mentioned having constipation but has never sought treatment for it. Two years ago, her previous doctor recommended a colonoscopy to investigate her symptoms, and found no signs of malignancy or inflammatory bowel disease. At that time, celiac disease and thyroid function testing was also negative. Her physical exam reveals mild left lower quadrant abdominal tenderness. Her medical history is significant for mild hypertension treated with hydrochlorothiazide, and she also takes a daily multivitamin and iron supplement. All values on her CBC were within the normal ranges.

#### **What is the role of fiber in IBS-C?**

- A. Soluble fiber (eg, psyllium) can improve pain and other IBS symptoms in some patients
- B. Insoluble fiber (eg, wheat bran) can improve pain, bloating, and other IBS symptoms in some patients
- C. Neither soluble nor insoluble fiber improve IBS symptoms or constipation
- D. Soluble and insoluble fiber are equally effective in improving IBS symptoms and constipation



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### Discussion Points

A diagnosis of IBS-C can be made based on the patient's symptoms of intermittent abdominal pain in association with hard or lumpy stools. The diagnostic criteria for IBS (Table 1), along with identification of alarm features that would indicate organic disease (Table 2), can identify most patients with IBS, without extensive diagnostic testing.<sup>21</sup> Although blood in the stool is an alarm feature that might normally warrant additional investigation, investigation of constipation alone is usually not sufficient justification for a colonoscopy; for this patient, her recent colonoscopy is sufficient to rule out organic disease.

Her diet and medications also should be reviewed to ensure they are not contributing to her symptoms (Table 4 and 5). Although she has increased her intake of dietary fiber, a recent

### Case 3 (part 2): Moderate IBS-C, follow-up and second-line treatment

Along with educational materials to help guide some modifications to her diet, Mariabella agrees to an 8-week trial of PEG. You recommend a starting dose of 17 g/day with instructions to increase the dose over the course of weeks up to 51 g/day taken over 3 doses until she sees improvement in her stool consistency, with the caution that PEG may not improve her abdominal cramping or discomfort. You also encourage her to try and exercise whenever she can, even if it is only taking a short walk, given her sedentary workday. You raise the issue of her reasons for using an iron supplement, and ask her to consider discontinuing it at least temporarily.

At her follow-up appointment, the patient reports that she gradually increased her PEG to 17 g 3 times per day. She did notice an increase in stool frequency to every other day. She states that her stools are softer but “sticky,” making it difficult to get clean after a bowel movement. In addition, she still does not feel fully evacuated after a bowel movement. At her mother's suggestion, she tried bisacodyl 10 mg twice-daily

meta-analysis suggests that not all fiber is equivalent.<sup>5,22</sup> Insoluble fiber found in whole-wheat, vegetables, and wheat bran may not have an effect on symptoms, and can contribute to abdominal discomfort and bloating.<sup>23</sup> Soluble fiber—found in psyllium, oat bran, legumes, and fruits—can reduce constipation symptom severity.<sup>5,22,23</sup> In addition, caffeine and alcohol can contribute to her constipation if her water intake is insufficient. Hydrochlorothiazide can cause diuresis in the initial weeks of therapy, but this effect diminishes with time.<sup>24</sup>

Polyethylene glycol (PEG) is commonly used in patients who have not improved with soluble fiber treatment, and would be a reasonable first attempt at treatment in this case.<sup>5,25</sup> This osmotic laxative can improve stool frequency and consistency, but may not improve (or can worsen) other abdominal symptoms such as pain, discomfort, or bloating.<sup>5</sup>

for a week. This also provided her with some benefit for her constipation-related complaints, but her abdominal cramping has become intolerable.

You discuss having Mariabella see a gastroenterologist. During her first visit, the gastroenterologist confirms that Mariabella has no history of previous abdominal or pelvic surgery. He performs a digital rectal examination, which demonstrates normal anal sphincter tone and normal relaxation of the puborectalis and anal sphincter, making dyssynergic defecation less likely.

### Which of the following statements about lubiprostone, linaclotide, and plecanatide is most accurate?

- A. None of these treatments have been compared in a randomized, head-to-head trial
- B. Diarrhea is a common side effect of prescription prosecretory treatments
- C. Plecanatide should only be considered for patients who have not responded to treatment with linaclotide
- D. Linaclotide should be discontinued in patients who still have abdominal symptoms 4 weeks after initiating treatment



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### Discussion Points

When fiber and/or PEG fail to improve a patient's symptoms, the prosecretory agents lubiprostone, linaclotide, or plecanatide can be considered. All 3 agents have been tested in phase 3, placebo-controlled clinical trials, but no head-to-head trials have been done.

Lubiprostone 8 µg twice daily stimulates intestinal fluid secretion by activation of chloride channels, and is approved for treating IBS-C in women over 18 years of age. In 2 phase 3 trials, more lubiprostone-treated patients reported an improvement in bowel and abdominal symptoms (eg, discomfort/pain, bloating, straining) than those who received a placebo (17.9% vs 10% of patients in the placebo group,  $P=0.001$ ).<sup>26</sup> The response rates to lubiprostone improved over time in a 52-week follow-up study: after 1 month of treatment, 16% of patients responded, and this increased to 37%-44% after 10-13 weeks.<sup>27</sup> At the doses used for patients with IBS (higher doses are used for other indications), nausea occurred in 8% of patients, but could be reduced when lubiprostone was taken at mealtimes; diarrhea occurred in 7% of patients (compared to 4% of placebo-treated patients).<sup>28</sup>

Linaclotide is also approved for treating IBS-C, and acts to increase intestinal chloride secretion through increased cyclic guanosine monophosphate production.<sup>29</sup> In a 26-week placebo-controlled trial of patients with IBS-C (N=804), 34% responded to treatment (defined as an improvement in abdominal pain and increase in the number of complete spontaneous bowel movements) compared to 14% who received placebo.<sup>30</sup> Patients also saw significant improvements in abdominal pain, bloating, bowel symptoms, straining, and stool consistency. The improvement in abdominal pain and bloating may be delayed 8-12 weeks, compared to the improvement in stool frequency. Diarrhea—which occurred in 20% of patients (compared to 3% of patients who received placebo)—can also

be a concern and lead to treatment discontinuation, but taking linaclotide 30-60 minutes before breakfast can reduce this adverse effect.<sup>31</sup>

Plecanatide was approved in January 2018 for IBS-C based on 2 phase 3 trials. In both studies, significantly more patients (22%-30%, compared to 14%-18% in the placebo groups) had an improvement in abdominal pain and an increase in complete spontaneous bowel movements for at least 6 weeks in the 12-week study. Diarrhea occurred in 4% of plecanatide-treated patients, compared to 1% of those receiving placebo.<sup>32</sup>

### William Chey, MD, Summary

In this final case we have a patient who presents on the other side of the clinical spectrum of IBS, that is with constipation. As with IBS-D the presence of abdominal pain leads us to suspect IBS rather than functional constipation or just typical chronic constipation. Remember that constipation is a multisymptom disorder; in other words, it's not just about stool frequency. I know that, as doctors, we tend to focus on how often a person is moving their bowels and use that to define whether they're constipated or not, but realize that many patients that endorse the clinical complaint of constipation actually move their bowels on an everyday or every other day basis, which is normal.

It's really other symptoms, things like straining, hard or lumpy stools, incomplete evacuation and sensation of incomplete evacuation or sensation of anal/rectal blockage that define constipation for some of these individuals. Another thing that patients will tell you if you ask them, is some of these patients actually endorse the use of so called digital maneuvers. That is, actual digital disimpaction and everybody's aware of that, but also 2 other digital maneuvers that clinicians need to be aware of: one is pressing around the anus to facilitate defecation, and





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vaginal splinting in women, which is a pretty clear sign that a woman has a significant rectocele.

So those digital maneuvers we'll talk about in just a moment, have some predictive value in identifying patients with so called outlet obstruction constipation. Remember that not a lot of testing is needed to identify patients with IBS-C. Certainly routine colorectal screening is always indicated in everybody, and patients with symptoms suggestive of IBS-C are no different. So, if a person is over the age of 50 and has never had a colonoscopy they should absolutely have a colonoscopy.

On the other hand, if a 29-year-old comes in with constipation, particularly if it's mild to moderate in severity, you probably don't need to do a colonoscopy unless they have so called warning signs or alarm features. More on that in a moment.

But in this case, the patient did report an important warning sign that is blood with her stool. Rectal bleeding is a warning sign or alarm feature, that is, it's a clinical feature that's thought to increase the likelihood of an organic diagnosis. Like colon cancer or inflammatory bowel disease, for example. There are obviously differences between patients who report a little spotting on the toilet tissue after a bowel movement and those that have true or frank rectal bleeding. For example, painless spotting of small amounts of blood on the toilet tissue after a bowel movement usually is a sign of hemorrhoids.

On the other hand, patients that describe painful defecation, and often, you know, with or without bleeding, you should be thinking about an anal fissure, which can occur in patients with really hard or lumpy stools or excessive straining, by the way. So, bottom line here is that you need to take a careful history as we've talked about, the multi symptoms that define constipation. We need to assess specifically for warning signs or alarm

features like rectal bleeding, a family history of important organic diseases like colon cancer, inflammatory bowel disease, and you need to do a careful physical examination. Not just of the abdomen but also a perianal inspection as well as a digital rectal examination. It's very important to do those things in patients that you see with the clinical complaint of constipation.

Relevant to colonoscopy, remember that if a patient has warning signs or alarm features, you're gonna want to do a colonoscopy even before that age of 50 that we typically recommend a colonoscopy for the purposes of colorectal cancer screening. One thing to say about this population though—that I see in my referral practice oftentimes—is patients that come in with complaints of constipation that have [had] multiple colonoscopies. You can make the argument that one colonoscopy is very reasonable but if a person has a high-quality colonoscopy with an adequate preparation they don't need repeated colonoscopies. It's not going to do anything to help in making your diagnosis and it's not going to help the patient to get better.

Now, dyssynergic defecation is a condition where patients are unable to coordinate the series of activities and events that affect the anal rectum and abdominal wall musculature that allows them to evacuate stool from the rectum. So, remember that to normally evacuate stool from the rectum one needs to contract their abdominal wall musculature. This increases intrarectal pressure. Now, concurrently, there needs to be relaxation of the puborectalis muscle, a muscular sling that goes around the distal portion of the rectum and creates and angulation that is an important incontinence mechanism. Relaxation of the puborectalis allows straightening of that anal-rectal angle, and then finally there needs to be relaxation of the anal sphincter So you need to have contraction of the abdominal wall musculature, relaxation of the puborectalis,



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straightening of the anal-rectal angle, and relaxation of the anal sphincter, to be able to normally defecate.

If one or more of those things go awry, patients can't normally defecate and that is so called "dyssynergic defecation." Now why am I spending so much time telling you about this? The reason for that is because patients with dyssynergic defecation typically don't improve with laxative therapy. So, a really important clinical pearl for all of you listening in the audience today is that patients with constipation who don't respond to over-the-counter or prescription laxative therapies are enriched for dyssynergic defecation, and these are precisely the patients that need to be referred to a gastroenterologist for detailed physiological testing. And if dyssynergia is found referred to a physical therapist for physical therapy and biofeedback training which is the optimal therapy for dyssynergic defecation. Remember, as well, that patients that don't get better with laxative therapy are also enriched with other forms of outlet obstruction constipation. So not just dyssynergic defecation but also mechanical causes of distal rectal obstruction. So, things like intussusception, rectal prolapse, enterocele, and rectoceles are all more common in populations of patients who are not responding to laxative therapy.

So, take home message for those of you in the audience, there are a number of different over-the-counter and prescription medications, which can be highly effective. If you're going to use over-the-counter and prescription medications, remember to give patients specific advice in regards on how to start and how to titrate up the therapy to optimize response, and that's true for fiber supplements as well as osmotic laxatives, stimulant laxatives, and the prescription medications, which now come in 2 or 3 different doses depending on which medication you're talking about.

If an individual doesn't respond to over-the-counter or prescription laxatives, those are individuals that need to be referred to a gastroenterologist for physiologic testing. Obviously, if a patient has so called warning signs or alarm features, they should be referred to a gastroenterologist for more detailed structural evaluation, with colonoscopy for example; patients who don't respond to laxatives are more likely to have any of a number of different causes of outlet obstruction constipation that are treated with either biofeedback training and physical therapy or surgical therapies if they are one of those problems that can lead to mechanical obstruction.

So, hopefully you found those comments helpful in terms of managing your patients with chronic constipation.



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**Table 1: Rome IV Criteria for Irritable Bowel Syndrome<sup>33</sup>**

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with at least 2 of the following:

- Related to defecation
- Associated with a change in the frequency of stool
- Associated with a change in the form/appearance of stool

These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

**Table 2: Alarm Features Suggesting Organic Disease<sup>33</sup>**

Symptom onset after age 50

Severe or progressively worsening symptoms

Unexplained weight loss

Nocturnal diarrhea

Family history of gastroenterological disease\*

Rectal bleeding or melena

Unexplained iron-deficiency anemia

\*Including colon cancer, celiac disease, or inflammatory bowel disease

**Table 3: Questions on the IBS Severity Score Table<sup>34</sup>**

How severe is your pain?

If currently in pain, how severe is your abdominal pain?

If you currently have abdominal distention, how severe is it?

How satisfied are you with your bowel habits?

How much does your IBS affect or interfere with your life in general?



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**Table 4: Medications Associated with Constipation**

Analgesics

Anticholinergics

(including antihistamines, antispasmodics, antidepressants, and antipsychotics)

Cation-containing agents (eg, iron supplements, antacids, barium)

Neurally active agents

(eg, opiates, antihypertensives and calcium channel blockers, and 5HT<sub>3</sub> antagonists)

**Table 5: Medications Associated with Diarrhea**

Antiarrhythmics

- Digoxin, procainamide, quinidine

Antihypertensives

- ACE-inhibitors, angiotensin II receptor blockers, beta-blockers, hydralazine, methyldopa

Cholesterol-lowering agents

- Clofibrate, gemfibrozil, statins

Diuretics

- Acetazolamide, ethacrynic acid, furosemide

CNS-active agents

- Anti-anxiety drugs (eg, alprazolam, meprobamate)
- Levodopa
- Anticholinergic drugs
- Fluoxetine
- Lithium
- Tacrine

Endocrine

- Metformin

Antacids

- H<sub>2</sub>-receptor antagonists, magnesium, misoprostol, proton pump inhibitors

Non-steroidal anti-inflammatory drugs

Antibiotics

Vitamin C

Magnesium





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