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Discontinued Products, Uncertain Data, Changing Options: Selecting Effective and Reliable Treatment for IBS

A Report of a Symposium Presented During
the American College of Gastroenterology
Annual Scientific Meeting
October 14, 2007
Philadelphia, Pennsylvania

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with irritable bowel syndrome.

Statement of Need/Program Overview: The Clinical Symposium Report *Discontinued Products, Uncertain Data, Changing Options: Selective, Effective and Reliable Treatment for IBS* will discuss the most recent updates emerging in this therapeutic area based on an ACG symposium, which took place in October 2007 in Philadelphia, PA. An abundance of new data has recently come to light in this area, and a distinct educational need exists in the gastroenterology & hepatology community for an updated understanding of the latest treatment strategies.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe current parameters for irritable bowel syndrome (IBS) diagnosis
2. Review the historic and current treatment options for the different IBS symptom patterns (constipation-predominant, diarrhea-predominant, mixed pattern)
3. Explain the current and potential role of antibiotics in the treatment of each symptomatic characterization of IBS

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and *Gastroenterology & Hepatology*.

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Discontinued Products, Uncertain Data, Changing Options: Selecting Effective and Reliable Treatment for IBS

A Report of a Symposium Presented During the American College of Gastroenterology Annual Scientific Meeting
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Case 1

Dr. Mark Pimentel presented a case of a 20-year-old woman who took a spring break trip to Cancun. Three days after arriving, she developed travelers' diarrhea, which was watery and without blood. The diarrhea resolved by the time she returned to college; however, she has lately been experiencing abdominal cramps and intermittent diarrhea, which has worsened since she started preparing for finals.

This appears to be a classic case of postinfectious irritable bowel syndrome (IBS). It is important to note that at least three months have passed since the acute infection so that residual infection can be ruled out.

Incidence of Postinfectious IBS

Dr. Pimentel noted that case outbreaks of food poisoning indicate that between 7% and 31% of individuals exposed to a pathogen subsequently develop postinfectious IBS or chronic altered bowel function.[1-7] Postinfectious IBS is generally defined as bowel dysfunction occurring at least 3 months after the original infection. Some controversy had surrounded the question of whether these symptoms are due to lingering infection rather than IBS. However, Neal and colleagues found that many patients diagnosed with postinfectious IBS still had symptoms after 6 years, at which point infection would no longer be a consideration.[4]

Two meta-analyses indicate that the average rate of IBS after gastroenteritis is approximately 10%, compared with 0.35–1.2% in the general population.[8,9] Risk factors for postinfectious IBS include female sex,[4] increased diarrhea during the acute infection, younger age with acute diarrhea, and absence of vomiting.[3] Psychology also appears to play a role; several studies have shown that a patient's psychologic disposition at the time of the acute infection affects his or her likelihood of developing postinfectious IBS.[2,10]

Mearin and colleagues evaluated outcomes following a large *Salmonella* enteritis outbreak in Spain and found that at one year, 12% of individuals developed postinfectious IBS (relative risk, 7.8; 95% confidence interval [CI], 3.1–19.7).[6] Moreover, 17% of individuals developed nonulcer dyspepsia (relative risk, 5.2; 95% CI, 2.7–9.8); nausea was a risk factor for dyspepsia.

Pathogenesis of Postinfectious IBS

Dr. Pimentel further stated that approximately 90% of people spontaneously recover following a case of acute gastroenteritis, while the other 10% develop postinfectious IBS. The mechanism of postinfectious IBS is unclear though contributing factors may include genetic susceptibility, an abnormal host response, and the intensity of the toxin (*Campylobacter* is worse than *Escherichia coli*, which is worse than *Salmonella*).

To investigate the pathogenesis of postinfectious IBS, Pimentel and colleagues conducted studies in which rats were randomized to be infected with *Campylobacter jejuni* 81-176 or placebo.[11] Three months after infection spontaneously cleared, stool form was altered in 57% of *Campylobacter*-infected rats versus 7.4% of mock-infected controls ($P<.001$) and 27% of the rats infected with *Campylobacter* had developed small intestinal bacterial overgrowth (SIBO). Moreover, nearly 90% of the

Campylobacter-infected rats that developed SIBO had altered stool form—a significantly higher proportion than observed in rats that were infected with *Campylobacter* but did not develop SIBO. These rats also weighed significantly less than rats who did not develop SIBO, whether they had been infected with *Campylobacter* ($P<.05$) or were mock-infected ($P<.001$). This study demonstrates an association between bacterial overgrowth following acute infection and the development of symptoms consistent with postinfectious IBS.

Postinfectious IBS is thought to begin with acute gastroenteritis, which exerts some effects on the small bowel. Some studies have suggested that *Campylobacter* toxin affects myoelectrical functioning of the small bowel, leading to dysmotility and bacterial overgrowth. Overgrowth of hydrogen-producing bacteria leads to diarrhea-predominant IBS (IBS-D) and IBS-mixed patterns. Conversely, the presence of methane leads to slow transit and the development of constipation-predominant IBS (IBS-C). Stress may contribute to the process by inducing corticotropin-releasing factor, which promotes dysmotility.

Mechanism of Treatment for Postinfectious IBS

Dr. Pimentel also discussed treatment options for patients with postinfectious IBS. In patients with postinfectious IBS, antibiotics are administered in hope of reducing or eliminating SIBO; a prokinetic agent is then used to enhance motility, resulting in a delayed recurrence of overgrowth. Pimentel and colleagues showed that administering tegaserod after treating overgrowth extends the average time to recurrence from 58 days to more than 200 days.

Several antibiotics have been used to treat SIBO; however, none of these antibiotics have been approved by the US Food and Drug Administration (FDA) for the treatment of IBS. Additionally, the value of a therapeutic trial of antibiotics in IBS patients without a history of preceding infectious gastroenteritis or travelers' diarrhea has not been established. Antibiotics that could be used for postinfectious IBS include metronidazole, tetracycline, ciprofloxacin, neomycin, and rifaximin. For the first three agents, data in IBS are limited. Neomycin was evaluated in a randomized, double-blind, placebo-controlled study of 111 patients with IBS.[12] Rifaximin is showing great promise in IBS due to its efficacy in reducing bacterial overgrowth, its safety profile, and its nonsystemic absorption.

Rifaximin has been evaluated in two randomized, double-blind, placebo-controlled studies in IBS.[13,14] One study enrolled 124 patients with abdominal bloating and flatulence, more than half of whom had IBS, and another study enrolled 87 patients with IBS. The trial of rifaximin in IBS enrolled patients aged 18–65 years who met the Rome I criteria for IBS.[14] Patients who had taken oral antibiotics in the previous three months or were currently taking tegaserod or antidepressants were excluded. Pimentel and colleagues randomized subjects to a 10-day treatment with rifaximin (n=43) or placebo (n=44) and evaluated them after 10 weeks. This delay between the study medication and the evaluation allowed the investigators to observe whether eradicating the bacterial overgrowth would improve IBS symptoms, not whether the drug would directly improve symptoms. Over the 10-week period, patients who had received a 10-day rifaximin regimen had significantly greater mean percent global improvements compared with placebo-treated patients ($P=.02$) (Figure 1). Rifaximin is the first drug to demonstrate a lasting effect in IBS.

Unanswered Questions Regarding Postinfectious IBS

Given how common food poisoning is, and given that about 1 in 10 patients with food poisoning develop IBS, could many cases of IBS in fact be due to food poisoning? This is a difficult question to answer because a patient presenting with IBS has often had symptoms for years and does not remember an initial acute gastroenteritis event. However, Dr. Pimentel has observed that in his own clinic 20% of patients do remember that event, which suggests that more than 20% of IBS is postinfectious. Could treating acute gastroenteritis with an antibiotic possibly prevent postinfectious IBS? Moreover, could treating travelers with prophylactic antibiotics prevent postinfectious IBS? Whether such strategies could reduce the burden of IBS in the community remains to be seen.

Case #2

Dr. Anthony Lembo presented a case of a 35-year-old slightly overweight woman presents with a 5-year history of abdominal pain and bloating associated with hard stools and gas. She had frequent abdominal pain during childhood. Her current pain is located in the lower abdomen and is often associated with bloating and visible abdominal distention to the point that she looks pregnant. She generally passes stool daily but with straining and incomplete evacuation. Stress and menstruation exacerbate her symptoms. Although her condition has had some effects on her quality of life, she denies any warning symptoms such as weight loss, blood in her stools, fevers, chills, or nocturnal symptoms. There is no family history of colorectal cancer or inflammatory bowel disease (IBD). Her limited workup included an extensive physical examination, including a negative rectal examination. Routine laboratory tests, including a complete blood count (CBC), chem-20, and celiac antibody test, were all normal. Based on this information, the patient appears to have IBS with constipation.

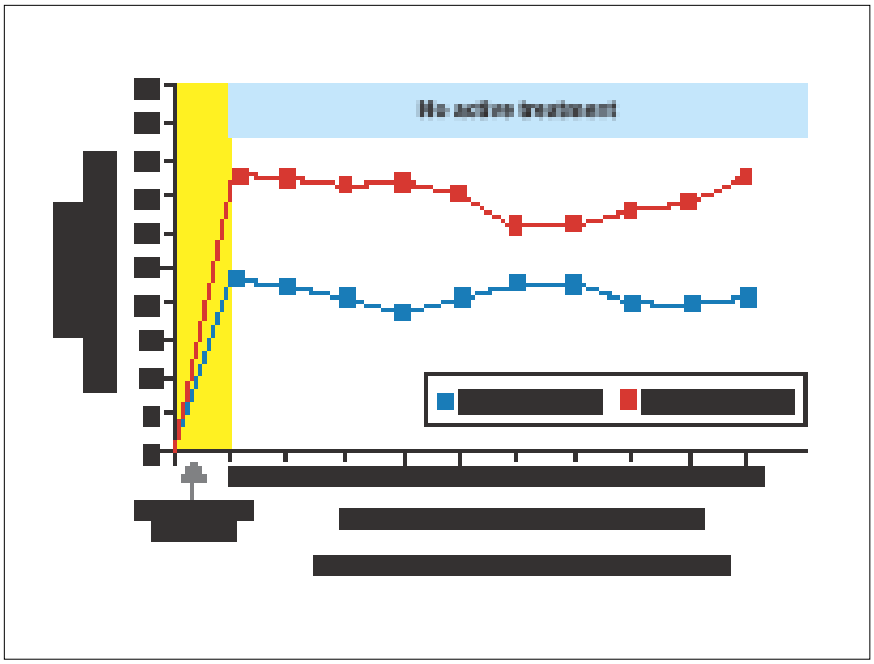

Figure 1. Rifaximin in irritable bowel syndrome: efficacy results.

Adapted from Pimental et al.[14]

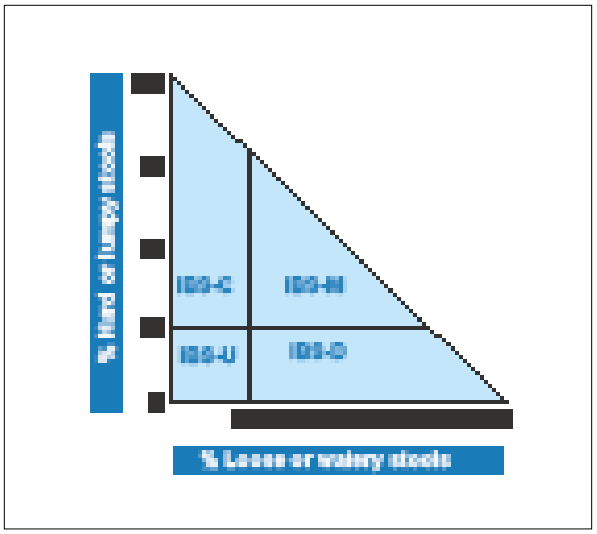

Figure 2. Subtypes of IBS according to bowel form.

IBS-C=constipation-predominant; IBS-D=diarrhea-predominant; IBS-M=mixed bowel pattern; IBS-U=unsubtyped.

Adapted from Longstreth et al.[15]

Diagnosing IBS

Dr. Lembo noted that the Rome III criteria for diagnosing IBS include recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with at least two of the following: improvement with defecation; onset associated with change in stool frequency; or onset associated with change in stool form.[15] The Rome III subtypes are based on bowel form, which refers to the proportion of stools that are hard or lumpy versus loose or watery (Figure 2). If more than 25% of bowel movements are associated with hard or lumpy stools and fewer than 25% are associated with loose stools, the patient meets the new definition for IBS-C. Conversely, if more than 25% of stools are loose or watery and less than 25% are hard or lumpy, the patient has IBS-D. These criteria differ from those in Rome II.

Factors Contributing to IBS

IBS is a heterogeneous disorder with multiple potential contributing and interacting factors, including visceral hypersensitivity, gastrointestinal dysmotility, genetic predisposition, infection, bacterial overgrowth, inflammation, brain-gut dysregulation, altered neuroendocrine function, and food sensitivity. Intestinal gas is also thought to be involved; it has been hypothesized that the dysmotility common in IBS may lead to gas retention, either through excessive swallowing of air or bacterial overgrowth.[16] This gas retention leads to increased wall tension in the small intestine and visceral hypersensitivity, which causes the symptoms associated with IBS.

Dr. Lembo further stated that data regarding the role of SIBO in the development of IBS have been mixed. Most, but not all, studies have shown that lactulose breath tests are more likely to be positive in patients with IBS

versus controls, with a prevalence ranging from 10% to 84%. A study investigating jejunal aspirates did not show significant differences in SIBO in patients with IBS versus controls at greater than 10^5 cfu/mL, a level considered the standard cutoff for SIBO. However, differences were seen at lower cutoffs, including greater than 10^4 cfu/mL (24% vs 4%; *P*=.02) and greater than 5000 cfu/mL (43% vs 12%; *P*=.002).17 Whether SIBO causes the symptoms of IBS remains to be determined, but data from Pimentel and colleagues suggest that a proportion of patients with IBS improve with rifaximin or neomycin.[12,18]

Treatment for IBS-C

Dr. Lembo went on to observe that treatment options for IBS-C are limited, though diet and lifestyle factors should be first addressed. Dietary recommendations include reducing lactose, sorbitol, and fructose, avoiding carbonated beverages, and reducing starches and legumes. For the case patient, stress appears to be a factor, and therefore stress relief may help improve symptoms. Pharmacologic treatment options include fiber, laxatives, tegaserod (available only through treatment IND [investigational new drug] program), antibiotics, probiotics, antidepressants, and, potentially, lubiprostone.

Efficacy of Pharmacologic Treatments in IBS

Fiber has been evaluated in 13 randomized clinical trials, with evaluated sources of fiber including wheat bran, corn fiber, calcium polycarbophil, ispaghula, and psyllium.[19] Most studies have been low to intermediate in quality with small sample sizes. Only ispaghula showed global improvements in IBS in four of five studies, with improvements in ease of passage of bowel movements but no changes in pain. Side effects associated with fiber include increased intestinal gas, bloating, and intestinal pain—the very symptoms the fiber is intended to treat. Therefore, although fiber is recommended, patients should be started on a low dose in anticipation of these side effects.

Laxatives have not been evaluated in clinical trials in IBS. However, a multitude of studies have investigated laxatives for the treatment of chronic constipation. The best-studied osmotic laxatives include polyethylene glycol and lactulose, which have received a Grade A recommendation for chronic constipation by the American College of Gastroenterology. Although stimulant laxatives are commonly used in chronic constipation, clinical trial data are insufficient to make recommendations in this indication.

Tegaserod initially showed promise, as it was associated with therapeutic gains of 5–19% over placebo in patients with IBS-C.[20-24] However, tegaserod was taken off the market in 2007 after a retrospective safety analysis of pooled clinical trials showed a significant increase in the incidence of cardiovascular ischemic events with tegaserod compared with placebo.[25] The overall incidence of cardiovascular events (including myocardial infarction, stroke, and unstable angina pectoris) was 13 of 11,614 patients treated with tegaserod versus 1 of 7,031 patients treated with placebo.

The efficacy of probiotics in IBS has been investigated by Whorwell and colleagues. In a study of 362 women with IBS, administration of *Bifidobacterium infantis* at a dose of 1×10^8 cfu/mL was associated with significantly greater improvements in global symptoms at 4 weeks compared with placebo (*P*<.02).[26] Interestingly, higher doses did not appear to confer greater improvements, possibly due to a manufacturing variance. This product is currently available over the counter.

Several classes of antidepressants have been evaluated in IBS. Meta-analyses of studies involving tricyclic antidepressants have shown conflicting results.[27,28] Because of their anticholinergic effects, these agents are probably more effective in IBS-D. Selective serotonin reuptake inhibitors are more likely to be considered for the treatment of IBS-C, although data with these agents are limited. They may cause patients with IBS-C to feel better, but have a limited effect on pain.[29]

With regard to antibiotics, rifaximin has also demonstrated efficacy in patients with bloating, which is a major symptom of IBS. Sharara and colleagues evaluated rifaximin at a slightly lower dose than was used in the IBS study (400 mg twice daily for 10 days vs 400 mg 3 times daily in the IBS study) and measured efficacy 10 days after the end of treatment.[13] For both the overall study population and for the subgroup of patients with IBS, rifaximin was superior to placebo in regard to the proportion of patients experiencing global relief ($P \leq .05$ for both; Figure 3).

Finally, lubiprostone is approved for the treatment of chronic constipation at a dose of 24 μg twice daily. At Digestive Disease Week 2007, Drossman and colleagues presented results from two phase III trials evaluating a lower dose of lubiprostone (8 μg twice daily) versus placebo in 1171 patients with IBS-C.[30] In a pooled intent-to-treat analysis, the proportion of patients with symptom relief was significantly higher with lubiprostone versus placebo after two months (*P*=.003) and three months (*P*=.003).

Case #3

Dr. William Chey presented a case of a 33-year-old woman who reports a longstanding history of intermittent abdominal cramping, bloating, and irregular bowel habits since adolescence. She typically passes 2–4 loose stools each day. Every two weeks she experiences "constipation."

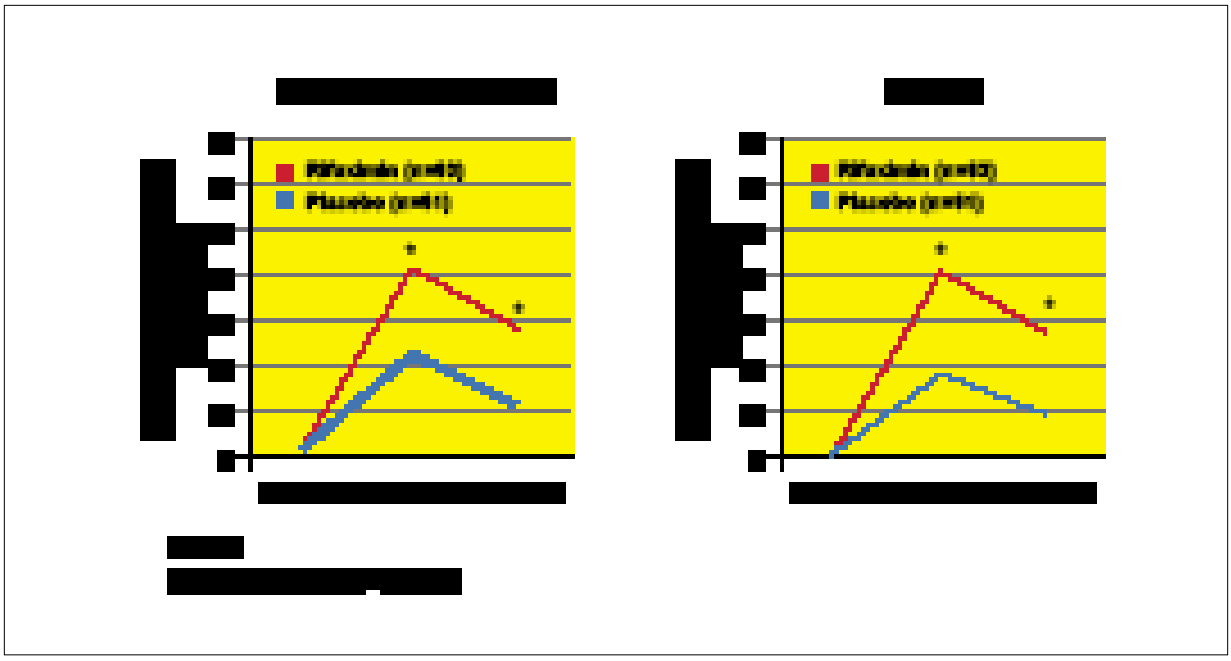

Figure 3. Effect of antibiotics in bloating.

After tx=after 10 days of treatment; Post-tx=10 days after end of treatment.

Adapted from Sharara et al.[13]

Although her symptoms worsen after eating, she has not identified specific food triggers. Excluding dairy products for several weeks did not affect her symptoms, which have been worsening in frequency and severity. She has lost 5 pounds in the last 6 months, but denies anorexia or gastrointestinal bleeding. Her mother has similar symptoms and has been treated for IBS. Her primary care provider has tried fiber, dicyclomine, and loperamide, none of which helped. She also has a history of infertility.

A physical examination of this patient reveals a well-developed white female, 5'4" and 125 pounds. Blood pressure is 110/60 and pulse is 66. Lower abdominal tenderness is noted and digital rectal examination reveals normal sphincter tone and hemoccult-negative brown stool. Screening blood tests ordered by her primary care provider—including CBC, metabolic profile, thyroid-stimulating hormone, and stool for ova and parasites (O & P)—were all normal.

IBS—A Diagnosis of Exclusion?

Dr. Chey concluded that the most probable clinical diagnosis for this patient is IBS. However, diagnostic evaluation in IBS remains a contentious issue. Clinicians can use a symptom-based approach such as the Rome criteria to first identify the patient's predominant symptoms and then to exclude alarm symptoms such as unexplained weight loss, fever, bleeding, or a family history of cancer, IBD, or celiac disease.[31] A detailed physical examination should then be performed to exclude organic conditions. The difficulty comes in discerning the broad differential diagnosis for symptoms that would otherwise constitute IBS. In a random survey of clinicians across the United States, Spiegel and colleagues found that a majority (76%) of primary care physicians considered IBS a diagnosis of exclusion, compared with 42% of gastroenterologists and 8% of experts.[32] Considering IBS a diagnosis of exclusion had significant financial consequences: providers who believe IBS is a diagnosis of exclusion on average order 1.6 more tests and spend $364 more than those who do not ($P<.0001$).

The case patient has several potential warning signs, with her borderline weight loss, history of worsening symptoms, and a family history of IBS. Cash and associates evaluated the utility of diagnostic tests by assessing the pretest probability of various organic diseases in patients with IBS symptoms versus the prevalence of these diseases in the general population.[33] The investigators found that the pretest probability of most organic gastrointestinal diseases, including IBD, colorectal cancer, and gastrointestinal infection, was less than 1%. Other conditions,

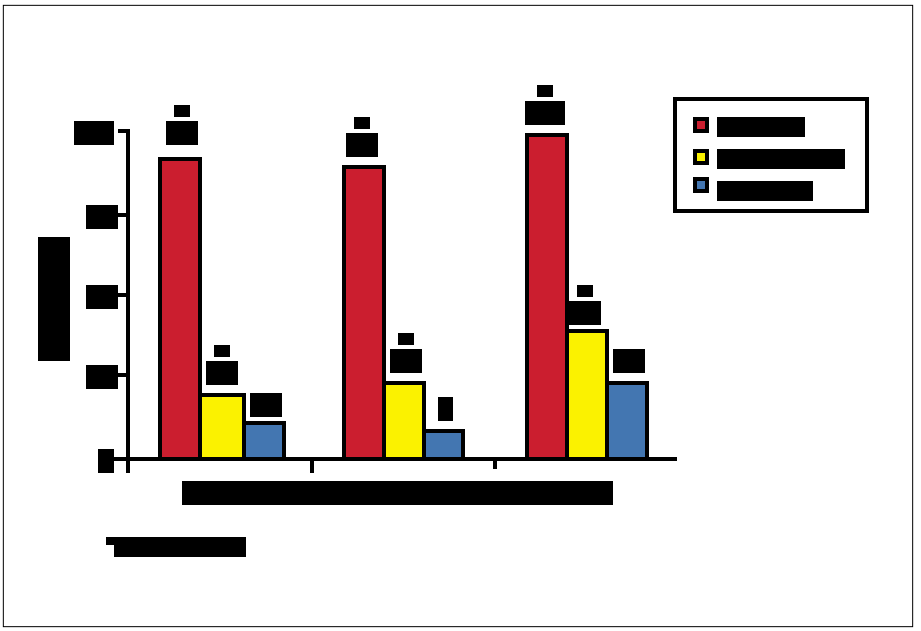

Figure 4. Prevalence of IgG celiac antibodies and HLA-DQ2 in celiac disease (CD), diarrhea-predominant irritable bowel syndrome (IBS-D), and inflammatory bowel disease (IBD).

AGA=antigliadin antibodies; TTG=tissue transglutanimase.

Adapted from Wahnschaffe et al.[38]

including thyroid dysfunction and lactose malabsorption, occurred at a similar rate in IBS patients versus the general population. However, celiac disease was 10 times more likely in the IBS patients versus the overall population, with probabilities of 4.67% versus 0.25–0.5%, respectively. Notably, the data for this review were obtained in the United Kingdom, which has the highest prevalence of celiac disease in the world.

The case patient underwent screening laboratory studies that revealed anemia (hemoglobin 9.2 g/dL) and microcytosis (mean corpuscular volume 78 microns). Albumin was 3.0 g/dL, endomysial antibody test was equivocal, and tissue transglutaminase was positive. Upper endoscopy showed some micronodularity and scalloping. Analysis of a small bowel biopsy showed villous splitting with hyperplasia, expansion of the lamina propria, and an increased number of intraepithelial lymphocytes.

Based on these additional findings, the patient appears to have classic celiac sprue. Indeed, the issue of discerning IBS from celiac sprue remains complicated. A US multicenter trial of 323 patients with IBS (Rome II criteria; no warning signs) and 241 controls reported that although celiac disease antibodies were significantly more common in IBS patients versus controls (7.2% vs 1.5%; *P*=.006), biopsy-proven celiac disease was not more common in IBS patients (1.24% vs 0.8%).[34,35] Most of these positive antibodies were in fact antigliadin antibodies.

Dr. Chey observed that many clinicians are moving away from testing for antigliadin antibodies, given that these antibodies are not specific for celiac disease. An analysis of different antibody tests showed that endomysium (EMA) and tissue transglutaminase (tTG), which are considered the gold standard serologies for celiac disease, are not as sensitive as once thought in individuals with biopsy-proven celiac disease—the sensitivity of both was 25%, indicating that the tests identified celiac disease in only one quarter of individuals with biopsy-proven celiac disease.[36] Abrams and colleagues also found suboptimal sensitivity with tissue IgA tTG testing versus endoscopy with biopsy in 122 patients with suspected celiac disease.[37] The overall sensitivity of tTG was 70.6% and the specificity was 65%. Sensitivity increased to 90% among patients with villous atrophy and decreased to 42.3% in patients with partial villous atrophy, suggesting that the lack of complete villous atrophy in many patients is probably the main driver of the lack of sensitivity of the test. Sensitivity and specificity also varied significantly between two different commercial laboratories, which brings into question the reliability of the tests. Abrams and colleagues reported a sensitivity and specificity of 40% and 100%, respectively, in Lab 1, and 100% and 41.7%, respectively, in Lab 2. Finally, expansion of lamina propria and the presence of intraepithelial lymphocytes also dramatically decrease the sensitivity of serologic testing.

HLA haplotype also appears to affect the development of celiac disease. In a study of 145 patients with IBS-D, 74 patients with celiac disease (treated and untreated), and 57 patients with active IBD, Wahnschaffe and colleagues found that individuals with HLA-DQ2 who fulfilled IBS criteria were more likely to test positive

for antigliadin antibodies and test negative for biopsy-proven celiac disease (Figure 4).[38] An important question is whether these individuals will respond to a gluten-free diet. In a preliminary evaluation of their data, Wahnschaffe and colleagues reported that patients with positive celiac antibodies but no evidence of biopsy-proven celiac disease were more likely to improve clinically on a gluten-free diet than were patients positive for HLA-DQ2 but negative for anti–celiac disease antibodies. Many of us have seen patients who appear to improve on a gluten-free diet. Current recommendation to screen for celiac disease without IgA, EMA, or tTG alone may not be adequate in clinical practice.

Dr. Chey concluded that the addition of antigliadin antibody testing will likely increase the diagnostic yield for celiac disease. The downside of this approach is that it will result in more esophagogastroduodenoscopies (EGDs) and biopsies. The meaning of those positive antibodies in the absence of biopsy-proven celiac disease remains uncertain. However, provocative data suggest that some of those patients may actually respond to a gluten-free diet. It remains unknown whether this is due to latent celiac disease or another cause. For patients with a high pretest probability for celiac disease—a family history or a great clinical suspicion—clinicians may choose to proceed directly to EGD and biopsy, foregoing antibody testing.

Case #4

Finally, Dr. Philip Schoenfeld presented a case of a 38-year-old man has been referred from his primary doctor with a 2-year history of diarrhea that is intermittent but occurs up to nine times a day with some bloating and occasional cramping. His past medical history is not contributory except for his frequent use of NSAIDs. He has no danger signs: no history of hematochezia, no weight loss, and no family history of colon cancer or IBD. The laboratory tests his primary care physician ordered were normal, including a normal complete blood count (CBC), negative fecal occult blood test, and normal erythrocyte sedimentation rate (ESR).

Confirming IBS Diagnosis

Dr. Schoenfeld noted that generally, when a patient presents with the symptoms of IBS, IBS is the diagnosis. If the patient has no alarm signs or symptoms, it is unlikely that a different diagnosis will be identified, regardless of how many diagnostic tests are undertaken. Tolliver and colleagues demonstrated this in a 1994 study in which they assessed the final diagnosis in 196 patients with IBS symptoms who underwent multiple diagnostic tests (CBC, ESR, serum chemistries, thyroid function test, urine, stool O & P; Figure 5).[39] In 99% of patients, workups were negative and the final diagnosis was IBS. The two exceptions included one patient over the age of 50 who was diagnosed with colon cancer and one patient who was diagnosed with IBD.

Diagnostic tests should certainly be performed in patients with alarm symptoms. The patient in this case study had diarrhea up to nine or ten times a day and even some nocturnal diarrhea, which might be considered to be alarm symptoms. Several studies have investigated the predictive value of different alarm features. Hammer and colleagues found that among 568 patients referred to an Australian gastroenterology clinic for signs of IBS, four clinical features were significantly predictive of a non-IBS organic disorder (Table 1): age greater than 50 years; blood on toilet tissue; frequent pain; and radiating pain.[40] Factors not predictive of other disorders included nocturnal pain, weight loss, and anorexia. Regarding the risk associated with blood on toilet tissue, it is difficult to determine whether this refers to true gross hematochezia. It is reasonable to consider a colonoscopy for a patient complaining of blood in their stool. However, for patients presenting with IBS symptoms with no other alarm signs or symptoms, routine diagnostic testing is likely not warranted.

The Bristol Stool Form Scale can be a useful guide for evaluating intestinal transit time when evaluating a patient for potential IBS. As patients describe their stool habits using the Type 1–Type 7 criteria, clinicians can better gauge their clinical situation. A patient with IBS can often discuss their bowel habits in detail, perhaps explaining that they have Type 1 stools for ten days followed by Type 6 or 7 for a few days and Type 4 around the time of menstruation.

Microscopic Colitis

Regarding the case patient, Dr. Schoenfeld further stated that the colonoscopy revealed a normal terminal ileum, as did random biopsies of the terminal ileum. The colonic mucosa appeared normal with no mucosal ulcerations. Random biopsies from the colon showed a thickened subepithelial collagenous band. All other diagnostic tests were normal.

This patient was diagnosed with microscopic colitis (collagenous colitis). Whereas 60% of these patients have an insidious onset of symptoms, the onset is sudden in 42% of patients.[41] Approximately 66% have 4–9 stools per day, and 27% have nocturnal diarrhea. The disease course is chronic and intermittent in 85% of patients and thus may mimic the disease course in IBS. Another 13% of patients have chronic, continuous disease, while 2% experience only a single episode.

Dr. Schoenfeld characterized data regarding effective therapies for microscopic colitis as limited, as no treat-

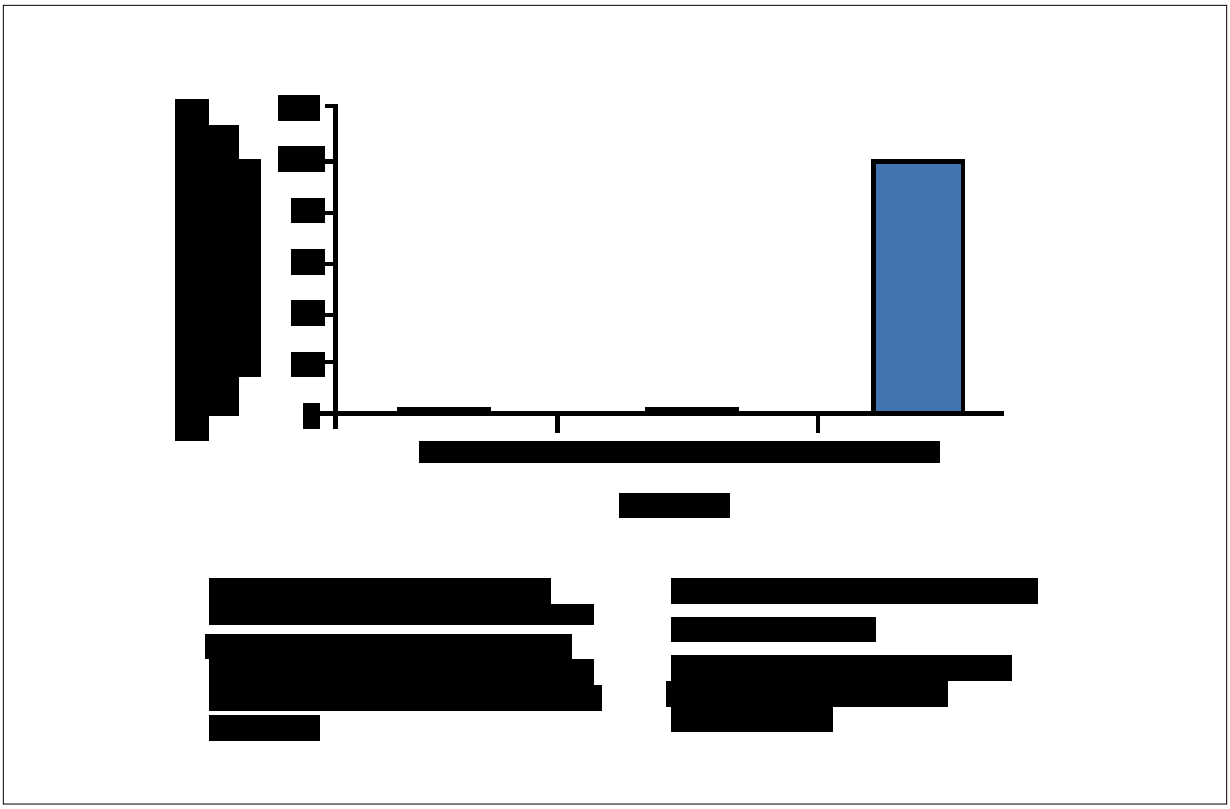

Figure 5. Evaluation of patients with IBS symptoms.

IBD=inflammatory bowel disease; IBS=irritable bowel syndrome.

Adapted from Tolliver et al.[39]

Table 1. Predictive Value of Alarm Features in Suspected IBS.

Clinical Feature	Odds Ratio	95% Confidence Interval
Age >50 years	2.96	1.47–5.94
Blood on the toilet tissue	2.19	1.06–4.52
Frequent pain	0.21	0.08–0.52
Radiating pain	0.38	0.16–0.88

568 patients referred to a gastrointestinal clinic in Australia completed a questionnaire and underwent a diagnostic evaluation. Nocturnal pain, weight loss, and anorexia were not predictive. A survey of 762,325 patients found an association between alarm symptoms (including rectal bleeding) and an increased likelihood of cancer. Of 15,289 cases of rectal bleeding, 338 patients were diagnosed with colorectal cancer within 3 years (positive predictive value, 2.0-2.4%).

Data from Hammer et al. *Gut.* 2004;53:666-672 and Jones et al. *BMJ.* 2007;334:1040.

ments for the disorder have been evaluated in large-scale randomized controlled trials. Experts have suggested several experience-based recommendations. First, patients should be started on loperamide to control diarrhea and should discontinue NSAIDs because some small case studies suggest an association between NSAID use and flaring of microscopic colitis symptoms.[42] For patients who do not respond to loperamide, budesonide is the agent of choice. A meta-analysis of three small randomized trials indicates that budesonide is significantly superior to placebo in improving stool frequency (OR, 20.1; 95% CI, 7.0–57.5).[43] In a randomized, controlled trial, budesonide 9 mg was clearly superior to placebo after 6 weeks, with 87% versus 14% of patients, respectively, achieving clinical remission.[44]

Despite the demonstrated short-term benefit of budesonide, the long-term benefit is unclear. Although most patients remain in remission for weeks to months following a course of budesonide, no clinical trials have investigated this issue. If neither budesonide nor loperamide are beneficial in these patients, open-label trials and small case studies suggest the following options: 5-ASA or sulfasalazine at standard IBD doses; cholestyramine 4 g daily; or prednisone at 0.5–1.0 mg/kg per day with taper.[41] Metronidazole, octreotide, and bismuth subsalicylate have also been reported to be beneficial in small case series.

Dr. Schoenfeld summarized his presentation, stating that evidence-based recommendations for the treatment of microscopic colitis are not available, though an experience-based recommendation includes the following measures: 1) discontinue NSAIDs and substitute acetaminophen; 2) start loperamide 2 mg once daily, with additional use as needed; 3) if these measures are ineffective, start budesonide 9 mg once daily for 6 weeks; 4) if budesonide is ineffective, consider a combination of cholestyramine and bismuth subsalicylate.

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Question and Answer Forum

Drs. Pimentel and Schoenfeld answer audience questions regarding treatment for IBS.

Based on the available data, what will be the most likely new indication for rifaximin?

Dr. Mark Pimentel I think the role of rifaximin in IBS is starting to expand dramatically. Physicians are using it regularly and in the next year or two an approval of rifaximin for IBS will likely be pursued on the basis of the latest multicenter clinical trials. A 75-center trial has just been completed and will be presented at an upcoming meeting. I think we will be hearing a lot more about rifaximin and IBS—and that is where the greatest impact of this agent will be.

How relevant are the cardiovascular events that have been associated with tegaserod?

MP I am not sure how relevant these events are. Although there was a numerical difference in cardiovascular events between tegaserod and placebo, it is not clear whether that represented the background rate of cardiovascular events in that patient population. The events do occur predominantly in patients with existing cardiovascular risk factors. I think the FDA will meet soon to evaluate the data in more detail.

What symptoms—IBS or other—would lead you to initiate more screening tests such as colonoscopy?

Dr. Philip Schoenfeld My two biggest factors are age greater than 50 years and gross hematochezia. I also initiate diagnostic tests in patients with IBS symptoms who have a family history of colon cancer or IBD and patients with a documented weight loss of more than ten pounds in the last six months. Although we sometimes consider complaints of frequent pain and of anorexia without associated weight loss to be danger signs, these do not appear to be associated with an increased risk of finding a non-IBS organic disorder.

Can antibiotics be used for postinfectious IBS prevention?

MP We are doing studies right now in animals to see if we can prevent IBS by using rifaximin or similar antibiotics. Although the data are not yet available, I believe it is likely that such agents may prevent IBS in the postinfectious setting.

Discontinued Products, Uncertain Data, Changing Options: Selecting Effective and Reliable Treatment for IBS

CME Post-Test: Circle the correct answer for each question below.

1. Approximately what proportion of individuals with gastroenteritis develops IBS?

   a. 1% b. 5% c. 10% d. 25%

2. The randomized, placebo-controlled trial of rifaximin in IBS excluded which of the following groups?

   a. Patients currently taking antidepressants
   b. Patients who had received oral antibiotics in the past 3 months
   c. Patients older than 65 years of age
   d. All of the above

3. Pimentel and colleagues found that a 10-day regimen of rifaximin was associated with improvements in IBS symptoms for what duration?

   a. 10 days
   b. 4 weeks
   c. 10 weeks
   d. 6 months

4. Which of the following fiber sources has demonstrated global improvements in IBS in multiple clinical trials?

   a. Ispaghula
   b. Wheat bran
   c. Corn fiber
   d. Psyllium

5. Why was tegaserod taken off the market?

   a. Liver toxicity
   b. Renal toxicity
   c. Cardiovascular ischemic events
   d. Central nervous system effects

6. Which of the following probiotics has demonstrated efficacy in global IBS symptoms?

   a. *Bifidobacterium infantis*
   b. *Bifidobacterium bifidus*
   c. *Lactobacillus acidophilus*
   d. *Saccharomyces boulardii*

7. True or false? Most experts consider IBS a diagnosis of exclusion.

   a. True
   b. False

8. According to a 2007 presentation by Chey and colleagues, what is the approximate sensitivity of EMA and tTG testing for detecting celiac disease?

   a. 25%
   b. 50%
   c. 75%
   d. 90%

9. Hammer and colleagues determined that which of the following features was most predictive of a non-IBS organic disorder after adjusting for other factors?

   a. Age greater than 50 years
   b. Nocturnal pain
   c. Weight loss
   d. Blood on toilet tissue

10. Which of the following disease patterns is most common in microscopic colitis?

    a. Chronic and continuous
    b. Chronic and intermittent
    c. Single episode
    d. No definitive pattern noted

Evaluation Form: Discontinued Products, Uncertain Data, Changing Options: Selecting Effective and Reliable Treatment for IBS

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe current parameters for irritable bowel syndrome (IBS) diagnosis.	1 2 3 4 5
2. Review the historic and current treatment options for the different IBS symptom patterns (constipation-predominant, diarrhea-predominant, mixed pattern).	1 2 3 4 5
3. Explain the current and potential role of antibiotics in the treatment of each symptomatic characterization of IBS.	1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1 2 3 4 5
Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Provided new ideas or information I expect to use	1 2 3 4 5
Addressed competencies identified by my specialty	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Posttest Answer Key

1	2	3	4	5	6	7	8	9	10

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