Treatment of Diarrhea in Patients With Inflammatory Bowel Disease: Concepts and Cautions

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Diarrhea continues to be a prevalent symptom in patients with inflammatory bowel disease (IBD), requiring a wide differential diagnosis to define the pathophysiologic mechanisms in individual patients. It is essential that physicians properly evaluate complaints of diarrhea by assessing both patient symptoms and potential physiologic impacts on fluid and electrolyte status. Underlying mechanisms of diarrhea with IBD are the location, extent, and severity of inflammation; malabsorption; altered motility; and iatrogenic causes such as medications, diet, and antibiotic-associated colitis (eg, Clostridium difficile). When treating diarrhea, physicians need to control inflammatory activity using appropriate treatment algorithms. Therapies include aminosalicylates, corticosteroids, immune modifiers, and, most recently, biologic treatment. Other medications, including loperamide, diphenoxylate, codeine sulfate, and tinctures of opium, slow motility and increase the absorption of fluids and nutrients. For iatrogenic issues, medications that cause diarrhea should be withdrawn and individual diets modified. Not all diarrheas in the IBD patient are the same; therefore, it is essential to tailor therapies according to presumed etiologies. Antidiarrheal agents are not recommended in extremely ill patients and those with known hypersensitivity or evidence of obstruction or colonic dilation, fever, or abdominal tenderness. Concomitant use of loperamide with diphenoxylate and atropine should be avoided in early pregnancy.

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Diarrhea remains one of the most common symptoms present in patients with inflammatory bowel disease (IBD), affecting up to 66% to 92% of patients. The severity of diarrhea ranges from a symptomatic nuisance affecting lifestyle and quality of life, to a severely debilitating life-threatening metabolic and physiologic crisis. It is imperative that physicians properly
Diarrhea in IBD is the result of arachidonic acid metabolism. Nearly all cells, including macrophages, neutrophils, eosinophils, and mast cells, are capable of synthesizing arachidonic acid metabolites.

**Mechanisms of Diarrhea**

**Inflammation**

The most important underlying mechanisms of diarrhea in IBD are the location, extent, and severity of inflammation. The most important underlying mechanisms of diarrhea include the stimulation of anion secretion and impaired absorption. Both of these processes are cumulatively referred to as net intestinal secretion. However, the primary pathophysiology of diarrhea associated with IBD is inhibition of fluid and electrolyte absorption as a result of altered regulation or impaired enterocyte function. Immune and inflammatory mediators inhibit the absorption of sodium and chloride through a cascade of biochemical events, increase and stimulate intestinal secretion of water and electrolytes, and stimulate the enteric nervous system, which directly affects the epithelium. Inflammation also causes denudation of the epithelium, which results in leakage of plasma and blood and increased secretion of water and electrolytes.

**Table 1**

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by immune cells, which then stimulate the release of neurotransmitters. In addition, these immune and inflammatory cells have receptors for neurotransmitters. The interaction of neural, immune, and inflammatory cells suggests the importance of communication between cells. Immune and inflammatory cells may reside close to enteric neurons in intestinal connective tissue. For example, mast cells are associated with neurons. Juxtacrine pathways are important in regulating intestinal water and electrolyte transport. This particular pathway includes many types of lamina propria cells and myofibroblasts that are located in the subepithelial region and release a variety of mediators in response to stimulation by enteric neurons and soluble mediators.

Many immune and inflammatory mediators have been shown to alter intestinal water and electrolyte transport by stimulating active anion secretion or inhibiting absorption of fluid and electrolytes. Metabolites of arachidonic acid affect electrolyte transport in both the small and large intestines. Agents such as bradykinin, interleukins 1 and 3, chemotactic peptides such as formyl-methionyl-leucyl-phenylalanine, and reactive oxygen metabolites stimulate the production of intestinal arachidonic acid metabolites. Some pharmacologic agonists, such as phorbol esters, activators of protein kinase C and calcium ionophore, also stimulate net secretion in part through the activation of arachidonic acid metabolism. Nearly all cells, including myofibroblasts, macrophages, neutrophils, eosinophils, and mast cells, are capable of synthesizing arachidonic acid metabolites.

Diarrhea in Crohn’s disease (CD) is also multifactorial and dependent on the anatomical distribution of disease extent and severity, as well as surgical resections affecting overall and local (eg, bile salt or fat) absorptive capacities. Diarrhea in the setting of Crohn’s colitis is similar to that in UC. However, the potential for small bowel disease further influences stool volume and electrolyte regulation. Even short-segment ileal resection can impact bile and/or fat absorption, contributing to steatorrhea or choleretic diarrhea. Thus, in CD the evaluation of disease activity and diarrhea based on symptomatic reports alone is often insufficient to assess the mechanisms of diarrhea. These assessments require more physiologic studies, including stool volume, presence of fecal leukocytes, and determination of fecal fat, osmolality, and electrolytes.

**Inflammation**

In ulcerative colitis (UC), the extent and severity of colitis within the colon are the 2 most important factors that determine overall signs and symptoms associated with disease activity. Extensive colitis often results in more diarrhea than bleeding. Patients with ulcerative proctitis may be constipated but still present a history of repeated trips to the toilet because of tenesmus, frequent passage of blood and mucus, and fear of passing flatus because of the inability to distinguish gas from liquids. Thus, it is relevant to query the patient regarding specific aspects of urgency, tenesmus, incontinence, and nocturnal diarrhea, as well as rectal bleeding and overall volume of stool.

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The most important underlying mechanisms of diarrhea in IBD are the location, extent, and severity of inflammation. In the setting of mucosal inflammation, important mechanisms of diarrhea include the stimulation of anion secretion and impaired absorption. Both of these processes are cumulatively referred to as net intestinal secretion. However, the primary pathophysiology of diarrhea associated with IBD is inhibition of fluid and electrolyte absorption as a result of altered regulation or impaired enterocyte function. Immune and inflammatory mediators inhibit the absorption of sodium and chloride through a cascade of biochemical events, increase and stimulate intestinal secretion of water and electrolytes, and stimulate the enteric nervous system, which directly affects the epithelium. Inflammation also causes denudation of the epithelium, which results in leakage of plasma and blood and increased secretion of water and electrolytes.

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Conversely, ileal involvement or resection can affect carbohydrate absorption by decreasing carbohydrate reabsorption. The intestine typically adapts to these changes by decreasing carbohydrate absorption, such that carbohydrate absorption is diminished after being “digested” by hydrolases and reaching the enterocytes as monosaccharides and/or length, then impaired absorption of sugars, amino acids, fat, and sodium pulls water out of the lumen through the epithelium. If there is loss of intestinal surface area and/or length, then impaired absorption results in osmotic diarrhea.6

Carbohydrates are absorbed across the enterocytes as monosaccharides after being “digested” by hydrolases located in the brush border of the duodenum and jejunum. Although intestinal resection can affect carbohydrate absorption by decreasing carbohydrate hydrolase, the intestine typically adapts such that carbohydrate absorption is adequate as long as there is residual small intestine up to mid-jejunum. Lactose malabsorption may occur with extensive proximal CD (eg, jejunoileitis) or after large jejunal resections because lactase is primarily located in this segment. Protein is primarily absorbed as amino acids (in the jejunum) and peptides (in the proximal ileum). In settings where less than 50 cm of small intestine remain, net protein absorption may be only 40% of dietary intake. Fat absorption takes place in the upper two thirds of the jejunum and is dependent on adequate absorptive surface area as well as optimal pancreatic function, intraluminal pH, bile salts, and mixed micelle diffusion into the microvilli.4

Malabsorption

Small bowel malabsorption is dependent upon the location and extent of inflammation or resection. The proximal small bowel processes 9 liters of fluid per day, of which 8 liters are absorbed. Normal jejunal luminal fluid is hypertonic and the osmolality is further increased by digestion of carbohydrates into simple sugars, leading to significant amounts of fluid crossing the epithelium into the lumen. In the distal jejunum and ileum, net fluid absorption occurs as absorption of sugars, amino acids, and sodium pulls water out of the lumen through the epithelium. If there is loss of intestinal surface area and/or length, then impaired absorption results in osmotic diarrhea.6

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Arachidonic acid is released from membrane phospholipids and metabolized by cyclooxygenase and 5-lipoxygenase. During mucosal inflammation, arachidonic acid metabolites are made. These metabolites may promote intestinal secretion by directly stimulating pathways of water and electrolyte transport or by having a direct effect on enterocytes. Some products, such as leukotriene \( \frac{1}{2} \), are proinflammatory mediators that can recruit additional cells to an inflamed area. By doing so, the inflammatory process is exaggerated, and there is an increase in inflammatory mediators, including other arachidonic acid metabolites such as phospholipase \( \frac{1}{2} \), prostaglandin, hydroperoxyecosatetraenoic acid, hydroxyeicosatetraenoic acid, and leukotriene.4

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CD patients with extensive small intestinal involvement have increased osmotic loads due to malabsorbed and maldigested nutrients, which worsen diarrhea. Patients with extensive small bowel resections and “short bowels” also have malabsorption of water, electrolytes, and nutrients due to a loss of absorptive surface area. Other factors that are involved include osmotic-induced diarrhea secondary to lactose and other carbohydrate malabsorption, concomitant bacterial overgrowth, and bile acid diarrhea from ileal resection. In the setting of a “short bowel,” and in contrast to the setting of osmotic diarrhea, diarrhea persists despite fasting, indicating a secretory component due to an absence of distal small bowel signals to inhibit proximal intestinal secretion.

Bile acid and fat malabsorption are contrasting and interrelated features of ileal disease or resection, producing diarrhea and/or steatorrhea. The nature of the diarrhea depends on whether bile acid losses exceed hepatic synthesis. Extensive ileal disease or ileal resection of greater than 100 cm usually results in bile acid malabsorption inadequately compensated by hepatic synthesis. Depletion of the bile acid pool then leads to steatorrhea as a result of decreased concentration of luminal bile acids, impaired micelle formation, and compromised fat digestion and absorption. Malabsorbed fats are rapidly metabolized to free fatty acids by colonic bacteria that stimulate net intestinal secretion. Conversely, ileal involvement or resections of less than 100 cm result in bile acid malabsorption that is compensated by increased hepatic synthesis.

Motility

Active colitis is accompanied by altered motility that decreases colonic absorption of water and electrolytes. Additional motility problems may arise from small bowel strictures in CD (contributing to SBBO) and concomitant irritable bowel syndrome (IBS)."
Treating Diarrhea in IBD Patients continued

IBS is differentiated from active UC based on a history of abdominal cramping, diarrhea, or constipation in the absence of rectal bleeding, but may require endoscopic evaluation or examination of stool for fecal leukocytes. The multiplicity and chronicity of symptoms and their relationship to altered bowel habits may also be helpful. Patients with a psychoneurotic disposition, anxiety, depression, or tendency to somatize are more likely to have IBS along with IBD, and even some patients with mild colitis have IBS symptoms that respond to IBS-directed treatment.

The diagnosis of IBS in CD can be challenging. The patient’s history is of primary importance if symptoms of IBS preceded those of IBD.

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Colonoscopy, small bowel radiographs, and inflammatory markers (eg, C-reactive protein) all aid in disease assessment. Cramping and diarrhea may also be related to complications of extensive small bowel disease or strictures leading to bile acid malabsorption, lactose intolerance, or SIBO.

After proctocolectomy and ileal pouch procedures, patients may experience diarrhea from intestinal spasms and loss of colonic absorptive capacity. These symptoms usually improve 6 to 12 months later, after the absorptive function of the ileal mucosa adapts and the ileal reservoir enlarges. Diarrhea following ileoanal anastomosis may be due to structural or inflammatory causes, as discussed, or to functional disorders such as irritable pouch syndrome (IPS). IPS patients have milder symptoms. In contrast, patients with “cuffitis” have active residual colitis manifested by rectal bleeding that may be associated with persisting or new extraintestinal manifestations. The diagnosis of pouch pathology relies on exclusion of a structural disorder by endoscopic and histological evaluations. Studies have shown that distention of ileal pouches in patients with IPS had lower volume thresholds for stool sensation, poorer compliance, and more frequent referred abdominal pain compared with distention of the rectum in normal healthy volunteers.

**Iatrogenic Causes**

Iatrogenic causes including medications, dietary factors, and antibiotic-associated colitis (eg, *Clostridium difficile*) should not be overlooked. Medications such as secretory aminosalicylates (eg, olsalazine), over-the-counter medications (eg, nonsteroidal anti-inflammatory drugs), antibiotics, and, rarely, mesalamine can cause diarrhea through a variety of mechanisms. Initial evaluation should include stool analysis for fecal volume and osmolality.

It is also important to review the patient’s diet history as it can provide insight into factors that may aggravate diarrhea in the setting of IBD. Although there is no clear association of lactose intolerance with IBD, lactose can induce symptoms in IBD patients who were previously tolerant because of impaired colonic absorption. Other dietary factors that increase diarrhea include fructose, large quantities of non-absorbed carbohydrates such as artificial fats and sorbitol, and stimulants such as caffeine. A thorough history should also be obtained from the patient in regard to vitamins, herbal supplements, homeopathic agents, laxatives, and other health foods.

Other iatrogenic causes that can affect the colon include toxin-producing bacteria such as *C. difficile*. Toxins stimulate net secretion of water and electrolytes by inducing mucosal inflammation and increasing cellular permeability. Incidences of *C. difficile* in IBD have increased and are higher than in the non-IBD population. In one study, antibiotic exposure was identified in 61% of IBD patients with *C. difficile* infection. Analysis of data identified use of immunomodulators and extent of colitis as independent risk factors for *C. difficile* infection in IBD.

**Treatment**

The most important approach to treatment of diarrhea in IBD is targeting the appropriate pathophysiological mechanism(s). These vary among individual patients according to the location and severity of inflammatory disease activity, intestinal complications such as fistulae or strictures, and surgical history. First and foremost, inflammatory activity needs to be controlled using treatment algorithms according to disease location, severity, and complications. Anti-inflammatory therapies include aminosalicylates, corticosteroids, immune modifiers, and, most recently, biologic therapies targeting tumor necrosis factor or adhesion molecules.

Patients with steatorrhea should be educated regarding a low-fat diet and may require supplements of calcium, magnesium, and fat-soluble vitamins. Ursodeoxycholic acid (15 to 20 mg/kg daily) may also help reduce diarrhea by improving fat malabsorption. Hydrogen blockers and proton pump inhibitors decrease jejunal fluid and potassium losses in response to transient hypergastrinemia that may ensue in the first 6 to 12 months following small bowel resection. An
Treating Diarrhea in IBD Patients

Increase in transit time may decrease absorption of some of these medications; therefore, higher doses may be necessary. Calcium supplementation may improve diarrhea by binding fatty acids, leading to excretion of calcium soaps. Other medications such as loperamide chloride and diphenoxylate, codeine sulfate, or tinctures of opium slow motility and thereby increase the absorption of fluids and nutrients. Loperamide and diphenoxylate are often used in the management of diarrhea in IBD. Pelemans and Vantrappen conducted a crossover study comparing patients with either CD or UC who received treatment of loperamide up to 10 mg daily or diphenoxylate/atropine up to 25 mg/0.25 mg daily. Both the frequency and consistency of stool improved more in patients treated with loperamide. Those patients who underwent colectomy and ileostomy also had a decrease in stool weight when placed on loperamide treatment as compared with diphenoxylate. Another crossover study evaluated 5 patients with chronic diarrhea secondary to either CD or UC. Both loperamide (up to 18 mg daily) and diphenoxylate (up to 22.5 mg daily) were titrated to relieve diarrhea. Although both treatments improved diarrhea, there was a shorter dose-titration period with loperamide. A double-blind, placebo-controlled, crossover study evaluated 21 patients with chronic diarrhea after ileocolic disease or resection. A dose of loperamide 6 mg daily was significantly superior to placebo in terms of decrease in stool frequency, consistency, and weight.

Cholestyramine reduces diarrhea in patients with ileal involvement or resection and compensates bile salt malabsorption by binding bile salts in the lumen and preventing conversion to bile acids. Relatively low divided doses (eg, 1 to 2 g/day) separate from meals and other medications are often sufficient. Higher doses can further deplete the bile salt pool leading to steatorrhea, or induce bloating or constipation. For patients intolerant of cholestyramine because of dyspepsia, an alternative is colestipol, which is a similar binding resin.

SBBO is treated with antibiotics targeting both aerobic and anaerobic enteric bacteria. Common antibiotics that are used for the treatment of SBBO include tetracyclines, sulfamethoxazole/trimethoprim, ciprofloxacin, metronidazole, and, more recently, rifaximin. A single course of 7 to 10 days of antibiotics may improve symptoms; however, some patients require a combination of antibiotics or longer therapy. Others may benefit from rotating courses of antibiotics or longer therapy. Others may benefit from rotating courses of several theories of the pathophysiology, including bacterial overgrowth or infections, bile acid toxicity, short-chain fatty acid deficiency, recurrent IBD, and ischemia.

**Differentiating and treating irritable bowel syndrome (IBS) in IBD patients may be difficult, but it is important to rule out active inflammation before attributing symptoms to IBS and to educate the patient in regard to both diseases.**
treating diarrhea in ibd patients continued

inflammation before attributing symptoms to ibs and to educate the patient in regard to both diseases. Antispasmodic agents directly affect intestinal smooth muscle relaxation or act via their anticholinergic or antimuscarinic properties (eg, dicyclomine and hyoscyamine). These medications can reduce colonic motor activity and may benefit patients with symptoms of postprandial abdominal pain, gas, bloating, and fecal urgency. Typical doses include dicyclomine (up to 20 mg orally [po] 4 times daily), hyoscymamine (up to 0.125 to 0.25 mg po or sublingually 3 times daily or 4 times daily) or sustained-release hyoscymamine (up to 0.375 to 0.75 mg po twice daily).

Alosetron, a 5-hydroxytryptamine-3 receptor antagonist, modulates visceral afferent activity from the gastrointestinal tract and decreases colonic motility and secretion. In clinical trials, this drug was most effective in females with diarrhea-predominant ibs. the us food and drug administration removed alosetron from the market because of reports of ischemic colitis and complications of severe constipation. however, it is now back on the market under tight control.

In a systematic review, 3 controlled trials evaluating loperamide in the treatment of IBS were reported.22 These trials suggest that loperamide is more effective than placebo for the treatment of diarrhea, but not for other irritable bowel symptoms. administering loperamide on an as-needed basis is preferred over scheduled dosing. For example, patients may benefit from taking it prior to a meal if they suffer with postprandial diarrhea. It should primarily be reserved for patients with diarrhea as their predominant symptom. Low-dose tricyclic antidepressants are used to treat functional abdominal pain as well as diarrhea. Treatment of underlying anxiety and depression is also imperative.

Iatrogenic causes of diarrhea in IBD patients should be appropriately identified and treated. Medications causing diarrhea should be withdrawn and diet that contributes to diarrhea should be modified. C. difficile should always be considered in IBD patients with diarrhea and appropriately treated with antibiotics. Antibiotics used for C. difficile include metronidazole 500 mg po 3 times a day or 250 mg PO 4 times daily. An alternative first-line agent is vancomycin 125 mg PO 4 times a day. Rifaximin has been found to be effective, although trials are ongoing. Duration of initial therapy is typically 10 to 14 days.

Again, not all diarrheas in the IBD patient are the same; therefore, it is important to tailor therapy according to the presumed etiologies. In addition to anti-inflammatory therapy to heal colonic inflammation, many patients warrant symptomatic treatment of their diarrhea. Opiate derivatives, including loperamide and diphenoxylate, stimulate muscle opiate receptors and thereby inhibit motor contraction and allow luminal content to have increased time for mucosal contact and absorption.23 Both loperamide and diphenoxylate may be helpful in controlling nocturnal diarrhea. Also, because of their relatively quick onset of action, they may be particularly useful in controlling diarrhea for anticipated social events. The primary mechanism of action is slowing small bowel transit and increasing anal sphincter tone, hence reducing incontinence. By decreasing small bowel transit there is an increase of mucosal contact time, allowing more time for the absorption of water and electrolytes.24 Loperamide may be safer and more effective than other opiates and other antidiarrheals, including diphenoxylate and bismuth salicylate.25

Distal colitis patients often have impaired proximal colonic motility and right colonic transit, so antimotility drugs may worsen their symptoms of constipation and bloating. These patients benefit from dietary fiber supplementation and treatment of their distal inflammation.26 Bulk agents such as psyllium, methylcellulose, or pectin can all be helpful in patients with diarrhea and they do not carry the additional risk of precipitating toxic megacolon.

Cautions

Antidiarrheal agents should be avoided in patients with known hypersensitivity or evidence of obstruction or colonic dilation, fever, or abdominal tenderness.27 These agents are not recommended as primary therapy in patients with acute dysentry, acute UC, and bacterial enterocolitis caused by invasive organisms, or in patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics. They should be avoided in extremely ill patients because they may precipitate toxic megacolon.

Animal studies suggest that diphenoxylate with atropine and loperamide are not shown to cause teratogenicity during pregnancy. However, there are case reports suggesting fetal malformations in those who were exposed to diphenoxylate with atropine during the first trimester. Diphenoxylate with atropine should be avoided in early pregnancy unless bulking agents and
differential diagnosis have failed to improve the patient’s diarrhea. Generally, they should be avoided with breastfeeding, although this recommendation comes from limited data. In contrast, loperamide is safe during pregnancy (Category C for prescription products) and breastfeeding. Bismuth subsalicylate and psyllium are also considered safe during pregnancy. High-fiber diets, bulking agents, and antispasmodics can be used to treat diarrhea and abdominal cramping, but should be avoided in patients with CD and a history of obstruction from strictures and upper gastrointestinal symptoms with gastric outlet obstruction. 30-33

Important data regarding the effects of loperamide can also be found in studies by Sun, Herbst, Oldfield, Emblem, and their respective associates. 30-33

Dr. Shah and Dr. Hanauer have indicated that they have no relationships or activities to disclose that could be perceived as potential conflicts of interest.

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Main Points
- Diarrhea in inflammatory bowel disease (IBD) is the result of complex physiologic and pathogenetic processes, and effective treatment requires targeting the appropriate pathophysiologic mechanism(s) in individual patients.
- The primary pathophysiology of diarrhea associated with IBD is inhibition of fluid and electrolyte absorption as a result of altered regulation or impaired enterocyte function. Immune and inflammatory mediators inhibit the absorption of sodium and chloride, increase and stimulate intestinal secretion of water and electrolytes, and stimulate the enteric nervous system, which directly affects the epithelium.
- Other mechanisms of diarrhea are malabsorption, which is dependent upon the location and extent of inflammation or resection; altered motility that decreases colonic absorption of water and electrolytes; and iatrogenic causes, including medications, dietary factors, and antibiotic-associated colitis.
- Treatment approaches to diarrhea vary according to the location and severity of inflammatory disease activity, intestinal complications such as fistulae or strictures, and surgical history. Anti-inflammtory therapies include aminosalicylates and corticosteroids; medications such as loperamide and diphenoxylate slow motility and increase the absorption of fluids and nutrients; and cholestyramine reduces diarrhea in patients with ileal involvement or resection, compensating bile salt malabsorption.
- It is important to remember that not all diarrheas in the IBD patient are the same; therefore, it is essential to tailor therapies according to the presumed etiologies.
- The use of anti diarrheal agents should be avoided in extremely ill patients or those with known hypersensitivity or evidence of obstruction or colonic dilation, fever, or abdominal tenderness. The use of diphenoxylate with atropine should be avoided in early pregnancy.