Evaluation and Treatment of Colonic Symptoms

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DIARRHEA

In the past, the definition of diarrhea relied on increased stool weight (>200–300 g/d) and increased frequency of stools (>3/day). However, most definitions now focus on loose or watery stool consistency and urgency because these are most consistent with patient self-reports of diarrhea.1 Probably the best description is that the stool takes the shape of the container in which it is collected. Diarrhea is considered acute if duration is less than 2 weeks, persistent if 2 to 4 weeks, and chronic if more than 4 weeks. Often, it is classified by the underlying pathologic process: inflammatory, watery, or malabsorptive.

Prevention

Although the focus of this article is the evaluation and management of bowel symptoms, several strategies may be effective in prevention of diarrhea. Clearly, careful...
hygiene and attention to food and water safety is critical. In addition, inappropriate antibiotic use should be minimized. However, when antibiotics are indicated, there may be a role for probiotic use to prevent both antibiotic-associated and *Clostridium difficile*-associated diarrhea. The most commonly studied probiotics include *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*. A systematic review of 63 randomized trials of probiotics, in which a broad range of antibiotics were used, found a 32% reduction in antibiotic-associated diarrhea. Therefore, a physician would need to treat 13 patients on antibiotics with probiotics to prevent one episode of diarrhea. In addition, a systematic review has shown an approximately 66% decrease in the number of cases of *C difficile*-associated diarrhea for those patients treated with probiotics (number needed to treat [NNT] 26).

**ACUTE DIARRHEA**

**Epidemiology**

In the United States, there are more than 300 million cases of diarrhea per year. However, accurate estimates of incidence are difficult because most patients do not present for evaluation. In addition, the yield of stool culture has been quite low, with historically only 1.5% to 5.8% returning a positive result. Most cases of acute diarrhea are due to infection, including viruses (norovirus or rotavirus), bacteria (*Staphylococcus*, *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli*, and *C difficile*), and parasites (*Giardia*, *Blastocystis*, and *Cryptosporidium*). In a recent study, adult subjects presenting to emergency departments with acute gastroenteritis were evaluated with extensive testing. Pathogens were identified in 25%, with yields up to nearly 50% when a whole stool specimen was submitted (compared with only rectal swabs). The most common pathogens identified were norovirus (26%), rotavirus (18%), salmonella (5.3%), *clostridium* (5.3%), campylobacter (3%), and parasites (3%).

**Patient History or Examination**

When evaluating a patient presenting with acute diarrhea, the important historical items help determine cause and assesses severity. Therefore, it is critical to get a detailed history of recent travel, antibiotic use, medication changes, ingestions (including raw or undercooked meats), ill contacts (including children), and underlying immune status. Further questions should concern the frequency and consistency of bowel movements, including the presence of blood or pus, as well as whether there is concomitant fever or abdominal pain. The physical examination is primarily focused on volume status and severity of illness. It should include, along with other modalities, orthostatic blood pressure measurement.

**DIAGNOSTIC TESTS**

In the immune-competent patient who presents in the first 2 to 3 days with acute diarrhea and no worrisome symptoms, no specific diagnostic testing is indicated. Evidence of a more inflammatory or invasive infection includes fever, severe abdominal pain, and blood and/or pus in the stool. If any of these are present, diagnostic testing is indicated. In addition, patients who are immunocompromised, elderly, generally unwell, or having severe symptoms are candidates for testing.

**Markers of Inflammation**

For years, various investigations have been performed in an attempt to better define cases of inflammatory diarrhea, including stool leukocytes and lactoferrin, a product of leukocytes. Existing guidelines recommend either performing or considering
inflammatory testing. The data on the usefulness of stool leukocytes have been inconsistent, with sensitivities ranging from 40% to 75% and specificity 50% to 88%. A meta-analysis focusing on data from developed countries found a sensitivity of 73% and specificity of 84%. Lactoferrin performed somewhat better, with sensitivity of 78% to 92% and specificity 54% to 79%, making it a reasonable test for ruling out an inflammatory cause.

**Stool Culture**

When done in a generalized population of patients with diarrhea, stool culture has limited usefulness. However, there is not consistent agreement on when or in whom to order stool cultures. Therefore, typically, cultures are performed in patients who have more significant underlying medical illness and in patients with severe cases (and at times of widespread involvement). The usefulness of routine stool culture in patients hospitalized for 3 days is extremely low and should not be routinely performed. Unless there is a clinical rationale, routine use of ova and parasite testing in patients with acute diarrhea should be discouraged. Possible indications include suspicious travel or exposure, immune-compromised state, or persistent symptoms (Box 1).

**Stool Toxin**

In certain patient populations, it is important to test stool directly for toxin. In a food-borne toxin-related illness (such as *Staphylococcus aureus*), there is not typically a need for testing because the course is self-limited. However, in patients recently treated with antibiotics, recently hospitalized, or residing in skilled-nursing facilities (include hospital staff in this group if they have taken antibiotics), checking for *C difficile* toxin is critical. In addition, Shiga toxin should be checked for in patients in whom the physician suspects possible enterohemorrhagic *E coli*, typically patients with bloody diarrhea but no fever.

**GENERAL TREATMENT**

**Supportive**

In severe diarrhea, the initial priority should be to assure adequate hydration. In the United States, this is often done intravenously. However, because most patients with diarrhea can tolerate oral intake, oral rehydration is possible with products such as Pedialyte (which has half the sugar and more than twice the sodium of Gatorade). Although the data are mixed, minimizing dairy intake given possible transient lactase deficiency is reasonable. Otherwise, a regular diet should be maintained because diets such as the BRAT (banana, rice, applesauce, and toast) are likely to be too nutritionally restrictive.

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**Box 1**

**Indications for stool culture**

- Severe illness
- Bloody diarrhea
- Abdominal pain (not just cramping-type pain)
- High fever
- Immune-compromised state
- Multiple comorbidities
**Antidiarrheals**

Loperamide, which binds gut wall receptors leading to decreased peristalsis and increased anal sphincter tone, is approved for use in both acute and chronic diarrhea. In acute diarrhea, most data are in patients with traveler’s diarrhea, in whom it has been tried in conjunction with antibiotics. In a systematic review, loperamide, when added to antibiotic therapy, was superior to antibiotic alone resulting in decreased illness duration, especially in subjects with increased pretreatment frequency of diarrhea. However, it should be avoided in severe or inflammatory cases. There are limited data on the usefulness of diphenoxylate-atropine in acute diarrhea.

**Probiotics**

As noted, probiotics may have a role in the prevention of diarrhea in patients on antibiotics. However, there may also be a role in the treatment of acute infectious diarrhea, although most studies have focused on infants and children. A Cochrane review found an approximately 24-hour reduction in duration of diarrhea, decreased stool frequency on day 2, and a lower risk of having diarrhea for 4 or more days (relative risk 0.41).

**TRAVELER’S DIARRHEA**

For patients who travel to resource-poor regions, the incidence of traveler’s diarrhea is 20% to 60%. For acute diarrhea in the traveler, bacterial pathogens are usually the cause. *E coli* (enterotoxigenic and enteroaggregative) is most commonly identified. In travelers with acute diarrhea, empiric antibiotic treatment for 3 to 5 days, usually with a quinolone, is recommended. For travelers with persistent diarrhea, *Giardia*, *Entamoeba*, *Strongyloides*, and *Schistosoma* should be considered.

**FOOD-BORNE DIARRHEA**

For food-borne illness, development of symptoms within 6 to 24 hours is most likely due to preformed toxin, as seen in *Staphylococcus*, *Bacillus*, and *Clostridium perfringens*. In addition, vomiting is frequently present as an initial symptom given upper gastrointestinal involvement. Typically, these patients only require supportive care.

**WATERY DIARRHEA**

Most watery diarrhea is due to viral gastroenteritis, such as norovirus or rotavirus. However, because there are no specific treatments, care is supportive. Diagnostic testing is not indicated unless there is either epidemiologic concern or history is inconclusive.

**INFLAMMATORY DIARRHEA**

Bloody diarrhea, fever, and abdominal pain are concerning for an invasive infection such as *Shigella*, *Salmonella*, *Campylobacter*, *C difficile*, or *Yersinia*. However, bloody diarrhea without fever is particularly worrisome for enterohemorrhagic *E coli* (including serotype 0157:H7). It is important to identify this variant of *E coli* because antibiotics should be avoided and the chance of developing hemolytic uremic syndrome is significant—up to 10% according to the World Health Organization. Antibiotics are also typically not needed in cases of salmonella and yersinia. However, in severe cases, and in cases of shigella and campylobacter, early antibiotics for 3 to 5 days can decrease duration of illness (norfloxacin 400 mg twice a day or, alternatively, quinolone or azithromycin 500 mg daily if quinolone-resistant campylobacter is suspected due to presumed a poultry source outside of the United States).
CHRONIC DIARRHEA

Chronic diarrhea is defined as the presence of loose stools with or without increased stool frequency for at least 4 weeks. As the definition has varied significantly, best estimates are that roughly 3% to 5% of the population suffers from chronic diarrhea. In these patients, the differential diagnosis is much longer than for those with an acute onset. In addition, initially it is important to determine exactly what the patient means by “diarrhea” because the term can be used in describing increased stool frequency, loosened stool consistency, a sense of incomplete emptying, or leakage. For instance, fecal incontinence, which might be reported as diarrhea, is quite common, affecting 8.3% of noninstitutionalized adults and up to 15% of those aged 70 or older. Many of these patients do not have true diarrhea (Box 2).

Patient History

Once it has been determined that a patient does have chronic diarrhea, history plays a major role in determining cause and subsequent diagnostic and therapeutic steps. Initially much of this rests on determining the presence of worrisome symptoms, such as weight loss or hematochezia. In addition, identification of medications that

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**Box 2**  
**Differential for chronic diarrhea**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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| Osmotic  | - Carbohydrate malabsorption (i.e., lactose intolerance)  
- Laxative or antacid use  
- Sugar alcohol intake (i.e., sorbitol) |
| Secretory| - Medications (including nonosmotic laxative use)  
- Non-inflammatory bowel disease (IBD) colitis (lymphocytic, collagenous)  
- Motility issues (IBS, diabetic enteropathy)  
- Neuroendocrine tumors (VIPoma, mastocytosis, carcinoid) |
| Inflammatory| - IBD  
- Infection (C difficile, invasive viral, bacterial, or parasitic infection)  
- Ischemic colitis  
- Malignancy (colon cancer or villous adenoma) |
| Fatty or malabsorption| - Celiac disease  
- Small intestine bacterial overgrowth  
- Giardia  
- Pancreatic insufficiency  
- Bile acid malabsorption |

*Data from* Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology 1999;116:1464–86.
might be contributing to diarrhea and diagnosing irritable bowel syndrome (IBS) are key early in the evaluation. After that, the goal of obtaining a detailed history is to categorize the diarrhea as watery, inflammatory, or fatty, realizing many patients have overlapping features. Common medications associated with diarrhea and the Rome III criteria are shown in Boxes 3 and 4.

**DIAGNOSTIC TESTS**

In patients with chronic diarrhea, it is reasonable to check a complete blood count (to evaluate for anemia and leukocytosis) and electrolytes. In appropriate situations, other testing may include autoantibodies for celiac disease, thyroid function, and protein levels. Although frequently checked, systemic inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, have limited data in the diagnostic work-up of chronic diarrhea. If a likely diagnosis is not immediately recognized, stool testing might be of benefit. Although osmotic diarrhea should usually be obvious by history, fecal osmotic gap can help differentiate osmotic from secretory diarrhea (especially when there is concern for factitious cause). In patients with watery diarrhea, a low stool pH (<5.6) suggests carbohydrate malabsorption (Box 5).13

The role of stool inflammatory markers, such as lactoferrin and calprotectin, to differentiate an inflammatory process from noninflammatory remains unclear. Fecal lactoferrin has been shown to have a sensitivity of approximately 80% and specificity 85% to 100% for abnormal endoscopy findings.15 More recently, there has been increased interest in calprotectin, a calcium-binding protein in white blood cells with both negative and positive predictive values of approximately 80% for histologic inflammation on colonoscopy.16,17

Testing for parasites, especially *Giardia* and *Cryptosporidium*, is appropriate in patients who may have been exposed. Stool antigen testing is more sensitive than routine ova and parasite examination for those organisms. Although bacteria other than *C difficile* are uncommon causes of chronic diarrhea, *Aeromonas, Plesiomonas*, and *Klebsiella oxytoca* have all been implicated. Other chronic infections to be aware of are the ulcerating viruses, most commonly in immunosuppressed patients. Stool statins for fat, such as the Sudan stain, and quantitative fat studies can be helpful in the diagnosis of malabsorption but may not add substantial information beyond visible fat in stool. Indications for colonoscopy are listed. There may be roles for other testing, including small bowel follow-through, abdominal-pelvic CT scan, and upper endoscopy (with small bowel biopsies) (Box 6).

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**Box 3**

**Common medications associated with diarrhea**

- Antidepressants (selective serotonin reuptake inhibitors)
- Diabetic medications (metformin, GLP-1 agonist exenatide, liraglutide)
- Antibiotics
- Laxatives (osmotic and stimulant)
- Nonsteroidal antiinflammatories
- Proton pump inhibitors
- Colchicine

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There are only a few disorders that are consistently osmotic and make evaluation straightforward. Use of fecal osmotic gap is rarely necessary. If history is compatible,
the physician can try eliminating lactose from the diet. If there is continued clinical concern for lactose intolerance, hydrogen breath testing can be performed. Otherwise, the most likely diagnosis is intentional or accidental ingestion of an osmotically active agent (or a mixed disorder). Some patients ingest a significant amount of sorbitol in candy and gum and can have diarrhea due to its ingestion.

SECRETORY

**IBS or Functional Diarrhea**

IBS is characterized by the presence of abdominal pain or discomfort in the setting of irregular bowel function. Functional diarrhea describes frequent loose stool but without the associated abdominal pain or other symptoms. Mucus is a common complaint. Features making IBS less likely include bloody or nocturnal diarrhea and weight loss. Testing on patients with IBS can show abnormal hydrogen and some patients respond to rifaximin, which suggests alteration in bacterial distribution.\(^{18,19}\) Treatments found to be effective in symptom management include exercise, antispasmodics, rifaximin, and probiotics.\(^{20}\) In patients with diarrhea, loperamide can decrease stool frequency but has limited effect on pain.

MICROSCOPIC COLITIS

Microscopic colitis is an increasingly recognized cause of chronic diarrhea, especially in older adults. Because diagnosis requires colonic biopsy in the setting of normal-appearing mucosa, it is a challenging and likely underreported diagnosis. Biopsy can show lymphocytic and/or collagenous infiltration, although there are newer reports of both eosinophilic and mast cell populations. The typical presentation is diffuse watery diarrhea, occasionally severe. Associated medications include nonsteroidal antiinflammatory drugs (NSAIDs), proton-pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), ticlopidine, and possibly statins.\(^{21}\) There also seems to be an association with celiac disease. Treatment is antidiarrheals such as loperamide for mild disease, bismuth subsalicylate for moderate disease, and budesonide for more severe symptoms.\(^{22}\)

**Neuroendocrine**

There are no clear guidelines on when testing for these very uncommon causes of diarrhea should be performed. Testing for plasma peptides (gastrin, vasoactive intestinal peptide, somatostatin, and calcitonin) and urine metabolites (5-hydroxyindoleacetic acid, metanephrine, and histamine) are most commonly ordered in atypical presentations or when radiographic studies suggest a cause.
INFLAMMATORY

Inflammatory Bowel Disease

One of the challenges is determining when colonoscopy is indicated to rule out inflammatory bowel disease (IBD) versus irritable bowel syndrome. Fecal calprotectin may aid in this decision. In a meta-analysis of subjects referred for colonoscopy for suspected IBD, calprotectin had a sensitivity of 93% and specificity of 96% in diagnosing IBD. A subsequent study, in which 41% of subjects had histologically confirmed inflammation, sensitivity and specificity were 75% and 88%, respectively. In a lower risk primary care population, a negative calprotectin would be reassuring that inflammation was very unlikely.

FATTY OR MALABSORPTION

Celiac Disease

Although not specifically outlined in the 1999 American Gastroenterological Association (AGA) guidelines, testing for celiac disease should be performed if the diagnosis is not immediately obvious. This is especially true if there is weight loss, steatorrhea, bloating, anemia, abnormal liver enzymes, or bone loss. Both IgA antiendomysial and IgA antitissue transglutaminase have excellent sensitivity in patients with abdominal symptoms (sensitivity 89%–90%, specificity 98%–99%). Gliadin antibodies should not be used for screening because it is inferior. Once diagnosed, if diarrhea persists, consider microscopic colitis (see previous discussion), pancreatic exocrine deficiency, or gastrointestinal lymphoma.

Small Intestine Bacterial Overgrowth

Typically, presentations of small intestine bacterial overgrowth include abdominal pain or cramping, bloating, diarrhea, and steatorrhea. However, because the standard for diagnosis is jejunal aspirate, the diagnosis is often not easily made. Hydrogen breath testing, often with lactulose, is used to help determine likelihood of bacterial overgrowth. If testing is positive, a trial of antibiotics is appropriate (rifaximin, amoxicillin-clavulanate, and norfloxacin). Because some patients with IBS respond to rifaximin, this is an attractive, albeit expensive, option.

Other malabsorptive causes of chronic diarrhea include pancreatic exocrine insufficiency and bile acid malabsorption. Fatty stools, either clinically or by testing, should suggest possible pancreatic or biliary cause of diarrhea. Patients in whom chronic pancreatitis or pancreatic insufficiency is a clinical concern may respond to treatment with pancreatic enzymes. Bile acid malabsorption is an underrecognized cause of chronic diarrhea in which bile is not resorbed properly in the distal ileum. Diarrhea due to increased colonic delivery of bile acids is common in patients who have had a cholecystectomy, causing persistent symptoms in 6% of patients.

Testing for bile issues is challenging and an empiric trial of cholestyramine, a bile acid sequestrant, is reasonable in persistent diarrhea of no other clear cause.

DIARRHEA SUMMARY

Important considerations for diarrhea include:

1. Chronic diarrhea can be due to a large number of underlying diagnoses but irritable bowel or functional disorders are the most common
2. History and examination help determine osmotic, secretory, inflammatory, or malabsorptive causes
3. Testing with fecal calprotectin may help differentiate inflammatory from noninflammatory causes
4. Treatment of chronic diarrhea is driven by diagnosis (Figs. 1 and 2)

CONSTIPATION

Chronic constipation is characterized by infrequent and/or difficult bowel movements that persist for at least 3 months. Associated symptoms can include hard or firm stool, incomplete evacuation, bloating, and abdominal discomfort. Although many studies and guidelines use fewer than three bowel movements per week as a criterion, this applies to a marked minority of patients who consider themselves constipated. As many as 50% of patients who report constipation actually have a daily bowel movement. Given variation in definition, precise prevalence is difficult. However, this is an extremely common condition, likely affecting 15% to 20% of adults in their lifetime and up to 33% of those older than 60 years of age. Women are affected more than
men and prevalence increases with age. In addition, quality of life is adversely affected, with associated loss of work productivity, activity impairment, and increased healthcare resource use (Box 7).30

Evaluation

History should include a detailed review of bowel habits, including frequency and consistency of bowel movements, the need to strain or use manual maneuvers, and sense of incomplete evacuation. It is important to identify the most bothersome symptom because it focuses the evaluation and treatment. Other abdominal symptoms, such as gastrointestinal bleeding, abdominal pain, and bloating, should also be ascertained. Relevant past history such as abdominal surgery, neurologic disorders (Parkinson disease and multiple sclerosis) and hypothyroidism should be collected. A complete medication history, including over-the-counter bulk agents and laxatives, along with other supplements, such as calcium and iron, should be obtained.
Adverse effect of medications can be a reversible cause of constipation. Common offenders include opioids, calcium and iron supplements, calcium channel blockers, anticholinergics (including inhaled agents such as tiotropium), and NSAIDs.

Physical Examination

Physical examination should include:

1. Careful abdominal examination with special attention to surgical scars and masses
2. Examination of the perianal region with attention to fissures and hemorrhoids
3. Perineal inspection during simulated evacuation
4. Rectal examination of sphincter tone, both at rest and with simulated bowel evacuation
5. In women, a pelvic examination may been needed to rule out rectocele

Laboratory Testing

In most patients, complete blood count should be checked. Blood sugar, calcium, and thyroid stimulating hormone can also be considered, although evidence of such an approach is lacking and this approach is not endorsed by AGA.

DEFECATORY DISORDERS

The initial goal of history, examination, and basic testing is to identify concerning symptoms as well as relevant medical or pharmacologic issues. After that, it is

<table>
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<th>Box 7</th>
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<tr>
<td>Differential for constipation</td>
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<td>Functional problems</td>
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<tr>
<td>• IBS with constipation</td>
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<tr>
<td>• Functional constipation</td>
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<td>Defecatory</td>
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<td>• Pelvic floor dysfunction</td>
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<td>• Dyssynergic defecation</td>
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<td>• Rectocele</td>
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<td>Diseases of the colon:</td>
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<td>• Stricture</td>
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<td>• Colorectal cancer</td>
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<td>Metabolic</td>
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<td>• Parkinson</td>
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<td>• Multiple sclerosis</td>
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<td>• Spinal cord lesions</td>
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important to determine if there is a defecatory disorder in which evacuation is the primary problem. Normal defecation requires relaxation of the puborectalis muscles, pelvic floor descent, abdominal wall muscle contraction, and, finally, relaxation of the anal sphincter.\textsuperscript{31} Issues with any of these actions can lead to difficulty with evacuation. In patients with pelvic floor dysfunction, there is a decrease in the strength of the pelvic floor muscles, impaired rectal sensation, and a subsequent decrease in rectal tone. Dyssynergic defecation refers to a lack of coordination of muscle relaxation and contraction. The precise cause of such disorders remains unclear. Other issues that can lead to defecatory difficulty are rectoceles, hemorrhoids, and anal fissure or stricture. Importantly, laxatives have limited effect on these disorders, making it critical to identify these patients (Box 8).

\textbf{Nonpharmacologic Therapy}

Constipation has been noted to be more prevalent in patients with limited physical activity and low dietary fiber. However, studies looking at dietary modifications with increased fiber intake (such as bran) have been conflicting. In at least one trial, abdominal pain and bloating actually worsened with added fiber. There have been some data supporting the benefit of prunes.\textsuperscript{32} However, soluble fiber (such as psyllium) led to improvements in global symptoms (86.5\% vs 47.4\%), straining (55.6\% vs 28.6\%), pain on defecation, and stool consistency compared with placebo.\textsuperscript{33} Biofeedback is an effective treatment in defecatory disorders with pelvic floor dysfunction, improving symptoms in up to 70\% of affected subjects.\textsuperscript{34}

\textbf{PHARMACOLOGIC THERAPY}

\textbf{Laxatives}

The mainstay of treatment over the years has been laxatives. Laxatives are either osmotic (polyethylene glycol, lactulose, and magnesium) or stimulatory (bisacodyl, senna, and cascara). Pooled data on osmotic laxatives reveal a significant effect with only 38\% failing to improve compared with 69\% for placebo, resulting in an

\begin{tabular}{|p{15cm}|}
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Box 8 & Diagnostic tests \\
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1. Anorectal manometry or balloon expulsion test: & \\
\hline
   a. Balloon test involves expulsion of a water-filled balloon, with expectation it will be completed within 1 to 5 minutes & \\
   b. Indicated for suspected defecatory disorder or those with poor response to laxatives & \\
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2. Defecography & \\
\hline
   a. Evacuation of barium is monitored by fluoroscopy & \\
   b. Reserved for inconclusive testing but concern for defecatory issue & \\
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3. Colon transit time & \\
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   a. Performed with radiopaque makers, with slow transit time defined as multiple retained markers on day 6; wireless motility capsules can also be used (more expensive) & \\
   b. Indicated if defecatory disorder ruled out, laboratory testing unremarkable and poor response to laxatives (or if symptoms persist after treatment of defecatory disorder) & \\
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4. Colonoscopy & \\
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   a. Indicated if due for routine screening, blood in stools, anemia, weight loss, or severe, persistent symptoms & \\
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\end{tabular}
NNT of 3. In direct comparisons, polyethylene glycol has been found to be more effective than lactulose in improving stool frequency and form, relief of abdominal pain, and need for other agents and, therefore, should be considered the preferred osmotic agent. Stimulant laxatives such as bisacodyl are also effective with 42% failing to improve versus 78% on placebo (NNT 3). Although there have been concerns regarding the long-term safety of stimulant laxatives, there is no convincing evidence of increased risk of cancer or worsening bowel function.

SECRETAGOGUES

There are two relatively new agents approved for use in patients with chronic constipation. Linaclotide is a peptide that stimulates cyclic guanosine monophosphate

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**Fig. 3.** American Gastroenterological Association (AGA) 2013 guidelines for initial evaluation and treatment algorithm for chronic constipation. (From American Gastroenterological Association, Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. Gastroenterology 2013;144:211–17.)
through the guanylate cyclase receptor. This results in chloride-rich fluid secretion into the intestinal lumen. Subjects with chronic constipation (average of 0.3 complete spontaneous bowel movements per week) were studied for 12 weeks with daily linaclotide or placebo. A return to normal bowel function (at least 3 complete spontaneous bowel movements per week in 75% of weeks) occurred in approximately 20% of treated subjects versus 5% with placebo (NNT ~ 6). Diarrhea led to discontinuation in approximately 4% of subjects.\textsuperscript{37} In addition, linaclotide has shown promise in subjects with IBS with constipation, with improvements in both spontaneous bowel movements and abdominal pain.\textsuperscript{38}

Fig. 4. AGA 2013 guidelines for treatment algorithm for defecating disorders. (From American Gastroenterological Association, Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. Gastroenterology 2013;144:211–17.)
Lubiprostone, which activates chloride channels leading to increased intestinal fluid secretion, has also been shown to increase the number of spontaneous bowel movements. A meta-analysis of three studies found an NNT of 4 to increase spontaneous bowel movement to at least 3 to 4 per week. The most common adverse effects were nausea and diarrhea.35

PROKINETICS

Cisapride and tegaserod, 5-HT₄ agonists used for constipation, have been removed from the US market due to concerns of excess cardiovascular events and QT prolongation. Prucalopride, a more selective 5-HT₄ agent, is now available in Canada and

Fig. 5. AGA 2013 guidelines for treatment algorithm for normal or slow transit constipation. GI, gastrointestinal. (From American Gastroenterological Association, Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. Gastroenterology 2013;144:211–17.)
Europe but has not been approved for use in the United States. In a meta-analysis, the NNT was 6 to return to normal bowel function. Thus far, there has been no significant effect on QT length or increase in adverse cardiovascular events.  

OTHERS

Probiotics may have a benefit in patients with functional constipation, with data suggesting improvement in defecation frequency and stool consistency. There are no convincing data on the efficacy of stool softeners such as docusate, although there may be a role in patients with hard stools.

SURGICAL TREATMENT

If slow transit constipation is documented, and a patient fails an aggressive trial of fiber, laxatives, and prokinetics, total colectomy is an option. Obviously, this needs to have been very carefully considered.

SUMMARY

Important considerations for constipation include:

1. Initial evaluation should evaluate for fecal incontinence, fecal impaction, medication side effects, concerning symptoms, underlying medical or metabolic issues and irritable bowel syndrome
2. History and examination should be used to determine if a defecatory disorder is most likely
   a. If defecatory disorder is likely, testing with balloon expulsion or anal manometry can be considered and, if confirmed, treatment with biofeedback (if testing not available, it is reasonable to trial fiber and laxatives because many patients have a mixed disorder)
   b. If it is unlikely, proceed with trial of fiber and/or osmotic laxatives
3. If continued symptoms, consider trial of newer agent (lubiprostone or linaclotide)
4. If ineffective, consider testing for colon transit time and referral to gastroenterology (Figs. 3–5)

REFERENCES


FURTHER READINGS


