JAMA | Review

Chronic, Noninfectious Diarrhea
A Review

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IMPORTANCE Chronic diarrhea is defined as loose or watery stools lasting longer than 4 weeks and affects approximately 6% to 7% of adults in the US. More than 90% of patients with chronic diarrhea have a noninfectious etiology.

OBSERVATIONS The most common causes of chronic, noninfectious diarrhea are irritable bowel syndrome with diarrhea (IBS-D) and functional diarrhea. IBS-D typically presents with recurrent abdominal pain relieved or worsened after defecation. Functional diarrhea is a condition in which more than 25% of bowel movements in the preceding 3 months are loose or watery, but it is not associated with significant abdominal pain. Chronic diarrhea due to a small-bowel source, such as celiac disease or small intestinal bacterial overgrowth, is typically associated with large-volume diarrhea and weight loss, with or without steatorrhea. Celiac disease is an autoimmune condition defined by enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals, and small intestinal bacterial overgrowth is characterized by excessive bacteria in the small bowel. Chronic diarrhea due to colon pathology, such as bile acid diarrhea and microscopic colitis, typically presents with frequent, low-volume stools, with or without urgency and excess mucus. Bile acid diarrhea is characterized by excess bile acids in the colon, and microscopic colitis is characterized by chronic inflammation on colon biopsies despite normal endoscopic appearance. Evaluation of chronic diarrhea includes serological testing for celiac disease (tissue transglutaminase immunoglobulin A, along with total immunoglobulin A) and stool testing for fecal calprotectin to evaluate for inflammatory bowel disease. Patients with gastrointestinal bleeding, unexplained weight loss, 45 years or older, nocturnal diarrhea, steatorrhea, and/or iron deficiency anemia should undergo colonoscopy to evaluate for colorectal cancer as well as upper endoscopy. During colonoscopy, random biopsies are recommended to evaluate for microscopic colitis, which affects 13% of patients with chronic diarrhea. If evaluation does not identify a cause of chronic diarrhea, likely diagnoses are IBS-D or functional diarrhea and the patient should be treated with lifestyle modification, such as regularly scheduled meals, exercise, intake of at least 8 cups of noncaffeinated fluids daily, limiting caffeine to 3 cups or fewer daily, and avoiding alcohol and carbonated beverages. For general treatment of chronic diarrhea, dietary modifications, such as consuming a diet low in fermentable oligosaccharides (legumes, wheat, onions, garlic), disaccharides (lactose), and monosaccharides (fructose), and polyols (sorbitol, mannitol), or medications, such as opiate agonists (loperamide), anticholinergics (hyoscyamine, dicyclomine), or 5-hydroxytryptamine 3 receptor (5-HT_3) antagonists (ondansetron), can be prescribed. These therapies typically improve diarrhea in 50% to 80% of patients.

CONCLUSIONS AND RELEVANCE The most common causes of chronic, noninfectious diarrhea include IBS-D and functional diarrhea. Diagnostic testing should include consideration of celiac disease, inflammatory bowel disease, and microscopic colitis. Empiric therapies for chronic diarrhea include lifestyle and dietary modifications and medications, including opiate agonists, anticholinergics, and 5-HT_3 antagonists.

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Chronic diarrhea is defined by recurrent loose or watery stools, with or without increased stool frequency, fecal urgency, or fecal incontinence, that lasts for at least 4 weeks. Chronic diarrhea affects approximately 6% to 7% of US adults.[1] Although a wide range of conditions can cause chronic, noninfectious diarrhea, irritable bowel syndrome with diarrhea (IBS-D) and functional diarrhea, a condition characterized by chronic diarrhea without abdominal pain, are the most common causes. This Review summarizes current evidence-based strategies to diagnose and treat the most common causes of chronic, noninfectious diarrhea in adults.

Methods

We searched PubMed, Scopus, and the Cochrane Library for English-language studies addressing the epidemiology, evaluation, diagnosis, and treatment of chronic diarrhea, using the search terms *chronic diarrhea* and *chronic, noninfectious diarrhea*. Meta-analyses, systematic reviews, clinical practice guidelines, and randomized clinical trials (RCTs) were prioritized for inclusion. The literature search was initially conducted on July 30, 2024, and updated on December 15, 2025. Of 238 articles identified, 90 were included, consisting of 26 meta-analyses or systematic reviews, 9 clinical practice guidelines, 15 RCTs, 11 longitudinal observational studies, and 29 cross-sectional studies.

Discussion

Pathophysiology

Oral fluid intake (2-3 L/d) and fluid secretion (7-8 L/d) by salivary glands, the stomach, pancreas, liver, and small intestine account for the fluid in the gastrointestinal (GI) tract. Under physiologic conditions, the small intestine reabsorbs approximately 7 to 9 L/d and the colon reabsorbs approximately 1.5 L/d, leaving 100 to 200 mL of fluid per day that is normally excreted in stool.

Chronic, noninfectious diarrhea due to small intestine pathology typically results from either conditions in which food is not fully digested in the small intestine, such as disaccharidase deficiency, exocrine pancreatic insufficiency (EPI), and small intestinal bacterial overgrowth (SIBO), or conditions in which the small intestine does not absorb nutrients from digested food (eg, celiac disease, short bowel syndrome). Diarrhea that occurs within 30 to 180 minutes after eating can result from either maldigestion or malabsorption in the small intestine, but can also arise from an overactive gastrocolonic reflex, in which gastric distention by food causes increased colonic motility.

Chronic diarrhea from colonic pathology is typically due to excess colonic fluid and electrolyte secretion and/or impaired absorption. For example, in bile acid diarrhea (BAD), excess bile acids stimulate colonic epithelial cells to secrete electrolytes while inhibiting fluid absorption. BAD is more common in people with cholecystectomy, terminal ileal disease or resection (eg, due to Crohn disease), EPI, and SIBO. Alternatively, mucosal inflammation due to microscopic or ulcerative colitis stimulates chloride and bicarbonate secretion and impairs absorption of water. Microscopic colitis is defined as microscopic chronic inflammation on colonic biopsies despite normal endoscopic appearance of mucosa, and ulcerative colitis is characterized by chronic inflammation on colonic biopsies, along with endoscopic changes suggestive of inflammation, that can involve any aspect of the colon, starting with the rectum and extending proximally in a continuous fashion. Rarely, secretory diarrhea is due to a hormone-secreting neuroendocrine tumor (eg, carcinoid, gastrin, glucagon, somatostatin, or vasoactive intestinal peptide–secreting tumors). Secretory diarrhea can awaken patients at night and occurs even during fasting states.

History

Patients with chronic diarrhea should be evaluated for stool consistency, frequency, volume, nocturnal diarrhea, factors that worsen diarrhea, factors that improve diarrhea, and associated symptoms, such as fecal urgency, tenesmus, or fecal incontinence (**Figure**). Stool consistency can be assessed with the Bristol Stool Form Scale, which provides standardized verbal and pictorial descriptors ranging from type 1 (hard stool) to type 7 (watery stool).

Steatorrhea, defined by excess fat in stools and characterized by large, foul-smelling stools that float, can result from small intestinal diseases (such as celiac disease) or EPI.

Medications Associated With Diarrhea

Common over-the-counter medicines that can cause diarrhea include magnesium-containing oral supplements or antacids and herbal teas containing plant-based laxatives, such as aloe, senna, rhubarb, or cascara. Prescription medications commonly associated with diarrhea include metformin, colchicine, immune checkpoint inhibitors (ipilimumab or nivolumab), and mycophenolate. Medical (diabetes, systemic sclerosis), surgical (small bowel or colon procedures, cholecystectomy), and family histories (celiac disease, inflammatory bowel disease [IBD]) may also provide important clues to the etiology of chronic diarrhea.

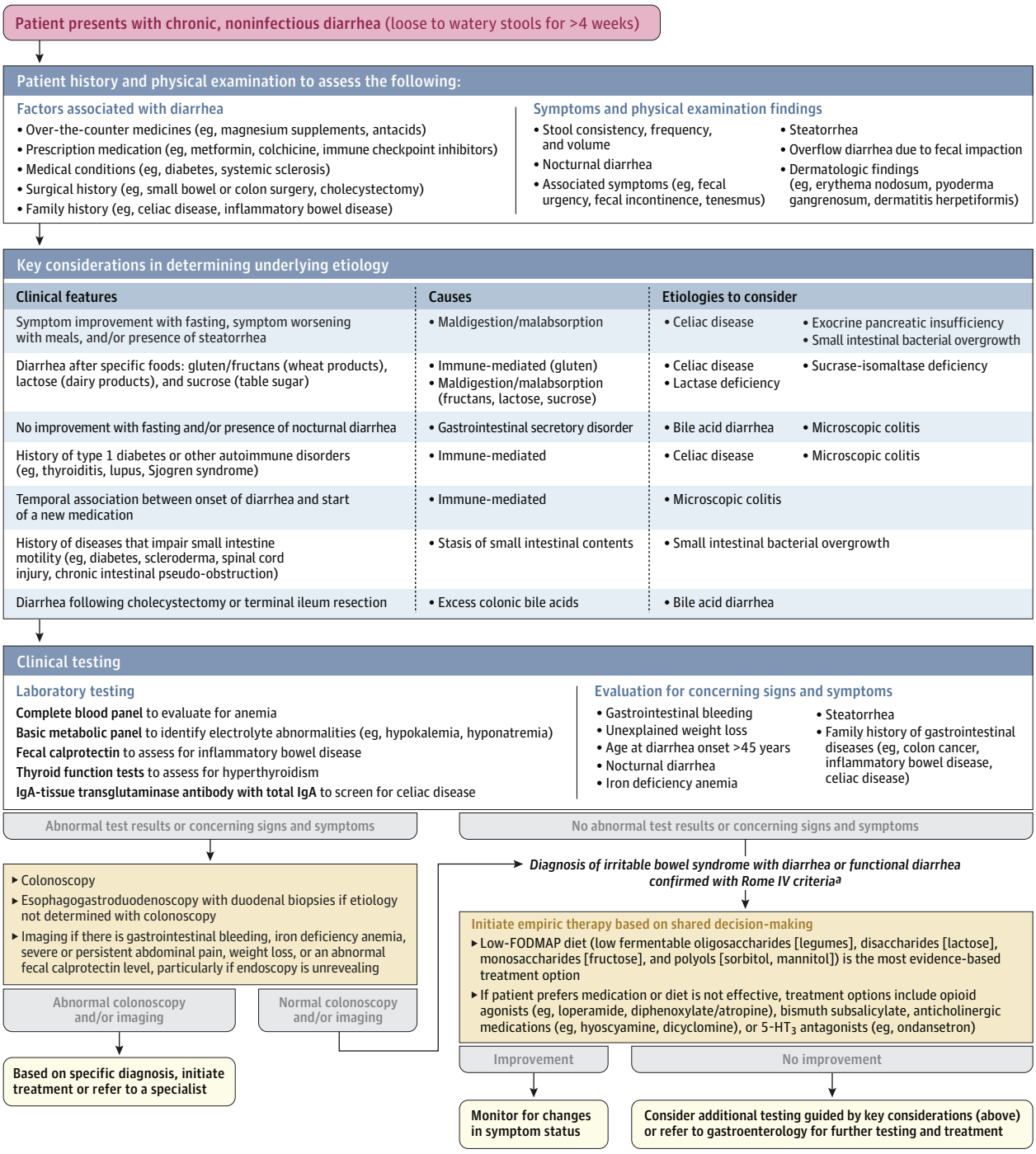
Physical Examination

Patients with chronic constipation can develop overflow diarrhea, in which liquid stool leaks around impacted feces in the sigmoid or rectum. A digital rectal examination can identify fecal impaction. Autoimmune diseases associated with chronic diarrhea may present characteristic dermatologic findings, such as erythema nodosum or pyoderma gangrenosum in IBD and dermatitis herpetiformis in celiac disease.

Laboratory Evaluation of Patients With Chronic Diarrhea

Clinical guidelines recommend that patients presenting with chronic diarrhea undergo a complete blood count to evaluate for anemia, a basic metabolic panel to identify electrolyte abnormalities (eg, hypokalemia, hyponatremia), fecal calprotectin to assess for IBD,[2,3] and immunoglobulin A (IgA)–tissue transglutaminase (IgA-tTG) antibody with total IgA to screen for celiac disease (Figure).[4] Patients with rectal bleeding, iron deficiency anemia, unexplained weight loss, age at onset of 45 years or older, or nocturnal diarrhea should undergo colonoscopy with biopsies to evaluate for colorectal cancer, IBD, and microscopic colitis (Figure). If colonoscopy does not identify the cause of diarrhea, upper endoscopy should be performed. If symptoms suggest a small intestinal source (eg, large-volume diarrhea or steatorrhea) or if the patient has signs of malabsorption, such as unexplained

Figure. Clinical History Elements That Aid in Determining the Underlying Etiology of Chronic, Noninfectious Diarrhea and Algorithm for Diagnosis



In patients with rectal bleeding, unexplained weight loss, older age at onset (>45 years), nocturnal diarrhea, steatorrhea, and/or iron deficiency anemia, further evaluation with colonoscopy, upper endoscopy, and/or imaging should be considered. In the absence of these features, a targeted workup can be considered. Once specific causes have been excluded, if symptoms are consistent with IBS-D or functional diarrhea, specific IBS-D or functional diarrhea treatment algorithms can be pursued. If patients do not meet the diagnoses for IBS-D or functional diarrhea, alternative causes can be considered based on specific risk factors. This algorithm has not been validated. 5-HT_3 indicates 5-hydroxytryptamine 3 receptor; IBS-D, irritable bowel syndrome with diarrhea; IgA, immunoglobulin A.

[a]Expert consensus definitions developed to diagnose and classify disorders of gut-brain interaction for clinical practice and research.

weight loss, muscle wasting or weakness, anemia, bone pain, or unexplained bruising or bleeding, upper endoscopy with duodenal biopsies should be performed to evaluate for celiac disease, Crohn disease, or other small intestinal pathology.[3]

Table 1. Common Causes of Chronic Diarrhea

Condition	Definition	Worldwide prevalence	Risk factors
Functional diarrhea	Defined by Rome IV Criteria[a] as loose or watery stools occurring in >25% of bowel movements without recurrent or predominant abdominal pain Diagnostic criteria include diarrhea for ≥3 mo, with onset ≥6 mo before diagnosis and symptoms unexplained by structural, infectious, or medication-related causes[5]	4.7% (95% CI, 4.2%-5.3%)[6]	NA
IBS-D	Recurrent abdominal pain on average ≥1 d/wk in the preceding 3 mo, with symptom onset ≥6 mo ago, associated with 2 or more of the following: related to defecation, change in stool frequency, and change in stool form For IBS-D specifically, >25% of bowel movements are loose or watery (Bristol Stool Form Scale types 6-7) and <25% are hard or lumpy (types 1-2)[5]	1.2% (95% CI, 1.1%-1.3%)[7]	Female sex (pooled prevalence rates for IBS 10.2% in females, 8.8% in males)[8] Depression (incidence of IBS 2.0 per 1000 person-years in individuals with depression vs 1.5 per 1000 person-years in individuals without depression)[9] Acute gastroenteritis (IBS diagnosed in 16.5% with acute gastroenteritis vs 2.6% in control individuals)[10]
Disaccharidase deficiency	Reduced or absent activity of ≥1 intestinal disaccharidase enzymes (lactase, sucrase, maltase, isomaltase) in the small intestinal brush border, resulting in malabsorption of corresponding sugars	Prevalence estimate[11,12] for loss of lactase enzyme activity is 60% globally in the adult population	Loss of lactase enzyme activity is associated with certain racial and ethnic populations (prevalence of 70%-100% in Asian, 80% in Black, and 66% in Native American populations)[11,12]
Microscopic colitis	Chronic inflammatory condition of the colon characterized by chronic watery diarrhea with a normal colonoscopic appearance, diagnosed by colonic biopsy	Approximately 197.9 to 246.2 per 100 000 persons[13,14]	Female sex (incidence was 11.0 per 100 000 person-years in female individuals vs 6.1 per 100 000 person-years in male individuals)[15] Increasing age (incidence was ≈3 per 100 000 person-years in ages 18-44.9 y; ≈11 per 100 000 person-years in ages 45-65 y; and ≈35 per 100 000 person-years in ages >65 y)[16] Autoimmune diseases (celiac disease; incidence in individuals with vs without celiac disease was 86.1 vs 7.5 per 100 000 person-years)[17] Medications (prevalence of microscopic colitis vs no microscopic colitis in individuals taking aspirin or nonsteroidal anti-inflammatory drugs was 54% vs 29%)[18]
Celiac disease	Chronic, immune-mediated enteropathy caused by ingestion of gluten in genetically susceptible individuals, characterized by small intestinal mucosal injury (villous atrophy)	1.4%[19] (95% CI, 1.1%-1.7%) based on positive celiac serologies 0.7% (95% CI, 0.5%-0.9%) with biopsy-proven celiac disease (N = 138 792; meta-analysis of 57 population-based studies worldwide)	First-degree relative with celiac disease (pooled prevalence of 7.5% [95% CI, 6.3%-8.8%])[20] Type 1 diabetes (prevalence of 6% [95% CI, 5%-6.9%])[21] Autoimmune thyroid disease (prevalence of 1.6% [95% CI, 1.3%-1.9%])[22]
EPI	Extremely reduced or absent pancreatic excretion of digestive enzymes and bicarbonate, resulting in maldigestion and malabsorption of nutrients, particularly fats, and fat-soluble vitamins	Unknown	Chronic pancreatitis (60%-90% have EPI),[23] cystic fibrosis (80%-90% have EPI),[24] and pancreatic carcinoma (70%-90% have EPI)[18]
SIBO	Abdominal pain, bloating, and/or diarrhea due to an abnormally high number of bacteria in the small intestine (>10^3 colony-forming units per milliliter of small bowel aspirate)	Unknown	Abnormal small bowel contractile activity (31% of patients with IBS have evidence of SIBO)[25] Other risk factors include hypochlorhydria or achlorhydria, EPI, small intestinal strictures, or resection of the ileocecal valve
BAD	Chronic watery diarrhea caused by excessive bile acids entering the colon, which stimulate colonic fluid and electrolyte secretion and increase colonic motility	Approximately 1% of the general population	Terminal ileal disease (28% of patients with Crohn disease, 90% with prior ileal resection)[26] Other risk factors (eg, dysregulated bile acid synthesis, impaired bile storage) have more limited data

Abbreviations: BAD, bile acid diarrhea; EPI, exocrine pancreatic insufficiency; IBS-D, irritable bowel syndrome with diarrhea; NA, not applicable; SIBO, small intestinal bacterial overgrowth.

[a] Expert consensus definitions developed to diagnose and classify disorders of gut-brain interaction for clinical practice and research.

Disorders of Gut-Brain Interaction Presenting With Diarrhea

IBS-D and Functional Diarrhea

Definition, Prevalence, and Risk Factors | Disorders of gut-brain interaction are defined by recurring GI symptoms that are not attributable to another disease or structural or biochemical abnormality. Although their pathogenesis remains incompletely understood, these disorders involve abnormalities in GI motility, visceral hypersensitivity, gut microbiome composition, intestinal permeability, and mucosal immune activation, resulting in disordered interaction between the GI tract and central nervous system (eg, perception and experience of pain, stressful events, and eating food).

Diarrhea-predominant disorders of gut-brain interaction include IBS-D and functional diarrhea, which are defined by the Rome IV Criteria, expert consensus definitions developed to diagnose and classify disorders of gut-brain interaction for clinical practice and

research[5] (**Table 1**).[5-26] IBS-D is defined by recurrent abdominal pain relieved by or worsened after defecation that is associated with more frequent than usual stools or recurring loose or watery stools. Functional diarrhea is characterized by more than 25% of bowel movements being loose or watery without significant abdominal pain. For both conditions, symptoms must be present for at least 8 weeks to make the diagnosis.[27]

In a population-based internet questionnaire that included 73 076 respondents from 24 countries, the combined prevalence of IBS-D and functional diarrhea using Rome IV Criteria was 6% to 9%.[7] The prevalence of functional diarrhea was similar between women and men (pooled prevalence of 4.1% in women vs 5.3% in men). In contrast, women were less likely than men to have IBS-D (meta-analysis of 56 studies including 188 229 participants: pooled prevalence in women was 31% vs 50% in men).[28]

Symptoms and Diagnosis | In addition to characteristic symptoms, patients with suspected IBS-D and functional diarrhea should undergo testing to evaluate for alternative diseases with overlapping presentations, such as fecal calprotectin to assess for IBD and IgA-tTG with total IgA to screen for celiac disease.

Treatment | Treatment of IBS-D and functional diarrhea includes dietary, pharmacologic, and behavioral interventions[29,30] (**Box**).[31-33] For patients with IBS, general dietary and lifestyle recommendations from the National Institute of Health and Care Excellence (NICE) include regularly scheduled mealtimes, physical activity, intake of at least 8 cups of noncaffeinated fluids daily, limiting caffeine to 3 cups or fewer daily, avoiding alcohol and carbonated beverages, restricting resistant starch (eg, potatoes, pasta, rice), limiting fresh fruit to 3 portions per day, reducing high-fiber foods (eg, high-fiber flour/breads, cereals high in bran and whole grains), and avoiding sorbitol-[34] or mannitol-containing products. Although RCTs comparing the NICE diet with a control diet are not available, studies comparing the NICE diet with other active diet interventions (eg, low fermentable oligosaccharides, disaccharides, and monosaccharides, and polyols [FODMAP] or Mediterranean diets) have reported response rates, defined as overall IBS symptom improvement, in 42% to 44% of participants.[35,36]

Among diets evaluated for IBS-D, the low-FODMAP diet has been most extensively studied. FODMAPs are short-chain carbohydrates that are poorly absorbed in the small intestine and are found in many foods, including wheat, garlic, onions, stone fruits (cherries, peaches, plums), some vegetables (legumes), and sugar alcohols (sorbitol, mannitol). These carbohydrates exert osmotic effects and undergo colonic fermentation, producing gas and short-chain fatty acids that may provoke diarrhea and/or abdominal pain. In a meta-analysis of 7 trials (N = 397 patients), a low-FODMAP diet was associated with greater improvement in IBS symptoms compared with a control diet (n = 86 [43.2%] still symptomatic with low-FODMAP diet vs n = 122 [61.6%] with control diet).[29] Patients who respond after 4 to 8 weeks of FODMAP restriction should undergo structured reintroduction of individual FODMAP groups, including fructans (wheat, onions, garlic), galactans (beans, chickpeas), lactose (milk), fructose (honey, agave, watermelon), and sugar alcohols (sugar-free gum or candy). A registered dietitian may be helpful in evaluating the restriction and reintroduction of foods. Foods tolerated during reintroduction can be incorporated into a personalized, long-term diet.

Box. Frequently Asked Questions About Chronic, Noninfectious Diarrhea

What are the most common causes of chronic, noninfectious diarrhea?

Among people with chronic diarrhea, the most common etiologies of noninfectious diarrhea are functional diarrhea, characterized by the absence of abdominal pain combined with more than 25% of stools with diarrhea over the preceding 3 months, and IBS-D (35% combined), lactase deficiency (35%),[31] bile acid diarrhea (25%-33%),[32] and celiac disease (12%).[33]

How should patients presenting with chronic, noninfectious diarrhea be evaluated?

Prior to diagnostic testing, all patients with chronic diarrhea should undergo a thorough history and physical examination, complete blood count to assess for anemia or iron deficiency, a basic metabolic panel to evaluate for electrolyte abnormalities, fecal calprotectin to evaluate for IBD, and serological testing for celiac disease (IgA-tTG and total IgA level). Patients with chronic diarrhea who are 45 years or older should undergo a colonoscopy to evaluate for colon cancer, and random biopsies should be obtained to rule out microscopic colitis.

Which therapies are recommended for IBS-D and functional diarrhea?

First-line treatment for patients with IBS-D and functional diarrhea include lifestyle changes (regularly scheduled meals and physical activity, intake of ≥8 cups of noncaffeinated fluids daily, limiting caffeine to ≤3 cups per day, and avoiding alcohol and carbonated beverages); dietary interventions, such as a diet low in fermentable oligosaccharides (legumes), disaccharides (lactose), and monosaccharides (fructose), and polyols (sorbitol, mannitol). Medications include opiate agonists (loperamide, diphenoxylate/atropine), antispasmodics (hyoscyamine, dicyclomine), and 5-HT_3 receptor antagonists (ondansetron). Second-line therapies, which may be effective in patients with IBS-D, include rifaximin, eluxadoline, and tricyclic antidepressants, such as amitriptyline.

Abbreviations: 5-HT_3, 5-hydroxytryptamine 3 receptor; IBS-D, irritable bowel syndrome with diarrhea; IgA, immunoglobulin A; tTG, tissue transglutaminase.

Medications

Although few high-quality RCTs exist, medications to treat diarrhea in patients with IBS-D and functional diarrhea include opiate agonists (loperamide, diphenoxylate-atropine), bismuth, anticholinergics (dicyclomine, hyoscyamine), and 5-hydroxytryptamine 3 receptor (5-HT_3) antagonists (ondansetron, granisetron)[30] (**Table 2**).[37,38] For patients with IBS-D with prominent abdominal pain and diarrhea, clinical trial evidence supports therapy with the poorly absorbed oral antibiotic rifaximin,[39] the mixed opioid agonist and antagonist eluxadoline,[40] or the tricyclic agent amitriptyline.[41] In 2 phase 3 RCTs (n = 623 [target 1] and n = 637 [target 2] nonconstipated patients with IBS), compared with placebo, rifaximin 550 mg 3 times daily for 2 weeks resulted in significant benefit for the primary outcome of the proportion of patients reporting adequate relief of IBS symptoms during the first 4 weeks after treatment (target 1: 40.8% vs 31.2% [P = .01]; target 2: 40.6% vs 32.2% [P = .03]).[39] In a secondary analysis, compared with placebo, rifaximin improved

Table 2. Medications for Chronic Diarrhea

Medication	Mechanism of action	Recommended dosing	Adverse events (with frequency[a])
Over-the-counter agents			
Bismuth subsalicylate	Prostaglandin inhibitor	524 mg Orally as needed, not to exceed 8 doses in 24-h period	Nausea (12.3%) Darkening of tongue and stools (89.5%)[37]
Loperamide	Peripherally acting μ-opioid receptor agonist	2-16 mg Daily in divided doses	Constipation (5.3%) Nausea (3.2%) Abdominal cramps (3%) Dizziness (1.4%) Overdose leading to central nervous system depression and arrhythmias (<1%)
Prescription agents			
Dicyclomine	Antispasmodics	10-20 mg Up to every 6 h as needed	Dry mouth/throat (>5%) Blurred vision (>5%)
Hyoscyamine		0.125-0.25 mg Up to every 6 h as needed	
Diphenoxylate-atropine	Peripherally acting μ-opioid receptor agonists	1-2 Tablets every 6 h, not to exceed 20 mg of diphenoxylate daily	Fatigue (45.5%)[38] Dizziness (36.4%) Nausea (27.3%) Abdominal pain (27.3%) Overdose and dependence can occur, particularly with tincture of opium
Tincture of opium		6 mg Every 4-6 h	
Ondansetron	5-Hydroxytryptamine 3 receptor agonists	4-8 mg Every 6-8 h, not to exceed 24 mg daily	Headache (≥5%) Constipation (≥2%) QT prolongation (<2%) Arrhythmias (<1%)
Granisetron		2-3 mg Daily in single or divided doses	
Amitriptyline	Tricyclic antidepressants[b]	10-100 mg Once daily	Dry mouth (54%) Drowsiness (53%) Difficulty urinating (22%) Blurry vision (17%)
Nortriptyline		10-100 mg Once daily	

[a] If available.

[b] The mechanism of action of tricyclic antidepressants in controlling chronic diarrhea is likely through their anticholinergic effects.

stool consistency measured daily using a 1 (hard) to 5 (watery) scale (target 1: n = 212 [67.5%] improved stool consistency for placebo vs n = 244 [79.0%] for rifaximin; target 2: n = 206 [64.4%] improved stool consistency for placebo vs n = 233 [74.0%] for rifaximin).[39] In 2 phase 3 RCTs, 1282 patients with IBS-D (study 3001) and 1146 patients (study 3002) were randomized to receive eluxadoline (75 or 100 mg) or placebo twice daily. The primary end point was attaining 50% or more days with a reduction of 30% or more in abdominal pain, with a stool consistency score of less than 5 on the same day abdominal pain improved. Between weeks 1 and 12, compared with placebo, eluxadoline significantly improved the primary end point responders (3001: 23.9% with 75 mg [P = .01] and 25.1% with 100 mg [P = .004] vs 17.1% with placebo; 3002: 28.9% with 75 mg [P < .001] and 29.6% with 100 mg [P < .001] vs 16.2% with placebo).[40] Because of an increased risk of acute pancreatitis and sphincter of Oddi spasm (right upper quadrant pain with elevated liver enzymes), eluxadoline, a μ and κ agonist and δ antagonist, should only be considered in patients with IBS-D and has not been studied in patients with functional diarrhea. Eluxadoline is contraindicated in patients without a gallbladder, those consuming 3 or more alcoholic beverages per day, and those with a history of pancreatitis or sphincter of Oddi spasm. In a meta-analysis of 7 trials (N = 796 patients with IBS), amitriptyline at doses of 10 to 75 mg per day improved overall IBS symptoms (n = 221 [64.4%] for amitriptyline vs n = 124 [36.3%] for placebo) and stool frequency and/or consistency (n = 78 [86.7%] for amitriptyline vs n = 40 [40.4%] for placebo).[42]

Inflammatory Causes of Chronic Diarrhea

Microscopic Colitis

Definition, Prevalence, and Risk Factors | Microscopic colitis is characterized by chronic watery diarrhea due to microscopic inflammation on colon biopsies despite normal-appearing mucosa on colonoscopy. Microscopic colitis accounts for 12.8% of chronic diarrhea cases and has a pooled US incidence of 11.4 (95% CI, 9.2-13.6) cases per 100 000 person-years.[43] Women are 3 times more likely than men to be affected, more than 80% of patients are older than 50 years, and more than 90% are White.[44] Approximately 30% to 50% of patients have coexisting autoimmune disorders, such as celiac disease or autoimmune thyroiditis.[17] In up to 10% of patients, microscopic colitis is associated with medication exposure, including selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors.[45]

Symptoms and Diagnosis | Patients with microscopic colitis typically present with chronic, nonbloody diarrhea, often with nocturnal symptoms; weight loss occurs in approximately 30% of patients.[46] Diagnosis requires colonoscopy with random biopsies (**Table 3**).[43,47-55] Subtypes of microscopic colitis include lymphocytic colitis (>20 intraepithelial lymphocytes per 100 epithelial cells) and collagenous colitis (subepithelial collagen band >10 μm).[56]

Treatment | Medications associated with microscopic colitis (eg, nonsteroidal anti-inflammatory drugs, proton pump inhibitors) should

Table 3. Causes of Chronic Diarrhea and Initial Diagnostic Tests

Test	Description	Diagnosis	Sensitivity	Specificity	Additional notes
Celiac disease					
IgA-tTG antibody	Antibodies directed against the target autoantigen (transglutaminase 2 enzyme that deamidates gliadin peptide) in celiac disease; normal result range depends on the reference ELISA test set by the manufacturer	Higher titer increases likelihood of true positive result[47]; titers >10 times upper limit of normal have a specificity of 100% for celiac disease	93% (95% CI, 90.3%-94.8%)[48]	97.9% (95% CI, 96.4%-98.8%)	Recommended first-line test given high sensitivity and specificity Measurement with total IgA level is recommended because IgA deficiency is more common in patients with celiac disease Patients should be eating a gluten-containing diet for ≥2-4 wk at the time of testing[49] In adults, diagnosis of celiac disease should be confirmed with duodenal biopsies
IgG DGP antibody	In the case of IgA deficiency, IgG antibodies directed against DGPs may be useful	Dependent on reference laboratory	80.1%-98.6%[50]	≥95%	IgG DGP should be ordered in patients with a negative IgA-tTG and IgA deficiency; IgG-tTG can be substituted if IgG DGP is unavailable Patients should be eating a gluten-containing diet In adults, diagnosis of celiac disease should be confirmed with duodenal biopsies
Microscopic colitis					
Colonoscopy with colon biopsies	Normal range for intraepithelial lymphocytes: <5 per 100 surface epithelial cells Normal range for collagen band: <5 µm	Lymphocytic colitis: ≥20 intraepithelial lymphocytes per 100 surface epithelial cells[51] Collagenous colitis: thickened collagen band (>10 µm) below the epithelium[51]	NA (histopathologic criteria are the standard)	NA (histopathologic criteria are the standard)	Diagnosis is based on histopathology
SIBO					
Glucose hydrogen breath test	Measures breath hydrogen (only produced by bacterial fermentation of carbohydrates) and methane (only produced by gut microorganisms that produce methane) after ingestion of 75 g of glucose[52]	≥20 ppm From baseline in hydrogen by 90 min suggests SIBO ≥10 ppm For methane at any time during the test suggests overgrowth of methane-producing microorganisms (intestinal methanogenic overgrowth)[53]	54.5%[54]	83.2%	Because glucose is readily absorbed by the small intestine and typically does not reach the colon, the glucose breath test is likely to be more accurate than the lactulose breath test; the large glucose dose makes this test inappropriate for patients with diabetes
Lactulose hydrogen breath test	Measures breath hydrogen (only produced by bacterial fermentation of carbohydrates) and methane (only produced by gut microorganisms that produce methane) after ingestion of 10 g of lactulose[52]	≥20 ppm From baseline in hydrogen by 90 min suggests SIBO ≥10 ppm For methane for any measure during the test suggests overgrowth of methane-producing microorganisms (intestinal methanogenic overgrowth)	42%[54]	70.6%	Lactulose is a synthetic disaccharide, which is not absorbed by the small intestine and thus reaches the colon, where it can be fermented by the microbiota; this can lead to false-positive test results for SIBO
EPI					
Fecal elastase	Measures elastase-1, which is secreted by the pancreas and correlates with pancreatic enzyme output	Fecal elastase levels <200 µg/g stool considered abnormal Fecal elastase levels <100 µg/g stool more specific for EPI	77% Compared with secretin stimulation test[55] 96% Compared with quantitative fecal fat	88% Compared with secretin stimulation test 88% Compared with quantitative fecal fat	Stable in feces for up to 1 wk at room temperature or up to 1 mo at 4 °C Should be performed on solid stool because false-positive results occur when testing is performed on liquid stool Not affected by diet, fasting, or pancreatic enzyme replacement therapy

Abbreviations: DGP, deamidated gliadin peptide; ELISA, enzyme-linked immunosorbent assay; EPI, exocrine pancreatic insufficiency; Ig, immunoglobulin; NA, not applicable; SIBO, small intestinal bacterial overgrowth; tTG, tissue transglutaminase.

be discontinued. Opioid agonists, such as loperamide or diphenoxylate-atropine, bismuth subsalicylate, or bile acid sequestrants (cholestyramine, colesevelam, colestipol), can be prescribed for diarrhea. Patients who do not improve with these treatments or who present with severe diarrhea should be prescribed the oral synthetic steroid budesonide (9 mg daily for 8 weeks) to induce clinical remission (<3 stools per day and <1 watery stool per day) (**Table 4**).[57-66] A meta-analysis of 3 RCTs (N = 94 patients with

Table 4. Available Therapies for Specific Causes of Chronic Diarrhea

Drug/treatment	Mechanism	Typical target daily dosing range	Efficacy of treatment	Adverse effects (with frequency[a])
Celiac disease				
Gluten-free diet	Foods must contain <20 ppm of gluten to be considered gluten-free[57]	NA	Symptoms improve within days or weeks of starting a gluten-free diet; at 6 mo, 22% of patients have persistent symptoms[58] Mucosal healing may take years; in 241 adults, mucosal healing occurred in 34% (95% CI, 27%-40%) within 2 y and 66% (95% CI, 58%-74%) within 5 y[59]	Constipation Weight gain
Bile acid diarrhea				
Bile acid sequestrants (off-label use)	Intraluminal bile acid binders	Starting doses: Cholestyramine: 1 g twice daily Colesevelam: 1250 mg twice daily Colestipol: 1 g twice daily Dose titration based on clinical response[60]	In a systematic review of 7 RCTs including 311 patients with bile acid malabsorption, 65.2% of patients randomized to receive bile acid sequestrants had resolution of diarrhea compared with 18.6% with placebo[61]	Constipation (11%) Dyspepsia (8.3%) Nausea (4.2%) Pharyngitis/rhinitis (3.2%) Myalgia (2.1%)
Microscopic colitis				
Budesonide (not FDA approved for this condition)	Anti-inflammatory treatment	9 mg Daily for 6-8 wk	In collagenous colitis, clinical response occurred in 81% (38/47) of patients taking budesonide vs 17% (8/47) taking placebo (RR, 4.56 [95% CI, 2.43-8.55])[62] In microscopic colitis, clinical response occurred in 88% (50/57) of patients taking budesonide vs 38% (22/57) taking placebo (RR, 2.03 [95% CI, 1.25-3.33])	Gastrointestinal (nausea, dyspepsia, bloating, flatulence) (12%) Arthralgia, myalgia, abdominal pain, leg cramps (6%) Weight gain (6%) Dizziness (4.5%)
Exocrine pancreatic insufficiency				
PERT (FDA approved for this use)	Porcine derived, including lipase, amylase, and a mixture of proteases	Initial dose: 40 000-50 000 *USP* units of lipase with meals and half-dose with snacks[63] Dose titration based on clinical response Nonenteric-coated enzyme preparations should be given with a proton pump inhibitor	Change in mean coefficient of fat absorption improved in patients receiving PERT compared with placebo (36.7% vs 12.1%)[64]	Nausea/vomiting (6%) Dizziness (4%) Cough (4%)
SIBO				
Rifaximin (off-label use)	Poorly absorbed antibiotic with gram-positive and -negative coverage	Standard dose and duration is 550 mg 3 times daily for 14 d but various regimens have been used, ranging from 600-1000 mg/d for 5-28 d	High-quality data for treatment of SIBO do not exist In 10 studies including 205 patients, improvement or resolution of symptoms in patients with eradication of SIBO occurred in 67.7% (95% CI, 44.7%-86.9%)[65]	Nausea (3%) Elevated liver enzymes (2%) 1 Case of *Clostridioides difficile* infection

Abbreviations: FDA, US Food and Drug Administration; NA, not applicable; PERT, pancreatic enzyme replacement therapy; RCT, randomized clinical trial; RR, relative risk; SIBO, small intestinal bacterial overgrowth; *USP*, *United States Pharmacopeia*.

[a] If available.

collagenous colitis) reported that, compared with placebo, budesonide was associated with significantly higher response rates (<3 bowel movements per day and/or a 50% improvement in stool frequency) at 81% vs 17%, respectively.[62] Similarly, a meta-analysis of 2 RCTs (N = 57 patients with lymphocytic colitis) reported that, compared with placebo, budesonide was associated with a higher clinical response (<3 bowel movements per day or >50% decrease in stool frequency) at 88% vs 38%, respectively.[62,67] Relapse occurs in up to 70% of patients after discontinuation of budesonide; many patients require low-dose maintenance therapy (eg, 3 mg daily or every other day). Combining budesonide with antidiarrheals, such as loperamide and diphenoxylate-atropine, may reduce the budesonide dose required to maintain remission.

Malabsorptive Diarrhea

Celiac Disease

Definition, Prevalence, and Risk Factors | Celiac disease is a chronic, immune-mediated enteropathy caused by dietary gluten ingestion in genetically predisposed individuals. Global prevalence in the general population is 0.7% based on duodenal biopsies and 1.4% based on serology,[19] with a prevalence of 12% among patients

with chronic diarrhea.[33] Risk is increased in patients with autoimmune disease (eg, type 1 diabetes, autoimmune thyroiditis, autoimmune liver disease, Sjogren disease) and those with a first-degree relative with celiac disease, with prevalences of 6% and 7.5%, respectively.[20,68] The aforementioned autoimmune diseases and celiac disease are strongly associated with the human leukocyte antigens DQ2 and DQ8. Although necessary, these haplotypes are insufficient for disease development. Approximately 40% of the US population has 1 or both of these haplotypes, but only 1% to 3% of people with the haplotype develop serological evidence of celiac disease.[69]

Symptoms and Diagnosis | Approximately 40% to 50% of patients with celiac disease present with diarrhea, often accompanied by weight loss, steatorrhea, and nutritional deficiencies, including iron and/or vitamin B_{12} deficiency. Up to 60% of patients have osteoporosis, unexplained anemia, or mild increases in liver enzymes. First-line testing includes serum IgA-tTG (enzymes that deamidate gliadin peptide) antibodies (sensitivity 93%, specificity 98%) (Table 3).[70] A quantitative IgA level should be measured to rule out IgA deficiency, which occurs in 2% to 3% of patients with celiac disease.[71] For patients with IgA deficiency, American College of Gastroenterology guidelines recommend an IgG-based antibody test (deamidated gliadin peptide or tTG), although high-quality data supporting this recommendation are lacking. In adults, diagnosis requires confirmatory upper endoscopy with duodenal biopsies while consuming a gluten-containing diet. Characteristic small bowel histology (>25 intraepithelial lymphocytes per high-power field, along with crypt hyperplasia and villous atrophy) with positive serology confirms the diagnosis of celiac disease.

Treatment | The only effective treatment for individuals with celiac disease is a lifelong gluten-free diet (Table 4). Although novel therapies that digest gluten or modify the immune response to gluten are in development, none are currently available.[72]

Disaccharidase Deficiency

Definition, Prevalence, and Risk Factors | Prior to absorption, disaccharides must be digested into monosaccharides by enzymes, including lactase, sucrase, maltase, and palatinase, located in the small intestinal brush border epithelium. Congenital forms of disaccharidase deficiencies are rare. The prevalence of congenital lactase deficiency is 0.002% and the prevalence of sucrase-isomaltase deficiency is 0.02%.[73] Acquired disaccharidase deficiencies may occur following mucosal injury (eg, acute gastroenteritis, celiac disease, Crohn disease) and can be transient or persistent.[74] In a multicenter US study of 199 adults diagnosed with IBS-D or functional diarrhea, lactase and sucrase deficiencies measured by disaccharidase assay performed on duodenal biopsies were identified in 72 (36.2%) and 17 (8.5%) patients, respectively.[31]

Symptoms and Diagnosis | Disaccharidase deficiencies typically present with chronic diarrhea (64%), abdominal pain (45%), and bloating (36%).[75,76] Diagnosis can be established using quantitative assessment of enzyme activities performed on duodenal biopsies. Breath tests indirectly assess for enzyme activity[53] and are less invasive and more accessible than the enzyme activity assay. The lactose breath test is commonly used to diagnose lactase deficiency and is recommended by the British Society of Gastroenterology. In this test, patients ingest 25 g of lactose. In patients with lactase deficiency, undigested lactose is fermented by colonic microbiota, producing hydrogen and/or methane, which is measured in exhaled breath. A meta-analysis of 17 studies (N = 1708 participants) reported sensitivity of 0.88 (95% CI, 0.85-0.90) and specificity of 0.85 (95% CI, 0.82-0.87) for lactase deficiency.[77]

Treatment | Treatment includes dietary restriction of the affected disaccharide—lactose (milk, cheese, ice cream) and/or sucrose (table sugar, fruits [mango, tangerine, pineapple, ripe banana]). An RCT of 47 patients with lactase deficiency reported that, compared with placebo, oral lactase replacement therapy[78,79] was associated with significant reductions in symptom severity scores measured with a visual analog scale 3 hours after lactose ingestion. RCTs of other disaccharidase replacement therapies are unavailable.

EPI

Definition, Prevalence, and Risk Factors | EPI is defined by inadequate release of pancreatic enzymes into the small intestine after a meal, resulting in maldigestion of fats, proteins, and carbohydrates. Chronic pancreatitis is the most common cause, with EPI developing in up to 60% to 90% of patients within 10 to 12 years of initial diagnosis of chronic pancreatitis.[23] Alcohol and tobacco use disorders are associated with an increased risk of EPI. Among 241 patients with chronic pancreatitis, EPI was diagnosed in 29% of people who smoked cigarettes compared with 16% for people who did not smoke cigarettes.[80,81] EPI also occurs in 80% to 90% of patients with cystic fibrosis[24] and 70% to 90% of those with pancreatic carcinoma.[18]

Symptoms and Diagnosis | Clinical features of EPI include steatorrhea, diarrhea, weight loss, bloating, and/or flatulence. Previously, the diagnosis of EPI required fecal fat excretion of more than 7 g in 24 hours on 72-hour stool collection, but this test requires a high-fat diet (100 g fat per day for 5 days). Currently, the American Gastroenterological Association (AGA) recommends fecal elastase as the preferred initial diagnostic test (threshold value for diagnosis of <100 µg/g stool) for EPI.[63] A meta-analysis of 6 observational studies (n = 428 individuals with and n = 673 without EPI) reported that fecal elastase had a sensitivity of 0.96 (95% CI, 0.79-0.99) and specificity of 0.88 (95% CI, 0.59-0.97) (Table 3).[55] Fecal elastase should be performed on solid stool because false-positive results occur in 11% of patients when stools are watery.[82]

Treatment | In addition to avoiding fatty foods and discontinuing alcohol and tobacco use, management of EPI includes pancreatic enzyme replacement therapy (PERT), which contains a combination of lipase, amylase, and protease to aid in the digestion of lipids, carbohydrates, and proteins, respectively. Orally ingested carbohydrates are partially digested with salivary amylase and ingested proteins are digested by gastric pepsin while lipid digestion is solely dependent on pancreatic lipase. For this reason, PERT prioritizes lipase replacement and correction of steatorrhea. Additional treatment goals include improving symptoms of steatorrhea and weight

loss and ensuring adequate fat-soluble vitamin availability. In an RCT of 62 patients with EPI, PERT significantly improved the primary outcome of fat absorption (100 × [(mean fat intake − mean stool fat)/mean fat intake]; pancreatic enzyme, 18.5% of fat absorbed vs placebo, 4.1% of fat absorbed [$P < .001$]).[83] In another RCT of 25 patients with EPI, PERT significantly improved the coefficient of fat absorption ([total fat eaten − total fat excreted]/total fat eaten × 100%) compared with placebo (mean [SD], 31.9% [18.6%] vs 8.7% [12.4%]; $P < .001$).[84] An initial starting dose of 40 000 to 50 000 lipase units with each meal and 20 000 to 25 000 lipase units with snacks is recommended by the AGA[63] (Table 4).

SIBO

Prevalence and Risk Factors | SIBO is characterized by excessive bacteria in the small intestine, which can cause symptoms including chronic diarrhea, abdominal pain, bloating, and flatulence. Several physiologic mechanisms prevent SIBO, including gastric acid, which destroys ingested bacteria, and pancreatic and biliary secretions, which exert antimicrobial effects and facilitate digestion and nutrient absorption, limiting nutrient availability to microbes as an energy source. The migrating motor complex, a physiologic process consisting of cyclical contractions in the stomach and small intestine during fasting that clear residual food debris and microbes as well as GI immune responses (eg, secretory IgA) also help prevent SIBO. Normal, unobstructed small intestine anatomy prevents luminal content stasis and an intact ileocecal valve prevents feces reflux from the colon into the ileum. Conditions in which these defensive mechanisms are impaired (eg, gastrectomy, EPI, systemic sclerosis, or ileocecectomy) increase the risk of SIBO. Up to 35% of patients diagnosed with IBS-D test positive for SIBO.[25]

Symptoms and Diagnosis | Symptoms of SIBO include abdominal bloating, pain or discomfort, and diarrhea. SIBO is diagnosed from a duodenal aspirate obtained during upper endoscopy and is defined by growth of more than 10^3 colony-forming units of bacteria per mL.[53] However, because of difficulty quantifying cultured bacteria due to contamination by oral flora, upper endoscopy requirement with sampling limited to the proximal small intestine, need for a microbiology laboratory, and the test cost, SIBO is more typically diagnosed using glucose or lactulose breath testing (Table 3). For breath testing, patients ingest glucose (75 g) or lactulose (10 g) and breath hydrogen levels are measured every 15 minutes for 2 to 3 hours. Patients with SIBO demonstrate an increase in breath hydrogen excretion (≥20 ppm over baseline) within 90 minutes of ingesting test sugar. The increased breath hydrogen results from fermentation of the ingested sugar by the excessive bacteria in the small intestine.

In a meta-analysis of 14 cross-sectional studies (N = 668 participants), glucose breath testing had a sensitivity of 54% (95% CI, 48.20%-60.70%) and specificity of 83% (95% CI, 79.10%-86.90%) for diagnosing SIBO. Meanwhile, a meta-analysis of 4 studies (N = 214 participants) demonstrated lactulose breath testing had a sensitivity of 42% (95% CI, 31.6%-53.0%) and specificity of 71% (95% CI, 61.9%-78.4%) for SIBO.[54]

Treatment | Successful treatment of SIBO is defined by symptom improvement rather than normalization of breath testing results. No RCTs have evaluated the treatment of SIBO in patients with chronic diarrhea. American College of Gastroenterology guidelines recommend rifaximin 550 mg 3 times daily for 14 days as first-line therapy for SIBO.[85]

Secretory Diarrhea

BAD

Prevalence and Risk Factors | BAD affects approximately 1% of the general population[86] and results from excess bile acids reaching the colon, due to increased bile acid synthesis (primary BAD), impaired ileal reabsorption (Crohn disease or terminal ileal resection), or decreased bile acid storage (post cholecystectomy). Excess bile acids stimulate colonic epithelial cells to secrete chloride and water and accelerate colonic transit.

Symptoms and Diagnosis | Symptoms of BAD include chronic diarrhea, occurring at night in 20% and associated with fecal urgency in up to one-third of patients. The selenium-75-homocholic acid taurine (75SeHCAT) test measures retention of radiolabeled bile acids within the GI tract 7 days after oral ingestion. Low retention indicates colonic bile acid loss consistent with BAD. A systematic review of 8 studies (N = 777 adults with chronic diarrhea) found that 75SeHCAT testing (<10% retention of radiolabeled bile acids) had a sensitivity of 87% and specificity of 93% for diagnosing BAD.[87] 75SeHCAT is the preferred initial diagnostic test for diagnosing BAD where available (eTable in the Supplement). Alternatively, diagnosis can be made by measuring excretion of total and primary bile acids (bile acids before they undergo bacterial deconjugation) in 48-hour stool collection.[88] Because of the limited availability of these tests, an empiric trial of bile acid sequestrants, such as cholestyramine, colesevelam, or colestipol, is suggested by the AGA, with clinical response (defined as a decrease in stool frequency and/or improvement in stool consistency) used as a proxy for diagnosing the condition.[89]

Treatment | Bile acid sequestrants, such as cholestyramine, colesevelam, or colestipol, are highly effective treatments for BAD (Table 4). In an RCT of 41 patients with BAD, colesevelam reduced diarrhea in 64% (14 of 22), compared with 16% (3 of 19) of patients in the placebo group (adjusted odds ratio, 9.1 [95% CI, 1.9-62.8]; $P = .01$).[90] In a meta-analysis of 7 RCTs (N = 311 patients with BAD), compared with placebo, bile acid sequestrants were associated with resolution of diarrheal symptoms (65.2% vs 18.6%).[61] An RCT of 52 patients with BAD reported that, compared with colesevelam 1875 mg twice daily, the glucagon-like peptide-1 analog liraglutide, a once-daily subcutaneous injection uptitrated from 0 × 6 mg to 1 × 8 mg per day over 3 weeks, significantly increased the rate of the primary end point (≥25% reduction in stool frequency) over 6 weeks (77% vs 50%; absolute difference, −27% [95% CI, −100% to −6%]).[91] However, the dropout rate in this clinical trial was 36.5%, with higher dropout in the colesevelam group.

Limitations

This Review has limitations. First, the quality of included studies was not evaluated. Second, the literature search may have missed some relevant articles. Third, some aspects of chronic diarrhea were not discussed or were not discussed in detail.

Conclusions

The most common causes of chronic, noninfectious diarrhea include IBS-D and functional diarrhea. Empiric therapies for chronic diarrhea include lifestyle modifications (regularly scheduled meals and physical activity, intake of ≥8 cups of noncaffeinated fluids daily, limiting caffeine to ≤3 cups per day, and avoiding alcohol and carbonated beverages); dietary interventions, such as a diet low in FODMAPs; and medications, including opiate agonists (loperamide and diphenoxylate-atropine), anticholinergics (dicyclomine and hyoscyamine), and 5-HT_3 antagonists (ondansetron).

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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