

PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Chronic Diarrhea: Diagnosis and Management



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Chronic diarrhea is a common problem affecting up to 5% of the population at a given time. Patients vary in their definition of diarrhea, citing loose stool consistency, increased frequency, urgency of bowel movements, or incontinence as key symptoms. Physicians have used increased frequency of defecation or increased stool weight as major criteria and distinguish acute diarrhea, often due to self-limited, acute infections, from chronic diarrhea, which has a broader differential diagnosis, by duration of symptoms; 4 weeks is a frequently used cutoff. Symptom clusters and settings can be used to assess the likelihood of particular causes of diarrhea. Irritable bowel syndrome can be distinguished from some other causes of chronic diarrhea by the presence of pain that peaks before defecation, is relieved by defecation, and is associated with changes in stool form or frequency (Rome criteria). Patients with chronic diarrhea usually need some evaluation, but history and physical examination may be sufficient to direct therapy in some. For example, diet, medications, and surgery or radiation therapy can be important causes of chronic diarrhea that can be suspected on the basis of history alone. Testing is indicated when alarm features are present, when there is no obvious cause evident, or the differential diagnosis needs further delineation. Testing of blood and stool, endoscopy, imaging studies, histology, and physiological testing all have roles to play but are not all needed in every patient. Categorizing patients after limited testing may allow more directed testing and more rapid diagnosis. Empiric antidiarrheal therapy can be used to mitigate symptoms in most patients for whom a specific treatment is not available.

Keywords: Diarrhea; Definitions; Classification; Diet; Diagnostic Testing; Therapy.

This clinical perspective addresses the definition, pathogenesis, diagnosis, and treatment of chronic diarrhea, which is based on a systematic review produced for the World Congress of Gastroenterology in 2013¹ and updated by the authors in 2016. Fifteen clinical questions are posed, followed by 24 recommendations pertinent to those questions with supporting evidence. In many instances there is not high-quality evidence to support the recommendations, and that is noted.

A search of PubMed for the years from 1975 to 2015 was conducted by using the following major search terms and

subheadings including “diarrhea,” “stool analysis,” “irritable bowel syndrome,” “chronic diarrhea AND diagnosis,” “chronic diarrhea AND therapy,” and “breath tests.” Systematic reviews and meta-analyses were given priority for each topic when available, followed by clinical trial evidence.

The GRADE system was used to evaluate the strength of the recommendations and the overall quality of evidence.² A recommendation was graded as “strong” when the desirable effects of an intervention clearly outweigh the undesirable effects and as “conditional” when there is uncertainty about the tradeoffs. The quality of evidence ranged from “high” (implying that further research is unlikely to change the authors’ confidence in the conclusion or in the estimate of the effect) to “moderate” (further research is unlikely to have an effect on the conclusion but might have an impact on the estimate of effect) or “low” (further research would be expected to have an important impact on the estimate of the effect or might change the conclusion altogether). For each recommendation, strength is abbreviated as “1” (strong) or “2” (conditional) and quality of evidence as “a” (high), “b” (moderate), or “c” (low).

How Is Chronic Diarrhea Defined?

Recommendations

1. Patients define diarrhea as loose stools, increased stool frequency, or urgency; physicians should note precisely what the patient means. (1b)
2. Chronic diarrhea is defined by a duration of >4 weeks. (2b)

Diarrhea can refer to urgency or high stool frequency, although most patients use the term to describe changes in

Abbreviations used in this paper: BAM, bile acid malabsorption; CD, celiac disease; CT, computed tomography; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; MR, magnetic resonance; SBS, short bowel syndrome; SIBO, small intestinal bacterial overgrowth.

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consistency (loose or watery stools).³ In fact, frequent defecation with normal consistency is termed *pseudodiarrhea*; therefore, abnormal stool form and not frequency should be used to define diarrhea.

Most diarrheal episodes in developed countries are acute and self-limited and are usually due to infections. In immunocompetent patients, acute infectious diarrhea typically resolves within 4 weeks (most commonly within 1 week). Therefore, chronic diarrhea is defined as that lasting longer than 4 weeks. It is estimated that 1%–5% of adults suffer from chronic diarrhea.⁴ In immunocompetent patients in developed countries, chronic diarrhea is generally not infectious. The challenge in managing these patients is the fact that the differential diagnosis is vast. However, a careful history and thorough physical examination with judicious use of selected tests often lead to a specific diagnosis and an appropriate treatment plan.

How Can Symptom Clusters and Settings Focus the Differential Diagnosis?

Recommendation

3. Consider comorbid symptoms and epidemiologic clues when constructing a differential diagnosis. (2c)

The main distinction in patients with chronic diarrhea is between functional and organic etiologies. The functional category includes irritable bowel syndrome (IBS), when abdominal pain accompanies the diarrhea, and functional diarrhea, when abdominal pain is absent.³ IBS can be prospectively characterized by symptoms such as those defined by the Rome IV criteria (recurrent abdominal pain at least 3 days per month in the last 3 months, associated with a change in stool frequency or form, and improvement with defecation).³ Functional diarrhea is defined as similar stool changes without prominent pain.³ However, many patients with organic causes of chronic diarrhea such as microscopic colitis often fulfill these criteria.⁵ Therefore, these criteria are not sufficiently specific to rule out organic etiologies. However, for patients with relatively mild symptoms and no alarm features such as gastrointestinal (GI) bleeding, fevers, or significant weight loss, those meeting the Rome IV criteria for IBS or functional diarrhea can be managed with empiric therapy. If empiric therapy fails, then further diagnostic testing may be considered.

Other symptom clusters can also be helpful in suggesting a specific diagnosis. Significant abdominal pain, fever, or GI bleeding suggests an inflammatory cause for diarrhea. Gas and bloating suggest carbohydrate malabsorption. Substantial weight loss suggests malabsorption, maldigestion, or a malignancy (particularly in an older person). Fatigue and night sweats suggest lymphoma, whereas anemia or change in stool caliber suggests colorectal malignancy. The positive predictive values of these symptoms for the underlying problems

causing chronic diarrhea are unknown but likely are low. Physical findings can indicate the impact of diarrhea on nutrition and sometimes suggest a specific diagnosis (Supplementary Table 1).

The characteristics of the stool also help. Small, frequent bowel movements with tenesmus and bleeding suggest proctitis, whereas larger volume, less frequent stools suggest a small bowel source of diarrhea. Steatorrhea indicates either fat maldigestion or malabsorption.

Epidemiologic associations and patient characteristics also help limit the differential diagnosis⁶ (Supplementary Table 2). Immunosuppressed patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome are at increased risk for common and uncommon, opportunistic infections. Recent travelers and migrants from endemic areas with chronic diarrhea should be tested for protozoa, atypical infections, *Strongyloides*, and tropical sprue. In patients with a history of constipation, the possibility of overflow diarrhea due to obstipation should be considered, especially if diarrhea worsens despite antidiarrheal therapy. Patients with diabetes or those attempting to lose weight should be questioned about consumption of diet foods containing poorly absorbed sugar alcohols.

How Can Clinicians Distinguish Irritable Bowel Syndrome From Other Causes of Chronic Diarrhea?

Recommendations

4. The Rome criteria provide a framework for the diagnosis of IBS and emphasize pain. Other etiologies should be sought when these criteria are not met. (1a)
5. Patients without alarm features who meet criteria for IBS should be treated without further testing. Those who do not respond should be evaluated further. (2b)

Criteria have been proposed to distinguish IBS from organic diseases; however, the utility of these criteria is only partially understood at present.³ The Rome criteria emphasize chronic abdominal pain that is relieved by defecation, associated with a change in stool frequency or consistency.³ IBS with diarrhea is diagnosed in patients who meet these criteria and have loose stools more than 25% of the time and hard stools less than 25% of the time. The specificity of symptom-based criteria for the diagnosis of IBS versus other colonic pathology is only moderate (~75%),^{7–9} but the incorporation of alarm features can improve specificity to ~90%.⁹ However, the predictive value of symptoms in identifying organic disease is less than 10%.¹⁰ The performance of symptom-based criteria was highly variable and might not be able to reliably distinguish IBS from other diseases.⁸ Thus, symptoms may be more useful in identifying patients requiring additional evaluation than in identifying patients with organic illnesses.¹¹

Because functional diarrheal problems are so common, the pretest probability of organic disease is low, suggesting that an extensive diagnostic evaluation is not needed in most patients.^{8,12}

Diagnostic tests such as radiography, serology, and biochemistries are generally not helpful in patients who meet criteria for IBS.^{13,14} One area of uncertainty is testing for celiac disease (CD). One meta-analysis suggested that the prevalence of CD in patients meeting criteria for IBS was more than 4-fold that of controls without IBS,¹⁵ whereas a more recent study showed no increased prevalence of CD in patients presenting with IBS.¹⁶ Likewise, microscopic colitis may be present in 1.5%–10% of patients meeting criteria for IBS^{17,18} and even higher in older patients. The yield of tests for small intestinal bacterial overgrowth (SIBO) is quite variable.¹⁹

What Is the Role of Diet in the Pathogenesis of Chronic Diarrhea?

Recommendations

6. Specific dietary components may cause or aggravate chronic diarrhea. A careful dietary history is essential. (1a)
7. True food allergies are rare causes of chronic diarrhea in adults. (2b)

Specific foods and diets are often incriminated as causes of diarrhea, some with good evidence and others less so.²⁰ In considering associations with foods, one must consider (1) substances that in sufficient quantities cause diarrhea in a normal gut (eg, fructose), (2) foods that cause diarrhea because of an underlying condition (eg, dairy products in lactase deficiency), (3) gut alterations that limit digestion or absorption (eg, short bowel, pancreatic insufficiency), and (4) idiosyncratic food intolerances. The identification of a dietary cause of diarrhea may be facilitated by a food diary.

Poorly absorbed carbohydrates are commonly linked to diarrhea.²⁰ For example, fructose is absorbed by facilitated diffusion with limited capacity; when the amount ingested exceeds that capacity, malabsorption and diarrhea may occur. Disaccharides must be split by disaccharidases such as sucrase or lactase, which may be insufficient because of mucosal disease or genetic downregulation. Unabsorbed carbohydrates lead to osmotic retention of fluid in the intestine and bacteria fermentation to gases. Therefore, flatus and bloating are important clues suggesting carbohydrate malabsorption. For many clinicians, concurrent diarrhea and bloating are taken as evidence of IBS, missing the opportunity to diagnose diet-induced diarrhea.

Lactose is a common cause of diet-induced diarrhea.²¹ Worldwide, most adults are lactose-intolerant and learn to avoid dairy products. Inadvertent lactose ingestion can occur from commercial foods fortified with milk. Lactose intolerance also can develop if the mucosa is diseased or bypassed.

Fructose is found in certain fruits, and it is difficult to exceed absorptive capacity with natural foods. However, high fructose corn syrup is widely used as a sweetener in processed foods and soft drinks, leading to a striking increase in fructose intake,²² which makes it easier to exceed the absorptive capacity of the gut.

Sugar alcohol malabsorption also is increasingly recognized as a cause of diarrhea. Sorbitol, mannitol, and xylitol are poorly absorbed non-nutritive sweeteners in items such as “sugar-free” chewing gum and candy; excessive intake may cause diarrhea.²³

The recognition that these carbohydrates can cause diarrhea and other symptoms led to development of the Fermentable Oligosaccharides, Disaccharides Mono-saccharides and Polyols (FODMAP) diet.²⁴ In a randomized trial, a FODMAP diet alleviated intestinal symptoms in 75% of IBS patients.²⁵

It is important to carefully quantify the amount of caffeine consumed in coffee and energy drinks.²⁶

Gluten intolerance. The diagnosis of CD is based on symptoms, serology, and intestinal histology.²⁷ It has become clear that CD can present with a wider range of symptoms than previously appreciated. Recently, it has been recognized that “gluten responsive symptoms” can be present in the absence of positive serologies or with less severe pathologic criteria (Marsh 1/2).²⁸ Non-celiac gluten sensitivity requires additional research, but it seems likely that gluten-free diets may benefit a broader segment of the population than previously thought. Most patients with chronic diarrhea should be screened for CD. It is less clear when a gluten-free diet should be tried in patients with diarrhea who do not have CD.²⁹

Fatty and fried foods frequently are implicated in the pathogenesis of diarrhea and other symptoms.³⁰ Although fat malabsorption stimulates colonic secretion to cause diarrhea,³¹ it seems that fat may precipitate symptoms without demonstrable steatorrhea.

Food allergies are immune reactions that may cause diarrhea and other symptoms. Food intolerances are not immune-based and are more common.³² Epidemiologic studies suggest that 1%–2% of adults have bona fide food allergy.³³ The frequency in children is higher.³⁴ Certain foods more frequently trigger allergic reactions. Recent studies have linked banana, avocado, walnut, and kiwi to a latex–food allergy syndrome.³⁵ Although true food allergy is uncommon in adults, it should be considered when other allergic features are present such as hives. Some food-allergic patients have elevated tryptase and eosinophilic cationic protein; however, fecal calprotectin is not elevated.^{33,36}

What Medications Are Common Causes of Diarrhea?

Recommendation

8. Many drugs cause diarrhea. Careful review of current medications is essential. (1a)

More than 700 drugs have been implicated as causing diarrhea, accounting for approximately 7% of drug adverse effects.³⁷ The mechanism by which some drugs cause diarrhea is unknown.³⁸

Some patients produce factitious diarrhea by taking laxatives. Osmotic agents usually produce typical changes on fecal electrolyte analysis. Laxatives producing secretory diarrhea may be detected in stool water by toxicologic tests. The key to diagnosis is keeping the possibility of factitious diarrhea in mind when the diagnosis is not forthcoming by routine testing, especially when the patient experiences a secondary gain from the illness.³⁸

What Other Therapies Cause Chronic Diarrhea?

Recommendations

9. Radiation can cause chronic diarrhea, sometimes starting years after exposure. Clinicians should ask about a history of radiation therapy. (1a)
10. Patients with chronic diarrhea who have had abdominal surgery may require empiric therapy or diagnostic evaluation. (1a)

Radiation enteritis. Radiation enteritis occurs in up to 20% of patients treated with pelvic irradiation, typically 1.5–6 years after irradiation, although later presentations are possible.³⁹ Risk factors include low body mass index, prior abdominal surgery, certain comorbidities, radiation dose, fractionation, and technique, as well as the concomitant chemotherapy.³⁹ Radiation enteritis is caused by direct damage to enterocytes and ischemia that is due to blood vessel damage. Submucosal fibrosis and lymphatic damage are commonly seen. The damaged bowel loses absorptive capacity and is predisposed to SIBO, particularly if strictures develop. If the distal ileum is involved, bile acid malabsorption (BAM) can be present. SIBO and BAM are discussed in more detail below.

Postsurgical diarrhea. GI surgeries can lead to diarrhea that is due to intentional or inadvertent vagotomy, SIBO, BAM, and short bowel syndrome (SBS).

Vagotomy. Truncal vagotomy results in rapid gastric emptying of liquids and diarrhea.⁴⁰ The incidence of diarrhea is increased if vagotomy is accompanied by antrectomy and decreased after highly selective vagotomy without antrectomy.⁴⁰

Bacterial overgrowth. In health, the bacterial count in the proximal jejunum is $<10^4$ /mL, and SIBO is typically defined as a bacterial count $>10^5$ /mL.⁴¹ Abdominal surgery predisposes to SIBO through disruption of the protective effect of stomach acid (eg, after vagotomy), stasis (eg, with an anastomotic stricture or partial bowel obstruction from adhesions), a blind limb (such as with an end-to-side anastomosis), or removal of the ileocecal valve. Bacterial overgrowth causes diarrhea by bile acid deconjugation, interfering with enzymatic action,

and damage to the mucosa.⁴¹ Bacterial overgrowth can be difficult to diagnose, because available tests are invasive and expensive (aspiration and culture of jejunal fluid) or have inadequate sensitivity and specificity (various breath tests).⁴² Because of these concerns, some clinicians use response to a trial of antibiotics as a diagnostic test. However, the operating characteristics of this practice are unknown.

Bile acid malabsorption. The majority of intraluminal bile acids are reabsorbed in the distal ileum. If this area is damaged (eg, Crohn's disease, radiation enteritis) or resected, BAM can occur. Malabsorbed bile acids stimulate fluid secretion and motility in the colon, resulting in diarrhea. The diagnosis of BAM is difficult; it is usually made empirically and is supported by response to a bile acid binder.⁴³ In individuals with >100 cm ileal resection, bile acid binder therapy may paradoxically worsen diarrhea by exacerbating fat malabsorption caused by depletion of the bile acid pool.⁴³ BAM is implicated in post-cholecystectomy diarrhea, although the exact mechanisms are obscure.

Short bowel syndrome. SBS occurs after resection of a large proportion of the small intestine. SBS is not likely if >200 cm of small intestine remains,⁴⁴ although longer lengths will not protect against SBS if the remaining bowel is abnormal (eg, Crohn's disease or radiation enteritis). In SBS, the remaining absorptive surface is insufficient to preserve nutrient, fluid, and/or electrolyte homeostasis.⁴⁴ The risk of SBS also relates to which part of the small bowel is resected and whether it is in continuity with the colon.⁴⁴

When Is Diagnostic Testing Indicated?

Recommendation

11. Testing should be done in the presence of alarm features, when the differential diagnosis can be effectively distinguished on the basis of test results, or when the differential diagnosis remains broad and initial testing will limit the number of additional tests needed. (2c)
12. For disorders without definitive diagnostic tests, therapeutic trials may be reasonable. (2c)

After interviewing and examining patients, the clinician may have a good idea of the likely cause of diarrhea. For some of these diagnoses, tests can confirm the diagnosis. For example, a patient with diarrhea, weight loss, and a tender abdominal mass might undergo computed tomography (CT) scanning and colonoscopy to establish a diagnosis of Crohn's disease. Testing also may be required to evaluate alarm features such as bleeding or weight loss. For other diagnoses no confirmatory tests are available. For example, a patient who developed diarrhea after cholecystectomy and had no alarm features might be tried on empiric bile acid binder therapy without further testing.

For many patients with chronic diarrhea, the pre-test probability of any specific diagnosis may not be high enough to allow focused testing or empiric therapy. In such cases, the clinician could conduct preliminary testing to categorize the diarrhea as discussed below and limit the differential diagnosis and subsequent testing. This approach has not been tested formally for chronic diarrhea; it is of value in guiding the evaluation of acute infectious diarrhea.⁴⁵

Is There Benefit From Categorizing Chronic Diarrhea by Stool Characteristics and Tests?

Recommendations

13. When the differential diagnosis is broad, stool testing to characterize diarrhea can direct further evaluation more precisely. (2c)
14. Stool chemistry tests can be used to categorize diarrhea and should be considered when the diagnosis remains obscure after initial assessment. (2c)
15. Fecal lactoferrin or calprotectin can be used as surrogate measures for fecal leukocytes. (1b) Stool chymotrypsin and elastase may have some utility as screening tests for pancreatic insufficiency. (2b)

The differential diagnosis of chronic diarrhea is lengthy and can be grouped by the kind of diarrhea that is produced: fatty, inflammatory, or watery. Watery stools can be subdivided into secretory and osmotic diarrheas, with different etiologies for each. Inspection of the stools and simple tests including measurement of fecal electrolytes, fat, occult blood, and leukocytes can distinguish these stool types (Supplementary Table 3). Characterizing diarrhea type

in a given patient should allow a more focused differential diagnosis.

Stool electrolytes. Fecal electrolytes can distinguish osmotic and secretory diarrhea on the basis of calculation of the osmotic gap⁴⁶: add fecal sodium and potassium concentrations, double that number to account for unmeasured anions, and subtract that number from 290 mOsm/kg (the expected osmolality of intraluminal contents). Measured stool osmolality is affected by fermentation and should not be used for this determination. A fecal osmotic gap <50 mOsm/kg indicates a secretory diarrhea. If the gap is >75 mOsm/kg, some non-electrolyte contributes substantially to fecal osmolality, indicating an osmotic diarrhea.⁴⁶

A low fecal pH (<7.0) may be due to colonic fermentation of malabsorbed carbohydrates to short chain fatty acids.⁴⁶

Blood or pus in the stool raises the possibility of an inflammatory diarrhea, although their absence does not exclude an inflammatory process.

Steatorrhea indicates a problem with fat absorption because of mucosal disease or luminal factors such as bile acid deficiency, SIBO, or pancreatic insufficiency. Although measurement of quantitative stool fat output on a 48- to 72-hour timed collection is ideal, qualitative stool fat content may be accurately assessed with a Sudan stain on a spot specimen.⁴⁷

A recent study evaluated the utility of measuring stool chemistries in patients referred to a tertiary center for evaluation of chronic diarrhea.⁴⁸ In this study, such stool analysis identified 6 patterns of stool composition with important impact on further diagnostic testing (Table 1). However, many of these patients had previous evaluations, and it is likely that the distribution of etiologies might be different than in a population-based sample.

Table 1. Patterns of Stool Composition in Chronic Diarrhea⁴⁸

Category/findings	Implications
Stool weight <200 g/24 h	
<ul style="list-style-type: none"> • No objective evidence of diarrhea 	Change in stool frequency, intermittent diarrhea, fecal incontinence, treatment with antidiarrheal drugs during collection
<ul style="list-style-type: none"> • Hyperdefecation (increased frequency without excess volume) 	Possible IBS, proctitis, abnormal rectal reservoir function
<ul style="list-style-type: none"> • Abnormal consistency (unformed to runny stools) 	Possible IBS
<ul style="list-style-type: none"> • Elevated fecal osmotic gap 	Presumed mild carbohydrate malabsorption or excess Mg intake from supplements
<ul style="list-style-type: none"> • Steatorrhea 	Malabsorption or maldigestion
Secretory diarrhea without steatorrhea (stool weight >200 g/24 h)	Microscopic colitis or other cause of secretory diarrhea
Carbohydrate malabsorption without steatorrhea	Ingestion of poorly absorbed carbohydrates, malabsorption
<ul style="list-style-type: none"> • High fecal osmotic gap • pH not always <5.5 	
Steatorrhea with or without carbohydrate malabsorption	Small bowel mucosal disease, pancreatic insufficiency, SIBO, bile acid deficiency
Osmotic diarrhea	Ingestion of poorly absorbed ions (eg, magnesium, phosphate, sulfate) or osmotically active polymers (eg, polyethylene glycol)
Unclassified (stool weight >200 g/24 h)	Blood or pus suggests inflammatory causes of diarrhea

Fecal lactoferrin and calprotectin. Microscopy for fecal leukocytes is operator-dependent. Measurement of leukocyte enzymes (lactoferrin or calprotectin) has been proposed as a surrogate for fecal leukocytes as a signal of mucosal inflammation. Fecal calprotectin appears to be more sensitive for this purpose.⁴⁹

Fecal chymotrypsin and elastase. Fecal concentrations of the pancreatic enzymes, chymotrypsin or elastase, have been proposed as tubeless tests of pancreatic exocrine function.⁵⁰ Most of the studies validating these assays were done in children and suggested that sensitivity and specificity were low (~70%),⁵¹ indicating that these tests might be suitable for screening but not for diagnosing pancreatic insufficiency.

What Is the Utility of Blood Tests?

Recommendations

16. Routine blood tests may provide clues to etiology and fluid and electrolyte status. Other blood tests should be obtained only when demanded by the clinical presentation. (2c)
17. Because of the rarity of peptide-secreting tumors, measurement of circulating peptide levels should be reserved for very select patients. (1b)

Routine blood tests (complete blood count and metabolic profile) can be used to evaluate fluid and electrolyte balance and nutritional sufficiency. Additional testing for entities such as CD, hyperthyroidism, amyloidosis, immunodeficiency, and mastocytosis can be considered on the basis of specific elements of each case.

Hormone-secreting tumors are rare causes of secretory diarrhea.⁵² In patients with classic tumor syndromes, evidence of tumor, or severe chronic diarrhea that remain undiagnosed after a detailed evaluation, measurement of serum chromogranin, gastrin, vasoactive intestinal polypeptide, or calcitonin levels, and/or urinary 5-hydroxyindoleacetic acid can be considered. However, because of the rarity of these tumors and low pretest probability of these disorders, most positive tests end up being false-positive results.⁵²

What Is the Utility of Imaging Studies?

Recommendation

18. Imaging studies are useful in some patients with steatorrhea and secretory or inflammatory diarrhea. (1b)

Imaging studies can play an important role in the evaluation of chronic diarrhea by (1) defining anatomic abnormalities such as strictures, fistulae, and diverticula; (2) delineating the degree and extent of inflammation in inflammatory bowel disease (IBD); (3) diagnosing chronic pancreatitis; and (4) demonstrating hormone-secreting tumors. CT enterography

and increasingly magnetic resonance (MR) enterography provide detailed small bowel imaging in Crohn's disease.⁵³ In patients with steatorrhea, abdominal CT or MR scanning, preferably with thin cuts through the pancreas, is useful to assess for chronic pancreatitis or pancreatic malignancy. Plain radiograms of the abdomen with radiopaque markers can be used to evaluate colon transit and the possibility of overflow diarrhea/incontinence.

Hormone-secreting tumors can also be assessed by CT scan, preferably multiphase helical CT or multi-detector CT with thin reconstructions.⁵⁴ Imaging with MR may be superior to CT for metastatic disease and tumors in the pancreas, although sensitivity for small tumors such as gastrinomas remains low.⁵⁴ Somatostatin receptor scanning has good sensitivity for many hormone subtypes associated with diarrhea⁵⁵ and can be used to identify the primary tumor and metastases, monitor treatment response, and select patients for radioreceptor therapy.⁵⁶ Positron emission tomography scanning, especially in combination with CT scanning, has become an important imaging modality in the rare patient with hormone-secreting tumors causing diarrhea.⁵⁶

What Is the Role of Endoscopy, Enteroscopy, Colonoscopy, and Mucosal Biopsy?

Recommendations

19. Lower gastrointestinal endoscopy with mucosal biopsy is valuable in inflammatory and secretory diarrheas. Colonoscopy has a greater yield than sigmoidoscopy, but multiple biopsies must be obtained. Biopsy of normal-appearing terminal ileum is not recommended. (1a)
20. Upper endoscopy or enteroscopy with biopsies of the duodenum or jejunum should be done in patients with unexplained steatorrhea. The role of aspiration of enteric contents for quantitative bacterial culture is unclear. (2c)

Although endoscopy and colonoscopy are not needed in every case, these tests often are useful in the evaluation of chronic diarrhea.

Lower gastrointestinal endoscopy. Colonoscopy with biopsy is valuable for diagnosing microscopic colitis, IBD, neoplasia, and other inflammatory conditions. Several studies have examined the diagnostic yield of colonoscopy in the evaluation of chronic diarrhea, with specific diagnoses found in 15%–31% of patients^{57,58}; microscopic colitis and IBD were common.

Whether sigmoidoscopy rather than colonoscopy should suffice is unsettled. The decision revolves around whether there is a significant increase in diagnostic yield beyond 60 cm; the data are conflicting, with some studies

finding a minimal increase with colonoscopy,⁵⁷ and other studies report a 10% chance of finding a specific diagnosis with inspection of the more proximal colon and ileum.⁵⁹ Therefore, colonoscopy with biopsies from the right and left colon rather than sigmoidoscopy generally is recommended.

There are few data on how many biopsies are sufficient for diagnosis of microscopic colitis; ≥ 8 biopsies are reasonable. There may be differences in collagen thickness and the extent of intraepithelial lymphocytosis in the rectum compared with the remainder of the colon; therefore, it is reasonable to obtain biopsies from above the rectum.⁶⁰ Although it is worthwhile to biopsy normal-appearing colon, biopsies from a normal terminal ileum are not often useful.⁶¹

Upper gastrointestinal endoscopy. There is relatively little information regarding the role of upper endoscopy in chronic diarrhea. Esophagogastroduodenoscopy (EGD) and duodenal biopsy can confirm a diagnosis of CD. However, these studies usually involve preselected individuals with positive celiac serologies and therefore do not address the diagnostic value of EGD in unselected patients with chronic diarrhea. In a large study evaluating the diagnostic value of duodenal biopsies, there was a significant finding in 8.6% of patients with diarrhea,⁶² all related to the spectrum of CD. For patients with suspected or confirmed sprue, the yield of small bowel biopsies was even higher, with intraepithelial lymphocytosis in 8.9%, variable villous atrophy in 11.2%, and overt sprue in 12%.⁶²

Endoscopic signs such as scalloping and furrowing have been linked to CD but are neither sensitive nor specific.⁶² Endoscopic clues may suggest other diagnoses (eg, aphthous ulcers in Crohn's disease or white punctate lesions in lymphangiectasia). Nevertheless, even a normal-appearing small bowel should be biopsied in a patient with chronic diarrhea.

The effectiveness of EGD in diagnosing CD may depend on the biopsy protocol. Villous atrophy in CD may occur in the duodenal bulb alone, and so biopsies should be obtained from the bulb and the distal duodenum.⁶³ Despite guidelines recommending >4 biopsies for the diagnosis of CD, this occurred infrequently in 1 study.⁶⁴ It may be reasonable to take 1 biopsy per pass to preserve architectural integrity.

Communication with the pathologist can ensure that appropriate histologic techniques are used when considering rare diagnoses (eg, Congo red staining for amyloidosis, polymerase chain reaction for *Tropheryma whippeli* for Whipple's disease, or immunohistochemical staining for lymphoma). Upper GI endoscopy may provide additional diagnostic methodologies beyond visualization and biopsy, including duodenal aspiration for *Giardia* or quantitative culture. The role of capsule endoscopy and deep enteroscopy remains to be delineated.⁶⁵

What Is the Role of Physiological and Microbiological Testing?

Recommendations

21. Breath tests can assist with the diagnosis of carbohydrate malabsorption and SIBO. Sensitivity and specificity are variable; therefore, breath tests are not recommended without local validation. (2b)
22. Idiopathic BAM may be more frequent than previously appreciated. Until more specific tests for BAM become widely available, empiric therapy may be the only option available in many clinical settings. (2b)
23. Direct pancreatic function testing is not widely available. Indirect testing (eg, serum trypsin, fecal chymotrypsin, and fecal elastase assays) has limited sensitivity. Imaging and empiric trials of pancreatic enzyme replacement therapy may be the best available methods for assessing the role of pancreatic insufficiency in patients with steatorrhea. (2c)

Hydrogen breath tests. Hydrogen (H_2) production in mammals is due to bacterial metabolism of carbohydrates, allowing development of technologies to detect malabsorption of carbohydrates and SIBO.⁶⁶ If carbohydrate, eg, lactose or fructose, is malabsorbed, colonic bacteria metabolize the carbohydrate and produce H_2 . Similarly, in SIBO, the bacteria in the small intestine degrade nutrients before they can be absorbed, again producing H_2 . The H_2 diffuses across the gut wall into the bloodstream, is excreted by the lungs, and can be detected in the breath.

SIBO is generally associated with anatomic or functional abnormalities of the intestine such as strictures, achlorhydria, motility disorders, or scleroderma. Symptoms related to SIBO include diarrhea, bloating, and weight loss. The diagnostic gold standard, quantitative culture of intestinal aspirates, is uncommonly performed in practice. Instead, hydrogen breath tests that use glucose or lactulose are more commonly used. However, sensitivity and specificity of these tests vary widely, resulting in questionable reliability.⁶⁶

SIBO has increasingly been implicated as a factor in IBS with diarrhea on the basis of lactulose hydrogen breath tests.⁶⁷ However, other studies have not confirmed the frequent diagnosis of SIBO in IBS patients.⁶⁸ Increased sensitivity and specificity may be gained by simultaneous measurement of intestinal transit time, which permits an accurate determination of whether the hydrogen signal arises from the small bowel or colon.⁶⁹

Bile acid malabsorption. Our understanding of the pathophysiology, clinical presentation, and treatment of BAM is changing rapidly. Although classic BAM as a result of ileal resection or disease remains uncommon, there has been an increasing interest in idiopathic BAM that may be related to functional diarrhea or diarrhea-predominant

IBS in as many as 33%–60% of cases.^{70,71} Emerging evidence suggests that there may be a paradoxical increase in the bile acid pool related to changes in the intestinal peptide FGF19.^{70,71} There are several promising diagnostic studies that unfortunately are not widely available.⁷² Whole-body retention of selenium-75-homocholic acid taurine is used in Europe and Canada as a measure of BAM, but it is not available in the United States.⁷³ Quantitative stool bile acids and measurement of C4, an indicator of bile acid synthesis and pool size, may be performed in a limited number of academic centers.⁷¹ Patients with an abnormal selenium-75-homocholic acid taurine test (<10% retention) predictably respond to bile acid binding drugs, whereas those with normal retention do not.^{71,72,74} Better understanding of the pathophysiology of BAM may lead to innovative therapies in the near future.^{75,76} If specific testing is not available, clinicians often resort to empiric trials, which not unexpectedly have a much less predictable response.^{74,75,77}

Pancreatic function testing. Testing for pancreatic insufficiency is difficult.⁵⁰ The gold standard, the secretin stimulation test, is cumbersome and rarely performed. In a modified, endoscopic secretin stimulation test, the pancreatic duct is cannulated during endoscopic retrograde cholangiopancreatography for fluid collection, but diagnostic accuracy is a concern.⁷⁸

Other tests of pancreatic function, including serum trypsin, fecal chymotrypsin, and fecal elastase,⁵⁰ are attractive because of their relative simplicity. However, they have limited ability to detect mild pancreatic insufficiency.

Imaging to diagnose chronic pancreatitis is based on detecting the abnormal anatomy, such as with endoscopic ultrasound and MR imaging without and with secretin.⁵⁰

In practice, many clinicians opt for an empiric trial of pancreatic enzyme replacement when pancreatic insufficiency is considered a potential cause for diarrhea. Although there are some intricacies to evaluating the results of empiric enzyme replacement therapy, a symptomatic response and reduction in steatorrhea may be sufficient to establish a diagnosis in the appropriate clinical setting.

What Is the Approach When Initial Efforts Fail to Make a Diagnosis?

Recommendation

- 24. Failure to make a diagnosis is more likely due to overlooking a common cause than missing a rare cause of chronic diarrhea. Physicians should repeat the history and physical examination and review studies already done before ordering additional tests. Repeating tests only should be done with cause. (2c)

Physicians sometimes fail to make a diagnosis despite an evaluation and may refer such patients to centers

interested in this condition.⁵³ Common diagnoses resulting from reevaluation of these patients are shown in Table 2.

Although unusual or obscure conditions might be expected in these patients, most of the eventual diagnoses are straightforward. Fecal incontinence and iatrogenic diarrhea could be recognized with a careful history. Surreptitious laxative ingestion and microscopic colitis could be diagnosed with appropriate testing (eg, laxative screen and colonic biopsy, respectively). Pancreatic insufficiency, BAM, SIBO, and carbohydrate malabsorption could be discovered with a detailed history and specific testing or properly conducted therapeutic trials. Peptide-secreting tumors are rare, but serum peptide assays and imaging (eg, CT scanning and octreotide scanning) are widely available. Failure to make a diagnosis typically results from failure to appreciate all the available evidence and from not considering the entire differential diagnosis of chronic diarrhea.

What Empiric Treatments Can Be Used for Symptomatic Management?

Recommendation

- 25. Opiate antidiarrheals are a mainstay of symptomatic management when specific treatment is not possible. Dosing should be scheduled rather than as needed. (1b)

Ideally, a work-up for chronic diarrhea will lead to a specific diagnosis and treatment. However, that is not always the case. Empiric treatment is necessary when testing does not find a specific diagnosis, when a specific diagnosis has no specific treatment, or treatment has failed. There are several options for empiric therapy (Supplementary Table 4); however, opiates are generally the first choice. Other “constipating” medicines may help individuals with chronic diarrhea.⁷⁹

Opiates. Treatment with opiates is effective and safe. Loperamide is μ -receptor agonist primarily affecting

Table 2. Frequent Diagnoses in Patients With Diarrhea of Obscure Origin⁵²

Bile acid malabsorption
Carbohydrate malabsorption
Chronic idiopathic secretory diarrhea
Fecal incontinence
Functional diarrhea
Iatrogenic diarrhea (drugs, surgery, radiation)
IBS
Microscopic colitis
Autonomic neuropathy
Pancreatic exocrine insufficiency
Peptide-secreting tumors
SIBO
Surreptitious laxative ingestion

intestinal motility.⁸⁰ Like all opiates, it slows intestinal transit time and increases net absorption. With minimal penetration into the brain, it has little potential for abuse. In chronic diarrhea, scheduled dosing is recommended. For example, if diarrhea occurs after meals, dosing before meals is used. Morning-predominant diarrhea can be improved by bedtime or early morning dosing.

Diphenoxylate and difenoxin have similar potency as loperamide but cross the blood-brain barrier and may produce central nervous system effects, especially at high doses. The potential for abuse is limited by combining these drugs with atropine.

More potent opiates are the most effective antidiarrheal drugs but are not prescribed frequently because of concern about misuse. Codeine, opium, or morphine preparations (eg, paregoric, tincture of opium, and morphine) can be very useful for severe diarrhea, such as

that resulting from bowel resection. The potential for abuse can be minimized by informing the patient about the risk of abuse, by starting with a low dose and titrating the dose gradually upward, and by refilling prescriptions only when the anticipated volume should have been used.

Other drugs. Bile acid binding resins (cholestyramine, colestipol, colesevelam) are effective in BAM⁷⁴ but also have nonspecific constipating effects. They also may bind other medications, and the dosing schedule should ensure that they are taken more than 2 hours away from other medications. Neither antibiotics nor probiotics are useful as nonspecific therapy in chronic diarrhea.

Clonidine, an α_2 -adrenergic agonist drug that stimulates absorption and slows intestinal transit, is used for diabetic diarrhea that is due to a loss of noradrenergic

Table 3. Summary of Recommendations

1. Patients define diarrhea as loose stools, increased stool frequency, or urgency; physicians should note precisely what the patient means. (1b)
2. Chronic diarrhea is defined by duration of >4 weeks. (2b)
3. Consider comorbid symptoms and epidemiologic clues when constructing a differential diagnosis. (2c)
4. The Rome criteria provide a framework for the diagnosis of IBS and emphasize pain. Other etiologies should be sought when these criteria are not met. (1a)
5. Patients without alarm features who meet criteria for IBS should be treated without further testing. Those who do not respond should be evaluated further. (2b)
6. Specific dietary components may cause or aggravate chronic diarrhea. A careful dietary history is essential. (1a)
7. True food allergies are rare causes of chronic diarrhea in adults. (2b)
8. Many drugs cause diarrhea. Careful review of current medications is essential. (1a)
9. Radiation can cause chronic diarrhea, sometimes starting years after exposure. Clinicians should ask about a history of radiation therapy in these patients. (1a)
10. Patients with chronic diarrhea who have had abdominal surgery may require empiric therapy or diagnostic evaluation. (1a)
11. Testing should be done in the presence of alarm features, when the differential diagnosis can be effectively distinguished on the basis of test results, or when the differential diagnosis remains broad and initial testing will limit the number of additional tests needed. (2c)
12. For disorders without definitive diagnostic tests, therapeutic trials may be reasonable. (2c)
13. When the differential diagnosis is broad, stool testing to characterize the diarrhea can direct further evaluation more precisely. (2c)
14. Stool tests can be used to categorize diarrhea and should be considered when the diagnosis remains obscure after initial assessment. (2c)
15. Fecal lactoferrin or calprotectin can be used as surrogate measures for fecal leukocytes. (1b) Stool chymotrypsin and elastase may have some utility as screening tests for pancreatic insufficiency. (2b)
16. Routine blood tests may provide clues to etiology and fluid and electrolyte status. Other blood tests should be obtained only when demanded by the clinical presentation. (2c)
17. Because of the rarity of peptide-secreting tumors, measurement of circulating peptide levels should be reserved for very select patients. (1b)
18. Imaging studies are useful in some patients with steatorrhea and secretory or inflammatory diarrhea. (1b)
19. Lower gastrointestinal endoscopy with mucosal biopsy is valuable in inflammatory and secretory diarrheas. Colonoscopy has a greater yield than sigmoidoscopy, but multiple biopsies must be obtained from the right and left colon. Biopsy of normal-appearing terminal ileum is not recommended. (1a)
20. Upper endoscopy or enteroscopy with biopsies of the duodenum or jejunum should be done in patients with unexplained steatorrhea. The role of aspiration of enteric contents for quantitative bacterial culture is unclear. (2c)
21. Breath tests can assist with the diagnosis of carbohydrate malabsorption and SIBO. Sensitivity and specificity are variable; therefore, breath tests are not recommended without local validation. (2b)
22. Idiopathic BAM may be more frequent than previously appreciated. Until more specific tests for BAM become widely available, empiric therapy may be the only option available in many clinical settings. (2b)
23. Direct pancreatic function testing is not widely available. Indirect testing (eg, serum trypsin, fecal chymotrypsin, and fecal elastase assays) has limited sensitivity. Imaging and empiric trials of pancreatic enzyme replacement therapy may be the best available methods for assessing the role of pancreatic insufficiency in patients with steatorrhea. (2c)
24. Failure to make a diagnosis is more likely due to overlooking a common cause than missing a rare cause of chronic diarrhea. Physicians should repeat the history and physical examination and review studies already done before ordering additional tests. Repeating tests only should be done with cause. (2c)
25. Opiate antidiarrheals are a mainstay of symptomatic management when specific treatment is not possible. Dosing should be scheduled rather than as needed. (1b)

innervation.⁸¹ It also may be useful in the diarrhea of opiate withdrawal. However, its use is often limited by its antihypertensive effect. Anticholinergic medications used to treat other conditions may mitigate diarrhea. For example, tricyclic antidepressants used to manage depression or pain may treat coexisting diarrhea.

Octreotide is used to treat diarrhea in patients with carcinoid syndrome or VIPomas, chemotherapy-induced diarrhea, HIV, and dumping syndrome after gastric surgery.⁸² It also has been tried as empiric therapy for nonspecific diarrhea, with mixed results. For this reason and its cost, empiric use of octreotide in nonspecific diarrhea is not recommended.

For small volume watery diarrhea and fecal incontinence, fiber supplementation or a hydrophilic, poorly fermentable colloid (calcium polycarbophil, carboxymethylcellulose) sometimes may be helpful.⁸³ Soluble fibers such as pectin increase the viscosity of luminal contents, slow gastric emptying, and slow intestinal transit. None of these agents reduce stool weight. However, a change from watery to semi-formed stool may alleviate symptoms.

Oral calcium supplementation also may treat mild chronic diarrhea. Bismuth subsalicylate is a frequently used over-the-counter treatment for diarrhea; however, there is some concern for safety with prolonged use. Bismuth also may be effective in the treatment of microscopic colitis.⁸⁴

Alonepton is a serotonin type 3 antagonist that slows colonic transit and increases fluid absorption.⁸⁵ It is useful in diarrhea-predominant IBS and functional diarrhea, but because of a risk of colonic ischemia and severe constipation, it is used infrequently. Another drug approved for IBS with diarrhea is the μ -opiate receptor agonist, eluxadoline.⁸⁶ It is unknown whether alonepton or eluxadoline has a beneficial effect in diarrhea that is not due to IBS.

Crofelemer, a chloride channel antagonist, is approved for the treatment of HIV-associated diarrhea but may be of use in a variety of diarrheal diseases in which the cystic fibrosis transmembrane receptor chloride channel is active.⁸⁷ However, this has not been tested.

There is no simple and logical algorithm to govern the empiric treatment of chronic diarrhea in every patient. Therefore, a thoughtful trial and error approach is frequently required to find the most effective therapy or combination of therapies for each patient.

A summary of all our recommendations is provided in Table 3.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2016.07.028>.

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Reprint requests

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Conflicts of interest

The authors have the following financial relationships: Dr Schiller has with AbbVie, Valeant, Ironwood, Allergan, Synergy, Takeda, Romark, and AstraZeneca. Dr Pardi has with Merck, Seres Therapeutics, Otsuka, Janssen, Atlantic, Salix, Rebiotix, and Takeda. Dr Sellin has with Forest, Ironwood, and Santarus.

Supplementary Table 1. Physical Findings of Interest in Chronic Diarrhea^{B8}

Findings	Potential implications
Orthostasis, hypotension	Dehydration, neuropathy
Muscle wasting, edema	Malnutrition
Urticaria pigmentosa, dermatographism	Mast cell disease (mastocytosis)
Pinch purpura, macroglossia	Amyloidosis
Hyperpigmentation	Addison's disease
Migratory necrotizing erythema	Glucagonoma
Flushing, heart murmur, wheezing	Carcinoid syndrome
Dermatitis herpetiformis	Celiac disease
Thyroid nodule, lymphadenopathy	Medullary carcinoma of the thyroid
Tremor, lid lag	Hyperthyroidism
Hepatomegaly	Endocrine tumor, amyloidosis
Arthritis	Inflammatory bowel disease, yersiniosis
Lymphadenopathy	HIV, lymphoma, cancer
Abdominal bruit	Chronic mesenteric ischemia
Anal sphincter weakness	Fecal incontinence

Supplementary Table 2. Epidemiologic Associations and Patient Characteristics⁶

Travelers
Bacterial infection (mostly acute)
Protozoal infections (eg, amebiasis, giardiasis)
Tropical sprue
Epidemics and outbreaks
Bacterial infection
Epidemic idiopathic secretory diarrhea (eg, Brainerd diarrhea)
Protozoal infection (eg, cryptosporidiosis)
Viral infection (eg, rotavirus)
Diabetic patients
Altered motility (increased or decreased)
Associated diseases
CD
Pancreatic exocrine insufficiency
SIBO
Drugs (especially acarbose, metformin)
Patients with acquired immunodeficiency syndrome
Drug side effects
Lymphoma
Opportunistic infections (eg, cryptosporidiosis, cytomegalovirus, herpesvirus, <i>Mycobacterium avium</i> complex)
Institutionalized and hospitalized patients
<i>Clostridium difficile</i> infection
Drug side effects
Fecal impaction with overflow diarrhea
Ischemic colitis
Tube feeding

Supplementary Table 3. Differential Diagnosis of Chronic Diarrhea by Stool Characteristics⁶

Watery diarrhea
Osmotic diarrhea
Carbohydrate malabsorption
Osmotic laxatives (eg, Mg ⁺⁺ , PO ₄ ⁻³ , SO ₄ ⁻²)
Secretory diarrhea
Bacterial toxins
Bile acid malabsorption
IBD (some cases)
Crohn's disease
Microscopic colitis
Collagenous colitis
Lymphocytic colitis
Medications and toxins
Disordered motility
Diabetic autonomic neuropathy
IBS
Postsympathectomy diarrhea
Postvagotomy diarrhea
Endocrinopathies
Addison's disease
Neuroendocrine tumors
Hyperthyroidism
Mastocytosis
Medullary carcinoma of the thyroid
Idiopathic secretory diarrhea (epidemic and sporadic)
Stimulant laxative abuse
Neoplasia
Colon carcinoma
Lymphoma
Villous adenoma
Vasculitis
Inflammatory diarrhea
Diverticulitis
Infectious diseases
Invasive bacterial infections (eg, tuberculosis, yersinosis)
Invasive parasitic infections (eg, amebiasis, strongyloidiasis)
Pseudomembranous colitis
Ulcerating viral infections (eg, cytomegalovirus, herpes simplex virus)
IBD (most cases)
Crohn's disease
Ulcerative colitis
Ulcerative jejunoileitis
Microscopic colitis (some cases)
Ischemic colitis
Neoplasia
Colon cancer
Lymphoma
Radiation colitis
Fatty diarrhea
Malabsorption syndromes
Mesenteric ischemia
Mucosal diseases (eg, CD, Whipple's disease)
SBS
SIBO
Maldigestion
Inadequate luminal bile acid concentration
Pancreatic exocrine insufficiency

Supplementary Table 4. Therapies for Chronic Diarrhea

Drug class	Agent	Dose
Opiates (μ -opiate receptor selective)	Diphenoxylate	2.5–5 mg 4 times a day
	Loperamide	2–4 mg 4 times a day
	Codeine	15–60 mg 4 times a day
	Opium tincture	2–20 drops 4 times a day
	Morphine	2–20 mg 4 times a day
Adrenergic agonist	Clonidine	0.1–0.3 mg 3 times a day
Somatostatin analogue	Octreotide	50–250 μ g 3 times a day (subcutaneously)
Bile acid-binding resin	Cholestyramine	4 g up to 4 times a day
	Colestipol	4 g up to 4 times a day
	Colesevelam	1875 mg up to twice a day
Fiber supplements	Calcium polycarbophil	5–10 g daily
	Psyllium	10–20 g daily