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Differential Diagnosis of Chronic Diarrhea

An Algorithm to Distinguish Irritable Bowel Syndrome With Diarrhea From Other Organic Gastrointestinal Diseases, With Special Focus on Exocrine Pancreatic Insufficiency

Darren M. Brenner, MD and J. Enrique Domínguez-Muñoz, MD, PhD†*

Abstract: Chronic diarrhea, defined as diarrhea persisting for more than 4 weeks, affects up to 5% of the population regardless of patient age, sex, race, or socioeconomic status. The impact on patient health and quality of life is substantial, and diagnosis and management of these patients have significant economic consequences for health care services. The differential diagnosis of chronic diarrhea is broad, with etiologies including infections, endocrinopathies, maldigestive/malabsorptive conditions, and disorders of gut-brain interaction. The considerable overlap of symptoms across this spectrum makes accurate diagnosis problematic and may lead to delays in diagnosis or misdiagnosis. In this narrative review, we consider the differential diagnosis of chronic diarrhea, focusing on irritable bowel syndrome with diarrhea and exocrine pancreatic insufficiency, two conditions that may present similarly but have very different underlying causes and require significantly different management strategies. We outline a 4-step diagnostic strategy and propose a straightforward algorithm to assist in efficiently differentiating irritable bowel syndrome from exocrine pancreatic insufficiency and other causes of chronic diarrhea. We anticipate that these aids will improve diagnostic accuracy, which ultimately should lead to improvements in patients' health-related quality of life and reduce the societal burden on health care services.

Key Words: diarrhea, exocrine pancreatic insufficiency, irritable bowel syndrome with diarrhea, differential diagnosis

From the *Division of Gastroenterology and Hepatology, Northwestern University—Feinberg School of Medicine, Chicago, IL; and †Department of Gastroenterology and Hepatology, University Hospital of Santiago de Compostela, Spain.

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Address correspondence to: Darren M. Brenner, MD, Division of Gastroenterology and Hepatology, Northwestern University—Feinberg School of Medicine, 676 N. Clair St, Suite 1400, Chicago, IL, 60611 USA (e-mail: Darren.Brenner@nm.org).

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Chronic diarrhea, defined as diarrhea persisting for more than 4 weeks, affects up to 5% of the population, regardless of age, sex, race, or socioeconomic status.[1] Findings from a recent global internet survey that included 25 countries revealed that, among 54,127 individuals surveyed, 4.7% reported functional diarrhea.[2] The humanistic and economic toll of diarrhea is substantial and imposes considerable burdens, including reductions in health-related quality of life, disruption of daily activities, and significantly increased health care resource utilization.[3,4] Recently, Peery et al summarized the burden and costs of gastrointestinal illnesses in the United States: in 2016, there were >36.8 million ambulatory visits for gastrointestinal symptoms and 43.4 million ambulatory visits with a primary gastrointestinal diagnosis.[5] Diarrhea was the fourth most common gastrointestinal symptom prompting an ambulatory health care visit (office and emergency department; $n=2,583,060$) and the sixth most common gastrointestinal-based physician diagnosis ($n=1,988,413$).[5]

The differential diagnosis of chronic diarrhea is vast and varied, including infections (eg, bacterial, parasitic, viral), endocrinopathies (eg, hyperthyroidism, diabetes), maldigestive and malabsorptive disorders (eg, celiac disease, lactose intolerance, exocrine pancreatic insufficiency [EPI]), disorders of gut-brain interaction (eg, irritable bowel syndrome [IBS]), inflammatory conditions (eg, Crohn's disease, ulcerative colitis), secondary precipitants such as medications (eg, laxatives), and ingestion of toxic substances (eg, alcohol abuse).[6,7] There is considerable overlap among the symptoms of this large range of conditions, making an accurate diagnosis at times difficult. Consequently, patients may experience delays in diagnosis or misdiagnosis, resulting in symptom persistence and other deleterious consequences.[8–12] Thus, efficient and accurate diagnoses are essential.

This narrative provides an overview of strategies to differentiate and accurately diagnose the myriad of diarrhea-related illnesses seen in clinical practice with a focus on IBS with diarrhea (IBS-D) and EPI. We review how IBS-D and EPI can best be distinguished from one another and from many other similarly presenting conditions, thus facilitating early diagnosis, more accurate treatment, improved quality of life, and reduced health care resource utilization.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is the most common cause of diarrhea in the developed world, with an estimated

prevalence in the United States of 4% to 9%, based on Rome III/IV criteria.[13,14] Although patients can present with IBS at any age, it is most common in women aged 20 to 40 years, with women being diagnosed about twice as often as men (14% vs. 8.9%).[15]

According to Rome IV clinical criteria, IBS may be diagnosed if abdominal pain is present at least 1 day per week, is associated with changes in visceral perception with defecation and/or alterations in stool form/frequency, and the symptoms affect patients' quality of life or their abilities to carry out normal activities of daily living. While these clinical criteria do not require symptoms to be present for a specific period of time, the practitioner must be confident that other diagnoses have been appropriately excluded. The Rome IV research-based criteria are more stringent, requiring symptoms to be present for the previous 3 months with onset >6 months before diagnosis (Table 1).[7,17] Symptoms not included in the definition of IBS-D, but commonly identified at presentation, include abdominal bloating and/or distension, fecal urgency, sensations of incomplete evacuation, and the passage of mucus in stools.[7] Stools are characteristically watery (Bristol Stool Form Scale 6-7, Fig. 1) and passed during waking hours. Stress is a well-known mediator.[6,18] Importantly, the development of symptoms in those older than 50 years, unintentional weight loss, acute unexplained symptom changes, recurrent bleeding and/or anemia, and a family history of inflammatory bowel disease, celiac disease, or colorectal cancer are considered alarm features or 'red flags' necessitating further diagnostic evaluation for organic causes other than IBS (Figs. 2 and 3).

Whereas the presence of chronic abdominal pain, the defining symptom of IBS, distinguishes these patients from those with functional diarrhea, there is significant overlap between the two; indeed, patients may oscillate between the diagnoses.[19,20] Patients with IBS, especially those with frequent pain, have been shown to experience increased psychological distress and somatic comorbidities compared with patients with functional diarrhea, and they should therefore be evaluated accordingly. Early treatment of these overlapping conditions may be beneficial.[21]

No universally accepted biomarker has been identified for diagnosing IBS, and exhaustive testing to rule out an organic cause is not recommended owing to high costs, inefficiency, and low yield.[19,22,23] Furthermore, an accurate diagnosis of IBS can usually be made based on subjective history alone. In a retrospective study by Vanner et al,[24] Rome Criteria for IBS, in the absence of alarm symptoms, yielded specificity and positive predictive values of 100%. None of the patients diagnosed with IBS required revised diagnoses during the subsequent 2 years. In a prospective analysis, positive predictive values approached 98%.[24] Consequently, guidelines have recommended minimizing diagnostic investigations and instead utilizing a positive diagnostic strategy.[16,19,25] Indeed, the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) recommend against routine colonoscopy except in patients older than 45 years (age-appropriate screening) or with warning signs of more serious illness.[16,22,26]

Recommended diagnostics are limited and include serologic testing to rule out celiac disease (specifically serum immunoglobulin [Ig] IgA and tissue transglutaminase IgA), fecal calprotectin (or lactoferrin), and C-reactive protein in patients without clinical signs suggestive of more serious disease to exclude inflammatory bowel disease, and a *Giardia* stool antigen in individuals travelling or emigrating from endemic countries, exposed to untreated or improperly treated water, or exposed in daycare settings.[16]

Irritable Bowel Syndrome Subtypes

Irritable bowel syndrome is categorized as one of four subtypes according to the predominant stool pattern: IBS-D, IBS with constipation, IBS with a mix of both diarrhea and constipation, or IBS unclassified.[7,8] Of these, IBS-D has the highest prevalence, affecting up to 40% of adults diagnosed with IBS.[27] Internationally, 1.2% of individuals experience IBS-D, and, like IBS overall, there is a slight preponderance of females compared with males (1.3% vs. 1.0%).[2]

Patients with IBS-D pass Bristol Stool Form Scale type 6 or type 7 stools (loose, mushy, watery) during more than 25% of bowel movements and types 1 and 2 stools (hard, lumpy, pellet-like) less than 25% of the time (Fig. 1).[7,19] Rome IV diagnostic criteria specify that stool texture should be assessed on days with abdominal pain to enable greater precision in differentiating the IBS subtype.[7,28]

Because the symptoms of IBS-D may overlap with those of other conditions, such as EPI, celiac disease, small intestinal bacterial overgrowth, disaccharidase deficiencies, Crohn's disease, ulcerative colitis, and infections, diagnosis is not always straightforward.[17] However, the initial classification of diarrhea as watery (indicative of IBS), fatty or/greasy (indicative of EPI), or inflammatory (indicative of inflammatory bowel disease) can begin to narrow the differential diagnosis (Table 2).[6]

TABLE 1. Rome IV Diagnostic Criteria for Irritable Bowel Syndrome[14,16]

Clinical diagnostic criteria	Criteria for patient inclusion in clinical trials, epidemiological studies, or pathophysiological studies
Recurrent abdominal pain on average at least 1 d/week, associated with two or more of the following criteria*: • Related to defecation • Associated with a change in frequency of stool • Associated with a change in form (appearance) of stool Bothersome symptoms: • Interfere with daily activities • Require attention • Cause worry or interfere with the quality of life	Recurrent abdominal pain on average at least 1 d/week in the last 3 mo, associated with two or more of the following criteria†: • Related to defecation • Associated with a change in frequency of stool • Associated with a change in the form (appearance) of stool

*For the last 8 weeks.
†For the last 3 months with symptom onset at least 6 months before diagnosis.

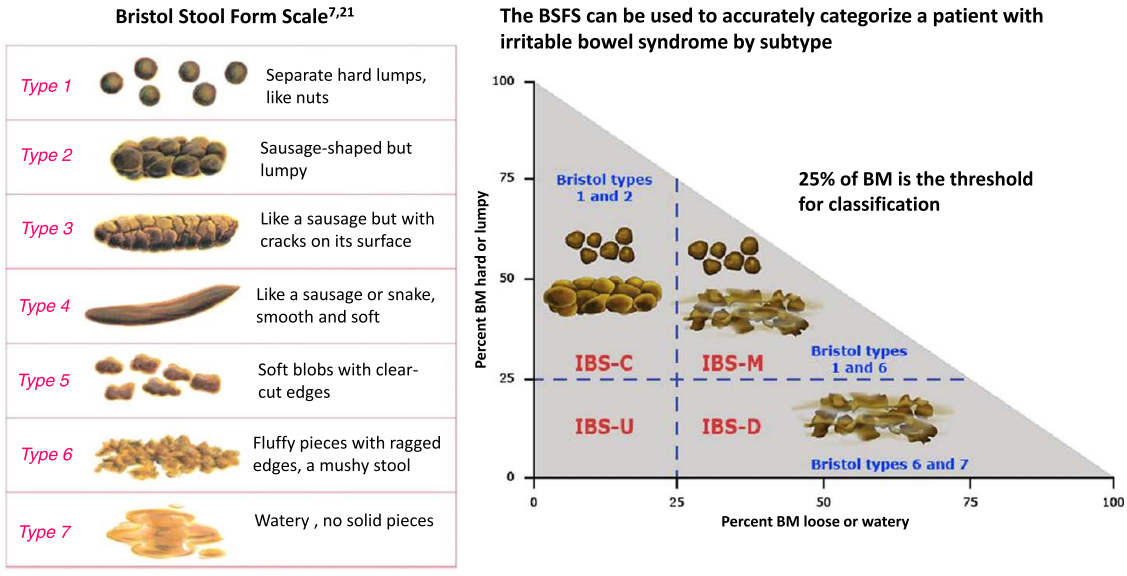

FIGURE 1. Bristol Stool Form Scale and IBS Subtypes BSFS indicates Bristol Stool Form Scale; BM, bowel movement; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, irritable bowel syndrome with a mix of both diarrhea and constipation; IBS-U, irritable bowel syndrome unclassified. Reprinted with permission from the Rome Foundation. ©2000 Rome Foundation. All Rights Reserved. All permission requests for this image should be made to the copyright holder.

EXOCRINE PANCREATIC INSUFFICIENCY

Although most commonly associated with diseases of the exocrine pancreas, EPI is also caused by a number of extrapancreatic diseases.[29] Approximately 80% of children with cystic fibrosis develop EPI within the first 2 years of life,[30] and between 10% and 30% of patients with mild and 85% of patients with severe chronic pancreatitis will develop EPI.[30,31] Among patients with pancreatic cancer, ~72% will develop EPI (this becomes 3.36 times more frequent if the tumor is located in the head of the pancreas rather than in the body or tail of the pancreas).[32] In patients with pancreatic disease, the low levels of secretion of pancreatic enzymes and bicarbonate are caused by loss of function of the parenchyma and/or obstruction of the main pancreatic duct.[33]

Patients with EPI have a reduced quantity or activity of pancreatic enzymes in the intestinal lumen, which results in failure to digest food normally.[29,34,35] The most clinically relevant feature of EPI is inadequate fat digestion[30]; for diarrhea to develop, the quantity and quality of ingested food overcomes the digestive ability of the exocrine pancreas. The prevalence of symptoms in patients with EPI is highly variable, owing mainly to different dietary habits and dietary restrictions. In clinical studies of patients with

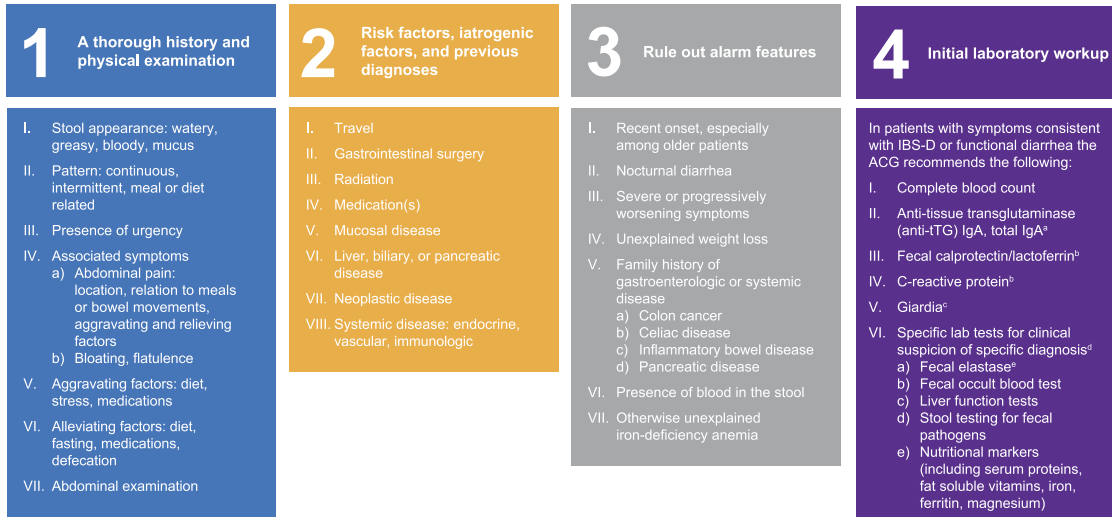

FIGURE 2. General Sequence for Differential Diagnosis of Chronic Diarrhea. ACG indicates American College of Gastroenterology; EPI, exocrine pancreatic insufficiency; IBS-D, irritable bowel syndrome with diarrhea; IgA, immunoglobulin A. [a]Indicative of celiac disease; [b]Indicative of IBS-D (lactoferrin if calprotectin unavailable, if neither available use C-reactive protein); [c]In specific populations; [d]Based on physician's clinical suspicion/differential diagnosis; [e]Pancreatic function test for suspected EPI.

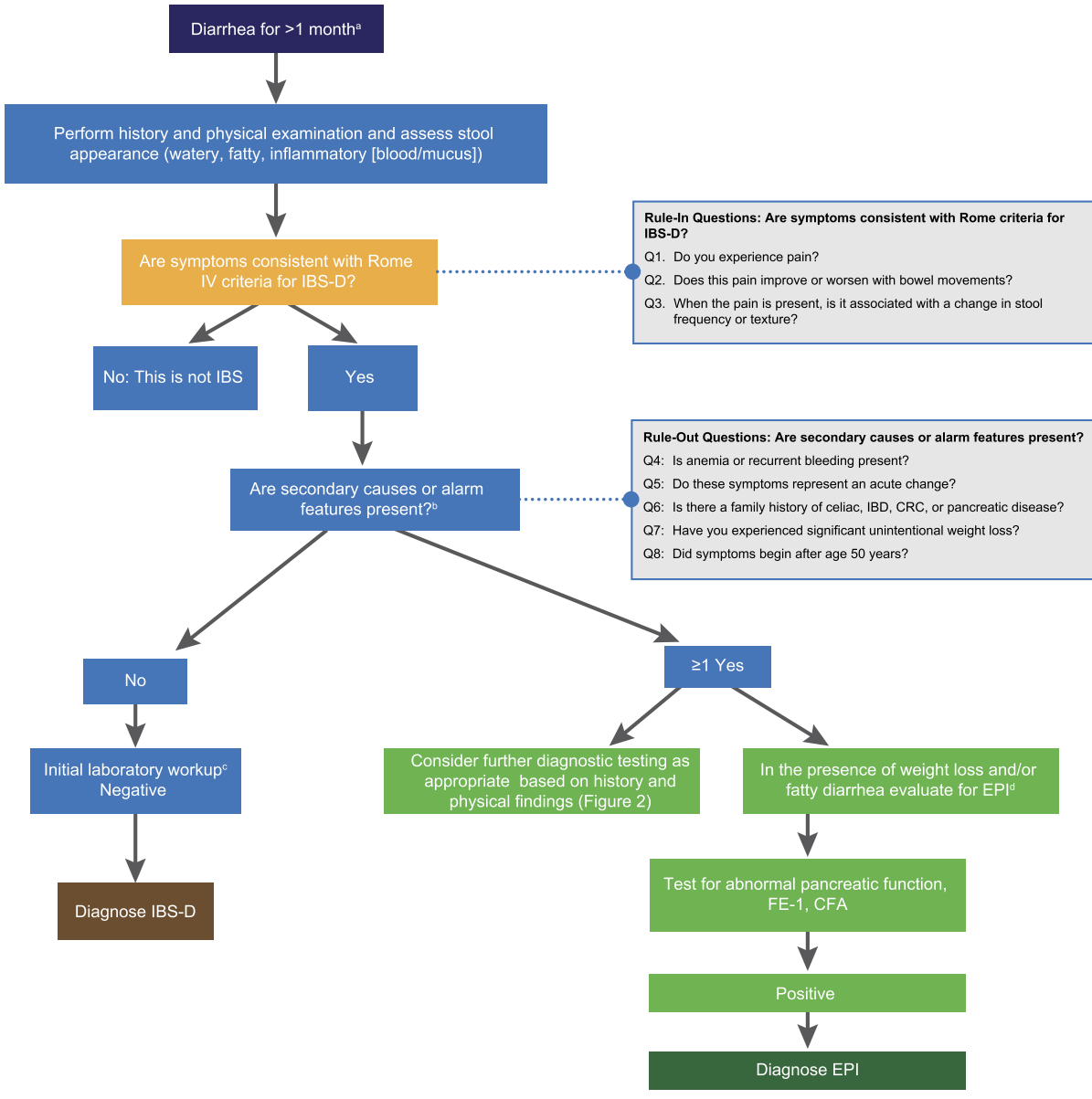

FIGURE 3. A General Strategy for the Differential Diagnosis of Patients with Chronic Diarrhea: EPI or IBS-D? CFA indicates coefficient of fat absorption; CRC, colorectal cancer; CRP, C-reactive protein; EPI, exocrine pancreatic insufficiency; FE-1, fecal elastase; IBD, inflammatory bowel disease; IBS-D, irritable bowel syndrome with diarrhea; IgA, immunoglobulin A. [a]IBS clinical diagnosis requires presence of diarrhea for >2 months; [b]If ≥ 1 alarm feature, further workup may be required; [c]Complete blood count, CRP, fecal calprotectin or fecal lactoferrin, anti-tissue transglutaminase IgA and total IgA; [d]Mainly in the presence of pancreatic disease, gastric or pancreatic surgery, or risk factors of pancreatic disease (alcohol abuse, smoking).

confirmed EPI, the frequency of clinically overt steatorrhea (fatty/oily loose stools) varied from 23% to 70% in chronic pancreatitis, 46% in pancreatic cancer before surgery, and 15% in cystic fibrosis.[36] It is necessary to obtain a detailed patient history because dietary restrictions are important confounding factors: for example, low fat intake, perhaps as a means of managing symptoms, may impede a diagnosis of EPI because a patient consuming a diet low in fat may be asymptomatic.[36]

Patients with EPI present with symptoms characteristic of malabsorption syndrome (diarrhea, abdominal distention and cramps, flatulence, weight loss) and nutritional deficiencies (fat-soluble vitamins, micronutrients, proteins).[33,34,37] Symptoms vary depending on the underlying cause, severity of enzyme deficit, and amount of fat intake, but the typical patient will report foul-smelling, fatty, loose stools; flatulence; and weight loss.[37] Longer-term consequences of EPI include sarcopenia, osteoporosis, low-trauma fractures, metabolic bone disease (especially with chronic pancreatitis), increased risk of infection, and cardiovascular disease.[30,34,35,38,39]

EPI should be considered in patients with chronic diarrhea in the presence of any of the following: history of pancreatic disease (acute, relapsing, or chronic pancreatitis; cystic fibrosis; pancreatic cancer; acute necrotizing pancreatitis; and type 1, 2, or 3c diabetes mellitus), risk factors of pancreatic disease (alcohol abuse and/or smoking), family

TABLE 2. Narrowing the Diagnosis According to Stool Characteristics

Watery	Fatty/Greasy	Inflammatory
Osmotic • Carbohydrate malabsorption • Celiac disease • Osmotic laxatives Secretory • Bile acid malabsorption • Microscopic colitis • Endocrinopathies (eg, diabetes, hyperthyroidism) • Medications (eg, metformin) Functional • Functional diarrhea • Irritable bowel syndrome	Malabsorption or maldigestion • Celiac disease • Small intestinal bacterial overgrowth • Giardiasis • Whipple disease • Inadequate luminal bile acid concentration • Exocrine pancreatic insufficiency	Inflammatory bowel disease • Segmental colitis associated with diverticulosis (SCAD) • Infectious disease • *Clostridium difficile* • Invasive bacterial infections • Invasive parasitic infections • Ischemic colitis • Radiation colitis • Lymphoma

history of pancreatic diseases (mainly chronic pancreatitis or pancreatic cancer), or pancreatic or gastric surgery.[32,33] Patients without a history of pancreatic disease should be tested for EPI only if there is a high level of clinical suspicion.

Definitive diagnosis of EPI, often challenging due to the lack of accurate tests, is extremely important to avoid complications. Diagnosis typically requires a combination of symptoms, nutritional markers, and a noninvasive pancreatic function test, such as coefficient of fat absorption (CFA) and fecal elastase (FE-1).[30,33,34] Although other pancreatic function tests exist, they are either invasive (eg, endoscopic pancreatic function test [ePFT]) or not readily available (eg, ^{13}C-labeled breath tests) for use in clinical practice.[37] The direct secretin-cholecystokinin (CCK) test is the most sensitive test for the diagnosis of reduced stimulated pancreatic secretion, but it is invasive, expensive, cumbersome, and time-consuming, and therefore it is not usually used in clinical practice.[40] The ePFT after intravenous secretin administration was developed as an alternative to the secretin-CCK test, but limitations persist.[41,42] Both the secretin-CCK test and the ePFT are used mainly for the functional diagnosis of chronic pancreatitis in patients with inconclusive imaging, but they are not appropriate for the diagnosis of EPI.[40,43]

The CFA test is regarded as the gold standard test for EPI,[34,37] but it requires the patient to consume a diet containing 100 g of fat/day for 5 days and to collect the total feces eliminated over days 3 to 5, which are then used for laboratory testing. Because this procedure is cumbersome, unpleasant, and difficult for patients to comply with, it is used rarely in clinical practice.[36,37] ^{13}C-labeled breath tests are an accurate and standardized alternative to CFA for the diagnosis of EPI in clinical practice but are not yet widely available.[44,45] Fecal concentration of elastase, a pancreatic-specific enzyme, reflects the amount of the enzyme that has been secreted by the pancreas, thus the FE-1 test is a pancreatic secretion test.[46] The concentration of FE-1 can be measured by an enzyme-linked immunosorbent assay in a small stool sample.[37] In addition, the FE-1 test is simple and widely available and therefore is the most frequently used test of pancreatic function.[37] The optimal cutoff and accuracy of FE-1 for the diagnosis of EPI, using CFA as the gold standard, are variable. By applying the optimal cutoff in each reported study, which ranges from 84 to 200 μg/g, the sensitivity of FE-1 is 68% to 94% and its specificity is 48% to 82%.[46–50]

In patients with chronic diarrhea and a high probability of EPI (eg, pancreatic cancer located in the head of the pancreas; advanced chronic calcifying pancreatitis; pancreatic surgery, such as pancreaticoduodenectomy, gastrectomy), the usefulness of pancreatic function tests for the diagnosis of EPI is limited and is not required for a diagnosis to be reached. In patients with chronic diarrhea but a low probability of EPI (eg, patients without a previous diagnosis of pancreatic disease or surgery, with no risk factor for pancreatic disease, and without weight loss or nutritional deficiencies), normal levels of FE-1 exclude EPI from the differential diagnosis; low levels may be indicative of EPI, and exploration of the pancreas is recommended to exclude pancreatic disease, but false-positive results of FE-1 are not infrequent.[46]

EPI is one of several organic gastrointestinal diseases that may mimic IBS.[12,51] EPI, as defined by a low FE-1 concentration, is present in 5% to 6% of patients fulfilling Rome criteria for IBS-D and 4.6% of patients with unexplained abdominal pain and/or diarrhea and/or IBS-D.[12,23,52] However, as false-positive FE-1 results are not rare in patients with watery diarrhea, low FE-1 levels do not completely exclude IBS-D.

DIFFERENTIAL DIAGNOSIS OF CHRONIC DIARRHEA

Early and accurate diagnosis is essential in disease management. A patient with chronic diarrhea may present with a spectrum of symptoms indicating one of several disorders, including IBS-D, EPI, celiac disease, small intestinal bacterial overgrowth, inflammatory bowel disease, and infections (eg, giardiasis). All of these conditions may include diarrhea, abdominal pain, bloating, and flatulence among their symptoms. To assist in the accurate diagnosis of patients presenting with chronic diarrhea, we suggest a four-step diagnostic process (Fig. 2).

Step 1: Thorough History and Physical Examination

Diagnosis should begin by taking a thorough history and physical examination.[6,10,53] Patients presenting with chronic diarrhea, defined as persisting for $\geq$4 weeks, should be questioned in detail on their symptoms and prior diarrhea history.[10,18,54] Although the clinical definition of diarrhea is loose or watery stools $\geq$3 times in a 24-hour period,[1,18] patients use various definitions (eg, loose stools, increased stool frequency, or fecal urgency), underscoring the

importance of an accurate and detailed patient history.[54] Abnormal stool form can be more important in defining diarrhea because patients with functional constipation will also present with a chief complaint of diarrhea owing to increased defecatory frequency. However, further questioning may cause illicit symptoms of straining, incomplete evacuation, obstruction, and the passage of hard stools.[1,55]

As an initial approach, we recommend determining if diarrhea can be categorized as watery (indicative of IBS, celiac disease, endocrinopathy, or laxative misuse), fatty or greasy (which may indicate a malabsorptive or maldigestion disease, such as celiac disease or EPI), or inflammatory (indicative of infectious or inflammatory bowel disease)[6]; however, definitive categorization is not always possible using these criteria because some conditions overlap (Table 2). Further questioning should include the following: What is the pattern of diarrhea? Is it continuous, intermittent, or meal-related (this may differentiate secretory from osmotic diarrhea)? When did it start? Was there a precipitating event? What is the volume of feces? Is there blood, mucus, or fat in the stool or toilet basin? Is there a nocturnal component to diarrhea? Is there fecal urgency or incontinence?[10,53,54,56] In addition, other gastrointestinal and extraintestinal symptoms should be explored, and potential aggravating factors, such as diet, stress, or medications,[10,18,56] and alleviating factors should be queried.[10,53]

Step 2: Identify Risk Factors, Iatrogenic Factors, and Previous Diagnoses

To rule out extrinsic risk factors as the cause of chronic diarrhea, it is important to establish if the patient has recently travelled (to regions with recognized specific diarrhea-related pathogens, such as *Giardia*), has undergone gastrointestinal surgery (eg, gall bladder removal, ileocecal resection, Roux-en-Y gastric bypass), received radiation treatment, or is taking medication that may induce diarrhea. In addition, the presence of mucosal (eg, celiac disease), hepatic, pancreaticobiliary, neoplastic, or systemic (endocrine, vascular, or immunologic) disease may indicate an increased risk for diarrhea development.[6,10,53,56]

Step 3: Rule Out Alarm Features

Several clinical features suggest the presence of a more serious disease. For this reason, it is important to rule out any of the following: recent onset, especially among older patients; nocturnal diarrhea; severe or progressively worsening symptoms; unexplained weight loss; a family history of gastroenterological or systemic disease, such as celiac disease, inflammatory bowel disease, or colorectal cancer; the presence of blood in the stool; and unexplained iron deficiency.[6,53,56]

Step 4: Initial Laboratory Workup

The history and physical examination should guide the diagnostic strategy. If alarm signs or symptoms are present, testing should be based on the most likely etiologic causes. For example, in individuals presenting with chronic meal-related fatty–greasy diarrhea in association with weight loss and fat-soluble vitamin deficiencies, a workup for EPI is warranted. Measurement of FE-1 levels is the most commonly used indirect test of exocrine pancreatic function; an FE-1 level <200 μg/g feces indicates a deficiency of FE-1 and is reflective of overall pancreatic output, correlating with the output of other pancreatic enzymes, such as lipase, amylase, and trypsin.[29,57] However, in patients presenting with symptoms consistent with functional diarrhea or IBS-D (where alarm signs/symptoms are absent), recent AGA and ACG guidelines are generally in agreement and recommend screening for celiac disease (anti-tissue transglutaminase IgA and total IgA), inflammatory bowel disease (fecal calprotectin or lactoferrin and C-reactive protein [ACG only]), and *Giardia* (in specific populations).[16,57] The AGA also suggests testing for bile acid diarrhea (48-hour fecal bile acid assay or serum fibroblast growth factor 19 level).[57]

AN ALGORITHM FOR THE DIFFERENTIAL DIAGNOSIS OF CHRONIC DIARRHEA: FOCUS ON IBS-D AND EPI

Using the four-step procedure described above, we have refined and developed a straightforward algorithm to assist clinicians in differentiating IBS-D and EPI from other diarrhea syndromes (Fig. 3). Use of this algorithm should minimize diagnostic testing and reduce health care expenditure by avoiding unnecessary investigations and may result in more timely and appropriate diagnosis and management. The algorithm provides a simple framework for making a rapid and accurate diagnosis of IBS-D. It begins with three "rule-in" questions to determine alignment with Rome IV criteria for IBS: (1) Do you experience pain? (2) Does the pain improve or worsen with defecation? and/or (3) Is the pain associated with changes in stool frequency or texture? If the answers to these three rule-in questions are positive, and in the absence of a few alarm symptoms/signs (Fig. 3), IBS-D can be diagnosed with an accuracy approaching 97%.[13] In this scenario, minimal diagnostic testing is warranted. However, if alarm symptoms are present (eg, weight loss) and if EPI is suspected as the cause of chronic diarrhea, nutritional markers, and FE-1 are indicated, with any abnormal results making exploration of the pancreas mandatory. If the pancreas looks normal, then a false positive FE-1 test is likely, EPI can be excluded, and another cause of chronic diarrhea should be sought.

DISCUSSION

Diarrhea is a common yet complex disorder precipitated by multiple etiologic and pathogenic mechanisms. Distinguishing these conditions from each other can be problematic, especially where symptoms overlap. This is highlighted in individuals with IBS-D: in the United States, up to 75% of patients meeting the criteria remain undiagnosed.[58] This is concerning because IBS is the most common cause of diarrhea and can be diagnosed with high accuracy based on a few simple binary questions and minimal diagnostic testing.

One of the most reported mimickers of IBS-D is EPI, and it is not uncommon for patients with EPI to be misdiagnosed with IBS-D. Consequently, we have proposed an algorithm designed specifically to help distinguish between these 2 disorders (Fig. 3) and differentiate them from other etiologies of chronic diarrhea. Most importantly, this algorithm incorporates recommendations from the recently published ACG and AGA IBS guidelines stressing a positive diagnostic strategy. This simple algorithm should assist practitioners in making timely diagnoses and reduce superfluous testing, thus reducing delays in treatment and improving patient health and quality of life.[58]

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