REVIEW

Evaluation of chronic diarrhea and irritable bowel syndrome with diarrhea in adults in the era of precision medicine

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Chronic diarrhea is a common clinical problem, affecting roughly 5% of the population in any given year. Evaluation and management of these patients can be difficult due to the extensive differential diagnosis of this symptom. Many patients with chronic diarrhea have structural problems, such as inflammatory bowel disease or celiac disease, that can be readily identified. Others do not, and often are given a diagnosis of irritable bowel syndrome with diarrhea (IBS-D). When based on generally accepted clinical criteria, a diagnosis of IBS-D identifies a group of patients who are unlikely to have disorders producing anatomical changes in the gut. It is less clear that a diagnosis of IBS-D identifies a specific pathophysiology or leads to better management of symptoms. Disorders such as small intestinal bacterial overgrowth, bile acid malabsorption, food intolerance, and motility disorders may account for symptoms in patients with IBS-D. More effective tests are being developed to identify the clinical problems underlying IBS-D and may lead to more specific diagnoses that may improve the results of therapy. Application of the principles of precision medicine (identifying a specific mechanism for disease and applying treatments that work on that mechanism) should lead to more expeditious diagnosis and treatment for patients with chronic diarrhea including IBS-D, but currently is limited by the availability of sufficiently sensitive and specific tests for underlying mechanisms that can predict response to treatment.

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CLINICAL DEFINITION

Most patients define diarrhea as passage of loose stools (consistencies ranging from pourable to watery), although abnormally frequent defecation (>2 bowel movements per day) often is present as well [1]. Diarrhea represents an alteration of bowel function in which stool water content is high because net absorption of water by the intestine is reduced, and can be due to a variety of causes [2]. Chronic diarrhea arbitrarily is distinguished from acute diarrhea by a duration > 4 weeks, and has a different differential diagnosis than acute diarrhea. Most acute diarrheas are due to self-limited infections or ingestion of preformed toxins. Chronic diarrhea has a much more extensive differential diagnosis that often requires clinical, radiographic, and laboratory evaluation to make a specific diagnosis and to provide specific treatment [3].

IRRITABLE BOWEL SYNDROME WITH DIARRHEA AS PART OF THE SPECTRUM OF CHRONIC DIARRHEA

Many patients with chronic diarrhea are given a diagnosis of irritable bowel syndrome with diarrhea (IBS-D), based on published criteria or clinical intuition. Published criteria identify the combination of chronic abdominal pain with altered bowel habits as the characteristic feature of irritable bowel syndrome [4]. The temporal connection between pain and bowel habits is what gives the criteria their specificity: the onset of abdominal pain in patients with IBS coincides with the change in bowel habit and is associated with altered stool consistency and/or frequency. Defecation often mitigates pain. Patients who meet the published criteria for IBS have a lower risk of an alternative structural diagnosis, such as inflammatory bowel disease or cancer [5]. Because of this, experts have advised a judicious evaluation for patients identified as having IBS, focused on identifying alarm features, such as weight loss and anemia, that might identify more serious conditions requiring further evaluation [6].

This judicious approach has two fundamental limitations: (1) it ignores the possibility of identifying an underlying cause of symptoms; and (2) it may delay application of effective therapy aimed at the specific underlying cause. In addition, once a diagnosis of IBS-D is made, physicians stop thinking about alternative diagnoses and press on with empiric treatment. Current treatments recommended for IBS-D have very specific mechanisms of action and

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are used sequentially until one is found to "work." Three drugs now have the Food and Drug Administration approval for IBS-D and several others have been used "off-label" [6, 7]. The best response rate for any individual treatment is only about 40%, however [6], probably because of the large number of potential mechanisms producing IBS-D symptoms, not all of which will respond to the same therapy (Table 1).

Trying to discover the specific mechanism producing symptoms in individual IBS-D patients has been difficult because of a lack of tests with sufficient sensitivity and specificity to identify those causes, and proof that identifying the mechanism can lead to expeditious therapy. This now may be changing, and so it makes some sense to bring the diagnostic evaluation of IBS-D within that of chronic diarrhea. This also may reduce the all-too-frequent practice of labeling every patient with chronic diarrhea with a diagnosis of IBS-D, delaying appropriate evaluation.

INITIAL EVALUATION

A detailed medical history is the best route toward making a diagnosis in patients with chronic diarrhea [1]. Important features to identify are listed in Table 2. It is essential to obtain a complete medication history, including over-the-counter drugs and supplements, since diarrhea is a common side effect of drug therapy. A thorough dietary intake history should be developed, since food intolerances may cause diarrhea also. Previous surgery or radiation therapy also should be noted. The presence of systemic diseases sometimes associated with diarrhea, such as diabetes, thyroid dysfunction, or collagen vascular diseases, should be ascertained.

Special note should be made of concurrent symptoms, such as abdominal pain, weight loss, edema, and bleeding. If abdominal pain is present, the relationship of pain to the occurrence of diarrhea should be documented. A diagnosis of IBS-D can be made from the history alone, but should be viewed as an intermediate diagnosis, suggesting a lower likelihood of structural disease, but not excluding the possibility of discovering a specific mechanism for symptoms.

Family history is important to review. Some illnesses producing chronic diarrhea, such as celiac disease, inflammatory bowel disease, and cancer, may be familial and may be more likely in a patient with a positive family history. These may need to be addressed, since they may be of concern to the patient.

Physical findings are not that common in patients with chronic diarrhea (other than evidence of weight loss), but if present, they may be significant [1]. For example, findings of flushing, hepatomegaly, and a heart murmur would suggest a diagnosis of

Table 1 Pathophysiological mechanisms and conditions proposed as contributing factors or mimics of irritable bowel syndrome with diarrhea (IBS-D) [6]

Psychosomatic disorders, somatization syndrome
Motility disorders
Hypersensitivity to gut distention
Brain–gut interactions
Altered intestinal permeability
Small intestinal bacterial overgrowth
Dysbiosis, chronic infection
Post-infection autoimmunity
Carbohydrate and other food intolerances
Bile acid malabsorption
Microscopic colitis
Celiac disease

Table 2 Key elements of the patient's history when diarrhea is chronic (>4-week duration) [1–3]

Patient's age, sex
Some conditions are more common in younger or older patients, and in men or women
Onset, duration
Stool frequency, appearance
Differentiate small, frequent bowel movements ("squirts") from more voluminous stools
Presence of urgency or fecal incontinence
Identify stools as watery, bloody or fatty
Periodicity and pattern of symptoms
Continuous vs. intermittent
Recognize factors that initiate or aggravate symptoms (diet, stress, other factors)
Epidemiological history and dietary exposures at time of onset
Ill contacts, travel, water source, restaurant meals, exposure to animals
Associated symptoms
Abdominal pain and its relationship to onset of diarrhea, bowel movements
Weight loss, edema
Bleeding
Medication history
Consider any medication (prescription, non-prescription, alternative) as possible cause
Review previous treatments for diarrhea
Prior surgeries, radiation therapy
These may have occurred years before onset of diarrhea
History of systematic illnesses
Diabetes, thyroid disease, immunological diseases, infectious diseases
Impact of illness on life and family
Quality of life
Attendance at work or school
Relationship issues
Secondary gain (potential for factitious illness or somatization syndrome). Obtain and review records of any previous evaluations for diarrhea

carcinoid syndrome. Physical findings that should be sought are listed in Table 3.

Basic laboratory tests should include a complete blood count, metabolic profile, testing for IgA anti-tissue transglutaminase and total IgA levels (if not previously tested for celiac disease), and C-reactive protein (CRP) [1–3]. Abnormal findings should be evaluated appropriately.

While it is unclear if the prevalence of celiac disease is higher in patients with IBS than in the normal population, a small percentage of patients has abnormal screening tests and needs further evaluation [8, 9]. The frequency of celiac disease in patients with chronic diarrhea is less well documented, but may be as much as 5%. All chronic diarrhea patients should be screened for celiac disease with IgA anti-tissue transglutaminase and total IgA levels, with further testing if positive or if IgA deficiency is documented.

High-sensitivity CRP has been touted as a marker for low-grade inflammation in groups of patients with IBS-D, but individual elevations tend to be modest and rarely are outside the normal laboratory range [10]. When more substantially above the normal range, CRP serves as a marker for traditionally recognized inflammatory conditions involving the bowel or other organ systems.

BASIC STOOL ANALYSIS

Most patients with chronic diarrhea should have stool collected for analysis. If not previously done, stool culture, fecal occult blood test, fecal calmodulin or lactoferrin activity (or fecal leukocytes by microscopy), ova and parasite assessment, *Clostridium difficile* toxin, and qualitative stool fat by microscopy should be considered. Fecal lactoferrin has a high specificity for inflammatory bowel disease, meaning that a negative test is likely to be a true negative result [11]. Although DNA multiplex assays for infectious agents may be useful for acute diarrhea, the tests selected for the multiplex panel only detect specific organisms that occur with high frequency in patients with acute diarrhea and may not catch all the potential infections causing chronic diarrhea [12].

Table 3 Physical findings of interest in chronic diarrhea [1]

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	Carcinoid syndrome
Malignant atrophic papulosis	Kohlmeier–Degos disease
Dermatitis herpetiformis	Celiac disease
Thyroid nodule, lymphadenopathy	Medullary carcinoma of the thyroid
Tremor, lid lag	Hyperthyroidism
Right-sided heart murmur, wheezing	Carcinoid syndrome
Hepatomegaly	Endocrine tumor, amyloidosis
Arthritis	Inflammatory bowel disease, yersinosis
Lymphadenopathy	HIV, lymphoma, cancer
Abdominal bruit	Chronic mesenteric ischemia
Anal sphincter weakness, perianal dermatitis	Fecal incontinence

Table from ref. 1

IMAGING

Patients with chronic diarrhea (including those with IBS-D who have alarm features or abnormal laboratory tests) should undergo cross-sectional abdominal imaging and enterography (either as part of the computed tomography (CT) or magnetic resonance imaging (MRI) study or as a traditional barium fluoroscopic test) to look for structural problems [1, 3]. Modern techniques are good at detecting both luminal and extraluminal problems that may cause chronic diarrhea. One such study usually is sufficient, however, and imaging should not be repeated without reviewing previous studies. Imaging might be delayed until a later time in patients with clear-cut IBS-D without alarm features, since the yield is likely to be low, but should be reconsidered if empiric therapy fails [6].

COLONOSCOPY AND ENDOSCOPY

Most patients with chronic diarrhea (and those with IBS-D with alarm features or poor response to therapy) should have colonoscopy with ileoscopy, if possible [1, 3]. When colonoscopy is done, colon biopsies should be obtained (at least six specimens from above the rectum)—even when the mucosa appears normal—to rule out microscopic colitis [13]. Patients with weight loss or clinical evidence of steatorrhea should have upper gastrointestinal endoscopy with duodenal biopsies to look for evidence of small intestinal mucosal disease. As with imaging studies, these procedures should not be repeated without cause, and may be delayed until empiric therapy fails in patients with IBS-D without alarm features.

FURTHER EVALUATION OF CHRONIC DIARRHEA PATIENTS WITHOUT STRUCTURAL DISEASE

Once structural disease has been excluded, an attempt should be made to identify the mechanism of diarrhea to narrow the differential diagnosis. This can be done with a timed stool collection which can give important information about the severity and pathogenesis of chronic diarrhea (Table 4). By analyzing stool for electrolyte concentrations, the presence of blood or fecal leukocytes, and fat content, the diarrhea can be categorized as being watery, inflammatory, or fatty, which will limit the differential diagnosis and direct further evaluation of the problem [14].

Table 4 Patterns of stool composition in chronic diarrhea [14]

Category/findings	Implications
Stool weight < 200 g/24 h	
No objective evidence of diarrhea	Change in stool frequency, intermittent diarrhea, fecal incontinence, treatment with antidiarrheal drugs during collection
Hyperdefecation (increased frequency without excess volume)	Possible IBS, proctitis, abnormal rectal reservoir function
Abnormal consistency (unformed-runny stools)	Possible IBS
Elevated fecal osmotic gap	Presumed mild carbohydrate malabsorption or excess Mg intake from supplements
Steatorrhea	Malabsorption or maldigestion
Stool weight > 200 g/24 h	
Secretory diarrhea without steatorrhea	Microscopic colitis or other cause of secretory diarrhea Carbohydrate malabsorption without steatorrhea
High fecal osmotic gap	Ingestion of poorly absorbed carbohydrates, malabsorption
Steatorrhea with or without carbohydrate malabsorption	Small bowel mucosal disease, small intestinal bacterial overgrowth, bile acid deficiency, pancreatic exocrine insufficiency
Osmotic diarrhea	Ingestion of poorly absorbed ions (e.g., magnesium, phosphate, sulfate) or osmotically active polymers (e.g., polyethylene glycol)
Unclassified	Blood or pus suggests inflammatory causes of diarrhea

Table from ref. [1], based on data from ref. [14]

Table 5 Differential diagnosis of chronic diarrhea

Watery	
Osmotic	
Medications	Osmotic laxatives (Mg, SO_4, PO_4)
Unabsorbed sugars/sugar alcohols	Diet foods/drinks/gum (sorbitol, mannitol, others)
	Enzyme dysfunction (e.g., lactase, sucrase)
Secretory	
Medications	Stimulant laxatives, antibiotics, many others
Small intestinal bacterial overgrowth	
Microscopic colitis	
Endocrine	
Tumors	Carcinoid, gastrinoma, medullary thyroid cancer, VIPoma
Systemic	Adrenal insufficiency, hyperthyroidism
Bile salt malabsorption	Ileal resection, postcholecystectomy, idiopathic
Non-invasive infections	Giardiasis, cryptosporidiosis
Fatty	
Maldigestion	Decreased duodenal bile salt concentration (cirrhosis, bile duct obstruction, ileal resection)
	Pancreatic dysfunction (chronic pancreatitis, cystic fibrosis, duct obstruction)
Malabsorption	Mucosal disease (celiac sprue, tropical sprue, giardiasis, Whipple's disease, chronic mesenteric ischemia)
	Short bowel syndrome
	Small intestinal bacterial overgrowth (diabetes mellitus, scleroderma, prior bowel surgery)
	Lymphatic obstruction
Inflammatory	
Inflammatory bowel disease	Ulcerative colitis, Crohn's disease
Malignancy	Colon cancer, lymphoma
Radiation colitis/enteritis	
Mastocytosis	
Invasive or inflammatory infections	*Clostridium difficile*, cytomegalovirus, *Entamoeba histolytica*, tuberculosis
Ischemia	

FURTHER EVALUATION OF WATERY DIARRHEA

The differential diagnosis of watery diarrhea is quite broad (Table 5). The key distinction between secretory diarrhea and osmotic diarrhea can be made by analyzing stool electrolyte concentrations and calculating the fecal osmotic gap [14]. A large, positive osmotic gap indicates an osmotic diarrhea due to ingestion of a poorly absorbed substance, such as magnesium salts, lactose in a patient with lactase deficiency, or polyethylene glycol (PEG). A negative osmotic gap suggests ingestion of sulfate or phosphate salts. If an osmotic diarrhea is detected, further analysis of stool can suggest the identity of the poorly absorbed ingested substance. Carbohydrate malabsorption is associated with stool pH < 6 due to fermentation of malabsorbed carbohydrate to short-chain fatty acids. High concentrations of PEG, magnesium, sulfate, or phosphate will be found in stool water when those substances are the culprits. Diarrhea with a small osmotic gap suggests a secretory diarrhea, which may be due one of many conditions (Table 5).

Food intolerances may be responsible for diarrhea in many patients, and should be suspected when diarrhea intensity fluctuates from day to day [15]. There is been great interest lately in poorly absorbable, fermentable carbohydrates, which may reach the colon and produce diarrhea, gas, and bloating by several potential mechanisms. Carbohydrate can be fermented to short-chain fatty acids, which can contribute to osmotic activity and a low fecal pH, if not absorbed by the colon mucosa or buffered by bicarbonate. This process also might stimulate peristalsis by

producing colon distention due to osmotic shifts of water and gas production. Symptoms of IBS-D can be mitigated by ingestion of a diet low in fermentable carbohydrates (low FODMAPs diet) [16]. Food intolerance also may be due to ingredients added to food, such as artificial sweeteners (e.g., sorbitol), or food allergy. Obtaining a food and symptom diary may shed light on the possibility of food intolerance. The physician should look back a few hours in time from the onset of loose stools to identify inciting foods. True food allergy often is associated with other acute allergic symptoms, such as urticaria, swelling of the mucous membranes of the mouth, or skin rash, and is felt to be an unusual cause of chronic diarrhea [17]. It has been estimated that non-allergic food intolerances may account for symptoms in at least 20% of patients with IBS-D [6, 15, 16, 18].

Microscopic colitis (lymphocytic or collagenous colitis) is a common cause of chronic secretory diarrhea and may be identified in up to 5–10% of IBS-D patients [13, 19, 20]. The only way to make this diagnosis is by obtaining mucosal biopsy specimens from the colon. Inflammatory markers, such as elevated serum CRP or fecal calprotectin, are not uniformly present; gross appearances of the colonic lining typically are normal. This means that is essential to obtain colon biopsy specimens in any patient with watery diarrhea who is undergoing colonoscopy or sigmoidoscopy. Multiple specimens should be obtained from the part of the colon proximal to the rectum to increase the likelihood of making an accurate diagnosis.

Another condition that can cause secretory diarrhea is bile acid malabsorption (BAM) [21–23]. This occurs when excess conjugated bile acid enters the colon and reaches a concentration of 3–5 mM. This reduces mucosal sodium absorption and may stimulate chloride secretion, producing watery secretory diarrhea. BAM can occur with ileal resection or disease (type 1), idiopathic BAM due to overproduction of bile acids by the liver or mutations in the ileal bile acid transporter (type 2), or various gastrointestinal diseases, such as small bowel bacterial overgrowth, cholecystectomy, and celiac disease (type 3). Diagnosis can be made by measuring excess fecal bile acid excretion in a timed stool collection [24], whole-body retention of radiolabeled SeHCAT (available in Europe and Canada) [25, 26], increased serum levels of C4 (7α-hydroxyl-4-cholesten-3-one) [27], or low serum levels of fibroblast growth factor 19 [28, 29]. Studies in patients with chronic idiopathic diarrhea or IBS-D suggests that up to 40% may have BAM as the mechanism for their diarrhea [25]. Bile acid-induced diarrhea responds well to bile acid sequestrants, such as cholestyramine, colstipol, and colesevelam with good long-term results in patients able to tolerate these agents [30–32]. When diagnostic tests for BAM are not available, an empiric trial of bile acid sequestrants showing improvement in diarrhea may support the diagnosis. Farnesoid X receptor agonists, such as obeticholic acid, are being studied and may also have a role in mitigating diarrhea in this condition [33].

Although the classical description of diarrhea with small intestinal bacterial overgrowth (SIBO) includes malabsorption with steatorrhea, it is likely that less dense overgrowth may be associated with watery diarrhea [34]. Some have claimed that this is a very common cause of IBS-D, but more recent studies suggest a lower, but still substantial prevalence of roughly 23–45% when stricter criteria are employed [35]. In part, this is due to limitations in our testing strategy for bacterial overgrowth. The classic form of SIBO with malabsorption is associated with $>10^5$ colony-forming units/mL on quantitative culture of proximal jejunal aspirate and positive glucose breath hydrogen tests in >80% of patients. Less dense or more distal bacterial overgrowth has been implicated in patients with IBS-D. In this situation, SIBO may not be severe enough or proximal enough to cause steatorrhea. SIBO has been diagnosed in IBS-D largely by lactulose breath hydrogen tests, which can be confounded by rapid small bowel transit or vagaries of the testing protocol [36]. Newer versions of breath tests for SIBO that use different substrates or simultaneous measurement of small bowel transit may improve the accuracy of the tests and their ability to predict responsiveness to antibiotic therapy [37].

Disordered motility, such as seen with diabetic autonomic neuropathy or post-vagotomy diarrhea, also may contribute to chronic diarrhea or IBS-D. Slow transit may predispose to SIBO and rapid transit may lead to intestinal hurry with incomplete absorption of fluid and nutrients in the small intestine [38–40]. Common endocrine diseases, such as hyperthyroidism and Addison's disease, also may affect motility, but also can produce diarrhea due to concurrent autoimmune enteropathy. Other systemic illnesses, such as vasculitis, may be associated with diarrhea through a number of mechanisms.

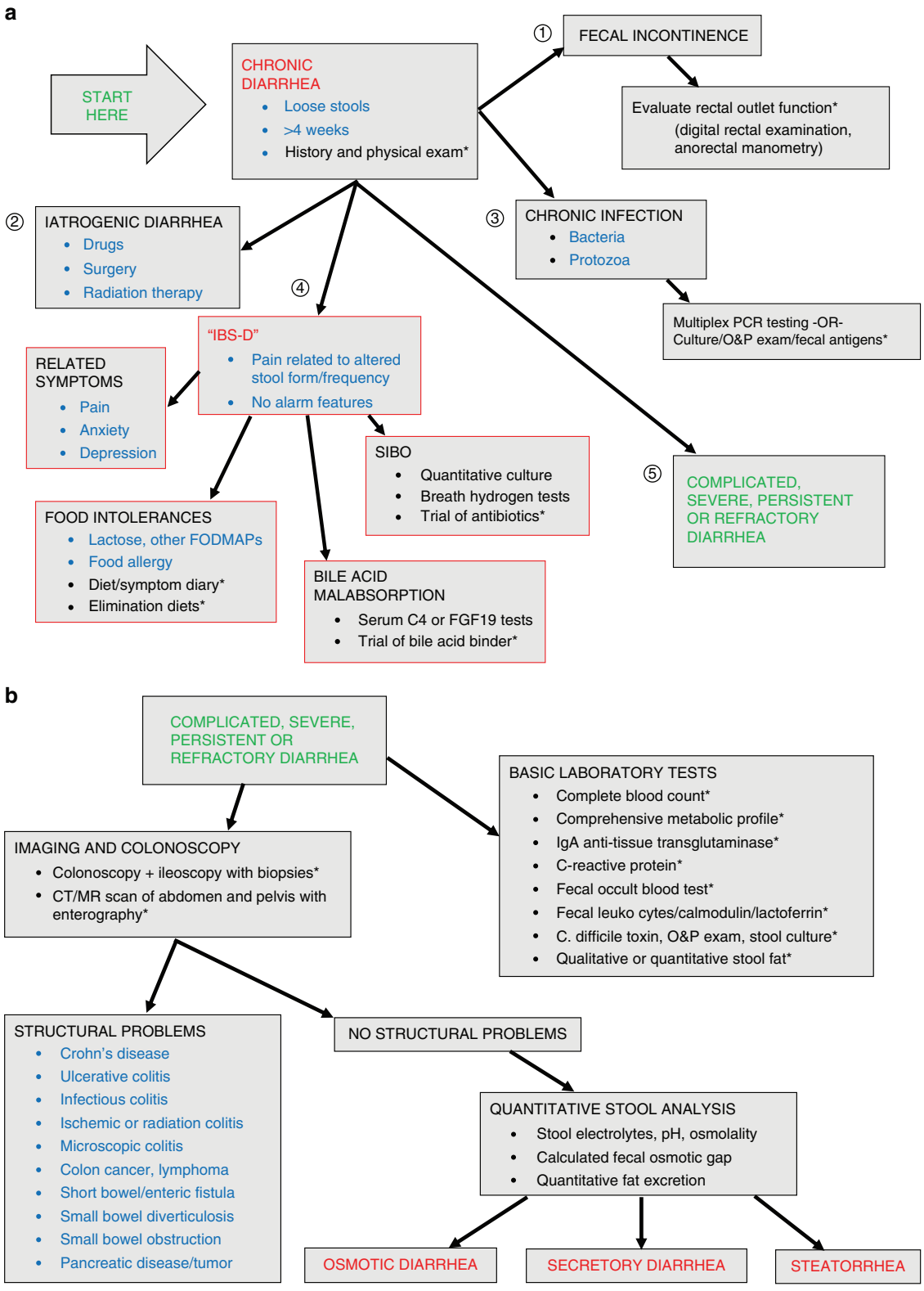
Gastroenterologists often consider endocrine tumors as a cause of watery diarrhea, but these are very rare. Testing should be limited to patients with chronic diarrhea that remains unexplained after more likely diagnoses have been excluded or those patients with abnormal cross-sectional imaging that suggests the presence of a tumor. If serum peptide levels are obtained in a broad cross section of patients with secretory diarrhea, false positive results will greatly outnumber true positive results [41].

Much more common is diarrhea due to the use or abuse of medications [42]. Diarrhea is a common side effect of many drugs, including proton pump inhibitors, beta blockers, metformin, olmesartan, and mycophenolate mofetil. Review of the patient's drug list is essential prior to instituting a major evaluation for chronic diarrhea. Surreptitious use of laxatives also must be considered in patients with chronic diarrhea. Factitious diarrhea due to laxative ingestion is particularly likely in patients with eating disorders, with secondary gain from illness, and with Munchausen syndrome [43].

A small group of patients with secretory diarrhea can be diagnosed with idiopathic secretory diarrhea once an extensive evaluation is negative [44]. These patients have a history characterized by sudden onset of watery diarrhea, persistence of diarrhea for months or years, and then a gradual return to normal. This may occur sporadically or in epidemics and seems to be related to ingestion of contaminated water or food. No causative organism has been identified despite careful efforts to do so during outbreaks. It does not respond to antibiotics typically used in the treatment of enteric infections and clears spontaneously.

FURTHER EVALUATION OF INFLAMMATORY DIARRHEA

Patients with blood or pus in their stools need further assessment for structural problems. In most cases, evaluation should



continue with cross-sectional imaging of the abdomen (CT or MRI scanning) and colonoscopy with ileoscopy [1]. In most instances, these tests will uncover evidence of inflammatory bowel disease, chronic infections, such as amebiasis or tuberculosis, malignancies, ischemia, or radiation enteritis, if those diseases are present.

FURTHER EVALUATION OF FATTY DIARRHEA

When excess fat is present in the stool, maldigestion or malabsorption is present. Common causes for steatorrhea include exocrine pancreatic insufficiency, decreased luminal bile salt concentration, classical SIBO, and small bowel mucosal diseases, such as

Fig. 1 Road map for the diagnostic evaluation of chronic diarrhea. **a** The initial assessment of patients presenting with chronic diarrhea, defined as having loose stools for at least 4 weeks. Like any road trip, not every road must be taken and not every roadside attraction needs to be visited during the evaluation of chronic diarrhea. Points of particular interest (readily available and useful tests) are indicated with an asterisk (*). First, a detailed medical history and physical examination should be done. Then, patients should be sorted into one of five groups and evaluated appropriately: (1) fecal incontinence should be distinguished from diarrhea and evaluated appropriately. (2) Iatrogenic causes for diarrhea should also be considered, including drugs, previous surgeries, and radiation therapy. (3) Chronic infections should be excluded by culture-independent methods, such as multiplex PCR testing, or by traditional stool culture, ova and parasite examination, and fecal antigen testing. (4) Patients meeting published criteria for irritable bowel syndrome with diarrhea and having no alarm features should be evaluated for common mechanisms of IBS-D, including food intolerances, bile acid malabsorption, and small intestinal bacterial overgrowth. Symptoms related to IBS, such as pain, anxiety, and depression also need attention. (5) Patients with alarm features, complicated, severe, persistent, or refractory diarrhea need further evaluation. **b** More detailed assessment, focused on basic blood and stool tests, imaging, and colonoscopy with biopsies. Structural problems can be identified by these tests and managed appropriately. If no structural problem is identified, quantitative stool analysis can help to categorize the type of diarrhea as osmotic diarrhea, secretory diarrhea, or steatorrhea. **c** The further assessment of each of these categories. Every test need not be done in every patient and care should be taken to review previous evaluations in detail to avoid needless repetition of studies

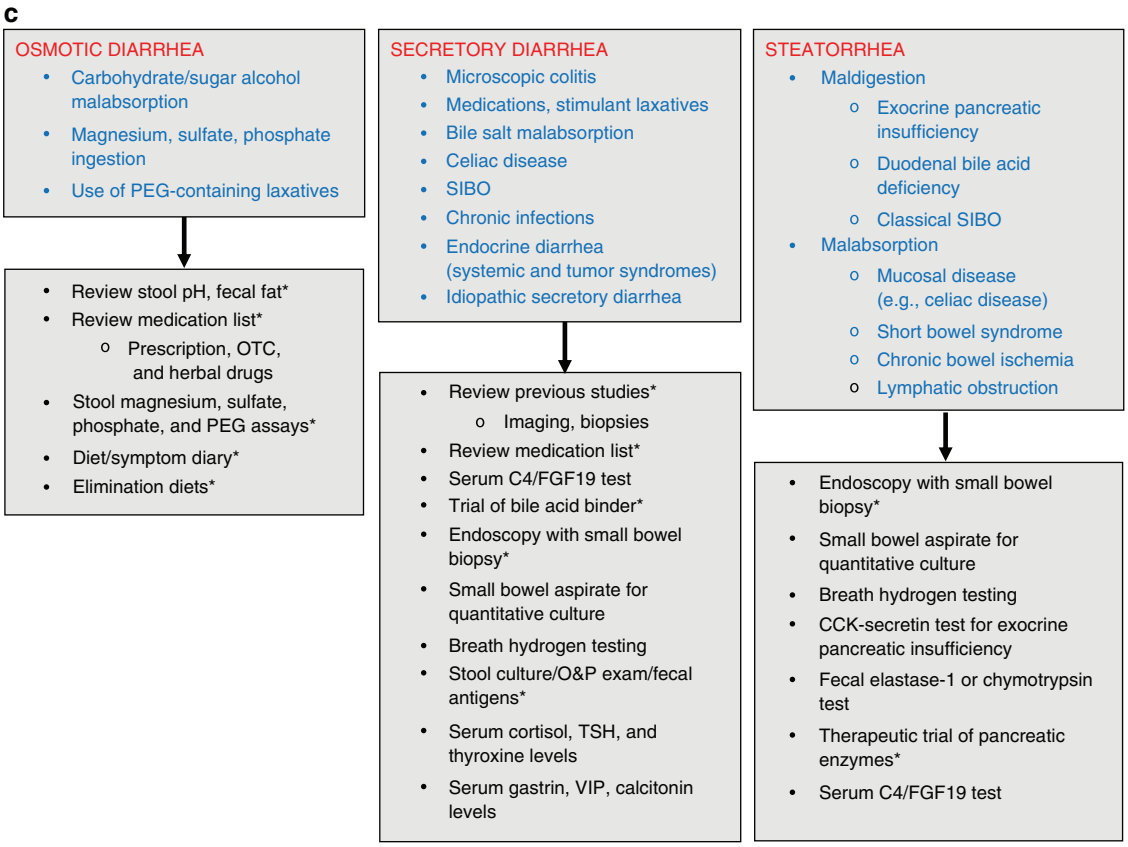


Fig. 1 Continued

celiac disease [45]. Cross-sectional imaging of the pancreas may show evidence of chronic pancreatitis, but does not eliminate the possibility of exocrine pancreatic insufficiency if normal. Indirect tests of pancreatic function, such as fecal elastase or chymotrypsin concentration, are not sufficiently sensitive or specific to make a diagnosis of pancreatic insufficiency, in part because of dilution of the enzymes by excess stool water in some patients, but can be suggestive [1, 46]. Formal pancreatic function testing (e.g., secretin test) is not widely available. Often the diagnosis of exocrine pancreatic insufficiency comes down to a therapeutic trial of pancreatic enzyme replacement therapy. If that is to be done, a sufficiently large dose of exogenous enzyme should be consumed and improvement in steatorrhea should be documented by stool testing. Endoscopy should be considered for most patients with steatorrhea to obtain mucosal biopsies from the small intestine and an aspirate of enteric contents for quantitative culture. With modern high-definition endoscopes mucosal abnormalities often can be appreciated grossly.

ROLE OF BIOMARKERS IN THE DIAGNOSIS OF IBS

Over the last 10 years attempts have been made to develop panels of serum tests that might identify patients with IBS. An initial effort identified 10 biomarkers that might identify organic disor-

Table 6 Differential diagnosis of IBS-D and diagnostic strategies

Diagnosis	Estimated prevalence in IBS-D	References	Diagnostic strategy
Food intolerances	20–67%	[18]	Diet and symptom diary→exclusion diet
Bile acid malabsorption	10–40%	[21–27]	SeCHAT retention, C4 or FGF-19 assay; trial of bile acid sequestrant
Small intestinal bacterial overgrowth	23–45%	[35]	Quantitative culture of small intestinal aspirate, breath hydrogen testing; trial of antibiotic therapy
Post-infectious IBS	28–58%	[49, 50]	Anti-cytolethal distending toxin B and anti-vinculin antibody assays
Microscopic colitis	5–10%	[19, 20]	Colon biopsies (from above rectum)
Celiac disease	0.4–4%	[9, 10]	IgA anti-tissue transglutaminase antibody and total IgA assays; duodenal biopsy
Pancreatic exocrine insufficiency	unknown	[7]	Fecal elastase-1 concentration; trial of pancreatic enzyme replacement
Rapid or slow intestinal transit	unknown	[39, 40]	Scintigraphic or capsule-based transit study

ders. These included cytokines, signaling molecules, inflammatory markers, and serologic tests that have been used to identify patients with inflammatory bowel disease and celiac disease [47]. In principle, if the tests were positive, organic disease would be more likely, and if the tests were negative, a functional problem would be more likely. A complex pattern-recognition algorithm was generated,which had a good positive predictive value when IBS was likely (95%) and a good negative predictive value when it was unlikely (93%) [47]. Thus, this test served to bolster the clinician's intuitive diagnosis, but only when the pretest probability was very high or very low. It did not help much when the pretest probability was in the intermediate range when it might be most useful clinically.

Another biomarker panel has been developed by Pimentel et al. based on the hypothesis that many patients with IBS-D have post-infectious IBS. Based on elegant animal studies [48] and supportive human studies [49], antibodies against cytolethal distending toxin B (CdtB), a common toxin produced by bacteria that cause acute gastroenteritis, cross-react with vinculin, a protein found in the gastrointestinal mucosa and enteric nervous system. High titers of anti-CdtB or anti-vinculin antibodies were associated with lower probabilities of being normal or having inflammatory bowel disease or celiac disease. High cutoff values were selected to improve the positive predictive value of the test so that physicians could make a confident diagnosis of post-infectious IBS-D, but the trade-off was a low sensitivity with fewer than 50% of all IBS-D patients having a positive test [49]. IBS-C patients had results no different than controls and IBS-M patients had results intermediate between IBS-D and normal controls [50]. Whether this test will minimize the need for additional diagnostic testing in practice or will indicate better responses to one treatment or another is uncertain at present.

A recent meta-analysis [51] and review [52] of these and other biomarkers for the diagnosis of IBS concluded that combinations of clinical criteria and biomarkers seemed to perform better than either approach individually in differentiating IBS from organic disease. A more robust multivariable statistical analysis combining many streams of clinical and laboratory data might perform even better [52], but requires population data and computation programs that do not currently exist.

The availability of tests to look for specific causes of chronic diarrhea is improving. One commercial laboratory has marketed a panel of blood and stool tests that may be useful in evaluating patients with chronic diarrhea. This includes multiplex assays for 14 microbial pathogens, a fecal calprotectin assay, a proprietary C4 assay for BAM, assays for celiac disease, and a high-sensitivity CRP test (personal communication, Prometheus Laboratories, San Diego, CA). The utility and cost-effectiveness of this panel has yet to be demonstrated, but—in theory—it could make the evaluation of chronic diarrhea more efficient.

NONSTANDARD TESTS

More than three dozen proprietary laboratories offer stool, blood, urine, and saliva tests that purport to measure digestive function, microbial ecology, intestinal permeability, and immune status in patients with digestive disorders, chronic fatigue, and other conditions. Most of these tests have not undergone vigorous scientific evaluation, and their utility in diagnosis and management is unproven. Clinicians should insist on evidence of good laboratory practice, reproducibility, established normal values, and clinical meaningfulness before ordering these tests.

SUMMARY

The diagnostic evaluation of chronic diarrhea can be complex, but as new and better diagnostic tests are developed, the evaluation should become simpler. A scheme for evaluating patients with chronic diarrhea is presented in Fig. **1**. All patients presenting with chronic diarrhea should be assessed for the presence of fecal incontinence, chronic infection, and iatrogenic causes for diarrhea, such as drugs, surgery, and radiation therapy. If a complete history and physical examination do not reveal any alarm features and the patient meets published criteria for irritable bowel syndrome, it is unlikely that inflammatory bowel disease or cancer is present, and an interim diagnosis of IBS-D can be made. This

should not be the end of the diagnostic thought process, however. Studies suggest that in aggregate up to 90% of IBS-D patients suffer with food intolerances, BAM, SIBO, or a handful of other defined conditions, such as microscopic colitis and celiac disease, that occur less frequently in this population (Table 6). Better diagnostic tests now allow us to recognize these conditions and provide more focused therapy when they are identified.

Patients with IBS-D with alarm features or patients with complicated, severe, persistent, or refractory diarrhea who do not meet the criteria for IBS-D need a more detailed evaluation. This deeper evaluation relies on basic blood and stool tests, and imaging and colonoscopy to identify structural problems that can cause chronic diarrhea. If no structural problems are identified, quantitative stool analysis can help categorize patients as having osmotic diarrhea, secretory diarrhea, or steatorrhea. This focuses the differential diagnosis on a smaller number of possibilities and usually allows for a definitive diagnosis.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Chronic diarrhea is a common clinical problem with many causes; diagnosis usually requires laboratory, imaging, and endoscopic testing
- ✓ Irritable bowel syndrome with diarrhea also is common; diagnosis of IBS can be made from symptoms alone
- ✓ Tests are now available for many of the mechanisms causing IBS symptoms

WHAT IS NEW HERE

- ✓ The initial evaluations of chronic diarrhea and IBS-D focused on a comprehensive medical history are similar
- ✓ Tests to discover underlying causes of IBS-D are increasingly available and should be considered, allowing treatment of the underlying causes
- ✓ Laboratory and structural assessments can identify the cause of chronic diarrhea in most patients

CONFLICT OF INTEREST

Guarantor of the article: Lawrence R. Schiller.

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