BMJ Best Practice

Evaluation of chronic diarrhea

Straight to the point of care

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Summary

Chronic diarrhea is defined as the presence of ≥3 loose stools per day for more than 4 weeks.[1] Although stool weight has been used in scientific studies, it is not useful in clinical practice, as some patients may have increased stool weight (higher than normal fecal weight of 200 g/day) but normal stool consistency, therefore do not complain of diarrhea.[2] Diagnosis can be challenging as a large number of etiologies present in a similar way and range from benign to life threatening. A systematic method of evaluation, knowledge of the common causes, and an understanding of the local epidemiology are crucial for efficient and effective diagnosis and management of chronic diarrhea.[3] [4]

THEORY

Etiology

Anatomical classification of causes of diarrhea

Colonic causes include:

- Inflammatory bowel disease (ulcerative colitis, Crohn colitis)
- Microscopic colitis (lymphocytic/collagenous/eosinophilic colitis)
- Infective gastroenteritis (bacterial/viral/parasitic)
- Ischemic colitis
- Colonic cancer/infiltrating malignancy
- Graft versus host disease.

Small bowel causes include:

- Celiac disease
- Crohn disease
- Bile salt malabsorption
- Brush border enzyme deficiency
- Small bowel bacterial overgrowth
- Radiation enteritis
- Eosinophilic enteritis
- Lymphoma
- Tropical sprue
- Lymphangiectasia/impaired lymphatic drainage
- Protein-losing enteropathy
- nonsteroidal anti-inflammatory drug enteropathy.

Pancreatic insufficiency causes include:

- Chronic pancreatitis
- Pancreatic carcinoma
- Cystic fibrosis.

Functional:

- Irritable bowel syndrome.

Endocrine causes include:

- Hyperthyroidism
- Diabetes
- Hypoparathyroidism
- Addison disease
- Hormone-secreting tumors (VIPoma, gastrinoma, carcinoid).

Systemic causes include:

- Drug effects
- Alcohol
- Abetalipoproteinemia

- Advanced liver disease
- Common variable immune deficiency
- Amyloidosis.

Finally, miscellaneous causes include:

- Surgical resections (short gut syndrome) or bypass
- Fecal impaction (overflow diarrhea).

Urgent considerations

(See **Differentials** for more details)
Most cases of chronic diarrhea can be evaluated in the outpatient setting; however, certain features require a faster approach.

Red flags

Individuals experiencing rapid weight loss, dehydration, gastrointestinal bleeding, anemia, or severe abdominal pain are more likely to have a serious cause of their diarrhea and should have an expedited evaluation, potentially in an inpatient setting.

Urgency of evaluation and treatment should be based on systemic signs. Any patients with signs of toxicity (tachycardia, dehydration, pyrexia, or hypotension) require urgent assessment. In these cases the patient should be admitted to the hospital for the following:

- Intravenous rehydration and correction of electrolyte imbalances
- Intravenous antibiotics if pyrexial
- Abdominal x-ray to exclude toxic dilatation
- Referral for a surgical consult
- Consideration of rigid or limited flexible sigmoidoscopy, provided no toxic dilatation
- Transfusion if necessary.

Approach

The evaluation of chronic diarrhea can be difficult and effective assessment requires significant clinical acumen. Approach to evaluation is initially for the most common and most serious conditions, adjusting for history and clinical presentation. If the initial evaluation fails to produce an etiology, then diagnosis can be pursued in a systematic fashion in order to search for each differential diagnosis.

Historical and symptomatic considerations

Evaluation begins with a thorough history with attention to symptoms, onset and duration, travel history, concurrent medical problems, diet (e.g., lactose, fructose, gluten, etc.), and medication use.[4] The documentation of stool consistency can be facilitated with the “Bristol stool chart”.[5] [Bristol stool chart] (https://en.wikipedia.org/wiki/Bristol_stool_scale)

The key components of the history include:

- Duration of diarrhea: more than 4 weeks in chronic diarrhea[1]
- Number of episodes per day: ≥3 loose stools per day in chronic diarrhea[1]
- Waking at night with symptoms: makes functional disorders less likely
- Presence of blood in the stool: may signify inflammatory bowel disease (IBD), malignancy, or ischemia.

Associated symptoms can include:

- Weight loss/failure to thrive (e.g., celiac disease, IBD, malignancy, small bowel bacterial overgrowth, chronic pancreatitis, hyperthyroidism, diabetes)
- Abdominal pain (e.g., celiac disease, Crohn disease, malignancy)
- Constipation alternating with diarrhea (e.g., IBD, fecal impaction with overflow)
- Nausea and vomiting (e.g., small bowel Crohn disease, small bowel bacterial overgrowth, diabetes, fecal impaction)
- Hematochezia or melena (IBD, ischemia, malignancy)
- Skin changes (celiac disease, inflammatory bowel disease).

Additional nonspecific symptoms can include:

- Steatorrhea (e.g., pancreatic insufficiency, celiac disease, liver disease, giardiasis)
- Abdominal distention/bloating (nonspecific, but beware irritable bowel syndrome and small bowel bacterial overgrowth)
- Flatulence (nonspecific, but beware irritable bowel syndrome and small bowel bacterial overgrowth)
- Borborygmi (nonspecific)
- Anorexia (nonspecific)
- Increased infections (common variable immune deficiency, HIV).

Medication use causing diarrhea can include:

- Laxative use (may not be volunteered by patient)
- Proton pump inhibitors
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Quinine
- Antibiotics (beware *Clostridium difficile* infection)

- Certain chemotherapies and other cancer treatments.[6]

Physical examination

Physical examination is usually nonspecific.

Key findings are:

- Skin rashes such as dermatitis herpetiformis, erythema nodosum, and pyoderma gangrenosum are consistent with celiac disease or IBD
- Lymphadenopathy or abdominal masses suggestive of infection or malignancy
- Blood on rectal exam, which is highly suggestive of a mucosal lesion such as IBD or malignancy.

Laboratory evaluation

Laboratory testing should be individualized for risk factors for disease. For instance, parasitic diseases are uncommon in North America and Western Europe in the absence of travel history.

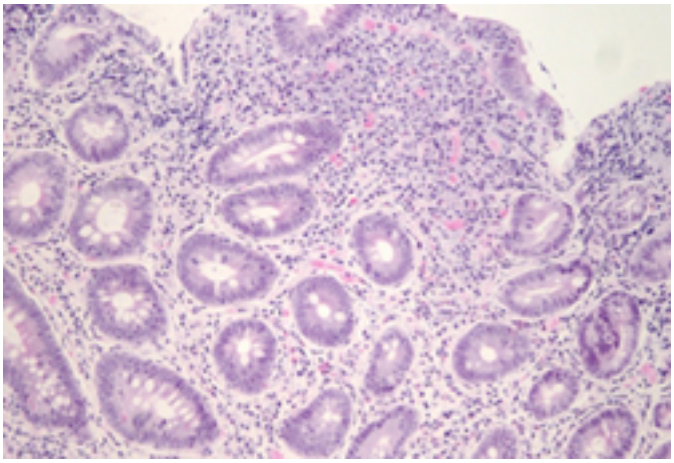
Basic laboratory tests, which are performed in all patients, include CBC, electrolytes, glucose, liver function tests, C-reactive protein, thyroid function tests, celiac serology, IgA level, and hematinics (B12, folate, ferritin). Fecal calprotectin testing may be considered if available. Fecal calprotectin has been shown to consistently differentiate IBD from irritable bowel syndrome because it has excellent negative predictive value in ruling out IBD in undiagnosed, symptomatic patients.[4] [7][8] However, fecal calprotectin can also be elevated in some cases of colorectal cancer, gastrointestinal (GI) infection, or with use of NSAIDs, limiting the test's specificity.[4]

There are few viral or bacterial infections that cause chronic diarrhea in an immunocompetent host, but certain parasites such as *Giardia* are common and should be tested for with a stool sample for microscopy, culture, and sensitivity. The number of stool samples necessary to achieve adequate specificity varies with diagnostic modality. A single sample may be adequate using direct immunofluorescence, whereas 3 samples will be necessary for microscopic examination.

Endoscopic evaluation

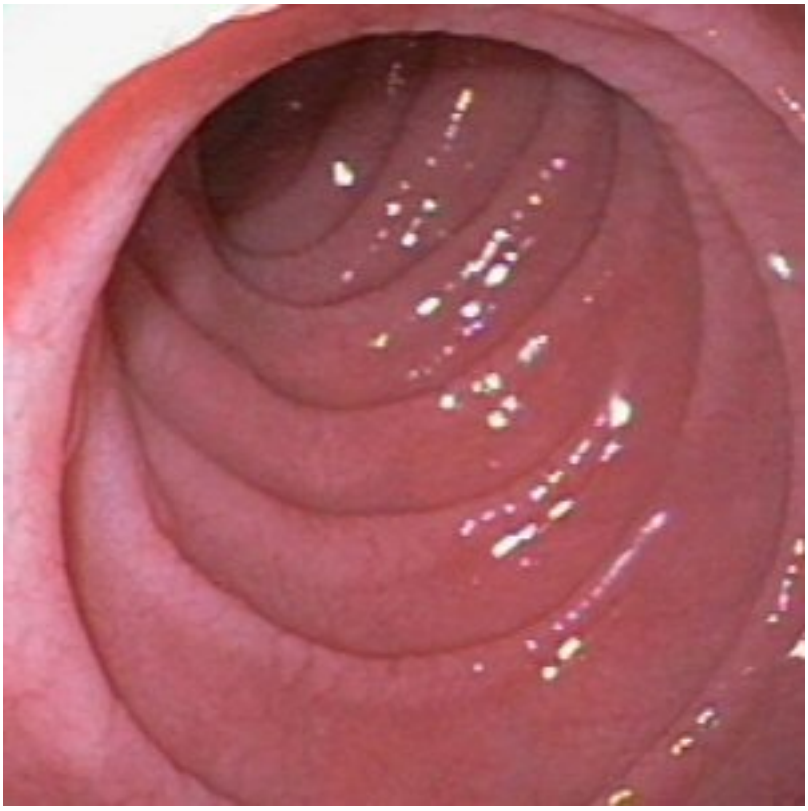
In the evaluation of chronic diarrhea, endoscopy is a valuable diagnostic tool and is often routinely requested unless other pathology is evident that requires treatment, for example, severe constipation (this also makes mucosal disease more unlikely).[9] Endoscopy allows the prompt visual assessment of disease severity and extent in IBD and can provide prognostic information.

Histologic assessment documents the presence of macroscopic and microscopic colitis. Inflammation on colonoscopy can direct future investigations, such as further small bowel evaluation if Crohn disease is suspected. A negative colonoscopy can allow reassurance to be given to patients who may be concerned they have IBD or cancer. If celiac disease is suspected, a gastroscopy with duodenal biopsies can be obtained at the same visit.



Photomicrograph of villous atrophy in celiac disease

Image courtesy of Daniel Leffler, MD and Ciaran Kelly, MD; used with permission



Endoscopic image of scalloping seen in the duodenal mucosa in celiac disease and other mucosal disorders including giardiasis

Image courtesy of Daniel Leffler, MD and Ciaran Kelly, MD; used with permission

Patients with evidence of GI blood loss, anemia, or significant weight loss should undergo urgent endoscopic assessment of the upper GI tract and large bowel.

Differentials overview

Common
Ulcerative colitis
Microscopic colitis (lymphocytic colitis and collagenous colitis)
Viral, bacterial, parasitic, HIV enteropathy
Irritable bowel syndrome
Drug effects
Fecal impaction
Celiac disease
Crohn disease
Bile salt malabsorption
Brush border enzyme deficiency (lactose, fructose, sucrose, isomaltase)
Small intestinal bacterial overgrowth
Pancreatic insufficiency
Alcohol
Hyperthyroidism
Diabetes mellitus
Radiation enteritis/colitis
Eosinophilic enteritis
Chronic ischemic colitis
Surgical bypass or resection
Uncommon
Nonsteroidal anti-inflammatory drug enteropathy

Uncommon

- Infiltrating malignancy
- Protein-losing enteropathy
- Graft versus host disease
- Hodgkin lymphoma
- Non-Hodgkin lymphoma
- Tropical sprue
- Lymphangiectasia/impaired lymphatic drainage
- Hypoparathyroidism
- Addison disease
- Gastrinoma
- Carcinoid tumors
- VIPomas
- Abetalipoproteinemia
- Advanced liver disease
- Common variable immune deficiency
- Amyloidosis

Differentials

Common

◊ Ulcerative colitis

History	Exam	1st Test	Other tests
hematochezia and tenesmus usually significant; diarrhea may be frequent but low volume; recent cessation of tobacco use associated with the onset of active ulcerative colitis; may be a family history[10] [11] [12] [13]	generally nonspecific; extraintestinal manifestations, such as erythema nodosum, pyoderma gangrenosum, uveitis, iritis, episcleritis, and arthritis	»**endoscopy/ colonoscopy with biopsy:** mucosal lesions consistent with colitis and/or enteritis[10] In the absence of granulomas, found in 30% of cases of Crohn disease, the differentiation between ulcerative colitis and Crohn disease is made primarily on clinical grounds and presence of lesions outside the colon. If diagnosis of Crohn disease still needs to be excluded after colonoscopy, further small bowel investigations (contrast study/CT/MRI/capsule endoscopy) may show stricture lesions in the small bowel.	»**abdominal radiograph:** transverse colon ≥6 cm in diameter in toxic megacolon Ordered in patients with acute severe disease to evaluate for toxic megacolon. »**fecal calprotectin:** elevated Has been shown to consistently differentiate inflammatory bowel disease from irritable bowel syndrome.[4] [7][8] However, fecal calprotectin can also be elevated in some cases of colorectal cancer, gastrointestinal infection, or with use of nonsteroidal anti-inflammatory drugs.[4]

◊ Microscopic colitis (lymphocytic colitis and collagenous colitis)

History	Exam	1st Test	Other tests
presence of celiac disease raises concern for lymphocytic colitis; diarrhea frequent and voluminous, may be associated with mild degrees of abdominal pain, weight loss, and	generally nonspecific	»**colonoscopy with colonic biopsies:** collagenous colitis: thickened subepithelial collagenous band >7 micrometer; lymphocytic colitis:	»**IgA-tissue transglutaminase (tTg):** elevated, if celiac disease also present (check local reference values) »**esophagogastroduodenoscopy with duodenal**

Common

◊ Microscopic colitis (lymphocytic colitis and collagenous colitis)

History	Exam	1st Test	Other tests
fatigue[14] [15] [16] [17] [18] [19] [20] [21] [22]		prominent subepithelial lymphocytic infiltrate Colon should appear visually normal.[17]	**biopsies:** increased intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia, if celiac disease also present

◊ Viral, bacterial, parasitic, HIV enteropathy

History	Exam	1st Test	Other tests
onset likely to be acute; may be history of travel, sick contacts, or immunosuppression[23] [24] [25] [26] [27] [28] [29] [30] [31]	usually nonspecific; specific infections may have systemic manifestations (e.g., rash in typhoid)	»**stool cultures with ova and parasites:** positive for pathogenic organisms[24] Multiple studies may be required to increase yield.	»**duodenal biopsy:** positive for pathogenic organisms[28] May be necessary especially in the immunosuppressed patient where organisms such as microsporidium may be found. »**CD4 cell count:** normal or low CD4 counts <200 x 10^6/L may raise suspicion of chronic *Cryptosporidium* infection.[32] Levels are also used to predict the risk of opportunistic infections and guide when to start prophylactic therapy.

◊ Irritable bowel syndrome

History	Exam	1st Test	Other tests
long history of diarrhea, constant or intermittent, without alarm features or night waking; bouts of diarrhea coincide with anxiety/stress,	mild abdominal distention or tenderness; patients may demonstrate hyperalgesia and allodynia (pain with	»**colonoscopy:** normal Should be completed if patient is positive for any "red flag" signs or	»**breath tests for bacterial overgrowth and lactose intolerance:** normal

DIAGNOSIS

Common

◊ Irritable bowel syndrome

History	Exam	1st Test	Other tests
family history of irritable bowel syndrome; bloating, flatulence, and crampy abdominal pain relieved by defecation may be present; diarrhea may coexist with periods of constipation; Rome criteria (set of guidelines that outlines symptoms and applies parameters such as frequency and duration to make possible a more accurate diagnosis) useful when considering irritable bowel syndrome[33] [34] [35]	nonpainful stimuli, e.g., on light palpation or touching the abdominal wall)	symptoms (rapid weight loss, dehydration, gastrointestinal bleeding, anemia, or severe abdominal pain) or if needed according to general colon cancer screening guidelines. »**IgA-tissue transglutaminase (tTG):** normal Recommended in some populations (family history of celiac disease or personal history of other autoimmune diseases, especially type 1 diabetes mellitus or autoimmune thyroid disease) to rule out celiac disease.	Treatment with antibiotics may be considered if positive. »**esophagogastroduodenoscopy:** normal Can rule out celiac disease or *Helicobacter pylori* gastritis. »**fecal calprotectin:** low Has been shown to consistently differentiate inflammatory bowel disease from irritable bowel syndrome in undiagnosed, symptomatic patients.[4] [7][8]

◊ Drug effects

History	Exam	1st Test	Other tests
on a medication that is known to cause diarrhea; typically proton pump inhibitors, nonsteroidal anti-inflammatory drugs, metformin, and quinine; in many cases, patients on multiple medications; possible laxative use/abuse; ingestion of candy sweetened with a nonabsorbable sugar such as sorbitol;[36] [37] [38] [39] time of onset can be very	generally nonspecific	»**trial of discontinuation of suspected medication:** improvement in symptoms upon discontinuation of drug If another cause is suggested by the history, then investigations may be necessary while empiric trial of medication	

Common

◊ Drug effects

History	Exam	1st Test	Other tests
variable, so can be difficult to pinpoint offending agent[1] [40] [41]		discontinuation is being tried.	

Fecal impaction

History	Exam	1st Test	Other tests
colonic obstruction due to malignancy or severe motility disorder causing fecal impaction and overflow diarrhea, usually history of severe or worsening constipation; cramping, gas, and abdominal pain common[1]	hard fecal mass may be noted on rectal exam	»**plain abdominal x-ray:** large amount of feces	

◊ Celiac disease

History	Exam	1st Test	Other tests
family history of celiac disease or personal history of other autoimmune diseases, especially type 1 diabetes mellitus or autoimmune thyroid disease; presenting symptoms, especially in adults, are highly variable; classic symptoms include diarrhea, abdominal pain, weight loss, fatigue or lethargy, nausea or vomiting, bloating or excess intestinal gas[42] [43] [44] [45]	nonspecific; dermatitis herpetiformis (a pruritic, vesicular rash over the extensor surfaces) if found, highly suggestive; aphthous mouth ulceration	»**IgA-tissue transglutaminase (tTG):** elevated (>20 units) >95% sensitive and specific, may be negative in patients with IgA deficiency.[45]	»**duodenal biopsy:** increased intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia Required in all cases of elevated IgA-tTG or in cases of high suspicion with a negative IgA-tTG.[45] »**capsule endoscopy:** villous atrophy, mosaic mucosal pattern, scalloping of folds, micronodularity

Common

Crohn disease

History	Exam	1st Test	Other tests
chronic abdominal pain, bloating, and weight loss may occur; family history of inflammatory bowel disease[10] [11] [12] [13]	generally nonspecific; may include distention consistent with a stricture and obstruction, abdominal masses secondary to abscess or phlegmon, abdominal or perirectal fistulae, or skin lesions including erythema nodosum or less commonly pyoderma gangrenosum	»**endoscopy/ colonoscopy with biopsy:** mucosal lesions consistent with colitis and/or enteritis[10] In the absence of granulomas, found in 30% of cases of Crohn disease, the differentiation between ulcerative colitis and Crohn disease is made primarily on clinical grounds and the presence of lesions outside the colon.	»**small bowel follow through:** strictures, lesions in small bowel »**capsule endoscopy:** inflammation, ulceration »**fecal calprotectin:** elevated Has been shown to consistently differentiate inflammatory bowel disease from irritable bowel syndrome.[4] [7][8] However, fecal calprotectin can also be elevated in some cases of colorectal cancer, gastrointestinal infection, or with use of nonsteroidal anti-inflammatory drugs.[4]

◊ Bile salt malabsorption

History	Exam	1st Test	Other tests
surgical history of resection of a section of ileum usually >50 cm; can occur in the absence of surgery and ileal disease (termed idiopathic bile salt malabsorption, it is believed to be due to abnormalities of the apical bile salt transporter located in ileal enterocytes)[1] [46] [47] [48] [49] [50] [51]	surgical scars on abdomen may be present	»**75-selenium-23-selena-25-homotaurocholic acid test (SeHCAT):** abnormally low retention level at 7 days is suggestive of bile salt malabsorption Ranges vary between hospitals.	»**trial of low-fat, medium-chain triglyceride-supplemented diet:** significant and lasting improvement of symptoms suggests cause related to bile salt deficiency or advanced liver disease »**serum 7-hydroxycholesterol:** elevated »**trial of cholestyramine:** diarrhea resolves

DIAGNOSIS

Common

◊ Brush border enzyme deficiency (lactose, fructose, sucrose, isomaltase)

History	Exam	1st Test	Other tests
diarrhea often occurs along with bloating, cramping, and gas; onset usually within 1 hour of ingesting offending substance; only lactose is typically easily identifiable as discrete exposures; symptoms often gradual, becoming increasingly severe in early adulthood; may present more suddenly after an acute insult (infectious gastroenteritis)[52] [53] [54]	usually nonspecific; signs of weight loss and anemia should not be present	»**diet record with elimination diet:** prompt resolution of symptoms with avoidance of offending substance	»**hydrogen breath testing:** rise of >20 ppm from baseline within 2 hours after the suspected offending sugar is ingested Demonstrates bacterial fermentation rather than host digestion of the tested sugar.[54] »**lactose tolerance test:** precipitation of symptoms by lactose ingestion Less sensitive and specific than breath testing.[54]

◊ Small intestinal bacterial overgrowth

History	Exam	1st Test	Other tests
history of diabetes, past surgery, celiac or Crohn disease; typical symptoms are bloating, gas, cramping, and mild to moderate diarrhea[1] [55] [56] [57] [58]	generally nonspecific	»**breath test:** a rise of >20 ppm of hydrogen or methane (or both) within 90 minutes is considered a positive result Bacterial fermentation of nondigestible sugars in the colon produces hydrogen and methane. If fermentation occurs in the small intestine, a rise in hydrogen and methane occurs earlier.[59] False positive tests can occur if gastrointestinal transit is rapid.[60]	

Common

◊ Small intestinal bacterial overgrowth

History	Exam	1st Test	Other tests
		Sensitivity is 42.0% to 54.5% and specificity is 70.6% to 83.2%.[61] Evidence for breath testing is contradictory, but recommended before antibiotic use in patients with weaker risk factors (e.g., proton pump inhibitor use, diabetes, gastroparesis). »**therapeutic trial of antibiotics:** significant and lasting improvement of symptoms suggests small intestinal bacterial overgrowth Recommended first-line by UK guidelines because of poor sensitivity and specificity of breath test.[4] Also used if breath testing not available and other etiologies ruled out.[57]	

◊ Pancreatic insufficiency

History	Exam	1st Test	Other tests
history of pancreatitis, alcohol misuse, or cystic fibrosis; onset typically gradual but progressive[1] [62] [63] [64]	generally nonspecific	»**fecal elastase:** positive if approximately ≤200 micrograms/g 70% to 90% sensitive and specific. This is a direct test of pancreatic enzyme production. Low level is suggestive of overall	»**fecal chymotrypsin:** positive if approximately ≤6 units/g 50% to 70% sensitive and specific. This is a direct test of pancreatic enzyme production. Low level is suggestive of overall

Common

◊ Pancreatic insufficiency

History	Exam	1st Test	Other tests
		pancreatic exocrine insufficiency.[63] Cutoff level is approximate as some patients with lower values will not have malabsorption and others with higher levels will develop symptoms.	pancreatic exocrine insufficiency.[64] Cutoff level is approximate as some patients with lower values will not have malabsorption and others with higher levels will develop symptoms. »**MRI abdomen:** may reveal pancreatic calcifications This result is suggestive of chronic pancreatitis, which is a leading cause of pancreatic insufficiency; it is not diagnostic for pancreatic insufficiency itself. »**CT abdomen:** may reveal pancreatic calcifications This result is suggestive of chronic pancreatitis, which is a leading cause of pancreatic insufficiency; it is not diagnostic for pancreatic insufficiency itself. »**ultrasound of pancreas:** may reveal pancreatic calcifications This result is suggestive of chronic pancreatitis, which is a leading cause of pancreatic insufficiency;

Common

◊ Pancreatic insufficiency

History	Exam	1st Test	Other tests
			it is not diagnostic for pancreatic insufficiency itself. »**therapeutic trial with pancreatic enzyme replacement:** significant and lasting improvement of symptoms suggests pancreatic insufficiency Necessary to exclude other etiologies.

◊ Alcohol

History	Exam	1st Test	Other tests
history of excessive alcohol ingestion	smell of alcohol present or intoxication evident; clinical features of liver disease (e.g., jaundice, spider angiomata, Dupuytren contractures, palmar erythema, gynecomastia, ascites)	»**blood alcohol level:** may be elevated »**LFTs:** all parameters may be elevated	»**hepatic ultrasound:** may show hepatomegaly, fatty liver, liver cirrhosis, liver mass, splenomegaly, ascites, evidence of portal hypertension

◊ Hyperthyroidism

History	Exam	1st Test	Other tests
may be history of other autoimmune disease, increased appetite, weight loss, heat intolerance, and hair loss[65] [66] [67]	fine tremor, goiter, exophthalmos, tachycardia, or hypertension in severe cases	»**thyroid stimulating hormone:** suppressed Thyroid stimulating hormone should be the initial test; if this is borderline or suppressed, additional testing such as free thyroid hormones should be requested.[67]	»**free thyroid hormones:** increased »**thyroid radioactive iodine or technetium-99 uptake scan:** diffuse increased uptake in Graves disease, reduced uptake in subacute thyroiditis

Common

◊ Diabetes mellitus

History	Exam	1st Test	Other tests
history diabetes mellitus usually known; nausea and early satiety may be present (indicating gastroparesis, suggesting long-standing diabetes); chronic diarrhea is uncommon as presenting symptom of new-onset diabetes[68] [69] [70]	generally nonspecific; in patients with diabetes, neuropathy, nephropathy, retinopathy are often present by the time gastrointestinal (GI) symptoms manifest	»**HbA1c:** 48 mmol/mol (6.5%) or greater »**plasma glucose:** elevated »**motility studies: gastric emptying, small intestinal transit time, colonic (sitz marker study, anorectal manometry):** evidence of abnormally fast or slow intestinal transit In a patient meeting Rome II or III criteria who does not have worrisome symptoms such as GI bleeding, weight loss, new-onset symptoms, or routine laboratory abnormalities, further testing is generally not necessary prior to empiric therapy.[35]	

◊ Radiation enteritis/colitis

History	Exam	1st Test	Other tests
significant radiation exposure to the abdomen, most commonly for prostate cancer in men and uterine cancer in women; hematochezia common[6] [71] [72]	generally nonspecific	»**fecal occult blood test:** may be positive Small bowel radiation enteritis may produce a positive result, while radiation to the colon commonly causes hematochezia making occult blood testing unnecessary. »**colonoscopy:** loss of normal mucosal	»**small bowel follow through:** areas of thickening, stenosis, adhesions, and occasional fistula Useful though not diagnostic in primary small bowel disease with normal colonoscopy and endoscopy.

Common

◊ Radiation enteritis/colitis

History	Exam	1st Test	Other tests
		vasculature markings with friability and telangiectasia Pathology is typically nondiagnostic and diagnosis is made on clinical grounds.	

◊ Eosinophilic enteritis

History	Exam	1st Test	Other tests
any area of gastrointestinal tract may be involved, symptoms nonspecific and variable including abdominal pain, nausea, vomiting, and diarrhea; patient may have history of other allergic conditions including food sensitivities[73] [74] [75] [76] [77] [78]	generally nonspecific	»**endoscopy and/or colonoscopy with biopsy:** histology should reveal a thickened submucosa with >20 eosinophils per high-powered field[74] Infections need to be ruled out before diagnosis of eosinophilic enteritis.	»**CT or small bowel follow through:** areas of thickening can occur in any area of the intestinal tract Findings are not specific as these changes may be seen in Crohn disease or malignancy. »**serum eosinophil count:** may be elevated

Chronic ischemic colitis

History	Exam	1st Test	Other tests
older patient with a history of vascular disease and on antihypertensive medications; cramping abdominal pain and mild to severe hematochezia common[79] [80] [81]	generally nonspecific; abdominal tenderness may be present and blood may be seen on rectal examination	»**colonoscopy:** mucosal congestion/hemorrhage in the area of the splenic flexure Biopsy is nonspecific and may include hemorrhage, thrombosis, crypt destruction, and granulation.	»**CT abdomen/pelvis:** thickening of the colon in the area of the splenic flexure Diffuse vascular calcifications also support this diagnosis.

Common

◊ Surgical bypass or resection

History	Exam	1st Test	Other tests
history of major gastrointestinal surgery; diarrhea from short gut syndrome due to long length resections or due to dumping syndrome in which the primary disorder is of motility[82] [83] [84] [85]	scars should be notable on the abdomen from prior surgery; otherwise, exam is generally nonspecific	»**no initial test:** diagnosis is based on history Typically no diagnostic test is necessary; however, other disorders such as bacterial overgrowth should be considered.	»**vitamin B12 levels following ileal resection:** low Depending on the area resected, nutritional deficiencies may be present; ileal resections can result in vitamin B12 deficiency. »**serum iron following large duodenal/jejunal resection:** low Large duodenal/jejunal resection may lead to iron or fat malabsorption.

Uncommon

◊ Nonsteroidal anti-inflammatory drug enteropathy

History	Exam	1st Test	Other tests
may be on Nonsteroidal anti-inflammatory drugs (NSAIDs) for any length of time prior to onset of symptoms; may present like inflammatory bowel disease with watery or bloody diarrhea[40] [86] [87] [88] [89]	generally nonspecific	»**endoscopy/colonoscopy:** absence of specific findings This test should be performed because alternate diagnoses need to be ruled out.	»**capsule endoscopy:** may reveal mucosal abnormalities/erosions »**cessation of NSAID:** resolution of symptoms within 2 to 4 weeks Resolution of symptoms is suggestive of NSAID enteropathy.

Infiltrating malignancy

History	Exam	1st Test	Other tests
rapid weight loss common; may be symptoms	usually nonspecific; cachexia and signs of	»**CT abdomen/pelvis:** may reveal mucosal	»**endoscopy/colonoscopy:** may be targeted for biopsy

DIAGNOSIS

Uncommon

Infiltrating malignancy

History	Exam	1st Test	Other tests
of anemia (e.g., fatigue, dizziness); hematochezia and/or pain may also be present depending on size and location of the lesions[1] [90] [91]	anemia (e.g., pallor) may be present	thickening or mass lesion	if lesion seen on prior imaging

◊ Protein-losing enteropathy

History	Exam	1st Test	Other tests
leg swelling, abdominal pain, weight loss, rectal bleeding, history immune deficiency with recurrent infections; history of the underlying disease (connective tissue disease, amyloidosis, congestive heart failure, constrictive pericarditis, ulcerative colitis)[92]	cachexia, pallor, edema; features of underlying disease (connective tissue disease, amyloidosis, congestive heart failure, constrictive pericarditis, ulcerative colitis)	»**stool alpha-1-antitrypsin:** present	»**endoscopy/colonoscopy:** evidence of underlying mucosal disease

Graft versus host disease

History	Exam	1st Test	Other tests
history of prior allogenic bone marrow transplant; may occur more than 1 year post-transplant; other manifestations, such as dermatitis and liver involvement, typical in patients who develop intestinal involvement[93] [94] [95]	generally nonspecific; patients will often have a maculopapular skin rash that may progress to generalized erythroderma and in severe cases bullous formation with desquamation	»**biopsy of affected area (skin/liver/intestine):** active colitis or enteritis with increased crypt apoptosis, degenerated crypts, and epithelial regeneration If diagnosis is confirmed in skin or liver, and symptoms are typical, intestinal biopsy need not be pursued in all situations.[95]	

Uncommon

◊ Hodgkin lymphoma

History	Exam	1st Test	Other tests
abdominal pain, nausea, vomiting, weight loss, anemia, fever, night sweats; history prolonged celiac disease, or clinical relapse of celiac disease after prolonged period of good response to gluten avoidance[96]	nonspecific; occasionally cachexia, pallor, lymphadenopathy, rash	»**CT scan:** staging tool; may show a mass, lymphadenopathy, or metastases »**lymph node biopsy:** diagnostic histology	»**endoscopy/ colonoscopy:** may show ulceration, nodules »**polymerase chain reaction:** clonal Ig and T-cell receptor gene rearrangement »**capsule endoscopy:** abnormal mucosal features »**deep small bowel biopsy:** diagnostic histology

◊ Non-Hodgkin lymphoma

History	Exam	1st Test	Other tests
abdominal pain, nausea, vomiting, weight loss, anemia, fever, night sweats; history prolonged celiac disease, or clinical relapse of celiac disease after prolonged period of good response to gluten avoidance[96]	nonspecific; occasionally cachexia, pallor, lymphadenopathy, rash	»**CT scan:** staging tool; may show a mass, lymphadenopathy, or metastases »**lymph node biopsy:** diagnostic histology	»**endoscopy/ colonoscopy:** may show ulceration, nodules »**polymerase chain reaction:** clonal Ig and T-cell receptor gene rearrangement »**capsule endoscopy:** abnormal mucosal features »**deep small bowel biopsy:** diagnostic histology

◊ Tropical sprue

History	Exam	1st Test	Other tests
residence or travel for longer than 1 month in endemic area, primarily south and south-east Asia and the Caribbean; steatorrhea and weight loss are	generally nonspecific	»**stool culture and serologic testing for infections:** negative for common pathogens Infectious diarrhea must be ruled out in all cases of suspected	»**endoscopy with duodenal biopsy:** macroscopic scalloping may be seen; histology reveals villous blunting, crypt hyperplasia, and increased intraepithelial lymphocytes

Uncommon

◊ Tropical sprue

History	Exam	1st Test	Other tests
often present[97] [98] [99]		tropical sprue for common pathogens including Giardia, entamebae, and cryptosporidium.[97] Testing should be directed according to local infectious epidemiology.	Villous atrophy is generally less severe than celiac disease, and generally affects individuals not predisposed to celiac disease. However, differentiation between the 2 disorders often requires serologic testing for celiac disease, and occasionally therapeutic trial of treatment for tropical sprue.[98]

◊ Lymphangiectasia/impaired lymphatic drainage

History	Exam	1st Test	Other tests
diarrhea with or without steatorrhea and nausea/vomiting in childhood or early adulthood; may be history of infection (e.g., tuberculosis), lymphoma, cardiac disease, or use of certain chemotherapeutic agents; easy bruising or night blindness may be noted[100]	peripheral edema may be present	»**alpha-1 antitrypsin excretion in 24-hour stool collection:** >24 mL/day without diarrhea or >56 mL/day with significant diarrhea Can be falsely negative in acid hypersecretory states.	»**CT scan with lymphangiography:** imaging constant with intestinal lymphangiectasia

◊ Hypoparathyroidism

History	Exam	1st Test	Other tests
fatigue, poor sleep, myalgias, unsteady gait, anxiety, depression, memory loss, constipation,	hyper-reflexia, tetany, surgical scars of thyroidectomy	»**serum intact parathyroid hormone:** low »**serum calcium:** low	»**bone radiography:** hyperostosis, soft tissue calcification

Uncommon

◊ Hypoparathyroidism

History	Exam	1st Test	Other tests
muscle cramps, paresthesias, abdominal pain; may be a history of osteopenia or osteoporosis and kidney stones		»**serum phosphate:** low or normal	»**brain CT:** may show basal ganglia calcification

◊ Addison disease

History	Exam	1st Test	Other tests
fatigue, weakness, weight loss, anorexia	skin hyperpigmentation, hypotension, hair loss in females	»**synthetic ACTH stimulation test:** low basal cortisol and/or failure to raise endogenous cortisol appropriately	»**adrenal CT:** normal or atrophy, calcification, or enlargement due to infiltration »**serum electrolytes:** low sodium, elevated potassium, elevated calcium »**insulin hypoglycemia test:** abnormal

Gastrinoma

History	Exam	1st Test	Other tests
may have history of weight loss or flushing; occurs in syndromes involving other endocrine tumors in family members or multiple tumors in an individual (e.g., multiple endocrine neoplasia syndrome)[66] [67] [101] [102]	hypertension, wheezing indicative of bronchospasm	»**24-hour urinary excretion of 5-hydroxyindoleacetic acid:** >100 mg/day Most useful for carcinoid syndrome. Highly sensitive and specific. »**fasting gut hormone profile:** abnormal Normal ranges: gastrin <40 picomol/L, glucagon <50 picomol/L, neurotensin <100 picomol/L, pancreatic polypeptide <300 picomol/L, vasoactive	»**octreotide scan (somatostatin receptor scintigraphy):** concentration of radioactivity at tumor site Will detect most gastroenteropancreatic neuroendocrine tumors. May be less sensitive for liver lesions and insulinomas.[66] »**gastrin level:** highly elevated Levels >1000 picogram/mL are highly suggestive.[103]

Uncommon

Gastrinoma

History	Exam	1st Test	Other tests
		intestinal peptide <30 picomol/L. However, check with local laboratory as reference intervals may vary.	Secretin stimulation results in paradoxic elevation in gastrin levels with gastrinoma.[101] »**secretin stimulation test:** rise in gastrin level of ≥200 picogram/mL or >50% from baseline within 30 minutes Secretin stimulation results in paradoxic elevation in gastrin levels with gastrinoma. »**glucose and electrolytes:** variable

Carcinoid tumors

History	Exam	1st Test	Other tests
may have history of weight loss or flushing; occurs in syndromes involving other endocrine tumors in family members or multiple tumors in an individual (e.g., multiple endocrine neoplasia syndrome)[66] [67] [101] [102]	hypertension, wheezing indicative of bronchospasm	»**24-hour urinary excretion of 5-hydroxyindoleacetic acid:** >100 mg/day Most useful for carcinoid syndrome.[103] Highly sensitive and specific. »**fasting gut hormone profile:** abnormal Normal ranges: gastrin <40 picomol/L, glucagon <50 picomol/L, neurotensin <100 picomol/L, pancreatic polypeptide <300 picomol/L, vasoactive intestinal peptide <30 picomol/L. However,	»**octreotide scan (somatostatin receptor scintigraphy):** concentration of radioactivity at tumor site Will detect most gastroenteropancreatic neuroendocrine tumors. May be less sensitive for liver lesions and insulinomas.[66] »**gastrin level:** highly elevated Levels >1000 picogram/mL are highly suggestive. Secretin stimulation results in paradoxic elevation

Uncommon

Carcinoid tumors

History	Exam	1st Test	Other tests
		check with local laboratory as reference intervals may vary.	in gastrin levels with gastrinoma.[101] »**secretin stimulation test:** rise in gastrin level of ≥200 picogram/mL or >50% from baseline within 30 minutes Secretin stimulation results in paradoxic elevation in gastrin levels with gastrinoma. »**glucose and electrolytes:** variable

VIPomas

History	Exam	1st Test	Other tests
may have history of weight loss or flushing; occurs in syndromes involving other endocrine tumors in family members or multiple tumors in an individual (e.g., multiple endocrine neoplasia syndrome)[66] [67] [101] [102]	hypertension, wheezing indicative of bronchospasm	»**24-hour urinary excretion of 5-hydroxyindoleacetic acid:** >100 mg/day Most useful for carcinoid syndrome. Highly sensitive and specific. »**fasting gut hormone profile:** abnormal Normal ranges: gastrin <40 picomol/L, glucagon <50 picomol/L, neurotensin <100 picomol/L, pancreatic polypeptide <300 picomol/L, vasoactive intestinal peptide <30 picomol/L. However, check with local	»**octreotide scan (somatostatin receptor scintigraphy):** concentration of radioactivity at tumor site Will detect most gastroenteropancreatic neuroendocrine tumors. May be less sensitive for liver lesions and insulinomas.[66] »**gastrin level:** highly elevated Levels >1000 picogram/mL are highly suggestive. Secretin stimulation results in paradoxic elevation in gastrin levels with gastrinoma.[101]

Uncommon

VIPomas

History	Exam	1st Test	Other tests
		laboratory as reference intervals may vary.	»**secretin stimulation test:** rise in gastrin level of ≥200 picogram/mL or >50% from baseline within 30 minutes Secretin stimulation results in paradoxic elevation in gastrin levels with gastrinoma. »**glucose and electrolytes:** variable

Abetalipoproteinemia

History	Exam	1st Test	Other tests
in infancy, diarrhea is associated with poor growth and poor weight gain; later in life poor muscle coordination, ataxia, and visual impairment common[104] [105]	physical exam may reveal ataxia, visual impairment, and other neurologic abnormalities	»**serum beta-lipoprotein:** absent	»**chylomicron level:** low »**MTTP gene testing:** presence of gene mutation

◊ Advanced liver disease

History	Exam	1st Test	Other tests
history of advanced liver disease from any cause including alcohol, fatty liver, autoimmune, and infectious; although the diarrhea associated with advanced liver disease is rarely life threatening, it often portends end-stage liver disease and evaluation and treatment should be expedited[1] [46] [47] [48] [49] [50]	stigmata of chronic liver disease may be present, including spider angioma, palmar erythema, jaundice, and ascites	»**trial of low-fat, medium-chain triglyceride-supplemented diet:** significant and lasting improvement of symptoms suggests cause related to bile salt deficiency or advanced liver disease	

Uncommon

◊ Common variable immune deficiency

History	Exam	1st Test	Other tests
can occur at any age; presence of multiple skin or respiratory tract infections common[106] [107] [108] [109]	generally nonspecific	»**serum Ig levels:** low IgG 700 mg/dL, IgA 70 mg/dL, and IgM 40 mg/dL.[107]	»**duodenal biopsy:** villous atrophy, crypt hyperplasia without increased intraepithelial lymphocytes May be mistaken for celiac disease.[108] Biopsy may also document *Giardia* , which commonly occurs in these patients.

Amyloidosis

History	Exam	1st Test	Other tests
presence of condition associated with developing amyloidosis such as multiple myeloma, chronic inflammatory diseases, and chronic renal failure; gastrointestinal (GI) bleeding, GI obstruction, and motility disorders[110] [111] [112]	generally nonspecific; however, macroglossia, enlargement of the anterior shoulder, ecchymoses, or subcutaneous nodules may be seen[111]	»**urine/serum protein analysis:** presence of monoclonal protein in the serum or urine (Bence Jones proteins)	»**tissue biopsy of duodenal or colorectal mucosa:** apple-green birefringence of amyloid under polarized light May be patchy in distribution. »**fat pad biopsy:** apple-green birefringence of amyloid under polarized light Less sensitive than GI biopsy.

Online resources

1. Bristol stool chart *(external link) (https://en.wikipedia.org/wiki/Bristol_stool_scale)*

Key articles

- Fernández-Bañares F, Esteve M, Salas A, et al. Systematic evaluation of the causes of chronic watery diarrhea with functional characteristics. Am J Gastroenterol. 2007;102:2520-2528. Abstract
- Arasaradnam RP, Brown S, Forbes A, et al. Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. Gut. 2018 Aug;67(8):1380-99. Full text (https://www.doi.org/10.1136/gutjnl-2017-315909) Abstract
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Images

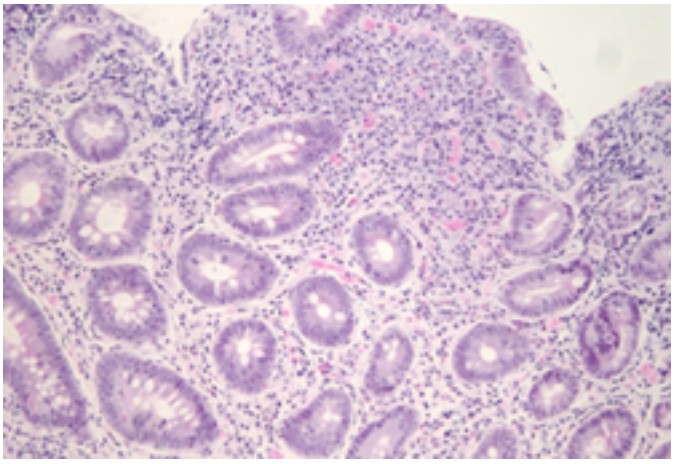

Figure 1: Photomicrograph of villous atrophy in celiac disease

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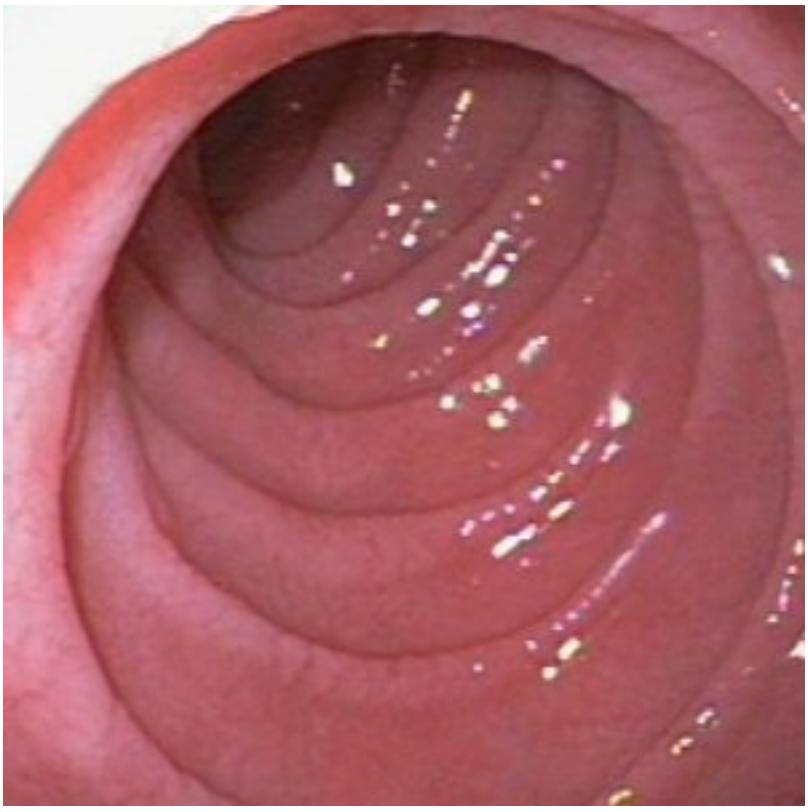

Figure 2: Endoscopic image of scalloping seen in the duodenal mucosa in celiac disease and other mucosal disorders including giardiasis

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Figure 1 – BMJ Best Practice Numeral Style

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

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Contributors:

// Authors:

Simon Campbell, MB ChB(Hons), MRCP(UK), MD(Edin.)

Consultant Gastroenterologist
Honorary Senior Lecturer, University of Manchester, Manchester, UK
DISCLOSURES: SC declares that he has no competing interests.

Rahul Kalla, MBChB, MRCP

Consultant Gastroenterologist
Royal Infirmary Edinburgh, Little France Crescent, Edinburgh, UK
DISCLOSURES: RK is the author of a reference cited in this topic. RK declares that he has no competing interests.

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// Peer Reviewers:

John Kepros, MD

Director
Trauma Services, Assistant Professor, Michigan State University, Lansing, MI
DISCLOSURES: JK declares that he has no competing interests.

Julian R.F. Walters, MA, MB, FRCP

Professor of Gastroenterology
Imperial College London, Hammersmith Hospital, London, UK
DISCLOSURES: JRFW has been a member of advisory boards and has received fees for arranging an educational programme from GE Healthcare, the manufacturer of 75SeHCAT. He is a member of the Health Advisory Network for Coeliac UK.