

Chronic diarrhoea – it happens!

GEORGE ERMERAK BMed, FRACP

CHRISTOPHER POKORNY MB BS, FRACP, FRCP

Diarrhoea that persists beyond a few weeks can be functionally debilitating and an indication of a significant underlying medical problem. A systematic approach to diagnosis involving a thorough history, examination and carefully targeted investigations allows for identification of cause in most cases. Appropriate treatment of the underlying problem is associated with improved outcomes for patients compared with symptomatic management alone.



Chronic diarrhoea is defined as three or more loose or watery stools per day, lasting beyond four weeks, although there is variation in what constitutes chronic diarrhoea in terms of stool consistency, volume and duration of symptoms. It affects approximately 5% of the population at any one time and not only has significant direct health implications for patients but is also associated with functional disability and significant economic cost.¹

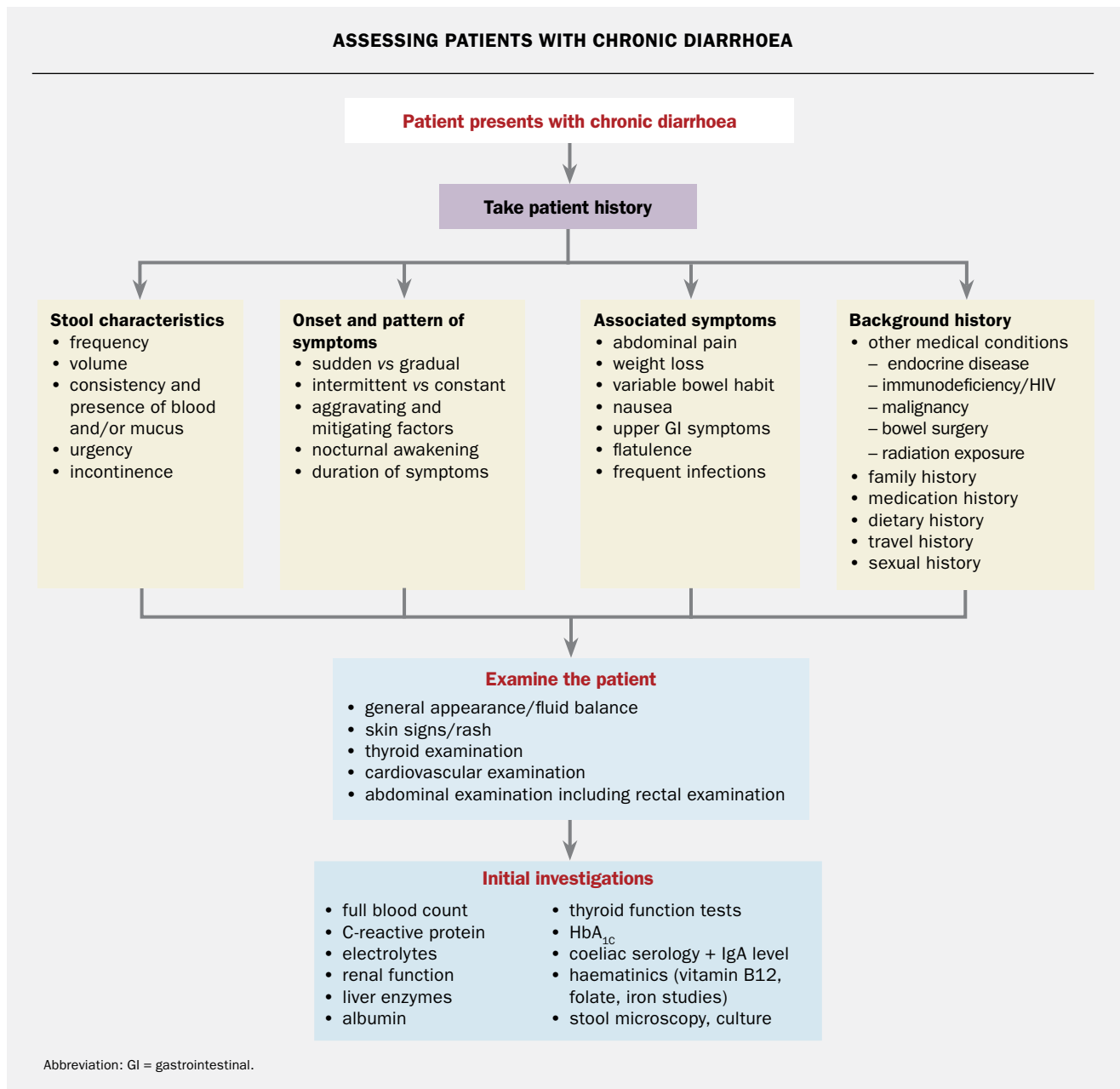
It can be difficult to manage chronic diarrhoea because there are a wide range of potential organic and functional causes with symptom overlap, which need to be distinguished before an accurate diagnosis is made. A thorough assessment focusing on the patient's history is often enough to identify the cause. Targeted investigation based on information from the history and examination can be helpful in diagnosing the underlying problem, although it is important to exclude common causes before pursuing the investigation of rare pathology. Occasionally, referral may be necessary, particularly where there are red flag symptoms, the differential diagnoses remain broad despite a thorough assessment, or when patients fail to respond to therapy. This review proposes a practical step-wise approach to the initial investigation and primary management of patients with chronic diarrhoea (Flowchart).

KEY POINTS

- Chronic diarrhoea is defined as the passage of at least three loose to watery stools per day for more than four weeks.
- Diarrhoea predominant IBS and functional diarrhoea are common, but organic causes need exclusion, particularly in the presence of red flag symptoms.
- Questioning patients on stool consistency, onset and pattern of diarrhoea and associated symptoms can help in diagnosis.
- Taking a thorough patient history, including family and medication history can help identify an underlying cause.
- Referral to a specialist is necessary if a common cause and treatment are not established on initial presentation, if further evaluation is required or if a patient presents with red flag symptoms.
- Treatment should be directed at the underlying cause.
- When an underlying cause of chronic diarrhoea cannot be established, empirical treatment guided by the patient's history may help improve symptoms.

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Dr Ermerak is an Interventional Endoscopy and Luminal Diseases Fellow at the Princess Alexandra Hospital, Brisbane, Qld. Associate Professor Pokorny is a VMO Gastroenterologist at the Sydney Eye Hospital, Sydney; and Conjoint Associate Professor of Medicine, UNSW, Sydney, NSW.



Symptoms of chronic diarrhoea

Although functional diarrhoea and irritable bowel syndrome (IBS) are common causes of chronic diarrhoea (Table 1), underlying organic causes should first be excluded, especially on presentation of red flag symptoms (Box 1). When assessing patients with chronic diarrhoea, it is important to consider the combination of presenting symptoms.

Typical symptom clusters that can help differentiate an underlying cause include:

- bloody diarrhoea, unintentional weight loss, anaemia and nocturnal waking, which suggest an organic cause;
- urgency and small volume stool, especially with blood, often indicate rectal pathology such as a proctitis, colitis or malignancy;

- profuse, watery, non-bloody diarrhoea points to a microscopic colitis (collagenous and lymphocytic colitis) and can only be diagnosed on colonic biopsies;
- pale, malodorous, oily stools, which suggest steatorrhoea as a result of malabsorption. Coeliac disease, bacterial overgrowth and bile salt malabsorption are also

common causes that should be considered.

Patient history

In most cases of chronic diarrhoea, the underlying cause can be established or narrowed to a short list of differential diagnoses based on patient history alone. Because of individual variability in defining diarrhoea, the most important initial element of the history is to clarify the patient's understanding of the term chronic diarrhoea, and establish if they are experiencing faecal incontinence and urgency.

Stool characteristics

Specific questioning about stool characteristics, including stool consistency, volume and frequency can help to identify the underlying cause of chronic diarrhoea; however, patients are often reluctant to discuss details of their bowel movements, and may not give a full or accurate account. Pale, malodorous, oily stools, can indicate malabsorption of fats (steatorrhoea); blood in the stool can indicate an inflammation of the bowel, which is a symptom of inflammatory bowel disease (IBD) or malignancy; profuse watery diarrhoea is suggestive of a microscopic colitis, namely collagenous or lymphocytic colitis. In addition, the duration of symptoms of chronic diarrhoea have a bearing on the possible cause, for example, the differential for diarrhoea that has been ongoing for several years is very different from diarrhoea that has been present for two to three months.

Onset and pattern of symptoms

Establishing the onset and pattern of symptoms can help to differentiate the underlying causes of chronic diarrhoea. For instance, intermittent diarrhoea is more likely to be associated with variable dietary causes or functional disorders, whereas ongoing symptoms are more suggestive of persisting organic pathology; nocturnal waking from diarrhoea is suggestive of an organic cause; urgency and

TABLE 1. CAUSES OF CHRONIC DIARRHOEA WITH ESTIMATED GLOBAL POPULATION PREVALENCE

Causes	Prevalence*
Frequent causes	
Brush border enzyme deficiency	1:4
Irritable bowel syndrome (IBS)	1:10
Coeliac disease	1:100
Bile salt malabsorption	1:100
Inflammatory bowel disease (IBD)	1:250
Hyperthyroidism	1:300
Colorectal cancer	1:300
Medications	n/a
Alcohol	n/a
Chronic infective causes	n/a
Overflow diarrhoea	n/a
Rarer causes	
Microscopic colitis	1:10,000
Pancreatic exocrine insufficiency	1:10,000
Chronic ischaemic colitis	1:10,000
Hypoparathyroidism	1:10,000
Common variable immunodeficiency	1:50,000
Carcinoid syndrome	1:100,000
Gastrinoma	<1:100,000
VIPoma	<1:100,000
Small intestinal bacterial overgrowth	n/a
Protein-losing enteropathy	n/a
Haematological transplant associated graft vs host disease	n/a

Abbreviation: n/a = variable or insufficient data.

* Prevalence is the global for average for most causes, although there are rare exceptions; e.g. coeliac disease is not common in Asia.

small volume stools are symptoms of IBD or a rectal cancer.

Identifying potential aggravating factors can help to further differentiate the underlying cause. The presence of aggravating factors such as diet can suggest an intolerance, whereas stress may indicate irritable bowel.

Associated symptoms

Distinguishing functional bowel disorders (which are highly prevalent) from organic pathology is a common early challenge in diagnosing the underlying cause of chronic diarrhoea. Symptoms associated with chronic diarrhoea can help differentiate the diagnosis and certain symptoms

1. RED FLAG SIGNS AND SYMPTOMS OF CHRONIC DIARRHOEA

- Gastrointestinal bleeding
- Unexplained weight loss
- Anaemia
- Severe abdominal pain
- Systemically unwell/unstable
- Severe malnutrition/dehydration

can indicate a more serious cause. It is therefore important to clarify associated symptoms when assessing patients.

Abdominal pain is a frequent and significant coexisting complaint in patients experiencing chronic diarrhoea and could indicate a range of underlying diagnoses including Crohn's disease, malignancy or irritable bowel syndrome (IBS). Investigating the nature of abdominal pain and its fluctuation with bowel movements can help clarify the diagnosis. For the diagnosis of IBS, as defined by the Rome IV criteria, a patient must have experienced abdominal pain for at least one day a week for the past three months, with two out of three of the following: pain related to defecation, change in stool frequency, or change in stool form or appearance.² Some organic causes of diarrhoea also fit these criteria; however, in the absence of red flag signs (Box 1), or if symptoms are mild, it is reasonable to treat the patient empirically and observe before undertaking further investigations.

Other associated symptoms indicative of a more serious underlying cause include:

- unintentional weight loss (a red flag symptom), which requires further interrogation and could be a sign of an underlying malabsorptive state, increased metabolic activity (for example, in hyperthyroidism) or malignancy;
- alternating periods of constipation and diarrhoea, which could indicate IBS or, rarely, faecal impaction with overflow;
- flatulence, although non-specific,

could be a sign of small bowel bacterial overgrowth in addition to IBS;

- the presence of peripheral arthritis, lower back pain, red eyes and skin ulcers, which raise the possibility of an extraintestinal manifestation of IBD.

Patient background and history

The patient's background, family history and medication history, both prescription and over the counter, need to be questioned when investigating underlying causes of chronic diarrhoea. Diarrhoea accounts for 7% of all adverse drug reactions, thus a thorough history of medications, particularly the temporal association of use to the onset of symptoms, needs to be considered.³ Exposure to laxatives, including weight loss preparations, should also be questioned separately. Patients may not be initially forthcoming about their medication usage, particularly laxative misuse, and may not provide all relevant details. Contributing factors that should be considered when taking the patient's history, including alcohol intake, past illness, surgery, sexual history, travel and family medical history, are summarised in Box 2.

Physical examination

A physical examination of patients suffering chronic diarrhoea should be done on initial presentation. Most findings are not diagnostic but can assist in differential diagnoses of the underlying cause. For instance, on examination:

- pathognomonic findings, such as dermatitis herpetiformis, suggest coeliac disease;
- general findings suggestive of malabsorption can include muscle wasting and peripheral oedema;
- IBD could be suggested by the presence of skin changes (such as erythema nodosum or pyoderma gangrenosum), mouth ulcers, episcleritis, abdominal tenderness or blood on digital rectal examination;

2. CONTRIBUTING FACTORS TO CONSIDER IN PATIENTS WITH CHRONIC DIARRHOEA

- Excessive alcohol intake – alcohol can act as an irritant to the gastrointestinal tract of some people
- Systemic illnesses including endocrine disorders (such as hyperthyroidism or diabetes) and immunodeficiency states (e.g. HIV) predisposing to chronic infection
- Bowel surgery can result in short gut or bile acid malabsorption if the terminal ileum is diseased or resected
- Radiation therapy can present with enteritis
- Medications including NSAIDs, laxatives containing magnesium, oral hypoglycaemic agents especially metformin proton pump inhibitors and antibiotics
- *Clostridium difficile* infection if a patient has recently used antibiotics
- A family history of autoimmune disease could suggest conditions such as coeliac disease, IBD or multiple endocrine neoplasia, which could predispose the patient to neuroendocrine tumours

- facial flushing in the presence of wheezing or a cardiac murmur could be an indication of carcinoid syndrome;
- the presence of a thyroid nodule with tachycardia may indicate hyperthyroidism;
- malignancy might be suggested by the presence of weight loss, abdominal masses or lymphadenopathy.

Initial investigations

Almost all patients with chronic diarrhoea warrant basic baseline laboratory testing including full blood count, C-reactive protein, electrolytes, liver enzymes, serum albumin and renal function analysis. Additional investigations such as haematinics, coeliac serology and endocrine testing are done depending on the clinical situation; HbA_{1c} testing can be considered in patients with poorly controlled diabetes

3. WHEN TO CONSIDER REFERRAL OF A PATIENT WITH CHRONIC DIARRHOEA

- If a patient presents with red flag symptoms (Box 1)
- For conditions requiring long-term management, such as IBD and chronic pancreatic exocrine insufficiency
- Where symptoms present a broad differential with unclear diagnosis
- If there is a need for endoscopic evaluation
- Where there is subjective concern regarding the severity of symptoms

if autonomic neuropathy is suspected as a cause for chronic diarrhoea. In cases of acute diarrhoea, stool testing (microscopy and culture) can be performed to exclude common infectious agents. Stool parasite testing could also be considered in patients who are returned travellers or immunocompromised. Stool calprotectin can help to differentiate IBD from IBS, but the test is not covered by the Medicare rebate.

When to refer

The underlying cause of chronic diarrhoea and a suitable treatment plan are often established after initial assessment; however, there are situations in which specialist consultation should be considered (Box 3). These include the presence of red flag symptoms (Box 1), if there is a need for endoscopic evaluation, to share the management of chronic conditions (such as IBD), in cases where a diagnosis is unclear or if there is concern over symptoms associated with chronic diarrhoea. The diagnosis of some underlying causes including IBD, colorectal malignancy (Figure 1), microscopic forms of colitis, coeliac disease (Figure 2) and laxative use (Figure 3) require a referral for endoscopic assessment. Occasionally, referral is required when the differential diagnosis after initial assessment remains broad and there is no improvement in the patient's signs or symptoms.



Figure 1. Colonoscopy identifying rectal cancer.



Figure 2. Gastroscopy showing the duodenum with scalloping, which is suggestive of coeliac disease.

Further testing and treatment

When a diagnosis is not apparent after initial investigations, distinguishing the stool as fatty, inflammatory or watery in nature can help narrow down the underlying cause. Stool analysis includes stool pH, stool culture, electrolyte analysis, calculation of stool osmotic gap, stool white cell count and stool fat content and composition. Watery diarrhoea accounts for a significant proportion of poorly differentiated chronic diarrhoea cases and can be separated further into secretory or osmotic in nature, although this distinction is infrequently required. If chronic infection has been excluded, as suggested by the absence of growth on serial stool cultures, additional testing to rule out neuroendocrine tumours (Box 2) could include abdominal imaging (including nuclear medicine studies), and hormone and metabolite testing. Neuroendocrine tumours are a rare cause of chronic diarrhoea and may only be incidentally picked up on imaging for other reasons. If patients develop symptoms or signs such as diarrhoea, facial flushing, and new onset hyper- or hypoglycaemia, this is usually because of the release of hormones from the tumour.

Bile acid malabsorption is an underlying cause of watery diarrhoea and is estimated to affect up to 1% of the population at any point in time.⁴ It is common in patients with ileal disease such as

Crohn's disease, and those who are thought to have diarrhoea-predominant IBS, but can also be idiopathic. The condition can be investigated using the ⁷⁵selenium homotaurocholic acid 7-day retention test (SeHCAT). The test involves ingestion of a radioactive synthetic analogue of a naturally occurring bile acid, followed by two nuclear medicine scans, a week apart; retention of less than 15% of the ingested agent at the second scan suggests bile acid malabsorption. Another test for measuring direct levels of faecal bile acid include a 48-hour stool collection. In reality, however, access to these investigations is usually limited and cost prohibitive. Most patients suspected of bile acid malabsorption are given a trial of a bile acid-binding resin such as cholestyramine and assessed for treatment response.

Pancreatic exocrine insufficiency causing chronic diarrhoea can result in steatorrhoea and can be assessed by measuring faecal elastase. However, it is best diagnosed based on a history of chronic pancreatitis rather than stool testing, because faecal elastase is only low in the very late stages of chronic pancreatitis or in significant pancreatic injury with loss of organ function. Inflammatory stool, identified by white cell count analysis, indicates intestinal irritation and in cases of chronic diarrhoea can be a sign of IBD. A raised white cell count in the stool suggests a microscopic colitis.



Figure 3. Colonoscopy showing tiger skin appearance of melanosis coli, which is associated with laxative use.

Empirical treatment

Although identification and treatment of the underlying causes of chronic diarrhoea are associated with improved patient outcomes, it may not always be possible to achieve and patients are often managed symptomatically.⁵ Antidiarrhoeal agents such as loperamide form the mainstay of treatment for undifferentiated non-infectious chronic diarrhoea. They work as a mu opioid receptor agonist and are considered safe, as there is minimal passage across the blood-brain barrier. Although other opioids such as codeine and morphine are potentially more effective, they are not suitable for use in chronic diarrhoea because of the potential for tolerance and misuse.

As mentioned above, an empiric trial of bile acid-binding agents such as cholestyramine is also beneficial for the management of chronic diarrhoea specifically related to bile acid resorption disorders. However, the usefulness of this medication is limited by the fact that it needs to be taken several hours apart from other medications to avoid binding interactions and the formulations are often not well tolerated or palatable. Octreotide is often used for the treatment of diarrhoea associated with neuroendocrine tumours such as VIPomas or

carcinoid syndrome, with variable success, and is available in both short-term and depot release formulations.

A number of other nonspecific measures that may be beneficial when a cause can't be established include:

- reducing excessive fibre and fluid intake
- trial of a bulking agent such as psyllium
- avoiding lactose can be helpful in patients with lactose intolerance
- dietary changes such as a low-FODMAP diet in patients diagnosed with IBS
- antibiotics for small intestinal bacterial overgrowth.

Conclusion

Chronic diarrhoea presents a diagnostic challenge because of variable patient reporting, a wide range of symptomatically overlapping functional as well as organic causes and potential for extensive, expensive investigations before a cause may be found. Patients can experience debilitating symptoms which result in poor health outcomes, functional decline and significant disease associated cost. In most cases however thorough history which guides a focused examination and targeted investigations can identify a diagnosis which results in improved patient outcomes. MT

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