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Mistakes in...

Mistakes in chronic diarrhoea and how to avoid them

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Chronic diarrhoea, lasting more than 3 or 4 weeks, is a common condition with a wide variety of different possible causes. Estimates suggest 5% of the population have experienced chronic diarrhoea and sought medical advice about it. All gastroenterologists see many patients whose principal complaint is frequent, loose stools, and will be aware of investigations that are needed to diagnose serious conditions such as inflammatory bowel disease (IBD) or colorectal cancer (CRC). Most people who present with chronic diarrhoea will not have these conditions and, if less common disorders are not considered, may be given a diagnosis of diarrhoea-predominant irritable bowel syndrome (IBS-D) or perhaps functional diarrhoea.[1] Many different treatments are used for IBS-D and often benefit only a small proportion of patients, leaving many with unmet needs, seeking further investigation, advice and treatment.

Guidelines for the investigation of chronic diarrhoea in adults have recently been updated.[2] These guidelines provide recommendations for investigating most patients who have chronic diarrhoea, and reflect the now greater availability of simple tests such as faecal calprotectin, coeliac serology, lower gastrointestinal endoscopy and tests for bile acid diarrhoea (BAD). The criteria for functional gastrointestinal disorders were revised in 2016 (Rome IV), with modifications made to the definitions of the various functional bowel disorders (FBD).[1] The revised criteria recognise a continuum between functional diarrhoea and IBS-D, and the usefulness of the Bristol stool form scale (BSFS) types 6 and 7 for defining diarrhoea. Approaches to the clinical evaluation of patients are indicated in those articles,[1–2] which provide much of the evidence discussed here, backed up by my clinical experience, highlighting certain mistakes that can be made in the management of chronic diarrhoea.

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Mistake 1 Not taking a clear history

Patients who are complaining of chronic diarrhoea can have a wide range of possible conditions (figure 1) and reaching a diagnosis is not always easy. When assessing a new patient it is crucial to take a full history and not just apply a standard set of investigations. A patient who has a 3-week history of diarrhoea is likely to have a different spectrum of possible diagnoses to one who has a 3-month or a 3-year history of diarrhoea.

The nature of the stool is extremely important, and the BSFS is very helpful in being sure that the patient is experiencing type 6 or 7 stool (figure 2).[3] The clinician needs to be aware that sometimes a patient will say 'diarrhoea' when they actually mean an increased frequency of hard bowel motions. Faecal urgency and incontinence can also be called diarrhoea. Be sure to ask explicitly about these symptoms as patients may be hesitant to admit to them. Documentation of frequency and BSFS type helps assess severity and future response to treatment.

As well as knowing how long the symptoms have been present, being aware of factors associated with their onset can be helpful. Has there been a recent episode of gastroenteritis, perhaps with vomiting?

- Inflammatory bowel disease (IBD)
- Colorectal cancer (CRC)
- Coeliac disease
- Diarrhoea-predominant irritable bowel syndrome (IBS-D) / functional diarrhoea
- Bile acid diarrhoea (BAD)
- Microscopic colitis
- Dietary factors (e.g. lactose, FODMAPs, alcohol, caffeine)
- Immunodeficiency (+/- infections)
- Drugs
- Surgery or radiation
- Small intestinal bacterial overgrowth (SIBO)
- Overflow diarrhoea
- Pancreatic exocrine insufficiency
- + many other rare causes

Figure 1 | Important and/or common causes of chronic diarrhoea. A full list of all causes of chronic diarrhoea – common, infrequent and rare – can be found elsewhere.[2]

Was there travel to an area where frequent, infectious diarrhoea is present? Did symtpoms start after surgery (possibly post-cholecystectomy) or new drugs (such as metformin, antibiotics, or proton pump inhibitors)? Treatments initiated many years before or that have been ongoing for many years can be relevant. Radiation enteropathy, drugs for HIV/AIDS or previous bariatric surgery may be overlooked. Immunocompromised patients, in particular, may have infectious

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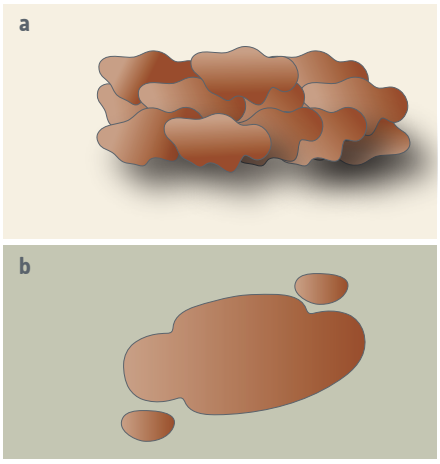

Figure 2 | Bristol stool form scale (BSFS) type 6 and 7 stool. **a** | Type 6 stool is mushy with ragged edges. **b** | Type 7 stool is watery with no solid pieces.

causes. Dietary changes, alcohol intake, and family history of related conditions can all provide clues to the underlying cause of symptoms.[2]

Mistake 2 Failing to investigate in severe, persistent cases

Patients who have severe diarrhoea are often unhappy that, after a few simple tests, they have been told they have IBS and not to worry. Their symptoms persist despite them being given a range of different medical treatments, and they may resort to alternative or complementary therapies. Further investigations should be considered in patients who have severe or persistent symptoms to ensure that a potential treatable diagnosis has not been missed.

Delayed diagnosis of coeliac disease is well recognised. For instance, in a series of 825 coeliac disease patients, 32% reported a diagnostic delay of more than 10 years, despite many having diarrhoea.[4] Serological testing for coeliac disease is now widely available, but it is important to be sure that it has been checked.

In a patient-organised survey of people who were eventually diagnosed with BAD, 44% had experienced symptoms for longer than 5 years and 39% had been told that nothing could be done for them.[5] Tests for BAD will be positive in more than 25% of patients investigated,[6] whereas standard screening tests such as C-reactive protein (CRP) and calprotectin will usually be negative. Furthermore, microscopic colitis will not be diagnosed unless it is specifically looked for.[7]

Clinical judgement is necessary to identify those patients who need further investigations so that no patient should experience undue delay in being diagnosed with coeliac disease, BAD or microscopic colitis.

Mistake 3 Missing colorectal cancer in a young patient

Young patients who have diarrhoea are much more likely to have IBS than anything more serious, but it is possible for diarrhoea in young patients to be caused by CRC. The incidence of CRC under the age of 50 is rising, and about 18% of young patients with CRC present with a change in bowel habit.[8] Unfortunately, most patients who have CRC and are under the age of 40 have been initially told they have IBS and reaching the correct diagnosis of cancer takes much longer than it should. For this reason, clinicians should be sure to ask their patients about, and then follow up on, the 'red flags' of anaemia, rectal bleeding, unintentional weight loss and a family history of CRC.

Measuring levels of faecal calprotectin can be reassuring, but the findings are not definitive. A colonoscopy will definitely make or exclude the diagnosis of CRC and give certainty to the patient and to the doctor. Whatever the guidelines say, clinical judgement should be used to ensure that a colonoscopy is performed if there is any doubt, or there is something unusual about the patient's history.

Mistake 4 Failing to consider bile acid diarrhoea as a common cause of chronic diarrhoea

The prevalence of BAD in patients with chronic diarrhoea is between 25% and 30%, depending on the test used.[6,9] BAD should always be considered because specific treatment exists in the form of bile acid sequestrants. The tests that are used to diagnose BAD are, however, not available in all countries.

The selenium homocholic acid taurine (SeHCAT) test, which looks at 7-day retention, and hence faecal loss, of the ^{75}Se-labelled bile acid, is recognised as the best investigation, and is now available in an increasing number of European countries. A SeHCAT result of less than 5% retention indicates severe bile acid loss, and over 90% of patients with severe bile acid loss will respond to a bile acid sequestrant.[9] Patients who have a SeHCAT result of 5–10% or 10–15% have moderate or mild bile acid loss, respectively, and the majority of these patients will also respond to bile acid sequestrants. An advantage of the SeHCAT test is that it provides an average of bile acid kinetics over 7 days and multiple cycles of secretion and reabsorption. Performing a SeHCAT test results in fewer subsequent investigations and reduces costs.[10,11]

An alternative test, which is becoming increasingly available in countries where the use of the SeHCAT test has not been approved, is to measure levels of the bile acid precursor 7α-OH-4-cholesten-3-one in the blood.[12] Levels of 7α-OH-4-cholesten-3-one are elevated when there is increased loss of bile acids.

Although it is unpopular with patients and laboratory staff, another method to diagnose BAD is to analyse bile acids in faecal collections. Research studies have suggested ways to improve this protocol by quantifying primary bile acids.[13]

Therapeutic trials of bile acid sequestrants can be performed when a definitive test is not available. However, as an individual's response to sequestrants can be very variable, such a trial can be hard to interpret. Frequently, patients have been prescribed a large dose of colestyramine or another sequestrant, which has worsened bloating or pain, even though it has helped the diarrhoea. Many patients do not tolerate the therapeutic trial for long, and the situation then is still unclear. If possible, it is preferable to make a definitive diagnosis, so that subsequent therapy is based on a clear, objective diagnosis. Patients can then be encouraged to find the most effective dose of colestyramine, titrating the anti-diarrhoeal effects against any side effects of pain, bloating or constipation. An alternative bile acid sequestrant such as colesevelam may be more easily tolerated.

Mistake 5 Performing colonoscopy without taking a biopsy sample

Patients who present with chronic diarrhoea are usually considered for colonoscopy (or perhaps flexible sigmoidoscopy depending on age and symptoms) to exclude CRC or IBD. CRC and IBD are important diagnoses and can be recognised by the macroscopic changes seen during colonoscopy. When colonoscopy findings are apparently normal, it is all too easy to tell the patient that there is nothing to worry about. Patients may, however, continue with symptoms and not appreciate that an essential test has not been done.

It is necessary to take colonic biopsy samples and to examine the histology to make the diagnosis of microscopic colitis. When assessing a new patient who describes having previously had a 'normal' colonoscopy, be certain that biopsy samples were taken and reviewed. Around 10% of colonic biopsy samples taken from patients who have diarrhoea show changes of lymphocytic or collagenous colitis–that is microscopic colitis.[2]

Many patients with microscopic colitis (25% overall) are under the age of 45 years; associated conditions or drugs do not need to be present.[2,14] Specific treatment with controlled-release budenoside formulations is very effective for treating the diarrhoea caused by microscopic colitis; all patients with diarrhoea need to be investigated for this so they can then be given appropriate, effective therapy.

Mistake 6 Not recognizing overflow diarrhoea or incontinence

The use of the term 'diarrhoea' by the patient may not just refer to what we recognise as mushy or watery stool types, increased faecal volumes or frequency, and changes in colonic absorption or secretion. It is important to be sure what the patient is describing as their symptoms.

Faecal urgency is frequently described and is related to both colonic transit times and rectal sensitivity. Overflow diarrhoea with faecal loading can be detected on clinical abdominal and rectal examination, and should be considered, especially in those patients who have neurological disorders, or those who describe alternating bowel functions. Imaging and colonic transit studies with markers (or scintigraphy) may help detect slow transit.

Faecal incontinence and anal leakage are worse with watery or soft diarrhoeal stools,[15] but anorectal function can be the primary problem. Evacuation disorders may need further assessment with manometry and different approaches to treatment may be required.[16]

Mistake 7 Providing inadequate or incorrect dietary advice

People who have diarrhoea that is diagnosed as IBS or functional diarrhoea have usually attempted to change aspects of their diet to try and improve their symptoms. They have often followed advice for 'healthy eating' and increased their intake of fruits and vegetables, or fibre in general. Going on a gluten-free diet is another step many people have taken. These changes may have made symptoms worse, rather than producing an improvement. A dietitian with expertise in functional bowel disorders can be particularly helpful in formulating effective dietary advice.

Awareness of foods that are high in fermentable oligosaccharides, disaccharides, monosaccharides and polyols–FODMAPs–is key, because avoiding or reducing their consumption can make a big difference to patients who are suffering from FBD with diarrhoea, bloating, flatulence and other symptoms.[17] Fructose (a monosaccharide) and sorbitol (a polyol [sugar alcohol]) are found in many foods, and various fruits and vegetables are abundant in fructans and galactans (both oligosaccharides). Ask if your patient has already found that consuming chickpeas or lentils makes their diarrhoea worse, and use that to lead into a full discussion and increased awareness of FODMAPs. The benefits of a gluten-free diet for a noncoeliac patient may be due to the reduced intake of fructans found in wheat and other cereals.[18] Adhering to a strict low FODMAP diet, with subsequent reintroduction of individual foods, under expert dietetic supervision, can be life changing.

Malabsorption of lactose (a disaccharide) is very common, but can be easily overlooked as a cause of chronic diarrhoea. Worldwide, lactase nonpersistence is the usual phenotype, but even in people of northern European genetic heritage, which favours lactose persistence, lactose malabsorption is more common than most other conditions that can lead to diarrhoea. Milk products should be avoided for a few weeks if lactose malabsorption is suspected, coupled with a lactose hydrogen breath test if there is any doubt.

In patients who have BAD, reducing fat in the diet to around 40g/day can help[19] by lowering bile acid secretion, which is regulated in part by cholecystokinin. This dietary fat reduction can help with dosing of bile acid sequestrants and also explain why some patients experience variation of their symptoms from day to day. Combining a low fat diet with a low FODMAP diet, which may also be beneficial for some patients in whom BAD is a factor but who are intolerant of other foods, is quite restrictive and needs expert help.

Mistake 8 Not persisting with therapeutic optimization

Diagnosing microscopic colitis, BAD, lactose intolerance or demonstrating a response to a low-FODMAP diet are all major findings that translate into great therapeutic benefit–as does diagnosing CRC, IBD or coeliac disease. However, patients may need encouragement to persist with treatment, or to combine first-line treatment with other approaches.

For instance, microscopic colitis will usually improve when budesonide is given for a few months; however, relapse may occur and patients may need further treatment to maintain clinical remission.[20] For patients who have BAD, titration of bile acid sequestrant therapy is needed–too large an initial dose can produce bloating and too small a dose may only lead to a partial response. Adding a low-fat diet, or possibly changing to a different bile acid sequestrant, can help.

The regular use of loperamide can help delay urgency, but patients need to be aware that its actions last only for a few hours. Other drugs such as eluxadoline, tricyclic antidepressants and ondansetron may help in some patients, and a role for antibiotics in small intestinal bacterial overgrowth (SIBO) should not be overlooked.

A gluten-free diet is hard to follow completely, even for patients diagnosed with coeliac disease, but the sources of FODMAPs are so numerous that optimising a low-FODMAP diet takes a long time. In patients who have chronic diarrhoea, the benefits of making a definitive diagnosis are clear, but even here many questions remain about the best treatment approaches to take for this large group of patients.

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Your chronic diarrhoea briefing

UEG Week

- 'Chronic diarrhoea' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=1982&conference=153].
- 'Microscopic colitis: A neglected entity' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=2019&conference=153].
- 'Chronic diarrhea: Diagnostic and therapeutic approach' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1872&conference=149].
- 'The role of the GI microenvironment in IBS' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1889&conference=149].
- 'Investigation of anaemia and malabsorption' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1361&conference=109].

UEG Summer School

- 'Session 2: Workup of diarrhoea | Bile acid malabsorption' at UEG Summer School 2015 [https://www.ueg.eu/education/document/session-2-workup-of-diarrhoea-bile-acid-malabsorption/126670/].

Society Conferences

- 'FODMAPs' presentation in the 'Diet and functional gastrointestinal disorders' session at NeuroGASTRO Meeting 2015 [https://www.ueg.eu/education/document/fodmaps/145320/].

Standards and Guidelines

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