Mistakes in the management of unexplained diarrhoea and how to avoid them

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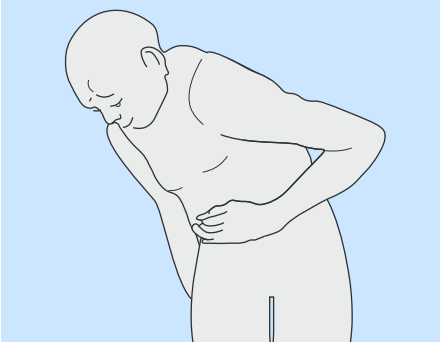
Diarrhoea, acute or chronic, is a common gastrointestinal symptom in healthcare. In most cases, acute diarrhoea in healthy individuals requires limited diagnostic and therapeutic efforts, except for the replacement of fluid electrolytes, and stool culture in severe occurrences. Acute diarrhoea is often self-limiting due to short-lived reactions to food intake and bacterial or viral infections. However, diarrhoea can persist and fulfil definitions of chronicity when a month or more has passed since the onset.[1]

Here we discuss some basic mistakes that should be avoided when managing unexplained non-bloody diarrhoea that persists beyond the acute setting. In this context, the term 'unexplained' refers to a patient without apparent alarm features and where initial consultations have failed at making a diagnosis. We used an evidence-based approach and included aspects predominantly based on clinical experience when appropriate.



Mistake 1 Miscommunicating and overlooking the clinical history

In clinical practice, obtaining a clear understanding of the patient's complaints about bowel habit abnormalities and its associated symptoms can be difficult. The number of differential diagnoses obtained using simple tools can be reduced without losing accuracy. Most doctors are familiar with the Bristol Stool Form Scale [2], which can be recommended for assessing bowel habits in research and clinical practice. In a patient that reports a loose or watery stool (types 6 and 7), it is more likely that the disturbed bowel habit is related to an accelerated gut transit time if normal (types 3-5) or hard (type 1 and 2) stool types are absent or uncommon. Therefore, it is essential to consider the type and number of investigations required before making an accurate diagnosis (see mistakes 2 and 3).

Furthermore, in case the patient does not respond to symptomatic treatment, such as loperamide, which can reduce diarrhoea and improve the diarrhoeal symptoms, a suspicion of a communication mismatch should be raised. In hard-to-understand cases, filling out a stool diary for 1-2 weeks is clinically helpful to complement a good clinical history (the diary can contain information on the frequency of bowel movements, stool consistency and time of the day). The presence of bowel movement clusters after meals does not implicate the exact pathophysiological mechanisms of diarrhoea (suspicion of a sensitive rectum). However, an evenly distributed watery bowel movement may affect sleep (suspicion of secretory diarrhoea).

Additional important features for understanding the more difficult to treat patients with diarrhoea can be obtained through a multidimensional clinical profile (MDCP).[3] This strategy involves adding layers of clinical information regarding detailed symptom descriptions and their emotional impact on the patient's life, psychosocial modifiers, and biomarkers (laboratory tests, transit time, and histopathology). Good communication skills form a fundamental basis for understanding why a patient presenting symptoms for an extended period has now decided to seek help from a doctor.[4] These efforts increase the possibility of educating the patient about the diagnosis and providing reassurance.[5] Moreover, this approach will lead to a diminished need for excessive health care consumption due to the misunderstanding of the intention of the treatment in irritable bowel syndrome with diarrhoea (IBS-D), where the abdominal pain component might not respond as well as the bowel habit abnormality to a specific type of treatment (e.g., loperamide).[6]

Mistake 2 Not recognising the epidemiology of chronic diarrhoea

A simple rule of thumb is that the most common causes underlying chronic diarrhoea will also be the most frequent diagnoses in clinical practice. (i.e., functional GI disorders).[7] In a recent internet-based global epidemiology study including twenty-six countries,[8] the prevalence of diarrhoea in adults with bowel disorders have a predominance of 5.9% and 8.8% in unspecified functional bowel disorder of whom a substantial proportion also had symptoms but did not rank them as the most bothersome symptom.[8]

It is also essential to consider that bile acid diarrhoea can be a contributing or fully explaining factor in 25-30% of cases of chronic diarrhoea.[10] This finding should guide further investigations, particularly in patients not responding well to first-line treatments such as loperamide.

Finally, basic clinical and epidemiological knowledge of microscopic colitis can guide the clinician in deciding when to consider this diagnosis in patients with chronic diarrhoea without overlooking biopsy retrieval from a normal mucosa at colonoscopy. This should be considered in patients with frequent watery, non-bloody diarrhoea, where pain and other GI

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symptoms are not dominant, despite the presence of symptoms. The diagnosis has a female preponderance, with increasing incidence and prevalence among the older age groups, and an association with the use of non-steroidal anti-inflammatory drugs, selective serotonin-reuptake inhibitors, and proton pump inhibitors.[11]

Mistake 3 Failing to select the right patient for further investigations

The number and type of investigations needed to end up with a correct diagnosis in patients with chronic diarrhoea will vary depending on the mode and age of onset, the duration of the associated symptoms, and alarm symptoms and signs. Selecting a limited number of relevant, evidence-based investigations and tests for symptoms compatible with a functional bowel disorder is essential. Factors supporting limited numbers of tests and investigations are young age (< 45 years), the fulfilment of the diagnostic criteria for one of the functional bowel disorders,[9] absence of alarm symptoms and no alarming findings when a thorough physical examination is performed. It is therefore considered sufficient to analyse for a complete blood count, C-reactive protein, coeliac serology, and a faecal calprotectin to exclude inflammatory bowel disease.[12] When the patient has a functional bowel disorder, this can be communicated at the first visit, and the preparation of the patient on a typical outcome of the tests can be confirmed (i.e., using a positive diagnostic approach). This strategy has been proven safe compared to a more comprehensive diagnostic strategy in patients with a suspected functional bowel disorder. It reduces the number of unnecessary investigations, including colonoscopy.[13,14] In register-based epidemiologic studies from Sweden using the ICD-10 code for IBS, it has been shown that the clinical use of this diagnostic code was not associated with increased mortality.[15] The number of diagnostic findings at endoscopy performed after receiving an IBS diagnosis was low in comparison to the one for non-IBS controls.[16] The latter was true for diagnoses such as inflammatory bowel disease, colorectal cancer or precancerous polyps, and coeliac disease, showing that the non-invasive tests and absence of alarm symptoms are safe to use in clinical practice. The odds ratio for diagnosing microscopic colitis in IBS-D patients ≥ 50 years old was significantly higher than in the younger age group. The proportion of IBS patients diagnosed with microscopic colitis after colonoscopy was more than 8% in those aged 70 years or older. This highlights the well-established recommendation to select older patients with watery diarrhoea for colonoscopy with biopsies without the prior use of faecal calprotectin.

Mistake 4 Failing to identify the less common causes of chronic diarrhoea

There are some infections to consider in patients with persisting diarrhoea. Some of these have an acute onset, with clinical features of an acute GI infection, but some may lack an apparent acute phase. *Giardia duodenalis* (formerly *G. lamblia* or *G. intestinalis*) is endemic worldwide. It is relatively common cause of travellers' diarrhoea, particularly among backpackers and campers, but should also be considered in immunocompromised patients and in men who have sex with men (MSM).[17] Even if symptoms usually resolve after 2-4 weeks, the infection may persist longer (chronic giardiasis) or becomes the starting point for post-infection IBS.[18] The diagnosis of chronic giardiasis relies on identifying the *Giardia* cysts or trophozoites in stool samples. Importantly, in the absence of travel in high-risk areas, routine stool testing for ova and parasites is unlikely to identify important causes of chronic diarrhoea.[19]

Whipple's disease caused by *Tropheryma whipplei* is uncommon, with an estimated prevalence of 1-6/106, even if asymptomatic carriage of the bacteria is much more common (1-10% in different geographical areas). However, this diagnosis should be considered for unexplained long-standing diarrhoea.[20] It is characterized by gastrointestinal manifestations secondary to malabsorption due to the affected small bowel mucosa, i.e., chronic diarrhoea, abdominal pain, and accompanying weight loss. In addition, arthralgia and arthritis mimicking rheumatoid arthritis most often precede the diarrhoea by years. The diagnosis is primarily obtained from multiple specimens' duodenal biopsies with histopathology (PAS staining, immunohistochemistry). Furthermore, depending on the symptom profile, PCR-based tests of mucosal tissue or other biologic material are highly recommended.

A somewhat debated bacterial aetiology explaining chronic diarrhoea is small intestinal bacterial overgrowth (SIBO),[21] mainly due to imprecise and not agreed-upon definitions with clinical relevance. The original description defines it as a malabsorption syndrome in predisposed individuals due to anatomic, pharmacologic, or other changes that promote stasis of intestinal contents and impaired resistance to bacteria. On the other hand, if SIBO is defined more widely by a pathologic glucose or lactulose hydrogen breath test, data supports the role of SIBO also in diarrhoea-dominated functional bowel disorders. However, its relative importance is still debatable. Widespread use of antibiotic treatment based on a combination of symptoms compatible with a functional bowel disorder and a positive hydrogen breath test does not have a worldwide consensus. This most probably mirrors a variation in microbiota composition and function, different from the original SIBO concept (figure 1).

Abnormal small intestinal motility	Anatomic abnormalities	Immune deficiency	Hypochlorhydria	Various
Diabetic visceral neuropathy	Small intestinal stricture	Inherited immune deficiencies (e.g. common variable immune deficiency)	Long-term acid suppression	Intestinal failure
Idiopathic intestinal pseudo-obstruction	Post-surgical alteration in anatomy (e.g. blind loop, ileocecal resection)	Acquired immune deficiency (AIDS, severe malnutrition)	Post-surgical	Coeliac disease
Systemic sclerosis				Irritable bowel syndrome
Amyloidosis				Radiation enteropathy
Muscular dystrophy	Intestinal fistulas			Cystic fibrosis
Chronic use of opioids or other motility suppressing drugs				End-stage liver or renal disease
				Chronic pancreatitis
				Old age

Figure 1 | Examples of diseases associated with small intestinal bacterial overgrowth.

Mistake 5 Misidentifying causes for diarrhoea in the elderly

The list of medication in elderly patients needs to be thoroughly checked for drugs that can cause diarrhoea, either by having a secretory or an osmotic effect (figure 2). Dietary components can also contribute to osmotic diarrhoea.
A person with lactase non-persistence at a higher age may experience a reduced tolerance to lactose-containing food.[22]

Coeliac disease can have a clinical onset late in life among the malabsorption syndromes. A recent review showed that a fifth of all diagnoses of coeliac disease is made in patients > 65 years and older.[23] The diagnostic strategy remains the same in younger age groups. However, knowing that tissue transglutaminase antibody titres may be lower in the elderly, the threshold for performing duodenal biopsies in seronegative patients is lowered. This strategy can help identify the histopathological features of mesenteric ischemia, a less common cause of chronic diarrhoea in the elderly.

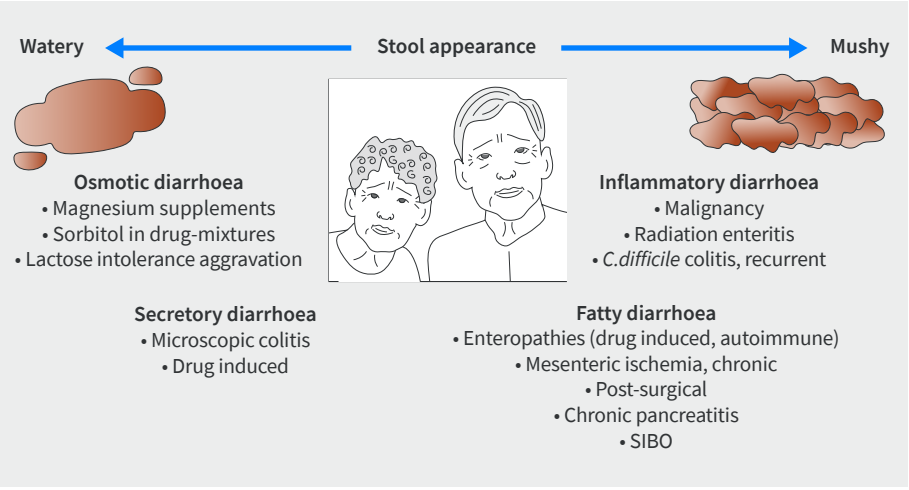

Figure 2 | Aetiologies of chronic diarrhoea that can be considered more frequently at an older age.

Faecal incontinence becomes more prevalent in older patients (> 65 years) and can be a contributing or significant cause for symptoms communicated as diarrhoea. A careful clinical history and a digital rectal exam will be crucial in diagnosing. If incontinence is frequent, especially with low-volume stools, these patients should primarily be evaluated for incontinence, not diarrhoea.

Among the inflammatory aetiologies explaining diarrhoea in the elderly, *Clostridioides difficile* infection is highly considered and tested for using glutamate dehydrogenase assay or nucleic acid amplification test,[24] where an enzyme immunoassay confirms positive results for *C. difficile* toxin A/B or toxigenic culture. Confirmation should involve toxin testing or toxigenic culture if considering a recurrent infection. The bacteria and spores can be excreted for an extended period (weeks) after the infection has been successfully treated.

Mistake 6 Improper use of medical therapy

The most common medication to treat chronic diarrhoea is the synthetic peripheral μ-opioid receptor agonist loperamide. It effectively reduces diarrhoea due to many aetiologies with a benign side effect profile (constipation) and a wide dose range of up to 16 mg/day. A mistake that needs to be avoided is that some patients are reluctant to use the doses needed due to a misconception of the risk for drug-dependency, which healthcare providers should firmly negate. Another problem is related to patients with IBS-D that may experience worsening in abdominal pain from loperamide.

Among treatments aimed at specific aetiologies of chronic diarrhoea, bile acid sequestrants can wrongfully be discarded as ineffective before their appropriate evaluation.[10] The most common treatment choice is cholestyramine, but it is unclear if this medication should be taken with a meal or not to achieve optimal effect. The recommendation regarding dosage with a meal is based on treating hypercholesterolemia and not on studies of bile acid diarrhoea. From a practical perspective, starting with a trial of 4 g twice daily if taken with a meal is recommended. If this approach is ineffective, adding a dose late in the evening can be considered. The dose range is also uncertain, but if tolerated, 4-24 g/day is harmless based on clinical experience and when doses are divided appropriately. The risk of interfering with other medications and reducing their absorption must be also acknowledged. This can be avoided by not administering bile acid sequestrants within an hour after, or 4-6 hours before intake of other medications. For those not responding to or not tolerating cholestyramine, colestipol and colesevelam are valid alternatives. It is encouraged to perform an objective test (golden standard selenium-75 homotaurocholic acid test [^{75}Se]Se-HCAT) for bile acid malabsorption if this has not been previously done i.e., in those where the treatment trial period also had a diagnostic purpose.

The 5-HT$_3$ antagonists alosetron and ramostron are effective for treating chronic diarrhoea but they are only available through prescription in parts of the world. Therefore, an off-label alternative in non-responders to loperamide is the 5-HT$_3$ antagonist ondansetron, used for chemotherapy-induced nausea and vomiting. There is little evidence supporting its use in patients with chronic diarrhoea. However, a randomized placebo-controlled trial in IBS-D supports the use of a wide dose range (4-24 mg/day) as a second-line treatment for diarrhoea.[25]

Antibiotic treatment in SIBO is not controversial if the clinical manifestation has a sound evidence base regarding its link to SIBO.[20] Generally, data supports the beneficial effect of a planned rotating treatment schedule in SIBO.[26] The use of rifaximin in patients with non-constipated IBS is still debated. It would be beneficial to identify a biomarker that better defines its proper use in a smaller proportion of patients with IBS. Considering the non-approval of rifaximin for IBS treatment by the European Medical Agency (EMA), it is advisable to avoid its widespread use for chronic diarrhoea.

Mistake 7 Failing to use dietary therapy properly

Many patients often highly appreciate dietary advice that can help reduce diarrhoea. There are no clear clinical or biological predictors for symptomatic response to dietary adjustments, but current knowledge gained from the IBS field may be of some help.[27] The best use of dietary advice should ensure that no unnecessary avoidance behaviour is promoted, and the general recommendation on healthy eating should be transferred to the patient. The first line of dietary treatment for diarrhoea that is not due to a readily identifiable cause, e.g., coeliac disease, milk protein allergy or other less common identifiable immune reactions to food items, should focus on the general guidelines of healthy eating. It includes not skipping meals, paying attention to the speed and the environment of where the patient eats, portions, and frequency of meals. Few scientific evidence exists on the effects of this advice on specific symptoms. However, clinical experience supports the effectiveness of this approach on some patients.

As a second step, exclusion diets can be tested. A mistake that should be avoided is not having the patient do this with the guidance of a trained dietitian. Among the exclusion diets, the scientific evidence is most robust for a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) that can lead to symptom reduction in IBS, in particular in IBS-D.[28] The short-term risks with this type of restrictive diet are probably negligible. However, long-term risks related to inadequate nutrition, socially restricting dietary habits, and fear related to eating must be prevented. Many patients, even before seeking healthcare, often test other diets, including gluten and a lactose-free diet. These are less restrictive, and healthcare providers should not contradict improvement symptoms experienced by the patient. However, this mechanism should be assessed further to appropriately treat the correct diagnosis: coeliac disease, non-coeliac gluten sensitivity, wheat sensitivity, lactose intolerance, food intolerance related to IBS, wheat allergy and others.

Mistake 8 Failing to use augmentation therapy

One therapeutic option might not lead to sufficient diarrhoea control for many patients. A severe mistake in such circumstances is to miss out on therapies that have had some effect, perhaps restricted by side effects in adequate doses, or have an overall good treatment

outcome. Instead of discarding them totally, the concept of augmentation therapy should be remembered. It refers to using treatment combinations of multiple drugs or a combination of drugs with non-pharmacological therapies such as dietary advice or psychological treatment options. In the context described here, good examples can consist of the following:

- A low dose of loperamide until the tolerance threshold for abdominal pain is reached in combination with dietary advice
- A bile acid sequestrant combined with loperamide
- Ondansetron and dietary advice
- Reintroduction of individual food items causing some problems (that patients appreciate) in combination with a single dose of loperamide

It is essential to reassess both reasons for using and not using different therapies over time so that smaller therapeutic gains among those suffering the most from difficult-to-treat diarrhoea are not overlooked.

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Your management of unexplained diarrhoea briefing

UEG Week

- 'Chronic diarrhoea in an older adult' session at PGT Virtual 2021 [https://ueg.eu/library/chronic-diarrhoea-in-an-older-adult/248582]
- 'Differential enteric glial cell phenotype in the jejunum of diarrhoea-prone irritable bowel syndrome and its association with clinical phenotype and symptom severity' [https://ueg.eu/library/differential-enteric-glial-cell-phenotype-in-the-jejunum-of-diarrhoea-prone-irritable-bowel-syndrome-and-its-association-with-clinical-phenotype-and-symptom-severity/248074]
- 'Mistakes in chronic diarrhoea' session at UEG Week Virtual 2020 [https://ueg.eu/library/mistakes-in-chronic-diarrhoea/234905]

Standards and Guidelines

- '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;67:1380-1399 [https://ueg.eu/library/guidelines-for-the-investigation-of-chronic-diarrhoea-in-adults-british-society-of-gastroenterology-3rd-edition/176624]
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- 'NICE Quality Standard Inflammatory bowel disease (QS81)' [https://ueg.eu/library/nice-quality-standard-inflammatory-bowel-disease/141824]
- 'NICE Quality Standard Irritable bowel syndrome in adults (QS114)' [https://ueg.eu/library/nice-quality-standard-irritable-bowel-syndrome-in-adults/141817]