Recommendations for the diagnosis and management of patients with chronic idiopathic diarrhea: Belgian multidisciplinary expert discussion based on a modified Delphi method

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Abstract

Background: **Chronic diarrhea is one of the more common reasons for referral to a gastro-enterologist. Chronic diarrhea can have a broad range of causes, making it a disease entity with a very extensive differential diagnosis. In a proportion of patients, however, a cause for the chronic diarrhea cannot be found and these patients are said to have chronic idiopathic diarrhea (CID).**

Methods: **A Delphi model was used to establish a diagnostic strategy for patients presenting with chronic diarrhea that maximizes the chance for a positive diagnosis while minimizing the number and invasiveness of the investigations. In addition, the participating experts sought consensus on the different treatment options that can be used in these patients.**

Results: **While a general consensus was reached on the required diagnostic tests for CID, marked differences were observed on the treatment preferences and strategies for these patients among the different experts. The main reason for this is the lack of solid scientific evidence with the different treatment options in this setting (i.e., most data have been generated in patients with IBS-D).**

Conclusion: **the Delphi-like process that was used for this initiative proved to be a useful vehicle to fuel discussions on the management of CID among experts with different backgrounds and to sketch the current clinical practice. (**Acta gastroenterol belg., **2025**, 88, **179-194**).

Keywords: chronic diarrhea; idiopathic diarrhea, Delphi process, IBS-D.

Introduction

Chronic diarrhea is one of the more common reasons for referral to a gastro-enterologist, with an estimated prevalence in Western populations of 4-5% (1). In the international literature, several definitions for diarrhea can be found, defining it in terms of stool consistency, frequency and/or stool volume. For most patients, however, diarrhea refers to 'loose stools'. Chronic diarrhea is generally distinguished from acute diarrhea by a duration of more than 4 weeks (2). Chronic diarrhea can have a broad range of causes, making it a disease entity with a very extensive differential diagnosis. In fact, chronic diarrhea can be the result of structural abnormalities or malignancies in the colon or small intestine, inflammation, small bowel malabsorption, maldigestion due to pancreatic insufficiency, motility disorders, laxative abuse, bacterial overgrowth in the small bowel, etc. In a proportion of patients, however, a cause for the chronic diarrhea cannot be found and these patients are said to have chronic idiopathic diarrhea (CID). In most of these patients, diarrhea is a sign of a disorder of the gut-brain interaction (DGBI), such as irritable bowel syndrome (IBS) or functional diarrhea. CID is in essence often a diagnosis of exclusion in which physicians use a range of clinical, laboratory and radiographic evaluations to rule out potential organic etiologies of diarrhea. Unfortunately, however, guidance on the essential tests that should be part of this diagnostic work-up and their optimal sequence is largely lacking. In addition, the therapeutic approach in patients with CID tends to vary between clinical centers and individual experts.

The aim of this initiative was therefore to establish a diagnostic strategy for patients presenting with chronic diarrhea that maximizes the chance for a positive diagnosis while minimizing the number and invasiveness of the investigations. In addition, the participating experts sought consensus on the different treatment options that can be used in these patients. To come to these recommendations, a Delphi model was used. This is a well described structured process for decision making using a series of questionnaires or 'rounds' to gather expert information in an anonymized fashion to work towards a consensus (3).

Materials and methods

Expert panel

The steering committee (SC), coordinating this independent Delphi process consisted of 2 gastro-enterologists, with expertise in the management of chronic diarrhea (RB and TV). These two experts were responsible for the composition of the expert

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panel and the desired level of expertise of the panelists. They also selected the topics to be addressed in the recommendations and created the content for the Delphi questionnaires. The selection of the participating experts was done on a national level. The SC aimed to include gastroenterologists, taking into consideration a good balance in the geographic and hospital (academic vs. non-academic) background of the panelists. Since the focus of the consensus was the management of chronic idiopathic diarrhea, rather than the management of well-established causes of chronic diarrhea such as celiac disease or inflammatory bowel disease (IBD), the majority of the included specialists have an background in functional gastrointestinal disorders, which could be viewed as a potential limitation. In total, 18 experts accepted the invitation to participate in the Delphi process. These experts had a median self-reported experience of 18 years and see a median of 15 patients with chronic diarrhea per month.

Delphi model

The Delphi-like process in this initiative was conducted over a 6-month period and was set up as a 3-round project. An independent third-party vendor was appointed for hosting and processing the online questionnaires and to gather and process the anonymized data. The different topics that were addressed in the questionnaires focused on definitions, diagnostic tests in the primary and refractory setting and the available treatment options in these two settings.

The first round of the process consisted of an electronic questionnaire including 54 statements that had to be answered on a 7-point Likert scale (strongly agree, agree, somewhat agree, neither agree or disagree, somewhat disagree, disagree, strongly disagree). In this approach the responses strongly agree and agree were considered as an 'agreement', while strongly disagree and disagree were grouped as a 'disagreement'. The levels in between (somewhat disagree, neither agree or disagree, to somewhat agree) were reported as 'neutral'. During the first voting round, participants were allowed to comment on certain statements to motivate their response. Following this first voting round, a face-to-face meeting was organized to confirm the consensus/dissensus of the different statements and to discuss, reformulate or further specify the statements on which no consensus/dissensus was reached. This discussion was chaired by the SC and the comments of participants on the first voting round were used to fuel the discussion.

Based on this face-to-face meeting, a second on-line voting round was organized including a total of 60 statements using a similar scoring system as in round 1. Compared to round 1, 6 new statements were added, and 43 statements were reformulated. In a third and last Delphi round, 23 statements for which no consensus was reached in round 2 were revoted during an interactive face-to-face meeting with anonymous voting.

Consensus definition

A 75% agreement with less than 15% disagreement, at least after 2 voting rounds, was identified as a minimum threshold for consensus.

Role of the funder

Ipsen sa/nv introduced the concept of organizing a modified Delphi panel on CID. The company was not involved in the selection of the panelists, the choice of the topics that were addressed, the development of the questionnaires, the analysis and interpretation of the results, and the content of the final manuscript. Ipsen sa/nv did provide funding for the SC members and the panelists and provided financial support to allow the involvement of a third party to manage the technical and statistical part of the Delphi process and a medical writer to support in the preparation of the final manuscript.

Results

Table 1 shows the statements for which consensus was reached and Table 2 the statements for which no consensus was reached.

1. Definitions

Statement 1: Chronic diarrhea is defined as loose or watery stool (Bristol Stool Form Scale 6 or 7) >3x per day or a total stool weight of >200 g/day, both persisting for >4 weeks

Statement endorsed (Round 2): Agreement 94.4%, Neutral 5.6%

In the literature, several definitions for chronic diarrhea can be found (2, 4-6). In general, these definitions use a combination of stool frequency, consistency, and volume/weight. Of these three factors, the latter is most controversial as stool weight can vary significantly and also 'normal' stool volumes can exceed this value depending on the diet. In addition, also a quantification of stool consistency may be challenging in clinical practice. To counter this, the expert group recommends the use of the Bristol Stool Form Scale (BSFS). Also, the required duration of symptoms to distinguish chronic from acute diarrhea has been subject to debate. However, most groups accept that symptoms persisting for longer than 4 weeks usually suggest a non-infectious etiology (4).

Statement 2: Chronic idiopathic diarrhea (the scope of these guidelines) is distinguished from irritable bowel syndrome with diarrhea (IBS-D) by a lack of predominant abdominal pain.

Statement endorsed (Round 2): Agreement 100%

The two most prominent bowel disorders that are associated with chronic diarrhea consist of functional diarrhea and irritable bowel syndrome (IBS). According to Rome IV criteria, the factor distinguishing these two entities is the presence of abdominal pain. In fact, the key criterion for IBS is recurrent abdominal pain on average at least 1 day/week in the last 3 months, whereas chronic functional (or idiopathic) diarrhea is defined as loose or watery stools in more than 25% of stools, without predominant abdominal pain (6).

Statement 3: Chronic idiopathic diarrhea and IBS-D should not be seen as two different disease entities but exist on a continuum

Statement endorsed (Round 3): Agreement 82.4%, neutral 11.8%, disagreement 5.8%

While the presence of abdominal pain has been acknowledged as a distinguishing factor between CID and IBS with diarrhea (IBS-D) by the Rome IV criteria, more recent data reported by Singh et al. suggest some overlap between these two disease entities and patients can shift between diagnostic categories over time. In fact, in this study, a significant proportion of patients with functional diarrhea also presented with abdominal pain (77.1%). Furthermore, no difference was seen in the incidence of concomitant symptoms such as abdominal bloating between patients with CID and IBS-D (7).

Statement 4: Refractory chronic idiopathic diarrhea is defined as a chronic diarrhea that was not resolved with standard first-line therapy

Statement endorsed (Round 4): Agreement 88.2%, neutral 5.9%, disagreement 5.9%

This definition of refractory CID was adopted for this paper. The nature of the standard first line treatment referred to in the definition will be clarified further.

2. Diagnosis

Initial presentation

Statement 5: Patients can mistake fecal incontinence for chronic diarrhea. This issue should be adequately addressed during the initial history taking

Statement endorsed (Round 2): Agreement 88.9%, neutral 11.1%

Fecal incontinence refers to recurring, uncontrolled passage of solid or liquid stool for an extended period of time (>3 months) (6, 8). The most common risk factor for fecal incontinence consists of diarrhea. Fecal incontinence is a prevalent debilitating symptom, affecting about 10% of adults worldwide (9). The incidence of fecal incontinence increases significantly with age, with an incidence of up to 40% among care home residents (10). Fecal incontinence is often an unspoken symptom and requires a different work-up compared to chronic diarrhea (11). Its high prevalence and the fact that patients may mistake fecal incontinence for chronic diarrhea require physicians to adequately address this issue during an initial history taking and carefully differentiate between both symptom presentations. Given the stigma surrounding fecal incontinence, it is important that the physician explicitly evaluates the presence or absence of incontinence and also uses the correct wording when addressing it. For example, it can be less confronting for patients to talk about 'accidental bowel leakage' rather than fecal incontinence.

In addition to fecal incontinence physicians should also think about the possibility of overflow incontinence as a result of fecal impaction in patients presenting with chronic diarrhea (12).

Statement 6: A detailed history is essential in the initial clinical assessment of a patient with chronic diarrhea

Statement endorsed (Round 2): Agreement 100%

A detailed medical and personal history is essential to come to a diagnosis of CID.(5) In this respect, the primary focus of physicians should be to rule out alarm signals, such as nocturnal diarrhea, unintentional weight loss, blood in stool, tenesmus, evidence of malnutrition, etc. (**statement 6a**: *statement endorsed [Round 2], agreement 94.4%, neutral 5.6%*). The presence of these alarm signals should prompt further investigation, including endoscopy. In patients without alarm signals, the abdominal and diarrheal symptoms need to be assessed together with a more general physical examination. An important aspect of this clinical assessment consists of an evaluation of the characteristics of the perceived chronic diarrhea (frequency, consistency [BSFS], duration, continuous or intermittent, etc.). (**statement 6f**: *statement endorsed [Round 3], agreement 88.9%, neutral 11.1%*).

Apart from this detailed symptom-based evaluation, the initial assessment of patients with chronic diarrhea needs to address a potential family history of gastro-intestinal disease (e.g., celiac disease, IBD, colorectal cancer) (**statement 6b:** *statement endorsed [Round 2], agreement 100%*) and should include a detailed analysis of the current and recent medication use, including over-the-counter drugs and supplements which can contribute to diarrhea (**statement 6c**: *statement endorsed [Round*

2], agreement 100%). Diarrhea is a very common side effect of medications, accounting for about 7% of all adverse events (13). The medications which are most commonly associated with diarrhea include antibiotics, magnesium-containing antacids, non-steroidal anti-inflammatory drugs, colchicine, anti-arrhythmic drugs, anti-depressants (especially selective serotonin reuptake inhibitors (SSRI)) and of course laxatives.

In addition to this, the recent travel history of the patient has to be addressed (**statement 6d**: *statement endorsed [Round 2], agreement 100%*) together with potential associations between specific food consumption and the occurrence of diarrhea (**statement 6e**: *statement endorsed [Round 3], agreement 100%*).

Statement 7: A whole blood count should be performed in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 88.9%, neutral 5.6%, disagreement 5.6%

A complete blood count should be performed in patients with chronic diarrhea to identify potential alarm signals such as anemia or leukocytosis that warrant further investigation.

Statement 8: C-reactive protein (CRP) should be evaluated in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 88.9%, neutral 11.1%

An evaluation of the C-reactive protein (CRP) level is an important test to discriminate IBD and other inflammatory conditions from CID. According to a systematic review and meta-analysis from 2015, patients with diarrhea and a CRP level ≤0.5 mg/dl have a likelihood of having IBD of less than 1% (14).

Statement 9: A thyroid function test should be performed in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 88.9%, neutral 5.6%, disagreement 5.6%

Hyperthyroidism can be associated with chronic diarrhea, even if chronic diarrhea as the sole presentation is uncommon (15). To rule out this etiology, a routine thyroid function test is warranted in patients with CID.

Statement 10: Serum electrolytes should be evaluated in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 94.4%, neutral 5.6%

Assessment of serum electrolytes is warranted to assess the impact of CID, since severe diarrhea can result in a significant loss of potassium and sodium.

Statement 11: Fecal calprotectin should be analyzed in all patients with chronic idiopathic diarrhea who do not require a colonoscopy

Statement endorsed (Round 2): Agreement 88.9%, neutral 11.1%

Calprotectin is released by the degranulation of neutrophil granulocytes in inflammatory processes. Fecal calprotectin is increased in different inflammatory gastrointestinal pathologies, and it is stable enough to be measured in stool samples. As a result, patients with low calprotectin levels are unlikely to have any active inflammatory processes at the time of sample collection. Confounders which can contribute to positive testing include the use of non-steroidal anti-inflammatory drugs (NSAID) and acute infection. As such, a low calprotectin level in feces (< 100mg/g feces) makes a diagnosis of inflammatory bowel disease (IBD) very unlikely (16, 17). In patients with a calprotectin level of 100-250mg/g feces, it is advised to remeasure the calprotectin after 2-3 months. If this test turns out to be normal, no colonoscopy is necessary.

Statement 12: Routine stool testing for C. difficile is not recommended in patients with chronic idiopathic diarrhea in the absence of risk factors

Statement endorsed (Round 2): Agreement 77.8%, neutral: 16.7%, disagreement 5.6%

While most infectious diarrhea is acute and self-limited, some infections can cause chronic symptoms. One of the most notable of these infectious agents in Western countries consists of toxin-producing Clostridioides difficile, which is commonly associated with antibiotic use and extended stays in a healthcare environment. However, the panel deems the yield of the test to be too low in patients without specific risk factors and in the absence of general symptoms (e.g., fever, abdominal pain) and therefore argues against its routine use in clinical practice.

Statement 13: A fecal occult blood test is not recommended in patients with chronic idiopathic diarrhea

Statement endorsed (Round 3): Agreement 82.4%, neutral 17.6%

The detection of excess blood in feces, using a fecal immunochemistry test (FIT) can be used in the

diagnosis of colorectal cancer. In this respect, studies indicate that FIT testing (cut-off 7-10 µg/g) has a high negative predictive value for colorectal cancer (CRC) in patients with lower gastro-intestinal symptoms suggestive of colorectal cancer (18, 19). However, in the setting of chronic idiopathic diarrhea in the absence of alarm symptoms, there are no data supporting the use of FIT testing. Moreover, FIT screening is indicated for asymptomatic individuals without a family history of CRC as a screening test for CRC to reduce the burden of this cancer type on society. In the setting of symptomatic patients with diarrhea, this is a priori not the case and has no other diagnostic value.

Statement 14: Serological tests for celiac disease (i.e., IgA tissue transglutaminase or IgG anti-deaminated gliadin peptide in case of IgA deficiency) should be performed in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 3): Agreement 100.0%

The prevalence of celiac disease in patients referred to secondary care with chronic diarrhea has been reported to range from 3% to 5% (20, 21). Several systematic reviews and meta-analyses have demonstrated the clinical utility and cost-effectiveness of celiac disease-associated antibody testing in patients with functional diarrhea or IBS-D (15-17). As such, all patients with CID should undergo an enzyme-linked immunosorbent assay to determine anti-tissue transglutaminase immunoglobin A (IgA) antibodies combined with a total IgA measurement while eating a gluten-containing diet. Of note, in case of IgA deficiency, which is present in about 2% of patients, the presence of anti-deaminated gliadin peptide IgG antibodies must be assessed (22).

Statement 15: In patients under the age of 45 with a suspicion for chronic idiopathic diarrhea there is no need for routine endoscopic examination in the absence of alarm signs or symptoms

Statement endorsed (Round 2): Agreement:77.8%, neutral 11.1%, disagreement: 11.1%

While a low threshold for the use of colonoscopy is acceptable in the context of the frequency and clinical significance of colonic malignancy in older individuals, there is less need if the probability of benign disease is high. In fact, studies indicate that the diagnostic yield of a colonoscopy is limited in the absence of alarm signals (23, 24). As such, a colonoscopy can be delayed until empiric treatment failure in younger patients (≤45 years old) who present with typical symptoms of a functional bowel disorder and do not exhibit alarm signs.

Statement 16: A colonoscopy is recommended in all patients with chronic diarrhea under the age of 45 presenting with alarm signals

Statement endorsed (Round 2): Agreement 100.0%

A colonoscopy can be used to exclude several gastrointestinal diseases that might be responsible for diarrhea in selected patients. This includes IBD, microscopic colitis (even if this is rare in this age group), and colorectal cancer (25). In this respect, the presence of alarm symptoms (unintentional weight loss, hematochezia, melena, a family history of IBD, family history of colorectal cancer or family history of other significant gastrointestinal diseases) is suggestive for an organic disorder in patients with chronic diarrhea. Therefore, the presence of such alarm signs warrants a colonoscopy in patients with chronic diarrhea, even if they are younger than 45 years of age (23).

Statement 17: Whenever a colonoscopy is performed in patients with chronic diarrhea, biopsies should be collected from the left and right colon to exclude microscopic colitis

Statement endorsed (Round 2): Agreement 100.0%

Microscopic colitis is a chronic inflammatory bowel disease characterized by normal or almost normal endoscopic appearance of the colon, and chronic watery, non-bloody diarrhea (26). While certain laboratory markers can be altered in patients with microscopic colitis, the only proven diagnostic approach to exclude it with an acceptable degree of confidence in patients with chronic diarrhea consists of a colonoscopy with random biopsies. As such, whenever a colonoscopy is being ordered in patients with chronic diarrhea, it is recommended to obtain biopsies to rule out microscopic colitis, even if the colon mucosa appears normal. As the histological findings in patients with microscopic colitis can be patchy rather than continuous, it is currently recommended to obtain multiple biopsy samples (>6) from different colonic segments (at least 3 in the left and 3 in the right colon) to establish or exclude its diagnosis (26-28).

Statement 18: Abdominal ultrasound is not routinely recommended in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 3): Agreement 94.1%, neutral 5.9%

Despite it being a non-invasive, broadly available and radiation-free imaging tool, ultrasound is not

commonly used in the initial evaluation of patients with chronic diarrhea. The main reasons for this are a lack of accuracy, the fact that this technique is unable to visualize the entire gastro-intestinal tract and its high inter-operator variability. Nevertheless, the use of intestinal ultrasound is a field in full development in the context of IBD (29) and may provide useful insights in patients with chronic diarrhea especially when used in combination with fecal calprotectin (30).

Statement 19: A lactose breath test is not routinely recommended in all patients with chronic idiopathic diarrhea to assess potential lactose malabsorption

Statement endorsed (Round 3): Agreement 88.2%, disagreement 11.8%

Statement 20: A fructose breath test is not recommended in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 94.4%, disagreement 5.6%

Maldigestion of carbohydrates, such as lactose or fructose, can be responsible for chronic diarrhea in a proportion of patients (31). Breath tests have been developed as a non-invasive method to identify carbohydrate malabsorption. These tests are based on the ability of bacteria to ferment carbohydrates with an end product of hydrogen, which is not produced by mammalian cells. While these breath tests are able to detect malabsorption, the existing consensus reports on the optimal challenge dose have not been widely adopted.(32, 33) Furthermore, the available data on the effect of lactose or fructose avoidance on symptoms in patients with chronic diarrhea are conflicting at best and isolated carbohydrate malabsorption rarely explains chronic diarrhea (34-36). Finally, fructose intolerance is a physiological phenomenon, present in the majority of healthy individuals due to the limited capacity of the GLUT5 fructose transporter (37). In addition to carbohydrate malabsorption, breath tests can theoretically also be used to detect small intestine bacterial overgrowth (SIBO). However, the diagnostic accuracy of these tests for the detection of SIBO is poor (38). As such, given the available data, carbohydrate breath tests are currently not recommended in the routine diagnostic work-up of patients with CID.

Statement 21: Routine testing for small intestinal bacterial overgrowth (SIBO) is not recommended in all patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 88.9%, neutral: 5.6%, disagreement 5.6%

SIBO can occur when an excess of bacteria builds up in the small intestine, with possible symptoms including bloating, diarrhea, and abdominal discomfort (39). While an association has been shown between SIBO and specific structural (e.g., blind loop syndrome) or neurological (e.g., chronic intestinal pseudo-obstruction) gastro-intestinal diseases, a link between SIBO and CID or IBS-D is less clear (40). Furthermore, the specificity and sensitivity of the available tests for SIBO (i.e., carbohydrate breath tests) is poor or not readily available (duodenal or jejunal aspirate culture). Indeed, the most commonly used lactulose breath test has been shown to measure transit time rather than SIBO and the glucose breath test is limited to testing of very proximal SIBO (41). As such, routine diagnostic testing for SIBO is currently not recommended in patients with chronic diarrhea without underlying conditions or diseases that predispose for SIBO (e.g., abnormal small intestine motility, anatomical abnormalities, hypochlorhydria, immune deficiency) (42).

Statement 22: Transit time studies are not recommended in the diagnostic work-up for patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 100.0%

Several diarrhea-conditions have been ascribed to abnormalities of gut motility and an increased intestinal transit time. However, assessing the contribution of transit times to diarrhea is hampered by the fact that the available tests are time consuming, require a specific expertise and have a limited ability to identify the cause of the symptoms. In addition to this, there is a wide variation in normal transit times between people. Furthermore, the available data in patients with chronic diarrhea and IBS-D rarely show an abnormal transit time. Hence, intestinal motility studies are only indicated in selected patients with chronic intestinal pseudo-obstruction, or other concomitant diseases that raise the suspicion of intestinal motility disorders as a cause of diarrhea.

Statement 23: Testing for microbiota composition is not recommended in the diagnostic work-up for patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 100.0%

The clinical relevance of alterations in gut microbiota composition and function in relation to CID remains unclear, and studies demonstrating that findings from microbiota composition studies can predict treatment outcome are lacking. Furthermore, alterations in gut microbiota composition in patients with unexplained

diarrhea may also be reflective of dietary changes rather than being the sole and direct explanation of the symptoms (43). Finally, most of these tests are performed in commercial laboratories with uncertain quality controls and validation. Until the cause-and-effect question regarding microbiota composition and diarrhea has been elucidated, testing for the microbiota composition should not be part of the routine diagnostic work-up.

Statement 24: Food allergy testing using an IgE test is not recommended in patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 100.0%

Patients with food allergy classically present with extra-intestinal symptoms (e.g., rhinosinusitis, rash, dyspnea, …) and therefore IgE testing should only be performed if the clinical history is compatible with an allergic condition (stereotypical symptoms, classically within minutes to 1 hour after ingestion of a specific food item).

Statement 25: Food allergy/intolerance testing using an IgG test is not recommended in patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 100.0%

There is no proven value of this test in this context whatsoever (44, 45). In fact, the only study that showed an effect with this test was flawed because of an inappropriately designed sham diet (46). Moreover, IgG-based tests stimulate restrictive food intake, which puts the patient at risk to develop malnutrition and eating disorders such as avoidant and restrictive food intake disorder (ARFID) (47).

Refractory setting

Statement 26: A colonoscopy is recommended in all patients with refractory chronic idiopathic diarrhea, regardless the presence of alarm signs or symptoms

Statement endorsed (Round 2): Agreement 83.3%, neutral: 11.1%, disagreement 5.6%

A colonoscopy allows the identification of macroscopic findings that imply mucosal damage (malignancy, IBD) and provides a source for biopsies to determine whether the diarrhea is caused by enteritis, microscopic colitis, or other inflammatory conditions. This procedure should be part of the routine work-up of all patients with CID in whom empiric first line therapy failed and who did not undergo a colonoscopy as part of the initial diagnostic process.

Statement 27: A 72h stool collection is recommended in patients with refractory chronic idiopathic diarrhea to assess stool volume and fat contents

Statement endorsed (Round 3): Agreement 82.4%, neutral: 11.8%, disagreement 5.9%

A 72-hour quantitative fecal fat estimation is the standard test to assess steatorrhea. Moreover, it also allows objectivation of the volume per day to assess whether the patient suffers from large vs. small stool diarrhea. Finally, in selected centers fecal bile acid concentrations can also be determined to diagnose bile acid diarrhea. However, given the burdensome and time-consuming nature of this test, and the poor availability it should be reserved for patients with refractory CID. In case the test is not available locally, patients should be referred to expert centers. Steatocrite determination is an alternative test to detect steatorrhea, with reasonable sensitivity and specificity, but does not allow analysis of stool volume and bile acid loss.(48) Moreover, analysis of one sample does not consider day-to-day variability. During the Delphi consensus, no agreement was reached over the use of the steatocrite test (35.3% agreement; see Table 2).

Statement 28: An upper GI endoscopy is recommended in all patients with refractory chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 83.3%, neutral: 16.7%

While the role of upper gastro-intestinal endoscopy in patients presenting with chronic diarrhea is not well-studied, it can provide additional information in patients with refractory disease. For example, serology-negative celiac disease occurring in about 2.5% of patients with celiac disease (49), parasitic infections (e.g., Giardia lamblia) or rare mucosal abnormalities (e.g., auto-immune enteropathy, Whipple's disease, amyloidosis, …) can be detected. Of note, whenever an upper GI endoscopy is performed, at least 4 biopsies should be obtained from multiple sites in the second part of the duodenum and 1 or 2 in the duodenal bulb, even in a macroscopically normal-appearing small bowel.

Statement 29: A routine video capsule endoscopy is not recommended in all patients with refractory chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 100.0%

While video capsule endoscopy may have a role in detecting, or confirming small-bowel abnormalities, this technique is not routinely available and not reimbursed for this indication in Belgium. As such, the expert panel does not recommend its use in patient with CID.

3. Treatment

Primary setting

Statement 30: Loperamide is a first-line treatment for patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 77.8%, neutral: 16.7%, disagreement: 5.6%

Loperamide is arguably the best known anti-diarrheal drug. Loperamide works by a number of different mechanisms of action, leading to a decreased peristalsis and fluid secretion, ultimately resulting in longer gastrointestinal transit time and increased absorption of fluids and electrolytes from the gastrointestinal tract. It is a phenylpiperidine derivative with a chemical structure similar to opiate receptor agonists such as diphenoxylate and haloperidol. It was designed to maintain the antidiarrheal activity of these drugs, but minimize the negative aspects associated with their effects on the opiate receptor. Because of the low oral absorption of loperamide and its inability to cross the blood-brain barrier, this agent also has a minimal effect on the central nervous system (50). The maximal daily dose according to the summary of product characteristics (SmPC) is 12mg, but this can be higher in individual cases, especially in case of diarrhea related to malabsorption.

Statement 31: Soluble fiber supplements (e.g., psyllium) are a first line treatment for patients with chronic idiopathic diarrhea

Statement endorsed (Round 3): Agreement 76.5%, neutral: 23.5%

Soluble dietary fibers, such as psyllium are a reasonable treatment choice in patients with chronic diarrhea. Dietary fibers are parts of carbohydrates derived from plant cell wall components, which are neither digested nor absorbed in the small intestine. Interestingly, soluble fibers have been demonstrated to improve the regularity of bowel movement due to their luminal water-holding property leading to bulky, soft, and easy-to-pass stools. In addition to improving bowel movements, insoluble fibers (e.g., wheat bran) can stimulate water and mucus secretion. As such, their use is more suited for treating constipation, while soluble fibers are preferred for diarrhea. Fibers provide an energy source to the colonocytes through the production of short-chain fatty acids, which have been associated with multiple health benefits (51, 52).

Statement 32: Spasmolytic agents are not recommended in patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 82.4%, neutral: 11.8%, disagreement 5.9%

While clinical studies with spasmolytic agents (e.g., peppermint oil, otilonium bromide) have shown a positive effect on abdominal pain and bloating in patients with IBS-D, these studies did not demonstrate an effect on diarrhea (53, 54). As such, the use of these agents is not recommended to treat diarrhea in patients with CID, although they can be helpful to treat concomitant pain.

Refractory setting

Statement 33: A low FODMAP diet is recommended in patients with refractory chronic idiopathic diarrhea in whom other measures have failed

Statement endorsed (Round 3): Agreement 82.4%, neutral: 5.9%, disagreement 11.8%

FODMAPs are carbohydrates and polyols that are incompletely absorbed in the small intestine and therefore attract water by their osmotic activity after which they undergo fermentation in the colon, resulting in flatulence, bloating, cramps and diarrhea (55). Several prospective and observational studies as well as multiple meta-analyses have demonstrated that a low-FODMAP diet reduces symptoms in patients with IBS-D, including diarrhea (56-61). While there are no specific data in patients with CID, a low FODMAP diet (under supervision of a dietician) seems a valid option in patients with refractory CID. Of note, the restrictive phase of this diet should be limited in time (2-4 weeks) and should be followed by a re-introduction phase.

Statement 34: A gluten-free diet is <u>not</u> recommended in patients with refractory chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 94.4%, neutral 5.6%

Several studies in patients with IBS-D have demonstrated symptom alleviation when a gluten-free diet was adopted (57, 62, 63). In these studies, a gluten-free diet also seemed to be associated with a reduced stool frequency. However, additional studies suggest that the benefit seen with a gluten-free diet were more

likely to be related to a decreased intake of wheat-related FODMAPs rather than gluten itself (64, 65). No specific data exist on the potential effect of a gluten-free diet in patients with CID. Hence, the experts argue against the adoption of such a diet in patients with refractory CID.

Statement 35: Bile acid sequestrants are recommended for patients with refractory chronic idiopathic diarrhea testing positive for bile acid diarrhea

Statement endorsed (Round 2): Agreement 94.4%, neutral 5.6%

Bile acid malabsorption (BAM) is a common, yet underestimated cause of chronic diarrhea. In patients with BAM, excessive amounts of bile acids are present in the colon, giving rise to bile acid diarrhea (BAD) (66). Bile acid sequestrants, such as colestyramine, bind bile acids in the intestine and were initially developed as cholesterol-lowering medication. Several studies have demonstrated a positive effect on diarrhea with cholestyramine in patients with CID or IBS-D with an abnormal result on a SeHCAT test (67-69). Based on these results, bile acid sequestrants are recommended in CID patients with a positive SeHCAT test result. During the Delphi panel, however, no consensus was found on the universal use of a SeHCAT test in patients with refractory chronic idiopathic diarrhea (76.5% agreement, See Table 2 with the list of statements on which no agreement was obtained). A possible explanation for this lack of consensus could be the limited availability and cost of the test. In the international literature, some experts also advise a short treatment course with a bile acid sequestrant in patients where a BAD test result is not available, as this may reveal whether or not the diarrhea is bile acid related (70).

Statement 36: Somatostatin analogues are recommended in the treatment of patients with refractory, large-stool chronic idiopathic diarrhea

Statement endorsed (Round 3): Agreement 76.5%, neutral 23.5%

Somatostatin analogues form the cornerstone for the treatment of patients with neuro-endocrine tumors (71). However, because of their inhibitory effect on intestinal secretion and motility, their clinical potential has also been evaluated in an open label clinical trial including patients with CID (72). In this trial, Lanreotide Autogel® 120 mg was shown to decrease symptoms in refractory CID patients, leading to a meaningfully improved QoL. While these findings warrant confirmation in a randomized setting, they do suggest a place for Somatostatin analogues in the treatment of patients with refractory CID, also taking into account the high healthcare cost of this drug.

Statement 37: 5-HT3 antagonists (e.g., ondansetron) are recommended in patients with refractory chronic idiopathic diarrhea

Statement endorsed (Round 3): Agreement 94.1%, neutral 5.9%

5-HT3 antagonists have extensively been studied in patients with IBS-D. In these studies, ondansetron was shown to have a significant effect on diarrhea and urgency, but not on abdominal pain (73-75). In addition, alosetron and ramosetron (not available in Europe) proved to be more effective than placebo in alleviating both pain and diarrhea in IBS-D patients (76). While these agents have not been tested in patients with CID, clinical experience supports their use in this condition as well. As such, the expert panel concluded that 5-HT3 antagonists are recommended in patients with refractory CID.

Statement 38: A fecal microbiota transplantation is not recommended in patients with chronic idiopathic diarrhea

Statement endorsed (Round 2): Agreement 88.9%, neutral 5.6%, disagreement 5.6%

A disturbed gut microbiome has been associated with chronic diarrhea. Based on this observation, probiotics, prebiotics, or antibiotics have been evaluated as treatment options for patients with chronic diarrhea. However, stool consistency itself is one of the most important determinants of microbiome composition. More recently, fecal microbiota transplantations have been evaluated in this setting, with mixed and at best short-term results (77-79). However, until more solid evidence has been generated in patients with CID, this therapeutic approach is not recommended in patients with refractory CID.

Conclusions

Chronic diarrhea can have a broad range of causes, making it a disease entity with a very extensive differential diagnosis. With this Delphi-based, multidisciplinary expert discussion we tried to generate some guidance on the different tests and evaluations that should be part of the diagnostic work up of patients with chronic diarrhea, both at initial presentation and after failure of empiric first line therapy. While a general consensus was reached on the required diagnostic tests for CID, marked differences were observed on the treatment preferences and strategies for these patients

Table 1. — **Overview of consensus statements -part 1.**

Definitions		
1	Chronic diarrhea is defined as loose or watery stool (Bristol Stool Form Scale 6 or 7) >3x per day or a total stool weight of >200 g/ day persisting for >4 weeks	Round 2: Agreement 94.4% Neutral 5.6%
2	Chronic idiopathic diarrhea (the scope of these guidelines) is distinguished from irritable bowel syndrome with diarrhea (IBS-D) by a lack of predominant abdominal pain.	Round 2: Agreement 100%
3	Chronic idiopathic diarrhea and IBS-D should not be seen as two different disease entities but exist on a continuum.	Round 3: Agreement 82.4% Neutral 11.8% Disagreement 5.8%
4	Refractory chronic idiopathic diarrhea is defined as a chronic diarrhea that was not resolved with standard first line therapy.	Round 3: Agreement 88.2% Neutral 5.9% Disagreement 5.9%
Diagnosis		
Initial presentation		
5	Patients can mistake fecal incontinence for chronic diarrhea. This issue should be adequately addressed during the initial history taking.	Round 2: Agreement 88.9% Neutral 11.1%
6	A detailed history is essential in the initial clinical assessment of a patient with chronic diarrhea.	Round 2: Agreement 100%
6a	The primary focus of physicians should be to rule out alarm signals, such as unexplained changes in bowel habits, nocturnal diarrhea, unintentional weight loss, blood in stool, tenesmus, evidence of malnutrition, etc.	Round 2: Agreement 94.4% Neutral 5.6%
6b	The initial assessment of patients with chronic diarrhea needs to address a potential family history of gastro-intestinal disease (e.g., celiac disease, IBD, colorectal cancer).	Round 2: Agreement 100%
6c	The initial assessment of patients with chronic diarrhea should include a detailed analysis of the current and recent medication use, including over-the-counter drugs and supplements	Round 2: Agreement 100%
6d	During the initial assessment of patients with chronic diarrhea the recent travel history of the patient has to be addressed	Round 2: Agreement 100%
6e	During the initial assessment of patients with chronic diarrhea potential associations between specific food consumption and the occurrence of diarrhea need to be assessed.	Round 3: Agreement 100%
6f	The initial clinical assessment of patients with chronic diarrhea should include an evaluation of the characteristics of the perceived chronic diarrhea (frequency, consistency [BSFS], duration, continuous or intermittent, etc.).	Round 3: Agreement 88.9% Neutral 11.1%
7	A whole blood count should be performed in all patients with chronic idiopathic diarrhea.	Round 2: Agreement 88.9% Neutral 5.6% Disagreement 5.6%
8	C-reactive protein (CRP) should be evaluated in all patients with chronic idiopathic diarrhea.	Round 2: Agreement 88.9% Neutral 5.6% Disagreement 5.6%
9	A thyroid function test should be performed in all patients with chronic idiopathic diarrhea.	Round 2: Agreement 88.9% Neutral 5.6% Disagreement 5.6%
10	Serum electrolytes should be evaluated in all patients with chronic idiopathic diarrhea.	Round 2: Agreement 94.4% Neutral 5.6%
11	Fecal calprotectin should be analyzed in all patients with chronic idiopathic diarrhea who do not require a colonoscopy.	Round 2: Agreement 88.9% Neutral 11.1%

Table 1. — **Overview of consensus statements -part 2.**

12	Routine stool testing for C. difficile is not recommended in patients with chronic idiopathic diarrhea in the absence of risk factors.	Round 2: Agreement 77.8% Neutral: 16.7% Disagreement 5.6%
13	A fecal occult blood test is not recommended in patients with chronic idiopathic diarrhea.	Round 3: Agreement 82.4% Neutral 17.6%
14	Serological tests for celiac disease (i.e., IgA tissue transglutaminase or IgG anti-deaminated gliadin peptide in case of IgA deficiency) should be performed in all patients with chronic idiopathic diarrhea.	Round 3: Agreement 82.4% Neutral 17.6%
15	In patients under the age of 45 with a suspicion for chronic idiopathic diarrhea there is no need for routine endoscopic examination in the absence of alarm signs or symptoms.	Round 2: Agreement 77.8% Neutral 11.1% Disagreement: 11.1%
16	A colonoscopy is recommended in all patients with chronic diarrhea under the age of 45 presenting with alarm signals.	Round 2: Agreement 100.0%
17	Whenever a colonoscopy is performed in patients with chronic diarrhea, biopsies should be collected from the left and right colon to exclude microscopic colitis.	Round 2: Agreement 100.0%
18	Abdominal ultrasound is not routinely recommended in all patients with chronic idiopathic diarrhea.	Round 3: Agreement 94.1% Neutral 5.9%
19	A lactose breath test is not routinely recommended in all patients with chronic idiopathic diarrhea to assess potential lactose malabsorption.	Round 3: Agreement 88.2% Disagreement 11.8%
20	A fructose breath test is not recommended in all patients with chronic idiopathic diarrhea.	Round 2: Agreement 94.4% Disagreement 5.6%
21	Routine testing for small intestinal bacterial overgrowth (SIBO) is not recommended in all patients with chronic idiopathic diarrhea	Round 2: Agreement 88.9% Neutral: 5.6% Disagreement 5.6%
22	Transit time studies are not recommended in the diagnostic work-up for patients with chronic idiopathic diarrhea	Round 2: Agreement 100.0%
23	Testing for microbiota composition is not recommended in the diagnostic work-up for patients with chronic idiopathic diarrhea.	Round 2: Agreement 100.0%
24	Food allergy testing using an IgE test is not recommended in patients with chronic idiopathic diarrhea.	Round 2: Agreement 100.0%
25	Food allergy testing using an IgG test is not recommended in patients with chronic idiopathic diarrhea.	Round 2: Agreement 100.0%
Refractory setting		
26	A colonoscopy is recommended in all patients with refractory chronic idiopathic diarrhea, regardless the presence of alarm signs or symptoms.	Round 2: Agreement 83.3% Neutral: 11.1% Disagreement 5.6%
27	A 72h stool collection is recommended in patients with refractory chronic idiopathic diarrhea to assess stool volume and fat contents.	Round 3: Agreement 82.4% Neutral: 11.8% Disagreement 5.9%
28	An upper GI endoscopy is recommended in all patients with refractory chronic idiopathic diarrhea	Round 2: Agreement 83.3% Neutral: 16.7%
29	A routine video capsule endoscopy is not recommended in all patients with refractory chronic idiopathic diarrhea.	Round 2: Agreement 100.0%

Table 1. — **Overview of consensus statements -part 3.**

Treatment		
Primary setting		
30	Loperamide is a first-line treatment for patients with chronic idiopathic diarrhea	Round 2: Agreement 77.8% Neutral: 16.7% Disagreement: 5.6%
31	Soluble fiber supplements (e.g., psyllium) are a first line treatment for patients with chronic idiopathic diarrhea.	Round 3: Agreement 76.5% Neutral: 23.5%
32	Spasmolytic agents are not recommended in patients with chronic idiopathic diarrhea.	Round 2: Agreement 82.4% Neutral: 11.8% Disagreement 5.9%
Refractory setting		
33	A low FODMAP diet is recommended in patients with refractory chronic idiopathic diarrhea in whom other measures have failed.	Round 3: Agreement 82.4% Neutral: 5.9% Disagreement 11.8%
34	A gluten-free diet is not recommended in patients with refractory chronic idiopathic diarrhea.	Round 2: Agreement 94.4% Neutral 5.6%
35	Bile acid sequestrants are recommended for patients with refractory chronic idiopathic diarrhea testing positive for bile acid diarrhea.	Round 2: Agreement 94.4% Neutral 5.6%
36	Somatostatin analogues (e.g., lanreotide autogel®) are recommended in the treatment of patients with refractory, large-stool chronic idiopathic diarrhea.	Round 3: Agreement 76.5% Neutral 23.5%
37	5-HT3 antagonists (e.g., ondansetron) are recommended in patients with refractory chronic idiopathic diarrhea.	Round 3: Agreement 94.1% Neutral 5.9%
38	A fecal microbiota transplantation is not recommended in patients with chronic idiopathic diarrhea.	Round 2: Agreement 88.9% Neutral 5.6% Disagreement 5.6%

Table 2. — **Overview of statements on which no consensus was reached - part 1.**

Statement	Agreement
Routine stool testing for ova, cysts, and parasites is not recommended in patients with chronic idiopathic diarrhea in the absence of risk factors.	Round 2: Agreement:50% Neutral: 33.3% Disagreement: 16.7%
Routine stool culture for conventional bacterial entero-pathogens is not recommended in patients with chronic idiopathic diarrhea in the absence of risk factors.	Round 2: Agreement: 61.1% Neutral 22.2% Disagreement: 16.7%
A spot stool acid steatocrit test should be performed in patients with chronic idiopathic diarrhea to rule out steatorrhea.	Round 3: Agreement: 35.3% Neutral: 41.2% Disagreement 23.5%
An exocrine pancreatic function test (e.g., fecal-elastase-1 or breath test) is recommended in patients with refractory chronic idiopathic diarrhea to assess the pancreatic exocrine function and secretion.	Round 3: Agreement 35.3% Neutral: 47.1% Disagreement 17.6%
Abdominal CT/MRI imaging is recommended in patients with refractory chronic idiopathic diarrhea.	Round 3: Agreement 52.9% Neutral: 29.4% Disagreement: 17.6%.

Table 2. — **Overview of statements on which no consensus was reached - part 2.**

Abdominal ultrasound imaging is recommended in patients with refractory chronic idiopathic diarrhea.	Round 3: Agreement 29.4% Neutral: 29.4% Disagreement: 41.2%.
SeHCAT testing is recommended in patients with refractory chronic idiopathic diarrhea to exclude bile acid diarrhea.	Round 3: Agreement 76.5% Neutral: 5.9% Disagreement: 17.6%
Screening for factitious diarrhea by laxative abuse (e.g., magnesium and phosphate analyses in stool or urine toxicology) is recommended in patients with refractory chronic idiopathic diarrhea.	Round 2: Agreement 44.4% Neutral: 50% Disagreement: 5.6%
Routine screening for neuroendocrine tumors with biochemical tests (e.g., 5-HIAA) is not recommended in patients with refractory chronic idiopathic diarrhea.	Round 2: Agreement 66.7% Neutral: 33.3%
Selected pro- and post-biotics are recommended in patients with chronic idiopathic diarrhea.	Round 3: Agreement 11.8% Neutral: 58.8% Disagreement 29.4%-
Xyloglucan-pea protein-xylo-oligosaccharides (e.g., Gelsectan) is recommended for patients with chronic idiopathic diarrhea.	Round 3: Agreement 17.6% Neutral: 76.5% Disagreement 5.9%
Selected antibiotics (e.g., doxycycline or rifaximin) are recommended in patients with refractory chronic idiopathic diarrhea.	Round 3: Agreement 5.9% Neutral 52.9% Disagreement 41.2%
Tricyclic antidepressants (e.g., amitriptyline, imipramine) are recommended in patients with refractory chronic idiopathic diarrhea.	Round 3: Agreement 35.3% Neutral 41.2% Disagreement 23.5%
Codeine is recommended in patients with refractory chronic idiopathic diarrhea.	Round 3: Agreement 35.3% Neutral 11.8% Disagreement 52.9%
Opium tincture is recommended in patients with refractory chronic idiopathic diarrhea.	Round 3: Agreement 47.1% Neutral 52.9%
Bile acid sequestrants are recommended for patients with refractory chronic idiopathic diarrhea in the absence of a test result for bile acid diarrhea.	Round 3: Agreement 76.5% Neutral 5.9% Disagreement 17.6%

among the different experts. The main reason for this is the lack of solid scientific evidence with the different treatment options in this setting (i.e., most data have been generated in patients with IBS-D). Nevertheless, the Delphi-like process that was used for this initiative proved to be a useful vehicle to fuel discussions on the management of CID among experts with different backgrounds and to sketch the current clinical practice.

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Conflict of interest

- TV: received lecturing fees from Abbott, Biocodex, Ipsen, Menarini, Microbiotica, MyHealth, Schwabe, Truvion. Participated in advisory boards for Biocodex, Ipsen, Norgine, PSI, Truvion. Received research grants from Danone, MyHealth.
- JA: nothing to declare
- VC: nothing to declare
- FdC: recieved speakers fees from: Truvion. Advisory boards: Abbvie and Dr Falk Farma

- DD: nothing to declare
- HD: nothing to declare
- KG:Received participation in advisory boards, received travel grants and research funding from Ipsen.
- MH: nothing to declare
- TH: nothing to declare
- HL: consultancy fees from Biocodex, Ipsen, Johnson & Johnson
- SK: Receipt of advisory, honoraria or consultation fees from Truvion Healthcare & Schwabe Pharma, president of BSNM which receives financial support from Truvion Healthcare, Kenvue, Mayoly, Schwabe, Myhealth and Biocodex.
- PL: nothing to declare
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- SN: received lecture and/or consulting fees from Truvion and Dr. Falk Pharma.
- HP: nothing to declare
- MS: nothing to declare
- JT: Jan Tack has given Scientific advice to Aclipse, Adare, AlfaSigma, Clasado, Danone, Falk, FitForMe, Ironwood, Kyowa Kirin, Menarini, Promed, Ricordati, Takeda, Truvion, Tsumura, Zealand Pharmaceuticals, has received research support from Biohit, Kiowa Kirin, ProMed, Sofar and Takeda, and has served on the Speaker bureau for Abbott, Bio-Codex, Mayoly, Menarini, ProMed, Schwabe, Takeda and Truvion Pharmaceuticals.
- RB: speaker fee and consultancy for Ipsen and Norgine.

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