Diagnostic approach to chronic diarrhoea and recent insights in treatment of functional diarrhoea including irritable bowel syndrome

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Abstract

Chronic diarrhoea is a common clinical problem with a plethora of possible causes and underlying pathophysiological mechanisms. The value of diagnostic assessment by laboratory testing, stool analysis, evaluation of bile acid malabsorption, endoscopy, breath testing and radiological imaging techniques is discussed. The decision to focus investigations on excluding certain pathologies remains a matter of clinical judgement. Functional diarrhoea and irritable bowel syndrome (IBS) being the most frequent causes of chronic diarrhoea, recent insights in the role of dietary management, management of dysbiosis by pre-, pro- and antibiotics and faecal microbiota transplantation, as well as targeted treatment by spasmolytics, 5-HT$_3$ receptor antagonists and eluxadoline will be reviewed. (Acta gastroenterol. belg., **2020**, 83, **461-474**).

Keywords : chronic diarrhoea, treatment, diagnosis, irritable bowel syndrome, review.

Abbreviations : 5-HT$_3$ 5-hydroxytryptamine, serotonin ; Anti-TTG, Anti-tissue transglutaminase ; BA, Bile acids ; BAD, Bile acid diarrhoea ; BAM, Bile acid malabsorption ; BSC, Bristol Stool Chart ; cfu, Colony forming unit ; CH_4, Methane ; CO_2, Carbon dioxide ; CT, Computed tomography ; CRP, C reactive protein ; EMEA, European Medicines Evaluation Agency ; EUS, Endoscopic ultrasound ; FBT, Fructose breath test ; FMT, Faecal microbiota transplantation ; FE-1, Faecal elastase-1 ; FOB, Faecal occult blood ; FODMAP, Fermentable oligo-, di- and monosaccharides and polyols ; GBT, Glucose Breath test ; GI, Gastrointestinal ; H_1, Histamine-1 ; H_2, Hydrogen gas ; IBD, Inflammatory bowel disease ; IBS, Irritable bowel syndrome ; IBS-D, Diarrhoea-predominant irritable bowel syndrome ; IgA, Immunoglobulin A ; LBT, Lactose breath test ; MRI, Magnetic resonance imaging ; NICE, National Institute for Health Care and Excellence ; PEI, Pancreatic exocrine insufficiency ; PPV, Positive predictive value ; RCT, Randomized controlled trial ; RNA, Ribonucleic acid ; SIBO, Small intestinal bacterial overgrowth ; SOS, Sphincter of Oddi spasm ; SSS, Symptom scale severity ; ^{75}SeHCAT, ^{75}Selenium-homotaurocholic acid test ; XOS,Xylo-oligo saccharides.

Introduction

Diarrhoea is a difficult to define entity; it may be defined in terms of stool consistency or frequency as well as stool volume or weight. However, for most patients the concept of diarrhoea refers to 'loose stools' and is thus defined in terms of stool consistency. The definition of stool consistency can be facilitated by using the Bristol Stool Chart (BSC) as shown in figure 1, which has shown substantial validity and reliability (1). Diarrhoea is defined as stool type 5 or above using the BSC.

It is of great importance to perform a thorough history as there may be a discrepancy between the medical and non-medical concepts of diarrhoea; for example, faecal incontinence may be misinterpreted as diarrhoea. These discrepancies need clarification at the initial patient history to avoid unnecessary investigations.

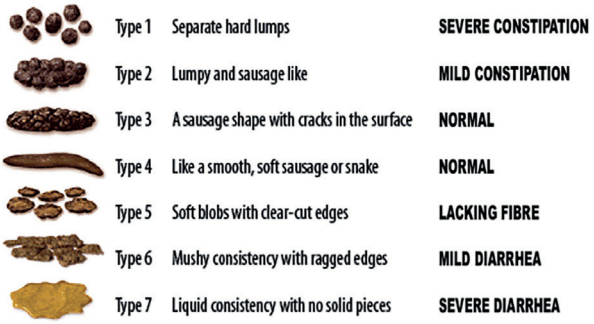

Figure 1. — Bristol Stool Chart.

Currently, there is no consensus on the duration of symptoms in chronic diarrhoea; symptoms persisting longer than 4 weeks is however a widely accepted duration to define chronic diarrhoea (2). On this basis the British Society of Gastroenterology defines chronic diarrhoea as "the persistent alteration from the norm with stool consistency between types 5 and 7 on the Bristol stool chart and increased frequency greater than 4 weeks' duration." (2)

Chronic diarrhoea is one of the most common reasons for a patient to seek expert help at a gastroenterology clinic. Prevalence rates are difficult to estimate in part because of difficulties in defining chronic diarrhoea, but also because of population differences. In 1992 the prevalence of chronic diarrhoea (based on excessive stool frequency without abdominal pain) in adults was estimated at 4-5% in a Western population (3); a more recent estimate is not (yet) available, neither is one based on the above-mentioned definition of chronic diarrhoea.

Clinical assessment and investigations

History and examination

A detailed history is essential in the initial clinical assessment of a patient presenting with chronic

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diarrhoea. A complete history should focus on alarm symptoms associated with diarrhoea such as blood loss in the stool, recent unexplained change in bowel habit and unintentional weight loss. With this history it should also be attempted to distinguish what the patient means by 'diarrhoea' (as noted above), as well as detecting symptoms suggestive of an organic cause of diarrhoea. Examples include diarrhoea of less than three months' duration, stools suggestive of steatorrhea, mucous discharge with stools and nocturnal or continuous (as opposed to intermittent) diarrhoea. Attention should be paid to the concomitant presence of oral, respiratory, dermatological, systemic or other gastrointestinal (GI) symptoms as these could be indicative of food allergy, especially when these symptoms occur reproducibly after exposure to specific food and are absent during avoidance (4). A thorough history should also include information on family history of GI diseases (in particular of neoplastic, inflammatory bowel disease (IBD) or coeliac disease), a personal history of abdominal surgery or radiation (e.g. small and/or large intestinal resection, cholecystectomy, abdominal radiation), pancreatic disease and systemic disease (e.g. hyperthyroidism, diabetes mellitus, parathyroid disease, adrenal disease, systemic sclerosis), diet, alcohol use, use of drugs (and recent antibiotic use) and also travel history. A non-exhaustive list of potential causes of chronic diarrhoea is listed in table 1. Several interesting case findings of rare causes of chronic diarrhoea have also been reported in this journal, for example olmesartan enteropathy, immunotherapy related colitis, histiocytic colitis, Whipple's disease, etc. (5-9).

1. Initial testing

An initial assessment using the combination of blood tests and examination of stool is recommended in all patients presenting with chronic diarrhoea to exclude or screen for common causes of chronic diarrhoea (2). Blood tests should include a full blood count, urea, serum creatinine, electrolytes (including calcium and phosphorus), liver function tests, C reactive protein (CRP), vitamin B12, folate, ferritin, thyroid function tests and serological tests for coeliac disease (with anti-tissue transglutaminase (anti-TTG) antibody being the most sensitive test in patients without immunoglobulin A (IgA) deficiency) (10). Stools should be tested for *Clostridioides difficile*, ova, cysts, parasites and calprotectin.

It is reasonable to make a positive diagnosis of functional diarrhoea or irritable bowel syndrome (IBS) with predominant diarrhoea (IBS-D, depending on the presence of associated abdo-minal pain) following negative results on the above-mentioned testing.

2. Further testing

Further testing should always be considered in patients with chronic diarrhoea who also present with worrisome features and those diagnosed with functional diarrhoea/ IBS-D unresponsive to treatment. Selection of one or more of the below mentioned testing modalities are to be made on a patient-to-patient basis. The decision to focus investigations on excluding certain pathologies is a matter of clinical judgement and should be founded on

Table 1. — **Causes of chronic diarrhoea (2,5-9)**

Common	**Infrequent**
IBS-diarrhoea	Small bowel bacterial overgrowth
Bile acid diarrhoea	Mesenteric ischemia
Diet	Lymphoma
- FODMAP malabsorption	Surgical causes (e.g. small bowel resections, internal fistulae)
- Lactase deficiency	Chronic pancreatitis
- Artificial sweeteners (e.g. sorbitol, xylol in chewing gum, soft drinks)	Radiation enteropathy
- Caffeine (e.g. coffee, coke, energy drinks)	Pancreatic carcinoma
- Excess alcohol	Hyperthyroidism
- Excess liquorice	Diabetes
Colonic neoplasia	Food allergy
Inflammatory bowel disease	Giardiasis (and other chronic infection)
- Ulcerative colitis	Cystic fibrosis
- Crohn's disease	Factitious diarrhoea
- Microscopic colitis	
Coeliac disease	**Rare**
Drugs	
- Antibiotics, in particular macrolides	Other small bowel enteropathies (e.g. Whipple's disease (9), tropical sprue, amyloid, intestinal lymphangiectasia)
- Non-steroidal anti-inflammatory drugs	Infectious colitis (e.g. histiocytic colitis) (8)
- Magnesium-containing products	Immunotherapy related colitis (7)
- Hypoglycemic agents (e.g. metformin, gliptins)	Hypoparathyroidism
- Antineoplastic agents	Addison's disease
- Others (e.g. furosemide, Olestra, Olmesartan (5,6))	Hormone secreting tumors (VIPoma, gastrinoma, carcinoid)
Overflow diarrhoea	Autonomic neuropathy
	Brainerd diarrhoea (possible infectious cause not identified)

FODMAP fermentable oligo-, di- and monosaccharides and polyols ; IBS irritable bowel syndrome ; VIPoma vasoactive intestinal peptide-producing tumor.

a thorough history.

a. Stool tests

As noted above, stools should be tested for *C. difficile*, ova, cysts and parasites in any patient presenting with chronic diarrhoea. Faecal calprotectin has also been suggested as a (first-line) stool test in patients with chronic diarrhoea to detect intestinal inflammation and to help differentiate between IBS and IBD in adults with lower GI symptoms in whom cancer is not suspected (2,11-13). Calprotectin is released by granulocytes, monocytes, macrophages and epithelial cells during an inflammatory response; when the inflammation occurs within the GI tract, calprotectin is released into the intestinal lumen. In the lumen it is mixed with the faeces and remains stable enough for 7 days at room temperature to be measured (2,11). It has a high negative predictive value in ruling out IBD, but it is not specific for IBD as it is a marker for intestinal inflammation; other causes of raised faecal calprotectin include colorectal cancer, microscopic colitis, diverticulitis and infectious gastroenteritis (2,11,13,14). The cut-off for faecal calprotectin is commonly set at 50 or 100µg/g faeces, with lower values indicative of functional disease, and higher values suggestive of inflammation (2,11). An exact cut-off value that distinguishes between functional intestinal disease and IBD does not exist, but the higher cut-off value of 150µg/g faeces suggested in a recent meta-analysis has potentially good diagnostic accuracy (12,13).

Another commonly used stool test is the faecal occult blood test (FOB); the most commonly used type of FOB uses an immunohistochemical technique to detect blood (2). This test is widely used as screening method for colorectal cancer, which is also the case in Belgium since 2013 for the Dutch-speaking part and 2016 for the French-speaking part of the country. Studies indicate that in patients with lower GI symptoms suggestive of colorectal cancer, the FOB-test has a high negative predictive value (2). This test may also reduce the burden of unnecessary endoscopic examination of the colon to exclude colorectal cancer in symptomatic patients when the test is negative (2).

The 72-hour quantitative faecal fat estimation is considered the golden standard for assessing steatorrhea which is defined as a faecal fat excretion of >7,0g per 24 hours (15). Yet this test is very laborious and time-consuming given the fact that patients are required to maintain a strict diet containing 100g of fat for five days and are to collect the total amount of faeces excreted over the last three days of the given five-day period. Therefore, it is largely abandoned for the diagnosis of steatorrhea.

The spot stool acid steatocrit is a more commonly and easily used stool test measuring stool fat content in a given stool sample after having maintained a diet containing 100g of fat for three days. The spot stool acid steatocrit correlates well with the 72-hour quantitative faecal fat estimation in terms of detection of steatorrhea (16,17). It has a sensitivity, specificity and positive predictive value (PPV) of respectively 100%, 95% and 90% for the assessment of steatorrhea (16,17). Given the ease of use of this test, it has largely replaced the 72-hour quantitative faecal fat estimation for the diagnosis of steatorrhea and fat malabsorption.

Another stool test is the faecal elastase-1 (FE-1) test which is used for the indirect and non-invasive evaluation of pancreatic exocrine function and secretion (18). It is a simple test in which elastase-1, a pancreatic protease, is detected in a single stool sample. It is stable in stool for up to one week at room temperature and is not affected by dietary modifications (2). The lower the FE-1 concentration, the higher the probability of pancreatic exocrine insufficiency (PEI); the threshold of 200µg/g faeces is mostly used as cut-off for detection of moderate to severe PEI (18). The FE-1 test does not allow the clinician to exclude mild PEI (sensitivity < 60%), although high values (>500µg/g faeces) exclude PEI (2,18). Also, in patients with diarrhoea, the possibility of false-positive results due to stool dilution (i.e. low levels of FE-1 in large volume liquid stool) should be considered (2,18,19).

The spot stool acid steatocrit method and the FE-1 test are both good and easy-to-use methods for the non-invasive evaluation of pancreatic exocrine function in patients with chronic pancreatitis (20). Although they correlate well to each other, the FE-1 test detected more patients with PEI than the spot stool acid steatocrit method in patients with chronic pancreatitis in the study of Kamath et. al, making it the preferred method for detection of PEI in chronic pancreatitis (18,20). On the other hand, the spot stool acid steatocrit method mostly demonstrated its diagnostic role in young patients with cystic fibrosis (21,22).

b. Endoscopic examinations

In most patients with chronic diarrhoea endoscopic investigation will be performed. In patients under the age of 40 with diarrhoea and other typical symptoms of a functional bowel disorder and negative results on initial testing, a diagnosis of functional diarrhoea or IBS with predominant diarrhoea (depending on the symptoms) may be made without the need for further endoscopic examinations (2). On the other hand, patients presenting with chronic diarrhoea who have severe symptoms and/or do not have typical symptoms of a functional bowel disorder should undergo further testing.

Colonoscopy is the most widely used first-line endoscopic examination in patients with chronic diarrhoea, and full colonoscopy (with routine ileoscopy) is preferred over sigmoidoscopy because of the higher chance of finding abnormalities and thus making a positive diagnosis with inspection of the more proximal colon and ileum (2,23-25). Colonoscopy (preferably with routine ileoscopy) with biopsies is a valuable exam for diagnosing neoplasia, IBD, microscopic colitis and other

inflammatory conditions causing chronic diarrhoea (2,23-25). There is no consensus about the number of biopsies for the diagnosis of microscopic colitis, yet it is reasonable to obtain eight or more biopsies from the right and left colon in a typically macroscopically normal-appearing colon (23). The biopsies are preferably taken above the rectum because of differences in collagen thickness and extent of lymphocytic intraepithelial infiltration between the rectum and the remainder of the colon (23). Routine biopsy of a macroscopically normal-appearing ileum is on the other hand not recommended as it rarely provided clinically relevant information according to the study of Melton et al. (26).

The role of upper GI endoscopy in patients presenting with chronic diarrhoea is not well studied and the diagnostic yield is thus unclear. It should not be routinely performed but restricted to patients with for example suspected coeliac disease, lymphoma (potentially associated with coeliac disease) or Whipple's disease (10,23). When performed, duodenal biopsies should always be obtained, even in a macroscopically normal-appearing small bowel (23).

In patients presenting with chronic diarrhoea suspected to arise from the small-bowel, capsule endoscopy may have a role to detect small-bowel abnormalities (as a first-line examination over radiological imaging), or may serve as a way to further asses the small bowel in negative or inconclusive radiological small-bowel imaging (27). The downside to capsule endoscopy is the inability to obtain a histological diagnosis; for this reason it is not recommended in patients with suspected coeliac disease (10,27). The role of small bowel enteroscopy in the diagnosis of patients presenting with chronic diarrhoea remains unclear. It is mostly reserved as a complementary examination in patients who have documented abnormalities of the small bowel through other modalities (e.g. small bowel imaging or capsule endoscopy); it is then used for targeting lesions, obtaining histology and/or therapeutic intervention (27).

a. Radiological imaging

Radiological imaging is mostly reserved for the evaluation of the small bowel and the pancreas. Historically, the small bowel barium follow through or barium enteroclysis was considered the standard to assess the small bowel. However, these examinations lack sensitivity and specificity in the detection of small bowel abnormalities and are largely abandoned in clinical practice (28).

Ultrasonography is another modality to assess the bowel, but it can also be used to evaluate the pancreas. Although its non-invasiveness, widespread availability and lack of radiation, it remains a lesser-used radiological modality to assess the small bowel and pancreas due to the difficulties of viewing the entirety of the GI tract, the lack of accuracy in diagnosing chronic pancreatitis, and the high operator dependency (18).

Computed tomography (CT) and magnetic resonance imaging (MRI), and especially the CT and MRI enterography, have become the preferred imaging modalities for the evaluation of the small bowel (2). The enterography techniques are based on imaging of the small bowel after ingestion of a large amount of oral contrast over a short period of time, allowing accurate evaluation of small bowel abnormalities (2,29). Because of high radiation burden when using CT enterography, and the higher sensitivity of MRI enterography in the detection of small bowel diseases and neoplasms when compared to CT enterography, MRI enterography should be the preferred initial test in patients with chronic diarrhoea and suspected small intestinal abnormalities (2,29).

Imaging studies are also applied for the evaluation of patients with (suspected) chronic pancreatitis. Ultrasonography is (as noted above) one modality to evaluate the pancreas. However, its value is limited to diagnose advanced chronic pancreatitis (18). Endoscopic ultrasound (EUS), CT and MRI all have comparable high diagnostic yield in the diagnosis of chronic pancreatitis (18). EUS is the most sensitive technique to diagnose chronic pancreatitis, especially in earlier stages of the disease (18). However, because of the more invasive character, EUS is not the preferred first-line examination in a patient with chronic diarrhoea with suspected chronic pancreatitis (2,18). In this case, CT and MRI are preferred; the choice between the two relies partly on the local availability and the cost.

b. Assessment of bile acid malabsorption

Bile acids (BA) are small molecules synthesized by the hepatocytes in the liver and secreted in the bile, mixing with meals in the intestinal lumen in order to absorb dietary fats and fat-soluble vitamins (30,31). In normal circumstances about 95% of the BA are reabsorbed in the ileum and are transported back through the portal vein to the liver for recycling, the so-called enterohepatic circulation (30,32,33). A small percentage of the unbound BA arrive in the colon, where a fraction is reabsorbed through the colonic mucosa and the remainder is lost with the faecal output (33). When an imbalance in the enterohepatic circulation resulting in bile acid malabsorption (BAM) occurs, excessive BA are present in the colon, giving way to what is called bile acid diarrhoea (BAD) (32,34).

Bile acid malabsorption is a common yet under-estimated cause of chronic diarrhoea; an estimate of 1% of the general population suffers from BAD (35). In patients with ileal disease (e.g. after ileal or ileocecal resection, Crohn's disease, radiation enteritis, etc.), BAM is especially common because of the disruption of the enterohepatic circulation of BA, and should always be considered as a causal factor in these patients presenting with chronic diarrhoea (32,34,36,37). Also, studies show that up to one third of patients diagnosed with IBS-D or functional diarrhoea actually have BAD (35,37). Bile acid

malabsorption has also been reported in other conditions such as in small intestinal bacterial overgrowth (SIBO), patients who have undergone cholecystectomy, patients with PEI, etc. (2,35).

For the diagnosis of BAM, several tests have been developed; the scintigraphic method ^{75}Selenium-homotaurocholic acid test (^{75}SeHCAT) is the most widely available and used test in Europe because it has the highest diagnostic yield for the diagnosis of BAM (34,38). This test is based on a two-phase (usually at 3 hours and 7 days), scintigraphic detection of gamma radiation after oral administration of ^{75}Selenium homotaurocholic acid which is a gamma-emitting, synthetic BA that follows the same enterohepatic cycle as endogenous BA (34). A retention of more than 15% of the gamma-emitting, synthetic BA after 7 days is defined as normal; retention of 10-15%, 5-10% and < 5% is usually defined as mild, moderate and severely abnormal BA loss respectively (2,32). These cut-offs also predict the probability of response to a treatment with BA sequestrant, with better response-rates with increasing BAM (2). Using the < 10% retention as cut-off, the ^{75}SeHCAT-test has an average sensitivity and specificity of 87% and 93% respectively for the diagnosis of BAM (34).

BAM can be assessed by other techniques as reviewed by Vijayvargiya and Camilleri (32). Direct measurement of bile acid content in a 48h stool collection is considered the best alternative when ^{75}SeHCAT is not available. Serum biomarkers have also been proposed, such as fasting 7 α-hydroxy-4-cholesten-3-One and fasting fibroblast growth factor 19, but they suffer from a lower diagnostic accuracy and are therefore infrequently used in Europe.

c. Lactose breath tests

Lactose malabsorption is a well-recognized cause of chronic diarrhoea. The ability to produce lactase, the enzyme responsible for intestinal hydrolysis of lactose, decreases with age. Genetic variances and continued exposure to dairy products beyond infancy also contribute to persistence of lactase beyond infancy, while GI infections, inflammatory bowel disease and abdominal surgery can lead to secondary lactase deficiency (39,40). The prevalence of lactose malabsorption has a wide geographical variability. Lactose intolerance resulting from lactose malabsorption should be suspected in case of repeated abdominal pain, flatulence, bloating and/or diarrhoea after intake of dairy products. Upon suspicion, some guidelines recommend an empirical trial of lactose free diet.

However, as complete avoidance of lactose is cumbersome in Western countries, most patients will undergo a lactose breath test (LBT). This test is based on the detection of metabolites such as hydrogen gas (H_2), methane (CH_4) and carbon dioxide (CO_2) resulting from the fermentation of lactose by colonic bacteria. Increasing concentrations of exhaled H_2 in breath samples obtained at different time points for 2-4 hours after ingestion of lactose are considered diagnostic for lactose malabsorption. Adding the measurement of CH_4-excretion increases the sensitivity of the lactose breath test by detecting patients with an excessive CH_4-production by the intestinal flora. For the indication, preparation, performance and interpretation of the breath test we refer to the North American consensus (41).

Noteworthy, some IBS patients will report symptoms after ingestion of lactose independently of lactose malabsorption, probably reflecting increased visceral sensitivity (42,43).

Other dissacharide malabsorptions, especially sucrase-isomaltase deficiency, are being investigated, but so far their role in the generation of symptoms such as diarrhoea and the therapeutic value of restriction diets targeting these malabsorptions remain uncertain (44,45).

d. Fructose breath test

Fructose malabsorption sometimes is believed to result in chronic diarrhoea. Similar to lactose malabsorption, diagnosis is obtained by a breath test, with the increase of H_2- or CH_4-excretion above a set threshold reflecting insufficient absorption of the substrate. When abdominal symptoms are recorded simultaneously, a distinction can be made between malabsorption (increased H_2- or CH_4-excretion) and intolerance (increased symptom severity). Upon confirmation of fructose malabsorption, a low fructose diet is believed to reduce symptoms of abdominal pain as well as diarrhoea. However, thorough validation of the fructose breath test (FBT) for clinical use by assessing its reproducibility and accuracy is lacking.

Test reproducibility implicates that a similar result should be obtained upon retesting. Yao et al. found no significant correlation in H_2-excretion during a 35 g fructose breath test upon retesting, with 27% of patients losing fructose malabsorption upon retesting (46). More recently, reproducibility for malabsorption as measured by a 25 g fructose breath test was noted to be poor, in contrast to the moderate reproducibility for intolerance status (47).

In order to verify the accuracy of the FBT and answering the question whether it measures what it intends to, its ability to predict the clinical response to a low fructose diet has been analysed. Already in 2013, consumption of a low fructose diet demonstrated an improvement in symptom scores as well as stool frequency in IBS patients diagnosed by ROME II criteria, but no change in stool consistency was observed (48). Similar results were obtained more recently by Melchior et al. and Helwig et al., with the authors of both studies concluding that a low fructose diet improved symptom scores in IBS independently of the results of a FBT (49,50). However, in the latter study a correlation between symptoms of fructose malabsorption and H_2-breath test measures was still observed (50).

Noteworthy, it is only recently that the North American consensus upon the test dose and the interpretation of the H_2- and CH_4-excretion was reached (41). As 25 g of fructose is now considered the preferred dose, this dose should be used by future studies assessing the validity of FBT. Meanwhile, in the absence of predictive value of this test and considering the insufficient data for reproducibility, a low fructose diet could be initiated without the hassle of prior testing. However, while improvement in abdominal symptoms can be expected from a low fructose diet, there is only scant data to support this diet for improvement in stool consistency.

e. Assessment of small intestinal bacterial overgrowth

In at least a subset of patients, chronic diarrhoea is attributed to SIBO. While SIBO is readily suspected after surgery associated with intestinal blind loops, e.g. after bariatric surgery or surgical reconstructions, an association with IBS-D (as described in a recent meta-analysis by Ghoshal et al.) and functional diarrhoea has been demonstrated (51-53). A recent meta-analysis of case-control studies identified a possible link between IBS and SIBO ; concomitantly the authors emphasized on the low quality of available evidence resulting from the heterogeneity in selection criteria and the limited sensitivity and specificity of the available diagnostic tests (54). On the other hand, others provided additional data to corroborate the link between IBS-D and SIBO by the identification of an increased abundance of *Prevotella sp*. as measured by 16S-RNA in IBS-D patients with a positive lactulose breath test (55).

While culture of jejunal aspirate is considered the golden standard, it suffers from major limitations. Its invasive nature and the lack of standardization limit its use to research. Breath tests have been proposed as an alternative for clinical use. Both glucose breath tests and lactulose breath tests are advocated, but similarly suffer from a lack of standardization of the test protocol. Between different studies dosage of glucose vary from 50 g up to 100 g. The amount of administered water can be as low as 100 ml or as high as 375 ml. Moreover, the criteria for a positive result differ significantly between studies as reviewed by Quigley et al. (56). Some studies consider any increase above 20 ppm as a positive, while others report 10 or 15 ppm, or an increase of 10 or 20 ppm above baseline. Adding CH_4-excretion to the equation only adds up to the interpretative complexity. Possibly the North American consensus on the topic will help tackle the issue (41).

When comparing both GBT and LBT to jejunal aspirate culture, irrespectively of the indication, a higher sensitivity and specificity was demonstrated for GBT, although sensitivity reached only 54,5% with GBT (57). These values increased when applying the test in patients with a history of GI surgery. A recent meta-analysis confirmed the superiority of GBT and jejunal aspirate over LBT for the diagnosis of SIBO in IBS, and additionally indicated the higher prevalence of a positive GBT in IBS-D patients (51).

Nevertheless, it remains to be proven whether a positive GBT actually identifies bacterial overload. Questioning this assumption, a study measured a similar bacterial load (being the number of bacterial genomes, colony counts or bacterial viability) in positive and negative GBT (58). Moreover, no correlation between H_2-excretion or jejunal bacterial load could be identified. However, an inverse correlation between H_2-excretion and bacterial viability was demonstrated.

f. Factitious diarrhoea

In Western populations, factitious diarrhoea by laxative abuse is a relatively common cause of chronic diarrhoea. In one study approximately 4% of patients presenting to gastroenterology clinics for chronic diarrhoea were diagnosed with factitious diarrhoea (59). This number was five times higher in patients presenting with chronic diarrhoea who had been evaluated in tertiary referral centres, making it the most common cause of diarrhoea of previously undetermined origin (59). The likelihood of this diagnosis increases with every additional negative examination and should always be kept in mind, especially when the patient has a secondary gain from the illness (2,23,60).

Alkalinisation assays used to be the only tests to detect laxative abuse, but are of insufficient sensitivity and are largely abandoned (2). Laxatives such as anthraquinones, bisacodyl and phenolphthalein can be detected in stool and urine and have been proposed as screening examination by the British Society of Gastroenterology together with measurement of magnesium and phosphate in stool of patients with suspected laxative abuse (2). Repeated analysis of stool and urine may be necessary as laxatives may be ingested intermittently.

Treatment

Upon identification of a treatable cause of chronic diarrhoea (e.g. colonic neoplasia, coeliac disease, IBD, microscopic colitis, etc.), directed treatment will be initiated. We refer to the specific guidelines of these entities. In the absence of a specific cause of diarrhoea, but also in the case of absence of a definitive treatment, symptomatic treatment will be initiated. Different therapeutic options are available to the clinician to improve stool consistency. An overview of therapeutic options is provided in table 2.

1. First-line treatment

a. Dietary modifications:

Dietary advice has been advocated for a long time in the management of chronic diarrhoea, with the first

Table 2. — **Therapeutic options for chronic diarrhoea in the absence of a specific cause**

First line	
Dietary management	
Dietary fibre supplements	
NICE-modified diet	
Low FODMAP diet	
Targeted treatment:	
Loperamide	Opioid-receptor agonist
Beyond first line	
Management of gut dysbiosis:	
Prebiotics	
Probiotics	
Faecal Microbiota transplantation *	
Rifaximin	
Targeted treatments:	
Otilonium Bromide *	Spasmolytic agent
Peppermint oil *	Spasmolytic agent
Alosetron $	5-HT_3-receptor antagonist
Ramosetron $	5-HT_3-receptor antagonist
Eluxadoline $	Opioid-receptor agonist and antagonist
Somatostatin analogues	Somatostatine receptor agonist
Cholestipol, colesevelam $, cholestyramine	Bile acid sequestrants
Chromoglycate, Ebastine *	Inhibition of mediator release by mast cell

* Studies demonstrating the efficacy of these drugs in the management of chronic diarrhoea are lacking. $ Not readily available in Belgium. 5-HT_3 5-hydroxytryptamine ; FODMAP fermentable oligo-, di- and monosaccharides and polyols ; NICE Natio-nal Institute for Health Care and Excellence.

publication referenced on Pubmed dating back to 1939 (61). More recently, the possible therapeutic effect of diets in IBS-D and functional diarrhoea has been galvanized by the publication by Halmos et al. on the beneficial effects of a diet low in fermentable oligo-, di-, monosaccharides and polyols (low FODMAP diet) in IBS (62,63). Different mechanisms by which food intake causes diarrhoea have been proposed. There is evidence for a role of fermentation of undigested saccharides, the osmotic activity of poorly absorbed carbohydrates and interaction with the GI motility (64-67).

However, the low FODMAP diet remains a very restrictive diet impacting daily life in terms of eating habits as well as costs. Although short term treatment does not result in major nutritional deficits, the effects of prolonged treatment remain a matter of debate (68,69). Moreover, the value of the low FODMAP diet – as well as a gluten-free diet – in the treatment of IBS symptoms has been questioned by a recent systematic review, pinpointing the very low quality of existing evidence (70).

Recently, more conflicting data on the role of diets in the treatment of abnormal stool consistency in IBS has been presented. Paduano et al. found that a low FODMAP diet, a gluten-free diet and a balanced diet equally reduced symptom severity, bloating and abdominal pain, while similarly increasing quality of life (71). When asked, a majority of patients expressed their preference for the balanced diet, which was reflected by a lower adherence with the other diets. However, only the low FODMAP diet demonstrated a significant improvement in stool consistency. Another study compared a brief advice on a commonly recommended diet with structural individual low-FODMAP dietary advice in IBS patients. The latter resulted in significantly lower global IBS symptoms score, but no difference was observed in the severity of individual symptoms or in the stool frequency in constipated as well as non-constipated patients, despite a significant reduction in the total intake of high-FODMAP items per week (72). Similarly, Eswaran et al. compared the low FODMAP diet with the National Institute for Health Care and Excellence (NICE) modified diet (73). The modified NICE diet included eating smaller, more frequent meals, limiting caffeine and alcohol, and avoiding foods that patients knew worsened their symptoms. While the proportion of patients reporting adequate relief of IBS-D was similar between diets, a greater reduction of daily scores of abdominal pain, bloating, urgency consistency and frequency was obtained with the low FODMAP diet. So, it seems that a low FODMAP diet has a therapeutic role in the treatment of abdominal symptoms, but whether it improves stool consistency remains a matter of debate.

g. Loperamide

Loperamide is probably the most known anti-diarrhoeal drug. As a peripherally acting μ-opioid receptor agonist, loperamide inhibits intestinal secretion and decreases intestinal motility. It only has limited absorption into the systemic circulation. Moreover, it cannot cross the blood-brain barrier. Its efficacy in controlling diarrhoea has been demonstrated in various diseases. Its efficacy in controlling diarrhoea in IBS has been demonstrated in

randomized-controlled trials, although it has no impact on the associated abdominal pain (74,75). The usual dosage is 2 mg b.i.d., but when necessary it can be increased up to 16 mg a day. There are anectodical reports in various diseases on the use of stronger opioid agents such as codeine sulphate or opium tincture for cases of chronic diarrhoea refractory to loperamide (76-78). However, the use of these molecules harbours an increased risk of side effects, mostly due to their addictive nature. Therefore, their use should be limited to severe cases of chronic diarrhoea refractory to other agents.

h. Dietary fibres

Dietary fibre supplements such as psyllium, Sterculia urens or Plantago ovata, are a reasonable choice in the treatment of diarrhoea (79). Although the mechanism underlying the beneficial effect will vary between supplements, the prebiotic properties of fibres, influence on gut motility and improved gut barrier function can all contribute to the beneficial effects (80-82). Despite the absence of studies, in clinical practice dietary fibres and loperamide are frequently combined for improved efficacy.

3. Beyond first line

Functional diarrhoea and IBS being the most frequent causes of chronic diarrhoea this part will largely focus on recent insights in the management of these disorders. Differences in gut microbiome in IBS vs. healthy volunteers have been described (83,84). Recent research has concentrated on the relationship between the gut microbiome and symptoms experienced by patients, such as abdominal pain or gut dysmotility, and the putative pathophysiological pathways (85). Different attempts at modulating the microbiome to improve GI symptoms have been made, leading to possible treatments involving dietary modifications, pre- or probiotics or even introduction of selected bacterial strains. Their ability to restore the so-called intestinal barrier – counterbalancing the effects of what is popularly known as leaking gut – has been proposed. The impact of existing treatments such as spasmolytic agents, somatostatine analogues and new therapeutic options such as 5-HT_3 receptor antagonists and eluxadoline in the management of functional diarrhoea and IBS-D will be discussed. Finally, the possible role of treatments targeting bile acid malabsorption and mast cells will also be presented.

a. Gut microbiome and gut dysbiosis

- Prebiotics

Where dietary modifications can influence abdominal symptoms, stool consistency and frequency directly by modifying the luminal contents or by activity on the intestinal wall, nutrients can also interact with the gut microbiome. So, it is not unexpected that this has led to the development of a huge array of prebiotics.

Xyloglucans have demonstrated film-forming protective barrier properties which is believed to restore the mucosal barrier (86). Xylo-oligosaccharides (XOS), on the other hand, selectively promote growth of certain strains of Firmicutes and Bifidobacteriae which are believed to play a role in gut health (87,88). Xyloglucans and XOS, together with tannins from grapeseed extract and pea protein (to which mucoprotective potential has been attributed) are now commercially available as Gelsectan®. Its beneficial effects have been studied in IBS with predominant diarrhoea in a randomized controlled crossover trial with astounding results (89). During active treatment about 90% of subjects experienced a normal stool pattern (Bristol Stool Scale 3 or 4), together with complete abolishment of abdominal pain. Despite symptom recurrence after the end of the treatment period, some patients remained symptom-free until the end of the study.

Another study investigated the effect of 8 weeks of glutamin in post-infectious IBS in a double-blind randomized placebo-controlled trial (90). The post-infectious nature required objective documentation in the year before inclusion. Additionally, an increased intestinal permeability defined by a 24 hours ratio of the urinary excretion of lactulose to mannitol superior to 0.7 was needed. The primary endpoint of more than 50 points improvement on the IBS-symptom scale severity (IBS-SSS) was reached in 79.6% of patients receiving glutamin vs. only 5.8% after placebo ($p < 0.0001$) (90). Interestingly, patients on glutamine also demonstrated a significant reduction of the stool frequency and a significant improvement of stool consistency compared to baseline over placebo. This was accompanied by a significant reduction of intestinal permeability, while no changes were observed after placebo. This effect could reflect the ability of glutamin to enhance expression of claudin-1 as demonstrated in in vitro studies (91). However, the measurement of differential excretion of lactulose vs. mannitol as a measure of intestinal permeability should be interpreted with caution (92).

- Probiotics

With the advancement in the ability to select and grow specific bacterial strains, the current clinical practice is overwhelmed by a variety of probiotics with potential beneficial effects on gut health. Most commercially available probiotics consist most frequently of the genera *Bifidobacterium* and *Lactobacillus* or a combination of both. Positive effects of probiotics have been demonstrated in various GI diseases. In IBD different bacterial strains have demonstrated efficacy in inducing and maintaining remission in ulcerative colitis, as well as in pouchitis (93,94). Probiotics help prevent antibiotic induced diarrhoea and *Clostridioides difficile* infections (95,96).

Different meta-analyses as well as a systematic review analysed the results from randomized controlled trials on probiotics for their effectiveness in IBS (97-99). Overall,

probiotics were favoured over placebo for their effect on the overall symptoms of IBS as well as on specific symptoms, with combination-probiotics demonstrating the most significant effect. This is in line with the updated evidence-based international consensus published in 2018 by Hungin et al. (100). In a network meta-analysis including 14 randomized placebo-controlled trials Liang et al. confirmed that probiotics resulted in a higher proportion of symptom relief, but this was attributable to probiotics combining *Lactobacillus* and *Bifidobacterium* species in a dose limited to less than 10^{10} cfu/day (101).

However according to the international consensus, to date no data support the reduction of diarrhoea by probiotics in IBS patients. Nevertheless, Ishaque et al. studied the effects of Bio-Kult®, a 14-strain probiotic, administered during 16 weeks in a double-blind design to 400 IBS-D patients (102). Bio-Kult® not only demonstrated positive effects on abdominal pain confirming previous reports on probiotics, but also significantly improved stool frequency from month 2 onward. This was accompanied by an improvement of the quality of life.

- Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) is yet another way to modulate the intestinal flora. As differences in gut microbiota are observed in GI as well as non-GI disorders, its potential is being investigated in various diseases (103). Its ability to alter the composition of the gut microbiota mostly reflected by an increased biodiversity and alteration towards the donor's microbial signature, has been verified by many studies in IBS patients, although this could not always be linked to improvement of IBS symptoms or symptom severity (104-108). Only one study failed to identify any significant change in diversity, challenging the therapeutic potential for FMT in IBS (109).

Likewise, various studies concentrated on the therapeutic role of FMT in IBS. In recent meta-analyses including 4 randomized controlled trials (RCT) including 240 patients, FMT was not more effective than placebo on IBS relief, symptom severity or quality of life, in contrast to findings in single arm trials (110,111). Various reasons could affect the response to FMT. The route of administration – by colonoscopy, oral ingestion, nasogastric tube of through an upper GI endoscope intraduodenally – and the amount of donor product differ between the different studies. Also, the application of fresh stool, frozen, lyophilized or capsule-based formulations could impact the therapeutic response (112). Finally, probably the most critical and least characterised factor is the donor selection, as indicated by success rates linked to stool from specific donors in some studies in IBD as reviewed by Wilson et al. in 2019 (113).

A meta-analysis including one more RCT than the aforementioned study of Myneedu et al. investigated the role of route of administration as well as the formulation. While the pooled analysis did not demonstrate a benefit of FMT in IBS, subgroup analysis indicated that delivery of fresh donor stool in the lower GI tract might be the preferred way of application (114). However, no benefit could be attributed to specific IBS subtypes. The importance of donor-selection for the success of FMT in IBS has been postulated before (115). A recent double-blind placebo-controlled trial in 165 patients receiving placebo, 30 g or 60 g FMT from one healthy donor with a well-characterised microbial signature profile provides additional proof to this assumption (116). Although frozen stool samples administered through a gastroscope were used, a very high response rate was obtained, and this response was associated with significant changes in intestinal bacterial signature. The same group investigated the effect of repeating FMT at a higher dose. It demonstrated that 70% of patients failing a first 30 g FMT could benefit from repeated treatment with 60 g transplant using the same protocol (117).

- Antibiotics

The use of antibiotics in the treatment of microbial dysbiosis has been a subject of discussion for a long time. Concerns have risen about emergence of microbial resistance and the associated risk of *Clostridioides difficile* infection. Nevertheless, our knowledge about the complex interaction between the host, the gut microbiota and antibiotics has increased in the last decade. This has led to the development of new antibiotics as a potential treatment for IBS with diarrhoea (118).

Already in 2006, the non-absorbable antibiotic rifaximin demonstrated efficacy in reduced severity of bloating and flatulence in a small study including 124 IBS patients (119). Later, its efficacy was demonstrated in phase 3 double-blind placebo-controlled trials with a 2 week treatment period (120). While the studies focused on global relief of IBS symptoms, significant improvement over placebo on daily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency were observed. More recently meta-analyses further confirmed the modest efficacy of rifaximin over placebo in non-constipated IBS patients, with low risk for side effects as compared to other treatment options (121,122). The therapeutic potential of other non-absorbable antibiotics in IBS-D is currently under investigation.

i. Targeted treatment

While much attention has been paid to manipulating the gut microbiota, inference with other pathophysiological pathways, by spasmolytic agents, 5-HT_3-receptor antagonists, novel opioid receptor agonists, somatostatin analogues, bile acid sequestrants and influencing the release of mediators by mast cells has been explored.

- Spasmolytic agents

Improvement in abdominal pain in IBS by peppermint oil has been demonstrated by RCT and recently confirmed by meta-analysis (123). However, these earlier studies used pooled data from both diarrhoea- and constipation-

predominant IBS patients. In contrast to these previous studies, in the recently published PERSUADE trial comparing small-intestinal-release or ileocolic-release formula of peppermint oil with placebo in IBS, Weerts et al. failed to demonstrate a difference in the primary endpoint of decreased weekly average of abdominal pain with at least 30% for at least half of the treatment period (124). Post-hoc analysis of IBS-D patients did not show any significant improvement of abdominal pain over placebo either. Concerning stool consistency, statistical analysis indicated significant improvement, but this seemed limited to the sixth week of treatment only.

Similarly, while the OBIS trial demonstrated the efficacy of otilonium bromide over placebo on abdominal pain in IBS, no significant impact on stool consistency and frequency was observed (125). When combining three independent clinical trials with otilonium bromide, none support its superiority over placebo for the management of diarrhoea (126).

The lack of efficacy of spasmolytic agents can be partly explained by the study design. All aforementioned studies focused on abdominal pain as primary endpoint and included IBS patients with constipation, diarrhoea as well as variable stool pattern.

- 5-HT_3 receptor antagonists

The efficacy of 5-HT_3-receptor antagonist in improving abdominal pain and stool consistency in severe diarrhoea-predominant IBS has been demonstrated with alosetron (127). However, fatal cases of ischemic colitis and severe constipation resulted in restricted use of this compound in women with severe IBS-D refractory to conventional therapy in the USA in 2002 (128). In an attempt to overcome these shortcomings, the more selective 5-HT_3-receptor antagonist ramosetron has been studied for the same indication. Abdominal pain and discomfort, stool form and stool consistency improved significantly as compared to placebo in women and men, without higher incidence of severe adverse effects (129-132). This was confirmed in a recent meta-analysis including 1623 participants (133). Despite these promising results, ramosetron remains unavailable outside of Japan and some Asian countries.

- Eluxadoline

Since September 2016, the μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist eluxadoline has been authorised by the European Medicines Evaluation Agency (EMEA) for the treatment of IBS with diarrhoea. Eluxadoline demonstrated its efficacy in phase 2 and phase 3 studies, independently of previous improvement of stool consistency with loperamide (134-136). Post-hoc analysis indicated that responders in the first month were more likely to maintain efficacy over 6 months of treatment (137). However, based on adverse events derived from these studies, concerns about sphincter of Oddi spasm (SOS) and consequent pancreatitis prohibits its use in patients with known SOS, with alcohol abuse or with a history of cholecystectomy or pancreatitis, resulting in the EMEA imposed requirement of additional monitoring (138).

More recently post-hoc analysis of aforementioned phase 3 trials confirmed the maintained improvement in health-related quality of life by eluxadoline over the 52 weeks follow-up period, as indicated by the significantly higher scores for the total as well as the different subscale scores of the disease-specific IBS-quality of life questionnaire (139). Recently, the results from a phase 4 study conducted in patients with intact gallbladder experiencing insufficient improvement with loperamide has been published (140). It confirmed the efficacy of eluxadoline vs. placebo administered for 12 weeks on the composite endpoint of improvement in abdominal pain and stool consistency. Similar rates of adverse events, with no treatment-associated SOS or pancreatitis, were observed.

- Somatostatin analogues

Somatostatin analogues are the mainstay of treatment of diarrhoea associated with metastatic neuro-endocrine tumours (141). Their therapeutic potential has also been assessed in chronic idiopathic diarrhoea in an open-label clinical trial (142). Their efficacy result from a multifactorial mode of action, with somatostatin analogues inhibiting intestinal chlorine secretion, while enhancing sodium and water absorption. Additionally, somatostatin analogues prolong oro-caecal transit time. Some of these effects are attributed to the reduced release of GI hormones. However, as sole treatment they are of little use in IBS-D as they lack impact on the associated abdominal pain.

- Bile acid sequestrants

Studies indicate that IBS-D patients have a significantly higher content of BA in their stool as compared with patients with constipation-dominant IBS or healthy volunteers and this was associated with objective measures of diarrhoea (143). Recent data point to the possible role of *Clostridioides*-rich microbiota in bile acid transformation in the gut, which leads to increased BA excretion (144).

The severity of BAM as assessed by ^{75}SeHCAT correlates with therapeutic response to bile acid sequestrants (145). In an open-label study with the bile acid sequestrant cholestipol in IBS, half of the patients experienced adequate relief (146). Similarly, treatment with colesevelam significantly improved stool consistency in IBS-D (147). However, recently a double-blind study of the same group failed to demonstrate improved stool consistency in IBS-D despite significant changes in the excretion of sequestered fecal bile acid contents and serum markers (148). This is in line with a prior retrospective survey indicating that a large proportion of patients with documented BAM still suffered from diarrhoea despite adequate treatment, irrespective of the underlying type of BAM (149).

- Role of mast cells

The implication of mast cells and their mediators in symptom generation and diarrhoea in IBS has been evidenced by various studies (150). The potential impact of the mast cell stabiliser sodium chromoglycate has been studied in IBS-D (151). The histamine-1 (H_1) receptor antagonist ebastine may also have therapeutic potential (152). However current evidence remains limited and the results from larger studies are eagerly awaited.

Conclusion - Summary

Many different pathophysiological pathways have been implicated in the development of chronic diarrhoea. Based on thorough history including drug use, clinical examination and limited testing the initial diagnostic steps should focus on the exclusion of cancer and inflammation. More elaborate tests should be reserved for patients with atypical symptoms, severe diarrhoea, or persistent symptoms despite treatment. Further testing should target the suspected underlying aetiology. However, in many cases, testing will fail to unravel a specific cause and patients will be diagnosed with functional diarrhoea or diarrhoea-predominant irritable bowel syndrome.

In the absence of an identifiable aetiology, different therapeutic options remain available, including dietary interventions, treatments influencing the gut microflora (e.g. prebiotics, probiotics or poorly absorbable antibiotics), bile acid sequestrants, spasmolytic agents, opioid receptor agonists and somatostatin analogues. Although a clear advantage has been demonstrated for 5-HT_3-receptor antagonists and the mixed opioid receptor agonist eluxadoline, their use has been restricted because of severe side effects and current unavailability in most countries. The role of faecal microbiota transplantation and treatments targeting mast cell mediators remain to be elucidated, but initial results hold some promise for the future.

Future studies should focus on clarifying how to adequately select pre- and probiotics, with a possible role of individualized treatment. Elucidating the role of donor-selection and resolving the safety issues will be of primordial importance for widespread application of faecal microbiota transplantation. Besides these options, the development of affordable and safe therapeutics with wide applicability targeting gut microbiota or specific pathways remains a viable option for future research.

Conflict of interest

None

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