Belgian consensus on irritable bowel syndrome

S. Kindt[1], H. Louis[2], H. De Schepper[3], J. Arts[4,5], P. Caenepeel[4,6,7], D. De Looze[8], A. Gerkens[9], T. Holvoet[8,10], P. Latour[11], T. Mahler[12], F. Mokaddem[13], S. Nullens[3], H. Piessevaux[14], P. Poortmans[1], G. Rasschaert[1], M. Surmont[1], H. Vafa[15], K. Van Malderen[3], T. Vanuytsel[4], F. Wuestenberghs[16], J. Tack[4]

(1) Department of gastroenterology and Hepatology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussel, Belgium; (2) Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme University Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium; (3) Department of Gastroenterology and Hepatology, University Hospital Antwerp, Antwerp, Belgium; (4) Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium; (5) Department of Gastroenterology, AZ Sint-Lucas, Brugge, Belgium; (6) Department of Gastroenterology, Ziekenhuis Oost-Limburg, Campus Sint-Jan, Genk, Belgium; (7) UHasselt, Hasselt, Belgium; (8) Department of Gastroenterology and Hepatology, University Hospital Ghent, Gent, Belgium; (9) Boitsfort Medical Center, Brussels, Belgium; (10) Department of Gastroenterology, AZ Nikolaas, Sint Niklaas, Belgium; (11) Department of Gastroenterology, Hepatology and Digestive Oncology, Centre Hospitalier Universitaire de Liège, Liège, Belgium; (12) Department of Pediatrics, Universitair Ziekenuis Brussel, Brussel, Belgium; (13) Department of Gastroenterology and Hepatology, Vivalia-Centre Sud Luxembourg, Arlon, Belgium; (14) Department of Hepato-gastroenterology, Cliniques universitaires St-Luc, Université catholique de Louvain, Brussels, Belgium; (15) Department of Gastroenterology and Hepatology, Chirec-Site Delta, Brussels, Belgium; (16) Department of Gastroenterology and Hepatology, CHU UCL Namur, Université catholique de Louvain, Yvoir, Belgium.

Abstract

Background: **Irritable bowel syndrome (IBS) is characterised by recurrent abdominal pain related to defaecation or associated with altered stool frequency or consistency. Despite its prevalence, major uncertainties in the diagnostic and therapeutic management persist in clinical practice.**

Methods: **A Delphi consensus was conducted by 20 experts from Belgium, and consisted of literature review and voting process on 78 statements. Grading of recommendations, assessment, development and evaluation criteria were applied to evaluate the quality of evidence. Consensus was defined as > 80 % agreement.**

Results: **Consensus was reached for 50 statements. The Belgian consensus agreed as to the multifactorial aetiology of IBS. According to the consensus abdominal discomfort also represents a cardinal symptom, while bloating and abdominal distension often coexist. IBS needs subtyping based on stool pattern. The importance of a positive diagnosis, relying on history and clinical examination is underlined, while additional testing should remain limited, except when alarm features are present. Explanation of IBS represents a crucial part of patient management. Lifestyle modification, spasmolytics and water-solube fibres are considered first-line agents. The low FODMAP diet, selected probiotics, cognitive behavioural therapy and specific treatments targeting diarrhoea and constipation are considered appropriate. There is a consensus to restrict faecal microbiota transplantation and gluten-free diet, while other treatments are strongly discouraged.**

Conclusions: **A panel of Belgian gastroenterologists summarised the current evidence on the aetiology, symptoms, diagnosis and treatment of IBS with attention for the specificities of the Belgian healthcare system** (Acta gastroenterol. belg., **2022,** 85, **360-382**).

Keywords: irritable bowel syndrome, Delphi consensus, diagnosis, treatment, review.

Abbreviations

5HT	5-hydroxytryptamine, Serotonin
BA	Bile acid
BAM	Bile acid malabsorption
BSFS	Bristol stool form scale
CBT	Cognitive Behavioural Therapy
FMT	Faecal microbiota transplantation
FODMAP	Fermentable oligo-, di-, and monosaccharides and polyols
GC-C	Guanylate cyclate-C
GI	Gastrointestinal
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant IBS
IBS-D	Diarrhoea-predominant IBS
MBSR	Mindfulness-based stress reduction
PEG	Poly-ethylene glycol
RCT	Randomised controlled trials
SNRI	Serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressants
QOL	Quality of life
XG	Xyloglucan

Introduction

The Rome IV consensus defines irritable bowel syndrome (IBS) as recurrent abdominal pain present for at least 3 months with onset 6 months before diagnosis and associated with at least two of the following criteria: change in stool form, change in stool frequency or in relation to defaecation (1). According to epidemiological studies, 4.1 % of the world population suffers from IBS (2). Despite its high prevalence, the exact aetiology remains elusive and is the topic of intensive research. Likewise, multiple pathophysiological mechanisms have been proposed. Despite these gaps in our knowledge of IBS, diverse therapeutic interventions are available. Treatment approaches can broadly be divided into general lifestyle advice, medical therapy, dietary and non-pharmaceutical interventions. Emerging evidence suggests possible novel future approaches. Finally, the large placebo response observed in most randomised controlled trials (RCT) further contributes to the challenges in IBS management.

The aim of this project was to develop a Belgian consensus on the definition of IBS, its clinical

Correspondence to: Sébastien Kindt, MD PhD, Department of Gastroenterology and Hepatology, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, B-1090 Brussel, Belgium. Fax: +32 2 477 6810.
Email: sebastien.kindt@uzbrussel.be

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characteristics, underlying pathophysiology and therapeutic options. The results provide guidance in the management of these patients, with focus on diagnosis and treatment in clinical practice, in order to improve overall care of these patients.

Methods

A steering group of Belgian gastroenterologists involved in the care of patients with disorders of gut brain interaction initiated a Delphi process to develop statements on different aspects of IBS, with Belgian healthcare professionals as target audience. The principles of the Delphi process have been published elsewhere (3). The primary purpose of the Delphi technique is to generate a reliable consensus opinion of a group of experts by an iterative process of questionnaires interspersed with controlled feedback (4). Its goal is to provide answers to complex medical problems insufficiently backed by evidence from controlled trials. The process involved multiple steps: 1/ selection of a steering committee of 3 Belgian gastro-enterologists involved in care of IBS patients and/ or the Delphi process, 2/ selection of a consensus group from Belgian gastro-enterologists involved in IBS patient care, 3/ drafting of statements pertaining to the current knowledge on IBS with focus on the Belgian situation, 4/ systematic literature review to identify the existing evidence for each statement, 5/ group discussion of the available evidence and voting with discussion to establish a stable level of consensus, and 6/ grading of the strength of evidence using accepted criteria.

The Belgian consensus group was established by contacting Belgian gastroenterology specialists with specific interest in IBS identified by their clinical or scientific activity. A total of 20 experts agreed to participate. The steering committee drafted a list of 60 statements covering different aspects of IBS. This list was evaluated during the initiatory meeting. The steering group adjusted the statements list based on the comments formulated during this meeting, generating a total of 75 statements. The consensus group was divided into 12 working groups consisting of 3 to 4 panellists each. Each working group was allocated statements, conducted a systematic literature search, and provided a narrative summary of the identified evidence. Summaries and references were made available to each member of the Belgian consensus group using cloud computing.

The consensus group met in September 2020 for the initiatory meeting. Four virtual meetings were organized in March-June 2021 to discuss statements. Based on these discussions, statements were reformulated if needed. The collected summaries with reference list were provided to all participants by June 2021, followed by an online voting round during which all members indicated their degree of agreement for each statement using a 6-point Likert scale. The voting outcomes were discussed during a meeting in September 2021, where it was decided to vote on 2 additional statements. Participants remained blinded to the votes of other panelists throughout the process. Truvion Healthcare and Mayoly Spindler provided financial support for the physical meetings, but were not further involved in the design of the statements, the discussions or the voting.

Table 1. — **6-point Likert scale**

Point	Description
A+	Agree strongly
A	Agree with minor reservation
A-	Agree with major reservation
D-	Disagree with minor reservation
D	Disagree with major reservation
D+	Strongly disagree

In accordance with the requisites of the Delphi process, consensus was defined as when at least 80% of the Consensus Group agreed (A+ or A) with a statement (Table 1). The strength of evidence for each statement was scored using the GRADE system by the members of the Steering Committee (Table 2) (5). Following the last voting round, a draft of the manuscript was circulated to all members for approval. The references presented with the statements in this manuscript only represents a selection of the articles reviewed during the Delphi process chosen to clarify the discussion.

Results

An overview of the statements with voting results, GRADE of evidence and associated references is provided in their respective tables. Evidence underlying the answer to the different statements is discussed further in the next topics.

Aetiology and impact

Statements on aetiology and impact are summarised in table 3.

IBS can be triggered by traumatic life events, psychological factors, gastrointestinal (GI) infection and/or perturbations in the gut microbiome (6,7). These events lead to alterations in both central and enteric nervous system activity, gut permeability and the mucosal immune system. The result is a disturbance of GI sensitivity, motility and/or secretion ultimately leading to abdominal discomfort and stool pattern alterations. These symptoms can be elicited or aggravated by intraluminal factors (food, microbiota, bile acids) or by central factors (stress, anxiety, somatisation). Ultimately, this chain of events will affect the bidirectional flow of information over the gut-brain axis and generate the chronic disease state that is IBS (8,9).

Table 2. — **Grading of recommendations assessment, development and evaluation system (Balshem 2011)**

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect • Several high-quality studies with consistent results • In special cases: one large, high-quality multicentre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate • One high-quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate • One or more studies with severe limitations
D	Very low	Any estimate of effect is very uncertain • Expert opinion • No direct research evidence • One or more studies with very severe limitations

Table 3. — **An overview of all statements on aetiology and impact with endorsement, grading of evidence and references**

1. Statements on aetiology and impact	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. The origin of symptoms in IBS is multi-factorial	100%, Yes	A	A+ 95%, A 5%, A- 0%, D- 0%, D 0%, D+ 0%	6-9,30
1.2. Increased intestinal permeability refers to a potential pathophysiological mechanism of IBS.	95%, Yes	B	A+ 55%, A 40%, A- 5%, D- 0%, D 0%, D+ 0%	10
1.3. Gut microbiota composition can contribute to IBS symptoms.	80%, Yes	B	A+ 45%, A 35%, A- 10%, D- 10%, D 0%, D+ 0%	17-19
1.4. Immune activation plays a role in the pathophysiology of IBS.	95%, Yes	B	A+ 60%, A 35%, A- 5%, D- 0%, D 0%, D+ 0%	11-16
1.5. Irrespective of specific food intolerance, eating can exacerbate symptoms in some IBS patients.	100%, Yes	B	A+ 80%, A 20%, A- 0%, D- 0%, D 0%, D+ 0%	20-23
1.6. Psychological stress is an important risk factor in IBS pathophysiology, can exacerbate symptoms in IBS and can influence IBS severity	100%, Yes	B	A+ 85%, A 15%, A- 0%, D- 0%, D 0%, D+ 0%	24-29
1.7. Patient's history should assess psychological comorbidities, lifestyle and dietary factors that may contribute to symptoms, as well as the impact of IBS on daily life	100%, Yes	C	A+ 95%, A 5%, A- 0%, D- 0%, D 0%, D+ 0%	8,9
1.8. Different aspects of quality of life are impaired in IBS patients	100%, Yes	A	A+ 90%, A 10%, A- 0%, D- 0%, D 0%, D+ 0%	31-33

Intestinal permeability is increased and tight junction proteins are expressed less abundantly in IBS patients compared to healthy controls. These phenomena are correlated with symptom severity (10). Dysfunction of both innate and adaptive immune responses has been identified in IBS patients, both by the number of immune cells present in the mucosa (mast cells, T-lymphocytes) (11) as well as their activity (secretion of cytokines such as TNF-α, IL-1β and IL-5) (12). Polymorphisms in genes encoding for inflammatory cytokines IL-6,IL-10, TNF-α have also been implicated (13-16). However, a recent genome-wide association study (GWAS) on 53,400 IBS patients revealed no genetic susceptibility loci involved in the immune system or inflammatory reactions (17). Mast cells are more abundant in both the colon and small intestine of IBS patients and are located more closely to afferent nerve endings (11,18,19). Additionally, a post-infectious origin is a well-characterised aetiology for IBS (20,21), which, according to some studies, results in a loss of lamina propria macrophages (22). More recently, the role of local immune response to food allergens triggered by a prior infection has been presented (23).

Several lines of evidence support a role for disturbances in the intestinal microbiota in the aetiology of IBS as well. In translational experiments, transplantation of faecal microbiota from IBS patients to germ free rats

can provoke IBS-like symptoms (24). Epidemiological studies show that bacterial or parasitic GI infections, disrupting the normal microbial balance, are associated with a 7-fold risk of developing IBS later in life (25). In a small prospective case-control study, the use of antibiotics increased the risk of developing IBS symptoms in the coming month (26). Additionally, several studies have shown that IBS patients exhibit a different microbiota composition compared to healthy subjects. One observation that appears consistent over several studies is the high *Firmicutes*/*Bacteroidetes* ratio of IBS patients compared to controls (27). Similarly, there appear to be changes in the viral microbiome as well. One study found a significant decrease in the abundance and diversity of the enteric virome in IBS patients compared to healthy individuals (particularly the Megavirales strain) (28).

Patients often report that their symptoms are triggered by food. Dedicated questionnaires show that in 60-84% of the IBS patients food intake causes abdominal symptoms (29-31). Food rich in FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols) received most attention in research (29). Undigested FODMAPs are osmotically active in the small bowel and delivered into the colon and fermented by the microbiota, resulting in the formation of osmotically active compounds, gas and short chain fatty acids. Hypersensitivity to the effects of these compounds seems to play a larger part than the specific compounds themselves (32).

Chronic stress is an important player in IBS pathophysiology and influences the severity of IBS symptoms. Stressful or traumatic life events often precede IBS development (33). Chronic stress affects brain-gut axis function (34), modulates the gut microbiota (35), and influences small intestinal permeability (36). Stress, anxiety, depression and traumatic life events all drive visceral sensitivity and symptom severity in IBS patients (35,37,38).

All these different influences are not mutually exclusive, contributing to the multifactorial aetiology of IBS symptoms. Simren et al showed that dysmotility, hypersensitivity and psychological disturbances have a cumulative effect on GI and non-GI symptoms, as well as on quality of life, in patients with IBS (39).

IBS is associated with increased morbidity but not mortality (40). Studies using a general questionnaire of quality of life (QOL) showed that the quality of life of IBS patients is lower than that of the general population and patients with several types of chronic organic disease. IBS affects work productivity and social integration. Patients' ability to be present and active at work depends on the IBS symptom severity, non-digestive somatic symptoms, anxiety and fatigue (41). IBS with predominant diarrhoea results in a greater reduction in QOL and greater impairments in daily activities but also in work productivity with higher rates of absenteeism and presenteeism (working while feeling sick) compared to controls (42).

Symptoms

Statements on symptoms on symptoms are summarised in table 4.

As per the Rome IV consensus, abdominal pain associated with defaecation and/or altered stool pattern, present over at least the last 6 months, defines IBS (1). In the Rome III consensus, discomfort related to stool pattern was also included in the definition of IBS (43). The issue of pain versus discomfort is to some extent

Table 4. — **An overview of all statements on symptoms with endorsement, grading of evidence and references**

1. Statements on symptoms	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. Abdominal pain present for longer than 6 months, related to defaecation, and associated with a change in stool frequency or stool consistency is a cardinal feature of IBS.	90%, Yes	B	A+ 45%, A 45%, A- 5%, D- 5%, D 0%, D+ 0%	1
1.2. Abdominal pain or discomfort present for longer than 6 months, related to defaecation, and associated with a change in stool frequency or stool consistency is a cardinal feature of IBS.	95%, Yes	B	A+ 75%, A 20%, A- 0%, D- 5%, D 0%, D+ 0%	34,35
1.3. Bloating and abdominal distension are part of the spectrum of IBS.	100%, Yes	B	A+ 95%, A 5%, A- 0%, D- 0%, D 0%, D+ 0%	36-52
1.4. There is a high inter-individual variability in symptom intensity and frequency	100%, Yes	B	A+ 100%, A 0%, A- 0%, D- 0%, D 0%, D+ 0%	53-55
1.5. Patients should be subtyped into IBS-C, IBS-D and IBS M/U according to stool characteristics.	100%, Yes	B	A+ 50%, A 50%, A- 0%, D- 0%, D 0%, D+ 0%	47,56-65
1.6. The Bristol Stool Scale is useful to identify IBS subtype.	95%, Yes	B	A+ 75%, A 20%, A- 5%, D- 0%, D 0%, D+ 0%	66,67

driven by linguistic issues, as the meaning of discomfort varies greatly among IBS patients (43,44). On the other hand, most of the available therapeutic studies in IBS included patients according to the Rome III consensus and evaluated effects not only on pain but also on bloating or discomfort. For these reasons, it remains acceptable to adhere to the Rome III definition for clinical practice, but Rome IV adherence is needed for research applications.

Apart from abdominal pain and altered bowel movements, bloating and abdominal distension are also part of the spectrum of IBS (45,46). According to Rome, abdominal bloating is defined as (subjective) symptoms of recurrent abdominal fullness, pressure or sensation of trapped gas. Abdominal distension refers to a measurable (visible) increase in abdominal girth.

However, bloating is not a cardinal feature of IBS. It is also reported by patients with other functional GI disorders – such as functional dyspepsia, functional abdominal bloating/distension, functional constipation – and is therefore not used in diagnostic criteria. The same pathogenic mechanisms are described for bloating and IBS (45,47-49). Bloating responds partially to most IBS treatments (50-61). Abdominal distension is also reported by IBS patients but less frequently than bloating (46).

In addition to the above-mentioned symptoms, IBS patients report a variety of symptoms which are subject to change over time (62), thus underlining the heterogeneity of IBS. Several studies assessing day-by-day symptoms using daily diaries showed variation among the frequency and intensity of symptomatic episodes of both abdominal pain and altered bowel patterns (63,64).

This symptomatic heterogeneity also translates in varying stool patterns among patients as well as within the same individual. The Rome committee differentiates between different subtypes based on the frequency of both constipation and diarrhoea. The subtyping into constipation-predominant IBS (IBS-C) and diarrhoea-predominant IBS (IBS-D) is justified by the different pathophysiological disturbances (65-71) and the different treatment options underlying both subtypes (56,72-74).

The Bristol stool form scale (BSFS) illustrates the common stool forms and consistency on a 7-point scale with simple visual descriptors (75). Patients can recognise and classify their stool type using the BSFS. The BSFS has been recommended by the Rome committee as a modality to subtype IBS patients. The validity and reliability have been verified in IBS-D and healthy adults, while its usefulness in the evaluation of treatment of IBS-C has been identified (76).

Testing: general - blood, faecal testing and endoscopy

Statements on testing are summarised in table 5.

Currently, there is no diagnostic test available for IBS. Therefore, a positive diagnosis should be made based on a careful history, physical examination and limited diagnostic testing based on a patient's individual case. The Rome IV criteria offer some structure and direction when diagnosing IBS but do have their limitations (1). Studies indicate that in the absence of alarm features, the ROME IV criteria harbour a sensitivity of over 85% for IBS in secondary care, although specificity is lower (77). Since other diseases can present with similar symptoms, limited testing could enhance the diagnostic accuracy.

In addition to symptom-driven history taking and careful physical examination, clinical practice guidelines

Table 5. — **An overview of all statements on testing with endorsement, grading of evidence and references**

2. Statements on testing	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. A positive diagnosis of IBS can be established in most patients by history and physical examination.	100%, Yes	B	A+ 55%, A 45%, A- 0%, D- 0%, D 0%, D+ 0%	1
1.2. Most IBS patients do not require routine laboratory testing	55%, No	B	A+ 40%, A 15%, A- 15%, D- 20%, D 5%, D+ 5%	68-72
1.3. A limited number of laboratory tests can be considered in selected patients depending on the clinical presentation.	90%, Yes	C	A+ 60%, A 30%, A- 10%, D- 0%, D 0%, D+ 0%	68-72
1.4. Colonoscopy is mandatory when alarm features are present.	100%, Yes	B	A+ 90%, A 10%, A- 0%, D- 0%, D 0%, D+ 0%	74,75
1.5. In the absence of improvement by initial treatment, additional testing to rule out other diseases is not routinely required.	85%, Yes	B	A+ 60%, A 25%, A- 5%, D- 10%, D 0%, D+ 0%	73,78-83
1.6. Upper GI endoscopy is recommended in IBS-D failing treatment.	50%, No	D	A+ 20%, A 30%, A- 15%, D- 10%, D 15%, D+ 10%	82,83
1.7. Lower GI endoscopy is recommended in IBS-D failing initial treatment.	75%, No	D	A+ 40%, A 35%, A- 15%, D- 5%, D 5%, D+ 0%	75-77

recommend limited laboratory testing. This may include complete blood count, C-reactive protein, coeliac disease serology, faecal calprotectin (78) and faecal hemoglobin (79). In case of constipation-predominant symptoms metabolic and endocrinologic disorders such as diabetes mellitus, hypothyroidism, hypercalcaemia and hypokalaemia could be considered with dosage of fasting glucose, thyroid stimulating hormone, calcium levels and ionogram (80). In case of diarrhoea-predominant symptoms, diabetes mellitus, hyperthyroïdism, hyperparathyroidism, giardiasis and other chronic infections can be tested by dosage of previous tests with addition of testing for malabsorption by dosing vitamin B12, folate and ferritin. Stool can be tested for *Clostridioides difficile* and parasites (81). It is reasonable to make a positive diagnosis of IBS-D following negative results on the above-mentioned testing (82).

Repeated laboratory testing should be avoided for patients with recurrent or persistent symptoms that are similar to their baseline symptoms (83). Repeat testing has a negative effect on patient management by undermining the diagnosis of IBS and the patient's confidence in their treating physician, amplifying anxiety in patients already carrying psychological comorbidities, while also increasing expenses for both patients and the healthcare system.

Careful follow-up is crucial to detect any changes in symptom patterns (1). The absence of red flag symptoms in addition to traditional symptoms increases the predictive value in diagnosing IBS. Alarm features that should prompt GI endoscopy to exclude organic disease include a family history of colon cancer, inflammatory bowel disease or coeliac disease, unintended weight loss, rectal bleeding in the absence of documented bleeding haemorrhoids or anal fissure, an abnormal physical examination, recent change in bowel habit in patients aged above 45 years, nocturnal diarrhoea, iron deficiency anaemia or evidence of inflammation on blood or stool testing (84,85). In the absence of alarm features, there is no evidence to support a colonoscopy in young IBS patients (85-87).

A poor response to therapy is frequently encountered in IBS patients, especially in patients with severe symptoms (88,89). Therefore, physicians should refrain from additional testing upon failure of initial treatment. Stability of IBS diagnosis has been shown in several studies, the diagnosis being durable and unlikely to be revised even after several years of follow-up (83,90,91). The risk of missing an organic disease is very low in young patients, who constitute the majority of IBS patients. Studies comparing a diagnostic strategy of exclusion and a positive strategy (limited to analyses of blood cell count and C-reactive protein) found a similar effect on symptoms, patient satisfaction and use of healthcare resources. Furthermore, a positive diagnostic strategy results in lower direct costs further supporting its use (92,93).

Food

Statements on food are summarised in table 6.

Patients often relate their symptoms to food allergy and ask for specific testing. According to the American National Institute of Allergy and Infectious Disease

Table 6. — **An overview of all statements on food with endorsement, grading of evidence and references**

3. Statements on food	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. Routine food allergy testing is not useful in IBS.	100%, Yes	B	A+ 95%, A 5%, A- 0%, D- 0%, D 0%, D+ 0%	84,85-91
1.2. Testing for food allergy should only be considered when GI symptoms are associated with stereotypical and repetitive symptoms across multiple organ systems or in case of an anaphylactic reaction immediately following food intake.	100%, Yes	B	A+ 80%, A 20%, A- 0%, D- 0%, D 0%, D+ 0%	84
1.3. Lactose malabsorption testing has a limited role in the work-up of IBS.	80%, Yes	C	A+ 45%, A 35%, A- 10%, D- 10%, D 0%, D+ 0%	93-95
1.4. The fructose breath test is not useful in the management of IBS.	100%, Yes	B	A+ 60%, A 40%, A- 0%, D- 0%, D 0%, D+ 0%	96-99
1.5. A fructose reduced diet is effective in the treatment of IBS.	65%, No	C	A+ 20%, A 45%, A- 15%, D- 10%, D 10%, D+ 0%	96-97
1.6. We advise against the gluten-free diet for the management of IBS.	85%, Yes	C	A+ 60%, A 25%, A- 10%, D- 0%, D 5%, D+ 0%	100-110
1.7. A low FODMAP diet is effective in the treatment of IBS.	100%, Yes	B	A+ 70%, A 30%, A- 0%, D- 0%, D 0%, D+ 0%	111-115
1.8. A low FODMAP diet is the preferred first-line treatment in IBS.	50%, No	D	A+ 15%, A 35%, A- 15%, D- 20%, D 5%, D+ 10%	111-117

(NIAID) guidelines only a combination of symptoms in different organ systems, including involvement of ocular symptoms, skin and/or cutaneous tissues, respiratory, GI or cardiovascular system within minutes to hours after ingesting food should prompt further investigation of food allergy (94). Evidently the possibility of food allergy should be ruled out in case of an anaphylactic reaction occurring after food intake.

Food allergy has been proposed in a subgroup of IBS patients who have a history of atopy or exacerbation of symptoms on ingesting specific foods (95). Where the role of IgE in diagnosing allergic reactions (with low yield in typical IBS) has long been recognised, different studies examined the relevance of IgG testing in IBS (96). Higher titers of IgG and IgG4 were observed in IBS. Guided by these elevated antibody titers, an elimination diet provided symptomatic improvement in small studies with criticism on the control diet arm (97,98). However, other studies could not detect an association between high levels of IgG to certain food and clinical symptoms (99,100). Moreover, an elimination diet based on results of IgG testing failed to improve IBS symptoms significantly better as compared to patients on a waiting list (101), questioning the validity of this approach. Finally, large exclusion diets harbour a risk of nutritional deficiencies as revealed by studies in patients with documented food allergy (102,103). Therefore, this consensus does not recommend IgG testing in IBS patients.

Food intolerances, such as fructose and lactose intolerance, are frequently suggested by patients. A lactose breath test is specific to diagnose lactose malabsorption (104). A correlation between the amount of gas production and the presence and severity of intestinal symptoms, like bloating and borborygmi, has been reported (105). However, not all IBS symptoms can be attributed to lactose malabsorption. Indeed, the incidence of lactose malabsorption in IBS is comparable to healthy controls (106,107). Also, the role of lactose breath testing in predicting symptom reduction by the lactose-free diet has not been demonstrated.

Different studies addressed the benefit of a fructose-reduced diet in at least a subset of IBS patients (108,109). Poor agreement was observed between symptoms and breath gas analysis during a fructose breath test, questioning the validity of the test. Furthermore, the fructose breath test suffers from a lack of standardisation. This has in the meanwhile been addressed by the North American and more recent European consensus (110,111). Finally, the symptomatic improvement provided by a fructose-reduced diet appeared independent from the results of the fructose breath test, questioning its utility in predicting the response to dietary intervention (108).

Irritable bowel syndrome patients frequently consider cereal-containing products as the cause of their symptoms (112). Patients with non-coeliac wheat sensitivity have symptoms that mimic those of IBS, such as abdominal pain, bloating, alternating bowel habits, constipation and diarrhoea (113). However, while some extra-intestinal manifestations (e.g. tiredness, lack of wellbeing, anxiety, fatigue, headache and joint pain), are reported in both disorders, associated aphthous stomatitis, dermatitis or asthma are uncommon in IBS. Even if some RCT concluded that avoiding gluten improved symptoms in IBS and non-coeliac wheat hypersensitivity (114-118), FODMAPs such as fructans are hypothesized to be the causative food component (119-122). Furthermore, physicians should also be aware that long-term avoidance of gluten increases the proportion of carbohydrate intake from non-milk extrinsic sugars and decreases intake of non-starch polysaccharides, while intakes of magnesium, iron, zinc, manganese, selenium and folate are reduced (123). Therefore, this consensus group does not recommend initiating a gluten-free diet in IBS patients.

Since the first publication 10 years ago (124), many studies confirmed that most IBS patients experience significant improvement in their GI symptoms with a low-FODMAP diet (125,126). While other diets also proved beneficial, often the low FODMAP diet appeared superior in most sub-analyses (127,128). The value of this approach is further substantiated by the superior efficacy in symptom control provided by a mobile application advising how to reduce dietary FODMAP intake over the spasmolytic agent otilonium bromide (Van Houtte et al. revised version submitted to Gut). Concerns about long-term efficacy and nutritional adequacy are not backed by recent evidence (129,130).

First-line approach

Statements on first-line approach are summarised in table 7.

Several studies highlighted the lack of information IBS patients receive concerning their disease and the misconceptions they hold (131-134). An effective management of IBS patients relies on physicians being able to provide information and instruction for the patient by naming the condition through a confident diagnosis, with a clear explanation of the benign nature of IBS, what they believe is causing symptoms and how they intend to target these factors with specific management strategies (84,135). Education on lifestyle, dietary and psychological (stress) factors that may contribute to the patient's symptoms will also help teach patients simple self-management strategies and alleviate symptom-related fears and anxiety (90,133,136,137). The beneficial effects of physical exercise on symptom severity have been demonstrated (138,139). However, the evidence remains scarce as these studies included only small numbers of patients.

The interval that should be considered before assessment of treatment efficacy has never been evaluated specifically. That is why one could consider relying on the observed timing of response from the respective study trials. As indicated in Table 14, a large variability exists between the different treatment options (61,76,125,140,141). Of course, the definitive timing

Table 7. — **An overview of all statements on first-line approach with endorsement, grading of evidence and references**

4. Statements on first-line approach	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. Explanation of IBS is a crucial part of the management.	100%, Yes	B	A+ 95%, A 5%, A- 0%, D- 0%, D 0%, D+ 0%	74,80, 118,120,122-124
1.2. First-line approach with lifestyle modification is effective in IBS.	95%, Yes	C	A+ 60%, A 35%, A- 0%, D- 0%, D 5%, D+ 0%	125-126
1.3. Treatment success evaluation should be timed in accordance with study results.	90%, Yes	D	A+ 55%, A 35%, A- 10%, D- 0%, D 0%, D+ 0%	--
1.4. Water-soluble fibres are effective in IBS.	85%, Yes	B	A+ 45%, A 40%, A- 15%, D- 0%, D 0%, D+ 0%	129-131
1.5. Spasmolytics are effective in IBS.	95%, Yes	B	A+ 65%, A 35%, A- 0%, D- 0%, D 0%, D+ 0%	52,64,133-139,141-143
1.6. Spasmolytics are the preferred first-line treatment in IBS.	80%, Yes	B	A+ 50%, A 30%, A- 20%, D- 0%, D 0%, D+ 0%	52,64,133-139,141-143
1.7. Simethicone in monotherapy is not effective in IBS.	90%, Yes	D	A+ 60%, A 30%, A- 0%, D- 5%, D 0%, D+ 5%	140
1.8. Herbal medicine is effective in IBS.	30%, No	C	A+ 15%, A 15%, A- 35%, D- 20%, D 5%, D+ 10%	144-148

should be weighted against the necessities in clinical practice.

Fibre supplementation is frequently advocated in the management of both diarrhoea and constipation in IBS. A Cochrane systematic review of 2011 concluded that there was no benefit from fibre in general, although there was a trend toward benefit for soluble fibre (142). In contrast, based on the data of two RCT, a significant improvement in IBS symptoms for the use of water-soluble fibre, such as psyllium or isphagula, as compared to insoluble fibre has been shown (143,144). The safety of fibre supplementation has been established, with no reported severe adverse events (143), making it a first-line strategy in the management of IBS.

Abnormal colonic motility or transit has been implicated in the pathophysiology of pain in IBS patients (145). Targeting the GI smooth muscle by means of spasmolytic agents is therefore a commonly used first-line treatment by many practitioners, and antispasmodics are among the most frequently used therapeutics in IBS, irrespective of its subtype. Guidelines acknowledge the beneficial effects of antispasmodics when compared to placebo, despite the high heterogeneity among included studies and the associated risk of publication bias (73,146).

Most data are available for otilonium bromide (Spasmomen®, recommended dose 40 mg t.i.d.), which provides significant improvement of bloating, pain and severity of abdominal distension (61). Otilonium bromide is well-tolerated, improves wellbeing but does not alter bowel symptoms. Of 12 agents compared in a meta-analysis, otilonium bromide had the strongest data (147).

Peppermint oil (Mentha x piperita Tempocol®, recommended dose 182 mg t.i.d.) represents another well-tolerated first-line treatment option in IBS, although it sometimes triggers reflux symptoms (148,149). In a systematic review analysis peppermint oil was ranked first for efficacy when global IBS symptoms were used as the outcome measure (150). However, the authors of this study judged that 5 out of the 8 included trials suffered from a high risk of bias. A recent multicenter study with peppermint oil in IBS failed to meet its primary endpoint (151). There is also evidence from 3 RCTs in favour of hyoscine (Buscopan®) over placebo (146,150).

Simethicone (Imonogas®), also known as activated dimethicone, reduces surface tension as a non-systemic surfactant (152). Evidence on therapeutic efficacy of simethicone as monotherapy for the management of IBS is limited to one single RCT pre-dating the Rome criteria (153). Concerning the combination of simethicone with alverine citrate (Simalviane®), limited data is currently available (154,155). Finally, only one double-blind placebo-controlled trial involving only 40 IBS patients found no statistically significant effect of mebeverine on IBS symptoms (156).

Herbal medicine has been used for decades in the treatment of IBS. Four large systematic reviews with subsequent meta-analysis have been published on this topic during the last decade (157-160). The most recent and most elaborate meta-analysis encompassed 33 different herbal formulae (157). Non-inferiority was found for herbal medicine compared to conventional pharmacological therapy in 5 trials, and subgroup analysis revealed that herbal medicine more efficaciously alleviated symptoms in IBS when compared to placebo (157). However, the low-quality of trials, the lack of regulation of these products and the potential side effects (161) have led to suggest against offering herbal remedies to IBS patients.

Management of diarrhoea

Statements on the management of diarrhoea are summarised in table 8.

Bile acid malabsorption (BAM) is a common, yet underdiagnosed cause of chronic diarrhoea (162). Several studies have demonstrated the increased prevalence of BAM in up to 25-30 % in patients diagnosed with functional diarrhoea or IBS-D (163-165). Several tests have been developed for the diagnosis of BAM; the ^{75}Selenium-homotaurocholic acid test (75SeHCAT) is the most widely available and used test in Europe because it holds the highest diagnostic yield for the diagnosis of BAM (163,164). Other diagnostic tests include direct measurement of bile acid (BA) content in a 48-hour stool collection and the use of biomarkers in the serum. Measurement of the BA content in stool is the best alternative when 75SeHCAT is not available.

Only one bile acid sequestrants is currently available in Belgium (colestyramine), while colestipol and colesevelam are not commercialised in Belgium. Treatment with colestyramine resulted in reduced stool frequency, harder stool consistency and prolonged small bowel and colon transit in a group of 13 patients (166). As for colestipol, treatment significantly improved IBS symptoms in an open-label trial including 27 patients (167). In a single-centre unblinded single dose trial, colesevelam (168) improved stool consistency. However, in a subsequent double-blind placebo-controlled randomised trial, no difference was found on stool consistency and frequency, colonic transit and permeability (169).

Because the limited availability of 75SeHCAT, empiric treatment with bile acid sequestrant is often attempted in patients suffering from IBS-D. However, evidence derived from RCT in this setting remains limited, resulting in guidelines advising against offering colestyramine in unselected IBS-D patients (73). Arguments in favour of prior 75SeHCAT are the correlation of BAM severity with response to treatment with BA sequestrants (166), making a positive diagnosis of BA diarrhoea justifying the long duration of treatment with BA sequestrants, and possibly avoiding unnecessary administration of BA sequestrants with possible side-effects. However, the degree of evidence on BA sequestrants is low because of the limited number of patients included in the studies until now.

Since its discovery over 50 years ago, loperamide has been used in the treatment of IBS-D despite the limited and contradictory data in this setting. Some studies indicated improvement in both stool consistency as well as significantly fewer painful days with loperamide (170,171). Combining these results in a systematic review revealed no statistical advantage of loperamide over placebo (172). Cann et al. confirmed the improvement in stool parameters, but failed to demonstrate any benefit in pain scores (173), while one group found an increase in nightly pain (174).

Mast cell stabilisation, thereby decreasing local histamine release, has been shown to decrease visceral hypersensitivity and reduce IBS symptoms thereby improving the QOL (175). In a prospective randomized trial involving 55 IBS patients, the H1-receptor antagonist ebastine reduced visceral hypersensitivity and improved the symptom burden (176). A RCT (clinicaltrials.gov: NCT01908465) is ongoing in non-constipated IBS. The consensus group recognises the preliminary evidence of efficacy of ebastine in IBS but awaits more data before making a formal recommendation on its use in clinical practice.

Mesalazine has a significant anti-inflammatory effect mediated through various pathways (177). In addition, mesalazine has an anti-microbial effect, which may influence the gut microbiome in IBS (178). Early underpowered and short-term studies have shown efficacy of mesalazine to decrease mucosal mast cell infiltration in IBS patients (179), whereas two RCT showed negative results regarding pre-specified outcomes (179,180). However, post-hoc subgroup analysis hints at an effect in a subgroup of patients either defined by symptom

Table 8. — **An overview of all statements on management of diarrhoea with endorsement, grading of evidence and references**

5. Statements on management of diarrhoea	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. Testing for bile acid diarrhoea is useful in the work-up of IBS patients with persisting diarrhoea despite initial treatment.	80%, Yes	C	A+ 55%, A 25%, A- 10%, D- 0%, D 5%, D+ 5%	64,149-153
1.2. Bile acid sequestrants are effective for diarrhoea in IBS.	80%, Yes	B	A+ 35%, A 45%, A- 15%, D- 5%, D 0%, D+ 0%	153-156
1.3. Loperamide is effective for diarrhoea in IBS but lacks efficacy on pain management.	100%, Yes	B	A+ 50%, A 50%, A- 0%, D- 0%, D 0%, D+ 0%	157-161
1.4. H1-receptor antagonists are effective in non-constipated IBS.	40%, No	C	A+ 10%, A 30%, A- 55%, D- 5%, D 0%, D+ 0%	162-163
1.5. Mesalazine is not effective in IBS.	100%, Yes	C	A+ 80%, A 20%, A- 0%, D- 0%, D 0%, D+ 0%	164-171

severity, immune infiltration of the mucosa (mast-cell infiltrate) or clinical onset (post-infectious IBS) (181). Two additional smaller studies (182,183) were included in a recent meta-analysis (184). The authors did not support the use of the drug in unselected IBS patients. Therefore, given the current state of the literature, we do not recommend treating IBS patients with this drug.

Management of constipation

Statements on the management of constipation are summarised in table 9.

Although most guidelines recommend the use of a laxative as first-line therapy in IBS-C, there is an appalling paucity of data on their efficacy in this indication. Only one study evaluated the use of poly-ethylene glycol (PEG) with electrolytes in a 4-week placebo-controlled trial in 139 IBS-C patients (185). There was a numerical improvement in the number of complete spontaneous bowel movements with PEG compared to placebo, but this was only significant in week 4. There was no impact of PEG over placebo on symptoms like pain and discomfort.

Measurement of transit would be useful in clinical practice if it would explain a relevant part of symptom generation in IBS-C, and if it would determine treatment choice or treatment response. In terms of explaining symptoms, the contribution of transit measurement is minimal. Radiopaque transit measurements in 359 consecutive IBS patients identified a normal transit time in 80% of IBS-C patients (186). Analysis of symptom correlation showed a relationship between transit time and stool frequency and consistency, but not with symptoms of pain, discomfort and bloating. In terms of treatment choice, one might argue that an enterokinetic might be chosen if there is a very slow colonic transit.

The 5HT-4 receptor agonist prucalopride (Resolor®) accelerates GI transit and has antinociceptive properties due to its action on 5HT4 receptors of intestinal afferent and spinal sensory neurons as well as the 5HT4 dependent activation of supraspinal structures involved in endogenous antinociceptive effect (187). However, there are no data on prucalopride in IBS, and in the extensive clinical data set with prucalopride in chronic constipation, use of the drug was not preceded by transit measurement in these patients (188,189). Its efficacy was initially demonstrated in chronic constipation in 3 large phase III trials (190-192) and confirmed by an integrated analysis of 6 RCTs (188). A later analysis of phase 3 trials also confirmed signficant improvement in abdominal pain, discomfort and bloating (189).

Similarly, in studies involving linaclotide, no stratification according to transit time is recommended or clinically used (193). Linaclotide is a Guanylate cyclase-C (GC-C) agonist which binds and activates GC-C on the luminal surface of the intestinal epithelium, induces secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased luminal fluid secretion and an acceleration of intestinal transit. There is also evidence from animal studies that activation of GC-C leads to cyclic guanylate monophosphate release, which inhibits nociceptors, leading to improvement in abdominal pain (194). Linaclotide improves bowel function and reduces abdominal pain and overall severity of IBS-C compared to placebo (195) with good safety and tolerability profile. By virtue of its effects in relieving abdominal pain by reducing visceral hypersensitivity and improving constipation symptoms by increasing intestinal secretion and accelerating transit, linaclotide may be uniquely positioned for a role in the management of IBS-C patients (72,196,197). Diarrhoea was the only dose-dependent adverse event and was usually of mild or

Table 9. — **An overview of all statements on management of constipation with endorsement, grading of evidence and references**

6. Statements on the management of constipation	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. Osmotic laxatives are effective for constipation in IBS-C.	95%, Yes	C	A+ 65%, A 30%, A- 5%, D- 0%, D 0%, D+ 0%	172
1.2. Investigating colonic transit is not useful in the management of IBS -C.	90%, Yes	C	A+ 60%, A 30%, A- 5%, D- 5%, D 0%, D+ 0%	173,175-176,180
1.3. Prucalopride is effective for severe constipation in IBS-C patients failing first-line treatment.	85%, Yes	A	A+ 55%, A 30%, A- 15%, D- 0%, D 0%, D+ 0%	175-179
1.4. Linaclotide is effective for severe constipation and abdominal pain in IBS-C failing first-line treatment.	100%, Yes	C	A+ 75%, A 25%, A- 0%, D- 0%, D 0%, D+ 0%	63,180-184
1.5. Assessment of evacuation disorders is useful in the management of IBS-C failing initial treatment.	85%, Yes	B	A+ 50%, A 35%, A- 5%, D- 0%, D 5%, D+ 5%	185-190
1.6. Biofeedback is effective in IBS-C patients with (suspected or documented) dyssynergic defaecation.	95%, Yes	C	A+ 60%, A 35%, A- 5%, D- 0%, D 0%, D+ 0%	191

moderate severity (196). Patients are therefore advised to take the drug 30 minutes before the meal and to adapt dosing in case of diarrhoea.

IBS-C and functional constipation are part of a continuum and hard to separate (198,199). A study indicated that outlet dysfunction is prevalent in a subset of non-diarrhoea-predominant IBS patients who have symptoms of outlet dysfunction (200). According to the criteria for functional constipation, symptoms suggestive of dyssynergic defaecation are straining, sensation of incomplete evacuation, sensation of anorectal obstruction, or manual manoeuvers to facilitate defaecation in more than 25% of defaecations. Evacuation disorders can be assessed using digital rectal examination (201), anorectal manometry (202) and with a balloon expulsion test (203). Biofeedback therapy has been assigned as a grade A recommendation for the treatment of dyssynergic defaecation by the American Neurogastroenterology and Motility Society and the European Society of Neurogastroenterology and Motility (204). The presence of IBS was not associated with poor biofeedback training results.

Management of intestinal permeability

Statements on the management of intestinal permeability are summarised in table 10.

An impaired intestinal barrier function represents a scientific concept which could contribute to symptom generation as several studies have shown a correlation between the degree of permeability and IBS symptoms (205-207), although a recent study reported an inverse correlation (208). Only Zhou et al. preselected IBS patients based on increased permeability in their treatment study with glutamine in the setting of post-infectious IBS-D (209). This is the only study to date in which an improvement of barrier function by glutamine translated into reduced symptoms. Nevertheless, most of the commercially available 'leaky gut' tests use indirect plasma markers of permeability which is not supported by scientific evidence (210-212). Therefore, at this moment, it is not advised to measure intestinal permeability in a diagnostic context because of the lack of impact on the management of IBS patients. Concerning glutamine, further larger studies are needed to determine its mechanisms of action, the optimal dose and duration of treatment, and if it has a place in other subsets of IBS patients. Moreover, it remains to be shown that the effect of glutamine is restricted to those patients with impaired barrier function.

Xyloglucan (XG) combined with a pea protein reticulated with tannins from grape seed extract and xylo-oligosaccharides (XOS) are the active components of Gelsectan®. Administration of Gelsectan® improved diarrhoea and abdominal pain in two RCTs (213,214). The effect was maintained during the follow-up period. Additional beneficial effects on flatulence and quality of life were observed. However, the unexpectedly low placebo response together with the very high clinical response rate observed in the study by Trifan et al. raise questions about selection bias and study blinding. Based on these uncertainties, the consensus group awaits confirmation by further larger studies before considering Gelsectan® as an established treatment for IBS-D.

Microbiome

Statements on the microbiome are summarised in table 11.

Although the gut microbiota composition is presumed to play an important role in the pathophysiology and future treatment of IBS (215), microbiome analysis for individual patients is currently not recommended. Lack of consistency in what represents the typical microbiome of IBS patients makes microbiome analysis not suitable as a discriminating biomarker (216,217). Lack of knowledge of the microbial community function renders microbiome analysis unusable as a tool for selecting therapeutic strategies (218). Commercially available microbiome testing dividing the microbiome in "good" and "bad" bacteria and offering supplements or other therapeutic options based on this distinction, is not supported by data.

Small intestinal bacterial overgrowth (SIBO) represents a condition characterised by symptoms arising from an increased number of bacteria in the small intestine. It has most commonly been described following abdominal surgery but is also recognised as a complication of diseases impacting intestinal motility or diseases characterised by intestinal stricturing such

Table 10. — **An overview of all statements on management of intestinal permeability with endorsement, grading of evidence and references**

7. Statements on the management of intestinal permeability	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. Testing for intestinal permeability is not useful in the management of IBS.	100%, Yes	C	A+ 90%, A 10%, A- 0%, D- 0%, D 0%, D+ 0%	192-199
1.2. Glutamine is effective in post-infectious IBS	50%, No	B	A+ 25%, A 25%, A- 30%, D- 10%, D 10%, D+ 0%	196
1.3. The combination of xyloglucan, pea protein, tannins and xylo-oligosaccharides is effective in IBS-D.	60%, No	D	A+ 30%, A 30%, A- 40%, D- 0%, D 0%, D+ 0%	200-201

Table 11. — **An overview of all statements on the microbiome with endorsement, grading of evidence and references**

8.	**Statements on the microbiome**	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1.	Microbiome analysis is not useful in the management of IBS.	100%, Yes	C	A+ 80%, A 20%, A- 0%, D- 0%, D 0%, D+ 0%	202-205
1.2.	Testing for SIBO is not useful in the management of IBS.	70%, No	C	A+ 35%, A 35%, A- 10%, D- 15%, D 5%, D+ 0%	50,206-212
1.3.	Testing for SIBO is useful in the management of IBS.	10%, No	C	A+ 0%, A 10%, A- 30%, D- 10%, D 20%, D+ 30%	50,206-212
1.4.	Prebiotics are not effective in IBS.	75%, No	D	A+ 30%, A 45%, A- 5%, D- 15%, D 5%, D+ 0%	213-215
1.5.	Selected probiotics are effective in IBS	80%, Yes	C	A+ 35%, A 45%, A- 15%, D- 0%, D 5%, D+ 0%	42,213,216-218
1.6.	Poorly resorbable antibiotics are effective in IBS-D.	75%, No	B	A+ 35%, A 40%, A- 25%, D- 0%, D 0%, D+ 0%	50,211,219-222
1.7.	Faecal microbiota transplantation may have a temporary effect in IBS.	70%, No	B	A+ 30%, A 40%, A- 30%, D- 0%, D 0%, D+ 0%	223-229
1.8.	Faecal microbiota transplantation is not effective in the treatment of IBS.	15%, No	B	A+ 10%, A 5%, A- 10%, D- 30%, D 30%, D+ 15%	223-229
1.9.	We advise against faecal microbiota transplantation for the treatment of IBS.	90%, Yes	B	A+ 70%, A 20%, A- 0%, D- 0%, D 10%, D+ 0%	223-229

as Crohn's disease or radiation enteritis. Culture of jejunal aspirate is considered the golden standard for the diagnosis of SIBO. However, because of its invasive and time-consuming nature, alternatives such as breath testing with glucose, lactulose, xylose or sucrose are preferred in clinical practice. According to 5 meta-analyses the prevalence of SIBO in IBS ranges from 32% to 72% (219-223), reflecting differences in sensitivity of the different techniques. Antibiotic treatment for demonstrated SIBO resulted in symptom improvement in 81.6% of the patients (222). Clearance of SIBO with rifaximin, as confirmed by a glucose breath test, was associated with symptomatic benefit according to most (59,224), but not all studies (225).

Different meta-analyses reviewed the effects of prebiotics (including fructo-oligosaccharides, galacto-oligosaccharides, inulin-type fructans, guar gum and pectin powder) on IBS symptoms (226-228). From these reviews, it became apparent that studies on prebiotics largely differ in prebiotic type and dose, treatment duration and outcome measures. Overall, prebiotics did not improve IBS symptoms or quality of life in general.

Many IBS patients will take probiotics to alleviate their symptoms, either bought over-the-counter, or based on the advice of healthcare professionals. Summary of meta-analyses and systematic reviews about effectiveness of probiotics have demonstrated that, as a group, they improve global abdominal symptoms and QOL of IBS patients, but the grade of evidence is low (51,226,229-231). Reduction of bloating and flatulence were consistently found without significant heterogeneity and both single-strain and multi-strain trials have demonstrated benefits. Moreover, it also seems likely that the meta-analyses have underestimated the efficacy of some strains or combinations due to the absence of subgroup analysis. Despite these results, concerns about strain accuracy, efficacy and safety of probiotics have been raised. Only a few probiotics available in Belgium have demonstrated efficacy (e.g. Bifidobacterium animalis subsp lactis (Activia), L plantarum 299v (Bion Transfit), Bifidobacterium bifidum HI-MIMBb75 (Kijimea Pro), Bifidobacterium infantis 35624 (Alflorex), Bacillus coagulans MTCC 5856 (SporixX Pro), Escherichia coli (Symbioflor 2)). Being branded as dietary supplements, and as such subject to less rigorous regulations, when prescribing probiotics in clinical practice, we recommend to verify their efficacy against specific target symptoms as well as the specific formulation with regard to strain and dosing.

Antibiotics represent another method to modulate the microbiome. Since only one trial studied neomycin and another norfloxacin, these antibiotics cannot be recommended in the treatment of IBS (232,233). Furthermore, both studies showed some efficacy in IBS patients that tested positive on lactulose breath testing at baseline, suggesting a correlation with SIBO. Four double-blind RCT indicated that rifaximin (Targaxan®) may have a modest efficacy over placebo in IBS-D patients, especially with associated bloating (59,224,234,235). The absence of financial reimbursement for this expensive drug in Belgium and the need for repeated treatment are limiting factors that hamper its use in this indication.

Seven double-blind, randomised, placebo-controlled trials have been published regarding the use of faecal microbiota transplantation (FMT) in IBS (236-242). The studies included patients from different IBS subgroups, used different delivery modes of faecal material and different primary endpoints. According to these RCTs

FMT may play a role in the short-term treatment of IBS, especially if the nasoduodenal route for administration is applied. However, FMT is not ready for routine clinical practice. Especially its short-term efficacy is a problem, although it has been shown that retransplantation can be beneficial (240). It also remains unclear how to select the donors. Furthermore, long-term safety remains uncertain. Until these issues are clarified, our consensus group does not recommend the use of FMT for IBS outside a clinical trial.

Neuromodulators and pain management

Statements on neuromodulators and pain management are summarised in table 12.

Central neuromodulators are increasingly used for the treatment of visceral pain in patients who are refractory to first-line treatments (243). Tricyclic antidepressants (TCAs) such as amitriptyline, imipramine, desipramine, nortriptyline and doxepin, are the first-line option for symptom improvement where visceral pain is a prominent feature, at lower doses than in their classical indication (243). Only TCAs have been shown to improve abdominal pain in patients without concomitant depression according to a recent meta-analysis (244). However, despite their efficacy, TCAs are not the first choice for the treatment of IBS and should be carefully used because of potential side effects (245). Adverse effects of TCAs include drowsiness, dry mouth, arrythmias, sexual dysfunction, and weight gain (246,247). Some side effects, particularly sedation and constipation, can prove beneficial to treat some aspects of disorders of gut-brain interaction such as sleep disturbance and diarrhoea (141,247). TCAs should be tested over a period of at least 4 weeks (see Table 14) and if effective continued 6 to 12 months following The Rome Foundation consensus, but without strong evidence about optimal duration.

Available data evaluating the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of IBS-related symptoms are conflicting. Fluoxetine, citalopram, and paroxetine have been studied. A recent meta-analysis including seven RCTs found a lower risk of persisting IBS symptoms with SSRIs (244). Altogether, the sensorimotor effects of SSRIs suggest that IBS-C patients in whom bloating or general discomfort, rather than pain, is the main symptom, are the target population. Moreover, SSRIs clearly have an anxiety-reducing effect, which is also useful in patients with comorbid psychiatric symptoms (243). Adverse effects include agitation, diarrhoea, insomnia and sexual dysfunction.

Data on serotonin and noradrenaline reuptake inhibitors (SNRIs) in IBS are limited to three small open-label studies with promising effects (248-250). Even if duloxetine is often used in clinical practice in patients with functional GI disorders, including IBS, a formal well-designed study is needed to assess its efficacy. Side effects mainly include nausea and impaired sleep.

Similar to SNRIs, there is evidence for delta ligands, like pregabalin, in other chronic pain conditions, including post-herpetic neuropathic pain, but the evidence in disorders of gut-brain interaction is limited (243). The only RCT with delta ligands demonstrated lower scores for pain, diarrhoea and bloating, with no effect on scores for adequate relief and quality of life (251). Adverse events such as blurred vision and dizziness were more common in the pregabalin-arm, which could be related to the very high dose. In regular practice, it is recommended to start at a low dose (e.g. 75mg bid) and slowly increase the dose based on efficacy and tolerance.

Centrally-acting opioids are potent analgesics, even in IBS (252) and are accepted for the treatment of patients with moderate to severe acute and chronic pain. Analgesic action of opioids is accompanied by significant adverse effects, including dependence, intoxication and respiratory depression, as a result from non-specific targeting of the central nervous system. In addition, opioids negatively affect the GI tract by causing nausea, vomiting, opioid-induced constipation and narcotic bowel syndrome, a paradoxical worsening of abdominal pain with escalating doses of opioids (245,253). There is no evidence for a long-term efficacy of centrally-acting opioids on IBS pain. Taking into account the side effect

Table 12. — **An overview of all statements on neuromodulators and pain management with endorsement, grading of evidence and references**

9. Statements on neuromodulators and pain management	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1. Tricyclic antidepressants are effective in IBS.	100%, Yes	B	A+ 85%, A 15%, A- 0%, D- 0%, D 0%, D+ 0%	128,230-234
1.2. Selective serotonin reuptake inhibitors are effective in IBS.	95%, Yes	B	A+ 70%, A 25%, A- 5%, D- 0%, D 0%, D+ 0%	230-231
1.3. Selective serotonin and noradrenalin reuptake inhibitors are effective in IBS.	65%, No	B	A+ 30%, A 35%, A- 25%, D- 5%, D 5%, D+ 0%	235-237
1.4. Delta-ligands (pregabalin and gabapentin) are effective in IBS.	65%, No	B	A+ 30%, A 35%, A- 20%, D- 10%, D 0%, D+ 5%	238
1.5. Centrally-acting opioids are not effective in IBS.	100%, Yes	D	A+ 80%, A 20%, A- 0%, D- 0%, D 0%, D+ 0%	232,239-240

Table 13. **An overview of all statements on non-pharmacological treatment targeting the brain-gut axis with endorsement, grading of evidence and references**

10.	**Statements on non-pharmacological treatment targeting the brain-gut axis**	Overall agreement, Endorsement	Grade of evidence	Voting distribution	References
1.1.	Cognitive behavioural therapy is effective in IBS.	95%, Yes	B	A+ 60%, A 35%, A- 5%, D- 0%, D 0%, D+ 0%	242,244-246
1.2.	Medical hypnotherapy is effective in IBS.	70%, No	B	A+ 35%, A 35%, A- 25%, D- 5%, D 0%, D+ 0%	248-254
1.3.	Yoga is effective in IBS.	35%, No	C	A+ 10%, A 25%, A- 40%, D- 0%, D 15%, D+ 10%	255-258
1.4.	Mindfulness is effective in IBS.	50%, No	C	A+ 10%, A 40%, A- 30%, D- 5%, D 15%, D+ 0%	260-263
1.5.	Osteopathy is not effective in IBS.	85%, Yes	C	A+ 40%, A 45%, A- 5%, D- 10%, D 0%, D+ 0%	265-266

profile, centrally-acting opioids should be avoided in the treatment of pain in IBS.

Non-pharmacological treatment targeting the brain-gut axis.

Statements on non-pharmacological treatment targeting the brain-gut axis are summarised in table 13.

Apart from dietary intervention and medical therapy, non-pharmacological intervention for IBS received attention from different research groups. Most data are available for cognitive behavioural therapy (CBT) and medical hypnotherapy, while data on mindfulness, yoga and osteopathy are limited or of low methodological quality.

Research has shown the benefit of complementary psychological interventions in reducing disease burden, healthcare costs and increasing coping and quality of life (254-256). CBT is one of the most extensively studied and substantiated methods (255,257-259). CBT focuses on the way patients process information about their environment to help them gain control and reduce symptoms. This therapy works by modifying thinking patterns and identifying cognitive errors and faulty logic. This can help patients control their difficulties and change the way they behave and feel better both emotionally and physically. In contrast to classic psychotherapy, CBT requires active participation and is more problem-focused, goal-directed and time-limited (257). Advantages of psychological treatment over the use of drugs are their safety and lasting effects beyond the duration of treatment (257).

Limitations of psychological treatment are the need for longer treatment durations, patients' motivation and the availability of specialised mental health professionals (257). Possible adverse events associated with psychological treatments are treatment failure, worsened symptoms, elevated distress levels, self-harm or even suicide (255). However, there is uncertainty on the causality of adverse events with psychological treatments.

Hypnosis represents a state of consciousness involving focused attention and reduced peripheral awareness characterised by an enhanced capacity for response to suggestion (260). Different studies, meta-analysis and even Cochrane reviews (261-266) recognise hypnosis as a potential and safe treatment for IBS patients resistant to standard therapy with a success rate somewhat above 50%. Studying hypnosis is obviously impossible in a well-blinded placebo-controlled trial. Nevertheless, the Superior Health Council of Belgium provides recommendations on the use of hypnosis for health care providers and its use in IBS (267). Despite the demonstrated positive response, patients in Belgium are rarely referred for medical hypnotherapy. The consensus group concurs that the lack of trained hypnotherapists and the resulting lack of experience in clinical practice contribute to the failure to reach a consensus position on this statement.

Yoga is a mind-body-breath practice that traditionally combines meditation postures and breathing control (268,269). Participants are immersed in their practice synchronising every movement to their breath leading to self-control and relaxation (269). Many studies have demonstrated a decrease in global symptom severity and improvement in QOL in IBS patients practising yoga (268-270). Assessment of efficacy is problematic due to study heterogeneity (session's length, intervention duration, diversity of yogic styles, and difficulties to have a sham group) (271). More studies are necessary to compare effectiveness of yoga to regular walking sessions or moderate regular physical activity that demonstrated improvement in IBS symptoms severity (139).

In training sessions of Mindfulness-Based Stress Reduction (MBSR) patients learn how to observe the present moment by noticing physical sensations, emotions and thoughts with compassion and without judgment. Active participation of patients is required. This awareness may facilitate enhanced emotional processing and coping regarding the effects of chronic illness and stress and improved self-efficacy and sense of control (272). It has been suggested that facilitating non-reactivity to GI-related anxiety may be a significant factor in positive outcomes from MBSR in IBS (273). According to PubMed, as of July 2021, 46 reports on the role of mindfulness in IBS have been published. The

Table 14. — **Suggested treatment duration before assessing its efficacy. A non-exhaustive list of frequently used IBS therapies**

Treatment	Assessment of treatment success	Reference
Otilonium bromide	10-15 weeks	52
Low FODMAP diet	1-2 weeks	112
Linaclotide	6 weeks	67
Amitriptyline	5-10 weeks	233
Citalopram	3-6 weeks	128

quality of the trials was not always optimal due to the small number of participants and the selection of a very specific group of patients. Three studies demonstrated a clear symptom reduction (274-276), warranting further research.

Osteopathy is based on manual contact between the therapist and the patient for diagnosis and treatment (277). Two systematic reviews (278,279) attempting to clarify the effectiveness of osteopathy in IBS concluded that further research is needed before any conclusions could be drawn. Therefore, this consensus group does not recommend osteopathy in the treatment of IBS.

Recommendations

Based on the statements that achieved consensus, different recommendations can be formulated, as summarised in Table 15 and Figure 1. These recommendations provide guidance in clinical practice how to approach a patient with suspected IBS with regard to the aetiology, pathophysiology, diagnostic approach and pharmacological, dietary or non-pharmacological treatment. Additionally, the recommendations point out which management strategies are insufficiently backed by evidence.

Areas of uncertainty were also identified. These should be addressed by future research. The biggest lack of consensus relates to testing of and treatment of the intestinal microbiome. Analysis of the microbiome is currently not useful in the management of IBS. However, no consensus was reached on the role of testing for and treating SIBO, possibly owing to the difficult distinction between SIBO and IBS and the lack of a validated test. The consensus agreed that probiotics should be selected according to their demonstrated effectiveness in treating IBS symptoms, while there was no consensus on the effectiveness of prebiotics and poorly resorbable antibiotics. At this stage, FMT is not recommended for routine clinical practice.

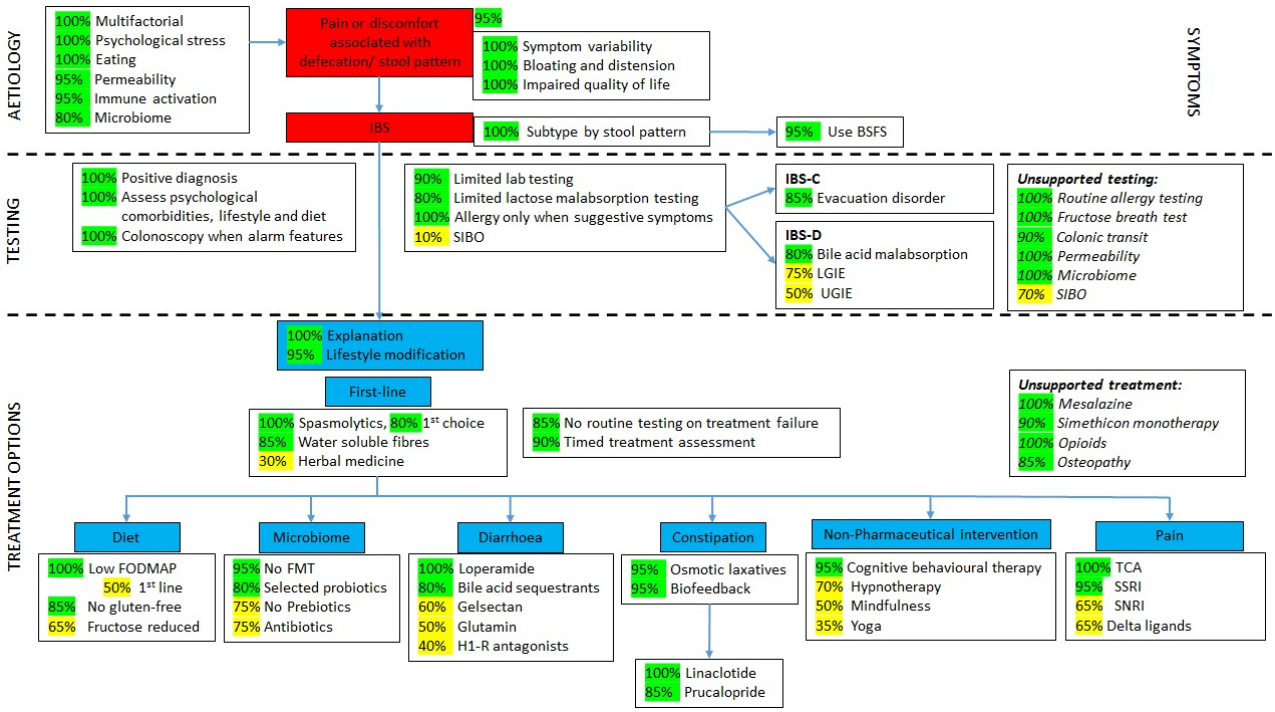

Figure 1. — Schematic representation of the outcome of the consensus on the management of IBS. The percentage of agreement is depicted by coloured rectangles, with green rectangles representing > 80% consensus. BSFS Bristol Stool Form Scale, FMT faecal microbiota transplantation, FODMAP fermentable oligo-, di-, polysaccharides and polyols, LGIE lower gastrointestinal endoscopy, UGIE upper gastrointestinal endoscopy, SIBO small intestinal bacterial overgrowth, SSRI selective serotonin reuptake inhibitor, SNRI serotonin and noradrenaline reuptake inhibitors, TCA tricylic antidepressant.

Table 15. — **Summary of recommendations**

Recommendations	**Based on statement(s)**
The aetiology of irritable bowel syndrome is multifactorial. Dietary factors, immune activation, increased intestinal permeability, gut microbiota composition and psychological stress can all contribute.	1.1, 1.2, 1.3, 1.4, 1.5, 1.6
History should address psychological comorbidities, lifestyle and dietary factors, as well as the impact on daily life.	1.7
Irritable bowel syndrome impacts quality of life.	1.8
Irritable bowel syndrome is characterised by recurrent abdominal pain or discomfort related to defaecation, and associated with a change of stool consistency or stool frequency. Symptom intensity and frequency vary between patients. Bloating and abdominal distension are frequently present in IBS patients.	2.1, 2.2, 2.3, 2.4
Irritable bowel syndrome should be subtyped according to the main stool pattern identified by the Bristol Stool Form Chart.	2.5, 2.6
A positive diagnosis of irritable bowel syndrome can be established in the majority of patients based on history and clinical examination. Limited laboratory testing can be considered in selected patients. Presence of alarm features warrant further testing by colonoscopy. Failure of initial therapy doesn't reject the diagnosis of irritable bowel syndrome.	3.1, 3.3, 3.4, 3.5
Routine food allergy testing is not useful. Food allergy testing should only be considered when GI symptoms are associated with stereotypical and repetitive symptoms across multiple organ systems.	4.1, 4.2
Lactose malabsorption testing has a limited role in the management of IBS.	4.3
We do not recommend fructose breath testing, colonic motility testing, assessment of intestinal permeability and microbiome analysis in IBS.	4.4, 7.2, 8.1, 9.1
Explanation is a crucial part of the management of IBS.	5.1
Lifestyle modifications are effective in the first-line approach of IBS.	5.2
Treatment evaluation should be timed in accordance to study results.	5.3
Water-soluble fibres and spasmolytics are effective in IBS. Spasmolytics are the preferred first-line treatment.	5.4, 5.5, 5.6
A low FODMAP diet is effective in the treatment of IBS.	4.8
Testing for bile acid diarrhoea is useful in persisting IBS-D despite initial treatment.	6.1
Selected probiotics are effective in IBS.	9.7
Bile acid sequestrants are effective for diarrhoea in IBS.	6.2
Loperamide is effective for diarrhoea in IBS, but not for pain	6.3
Osmotic laxatives are effective in IBS-C.	7.1
Linaclotide and prucalopride are effective for severe constipation in IBS-C failing initial treatment.	7.3,7.4
Assessment of evacuation disorders is useful in IBS-C failing initial treatment.	7.5
Biofeedback is effective in IBS-C with dyssynergic defaecation.	7.6
Tricyclic antidepressants and selective serotonin reuptake inhibitors are effective in IBS.	10.1, 10.2
Cognitive behavioural therapy is effective in IBS.	11.1
We advise against the gluten-free diet for the management of IBS.	4.7
We advise against faecal microbiota transplantation for the treatment of IBS.	9.11
Simethicone monotherapy, H1-receptor antagonists, mesalazine and centrally-acting opioids are not effective in IBS.	5.7,6.4, 6.5, 10.5
Osteopathy is not effective in IBS.	11.5

Different areas of uncertainty in IBS were highlighted. Most importantly, despite the recognition of multiple pathophysiological pathways and a multitude of treatments targeting these pathways, there is an unmet need for a mechanistic basis guiding treatment selection. Up to some point a selection based on predominant stool pattern or presence of pain is possible. However, this approach does not necessarily relate to the involved underlying pathophysiological mechanism in a specific patient. Future therapeutic trials including mechanistic testing could solve this issue.

Second, the consensus uncovered uncertain roles for upper and lower GI endoscopy in IBS-D patients failing initial treatment. This is emphasised by the fact that 75% of panelists were in favour of colonoscopy in this setting, despite the fact that 85% supported the statement

rejecting the need for routine testing in case of initial treatment failure. Intrinsic uncertainties associated with the symptom-based diagnosis of IBS could explain this contradictory result. Future research on possible markers for IBS undeniably would further the confidence in its diagnosis.

Lastly, from the results of the literature search of the different working groups, it became apparent that many interventional studies in IBS suffer from methodological flaws including poor endpoint selection and/or a small number of patients. This hampers comparison across studies and explains the contradictory results of different RCTs. These limitations underline the need for high-quality therapeutic studies with commonly accepted endpoints, preferentially in a multicenter setting. Undeniably, policy makers should play an important role in attaining these objectives by recognising the importance of IBS and facilitating research in this area.

Conclusion

IBS is a highly prevalent disorder with a high disease burden for patients and the healthcare system. Following a Delphi process, a group of Belgian IBS experts summarised the current evidence on the definition, symptom characteristics, pathophysiology, diagnosis and treatment of IBS with focus on the Belgian healthcare specificities. The voting results on the different statements can guide clinicians in recognising, diagnosing and treating IBS patients in clinical practice. Statements without consensus indicate areas of uncertainty warranting further research.

Conflict of interest

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References

1. LACY BE, MEARIN F, CHANG L, CHEY WD, LEMBO AJ, SIMREN M, *et al.* Bowel disorders. *Gastroenterology*, 2016, **150**: 1393-1407.e5.
2. SPERBER AD, BANGDIWALA SI, DROSSMAN DA, GHOSHAL UC, SIMREN M, TACK J, *et al.* Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology*, 2021, **160**: 99-114.e3.
3. MULLEN PM. Delphi: Myths and reality. *J Health Organ Manag*, 2003, **17**: 37-52.
4. NASA P, JAIN R, JUNEJA D. Delphi methodology in healthcare research: How to decide its appropriateness. *World J Methodol*, 2021, **11**: 116-29.
5. BALSHEM H, HELFAND M, SCHÜNEMANN HJ, OXMAN AD, KUNZ R, BROZEK J, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*, 2011, **64**: 401-406.
6. FORD A, SPERBER A, CORSETTI M, CAMILLERI M. Irritable bowel syndrome. *Lancet*, 2020, **396**: 1675-1688.
7. DEITEREN A, DE WIT A, VAN DER LINDEN L, DE MAN J, PELCKMANS P, DE WINTER B. Irritable bowel syndrome and visceral hypersensitivity : risk factors and pathophysiological mechanisms. *Acta gastroenterol Belg*, 2016, **79**: 29-38.
8. CHANG L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology*, 2011, **140**: 761-765.
9. KOLOSKI NA, JONES M, KALANTAR J, WELTMAN M, ZAGUIRRE J, TALLEY NJ. The brain - Gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. *Gut*, 2012, **61**: 1284-1290.
10. BERTIAUX-VANDAËLE N, YOUMBA S, BELMONTE L, LECLEIRE S, ANTONIETTI M, GOURCEROL G, *et al.* The expression and the cellular distribution of the tight junction proteins are altered in irritable bowel syndrome patients with differences according to the disease subtype. *Am J Gastroenterol*, 2011, **106**: 2165-2173.
11. BASHASHATI M, MOOSSAVI S, CREMON C, BARBARO M, MORAVEJI S, TALMON G, *et al.* Colonic immune cells in irritable bowel syndrome: A systematic review and meta-analysis. *Neurogastroenterol Motil*, 2018, **30**: e13192.
12. HUGHES PA, HARRINGTON AM, CASTRO J, LIEBREGTS T, ADAM B, GRASBY DJ, *et al.* Sensory neuro-immune interactions differ between Irritable Bowel Syndrome subtypes. *Gut*, 2013, **62**: 1456-1465.
13. BASHASHATI M, REZAEI N, BASHASHATI H, SHAFIEYOUN A, DARYANI NE, SHARKEY KA, *et al.* Cytokine gene polymorphisms are associated with irritable bowel syndrome: A systematic review and meta-analysis. *Neurogastroenterol Motil*, 2012, **24**: 1102-e566.
14. VILLANI A-C, LEMIRE M, THABANE M, BELISLE A, GENEAU G, GARG AX, *et al.* Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. *Gastroenterology*, 2010, **138**: 1502-1513.
15. BARKHORDARI E, REZAEI N, MAHMOUDI M, LARKI P, AHMADI-ASHTIANI HR, ANSARIPOUR B, *et al.* T-helper 1, T-helper 2, and T-regulatory cytokines gene polymorphisms in irritable bowel syndrome. *Inflammation*, 2010, **33**: 281-286.
16. BARKHORDARI E, REZAEI N, ANSARIPOUR B, LARKI P, ALIGHARDASHI M, AHMADI-ASHTIANI HR, *et al.* Proinflammatory cytokine gene polymorphisms in irritable bowel syndrome. *J Clin Immunol*, 2010, **30**: 74-79.
17. EIJSBOUTS C, ZHENG T, KENNEDY NA, BONFIGLIO F, ANDERSON CA, MOUTSIANAS L, *et al.* Genome-wide analysis of 53,400 people with irritable bowel syndrome highlights shared genetic pathways with mood and anxiety disorders. *Nat Genet*, 2021, **53**: 1543-1552.
18. BARBARA G, STANGHELLINI V, DE GIORGIO R, CREMON C, COTTRELL GS, SANTINI D, *et al.* Activated Mast Cells in Proximity to Colonic Nerves Correlate with Abdominal Pain in Irritable Bowel Syndrome. *Gastroenterology*, 2004, **126**: 693-702.
19. ROBLES A, PEREZ INGLES D, MYNEEDU K, DEOKER A, SAROSIEK I, ZUCKERMAN M, *et al.* Mast cells are increased in the small intestinal

mucosa of patients with irritable bowel syndrome: A systematic review and meta-analysis. *Neurogastroenterol Motil*, 2019, **31**: e13718.
20. SPILLER RC. Postinfectious irritable bowel syndrome. *Gastroenterology*, 2003, **124**: 1662-1671.
21. KLEM F, WADHWA A, PROKOP L, SUNDT W, FARRUGIA G, CAMILLERI M, *et al.* Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. *Gastroenterology*, 2017, **152**: 1042-1054.e1.
22. SASAKAWA C. A new paradigm of bacteria-gut interplay brought through the study of Shigella. *Proc Jpn Acad Ser B Physl Biol Sci*, 2010 ,**86**: 229-243.
23. AGUILERA-LIZARRAGA J, FLORENS M, HUSSEIN H, BOECKXSTAENS G. Local immune response as novel disease mechanism underlying abdominal pain in patients with irritable bowel syndrome. *Acta Clin Belgica*, 2021, 1-8.
24. CROUZET L, GAULTIER E, DEL'HOMME C, CARTIER C, DELMAS E, DAPOIGNY M, *et al.* The hypersensitivity to colonic distension of IBS patients can be transferred to rats through their fecal microbiota. *Neurogastroenterol Motil*, 2013, **25**: e272-282.
25. RINGEL Y, RINGEL-KULKA T. The intestinal microbiota and irritable bowel syndrome. *J Clin Gastroenterology*, 2015, **49**: S56-59.
26. MAXWELL PR, RINK E, KUMAR D, MENDALL MA. Antibiotics increase functional abdominal symptoms. *Am J Gastroenterol*, 2002, **97**: 104-108.
27. LEE KJ, TACK J. Altered intestinal microbiota in irritable bowel syndrome. *Neurogastroenterol Motil*, 2010, **22**: 493-498.
28. ANSARI MH, EBRAHIMI M, FATTAHI MR, GARDNER MG, SAFARPOUR AR, FAGHIHI MA, *et al.* Viral metagenomic analysis of fecal samples reveals an enteric virome signature in irritable bowel syndrome. *BMC Microbiol*, 2020, **20**: 123.
29. BÖHN L, STÖRSRUD S, TÖRNBLOM H, BENGTSSON U, SIMRÉN M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol*, 2013, **108**: 634-641.
30. MONSBAKKEN KW, VANDVIK PO, FARUP PG. Perceived food intolerance in subjects with irritable bowel syndrome - Etiology, prevalence and consequences. *Eur J Clin Nutr*, 2006, **60**: 667-672.
31. BÖHN L, STÖRSRUD S, TÖRNBLOM H, BENGTSSON U, SIMRÉN M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol*, 2013, **108**: 634-641.
32. MAJOR G, PRITCHARD S, MURRAY K, ALAPPADAN JP, HOAD CL, MARCIANI L, *et al.* Colon Hypersensitivity to Distension, Rather Than Excessive Gas Production, Produces Carbohydrate-Related Symptoms in Individuals With Irritable Bowel Syndrome. *Gastroenterology*, 2017, **152**: 124-133.e2.
33. BRADFORD K, SHIH W, VIDELOCK EJ, PRESSON AP, NALIBOFF BD, MAYER EA, *et al.* Association Between Early Adverse Life Events and Irritable Bowel Syndrome. *Clin Gastroenterol Hepatol,* 2012, **10**: 385-390. e3.
34. CHANG L, SUNDARESH S, ELLIOTT J, ANTON P, BALDI P, LICUDINE A, *et al.* Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in irritable bowel syndrome. *Neurogastroenterol Motil*, 2009, **21**: 149-159.
35. MOLONEY RD, JOHNSON AC, O'MAHONY SM, DINAN TG, GREENWOOD-VAN MEERVELD B, CRYAN JF. Stress and the Microbiota-Gut-Brain Axis in Visceral Pain: Relevance to Irritable Bowel Syndrome. *CNS Neurosci Ther,* 2016, **22**: 102-117.
36. VANUYTSEL T, VAN WANROOY S, VANHEEL H, VANORMELINGEN C, VERSCHUEREN S, HOUBEN E, *et al.* Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. *Gut*, 2014, **63**: 1293-1299.
37. PARK SH, VIDELOCK EJ, SHIH W, PRESSON AP, MAYER EA, CHANG L. Adverse childhood experiences are associated with irritable bowel syndrome and gastrointestinal symptom severity. *Neurogastroenterol Motil*, 2016, **28**: 1252-1260.
38. GRINSVALL C, TÖRNBLOM H, TACK J, VAN OUDENHOVE L, SIMRÉN M. Relationships between psychological state, abuse, somatization and visceral pain sensitivity in irritable bowel syndrome. *United European Gastroenterol J,* 2018, **6**: 300-309.
39. SIMRÉN M, TÖRNBLOM H, PALSSON OS, VAN OUDENHOVE L, WHITEHEAD WE, TACK J. Cumulative Effects of Psychologic Distress, Visceral Hypersensitivity, and Abnormal Transit on Patient-reported Outcomes in Irritable Bowel Syndrome. *Gastroenterology*, 2019, **157**: 391-402. e2.
40. CHANG JY, LOCKE GR, MCNALLY MA, HALDER SL, SCHLECK CD, ZINSMEISTER AR, *et al.* Impact of functional gastrointestinal disorders on survival in the community. *Am J Gastroenterol*, 2010, **105**: 822-832.
41. FRÄNDEMARK Å, TÖRNBLOM H, JAKOBSSON S, SIMRÉN M. Work Productivity and Activity Impairment in Irritable Bowel Syndrome (IBS): A Multifaceted Problem. *Am J Gastroenterol*, 2018, **113**: 1540-1549.
42. BUONO JL, CARSON RT, FLORES NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes*, 2017, **15**: 35.
43. LONGSTRETH GF, THOMPSON WG, CHEY WD, HOUGHTON LA, MEARIN F, SPILLER RC. Functional Bowel Disorders. *Gastroenterology*, 2006, **130**: 1480-1491.
44. SPIEGEL BMR, BOLUS R, AGARWAL N, SAYUK G, HARRIS LA, LUCAK S, *et al.* Measuring symptoms in the irritable bowel syndrome: Development of a framework for clinical trials. *Aliment Pharmacol Ther*, 2010, **32**: 1275-1291.
45. ZHU Y, ZHENG X, CONG Y, CHU H, FRIED M, DAI N, *et al.* Bloating and distention in irritable bowel syndrome: The role of gas production and visceral sensation after lactose ingestion in a population with lactase deficiency. *Am J Gastroenterol*, 2013, **108**: 1516-1525.
46. HOUGHTON LA, LEA R, AGRAWAL A, REILLY B, WHORWELL PJ. Relationship of Abdominal Bloating to Distention in Irritable Bowel Syndrome and Effect of Bowel Habit. *Gastroenterology*, 2006, **131**: 1003-1010.
47. CHANG L, LEE OY, NALIBOFF B, SCHMULSON M, MAYER EA. Sensation of bloating and visible abdominal distension in patients with irritable bowel syndrome. *Am J Gastroenterol*, 2001, **96**: 3341-3347.
48. TREMOLATERRA F, VILLORIA A, AZPIROZ F, SERRA J, AGUADÉ S, MALAGELADA JR. Impaired Viscerosomatic Reflexes and Abdominal-Wall Dystony Associated With Bloating. *Gastroenterology*, 2006, **130**: 1062-1068.
49. ACCARINO A, PEREZ F, AZPIROZ F, QUIROGA S, MALAGELADA JR. Abdominal Distention Results From Caudo-ventral Redistribution of Contents. *Gastroenterology*, 2009, **136**: 1544-1551.
50. MARSH A, ESLICK EM, ESLICK GD. Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis. *Eur J Nutr,* 2016, **55**: 897-906.
51. FORD AC, QUIGLEY EMM, LACY BE, LEMBO AJ, SAITO YA, SCHILLER LR, *et al.* Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol*, 2014, **109**: 1547-1562.
52. MÜLLER-LISSNER S, HOLTMANN G, RUEEGG P, WEIDINGER G, LÖFFLER H. Tegaserod is effective in the initial and retreatment of irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*, 2005, **21**: 11-20.
53. QUIGLEY EMM, TACK J, CHEY WD, RAO SS, FORTEA J, FALQUES M, *et al.* Randomised clinical trials: Linaclotide phase 3 studies in IBS-C - A prespecified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther*, 2013, **37**: 49-61.
54. CORSETTI M, TACK J. Linaclotide: A new drug for the treatment of chronic constipation and irritable bowel syndrome with constipation. *United European Gastroenterol J,* 2013, **1**: 7-20.
55. CHANG L, CHEY WD, DROSSMAN D, LOSCH-BERIDON T, WANG M, LICHTLEN P, *et al.* Effects of baseline abdominal pain and bloating on response to lubiprostone in patients with irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*, 2016, **44**: 1114-1122.
56. TACK J, STANGHELLINI V, DUBOIS D, JOSEPH A, VANDEPLASSCHE L, KERSTENS R. Effect of prucalopride on symptoms of chronic constipation. *Neurogastroenterol Motil*, 2014, **26**: 21-27.
57. LEMBO AJ, LACY BE, ZUCKERMAN MJ, SCHEY R, DOVE LS, ANDRAE DA, *et al.* Eluxadoline for Irritable Bowel Syndrome with Diarrhea. *N Engl J Med*, 2016, **374**: 242-253.
58. MENEES SB, MANEERATTANNAPORN M, KIM HM, CHEY WD. The efficacy and safety of rifaximin for the irritable bowel syndrome: A systematic review and meta-analysis. *Am J Gastroenterol*, 2012, **107**: 28-35.
59. PIMENTEL M, LEMBO A, CHEY WD, ZAKKO S, RINGEL Y, YU J, *et al.* Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation. *N Engl J Med*, 2011, **364**: 22-32.
60. GLENDE M, MORSELLI-LABATE A, BATTAGLIA G, EVANGELISTA S. Extended analysis of a double-blind, placebo-controlled, 15-week study with otilonium bromide in irritable bowel syndrome. *Eur J Gastroenterol Hepatol*, 2002, **14**: 1331-1338.
61. CLAVÉ P, ACALOVSCHI M, TRIANTAFILLIDIS JK, USPENSKY YP, KALAYCI C, SHEE V, *et al.* Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*, 2011, **34**: 432-442.
62. MEARIN F, BARÓ E, ROSET M, BADÍA X, ZÁRATE N, PÉREZ I. Clinical patterns over time in irritable bowel syndrome: Symptom instability and severity variability. *Am J Gastroenterol*, 2004, **99**: 113-121.
63. HEITKEMPER M, CAIN KC, SHULMAN R, BURR R, POPPE A, JARRETT M. Subtypes of irritable bowel syndrome based on abdominal pain/discomfort severity and bowel pattern. *Dig Dis Sci*, 2011, **56**: 2050-2058.

64. HAHN B, WATSON M, YAN S, GUNPUT D, HEUIJERJANS J. Irritable bowel syndrome symptom patterns: frequency, duration, and severity. *Dig Dis Sci*, 1998, **43**: 2715-2718.
65. PETERS SA, EDOGAWA S, SUNDT WJ, DYER RB, DALENBERG DA, MAZZONE A, *et al.* Constipation-Predominant Irritable Bowel Syndrome Females Have Normal Colonic Barrier and Secretory Function. *Am J Gastroenterol*, 2017, **112**: 913-923.
66. ISHIMOTO H, OSHIMA T, SEI H, YAMASAKI T, KONDO T, TOZAWA K, *et al.* Claudin-2 expression is upregulated in the ileum of diarrhea predominant irritable bowel syndrome patients. *J Clin Biochem Nutr*, 2017, **60**: 146-150.
67. CAMILLERI M, MCKINZIE S, BUSCIGLIO I, LOW PA, SWEETSER S, BURTON D, *et al.* Prospective Study of Motor, Sensory, Psychologic, and Autonomic Functions in Patients With Irritable Bowel Syndrome. *Clin Gastroenterol Hepatol,* 2008, **6**: 772-781.
68. CAMILLERI M. Intestinal Secretory Mechanisms in Irritable Bowel Syndrome-Diarrhea. *Clin Gastroenterol Hepatol,* 2015, **13**: 1051-1057.
69. AZIZ I, MUMTAZ S, BHOLAH H, CHOWDHURY FU, SANDERS DS, FORD AC. High Prevalence of Idiopathic Bile Acid Diarrhea Among Patients With Diarrhea-Predominant Irritable Bowel Syndrome Based on Rome III Criteria. *Clin Gastroenterol Hepatol*, 2015, **13**: 1650-1655.e2.
70. SURAWICZ CM. Mechanisms of diarrhea. *Curr Gastroenterol Rep*, 2010, **12**: 236-241.
71. HANNING N, EDWINSON A, CEULEERS H, PETERS S, DE MAN J, HASSETT L, *et al.* Intestinal barrier dysfunction in irritable bowel syndrome: a systematic review. *Therap Adv Gastroenterol*, 2021, **14**: 1756284821993586.
72. VIDELOCK EJ, CHENG V, CREMONINI F. Effects of Linaclotide in Patients With Irritable Bowel Syndrome With Constipation or Chronic Constipation: A Meta-analysis. *Clin Gastroenterol Hepatol,* 2013, **11**: 1084-1092.e3.
73. MOAYYEDI P, ANDREWS CN, MACQUEEN G, KOROWNYK C, MARSIGLIO M, GRAFF L, *et al.* Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). *J Can Assoc Gastroenterol*, 2019, **2**: 6-29.
74. COLOMIER E, ALGERA J, MELCHIOR C. Pharmacological Therapies and Their Clinical Targets in Irritable Bowel Syndrome With Diarrhea. *Front Pharmacol*, 2021, **18**, 11: 629026.
75. O'DONNELL L, VIRJEE J, HEATON K. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. *BMJ*, 1990, **300**: 439-440.
76. CHEY W, LEMBO A, LAVINS B, SHIFF S, KURTZ C, CURRIE M, *et al.* Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*, 2012, **107**: 1702-1712.
77. BLACK CJ, CRAIG O, GRACIE DJ, FORD AC. COMPARISON of the Rome IV criteria with the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gut*, 2021, **70**: 1110-1116.
78. LOZOYA ANGULO M, DE LAS HERAS GÓMEZ I, MARTINEZ VILLANUEVA M, NOGUERA VELASCO J, AVILÉS PLAZA F. Faecal calprotectin, an useful marker in discriminating between inflammatory bowel disease and functional gastrointestinal disorders. *Gastroenterol Hepatol*, 2017, **40**: 125-131.
79. MOWAT C, DIGBY J, STRACHAN JA, MCCANN R, HALL C, HEATHER D, *et al.* Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: A prospective cohort study. *BMJ Open Gastroenterol*, 2019, **6**: e000293.
80. MEARIN F, CIRIZA C, MÍNGUEZ M, REY E, MASCORT JJ, PEÑA E, *et al.* Clinical Practice Guideline: Irritable bowel syndrome with constipation and functional constipation in the adult. *Rev Esp Enferm Dig*, 2016, **108**: 332-363.
81. ARASARADNAM RP, BROWN S, FORBES A, FOX MR, HUNGIN P, KELMAN L, *et al.* Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. *Gut*, 2018, **67**: 1380-1399.
82. POORTMANS P, KINDT S. Diagnostic approach to chronic diarrhoea and recent insights in treatment of functional diarrhoea including irritable bowel syndrome. *Acta gastroenterol Belg*, 2020, **83**: 461-474.
83. EL-SERAG HB, PILGRIM P, SCHOENFELD P. Systematic review: Natural history of irritable bowel syndrome. *Aliment Pharmacol Ther*, 2004, **19**: 861-870.
84. MOAYYEDI P, MEARIN F, AZPIROZ F, ANDRESEN V, BARBARA G, CORSETTI M, *et al.* Irritable bowel syndrome diagnosis and management: A simplified algorithm for clinical practice. *United European Gastroenterol J,* 2017, **5**: 773-788.
85. ASGHAR Z, THOUFEEQ M, KURIEN M, BALL AJ, REJ A, DAVID TAI FW, *et al.* Diagnostic Yield of Colonoscopy in Patients With Symptoms Compatible With Rome IV Functional Bowel Disorders. *Clin Gastroenterol Hepatol,* 2022, **20**: 334-341.
86. CHEY WD, NOJKOV B, RUBENSTEIN JH, DOBHAN RR, GREENSON JK, CASH BD. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: Results from a prospective, controlled US trial. *Am J Gastroenterol*, 2010, **105**: 859-865.
87. LACY BE, PIMENTEL M, BRENNER DM, CHEY WD, KEEFER LA, LONG MD, *et al.* ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am J Gastroenterol*, 2021, **116**: 17-44.
88. OLDEN KW. Approach to the patient with severe, refractory irritable bowel syndrome. *Curr Treat Options Gastroenterol*, 2003, **6**: 311-317.
89. YAMADA E, TSUNODA S, ABE T, UCHIDA E, TERAOKA H, WATANABE S, *et al.* Factors associated with poor therapeutic response in outpatients with irritable bowel syndrome: a multicenter study in Japan. *J Gastroenterol*, 2017, **52**: 301-307.
90. OWENS DM, NELSON, DK, TALLEY NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. *Ann Intern Med,* 1995, **122**: 107-112.
91. ADENIJI O, BARNETT C, DI PALMA J. Durability of the diagnosis of irritable bowel syndrome based on clinical criteria. *Dig Dis Sci*, 2004, **49**: 572-574.
92. BEGTRUP LM, ENGSBRO AL, KJELDSEN J, LARSEN P V., SCHAFFALITZKY DE MUCKADELL O, BYTZER P, *et al.* A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol,* 2013, **11**: 956-962.
93. ENGSBRO AL, BEGTRUP LM, HAASTRUP P, STORSVEEN MM, BYTZER P, KJELDSEN J, *et al.* A positive diagnostic strategy is safe and saves endoscopies in patients with irritable bowel syndrome: A five-year follow-up of a randomized controlled trial. *Neurogastroentero Motil*, 2021, **33**: e14004.
94. BOYCE J, ASSA'AD A, BURKS A, JONES S, SAMPSON H, WOOD R, *et al.* Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*, 2010, **126**: S1-58.
95. PARK MI, CAMILLERI M. Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review. *Neurogastroenterol Motil*, 2006,**18**: 595-607.
96. MULLIN G, SWIFT K, LIPSKI L, TURNBULL L, RAMPERTAB S. Testing for food reactions: the good, the bad, and the ugly. *Nutr Clin Pract*, 2010, **25**: 192-198.
97. ATKINSON W, SHELDON TA, SHAATH N, WHORWELL PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut*, 2004, **53**: 1459-1464.
98. ZAR S, MINCHER L, BENSON MJ, KUMAR D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol*, 2005, **40**: 800-807.
99. LIGAARDEN S, LYDERSEN S, FARUP P. IgG and IgG4 antibodies in subjects with irritable bowel syndrome: a case control study in the general population. *BMC gastroenterol*, 2012, **12**: 166.
100. ZUO X, LI Y, LI W, GUO Y, LU X, LI J, *et al.* Alterations of food antigen-specific serum immunoglobulins G and E antibodies in patients with irritable bowel syndrome and functional dyspepsia. *Clin Exp Allergy*, 2007, **37**: 823-830.
101. NEUENDORF R, CORN J, HANES D, BRADLEY R. Impact of Food Immunoglobulin G-Based Elimination Diet on Subsequent Food Immunoglobulin G and Quality of Life in Overweight/Obese Adults. *J Altern Complement Med*, 2019, **25**: 241-248.
102. MASLIN K, VENTER C, MACKENZIE H, VLIEG-BOERSTRA B, DEAN T, SOMMER I. Comparison of nutrient intake in adolescents and adults with and without food allergies. *J Hum Nutr Diet*, 2018, **31**: 209-217.
103. SOVA C, FEULING MB, BAUMLER M, GLEASON L, TAM JS, ZAFRA H, *et al.* Systematic review of nutrient intake and growth in children with multiple IgE-mediated food allergies. *Nutr Clin Pract*, 2013, **28**: 669-675.
104. GASBARRINI A, CORAZZA GR, GASBARRINI G, MONTALTO M, DI STEFANO M, BASILISCO G, *et al.* Methodology and indications of H2-breath testing in gastrointestinal diseases: The Rome consensus conference. *Aliment Pharmacol Ther*, 2009, **29**: 1-49.
105. ZHU Y, ZHENG X, CONG Y, CHU H, FRIED M, DAI N, *et al.* Bloating and distention in irritable bowel syndrome: the role of gas production and visceral sensation after lactose ingestion in a population with lactase deficiency. *Am J Gastroenterol*, 2013, **108**: 1516-1525.
106. VERNIA P, DI CAMILLO M, MARINARO V. Lactose malabsorption, irritable bowel syndrome and self-reported milk intolerance. *Dig Liver Di,* 2001, **33**: 234-239.
107. XIONG L, WANG Y, GONG X, CHEN M. Prevalence of lactose intolerance in patients with diarrhea-predominant irritable bowel syndrome: data from a tertiary center in southern China. *J Health Popul Nutr,* 2017, **36**: 38.

108. MELCHIOR C, DESPREZ C, HOUIVET E, DEBEIR L, BRIL L, MACCARONE M, *et al.* Is abnormal 25 g fructose breath test a predictor of symptomatic response to a low fructose diet in irritable bowel syndrome? *Clin Nutr*, 2020, **39**: 1155-1160.
109. BERG L, FAGERLI E, MARTINUSSEN M, MYHRE A, FLORHOLMEN J, GOLL R. Effect of fructose-reduced diet in patients with irritable bowel syndrome, and its correlation to a standard fructose breath test. *Scan J Gastroenterol* 2013, **48**: 936-943.
110. HAMMER HF, FOX MR, KELLER J, SALVATORE S, BASILISCO G, HAMMER J, *et al.* European guideline on indications, performance, and clinical impact of hydrogen and methane breath tests in adult and pediatric patients: European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Neurogastroenterology and Motility, and European Society for Paediatric Gastroenterology Hepatology and Nutrition consensus. *United European Gastroenterol J,* 2021, Epub.
111. REZAIE A, BURESI M, LEMBO A, LIN H, MCCALLUM R, RAO S, *et al.* Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. *Am J Gastroenterol*, 2017, **112**: 775-784.
112. HAYES P, CORISH C, O'MAHONY E, QUIGLEY EMM. A dietary survey of patients with irritable bowel syndrome. *J Hum Nutr Diet*, 2014, **27**: 36-47.
113. CATASSI C, ELLI L, BONAZ B, BOUMA G, CARROCCIO A, CASTILLEJO G, *et al.* Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. *Nutrients*, 2015, **7**: 4966-4977.
114. VAZQUEZ-ROQUE MI, CAMILLERI M, SMYRK T, MURRAY JA, MARIETTA E, O'NEILL J, *et al.* A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: Effects on bowel frequency and intestinal function. *Gastroenterology*, 2013, **144**: 903-911.
115. HAJIANI E, MASJEDIZADEH A, SHAYESTEH A, BABAZADEH S, SEYEDIAN S. Comparison between gluten-free regime and regime with gluten in symptoms of patients with irritable bowel syndrome (IBS). *J Family Med Prim Care*, 2019, **8**: 1691-1695.
116. ZANWAR VG, PAWAR S V., GAMBHIRE PA, JAIN SS, SURUDE RG, SHAH VB, *et al.* Symptomatic improvement with gluten restriction in irritable bowel syndrome: A prospective, randomized, double blinded placebo controlled trial. *Intest Res*. 2016, **14**: 343-350.
117. DI SABATINO A, VOLTA U, SALVATORE C, BIANCHERI P, CAIO G, DE GIORGIO R, *et al.* Small Amounts of Gluten in Subjects With Suspected Nonceliac Gluten Sensitivity: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial. *Clin Gastroenterol Hepatol,* 2015, **13**: 1604-1612.e3.
118. SHAHBAZKHANI B, SADEGHI A, MALEKZADEH R, KHATAVI F, ETEMADI M, KALANTRI E, *et al.* Non-celiac gluten sensitivity has narrowed the spectrum of irritable bowel syndrome: A double-blind randomized placebo-controlled trial. *Nutrients*, 2015, **7**: 4542-54.
119. BIESIEKIERSKI JR, PETERS SL, NEWNHAM ED, ROSELLA O, MUIR JG, GIBSON PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology*, 2013, **145**: 230-328.
120. SKODJE GI, SARNA VK, MINELLE IH, ROLFSEN KL, MUIR JG, GIBSON PR, *et al.* Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity. *Gastroenterology*, 2018, **154**: 529-539.e2.
121. MOLESKI SM, SHAH A, DURNEY P, MATTHEWS M, KAUSHAL G, SMITH C, *et al.* Symptoms of gluten ingestion in patients with non-celiac gluten sensitivity: A randomized clinical trial. *Nutrition*, 2021, **81**: 110944.
122. DALE HF, HATLEBAKK JG, HOVDENAK N, YSTAD SO, LIED GA. The effect of a controlled gluten challenge in a group of patients with suspected non-coeliac gluten sensitivity: A randomized, double-blind placebo-controlled challenge. *Neurogastroenterol Motil*, 2018: Epub.
123. WILD D, ROBINS GG, BURLEY VJ, HOWDLE PD. Evidence of high sugar intake, and low fibre and mineral intake, in the gluten-free diet. *Aliment Pharmacol Ther*, 2010, **32**: 573-581.
124. STAUDACHER HM, WHELAN K, IRVING PM, LOMER MCE. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet*, 2011, **24**: 487-495.
125. HALMOS EP, POWER VA, SHEPHERD SJ, GIBSON PR, MUIR JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*, 2014, **146**: 67-75.
126. DE ROEST RH, DOBBS BR, CHAPMAN BA, BATMAN B, O'BRIEN LA, LEEPER JA, *et al.* The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: A prospective study. *Int J Clin Pract*, 2013, **67**: 895-903.
127. PATCHARATRAKUL T, JUNTRAPIRAT A, LAKANANURAK N, GONLACHANVIT S. Effect of structural individual low-fodmap dietary advice vs. Brief advice on a commonly recommended diet on ibs symptoms and intestinal gas production. *Nutrients*, 2019, **11**: 2586.
128. ESWARAN SL, CHEY WD, HAN-MARKEY T, BALL S, JACKSON K. A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D. *American Journal of Gastroenterology*, 2016, **111**: 1824-1832.
129. MAAGAARD L, ANKERSEN D, VÉGH Z, BURISCH J, JENSEN L, PEDERSEN N, *et al.* Follow-up of patients with functional bowel symptoms treated with a low FODMAP diet. *World J Gastroenterol*, 2016, **22**: 4009-4019.
130. O'KEEFFE M, JANSEN C, MARTIN L, WILLIAMS M, SEAMARK L, STAUDACHER H, *et al.* Long-term impact of the low-FODMAP diet on gastrointestinal symptoms, dietary intake, patient acceptability, and healthcare utilization in irritable bowel syndrome. *Neurogastroenterol Motil*, 2018, **30**: Epub.
131. O'SULLIVAN MA, MAHMUD N, KELLEHER DP, LOVETT E, O'MORAIN CA. Patient knowledge and educational needs in irritable bowel syndrome. *Eur J Gastroenterol Hepatol*, 2000, **12**: 39-43.
132. WEISER KT, LACY BE, NODDIN L, CROWELL MD. Patient knowledge and perspective on irritable bowel syndrome: Development of a survey instrument. *Dig Dis Sci*, 2008, **53**: 284-95.
133. HALPERT A. Irritable bowel syndrome: Patient-provider interaction and patient education. *J Clin Med*, 2018, **7**: 3.
134. FLIK CE, VAN ROOD YR, DE WIT NJ. Systematic review: Knowledge and educational needs of patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol*, 2015, **27**: 367-371.
135. HUNGIN APS, BECHER A, CAYLEY B, HEIDELBAUGH JJ, MURIS JWM, RUBIN G, *et al.* Irritable bowel syndrome: An integrated explanatory model for clinical practice. *Neurogastroenterol Motil*, 2015, **27**: 750-763.
136. LABUS J, GUPTA A, GILL HK, POSSERUD I, MAYER M, RAEEN H, *et al.* Randomised clinical trial: Symptoms of the irritable bowel syndrome are improved by a psycho-education group intervention. *Aliment Ther,* 2013, **37**: 304-315.
137. DROSSMAN DA, RUDDY J. Improving Patient-Provider Relationships to Improve Health Care. *Clin Gastroenterol Hepatol,* 2020, **18**: 1417-426.
138. JOHANNESSON E. Intervention to increase physical activity in irritable bowel syndrome shows long-term positive effects. *World J Gastroenterol*, 2015, **21**: 600-608.
139. JOHANNESSON E, SIMRÉN M, STRID H, BAJOR A, SADIK R. Physical activity improves symptoms in irritable bowel syndrome: A randomized controlled trial. *Am J Gastroenterol*, 2011, **106**: 915-922.
140. TACK J, BROEKAERT D, FISCHLER B, VAN OUDENHOVE L, GEVERS AM, JANSSENS J. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*, 2006, **55**: 1095-1103.
141. VAHEDI H, MERAT S, MOMTAHEN S, KAZZAZI AS, GHAFFARI N, OLFATI G, *et al.* Clinical trial: The effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*, 2008, **27**: 678-684.
142. RUEPERT L, QUARTERO AO, DE WIT NJ, VAN DER HEIJDEN GJ, RUBIN G, MURIS JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev,* 2011, **2011**: CD003460.
143. MOAYYEDI P, QUIGLEY EMM, LACY BE, LEMBO AJ, SAITO YA, SCHILLER LR, *et al.* The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol*, 2014, **109**: 1367-1374.
144. NAGARAJAN N, MORDEN A, BISCHOF D, KING EA, KOSZTOWSKI M, WICK EC, *et al.* The role of fiber supplementation in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*, 2015, **27**: 1002-1010.
145. CAMILLERI M. Management Options for Irritable Bowel Syndrome. *Mayo Clin Proc*, 2018, **93**: 1858-1872.
146. FORD AC, MOAYYEDI P, CHEY WD, HARRIS LA, LACY BE, SAITO YA, *et al.* American college of gastroenterology monograph on management of irritable bowel syndrome. *Am J Gastroenterol*, 2018, **113**: 1-18.
147. FORD AC, TALLEY NJ, SPIEGEL BMR, FOXX-ORENSTEIN AE, SCHILLER L, QUIGLEY EMM, *et al.* Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: Systematic review and meta-analysis. *BMJ*, 2008, **337**: 1388-1392.
148. CHEY WD, KURLANDER J, ESWARAN S. Irritable bowel syndrome: A clinical review. *JAMA* , 2015, **313**: 949-958.
149. KHANNA R, MACDONALD JK, LEVESQUE BG. Peppermint oil for the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *J Clin Gastroenterol*, 2014, **48**: 505-512.
150. BLACK C, YUAN Y, SELINGER C, CAMILLERI M, QUIGLEY E, MOAYYEDI P, *et al.* Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: a systematic review

and network meta-analysis. *Lancet Gastroenterol Hepatol*, 2020, **5**: 117-131.
151. WEERTS ZZRM, MASCLEE AAM, WITTEMAN BJM, CLEMENS CHM, WINKENS B, BROUWERS JRBJ, *et al.* Efficacy and Safety of Peppermint Oil in a Randomized, Double-Blind Trial of Patients With Irritable Bowel Syndrome. *Gastroenterology*, 2020, 158: 123-136.
152. INGOLD CJ, AKHONDI H. Simethicone. StatPearls, Treasure Island: StatPearls Publishing, 2021.
153. BERNSTEIN JE, KASICH AM. A Double-Blind Trial of Simethicone in Functional Disease of the Upper Gastrointestinal *Tract. J Clin Pharmacol*, 1974, **14**: 617-623.
154. WITTMANN T, PARADOWSKI L, DUCROTTÉ P, BUENO L, ANDRO DELESTRAIN M. Clinical trial: the efficacy of alverine citrate/simeticone combination on abdominal pain/discomfort in irritable bowel syndrome--a randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*, 2010, **31**: 615-624.
155. DUCROTTE P, GRIMAUD JC, DAPOIGNY M, PERSONNIC S, O'MAHONY V, ANDRO-DELESTRAIN MC. On-demand treatment with alverine citrate/simeticone compared with standard treatments for irritable bowel syndrome: Results of a randomised pragmatic study. *Int J Clin Pract*, 2014, **68**: 245-254.
156. KRUIS W, WEINZIERL M, SCHÜSSLER P, HOLL J. Comparison of the therapeutic effect of wheat bran, mebeverine and placebo in patients with the irritable bowel syndrome. *Digestion*, 1986, **34**: 196-201.
157. TAN N, GWEE K, TACK J, ZHANG M, LI Y, CHEN M, *et al.* Herbal medicine in the treatment of functional gastrointestinal disorders: A systematic review with meta-analysis. *J Gastroenterol Hepatol,* 2020, **35**: 544-456.
158. LI C, AIN MOHD TAHIR N, LI S. A systematic review of integrated traditional Chinese and Western medicine for managing irritable bowel syndrome. *Am J Chin Med*, 2015, **43**: 385-406.
159. RAHIMI R, ABDOLLAHI M. Herbal medicines for the management of irritable bowel syndrome: A comprehensive review. *World J Gastroenterol*, 2012, **18**: 589-600.
160. SHI J, TONG Y, SHEN JG, LI HX. Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: A systematic review. *World J Gastroenterol*, 2008, **14**: 454-462.
161. CHEN M, QIN D, HUANG S LE, TANG TC, ZHENG H. Chinese herbal medicine versus antispasmodics in the treatment of irritable bowel syndrome: A network meta-analysis. *Neurogastroenterol Motil*, 2021, **33**: e14107.
162. WALTERS J, PATTNI S. Managing bile acid diarrhoea. *Therap Adv Gastroenterol,* 2010, **3**: 349-357.
163. VALENTIN N, CAMILLERI M, ALTAYAR O, VIJAYVARGIYA P, ACOSTA A, NELSON AD, *et al.* Biomarkers for bile acid diarrhoea in functional bowel disorder with diarrhoea: A systematic review and meta-analysis. *Gut*, 2016, **65**: 1951-1959.
164. WEDLAKE L, A'HERN R, RUSSELL D, THOMAS K, WALTERS J, ANDREYEV H. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*, 2009, **30**: 707-717.
165. SLATTERY SA, NIAZ O, AZIZ Q, FORD AC, FARMER AD. Systematic review with meta-analysis: The prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. *Aliment Pharmacol Ther*, 2015, **42**: 3-11.
166. STOTZER P-O, ABRAHAMSSON H, BAJOR A, SADIK R. Effect of Cholestyramine on Gastrointestinal Transit in Patients with Idiopathic Bile Acid Diarrhea: A Prospective, Open-Label Study. *Neuroenterology*. 2013, **2**.
167. BAJOR A, TÖRNBLOM H, RUDLING M, UNG K, SIMRÉN M. Increased colonic bile acid exposure: a relevant factor for symptoms and treatment in IBS. *Gut*, 2015, **64**: 84-92.
168. CAMILLERI M. Bile acid diarrhea: Prevalence, pathogenesis, and therapy. *Gut Liver*, 2015, **9**: 332-339.
169. VIJAYVARGIYA P, CAMILLERI M, CARLSON P, NAIR A, NORD SL, RYKS M, *et al.* Effects of Colesevelam on Bowel Symptoms, Biomarkers, and Colonic Mucosal Gene Expression in Patients With Bile Acid Diarrhea in a Randomized Trial. *Clin Gastroenterol Hepatol,* 2020, **18**: 2962-2970.e6.
170. HOVDENAK N. Loperamide treatment of the irritable bowel syndrome. *Scand J Gastroenterol*, 1987, **130**: 81-84.
171. LAVÖ B, STENSTAM M, NIELSEN A. Loperamide in treatment of irritable bowel syndrome--a double-blind placebo controlled study. *Scand J Gastroenterol*, 1987, **130**: 77-80.
172. FORD A, VANDVIK P. Irritable bowel syndrome. *BMJ Clin Evid,* 2010, **2010**: 0410.
173. CANN PA, READ NW, HOLDSWORTH CD, BARENDS D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci*, 1984, **29**: 239-247.
174. EFSKIND P, BERNKLEV T, VATN M. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol*, 1996, **31**: 463-468.
175. KLOOKER TK, BRAAK B, KOOPMAN KE, WELTING O, WOUTERS MM, VAN DER HEIDE S, *et al.* The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut*, 2010, **59**: 1213-1221.
176. WOUTERS M, BALEMANS D, VAN WANROOY S, DOOLEY J, CIBERT-GOTON V, ALPIZAR Y, *et al.* Histamine Receptor H1-Mediated Sensitization of TRPV1 Mediates Visceral Hypersensitivity and Symptoms in Patients With Irritable Bowel Syndrome. *Gastroenterology*, 2016, **150**: 875-887.e9.
177. BANTEL H, BERG C, VIETH M, STOLTE M, KRUIS W, SCHULZE-OSTHOFF K. Mesalazine inhibits activation of transcription factor NF-kappaB in inflamed mucosa of patients with ulcerative colitis. *Am J Gastroenterol*, 2000, **95**: 3452-3457.
178. ANDREWS CN, GRIFFITHS TA, KAUFMAN J, VERGNOLLE N, SURETTE MG, RIOUX KP. Mesalazine (5-aminosalicylic acid) alters faecal bacterial profiles, but not mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*, 2011, **34**: 374-383.
179. CORINALDESI R, STANGHELLINI V, CREMON C, GARGANO L, COGLIANDRO RF, DE GIORGIO R, *et al.* Effect of mesalazine on mucosal immune biomarkers in irritable bowel syndrome: A randomized controlled proof-of-concept study. *Aliment Pharmacol Ther*, 2009, **30**: 245-52.
180. LAM C, TAN W, LEIGHTON M, HASTINGS M, LINGAYA M, FALCONE Y, *et al.* A mechanistic multicentre, parallel group, randomised placebo-controlled trial of mesalazine for the treatment of IBS with diarrhoea (IBS-D). *Gut*, 2016, **65**: 91-99.
181. TÖRNBLOM H, SIMRÉN M. In search for a disease-modifying treatment in irritable bowel syndrome. *Gut*, 2016, **65**: 2-3.
182. TUTEJA A, FANG J, AL-SUQI M, STODDARD G, HALE D. Double-blind placebo-controlled study of mesalamine in post-infective irritable bowel syndrome--a pilot study. *Scand J Gastroenterol*, 2012, **47**: 1159-1164.
183. GHADIR M, PORADINEH M, SOTODEH M, ANSARI R, KOLAHDOOZAN S, HORMATI A, *et al.* Mesalazine Has No Effect on Mucosal Immune Biomarkers in Patients with Diarrhea-Dominant Irritable Bowel Syndrome Referred to Shariati Hospital: A Randomized Double-Blind, Placebo-Controlled Trial. *Middle East J Dig Dis*, 2017, **9**: 20-25.
184. ZHANG FM, LI S, DING L, XIANG SH, ZHU HT, YU JH, *et al.* Effectiveness of mesalazine to treat irritable bowel syndrome: A meta-Analysis. *Medicine* (Baltimore), 2019, **98**: e16297.
185. CHAPMAN RW, STANGHELLINI V, GERAINT M, HALPHEN M. Randomized clinical trial: Macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol*, 2013, **108**: 1508-1515.
186. TÖRNBLOM H, VAN OUDENHOVE L, SADIK R, ABRAHAMSSON H, TACK J, SIMRÉN M. Colonic transit time and IBS symptoms: what's the link? *Am J Gastroenterol*, 2012, **107**: 754-760.
187. LYUBASHINA OA, BUSYGINA II, PANTELEEV SS, NOZDRACHEV AD. The 5HT4 receptor agonist prucalopride suppresses abdominal nociception. *Dokl Biol Sci*, 2015, **461**: 76-79.
188. CAMILLERI M, PIESSEVAUX H, YIANNAKOU Y, TACK J, KERSTENS R, QUIGLEY E, *et al.* Efficacy and Safety of Prucalopride in Chronic Constipation: An Integrated Analysis of Six Randomized, Controlled Clinical Trials. *Dig Dis Sci*, 2016, **61**: 2357-2372.
189. TACK J, STANGHELLINI V, DUBOIS D, JOSEPH A, VANDEPLASSCHE L, KERSTENS R. Effect of prucalopride on symptoms of chronic constipation. *Neurogastroenterol Motil*, 2014, **26**: 21-27.
190. QUIGLEY EMM, VANDEPLASSCHE L, KERSTENS R, AUSMA J. Clinical trial: The efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation - A 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*, 2009, **29**: 315-328.
191. TACK J, VAN OUTRYVE M, BEYENS G, KERSTENS R, VANDEPLASSCHE L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut*, 2009, **58**: 357-365.
192. CAMILLERI M, KERSTENS R, RYKX A, VANDEPLASSCHE L. A Placebo-Controlled Trial of Prucalopride for Severe Chronic Constipation. *N Engl J Med*, 2008, **358**: 2344-2354.
193. CORSETTI M, TACK J. Linaclotide: A new drug for the treatment of chronic constipation and irritable bowel syndrome with constipation. *United European Gastroenterol J,* 2013, **1**: 7-20.
194. EUTAMENE H, BRADESI S, LARAUCHE M, THEODOROU V, BEAUFRAND C, OHNING G, *et al.* Guanylate cyclase C-mediated

antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol Motil*, 2010, **22**: 312-e84.
195. LACY BE, PIMENTEL M, BRENNER DM, CHEY WD, KEEFER LA, LONG MD, *et al.* ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am J Gastroenterol*, 2021, **116**: 17-44.
196. JOHNSTON JM, SHIFF SJ, QUIGLEY EMM. A review of the clinical efficacy of linaclotide in irritable bowel syndrome with constipation. *Curr Med Res Opin*, 2013, **29**: 149-160.
197. LACY B, LEMBO A, MACDOUGALL J, SHIFF S, KURTZ C, CURRIE M, *et al.* Responders vs clinical response: a critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. *Neurogastroenterol Motil*, 2014, **26**: 326-333.
198. SIAH KTH, WONG RK, WHITEHEAD WE. Chronic Constipation and Constipation-Predominant IBS: Separate and Distinct Disorders or a Spectrum of Disease? *Gastroenterol Hepatol* (N Y), 2016, **12**: 171-178.
199. CAMILLERI M. Irritable Bowel Syndrome: Straightening the road from the Rome criteria. *Neurogastroenterol Motil*, 2020, **32**: e13957.
200. SUTTOR V, PROTT G, HANSEN R, KELLOW J, MALCOLM A. Evidence for pelvic floor dyssynergia in patients with irritable bowel syndrome. *Dis Colon Rectum*, 2010, **53**: 156-160.
201. TANTIPHLACHIVA K, RAO P, ATTALURI A, RAO SSC. Digital rectal examination is a useful tool for identifying patients with dyssynergia. *Clin Gastroenterol Hepatol,* 2010, **8**: 955-960.
202. GROSSI U, CARRINGTON E V., BHARUCHA AE, HORROCKS EJ, SCOTT SM, KNOWLES CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defecation, *Gut*, 2016, **65**: 447-455.
203. JAIN M, SINGH S, BAIJAL R. Diagnostic value of the balloon expulsion test compared with anorectal manometry in Indian patients with dyssynergic defecation. *Prz Gastroenterol*, 2020, **15**: 151-155.
204. RAO S, BENNINGA M, BHARUCHA A, CHIARIONI G, DI LORENZO C, WHITEHEAD W. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. *Neurogastroenterol Motil*, 2015, **27**: 594-609.
205. VIVINUS-NÉBOT M, FRIN-MATHY G, BZIOUECHE H, DAINESE R, BERNARD G, ANTY R, *et al.* Functional bowel symptoms in quiescent inflammatory bowel diseases: Role of epithelial barrier disruption and low-grade inflammation, *Gut*, 2014, **63**: 744-752.
206. VIVINUS-NÉBOT M, DAINESE R, ANTY R, SAINT-PAUL MC, NANO JL, GONTHIER N, *et al.* Combination of allergic factors can worsen diarrheic irritable bowel syndrome: Role of barrier defects and mast cells. *Am J Gastroenterol*, 2012, **107**: 75-81.
207. ZHOU QQ, ZHANG B, NICHOLAS VERNE G. Intestinal membrane permeability and hypersensitivity in the irritable bowel syndrome. *Pain*, 2009, **146**: 41-46.
208. WITT S, BEDNARSKA O, KEITA Å, ICENHOUR A, JONES M, ELSENBRUCH S, *et al.* Interactions between gut permeability and brain structure and function in health and irritable bowel syndrome. *NeuroImage Clin*, 2019, **21**: 101602.
209. ZHOU QQ, VERNE ML, FIELDS JZ, LEFANTE JJ, BASRA S, SALAMEH H, *et al.* Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. *Gut*, 2019, **68**: 996-1002.
210. TATUCU-BABET OA, FORSYTH A, OWEN E, NAVARRO-PEREZ D, RADCLIFFE J, BENHEIM D, *et al.* Serum zonulin measured by enzyme-linked immunosorbent assay may not be a reliable marker of small intestinal permeability in healthy adults. *Nutr Res*, 2020, **78**: 82-92.
211. FASANO A. Zonulin measurement conundrum: Add confusion to confusion does not lead to clarity. *Gut*, 2021, **70**: 2007-2008.
212. SCHEFFLER L, CRANE A, HEYNE H, TÖNJES A, SCHLEINITZ D, IHLING CH, *et al.* Widely used commercial ELISA does not detect precursor of haptoglobin2, but recognizes properdin as a potential second member of the zonulin family. *Front Endocrinol* (Lausanne), 2018, **9**: 22.
213. TRIFAN A, BURTA O, TIUCA N, PETRISOR D, LENGHEL A, SANTOS J. Efficacy and safety of Gelsectan for diarrhoea-predominant irritable bowel syndrome: A randomised, crossover clinical trial. *United European Gastroenterol J,* 2019, **7**: 1093-1101.
214. ALEXEA O, BACAREA V, PIQUÉ N. The combination of oligo- and polysaccharides and reticulated protein for the control of symptoms in patients with irritable bowel syndrome: Results of a randomised, placebo-controlled, double-blind, parallel group, multicentre clinical trial. *United European Gastroenterol J,* 2016, **4**: 455-465.
215. DAHLQVIST G, PIESSEVAUX H. Irritable bowel syndrome: The role of the intestinal microbiota, pathogenesis and therapeutic targets. *Acta gastroenterol Belg*, 2011, **74**: 375-380.
216. CAMILLERI M, HALAWI H, ODUYEBO I. Biomarkers as a diagnostic tool for irritable bowel syndrome: where are we? *Exp Rev Gastroenterol Hepatol*, 2017, **11**: 303-316.
217. JEFFERY IB, O'TOOLE PW, ÖHMAN L, CLAESSON MJ, DEANE J, QUIGLEY EMM, *et al.* An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut*, 2012, **61**: 997-1006.
218. STALEY C, KAISER T, KHORUTS A. Clinician Guide to Microbiome Testing. *Dig Dis Sci*, 2018, **63**: 3167-3177.
219. FORD A, SPIEGEL B, TALLEY N, MOAYYEDI P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. *Clin Gastroenterol Hepatol,* 2009, **7**: 1279-1286.
220. GHOSHAL U, NEHRA A, MATHUR A, RAI S. A meta-analysis on small intestinal bacterial overgrowth in patients with different subtypes of irritable bowel syndrome. *J Gastroenterol Hepatol*, 2020, **35**: 922-931.
221. CHEN B, KIM J, ZHANG Y, DU L, DAI N. Prevalence and predictors of small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis. *J Gastroenterol*, 2018, **53** : 807-818.
222. SHAH A, TALLEY N, JONES M, KENDALL B, KOLOSKI N, WALKER M, *et al.* Small Intestinal Bacterial Overgrowth in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies. *Am J Gastroenterol*, 2020, **115**: 190-201.
223. SHAH E, BASSERI R, CHONG K, PIMENTEL M. Abnormal breath testing in IBS: a meta-analysis. *Dig Dis Sci*, 2010, **55**: 2441-2449.
224. LEMBO A, PIMENTEL M, RAO S, SCHOENFELD P, CASH B, WEINSTOCK L, *et al.* Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome. *Gastroenterology*, 2016, **151**: 1113-1121.
225. TUTEJA A, TALLEY N, STODDARD G, VERNE G. Double-Blind Placebo-Controlled Study of Rifaximin and Lactulose Hydrogen Breath Test in Gulf War Veterans with Irritable Bowel Syndrome. *Dig Dis Sci*, 2019, **64**: 838-845.
226. FORD A, HARRIS L, LACY B, QUIGLEY A, MOAYYEDI P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther*, 2018, **48**: 1044-1060.
227. ASHA M, KHALIL S. Efficacy and Safety of Probiotics, Prebiotics and Synbiotics in the Treatment of Irritable Bowel Syndrome: A systematic review and meta-analysis. *Sultan Qaboos Univ Med J*, 2020, **20**: e13-24.
228. WILSON B, ROSSI M, DIMIDI E, WHELAN K. Prebiotics in irritable bowel syndrome and other functional bowel disorders in adults: a systematic review and meta-analysis of randomized controlled trials. *The Am J Clin Nutr*, 2019, **109**: 1098-1111.
229. DALE HF, RASMUSSEN SH, ASILLER ÖÖ, LIED GA. Probiotics in irritable bowel syndrome: An up-to-date systematic review. *Nutrients*, 2019, **11**: 2048.
230. SHAPIRO J, BERNICA J, HERNAEZ R. Risk of Bias Analysis of Systematic Reviews of Probiotics for Treatment of Irritable Bowel Syndrome. *Clin Gastroenterol Hepatol,* 2019, **17**: 784-578.
231. LI B, LIANG L, DENG H, GUO J, SHU H, ZHANG L. Efficacy and Safety of Probiotics in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *Front Pharmacol*, 2020, **11**: 332.
232. GHOSHAL U, SRIVASTAVA D, MISRA A, GHOSHAL U. A proof-of-concept study showing antibiotics to be more effective in irritable bowel syndrome with than without small-intestinal bacterial overgrowth: a randomized, double-blind, placebo-controlled trial. *Eur J Gastroenterol Hepatol*, 2016, **28**: 281-289.
233. PIMENTEL M, CHOW EJ, LIN HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol*, 2003, **98**: 412-419.
234. SHARARA AI, AOUN E, ABDUL-BAKI H, MOUNZER R, SIDANI S, ELHAJJ I. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. *Am J Gastroenterol*, 2006, **101**: 326-333.
235. PIMENTEL M, PARK S, MIROCHA J, KANE S, KONG Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med*, 2006, **145**: 557-563.
236. ARONIADIS OC, BRANDT LJ, ONETO C, FEUERSTADT P, SHERMAN A, WOLKOFF AW, *et al.* Faecal microbiota transplantation for diarrhoea-predominant irritable bowel syndrome: a double-blind, randomised, placebo-controlled trial. *Lancet Gastroenterol Hepatol*, 2019, **4**: 675-685.
237. HOLSTER S, LINDQVIST CM, REPSILBER D, SALONEN A, DE VOS WM, KONIG J, *et al.* The effect of allogenic versus autologous fecal microbiota transfer on symptoms, visceral perception and fecal and mucosal microbiota in irritable bowel syndrome: a randomized controlled study. *Clin Transll Gastroenterol*, 2019, **10**: e00034.
238. LAHTINEN P, JALANKA J, HARTIKAINEN A, MATTILA E, HILLILÄ M, PUNKKINEN J, *et al.* Randomised clinical trial: faecal microbiota transplantation versus autologous placebo administered via colonoscopy in irritable bowel syndrome. *Aliment Pharmacol Ther*, 2020, **51**: 1321-1131.

239. EL-SALHY M, HATLEBAKK JG, GILJA OH, BRÅTHEN KRISTOFFERSEN A, HAUSKEN T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. *Gut*, 2020, **69**: 859-867.
240. HOLVOET T, JOOSSENS M, VÁZQUEZ-CASTELLANOS JF, CHRISTIAENS E, HEYERICK L, BOELENS J, *et al.* Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome With Predominant Abdominal Bloating: Short- and Long-term Results From a Placebo-Controlled Randomized Trial. *Gastroenterology*, 2021, **160**: 145-157.e8.
241. HALKJÆR S, CHRISTENSEN A, LO B, BROWNE P, GÜNTHER S, HANSEN L, *et al.* Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results from a randomised, double-blind placebo-controlled study. *Gut*, 2018, **67**: 2107-2115.
242. JOHNSEN P, HILPÜSCH F, CAVANAGH J, LEIKANGER I, KOLSTAD C, VALLE P, *et al.* Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol*, 2018, **3**: 17-24.
243. DROSSMAN DA, TACK J, FORD AC, SZIGETHY E, TÖRNBLOM H, VAN OUDENHOVE L. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut−Brain Interaction): A Rome Foundation Working Team Report. *Gastroenterology*, 2018, **154**: 1140-1171.e1.
244. FORD AC, LACY BE, HARRIS LA, QUIGLEY EMM, MOAYYEDI P. Effect of Antidepressants and Psychological Therapies in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-Analysis. *Am J Gastroenterol*, 2019, **114**: 21-39.
245. CHEN L, ILHAM SJ, FENG B. Pharmacological approach for managing pain in irritable bowel syndrome: A review article. *Anesth Pain Med*, 2017, **7**: e42747.
246. VANUYTSEL T, TACK JF, BOECKXSTAENS GE. Treatment of abdominal pain in irritable bowel syndrome. *J Gastroenterol*, 2014, **49**: 1193-1205.
247. TÖRNBLOM H, DROSSMAN DA. Psychotropics, Antidepressants, and Visceral Analgesics in Functional Gastrointestinal Disorders. *Curr Gastroenterol Rep*, 2018, **20**: 58.
248. BRENNAN BP, FOGARTY KV., ROBERTS JL, REYNOLDS KA, POPE HG, Hudson JI. Duloxetine in the treatment of irritable bowel syndrome: An open-label pilot study. *Hum Psychopharmacol*, 2009, **24**: 423-428.
249. KAPLAN A, FRANZEN MD, NICKELL P V., RANSOM D, LEBOVITZ PJ. An open-label trial of duloxetine in patients with irritable bowel syndrome and comorbid generalized anxiety disorder. *Int J Psychiatry Clin Pract*, 2014, **18**: 11-15.
250. LEWIS-FERNÁNDEZ R, LAM P, LUCAK S, GALFALVY H, JACKSON E, FRIED J, *et al.* An Open-Label Pilot Study of Duloxetine in Patients with Irritable Bowel Syndrome and Comorbid Major Depressive Disorder. *J Clin Psychopharmacol*, 2016, **36**: 710-715.
251. SAITO YA, ALMAZAR AE, TILKES KE, CHOUNG RS, VAN NORSTRAND MD, SCHLECK CD, *et al.* Randomised clinical trial: pregabalin vs placebo for irritable bowel syndrome. *Aliment Pharmacol Ther*,. 2019, **49**: 389-397.
252. LEMBO T, NALIBOFF BD, MATIN K, MUNAKATA J, PARKER RA, GRACELY RH, *et al.* Irritable bowel syndrome patients show altered sensitivity to exogenous opioids. *Pain*, 2000, **87**: 137-147.
253. SZIGETHY E, SCHWARTZ M, DROSSMAN D. Narcotic Bowel Syndrome and Opioid-Induced Constipation. Curr Gastroenterol Rep, 2014, 16: 1-11.
254. MONTERO AM, JONES S. Roles and Impact of Psychologists in Interdisciplinary Gastroenterology Care. *Clin Gastroenterol Hepatol,* 2020, **18**: 290-293.
255. BLACK CJ, THAKUR ER, HOUGHTON LA, QUIGLEY EMM, MOAYYEDI P, FORD AC. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. *Gut*, 2020, **69**: 1441-1151.
256. BASNAYAKE C, KAMM MA, STANLEY A, WILSON-O'BRIEN A, BURRELL K, LEES-TRINCA I, *et al.* Standard gastroenterologist versus multidisciplinary treatment for functional gastrointestinal disorders (MANTRA): an open-label, single-centre, randomised controlled trial. *Lancet Gastroenterol Hepatol*, 2020, **5**: 890-899.
257. VAN OUDENHOVE L, LEVY RL, CROWELL MD, DROSSMAN DA, HALPERT AD, KEEFER L, *et al.* Biopsychosocial Aspects of Functional Gastrointestinal Disorders. *Gastroenterology*, 2016, **150**: 1355-1367.e2.
258. LACKNER JM. Skills over pills? A clinical gastroenterologist's primer in cognitive behavioral therapy for irritable bowel syndrome. *Exp Rev Gastroenterol Hepatol*, 2020, **14**: 601-618.
259. EVERITT HA, LANDAU S, O'REILLY G, SIBELLI A, HUGHES S, WINDGASSEN S, *et al.* Cognitive behavioural therapy for irritable bowel syndrome: 24-month follow-up of participants in the ACTIB randomised trial. *Lancet Gastroenterol Hepatol*, 2019, **4**: 863-872.
260. ELKINS G, BARABASZ A, COUNCIL J, SPIEGEL D. Advancing research and practice: the revised APA Division 30 definition of hypnosis. *International J Clin Exp Hypn*, 2015, **63**: 1-9.
261. MOSER G, TRÄGNER S, GAJOWNICZEK E, MIKULITS A, MICHALSKI M, KAZEMI-SHIRAZI L, *et al.* Long-term success of GUT-directed group hypnosis for patients with refractory irritable bowel syndrome: a randomized controlled trial. *American J Gastroenterol*, 2013, **108**: 602-609.
262. LINDFORS P, LJÓTSSON B, BJORNSSON E, ABRAHAMSSON H, SIMRÉN M. Patient satisfaction after gut-directed hypnotherapy in irritable bowel syndrome. *Neurogastroenterol Motil*, 2013, **25**: 169-e86.
263. LEE HH, CHOI YY, CHOI MG. The efficacy of hypnotherapy in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *J Neurogastroenterol Motil*, 2014, **20**: 152-162.
264. WEBB A, KUKURUZOVIC R, CATTO-SMITH A, SAWYER S. Hypnotherapy for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*, 2007, CD005110.
265. ABBOTT RA, MARTIN AE, NEWLOVE-DELGADO T V., BETHEL A, THOMPSON-COON J, WHEAR R, *et al.* Psychosocial interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst Rev*, 2017, **1**: CD010971.
266. GUEGUEN J, BARRY C, HASSLER C, FALISSARD B. Evaluation de l'efficacité de la pratique de l'hypnose. 2015.
267. Hoge Gezondheidsraad. Verantwoord gebruik van hypnose in de gezondheidszorg. HGR. Brussel, 2020.
268. D'SILVA A, MACQUEEN G, NASSER Y, TAYLOR LM, VALLANCE JK, RAMAN M. Yoga as a Therapy for Irritable Bowel Syndrome. *Dig Dis Sci*, 2020, **65**: 2503-2514.
269. KAVURI V, RAGHURAM N, MALAMUD A, SELVAN S. Irritable Bowel Syndrome: Yoga as Remedial Therapy. Evid Based Complement Alternat Med, 2015, **2015**: 398156.
270. SCHUMANN D, ANHEYER D, LAUCHE R, DOBOS G, LANGHORST J, CRAMER H. Effect of Yoga in the Therapy of Irritable Bowel Syndrome: A Systematic Review. *Clin Gastroenterol Hepatol,* 2016, **14**: 1720-1731.
271. PATEL N, LACY B. Does Yoga Help Patients With Irritable Bowel Syndrome? *Clin Gastroenterol Hepatol,* 2016, **14**: 1732-1734.
272. KABAT-ZINN. Full catastrophe living. Bantam Dell. New York, 1990.
273. GARLAND E, GAYLORD S, PALSSON O, FAUROT K, DOUGLAS MANN J, WHITEHEAD W. Therapeutic mechanisms of a mindfulness-based treatment for IBS: effects on visceral sensitivity, catastrophizing, and affective processing of pain sensations. *J Behav Med*, 2012, **35**: 591-602.
274. GAYLORD SA, PALSSON OS, GARLAND EL, FAUROT KR, COBLE RS, MANN JD, *et al.* Mindfulness training reduces the severity of irritable bowel syndrome in women: Results of a randomized controlled trial. *Am J Gastroenterol*, 2011, **106**: 1678-1688.
275. ZERNICKE KA, CAMPBELL TS, BLUSTEIN PK, FUNG TS, JOHNSON JA, BACON SL, *et al.* Mindfulness-based stress reduction for the treatment of irritable bowel syndrome symptoms: A randomized wait-list controlled trial. *Int J Behav Med*, 2013, **20**: 385-396.
276. NALIBOFF BD, SMITH SR, SERPA JG, LAIRD KT, STAINS J, CONNOLLY LS, *et al.* Mindfulness-based stress reduction improves irritable bowel syndrome (IBS) symptoms via specific aspects of mindfulness. *Neurogastroenterol Motil*, 2020, **32**: e13828.
277. HUNDSCHEID H, PEPELS M, ENGELS L, LOFFELD R. Treatment of irritable bowel syndrome with osteopathy: results of a randomized controlled pilot study. *J Gastroenterol Hepatol*, 2007, **22**: 1394-1398.
278. GUILLAUD A, DARBOIS N, MONVOISIN R, PINSAULT N. Reliability of diagnosis and clinical efficacy of cranial osteopathy: A systematic review. *PLoS One*, 2016, **11**: e0167823.
279. MÜLLER A, FRANKE H, RESCH KL, FRYER G. Effectiveness of osteopathic manipulative therapy for managing symptoms of irritable bowel syndrome: A systematic review. *J Am Osteopath Assoc*, 2014, **114**: 470-479.