Italian guidelines for the management of irritable bowel syndrome: Joint Consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG),

Italian Guidelines for the Management of Irritable Bowel Syndrome

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ABSTRACT

The irritable bowel syndrome (IBS) is a chronic disorder of gut-brain interaction. IBS is still associated with areas of uncertainties, especially regarding the optimal diagnostic work-up and the more appropriate management. Experts from 7 Italian Societies conducted a Delphi consensus with literature summary and voting process on 27 statements. Recommendations and quality of evidence were evaluated using the grading of recommendations, assessment, development, and evaluation (GRADE) criteria. Consensus was defined as >80% agreement and reached for all statements.

In terms of diagnosis, the consensus supports a positive diagnostic strategy with a symptom-based approach, including the psychological comorbidities assessment and the exclusion of alarm symptoms, together with the digital rectal examination, full blood count, C-reactive protein, serology for coeliac disease, and fecal calprotectin assessment. Colonoscopy should be recommended in patients with alarm features. Regarding treatment, the consensus strongly supports a dietary approach for patients with IBS, the use of soluble fiber, secretagogues, tricyclic antidepressants, psychologically directed therapies and, only in specific IBS subtypes, rifaximin. A conditional recommendation was achieved for probiotics, polyethylene glycol, antispasmodics, selective serotonin reuptake inhibitors and, only in specific IBS subtypes, 5-HT3 antagonists, 5-HT4 agonists, bile acid sequestrants.

Keywords: irritable bowel syndrome; diarrhea; constipation; disorders of gut-brain interaction.

INTRODUCTION

The irritable bowel syndrome (IBS) is a chronic and often debilitating disorder of gut-brain interaction (DGBI), formerly known as functional gastrointestinal disorders (FGID) [1]. IBS is defined by symptom-based diagnostic criteria, known as the "Rome criteria", derived by consensus from a multinational group of experts, currently in their IV iteration reported in Table 1[1].

IBS is one of the most frequent DGBI, affecting up to about 3-5% of the Western population[2]. It is difficult to obtain a reliable estimation of IBS prevalence since there are no objective biomarkers for this condition. Its prevalence changes among different geographical regions due to variations in symptoms interpretation and reporting[3]. A recent a cross-sectional survey promoted by the Rome Foundation [2], reported that IBS prevalence rates ranged between 1.3% and 7.6%, with a pooled prevalence of 4.1% using Rome IV criteria. Even if IBS it is not a life-threatening condition, it impacts significantly quality of life of the patients affected, and places a considerable burden on health care systems[4]. Health care resource utilization, unnecessary testing and lack of consensus on treatment approaches additionally contribute to IBS costs[5]. IBS is associated with areas of uncertainties, especially regarding the optimal diagnostic work-up and the more appropriate management. Consequently, a joint group of experts of the Italian Societies of Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP) identified the need to formally evaluate and develop diagnostic and treatment recommendations for IBS, using a rigorous methodology. This guideline was developed to increase the awareness for this disease and support clinicians in the diagnosis and management of patient with IBS, in order to optimize clinical outcomes. Statements and summary of evidence on pediatric age are reported in Supplementary material 1.

METHODS

Methods are reported in Supplementary material 2 and Supplementary Table 1.

RESULTS

Table 2 reports all PICO and statements with endorsement, level of evidence, grade of recommendation and agreement

DIAGNOSIS

Statement 1.1: We recommend for the assessment of clinical history and patient's phenotyping due to their relevance for diagnosis and management of patients with IBS.

Statement endorsed, overall agreement: 100%: A+ 87.5%, A 12.5%, A- 0%, D- 0%, D 0%, D+ 0%.

LE: unable to assess using GRADE methodology; GR: consensus recommendation.

Summary of evidence: in the absence of alarm features, an accurate clinical history, focused on key abdominal symptoms, bowel habits (frequency and stool consistency), duration of symptoms and associated illness, combined with physical examination and minimal diagnostic testing is sufficient as a positive diagnostic strategy for IBS [1,6]. Alarm features, including a positive family history of colorectal cancer, inflammatory bowel disease or celiac disease, rectal bleeding or anemia, unintentional weight loss, abdominal mass, nocturnal symptom or a short history of symptoms, do not exclude the diagnosis of IBS *per se*, however, their presence warrants further investigation [6,7]. A systematic review and meta-analysis involving more than 1,000 patients showed that the accuracy of the Rome III criteria associated with clinical history and limited diagnostic evaluation enhanced the specificity of diagnostic performance of symptom-based criteria to more than 95% [8]. A study assessing 300 primary care patients with suspected IBS without alarm signs, randomized to either a diagnostic strategy of exclusion or to a positive diagnostic strategy [included only a complete blood count and C-reactive protein (CRP)], showed that a positive diagnostic strategy was non-inferior to a diagnosis of exclusion [9]. In addition, a positive diagnostic strategy can substantially shorten health care costs and time to appropriate therapy [10].

The Bristol Stool Form Scale (BSFS) and the Rome IV diagnostic questionnaires for adults, irritable bowel syndrome module, are the most commonly used diagnostic criteria to record stool consistency and to perform IBS diagnosis, respectively [6,7]. Although recurrent abdominal pain is the key IBS symptom, identification of predominant stool pattern based on BSFS on days with abnormal stools is crucial to select appropriate diagnostic testing and to guide treatment. In fact, current pharmacological treatments are based on predominant symptoms, usually targeting diarrhea or constipation [1]. According to the Rome classification, IBS is categorized in 4 distinct subtypes: IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), IBS with mixed bowel habits (IBS-M), and IBS unclassified (IBS-U) [1]. Only a very limited number of RCTs evaluated treatment effect in patients with IBS-M or IBS-U. Furthermore, other gastrointestinal symptoms (e.g., dyspepsia) and non-gastrointestinal complaints (i.e., psychological symptoms, migraine, headaches, fibromyalgia, interstitial cystitis, dyspareunia) are frequently overlapping with IBS [11,12]. All together these

aspects need to be considered in the diagnostic process as they play a crucial role in patient's phenotyping and are relevant for the proper management of this disorder [12].

Statement 1.2: We recommend for psychological comorbidities assessment in patients with IBS.

Statement endorsed, overall agreement: 93.8%: A+ 68.8%, A 25%, A- 6.2%, D- 0%, D 0%, D+ 0%.

LE: unable to assess using GRADE methodology; GR: consensus recommendation.

Summary of evidence: a number of patients with IBS have a concomitant mood disorder co-existing with the peripheral gut symptoms [13,14]. Indeed, IBS has been associated with impaired quality of life, distress [15] and anxiety [16]. However, the prevalence of overlapping psychological comorbidities in patients with IBS is controversial [17].

A recent systematic review and metanalysis including 73 studies [18] assessed the prevalence of anxiety and depression in patients with IBS. The authors found that the prevalence rates of anxiety symptoms and disorders in patients with IBS were 39.1% [95% Confidence Interval (CI): 32.4-45.8] and 23% (95%CI: 17.2-28.8), respectively. The Odds Ratios (ORs) for anxiety symptoms and disorders in patients with IBS compared with healthy subjects were 3.11 (95%CI: 2.43-3.98) and 2.52 (95%CI: 1.99-3.20), respectively. On the other hand, the prevalence estimates of depressive symptoms and disorders in patients with IBS was 28.8% and 23.3%, respectively. The ORs for depressive symptoms and disorders in patients with IBS compared to healthy subjects were 3.04 (95%CI: 2.37-3.91) and 2.72 (95%CI: 2.45-3.02), respectively. Subgroup analyses showed a higher prevalence of anxiety and depressive symptoms in female individuals than in male individuals.[18]

Regarding specific IBS subtypes, a meta-analysis[16] showed that patients with IBS with high levels of anxiety were mostly those with IBS-C and IBS-D, while depression was associated only to IBS-D [Standardized mean differences (SMD) 1.75, 95 % CI 0.20–3.31, p=0.027]. Besides, IBS severity has been shown to be dependent to psychological mechanism such as catastrophizing and somatization [19]. Somatization may also underlie the extraintestinal manifestations reported by patients with IBS, such as urinary and sexual symptoms, headache, and fatigue [20]. Conversely, stress and maladaptive coping mechanisms can increase the frequency and severity of IBS symptoms.[17,21]

Thus, IBS symptoms may themselves increase distress levels generating anxiety and depression not fulfilling criteria for a psychiatric diagnosis.

Statement 1.3: We recommend for a positive diagnostic strategy in patients with symptoms suggestive of IBS.

Statement endorsed, overall agreement: 93.8%: A+ 75%, A 18.8%, A- 6.2%, D- 0%, D 0%, D+ 0%.

LE: unable to assess using GRADE methodology; GR: consensus recommendation.

Summary of evidence: justification for a positive diagnosis of IBS as opposed to a diagnosis of exclusion is based on consensus and data from studies which show a low diagnostic yield of additional diagnostic studies in patients with IBS symptoms without alarm features and a minimal impact on patient outcomes or satisfaction. Nevertheless, many community providers (general practitioners and specialists) still consider IBS to be a diagnosis of exclusion [22]. This is confirmed also by data obtained in Italy both in general practice [23] and at hospital level [24]. Available data on the cost-effectiveness ratio of a positive strategy versus an exclusion strategy are limited, due to the difficulty of gathering the necessary information, the length of follow up, organizational and regulatory differences among countries.

A rigorous Danish study evaluated patients aged 18-50 years fulfilling the Rome III criteria for IBS without alarm signals seen in primary care setting [9]. Patients were randomized to a positive diagnostic strategy (limited blood tests) or a strategy of exclusion (extensive laboratory tests and sigmoidoscopy with biopsies). The initial costs of the investigations per patient for the two diagnostic strategies were 50.11$ and 913.59$, respectively, mainly related to endoscopy costs in the strategy of exclusion. After 1 year, overall there were no differences in gastrointestinal symptoms or patient satisfaction and there were no cases of inflammatory bowel disease (IBD), celiac disease (CD), or cancer discovered through either diagnostic strategy. There were no differences in health care costs in the year of follow up between groups in terms of either direct or indirect (sick days) costs.

Data about the 5 year follow-up of these patients [25] confirmed the absence in both groups of diagnosis of CD or cancers, with a similar Health-Related Quality of Life (HRQoL) and number of visits to the general practitioner, but a slight difference in hospital outpatient visits due to an IBS-related diagnosis (P=0.024). There was no economic analysis reported, however the positive strategy overall saved endoscopies. However, since the economic costs of the diagnostic strategies depend on the number and type of initial investigations and above all on their local cost, the generalizability of these data requires caution.

Statement 1.4: We recommend for the use of digital rectal examination and anorectal physiology tests in selected adult patients with IBS referred for refractory symptoms to exclude functional defecation disorder or fecal incontinence.

Statement endorsed, overall agreement: 87.5%: A+ 75%, A 12.5%, A- 12.5%, D- 0%, D 0%, D+ 0%.
LE: unable to assess using GRADE methodology; GR: consensus recommendation.

Summary of evidence: functional defecation disorders can be present in a relevant proportion of both adults and children patients with IBS [1,26]. Digital rectal examination (DRE) can help providing useful information about anal tone and sensitivity, and the ability to squeeze and strain, thus resulting in a firm suspicion of a functional anorectal disorder in adults [27–31]. However, DRE is seldomly performed in this kind of patients, even in gastroenterological referral centers [27,32]. A recent Italian survey reported that about 56.4% patients with functional constipation and IBS-C, referred to a secondary/tertiary gastroenterological center underwent a DRE [32].
Anorectal physiology tests, mainly anorectal manometry with balloon expulsion test and defecography should always be considered in adults with coexisting symptoms and signs of functional defecation disorder or fecal incontinence and/or refractory to conservative treatment, although there is limited agreement among the different tests [31]. These tests help in selecting subjects that likely benefit from a tailored pelvic floor rehabilitation which can be carried out by means of a multimodal approach, including kinesiotherapy associated with biofeedback, electrical functional stimulation and, in those with a change in rectal sensitivity, also volumetric rehabilitation [33]. The improvement in abdominal pain and bloating reported by IBS adult patients treated with a rehabilitative approach could further support this therapeutic option [34,35].
In conclusion if medical therapies have failed and/or a DRE raises the suspicion of an anorectal functional disorder, anorectal physiology tests should be considered for a tailored management of patients with IBS.

Statement 1.5: We recommend serologic testing for celiac disease if the prevalence in the population is >1%. If tests are positive, upper endoscopy with duodenal biopsies should be performed.

Statement endorsed, overall agreement: 100%: A+ 68.8%, A 31.2%, A- 0%, D- 0%, D 0%, D+ 0%.

LE: Moderate; GR: Strong.

Summary of evidence: celiac disease is an immune-mediated disease triggered by dietary gluten, a storage protein found in cereals such as wheat, rye, and barley. The disorder is characterized by an intestinal enteropathy leading to an extremely diversified clinical presentation ranging from no symptoms to a variety of gastrointestinal and extra-gastrointestinal manifestations [36,37]. The measurement of serum anti-tissue transglutaminase (tTG) antibodies and/or anti-endomysium are extremely sensitive and specific for the diagnosis and follow-up of CD, although at least in adults confirmation with duodenal biopsy is still mandatory. The seroprevalence of CD was recently estimated at 1.4% worldwide, ranging from 1.1 to 1.8% across geographical areas**,** whereas the pooled global prevalence of biopsy-confirmed CD was 0.7% (95%CI, 0.5%-0.9%) in 138,792 individuals [38].

Patients with CD often complain of abdominal pain, bloating, and/or modification in bowel habit that may be undistinguishable from IBS symptoms [39]. A gluten-free diet over a lifetime is protective, alleviates symptoms and prevents complications [36,40]. Hence, missing the diagnosis of CD in individuals reporting IBS-like symptoms might have significant potential consequences.

As demonstrated in a meta-analysis that included 36 studies with 9,275 subjects fulfilling criteria for IBS, the prevalence of abnormal serological testing for CD was significantly increased among patients fulfilling criteria for IBS irrespective of bowel habit, as compared with controls who did not have IBS [41]. In particular, the overall ORs for a positive anti-endomysium and/or tTG antibodies and biopsy-proven CD was 2.75 (95%CI 1.35–5.61) and 4.48, (95%CI 2.33–4.60) in patients with IBS symptoms compared with controls, respectively [41]. However, in this meta-analysis, data from North America found that a diagnosis of CD was uncommon in both IBS cases and controls without IBS. This result is consistent with another most recent study from United States (US) [42] and might be explained by a lower prevalence of CD in US compared with Europe. The OR for a positive serological test for CD was significantly higher among patients with IBS-D (OR 6.09; 95%CI 1.88-19.7) and IBS-C (OR 4.84; 95%CI 1.32-17.7). In addition, the OR for biopsy-proven CD was consistently elevated across all IBS subtypes when compared to controls without symptoms meeting criteria for IBS. Furthermore, since immunoglobulin A (IgA) deficiency causes false-negative IgA-based celiac serology tests and 2-3% of CD patients might have IgA deficiency, CD screening should combine IgA-tTG testing with a second test such as quantitative IgA levels to avoid the underdiagnosis of CD [43].

In summary, given the increased odds of CD among patients with IBS symptoms, independent from the predominant bowel habit pattern, the significant potential consequences of missing the diagnosis

of CD, the availability of highly effective treatment, and the apparent cost effectiveness of an early diagnosis [44], we recommend serologic testing with quantitative IgA levels and IgA anti-tTG to rule out CD in patients with any IBS subtype. This is mandatory, if CD prevalence in the population is >1% (as in Italy), since it has an acceptable cost and is worthwhile [44]. If tests are positive, upper endoscopy with duodenal biopsies should be performed in all adults.

Statement 1.6: We recommend for the use of fecal calprotectin[1] and C-reactive protein[2] to exclude inflammatory bowel disease in patients with IBS symptoms and diarrhea without alarm features.

Statement endorsed, overall agreement: 100%: A+ 93.8%, A 6.2%, A- 0%, D- 0%, D 0%, D+ 0%.

[1]LE: Very low; GR: Strong.

[2]LE: Very low; GR: Conditional.

Summary of evidence: although symptom based criteria for IBS may miss some patients with IBD [45], the risk in patients without alarm features is very low as the prevalence of IBD in such patients is only 0.5-2%.[46,47]. The addition of non-invasive tests in the workup of patients presenting with IBS like symptoms can help identifying this marginal proportion of misdiagnosed IBD patients and should be considered in clinical practice.

Fecal calprotectin is a non-invasive, simple and widely available marker of intestinal inflammation. This test has been indicated to be more accurate than serum biomarkers in ruling-out IBD and provides helpful prognostic information [48–52]. A meta-analysis evaluated the diagnostic performance of fecal calprotectin in identifying patients with IBD among those with IBS symptoms, using endoscopy as a reference test. The summary sensitivity was 93% (95%CI: 85-97) and specificity 96% (95%CI: 79-99%) for IBD diagnosis [53]. Rapid fecal calprotectin tests have been recently shown comparable to the enzyme-linked immunosorbent assay [54,55], but they are not widely available.

Serology tests of inflammation, such as CRP, are easy to perform and inexpensive. Although these tests are non-specific for IBD, they have been largely investigated for distinguishing between IBS and IBD patients [48,49,56,57]. A meta-analysis showed that CRP ≤0,5 mg/dL yields a 1% probability of IBD among patients with IBS symptoms [56]. In conclusion, fecal calprotectin and CRP are reliable non-invasive tools that can be used for the diagnosis of IBD among patients with IBS symptoms without alarms symptoms in clinical practice.

Statement 1.7: We recommend against routine stool testing for enteric pathogens in adults with IBS

Statement endorsed, overall agreement: 82.5%: A+ 75%, A 12.5%, A- 12.5%, D- 0%, D 0%, D+ 0%.
LE: Low; GR: Conditional.

Summary of evidence: acute infectious gastroenteritis is the strongest known risk factors for the development of IBS, the so-called post-infection IBS (PI-IBS), however infection in these cases is consistently transient and stool testing for enteric pathogens in the long run is not required [58,59]. Chronic parasite gastrointestinal infections elicit a wide range of clinical manifestations ranging from asymptomatic, to severe chronic symptoms such as bloating, diarrhea, and abdominal pain. While there are data in the literature linking parasite infections with IBS, most of the literature is focused on Giardiasis. A multinational RCT found that 2% of 1452 patients with established IBS diagnosis had a positive fecal ova and/or parasite testing [60]. Tests for fecal ova and parasites are widely requested by general practitioners and community gastroenterologists as compared to IBS experts, despite the lack of evidence demonstrating a change in diagnosis or outcome [22]. However, testing is indicated in patients with risk factors for Giardiasis such as patients from developing countries, travelling to endemic areas or drinking water of poor quality. [61,62]. In summary, due to the low evidence and quality of studies available, routine testing for Giardia is not recommend in all patients with IBS, except for those at high risk.

Statement 1.8: We recommend for colonoscopy in patients with IBS symptoms and alarm features.

Statement endorsed, overall agreement: 93.8%: A+ 93.8%, A 0%, A- 0%, D- 0%, D 0%, D+ 6.2%.
LE: Moderate; GR: Strong.

Summary of evidence: colonoscopy is frequently prescribed in patients with symptoms suggestive for IBS. However, colonoscopy should be indicated in patients with IBS symptoms and alarm features only, as well as according to local colorectal cancer-screening programs [63].

Indeed, according to several prospective and retrospective studies, in absence of alarm features the diagnostic yield of colonoscopy is low. Of note, a high heterogeneity across studies as concern design, definition of alarm features and Rome criteria used for the definition of IBS should be mentioned. When Rome IV criteria are adopted, the range is narrowed to 0-3.5% [64,65]. In case of diarrhea as the predominant symptom, colonoscopy with biopsies should be considered in case of suspected microscopic colitis, although its prevalence is low (up to 4%) [64,66].

Statement 1.9: We recommend against testing for food and lactose intolerance in patients with IBS.

Statement endorsed, overall agreement: 93.8%: A+ 87.5%, A 6.3%, A- 0%, D- 0%, D 6.2%, D+ 0%.
LE: Very low; GR: Strong.

Summary of evidence: food intolerance can be defined as a non-immune mediated reaction to food, either secondary to the pharmacologic effects of some substances contained in foods (e.g. salicylates, vasoactive amines, caffeine, glutamate, serotonin, tyramine, and capsaicin) or, more commonly, to the effects of poorly digestible/absorbable carbohydrates, leading to alterations of bowel frequency, bloating and changes in fecal consistency [67]. Although many tests have been proposed to detect food intolerances, [e.g. serum Immunoglobulin G (IgG) panels, leukocyte activation test], they are affected by limited validation, low specificity and lack of cost-effectiveness analysis [68–70]. Malabsorption of certain carbohydrates (e.g., lactose, sucrose) can be detected with hydrogen breath testing. As both IBS and lactose intolerance are highly prevalent in the general population, they can be simultaneous, but not necessarily interdependent. In fact, a recent meta-analysis of 34 case series including 9041 patients with IBS, reported a prevalence of a positive lactose breath test (LBT) of 56% (95%CI: 43-69%) in South Asia, 50% (95%CI: 43%-56%) in Europe, and 21% (95%CI: 14-29%) in the USA [71]. However, the same authors, analyzing 10 case control studies, including 2008 subjects, did not find significant difference in the prevalence of lactose malabsorption in patients with IBS compared with controls (OR 1.68; 95%CI 0.95–2.94, P=0.07) [71]. No significant difference in lactose malabsorption prevalence between patients with IBS and the general population is currently available and discrepancy between the prevalence of IBS symptoms and a positive lactose hydrogen breath test has been reported [72]. Therefore, routinely carrying out a hydrogen breath test to exclude lactose intolerance in patients with IBS is not advisable.

Statement 1.10: We recommend against routine testing for food allergies in both adult and pediatric patients with IBS unless there are reproducible symptoms suggestive of a food allergy.

Statement endorsed, overall agreement: 93.8%: A+ 68.8%, A 25%, A- 6.2%, D- 0%, D 0%, D+ 0%.
LE: unable to assess using GRADE methodology; GR: Conditional.

Summary of evidence: food allergies are an immune-mediated reactions to proteins contained in foods which can be 1) related to an Immunoglobulin E (IgE)-mediated response (upon sensitization with development of specific IgE antibodies to a food allergen, e.g., nuts), 2) unrelated to IgE mechanisms (mediated by T cells, e.g., food protein–induced enterocolitis syndrome), or 3) secondary to a mixed (IgE and non-IgE) response (e.g., milk protein allergy) [37,73,74]. True food allergies are rare, as they occur in only 1%–3% of adults with the most common food allergens being related to cow's milk, soy, peanuts, eggs, seafood and wheat [74–77]. The diagnosis of a food allergy is usually clinical, when symptoms (e.g. urticaria, itching, angioedema, rhinorrhea, laryngospasm, bronchospasm, abdominal pain, nausea, vomiting and diarrhea, dizziness, tachycardia and hypotension) occur rapidly after exposure to a certain food, are absent during avoidance and are reproducible after rechallenge [73]. Unfortunately, diagnostic tests including skin prick tests or serum IgE levels yield a low sensitivity (50-75%) and do not always correlate with the intensity of the reaction [73,78,79]. Adverse reactions to food are very common in the general population (up to 20-30%) and could negatively affect quality of life and costs [75,80–82]. However, even though the default interpretation is that of an allergic reaction, only 2-3% of the subjects develop recurrent symptoms when rechallenged with the offending food [82]. In fact, most adverse reactions to foods represent food intolerance or are the expression of visceral hypersensitivity [81–83]. Patients with IBS are more likely than the general population to report adverse reactions to food, with prevalence rates as high as 50%[73,83,84]. However, there are no case-control studies assessing the putative association between true food allergies and IBS. In conclusion, given the lack of evidence supporting an association between food allergies and IBS and the poor diagnostic performance of available tests, routine testing for food allergies in patients with IBS is not recommended, unless symptoms are reproducible after re-challenge and absent during avoidance.

Statement 1.11: We recommend against routine testing for small intestinal bacterial overgrowth in adult patients with IBS symptoms

Statement endorsed, overall agreement: 100%: A+ 93.8%, A 6.2%, A- 0%, D- 0%, D 0%, D+ 0%.

LE: Very low; GR: Strong.

Summary of evidence: small intestinal bacterial overgrowth (SIBO) has been frequently reported in patients with IBS, however it remains unclear whether SIBO represents a major pathogenetic mechanism underlying IBS [85]. Results of the studies are strongly influenced by the diagnostic methods [86]. Culture of duodenal aspirates represents an invasive approach and present a risk of contamination of the samples. Breath tests are considered scarcely accurate, poorly correlated with intestinal aspiration methods and affected by a high frequency of false positives (lactulose test) and low sensitivity (glucose test) [87–89].

A recent meta-analysis included 25 case-control studies (3192 IBS subjects and 3320 controls) taking into account different definitions of SIBO and several IBS diagnostic criteria [90]. The results showed that the overall prevalence of SIBO in IBS was 31.0% (95%CI 29.4–32.6) with an OR of 3.5 (95%CI 2.2-5.7.0, p=0.001) compared to a mix of controls (healthy subjects and non-patients with IBS). When comparing SIBO rates in IBS versus healthy controls (i.e., excluding non-patients with IBS) the OR increased to 4.9 (95%CI 2.8–8.6, p=0.001). The OR was 3.5 (95%CI 1.0-12.9; p<0.06) for the lactulose breath test, 6.0 (95%CI 4.1-8.8, p<0.001) for glucose, and 1.9 (95%CI 0.6-6.3; p<0.27) for small intestinal aspiration, with a high heterogeneity among studies [90]. In another meta-analysis, patients with IBS were 4.2 (95%CI 3.0-5.9 p<0.001), 3.0 (95%CI 1.3-6.9 p=0.009) and 1.3 (95%CI 0.8-1.9 p=0.25) times more likely to have a positive test for SIBO as compared with healthy controls using glucose test, jejunal aspirate culture and lactulose test, respectively [87]. The association between SIBO and IBS seems to be stronger for IBS-D vs IBS-C [90,91].

In conclusion, patients with IBS were more likely to have a positive test for SIBO as compared with healthy subjects. However, although a difference in the prevalence of SIBO was found between patients with IBS and healthy controls and SIBO may be an explanation for IBS symptoms for some patients, available data do not support the routine testing for SIBO in both adult and pediatric patients with IBS.

Figure 1 reports a diagnostic algorithm for IBS.

TREATMENT

Statement 2.1: We recommend for a dietary approach for patients with IBS. Traditional dietary advice is suggested as first line approach[1], while a low FODMAP diet as a second line approach[2]. A gluten free diet is not recommended in patients with IBS[3].

Statement endorsed, overall agreement: 100%: A+ 81.3%, A 18.7%, A- 0%, D- 0%, D 0%, D+ 0%.

[1]LE: Very low; GR: Strong.

[2]LE: Low; GR: Conditional.

[3]LE: Very low; GR: Strong.

Summary of evidence: food can induce symptoms in patients with IBS through many different mechanisms [92]**.** Therefore, dietary and lifestyle suggestions are the most frequently used advice for patients with IBS [24]. Currently, among the different possible dietary approaches, three diets are the most popular and are frequently prescribed: the traditional dietary advice (TDA) produced by NICE (National Institute for Health and Care Excellence) and The British Dietetic Association (BDA), the Low FODMAP (Fermentable Oligo-, Di- and Mono-saccharides And Polyols) Diet (LFD) and the Gluten-Free Diet (GFD). The TDA is considered a first-line dietary approach and it consists in adopting healthy eating patterns (e.g. having regular meals, adjustment of fiber and fluid intake, decreasing fat, alcohol and caffeine intake), however evidence for this dietary choice comes mainly from clinical experience and indirect data from RCTs assessing other dietary approaches [93–97].

The LFD, usually recommended as a second-line diet consisting in the reduction of highly fermentable carbohydrates [98,99]. Several trials enrolling a total of 658 subjects have compared a LFD with other therapeutic choices, mainly dietary interventions [94–97,100–106] showing that the LFD was associated with a reduction in the risk of remaining symptomatic [Risk Ratio (RR)=0.71; 95%CI 0.61-0.83]. Among these studies, trials comparing the LFD with the TDA showed the least heterogeneity and magnitude of effect when pooled together and no difference in the efficacy between the two dietary intervention (RR=0.82, 95%CI 0.67-1.01)[107]. A recent systematic review and metanalysis reported that LFD is able to reduce gastrointestinal symptoms and to improve quality of life [108]. However, evidence concerning the efficacy of most trials involving LFD and other dietary options is very scarce. In fact, most studies do not meet the GRADE guidelines level for high quality evidence [98,109]. Moreover, most trials reported the results at the end of the starting of the elimination phase, the so called “strict LFD”, usually lasting 4-6 weeks. Up to now only four studies have reported results in the medium-long term (6-44 months) of an adapted LFD, (i.e. only excluding trigger foods) showing symptom improvement in up to 60% of patients with IBS[103,110–112].

However, the complexity of the low FODMAP diet, its potential for nutritional deficiencies and the risk for the development of restrictive eating habit, which require counselling by a specialist dietician, led to the recommendation of LFD as a second-line approach in this guideline and others[93,107]
A recent meta-analysis, including 11 trials (three prospective studies, six RCTs, one retrospective study and one study in the pediatric population) stated that gluten might contribute to the occurrence of gastrointestinal symptoms in patients with IBS [113]. However, improvement reported by some patients on a GFD could be due also to the reduction of the fructans contained in wheat, which are FODMAPs, rather than to the withdrawal of gluten. In clinical practice some patients with IBS report an improvement of symptoms and QoL when adopting a GFD[114]. In 2018, a systematic review and meta-analysis by Dionne et al.[109] identified two RCTs including 111 IBS subjects[115,116]. The GFD was not associated with a significant improvement in global IBS symptoms in comparison with a control gluten containing diet (RR=0.42, 95%CI 0.11-1.55). Therefore, as for now there is too little evidence to suggest the adoption of a GFD in patients with IBS.

Statement 2.2: We recommend for soluble but not insoluble fiber supplementation to treat global IBS symptoms.

Statement endorsed, overall agreement: 93.8%: A+ 87.5%, A 6.3%, A- 6.2%, D- 0%, D 0%, D+ 0%.
LE: Low; GR: Strong.

Summary of evidence: intake of 25–35 g of fiber per day is usually recommended due to general health benefits [117,118]. Different types of fiber can be distinguished based on their solubility, viscosity, and ability to resist fermentation in the colon, with different effects on gut microbiome, metabolism, transit time, stool consistency, bile acid absorption, immune-mediated and anti-inflammatory pathways [118,119]. Insoluble fiber (e.g., wheat bran) undergoes little physical change as it passes through the gut, bulks stools, and increases stool water content, with the potential to accelerate intestinal transit times [120]. Soluble fibers form a gel that interacts with gut bacteria, resulting in the production of metabolites, including short-chain fatty acids and secondary bile acids [118,120]. Soluble fiber is found in ispaghula husk/psyllium, oat bran, barley, and beans. The major adverse effects of fiber intake are bloating, abdominal distension, and flatulence[121], which however, are less prominent with soluble than with insoluble fibers [119].
A systematic review and meta-analysis on fiber in IBS [68] identified 15 RCTs, involving 946 patients, most with high risk of bias. There was a statistically significant effect in favor of fiber

compared with placebo (RR of IBS not improving =0.87, 95%CI 0.80-0.94 p=0.003) with a number needed to treat (NNT) of 11 (95%CI 7-25). There was no significant heterogeneity between results (I^2=0%, P=0.53). Six studies used bran (411 patients), seven studies ispaghula husk/psyllium (499 patients), and the remaining three studies used "concentrated fiber", linseeds, or rice bran. Bran had no significant effect on treatment of IBS (RR of IBS not improving=0.90, 95%CI 0.79-1.03 p=0.14), but ispaghula husk/psyllium was effective in treating IBS (RR=0.83, 95%CI 0.73-0.94 p=0.005) with a NNT of 7 (95%CI 4-25). Data on overall adverse events were only provided by seven trials. A total of 130 of 355 patients (36.6%) receiving fiber reported adverse events, compared with 63 of 251 (25.1%) in the placebo arm (RR=1.06, 95%CI 0.92-1.22). There were insufficient data to assess adverse events according to type of fiber administered, although authors concluded that insoluble fiber may exacerbate pain and bloating in IBS.

Due to the effect on intestinal transit, the use of fibers could potentially be useful in patients with IBS and constipation. A systematic review was unable to perform a meta-analysis due to study heterogeneity and methodological quality. However, fiber was beneficial in all the three studies[122]. At present the evidence suggests that only soluble (e.g., ispaghula husk/psyllium) but not insoluble (e.g., wheat bran) fibers have a significant effect for the treatment of IBS symptoms. The low cost and lack of significant side effects makes soluble fiber a reasonable first-line therapy for patients with IBS.

Statement 2.3: We recommend for the use of probiotics, as a group, for improving overall symptoms or abdominal pain in patients with IBS

Statement endorsed, overall agreement: 87.5%: A+ 37.5%, A 50%, A- 12.5%, D- 0%, D 0%, D+ 0%.

LE: Low; GR: Conditional.

Summary of evidence: probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [123]. Major claims of probiotics include modulation of gastrointestinal motility, reduction of visceral hypersensitivity and pain as well as low grade mucosal immune activation, improvement of epithelial permeability, enhancement of gut-brain communication, modulation of gut microbial metabolites production with potential impact on restoring intestinal dysbiosis, all mechanisms potentially involved in IBS pathophysiology [124,125]. A meta-analysis of 37 RCTs [126] which has been recently updated with data from 8 new trials[127], included a total of 6352 patients, of whom 3401 treated with probiotics and 2951 with placebo. A

significant effect on global symptoms or abdominal pain has been demonstrated for probiotics as a group, with RR=0.78 (CI 95%: 0.63-0.95). Subgroup analyses according to type of probiotic showed a significant effect for combinations of probiotics, *Lactobacillus*, *Bifidobacterium*, and *Escherichia* [127]. Interestingly, of the new 8 RCTs updating this meta-analysis, a RCT performed in 445 Rome III patients with IBS showed that a specific strain of heat-inactivated probiotic significantly improves IBS symptoms fulfilling the primary composite endpoint (i.e., the combination of at least 30% improvement of abdominal pain and adequate relief of overall IBS symptoms for at least 50% of weeks during treatment) as recommended by the European Medicines Agency (EMA)[128]. Due to the lack of rigorous trials fulfilling stringent regulatory agency endpoints [e.g., Food and Drug Administration (FDA) or EMA], this can be considered a first important step forward trials with validated outcomes.

In addition, five new RCTs which were not included in the meta-analysis due to different outcomes were recently published [129–133]. Out of them, two studies, involving 284 and 80 patients, showed negative or mixed results without a clear effect on IBS symptoms[129,130], while 3 small trials, including less than 50 patients, showed a significant effect of probiotics in improving severity of IBS symptoms [131–133].

While the results of meta-analysis and RCTs suggest that probiotics as a group may be effective in the management of global IBS symptoms, specific recommendations cannot be given due to different study design (including different comparators, inclusion criteria, comorbidity, outcomes and endpoints), various strains, formulation, combination, or mixture of probiotics assessed, and heterogeneity among studies.

Statement 2.4: We suggest for the use of polyethylene glycol for the treatment of constipation in patients with IBS-C. The dose should be titrated according to stool consistency.

Statement endorsed, overall agreement: 100%: A+ 93.8%, A 6.2%, A- 0%, D- 0%, D 0%, D+ 0%.

LE: Very low; GR: Conditional.

Summary of evidence: polyethylene glycol (PEG) is a minimally adsorbed osmotically acting laxative, commonly used to manage constipation in both adults and children. PEG exerts its laxative action by increasing water content of stools due to its ability to interact with water molecules [134]. The clinical effectiveness of PEG in the management of constipation in adults has been confirmed in a recent meta-analysis. The NNT with osmotic laxatives was 3 (95%CI 2-4)[135]. PEG is well

tolerated with most adverse events being mild to moderate in severity, including abdominal pain, diarrhea, loose stools, nausea and abdominal distension, mostly occurring in a dose-dependent manner [136–138]. In chronic constipation patients older than 70 years of age, long-term PEG was well tolerated without nutritional deficiencies or biochemical abnormalities[139]. PEG has been evaluated in 2 RCTs recruiting patients with IBS-C. One was a mechanistic study that evaluated 47 patients with IBS-C according to Rome II criteria. The primary endpoint was the effects of PEG 3350 over fasting and post prandial recto-anal tone and sensitivity before and at the end of 30 days of treatment with PEG 3.45 g t.i.d., p.o. or placebo. No changes in fasting and post prandial rectal tone and thresholds for first sensation, gas sensation, urge to defecate, and pain was observed with PEG. However, PEG improved stool consistency. The second study was a multicenter RCT that studied 139 patients with IBS-C for 28 days. The primary endpoint, that was the mean number of spontaneous bowel movements (SBMs) per day in the last treatment week, was met. Abdominal discomfort/pain, the secondary endpoint, however, was not improved in PEG treated patients compared with placebo. Moreover, in the post-hoc analysis when compared with placebo, PEG did not demonstrate a significant lower failure rate of symptom relief using the modified FDA responder definition (patients with pain reduction of >30%, >3 SBMs per week, and an increase of 1 SBM per week) (RR=0.9; 95%CI, 0.66–1.2)[140]. The most common treatment-emergent adverse events were abdominal pain and diarrhea and were more frequent in patients treated with PEG compared with placebo, but most of these were mild or moderate. An American College of Gastroenterology monograph in 2014 concluded that there is no evidence that PEG formulations alleviate pain or provide overall symptom relief in IBS [6] and, no other RCTs were conducted.

In summary, the 2 RCTs that studied the beneficial effect of PEG in IBS-C patients were heterogeneous in trials design and endpoint and were only 4 weeks duration, thus there is no evidence that PEG alone alleviates neither abdominal pain or global symptoms in patients with IBS-C. PEG should be considered for the treatment of constipation in people with IBS-C acting as osmotic laxative. The dose should be titrated according to stool consistency. The side effect of abdominal pain should be taken into account and the long-term efficacy in IBS-C is unknown.

Statement 2.5: Secretagogues are useful for the treatment of global symptoms and constipation in patients with IBS-C. Diarrhea is a frequent side effect.

Statement endorsed, overall agreement: 93.8%: A+ 75%, A 18.8%, A- 6.2%, D- 0%, D 0%, D+ 0%.

LE: High; GR: Strong.

Summary of evidence: four secretagogues (i.e., lubiprostone, linaclotide, plecanatide, tenapanor) have been studied and approved by the FDA for the treatment of IBS-C, but only linaclotide has been authorised by EMA for this indication and is available in Italy.

Lubiprostone is an activator of chloride type 2 channels in the intestine and was approved by FDA in 2008 for the treatment of adult women with IBS-C at a dosage of 8 mg twice daily. The efficacy and safety of lubiprostone has been assessed in 3 RCTs [141,142] In particular, the most robust data derive from a combined analysis of two different phase-3 RCTs (registration IDs NCT00380250, NCT00399542) [142]. These studies involved 1,171 patients meeting Rome II criteria for IBS-C who were randomized to receive 8 mg of lubiprostone or placebo twice daily for 12 weeks. The primary endpoint, i.e., the total number of overall responders, was achieved by 17.9% in the lubiprostone group as compared with 10.1% in the placebo group (P<0.0001), In addition, secondary endpoints demonstrated a significant efficacy of the active treatment in the improvement of abdominal pain/discomfort, bloating, straining, stool frequency, and consistency. In a post-hoc analysis based on 2012 FDA updated guidance document recommending composite endpoints (with both abdominal pain and stool frequency), lubiprostone was significantly more effective than placebo in improving composite end-points, abdominal pain, bloating and stool frequency [143]. High quality systematic reviews/meta-analyses confirmed that lubiprostone was more effective than placebo for overall IBS-C symptoms. Differently from other secretagogues, nausea but not diarrhea is the most frequently reported side effect with this treatment.

Linaclotide is a guanylate-cyclase agonist which activates human guanylate cyclase-C, a transmembrane protein located in the intestinal epithelium, that in turn increases fluid secretion. Moreover, guanylate cyclase-C activation led to the production and release of cyclic guanosine-3',5'-monophosphate (cGMP) which may act in the extracellular compartment inhibiting nociceptors, thereby reducing nociception. Linaclotide was approved by the FDA and EMA in 2012 for the symptomatic treatment of adults with moderate-to-severe IBS-C. The efficacy and safety of linaclotide was assessed in 3 North American phase IIb/III trials [144–146] and later evaluated in several systematic reviews/meta-analyses. In particular, a phase 3 RCT (Trial 31, NCT00948818) [146] was performed in 800 patients with IBS-C and assessed the efficacy and safety of 290 μg linaclotide once daily in a 12-week treatment period, followed by a 4-week randomized withdrawal period [146]. Linaclotide significantly improved abdominal pain and bowel symptoms for at least 12 weeks (primary endpoint achieved in 33.6% of patients treated with linaclotide as compared with 21.0% of placebo-treated patients, P<0.0001). During the withdrawal period, patients remaining on linaclotide showed sustained symptom improvement, while patients passing from linaclotide to

placebo showed return of symptoms to baseline level without worsening. A similar phase 3 study (Trial 302, NCT00938717) [145] was performed in 804 adult patients with IBS-C and showed that linaclotide 290 μg once daily significantly improved abdominal and bowel symptoms over 26 weeks of treatment (primary end-point achieved in 33.7% of patients treated with linaclotide as compared with 13.9% of placebo-treated patients, P<0.0001). These trials, although conducted in the US and Canada between July 2009 and September 2010, were designed in accordance with both FDA and EMA guidelines for the treatment of patients with IBS-C. Also applying the pre-specified EMA-recommended co-primary endpoints, linaclotide significantly improved abdominal pain/discomfort and degree-of-relief of IBS-C symptoms over 12 and 26 weeks [147]. In both the pivot studies, diarrhea was the most common adverse event, resulted in discontinuation of about 5% of linaclotide patients.

Plecanatide is another guanylate cyclase-C agonist that has been approved in 2017 by FDA for the treatment of IBS-C (at the dosage of 3 mg). The efficacy and safety of this agent has been evaluated in 3 individual phase IIb/III studies. In particular, the 2 identical phase 3 studies involved a total of 2189 Rome III IBS-C patients randomized to placebo or plecanatide (3 or 6 mg) for 12 weeks[13]. Both doses showed superior efficacy when compared to placebo as concern the achievement of the study primary end point [148,149]. Similarly, all secondary end points (stool frequency/consistency, straining, abdominal symptoms) showed statistically significant improvements after the active treatment as compared with placebo. Similar to other secretagogues, diarrhea was the most frequently reported side effect.

Tenapanor, recently approved by FDA for IBS-C, is a first in class inhibitor of the sodium/hydrogen exchanger isoform 3 that reduces intestinal sodium and phosphate absorption. A phase 3, double-blind study in patients with IBS-C according to Rome III criteria, included a total of 610 patients in the safety analysis, of whom 309 received tenapanor 50 mg two per day and 301 received placebo [150]. In the intention-to-treat analysis, a significantly greater proportion of patients treated with tenapanor showed a reduction in average weekly worst abdominal pain of ≥30.0% and an increase of complete spontaneous bowel movements ≥1 per week from baseline than placebo group at 6/12-week (27.0% vs 18.7%, P=0.020) and at 9/12-week (13.7% vs 3.3%). During the 12-week treatment period, treatment with tenapanor compared with placebo resulted in significantly higher durable abdominal pain responder (P=0.006) and durable complete SBMs responder rates; diarrhea was the most commonly reported adverse event, confirming a safety profile for this new treatment option for patients with IBS-C. Similar results were obtained in a more recent RCT showing that tenapanor 50 mg b.i.d. improved IBS-C symptoms over 26 weeks[151].

A network meta-analysis by Black et al.[149] compared the efficacy of the four secretagogues (linaclotide, lubiprostone, plecanatide, and tenapanor) FDA-approved for IBS-C. Although all drugs resulted superior to placebo for the treatment of IBS-C symptoms, this meta-analysis ranked linaclotide 290 mg once daily first in efficacy profile overall (RR=0.81, 95% CI 0.76-0.86) and across several different endpoints, including improvement in abdominal pain and increase of CSBMs. In particular, linaclotide was superior to placebo in 5 RCTs, including 3193 patients, for the FDA composite end point for IBS-C (improvement in abdominal pain and increase of ≥1 CSBMs per week from baseline [RR=0.82, 95%CI 0.78-0.87]). Adverse events were significantly more common with linaclotide, with diarrhea being the most common.

Statement 2.6: We suggest for the use of 5-HT4 agonists in selected IBS-C patients who have failed conventional therapy.

Statement endorsed, overall agreement: 100%: A+ 68.8%, A 31.2%, A- 0%, D- 0%, D 0%, D+ 0%.
LE: Low; GR: Conditional.

Summary of evidence: 5-HT4 receptors play a key role in the modulation of human gut motility and have been the target of drug development in both chronic constipation and IBS-C since long time [152]. Only two drugs of this class, tegaserod and prucalopride, are currently approved for the treatment respectively of IBS-C in USA and chronic idiopathic constipation both in Europe and USA. Tegaserod is a partial 5-HT4 agonist found to stimulate gastric, oro-cecal and colonic transit [153]. A meta-analysis[154] has evaluated all the 11 RCTs including 9242 patients conducted in the past with tegaserod with dose ranging from 0.5 to 12 mg bid. Eight of these enrolled only IBS-C while the others excluded IBS-D but not IBS-M. All the studies used as endpoint the global or overall relief of IBS-C symptoms. Tegaserod resulted more effective than placebo in in treating IBS-C symptoms (RR of symptoms persisting=0.85, 95%CI 0.80–0.90) [154]. Most common treatment-emergent adverse event was diarrhea (RR of diarrhea=3.60, 95%CI 2.45 –5.30).
However, the drug was withdrawn by the company in 2007 because of a small increased risk of cerebrovascular and cardiovascular ischemic events [155]. In 2019, after a re-evaluation of the safety data and a post-hoc analysis conducted according to the recent FDA composite endpoints, FDA has reintroduced the drug [155]. As all confirmed cardiovascular ischemic events occurred in patients with risk for these, the current indication is for females IBS-C, <65 years old, without pre-existing cerebrovascular and cardiovascular disease [155]. Tegaserod has not been re-introduced by EMA.

Prucalopride is selective for 5-HT4 receptors approved by EMA for the treatment of chronic idiopathic constipation not responding to laxatives [152], with a low affinity for hERG potassium channel (relevant to cisapride-induced arrhythmias), thus minimizing potential cardiac side effects both in animal and human studies [152]. Mechanistic studies both in healthy subjects and constipated patients have shown that prucalopride stimulates gastric emptying, small bowel and colonic transit time [152]. A recent network meta-analysis [156] has evaluated 8 RCTs assessing the effectiveness of prucalopride in patients with chronic idiopathic constipation, finding that 2 mg daily was more effective than placebo, both at 4 and 12 weeks. The most common treatment-emergent adverse events of prucalopride are nausea, diarrhea and headache (RR=1.20, 95%CI 1.08-1.34) [156]. So far there have been no RCTs of prucalopride in patients with IBS-C.

Statement 2.7: We suggest for the use of bile acid sequestrants to treat IBS-D symptoms in case of proven bile acid malabsorption. If testing is not available, in patients with IBS-D, not otherwise manageable with first line treatments, a trial of bile acid sequestrants is advisable.

Statement endorsed, overall agreement: 93.8%: A+ 87.5%, A 6.3%, A- 6.2%, D- 0%, D 0%, D+ 0%.
LE: Very low; GR: Conditional.

Summary of evidence: excessive bile acids entering the colon increases colonic secretion of fluid resulting in diarrhea [157]. A meta-analysis based on 6 studies [158] showed that the 75-selenium homocholic acid taurine test (SeHCAT) testing was positive for bile acid malabsorption (BAM) in 28.1% (CI 22.6%–34%) of patients with IBS-D. Bile acid sequestrants, including colestyramine, colestipol, and colesevelam, binding bile acids in the intestinal lumen, were developed initially to lower hypercholesterolemia. Subsequently, they were shown to relieve diarrhea in patients with ileal resection and associated BAM [159].
The effectiveness of cholestyramine has been mainly studied in patients with BAM, while data in patients with IBS-D are scanty. Nonetheless, in the latter category, in the presence of abnormal SeHCAT, an improvement of diarrhea has been reported [160,161]. Using SeHCAT, Fibroblast growth factor (FGF)-19, and C4 testing, Bajor et al., showed the presence of BAM in a cohort of patients with IBS-D [162]. Treatment with colestipol in an open-label fashion demonstrated a significant improvement in IBS severity scores in 15 over 27 patients (55.5%).
An open-label single-center trial in 12 patients with IBS-D showed that 1.875 mg of colesevelam daily determined a modest reduction in the Bristol Stool Score (P=0.043) [6]. On the other hand, a

randomized, double-blind, placebo-controlled study [163] in 24 patients with IBS-D showed that colesevelam at dose of 1.875 mg b.i.d. was associated with a greater ease of stool passage (P=0.048) and firmer stool consistency [163].

Given the fact that there is limited evidence on randomized controlled trials evaluating the utility of tests to diagnose BAM in patients with IBS-D nor the usefulness of empirical therapy with bile acid sequestrants in these patients, the recommendation to use bile acid sequestrants can be advised but is based on low quality of evidence.

Statement 2.8: We suggest for the use of rifaximin to treat global symptoms in patients with IBS without constipation

Statement endorsed, overall agreement: 93.8%: A+ 75%, A 18.8%, A- 6.2%, D- 0%, D 0%, D+ 0%.

LE: Moderate; GR: Strong.

Summary of evidence: rifaximin is a poorly absorbable antibiotic licensed in Italy for the treatment of acute diarrhea and prevention of porto-systemic encephalopathy [164]. Its use in IBS has been proposed according with the hypothesis that a portion of patients with IBS suffers from altered intestinal microbiota.

The effect of rifaximin was first evaluated in a retrospective chart review and in a small trial showing a global symptom improvement [165–167]. These observations have been confirmed in two large, identically designed, phase 3 trials, involving totally 1258 patients with IBS without constipation, showing that rifaximin 550 mg t.i.d. for 2 weeks improved global symptoms in 40.7% of patients compared to 30.7% of patients receiving placebo [168].

The same group subsequently analyzed the response to rifaximin retreatment in IBS-D patients with clinical relapse after the first treatment. Among relapsing patients, 38.1% responded to a second treatment with rifaximin, vs 31.5 % receiving placebo[169]. In the same study, abdominal pain improvement was observed in 1384 patients (56.8%). In the long-term follow-up after treatment, 35% of patients were still pain-free[170]. In a secondary analysis on the open label arm of the study, rifaximin could also ameliorate quality of life [169].

A recent metanalysis on the efficacy of rifaximin in IBS without constipation, including 5 trials (1805 patients) showed a greater effect of rifaximin compared with placebo (RR of symptoms persisting 0.84, 95%CI 0.79–0.90) [126].

Also, in a study including 93 IBS-D patients, a higher response rate (56%) was observed in patients with a positive vs negative LBT (59.7% vs 25.8%, OR 4.3, 95%CI 1.5-12.7, p=0.002), suggesting that altered baseline microbiota might predict rifaximin response [171].

Risks of adverse events of rifaximin have been reported in a meta-analysis of 5 studies involving 1187 patients, showing not significant risks compared with placebo, with a number needed to harm (NNH) of 8971 and a pooled of RR=1.01, 95%CI 0.5-2.02[172]. In a post hoc analysis from the phase 2b-phase 3 trials, patients were followed-up to 12 weeks, showing similar incidence of adverse events in patients treated with rifaximin or placebo. In addition, no case of *C. difficile* colitis or deaths were described [173]. Rifaximin also showed the best safety profile compared with other treatment for IBS, such as alosetron, ramosetron and eluxadoline[174].

Furthermore, no effect of rifaximin on stool microbial susceptibility was observed [175]. There are very few data on the effect of rifaximin in IBS-C: a small study found that rifaximin in combination with neomycin significantly improved constipation, bloating and straining but not pain compared with neomycin alone, and the effect as accompanied by a reduction in breath methane [176].

In conclusion, data from the literature in adults support the beneficial effect of rifaximin on IBS without constipation, being the treatment both effective and safe. Further studies are needed to confirm the efficacy of rifaximin in the pediatric population.

Statement 2.9: We suggest for the use of 5-HT3 antagonists for global IBS-D symptoms in patients who have failed conventional therapy.

Statement endorsed, overall agreement: 87.5%: A+ 62.5%, A 25%, A- 12.5%, D- 0%, D 0%, D+ 0%.

LE: Low; GR: Conditional.

Summary of evidence: 5-HT3 receptor antagonists, comprising alosetron and ramosetron, were licensed for IBS-D treatment. These drugs delay gastrointestinal transit, reduce visceral hypersensitivity and alter rectal compliance [177,178]. In a previous meta-analysis,[174] both alosetron (1 mg b.i.d.) and ramosetron (2.5 μg or 5 μg once daily) were superior to placebo across various end points, including the FDA composite endpoint for IBS-D (3 RCTs of alosetron 1 mg b.i.d., 787 patients, RR=0.69; 95%CI 0.60-0.80, and 1 RCT of ramosetron 2.5 μg once a day, 348 patients, RR=0.78, 95%CI 0.67-0.91). Both drugs were also more effective than placebo in improving IBS global symptoms, abdominal pain and stool consistency. The rate of reported side effects was higher in the active arm than in the placebo group and comprised constipation, nausea and headache.

Alosetron was withdrawn from the market in 2001 due to reports of ischemic colitis [179]. It was however reintroduced in the US via a risk evaluation and mitigation strategy, at a lower dose of 0.5 mg b.i.d., for women with severe IBS-D. At these doses, the rates of ischemic colitis were no higher than those expected in female patients with IBS [180].

Ramosetron is associated with a low incidence of adverse events, such as abdominal distension and hard stools, and is unlikely to cause ischemic colitis. Based on the above, ramosetron is considered safe for treating IBS without constipation. However, clinical research on ramosetron was conducted in Japan and Korea, therefore these findings cannot be generalizable to Western populations. Alosetron and ramosetron remain unavailable in many countries [181].

Ondansetron, a widely available 5-HT3 receptor antagonist with a good safety profile, has been evaluated in several trials. A small crossover trial of ondansetron, titrated from 4 mg up to 8 mg t.i.d., showed significantly higher rates of improvement in urgency, bloating and stool consistency, but not abdominal pain [182]. A subsequent RCT of 12 mg once a day of bimodal release ondansetron also demonstrated superiority over placebo in improving stool consistency, but not abdominal pain[183]. Constipation was the most reported side effect.

However, there are noticeable individual differences in 5-HT3 receptor antagonists' responsiveness which have been correlated with common polymorphisms in key genes regulating the synthesis and reuptake of 5-HT, as well as the structure of the 5-HT receptors. Therefore, the sensitivity to 5-HT3 receptor antagonists, such as ondansetron, might be partly dependent on genetic variability due to polymorphisms in these genes. In 2019 Gunn et al.,[184] carried out a randomized, placebo-controlled, cross-over trial of 5 weeks of ondansetron versus placebo in 125 IBS-D patients. IBS-D patients had significant abnormalities in mucosal 5-HT metabolism and those with the lowest concentration of 5-HT in rectal biopsies showed the greatest responsiveness to ondansetron.

Ondansetron is a safe 5-HT3 receptor antagonist and worldwide available, which could improve mild to moderate IBS-D symptoms. These data suggest either that access to existing, licensed 5-HT3 antagonists should be improved, or large trials of older 5-HT3 antagonists, such as ondansetron, are needed in patients with IBS-D and IBS-M.

Statement 2.10: We recommend for the use of opioid agonists to manage diarrhea in IBS-D.[1] We recommend for the use of mixed opioid agonists/antagonists to treat global symptoms in IBS-D.[2]

Statement endorsed, overall agreement: 100%: A+ 62.5%, A 37.5%, A- 0%, D- 0%, D 0%, D+ 0%.

[1]LE: Low; GR: Conditional.

[2]LE: High; GR: Strong.

Summary of evidence: antidiarrheal drugs generally reduce diarrhea by decreasing stool frequency, improving stool consistency, and/or reducing stool weight. Loperamide, one of the most prescribed anti-diarrheal agents, is a synthetic μ-opioid agonist that increases intestinal transit time and decrease secretion. A prior systematic review identified only 2 RCTs of loperamide in IBS-D and IBS-M including overall 42 patients [68]. This study shows that loperamide improved stool frequency and consistency, without effects on abdominal pain bloating or global symptoms (RR=0.44, 95%CI 0.14-1.42). Furthermore, in clinical practice common side effects of loperamide, as abdominal pain, bloating, nausea and constipation may limit tolerability. These effects can be mitigated by titrating the dose. However, the risk of prolonged QTc suggests caution, particularly for chronic use with high doses in patients with long QT or in comedication with other drugs prolonging QT [185]. Another randomized-controlled study by Cann et al. [186], showed that loperamide improved daily stool frequency compared with placebo after 5 weeks of treatment (1.3 versus 1.9 stools/day, respectively). Moreover, patients reported a significant reduction in the percentage of loose stools ($P<0.01$), and incidence of urgency ($P <0.001$) [186]. Taken together, these data suggest that loperamide may be effective in the treatment of diarrhea in patients with IBS-D, although its chronic use should be avoided due to poor tolerability and the risk of tachyphylaxis and serious adverse events.

Eluxadoline is a peripherally acting, mixed mu- and kappa-opioid receptor agonist/delta-opioid receptor antagonist, effective in slowing intestinal transit and reducing visceral hypersensitivity [187]. A recent metanalysis including 3122 patients from four RCT studies [174] demonstrated that eluxadoline, (both 75 mg b.i.d. and 100 mg b.i.d.) was superior to placebo in improving IBS-D symptoms as assessed by the FDA-approved composite endpoints. Moreover, eluxadoline 100 mg b.i.d. was also superior to placebo in improving abdominal pain. Adverse events included constipation, nausea and headache, and adverse events leading to drop out were significantly higher with active drug than placebo. In addition, serious adverse events, including pancreatitis and sphincter of Oddi spasm, occurred in 0.5% of patients included in these trials[188]. For this reason, the drug is contraindicated in patients with prior sphincter of Oddi problems or in presence of cholecystectomy, alcohol abuse, pancreatitis or severe liver impairment. Although EMA approved for IBS-D, eluxadoline is currently unavailable in European countries.

Statement 2.11: We recommend against the use of fecal microbiota transplantation in patients with IBS.

Statement endorsed, overall agreement: 100%: A+ 75%, A 25%, A- 0%, D- 0%, D 0%, D+ 0%. LE: Low; GR: Strong.

Summary of evidence: there is enough evidence to suggest that changes in gut microbiota ecosystem may play an important role in the pathophysiology of IBS. Antibiotic therapy and other therapeutic modulators of the gut microbiota, such as probiotics and prebiotics, have beneficial effects in patients with IBS [58]. In addition, gut microbiota has been shown to be altered in patients with IBS, and certain microbial signatures have been associated with the severity of IBS symptoms [189,190].

In the last decade, fecal microbiota transplantation (FMT), namely the process of transferring fecal bacteria and other microbes from a healthy individual into another individual, has been investigated in the context of IBS.

Two meta-analyses did not observed a clear benefit of FMT for the relief of IBS symptoms [191,192]. Of note, over 90% of patients had IBS-D or IBS-M. Myneedu et al.[192] included 8 single arm trials reporting 59.5% (95%CI 49.1–69.3) of patients with IBS, showing a significant improvement of IBS symptoms. Pooling the results of the 4 RCTs a reduction of at least 50 points on IBS-Symptom Severity Score (IBS-SSS score) was not observed (RR=0.93, 95%CI 0.50–1.75). Similarly, in the meta-analysis by Ianiro et al. [191] including a total of 5 RCTs reporting on 267 patients, the effect of FMT over controls for the improvement of IBS symptoms yielded a RR=0.98 (95%CI 0.58-1.66). However, 92.2% of included patients had IBS-D or IBS-M, and only 7.8% IBS-C. FMT from donor stool delivered via colonoscopy was superior to autologous stool in 2 RCTs (RR=0.63, 95%CI 0.43-0.93) [191]. Interestingly, FMT from donor stool via naso-jejunal tube showed a trend towards a benefit over autologous stool in one trial (RR=0.69, 95%CI 0.46-1.02). However, none of the studies included showed a low risk of bias, thus precluding definitive conclusions.

In addition, a recent RCT carried out on 49 patients with IBS (51% IBS-D) using FMT via colonoscopy, failed in achieving a reduction in the IBS-SSS throughout the 52-week follow-up period [193]. In another RCT[194], FMT from a single healthy, well-characterized donor was administered via gastroscope in 164 patients with IBS. This study found that patients who received placebo, 30 g FMT or 60 g FMT were responders in 23.6%, 76.9% ($p<0.0001$) and 89.1% ($p<0.0001$), respectively. Future studies should test FMT in IBS to understand its efficacy, determine the optimal donor and delivery formulation and technique.

Statement 2.12: We recommend for the use of antispasmodics for global symptom improvement in patients with IBS.

Statement endorsed, overall agreement: 100%: A+ 81.3%, A 18.2%, A- 0%, D- 0%, D 0%, D+ 0%.
LE: Low; GR: Conditional.

Summary of evidence: antispasmodics are among the most frequently used treatments for IBS although their availability in the different countries is very diversified. The rationale for using these drugs is based on the fact that that some IBS symptoms are believed to be the result of gastrointestinal spasm and dysmotility [195]. Antispasmodics are an heterogeneous group of substances that include direct smooth muscle relaxants (e.g.papaverine, mebeverine), anticholinergic agents (e.g., butylscopolamine, hyoscine, cimetropium bromide, pirenzepine) and calcium channel blockers (e.g., alverine citrate, otilonium bromide, pinaverium bromide, peppermint oil). For some of these molecules the pharmacological action is not fully known and the mechanisms are often mixed [196]. Data on the efficacy of antispasmodics were analyzed in a meta-analysis that included 26 RCTs, evaluating 2811 patients with IBS. Thirteen different antispasmodics were compared with placebo [68]. Antispasmodic therapy had a statistically significant effect in improving global IBS symptoms (RR of IBS symptoms not improving=0.65, 95%CI 0.56-0.76) and the NNT was 5 (95%CI 4-8). The overall rates of adverse events were significantly higher with antispasmodics compared with placebo, most notably dry mouth, visual disturbance and dizziness, essentially linked to the anticholinergic effects, but no serious adverse events were reported. Statistically significant effect on improving global IBS symptoms were demonstrated for cimetropium (NNT=3), dicyclomine (NNT=4), drotaverine (NNT=2), hyoscine (NNT=3), otilonium (NNT=5), pinaverium (NNT=4), but not for mebeverine, trimebutine, pirenzepine, alverine, rociverine, prifinium, and propinox. In a Cochrane review, trimebutine was effective for abdominal pain, pinaverium for abdominal pain, global assessment and IBS symptom score, cimetropium/dicyclomine for global assessment, while no statistically significant effect was reported for mebeverine and scopolamine derivatives [197]. In a pooled analysis comprising 3 clinical trials, otilonium bromide demonstrated a significant reduction of intensity and frequency of abdominal pain and of severity of bloating at 10 and 15 weeks of treatment. No significant effect was observed in stool frequency and consistency [198].
Peppermint oil is used in the treatment of IBS symptoms due to its main action as a calcium channel blocker, but several other physiological effects are reported. In Ford's meta-analysis it is suggested a benefit of peppermint oil for overall symptom improvement in IBS patients and, in a subsequent

meta-analysis, it is reported a NNT=3 for overall IBS symptoms and NNT=4 for abdominal pain[199]. Peppermint oil was well tolerated but some patients experienced heartburn probably due to relaxation of the lower esophageal sphincter. In a recent RCT, small bowel release peppermint oil led to significant improvements in the secondary outcomes including abdominal pain, discomfort and IBS severity, compared with placebo[200]. The results obtained in these studies cannot be extended to many products containing Peppermint oil, variously formulated, and enteric-coated formulations must be used to minimize heartburn. In conclusion, published studies support the use of antispasmodics to treat global and troublesome IBS symptoms. However, published data mainly came from small sample size and dated studies, with bias in selection of patients and variability in end points. Also, no data on head-to-head efficacy are available. In Italy, medications registered for use in patients with IBS include cimetropium, hyoscine, mebeverine, otilonium, pinaverium, trimebutine, and peppermint oil, while other compounds (e.g., prifinium, dicycloverine, drotaverine) are marketed, alone or in combination, in many over-the-counter products.

Statement 2.13: We recommend for the use of tricyclic antidepressant (TCAs) in adult patients with IBS to induce global relief of symptoms and to treat abdominal pain alone[1]. We recommend FOR the use of selective serotonin reuptake inhibitors (SSRIs) in adult patients with IBS to induce global relief of symptoms[2].

Statement endorsed, overall agreement: 100%: A+ 81.3%, A 18.2%, A- 0%, D- 0%, D 0%, D+ 0%.

[1]LE: Moderate; GR: Strong.

[2]LE: Low; GR: Conditional.

Summary of evidence: a recent Rome Foundation Working Team Report has recommended replacing the term antidepressants with that of gut-brain neuromodulators[201]. This has been motived by two main reasons. The first is that it is now recognized that gut-brain interaction plays a relevant role in the pathophysiology of functional bowel disorders. This means that clinicians need to be aware these medications are not prescribed only to treat psychological factors like anxiety and depression in IBS. Second but maybe more relevant reason is that the term “antidepressants” associates with a stigma that has profound implication in clinical practice and is responsible for emotional distress, medication non-adherence and increase in symptoms[202].

Different classes of neuromodulators exist but only TCAs, SSRIs and gabapentin have been applied in RCTs in IBS. The most accepted mechanism of action of TCA and SSRI at central level is through the modulation of three main monoamines: serotonin, noradrenalin, and dopamine [201].
A recent metanalysis have evaluated the RCTs conducted with these medications in patients with IBS and has identified 12 studies with TCA (including a total of 787 patients) and 7 with SSRI (including a total of 356 patients) [203]. The study endpoints were mainly relief of global symptoms.
TCA resulted more effective than placebo in treating IBS symptoms (RR=0.65, 95%CI 0.55–0.77). Only in four studies, the duration of treatment was longer than 2 months, and the maximum duration was 12 weeks [203]. SSRI resulted more effective than placebo in treating IBS symptoms (RR=0.68, 95%CI 0.51–0.91). Although not always reported, adverse events were not serious and drowsiness and dry mouth were more frequent in patients treated with TCAs. These medications need to be started at low dosage and titrated according to the patients' symptoms response and tolerability.
A recent study has evaluated the efficacy and safety of pregabalin in IBS including all the different subtypes[204]. Pregabalin is a calcium channel α2δ ligand previously demonstrated to act on visceral hypersensitivity in IBS[204]. Pregabalin 225 mg was found to be more effective than placebo in reducing the average pain score (25 vs 42, P=0.008) and overall severity score (26 vs 42, P=0.009) as measured by Bowel Symptoms Scale in 85 patients with IBS over 12 weeks treatment. Most common adverse events were blurred vision, dizziness and altered sensation.

Statement 2.14: We recommend against the use of cannabinoid and endocannabinoid modulators to treat IBS symptoms.

Statement endorsed, overall agreement: 100%: A+ 75%, A 25%, A- 0%, D- 0%, D 0%, D+ 0%. LE: Low; GR: Conditional.

Summary of evidence: in the gastrointestinal tract the endocannabinoid system consists of endogenous agonists and two receptors, namely, CB1 and CB2. The activation of these receptors is potentially involved in the regulation of key factors implicated in IBS pathophysiology, including visceral hypersensitivity, pain, inflammation, secretion, motility and microbiota[205]. However, little is known on this system in patients with IBS, consequently, few RCTs have been conducted on these patients.
Wong et al.[206] assessed the effects of dronabinol, an isomer of tetrahydrocannabinol (THC) that is the main and most active isomer found in the Cannabis sativa on colonic sensory and motor functions in 75 cannabinoid naïve patients with IBS. Patients randomly received placebo, dronabinol (2.5 mg

or 5 mg). Compared with placebo, dronabinol decreased fasting proximal left and distal colonic motility index and increased colonic compliance. These effects were greater in IBS-D and IBS-M patients with a significant correlation with genetic variants of the cannabinoid system. However, a subsequent RCT [207] in 36 CB-naive IBS-D patients failed to identify significant effects on gastrointestinal transit. Cremon et al.[205] in a pilot study evaluated the efficacy and safety of dietary compounds palmitoylethanolamide/polydatin, (acting mainly as PPR-a agonist) in patients with IBS. Compared with placebo, palmitoylethanolamide/polydatin treatment (200 mg/20 mg, b.i.d for 12 weeks) showed a significant decrease in the severity of abdominal pain/discomfort over time (P=0.001). The RCT CANdidate Study [208], assessed the effect of cannabidiol (CBD)-containing chewing-gum in 32 patients with IBS. The results showed no statistically significant difference in abdominal pain scores between CBD and placebo.

In summary, although there is some evidence in favor of the usefulness of cannabinoids and endocannabinoids in patients with IBS. Future studies of safe and selective cannabinoid receptor agonists or antagonists are warranted.

Statement 2.15: We recommend against the use of complementary alternative therapies, although some reasonably good quality evidence exists for specific approaches.

Statement endorsed, overall agreement: 93.8%: A+ 75%, A 18.8%, A- 6.2%, D- 0%, D 0%, D+ 0%.

LE: Low; GR: Conditional.

Summary of evidence: patients and providers are often unsatisfied with conventional IBS treatments and may be inclined to seek complementary and alternative medicine (CAM) [209,210].

The mechanisms by which CAM therapies confer benefits for IBS symptoms are still unclear. Mind-body based interventions, such as hypnotherapy, may benefit IBS symptoms via the brain-gut axis by targeting psychological factors and central pain processing and perceptual responses. Mechanisms of action that have been proposed for acupuncture include pain modulation and intestinal motility regulation; herbal and dietary interventions may potentially exert helpful effects by affecting visceral hypersensitivity, intestinal permeability and smooth muscle contractility[205,211].

A recent meta-analysis [212] of randomized placebo or sham controlled trials summarizes the effects of CAM therapies on key patient-reported outcomes of abdominal pain and overall response in IBS. CAM were classified in: body based therapy (biofeedback and visceral osteopathy); dietary supplements [Aloe vera, berberine, palmitoylethanolamide and polydatin, cod protein (Gadus

morhua) hydrolysate, biobran, enteric coated anise oil, ginger, melatonin, alkaline water]; energy healing therapy (acupuncture, moxibustion and electroacupuncture); herbal therapies (Curcuma, furmitory, caraway oil, peppermint oil, fennel, STW 5, Tong-Xie, Chinese herbal medicine, Ayurvedic herbal compound, boswellia caterii, carmint) and Mind-body based therapy (Hypnotherapy). This meta-analysis included 66 RCT: herbal therapy (SMD=0.47, 95%CI 0.20-0.75, I^2=82%) showed significant benefit over placebo for abdominal pain. Benefit with mind-body based therapy for abdominal pain was of borderline significance (SMD=0.29, 95%CI -0.01-0.59, I^2=78%). Overall, clinical response to herbal therapy (RR=1.57, 95%CI 1.31-1.88, I^2=77%), dietary supplements (RR=1.95, 95%CI 1.02-3.73, I^2=75%), and mind-body based therapy (RR=1.67, 95%CI 1.13-2.49, I^2=63%) was superior to placebo. Healing therapies based on body and energy also demonstrated no significant benefit over placebo or sham for abdominal pain or overall response [212]. Not all studies reported adverse effects (AEs), and many reported AEs overlapped with IBS symptoms. No major AEs were reported, suggesting that overall, CAM therapies show a reasonable safety profile in IBS.

In addition, a recent meta-analysis [213] assessed the efficacy of Western herbal medicines in the treatment of IBS. Several herbal medicines were effective in relieving IBS symptoms. Aloe vera and asafoetida were proven effective in reducing global IBS symptoms in meta-analyses. Herbal formulations such as STW 5, STW 5-II and Carmint, along with Ferula assa-foetida, Pimpenella anisum oil, the combination of Curcumin and Foeniculum vulgare oil, and the blend of Schinopsis lorentzii, Aesculus hippocastanum and peppermint essential oil, were also effective. In conclusion, many herbal medicines show promise in the treatment of IBS. However, with the exception of peppermint essential oil, Aloe vera, and asafoetida, none of the positive trials have been replicated.

Therapy options should also align with patients' preferences, who in many cases may be willing to and interested in exploring CAM. CAM may also serve as a useful aid for patients refractory to traditional approaches. The downside is that the strength of the evidence is low and additional high quality RCTs are needed. Moving forward, future studies on CAM therapy in IBS should adopt the FDA's guidance on pharmaceutical treatments for IBS to provide more rigorous quality evidence.

Statement 2.16: We recommend for the use of psychologically directed therapies for the treatment of global symptoms in patients with IBS.

Statement endorsed, overall agreement: 100%: A+ 68.8%, A 31.2%, A- 0%, D- 0%, D 0%, D+ 0%.

LE: Low; GR: Strong.

Summary of evidence: several evidence suggest a key-role of the interaction between brain and gut (brain-gut axis) and the importance of the so-called ‘‘biopsychosocial model’’ in the pathophysiology of IBS. Ford et al. [203] in a systematic review and meta-analysis of 36 RCTs demonstrated that IBS symptoms did not improve in patients receiving psychological therapies (52.2%, RR=0.69; 95%CI 0.62–0.76), compared with those receiving control (75.9%, symptom monitoring, physician’s “usual management”, supportive therapy, or placebo) with considerable heterogeneity detected between studies (I^2=69%, P<0.001). Contradictory results were found in a subsequent network meta-analysis [214] that investigated the efficacy of all psychological therapies and control interventions in IBS, evaluating 41 RCTs including 4072 participants. The psychological interventions including self-administered or minimal contact cognitive behavioral therapy (CBT) (RR=0.61, 95%CI 0.45-0.83, P score 0.66), face-to-face CBT (RR 0.62, 95%CI 0.48-0.80, P=0.65) and gut-directed hypnotherapy (RR 0.67, 95%CI 0.49-0.91, P=0.57) demonstrated efficacy. Similar results were found in trials recruiting only patients with refractory symptoms, showing that group CBT and gut-directed hypnotherapy were more effective than either education and/or support or routine care. CBT via the telephone, contingency management, CBT via the internet and dynamic psychotherapy were superior compared to control interventions. Among the most recent RCTs, Everitt et al. evaluated the clinical effectiveness of two modes of cognitive–behavioral therapy, telephone (TCBT) or web-based (WCBT) delivery for refractory IBS showing improvement in IBS-SSS at 12 months[215]and at 24 months [216] compared with treatment as usual (TAU). This approach has also been shown to be cost-effective [217].

The randomized trial Irritable Bowel Syndrome Outcome Study (IBSOS)[218]evaluated the efficacy of CBT or IBS education (EDU) in 436 patients. Only CBT treated patients with lower levels of trait anxiety and state anxiety evidenced greater symptomatic improvement than EDU-treated patients. Mohsenabadi et al. [219] evaluated the efficacy of the Unified Protocol for transdiagnostic treatment of emotional disorders demonstrating that this protocol decreased anxiety, depression, stress, and gastrointestinal symptoms and improved emotion regulation.

Three RCTs compared the efficacy of mindfulness-based therapy (e.g. meditation, mindfulness practices, mindfulness stretching, yoga) with other psychological therapies on the quality of life and severity of symptoms in patients with IBS [220–222] demonstrating efficacy although on a small number of patients. A recent RCT [223] investigated the relief of IBS symptoms in patients receiving six sessions of individual or group hypnotherapy or group educational supportive therapy (control group). At 12 months, there was a significant improvement in the hypnotherapy group compared with the control group. In summary, we suggest the use of psychologically direct therapy in all IBS adult

and pediatric patients who exhibit cognitive-affective drivers of IBS symptoms and stress-related psychological disorders because studies demonstrated a positive effect on global IBS symptoms and quality of life.

Figure 2 reports available therapeutic approaches for IBS and their grade of recommendation.

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TABLES

Table 1. Rome IV Diagnostic Criteria for IBS.

Rome IV IBS Diagnostic Criteria
1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and associated with two or more or the following:
a. Related to defecation
b. Associated with a change in frequency of stool
c. Associated with a change in the form (appearance) of stool
2. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Abbreviations: IBS: Irritable Bowel Syndrome

Table 2. All PICO and statements with endorsement, level of evidence, grade of recommendation and agreement.

PICO/Statement number	PICO	Statement	Endorsement	Level of evidence	Grade of recommendation	Agreement
Diagnosis						
1.1	Is clinical history and patient's phenotyping relevant for diagnosis and management?	We recommend for the assessment of clinical history and patient's phenotyping due to their relevance for diagnosis and management of patients with IBS.	Yes	NA	Consensus	100%
1.2	Should patients with IBS be assessed for psychological comorbidities?	We recommend for psychological comorbidities assessment in patients with IBS.	Yes	NA	Consensus	93.8%
1.3	Is it more cost-effective a positive or an exclusion diagnostic strategy in patients with symptoms suggestive of IBS?	We recommend for a positive diagnostic strategy in patients with symptoms suggestive of IBS.	Yes	NA	Consensus	93.8%
1.4	Should an anorectal functional evaluation be performed in patients with IBS?	We recommend for the use of digital rectal examination and anorectal physiology tests in selected adult patients with IBS referred for refractory symptoms to exclude functional defecation disorder or fecal incontinence.	Yes	NA	Consensus	87.5%
1.5	Should patients with IBS symptoms be checked for celiac disease?	We recommend serologic testing for celiac disease if the prevalence in the population is >1% (as in Italy). If tests are positive, upper endoscopy with duodenal biopsies should be performed.	Yes	Moderate	Strong	100%
1.6	Can fecal calprotectin, and/or C-reactive protein be used to rule out IBD in patients with IBS symptoms?	We recommend for the use of fecal calprotectin[1] and C-reactive protein[2] to exclude inflammatory bowel disease in patients with IBS symptoms and diarrhea without alarm features.	Yes	[1]Very low [2]Very low	[1]Strong [2]Conditional	100%

1.7	Should patients with IBS be routinely checked for stool pathogens?	We recommend against routine stool testing for enteric pathogens in adults with IBS.	Yes	Low	Conditional	82.5%
1.8	When is colonoscopy indicated in patients with IBS symptoms?	We recommend for colonoscopy in patients with IBS symptoms and alarm features.	Yes	Moderate	Strong	93.8%
1.9	Should patients with IBS be tested for food intolerance?	We recommend against testing for food and lactose intolerance in patients with IBS.	Yes	Very low	Strong	93.8%
1.10	Should patients with IBS be tested for allergies?	We recommend against routine testing for food allergies in both adult and pediatric patients with IBS unless there are reproducible symptoms suggestive of a food allergy.	Yes	NA	Conditional	93.8%
1.11	Should patients be tested for small intestinal bacterial overgrowth?	We recommend against routine testing for small intestinal bacterial overgrowth in adult patients with IBS symptoms.	Yes	Very low	Strong	100%
Treatment						
2.1	Should dietary approaches be used in patients with IBS?	We recommend for a dietary approach for patients with IBS. Traditional dietary advice is suggested as first line approach[1], while a low FODMAP diet as a second line approach[2]. A gluten free diet is not recommended in patients with IBS[3].	Yes	[1]Very low [2]Low [3]Very low	[1]Strong [2]Conditional [3]Strong	100%
2.2	Should fiber supplementation be used to treat global IBS symptoms?	We recommend for soluble but not insoluble fiber supplementation to treat global IBS symptoms.	Yes	Low	Strong	93.8%
2.3	Should probiotics be used to treat global IBS symptoms?	We recommend for the use of probiotics, as a group, for improving overall symptoms or abdominal pain in patients with IBS.	Yes	Low	Conditional	87.5%
2.4	Should polyethylene glycol be used to treat IBS-C symptoms?	We suggest for the use of polyethylene glycol for the treatment of constipation in patients with IBS-C. The dose should be titrated according to stool consistency.	Yes	Very low	Conditional	100%

2.5	Should secretagogues be used to treat IBS-C symptoms?	Secretagogues are useful for the treatment of global symptoms and constipation in patients with IBS-C. Diarrhea is a frequent side effect.	Yes	High	Strong	93.8%
2.6	Should 5-HT4 agonists be used to treat IBS-C symptoms?	We suggest for the use of 5-HT4 agonists in selected IBS-C patients who have failed conventional therapy.	Yes	Low	Conditional	100%
2.7	Should bile acid sequestrants be used to treat IBS-D symptoms?	We suggest for the use of bile acid sequestrants to treat IBS-D symptoms in case of proven bile acid malabsorption. If testing is not available, in patients with IBS-D, not otherwise manageable with first line treatments, a trial of bile acid sequestrants is advisable.	Yes	Very low	Conditional	93.8%
2.8	Should rifaximin be used to treat global IBS symptoms?	We suggest for the use of rifaximin to treat global symptoms in patients with IBS without constipation.	Yes	Moderate	Strong	93.8%
2.9	Should 5-HT3 antagonists be used to treat IBS-D symptoms?	We suggest for the use of 5-HT3 antagonists for global IBS-D symptoms in patients who have failed conventional therapy.	Yes	Low	Conditional	87.5%
2.10	Should opioid agonists/mixed antagonists be used to treat IBS-D symptoms?	We recommend for the use of opioid agonists to manage diarrhea in IBS-D.[1] We recommend for the use of mixed opioid agonists/antagonists to treat global symptoms in IBS-D.[2]	Yes	[1]Low [2]High	[1]Conditional [2]Strong	100%
2.11	Should fecal microbial transplantation be performed to treat IBS symptoms?	We recommend against the use of fecal microbiota transplantation in patients with IBS.	Yes	Low	Strong	100%
2.12	Should antispasmodics be used to treat global IBS symptoms?	We recommend for the use of antispasmodics for global symptom improvement in patients with IBS.	Yes	Low	Conditional	100%
2.13	Should antidepressants be	We recommend for the use of tricyclic antidepressant (TCAs) in adult patients	Yes	[1]Moderate [2]Low	[1]Strong [2]Conditional	100%

	used to treat IBS symptoms?	with IBS to induce global relief of symptoms and to treat abdominal pain alone[1]. We recommend for the use of selective serotonin reuptake inhibitors (SSRIs) in adult patients with IBS to induce global relief of symptoms[2].				
2.14	Should cannabinoid and endocannabinoid modulators be used to treat IBS symptoms?	We recommend against the use of cannabinoid and endocannabinoid modulators to treat IBS symptoms.	Yes	Low	Conditional	100%
2.15	Should complementary alternative therapies be used to treat IBS symptoms?	We recommend against the use of complementary alternative therapies, although some reasonably good quality evidence exists for specific approaches.	Yes	Low	Conditional	93.8%
2.16	Should psychologically directed therapies be used to treat global IBS symptoms?	We recommend for the use of psychologically directed therapies for the treatment of global symptoms in patients with IBS.	Yes	Low	Strong	100%

Abbreviations: PICO: patient, intervention, control, and outcome. NA: not available: unable to assess using GRADE methodology. IBS: Irritable Bowel Syndrome. IBD: inflammatory bowel disease.

FIGURE LEGEND

Figure 1. Diagnostic algorithm for irritable bowel syndrome. Abbreviations: IBS, irritable bowel syndrome; IBS-D, IBS with predominant diarrhea; IBS-C, IBS with predominant constipation; IBS-M, IBS with mixed bowel habits; IBS-U, unclassified IBS; BM, bowel movements; BSS, Bristol Stool Scale.

Figure 2. Therapeutic approach for irritable bowel syndrome.