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Irritable Bowel Syndrome: News from an Old Disorder

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Abstract
Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder, which can affect all members of a society, regardless of age, sex, race or socioeconomic status. Because of its high prevalence and chronic nature, it represents a significant economic burden. In fact, these patients have a relevant impairment of their quality of life, which limits their work productivity and daily social activities, especially when it is associated with other disorders, such as anxiety and depression. The diagnosis of IBS relies on symptom-based diagnostic criteria with normal results on a limited number of complementary tests that rule out other possible diagnoses. The aetiology of this condition is incompletely established. However, evidence suggests that it is a multifactorial disorder with several different mechanisms that have been implicated as responsible for the symptoms. Since the treatment strategy is usually based on predominant symptoms and their severity, it is important to recognise the underlying mechanisms in order to successfully relief the visceral pain and altered bowel habits. The aim of this non-systematic review of the literature was to explore the pathophysiology and treatment options of IBS, highlighting the most recent evidence, from the new Rome IV criteria to the new drug armamentarium.

Síndrome do intestino irritável: novidades de uma doença antiga

Palavras Chave
Síndrome do intestino irritável · Revisão · Critérios Rome

Resumo
A síndrome do intestino irritável é um distúrbio gastrointestinal funcional, que pode afetar todos os membros da sociedade, independentemente da idade, sexo, raça ou estrato socioeconómico. Devido à sua elevada prevalência e natureza crónica, representa um encargo económico significativo. De facto, estes doentes apresentam uma alteração relevante da sua qualidade de vida, o que limita a sua produtividade laboral e atividades de vida diárias, sobretudo quando está associada a outros distúrbios, tais como ansiedade e depressão. O diagnóstico da síndrome do intestino irritável depende de critérios diagnósticos baseados em sintomas, com resultados normais num número limitado de testes complementares que exluem outros diagnósticos possíveis. A etiologia desta doença não está completamente estabelecida. No entanto, a evidência sugere que se trata de um distúrbio multifatorial com vários mecanismos diferentes que têm sido implicados como responsáveis pelos sintomas. Visto que a estratégia terapêutica é geralmente baseada nos sintomas predominantes e sua gravidade, é importante reconhecer

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os mecanismos subjacentes para aliviar com sucesso a dor visceral e a alteração dos hábitos intestinais. O objetivo desta revisão literária não sistemática consistiu em explorar a fisiopatologia e opções terapêuticas disponíveis para a síndrome do intestino irritável, realçando a evidência mais recente, desde os novos critérios Roma IV até ao novo arsenal farmacológico.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder which can affect all members of a society, regardless of age, sex, race or socioeconomic status [1]. Because of its chronic nature and impairment of quality of life, this condition represents a significant economic burden and these patients are more likely to resort to health services and to require time off work [2]. Traditionally labelled as a functional GI disorder without evident structural or pathological changes, new insights suggest a disturbed GI physiology with impairment of GI motor function, visceral sensation and secretion, all of them potential therapeutic targets to improve symptoms and quality of life of these patients.

The aim of this non-systematic review of the literature was to explore the pathophysiology and treatment options of IBS, highlighting the most recent evidence, from the new Rome IV criteria to the new drug armamentarium.

The methodology applied was a bibliographic search on PUBMED of systematic reviews, meta-analyses, case-control or cohort studies and guidelines, published in English language preferably in the last 10 years.

Epidemiology

The worldwide estimated prevalence of IBS is 11.2% and vary based on the geographic region, age, gender and diagnostic criteria [3].

The prevalence of IBS is higher in younger age groups from 26 to 55 years [4] and in women, who appear to have more frequent and severe IBS symptoms during menses due to low ovarian hormone levels, which are associated with a decreased sensory threshold to rectal distension. Additionally, symptoms vary between genders with women reporting more commonly symptoms of constipation (IBS-C) and men having more diarrhoea-associated symptoms (IBS-D) [5]. Constipation symptoms are also more frequent in older patients, most likely because these patients show more comorbidities and less mobility [6].

There is little information about subtype-specific prevalence because patients with IBS vary over time in terms of symptoms, switching subtype [4]. However, some studies suggest IBS with mixed bowel habits (IBS-M) as being the most common [6].

Association between IBS and Other Disorders

IBS is commonly associated with other functional, somatoform and mental disorders [7]. In >20% of the cases, there is an overlap of IBS with functional GI disorders of the upper GI system – particularly functional dyspepsia and gastroesophageal reflux disease – and of the lower GI system – such as diarrhoea, incontinence, pelvic floor dyssynergia and constipation [8]. Psychiatric comorbidities are present in approximately 50% of IBS patients and include depressive symptoms, anxiety and eating disorders [7].

IBS patients appear to have an increase of the incidence rate of other diseases, including stroke, osteoarthritis and infections, probably because these patients are hypervigilant in detecting somatic symptoms [9].

Post-Infectious IBS

A strong association between GI infections and the development of IBS has been established [10]. Around 1 in 9 patients exposed to infectious enteritis may develop IBS, at a rate 4 times higher than non-exposed individuals. The greatest risk is associated with protozoal and bacterial infections, with viral infections having a lower risk of development of IBS. The severity of the acute gastroenteritis increases the risk of developing IBS [11, 12], but symptoms usually decrease over time [12].

Pathophysiology

IBS is a functional GI disorder without evident structural or pathological changes; still there is evidence of a disturbed GI physiology because GI motor function, visceral sensation and secretion are altered [13]. Evidence suggests that it is a multifactorial disorder with several different underlying mechanisms responsible for the symptoms reported by the patients (Fig. 1). In IBS, the epithelial barrier, gut microbiota, food antigens and bile acids give rise to abnormal responses in the main regulators of sensorial and motor functions, such as the hypothalamus-pituitary-adrenal axis, the immune system, the brain-gut axis and the enteric nervous system (ENS) [14]. In addi-

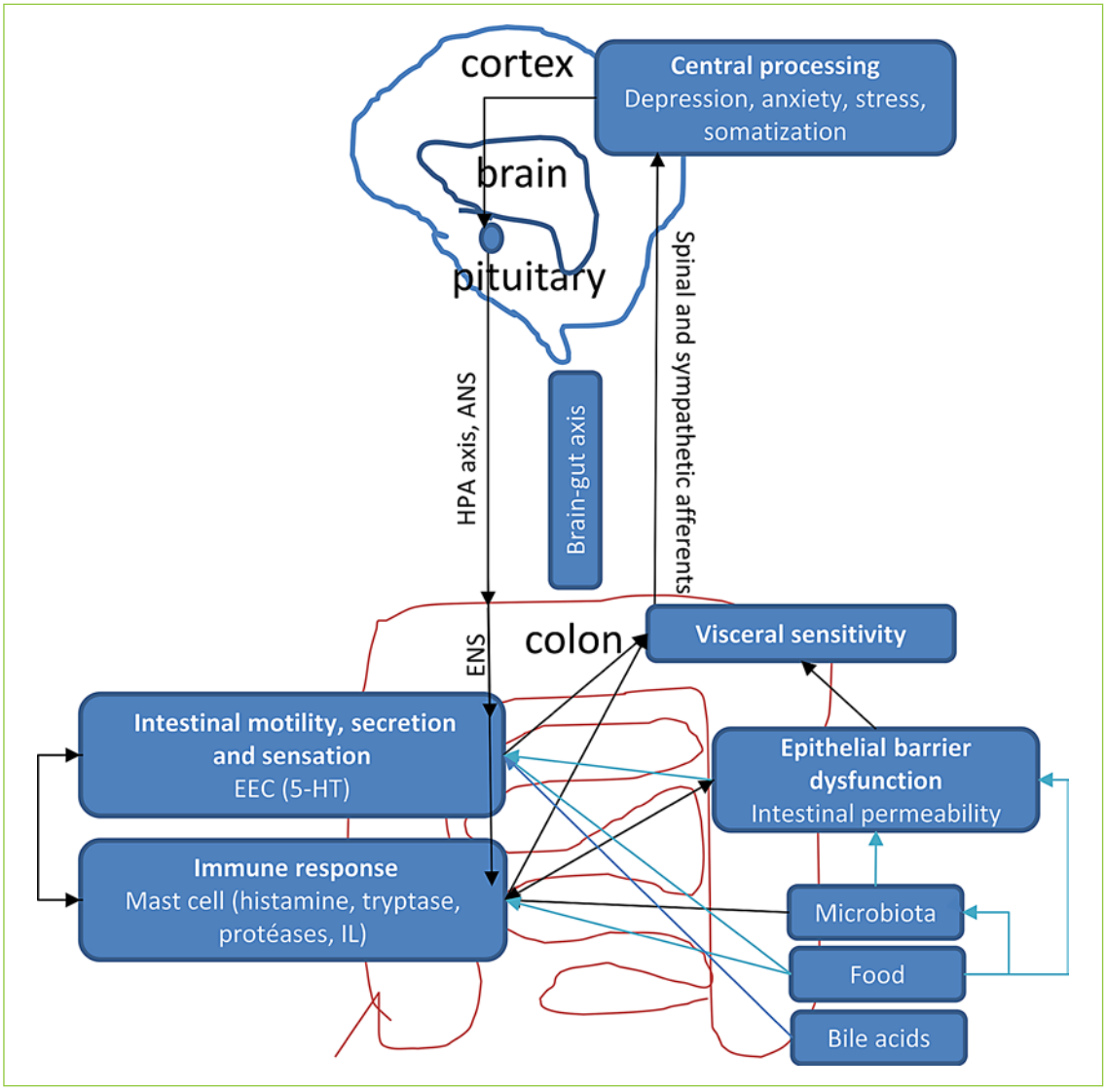

Fig. 1. Overview of the pathophysiology of IBS. Several underlying mechanisms have a role in pathophysiology of IBS and its symptoms. Food antigens, gut microbiota, bile acids and the brain, via the ANS-ENS and the HPA axis, give rise to abnormal responses in the bowel at the level of motility, secretion and sensation, directly or mediated through epithelial barrier dysfunction with increased intestinal permeability or immune cell reactivity. 5-HT, 5-hydroxytryptamine; ANS, autonomic nervous system; EEC, enteroendocrine cell; ENS, enteric nervous system; HPA, hypothalamus-pituitary-adrenal; IL, interleukin.

tion, it is well recognized the association of psychological factors, particularly anxiety and depression, and the development of IBS, with the corticotropin-releasing factor being one of the key mediators between the two [15].

Epithelial Barrier

Intestinal barrier dysfunction has been proven to have a pathogenic role in IBS and is considered an early event in the course of this disorder [16]. Increased intestinal permeability can be triggered by different factors, such as stress, food allergies, bile acids, infections and dysbiosis, genetic and epigenetic factors. This mechanism is associated with low-grade inflammation, visceral hypersensitivity and pain, with evidence suggesting that increased levels of mast cell mediators may be involved in increased epithelial permeability [15, 17].

Bile Acids

It has been suggested that one of the mechanisms for symptom generation in patients with IBS-D is the in-

creased bile acid exposure at the colon. Among patients with IBS, faecal bile acid levels are higher in patients with IBS-D and lower in patients with IBS-C [18]. Approximately 25% of patients with IBS-D have excessive levels of total faecal bile acids [19] because of both bile acid absorption and synthesis dysregulation [20].

The increased levels of total faecal bile acids in patients with IBS-D are associated with increased concentrations of serum 7α-hydroxy-4-cholesten-3-one (C4), being a potential non-invasive test for bile acid malabsorption in IBS [21, 22].

Immune Response

Evidence suggests that systemic or intestinal immune activation has a role in the pathophysiology of IBS shown by both increased infiltration of inflammatory cells (T cells and mast cells) and increased humoral activity (higher density of activated B lymphocytes and plasma cells and a higher local production of immunoglobulin G) in the mucosa of small and large intestine of some patients with IBS, findings positively associated with the number of bowel movements per day and stool form, but not with the intensity and frequency of abdominal pain [23]. Mast cells are a key component in inducing and maintaining a low-grade immune activation. Peripherally elevated cytokine levels like tumour necrosis factor α and toll-like receptor activity of patients with IBS demonstrate the immune dysfunction present in these patients [13, 24].

Neuroimmune Interactions

The ENS is sometimes called the "second brain" because of the diversity of neuronal cell types and complex, integrated circuits that permit the ENS to autonomously regulate many processes in the bowel [25]. IBS patients have a higher density of mucosal nerve fibres and increased nerve outgrowth with functional and structural alterations in the ENS that might be responsible for the visceral hypersensitivity [26]. Also, the release of pro-inflammatory mediators by persistently activated immune cells such as mast cells are crucial in the mechanisms underlying abdominal pain and dysmotility in IBS patients [27, 28].

Serotonin Metabolism

Serotonin 5-hydroxytryptamine (5-HT) is an important neurotransmitter present in the brain and the ENS. Up to 90% of the total body serotonin is produced by the enteroendocrine cells present in the GI tract and regulates intestinal motor and secretory functions. 5-HT can make the bowel contract or relax, depending on the activation of cholinergic excitatory neurons – mediated by 5-HT_3 or 5-HT_4 receptors – or nitric oxide inhibitory enteric motor neurons – mediated by 5-HT_4, 5-HT_{1A} or 5-HT_{1D} receptors. Serotonin is also a potent intestinal secretagogue [29, 30].

Patients with IBS, regardless of bowel habit, have a higher colonic mucosa 5-HT availability, which was associated with mucosal mast cell infiltration, suggesting that the immune activation can lead to 5-HT release. The increased colonic 5-HT release was correlated with the severity of abdominal pain [31].

Microbiota

The dysbiosis of microbiota in IBS has been recognized by the Rome Foundation Working Team as a plausible contributing factor to this condition [32]. IBS symptom severity has been associated with a distinct faecal microbiota signature and patients with severe IBS have lower microbial richness and exhaled methane, as well as reduced presence of Methanobacteriales and Prevotella enterotype, but increased presence of Bacteroides enterotype [33].

Diet plays a major role in the pathogenesis of IBS [34], and it can rapidly change the intestinal microbiota, affecting the abundance of specific microbial groups [35].

The dysbiosis of microbiota present in some individuals with IBS results in abnormal levels of intestinal fermentation. The colonic pH was reported to be significantly lower in patients with IBS, compared to healthy controls, which suggests a higher proportion of colonic fermentation [36]. In these patients, the presence of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) can induce IBS symptoms because these products increase the intraluminal osmotic pressure and provide a substrate for bacterial fermentation, resulting in gas production, abdominal distension and abdominal pain [34]. In addition, the overproduction of gas can lead to faster colonic transit in patients with IBS-D, due to the increased sensitivity to the augment of intestinal volume [37].

Brain and Behaviour

One of the key mechanisms in the development of IBS is believed to be a dysregulation of the axis between the brain and the gut as a consequence of peripheral and central mechanisms [38]. The brain, through the hypothalamus-pituitary-adrenal axis and the autonomic nervous system, can influence intestinal motility, fluid secretion, intestinal epithelial permeability, immune function and gut microbiota [14].

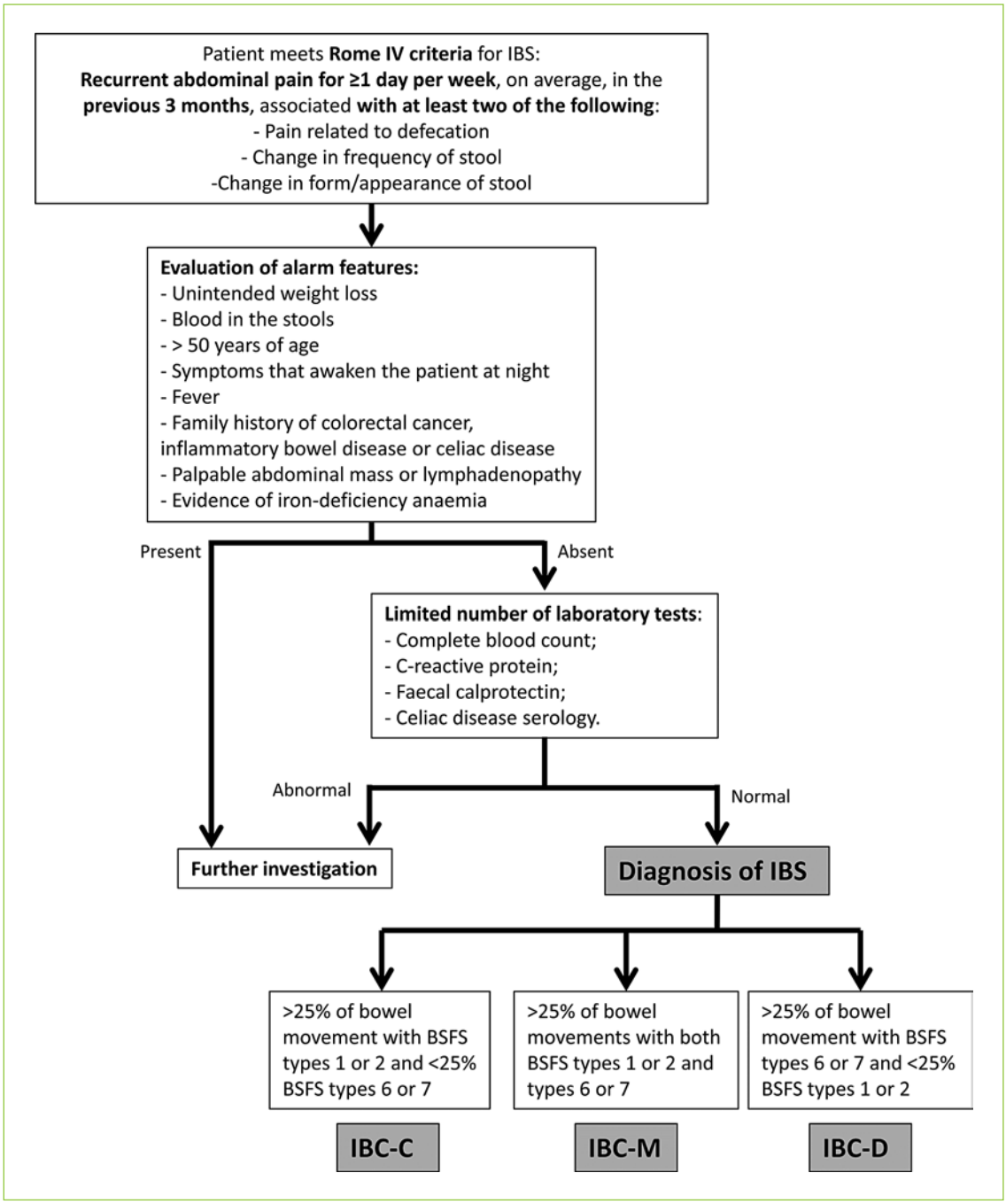

Fig. 2. Algorithm for the diagnosis of IBS. IBS, irritable bowel syndrome; BSFS, Bristol Stool Form Scale; IBS-C, irritable bowel syndrome with predominant constipation; IBS-D, irritable bowel syndrome with predominant diarrhoea; IBS-M, irritable bowel syndrome with predominant irregular bowel habits (mixed C/D).

On the one hand, central mechanisms are based on depression, anxiety and somatisation [38]. Patients with IBS have reported a higher prevalence of somatisation, compared with controls without IBS, which can be partly explained by the increased levels of depression and anxiety that lead to a greater awareness of any physical symptoms [39]. Stressful life events may alter the central processing of afferent stimuli and have been directly associated with neuroticism and higher rates of functional bowel disorders [40].

On the other hand, peripheral mechanisms are characterized by changes in intestinal motility and secretion, as well as visceral hypersensitivity [38]. These peripheral changes can influence brain structure and function [14]. Alterations in the volume of grey matter were identified in patients with IBS and may be linked with the increased sensitivity to somatic and visceral stimuli, as well as an increase in emotional arousal [41]. In fact, epidemiological evidence suggests that, in about half of the patients, the GI symptoms arise first and then the mood disorders become apparent [40].

Genetic and Epigenetic Data

IBS has familial aggregation and higher concordance between monozygotic twins compared to dizygotic twins, which demonstrates that genetic factors play a role [42]. Polymorphisms and variants of several genes involved in neuronal signal transduction, immune response and intestinal barrier, as well as mutations in genes encoding proteins involving the serotonergic system and bile acid synthesis regulation, have been associated with IBS [22, 43].

Although only a few studies have been performed, miRNA studies have linked target genes to increased gut permeability, visceral sensitivity and colonic motility [14].

Diagnosis

Diagnostic Criteria

The diagnosis of IBS relies on symptom-based diagnostic criteria with normal results on a limited number of complementary tests that rule out other possible diagnoses [14]. These criteria were first established in 1978, the Manning criteria [44], but the current gold standard criteria for the diagnosis of IBS are the Rome IV criteria (Fig. 2), updated in 2016 [1]. When these criteria are present and alarm features are absent, only a limited number of laboratory tests are recommended without any need to perform invasive investigations. Currently, there is no valid biomarker for IBS [45].

In the new Rome IV criteria, "discomfort" was eliminated from the criteria because it is non-specific and has different meanings in different languages. Now pain related to bowel movements is required, rather than just improving with bowel movements, because, in some cases, pain can worsen after bowel movements [46]. Furthermore, the frequency of abdominal pain was increased from 3 days per month to 1 day per week on average [47].

Clinical Features

Abdominal pain must be present anywhere throughout the abdomen, but it is more common in the lower quadrants; the absence of this feature excludes the diagnosis of IBS. Abdominal pain is associated with abnormal bowel habit, such as diarrhoea, constipation or alternating diarrhoea and constipation [1].

Abnormal stool frequency (>3 bowel movements per day or <3 bowel movements per week), abnormal stool form in the Bristol Stool Form Scale (types 1–2 or 6–7), excessive straining during defecation, urgency, feelings of incomplete evacuation and mucus with bowel movements are common symptoms but are not specific of IBS [14]. The same applies to abdominal bloating and abdominal distension that are present in most IBS patients [1].

Physical Examination

Physical examination should be performed in every patient evaluated for IBS since it helps to exclude organic causes for the symptoms [1], although abdominal examination rarely gives information to support a specific diagnosis. Digital rectal examination can exclude rectal cancer and can identify patients with dyssynergic defecation, which has to be ruled out in patients with constipation. Perianal inspection is also an important part of the physical examination to exclude perianal fistulas and other relevant anal pathology. The absence of objective findings on physical examination supports a diagnosis of IBS [14].

Laboratory Tests

At the time, there is not sufficient evidence to recommend which laboratory tests should be used for the diagnostic work-up of patients with IBS. It is important to perform limited laboratory studies, starting with a complete blood count [14]. C-reactive protein or faecal calprotectin must be measured because normal levels help exclude IBD in patients with non-constipated symptoms of IBS [48].

In the clinical suspicion of thyroid disease, a thyroid profile should be performed. Serologic tests for celiac disease should be used to exclude this condition in patients with symptoms of IBS-D and IBS-M [1, 49]. Other differential diagnoses include bile-acid-induced diarrhoea and carbohydrate malabsorption. Furthermore, stool analysis for bacteria, parasites and ova may be considered to detect GI infections in patients with diarrhoea [1].

Colonoscopy is indicated in the presence of alarm features and persistent diarrhoea, in the suspicion of IBD and in cases of a family history of colorectal cancer [1]. In

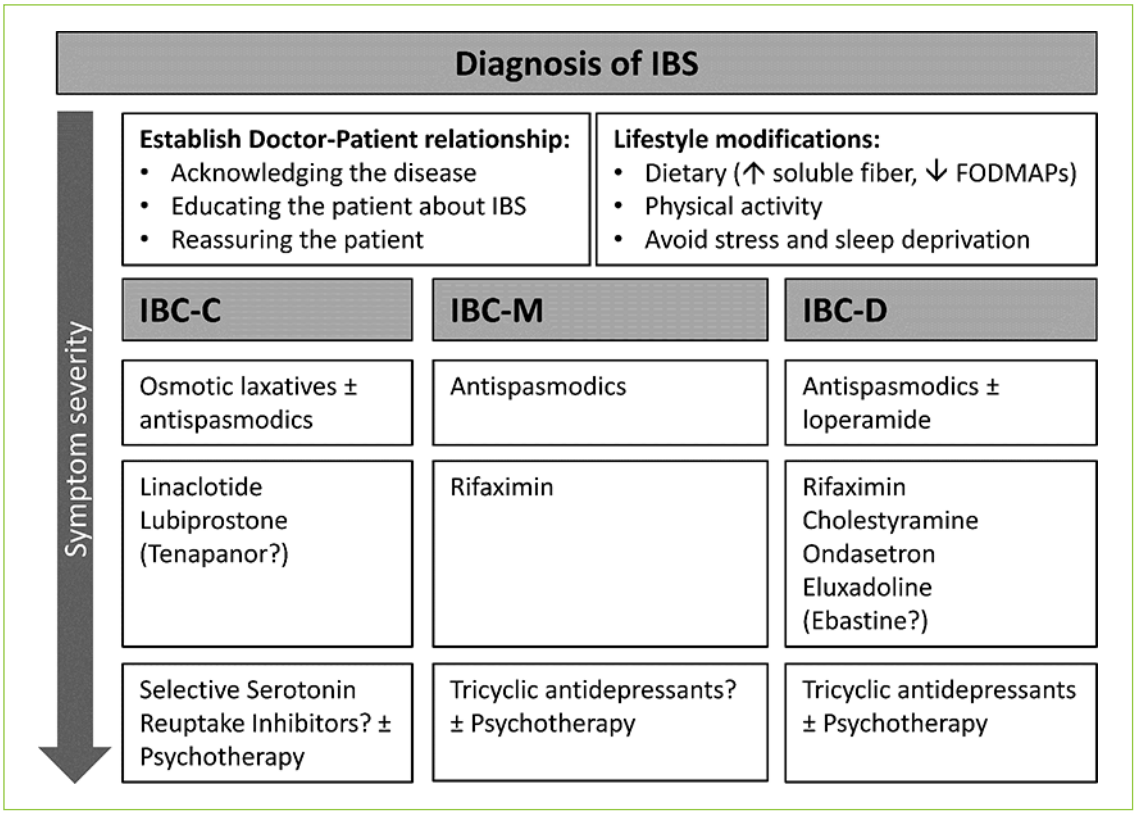

Fig. 3. Treatment options for IBS according to predominant symptoms and their severity. Doctor–patient relationship and lifestyle modifications are the mainstay of treatment regardless of symptom severity and probably sufficient in the management of mild symptoms. For moderate symptoms, pharmacological therapies may be added and aim to relief predominant bowel habits and visceral pain. For severe symptoms and patients with refractory symptoms, psychopharmacologic agents and psychotherapy can be used. IBS, irritable bowel syndrome; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; IBS-C, irritable bowel syndrome with predominant constipation; IBS-D, irritable bowel syndrome with predominant diarrhoea; IBS-M, irritable bowel syndrome with predominant irregular bowel habits (mixed C/D).

patients with watery diarrhoea if symptoms are not controlled by empiric treatment, biopsies of the colon might be required to exclude microscopic colitis [50].

All described biomarkers were not superior to symptom-based criteria for the diagnosis of IBS [51]. Serum biomarkers such as antibodies to a bacterial toxin produced by *Campylobacter jejuni* called cytolethal distending toxin B and vinculin have been studied and permit the distinction between IBS and non-IBS subjects with high specificity but low sensitivity [52].

Management

The first step after the diagnosis of IBS is explaining the natural history of the disease and providing reassurance that it is a benign condition. Establishing of a good rapport with a patient is an essential step in the management of this condition, making sure the patient feels heard as well as validating their symptoms. A trust relationship between a doctor and his patient will lead to a more effective treatment [1].

The heterogeneity of IBS complicates the development of an algorithm to all patients, even within individual IBS subtypes. Management of IBS involves an integrated approach [53] and treatment options include establishment of an effective patient-provider relationship, education, reassurance, nutritional interventions, drug therapy and psychological therapy [8]. In fact, patients who received information about the course of the disease, disease-related diet and lifestyle, medications and check-ups had their quality of life improved [54].

Treatment strategy should be based on predominant symptoms and their severity [8] (Fig. 3). For mild symp-

toms, reassurance, education and dietary modifications are probably enough. Complementing the dietary changes, it is important that IBS patients exercise and reduce stress and sleep deprivation [1]. For moderate symptoms, more specific actions are recommended, such as identification and alteration of exacerbating factors and pharmacological therapy aimed at the predominant symptoms (Table 1). For severe symptoms and patients with refractory symptoms, psychopharmacologic agents and psychotherapy can be added [53].

Dietary Modifications

Food ingestion is one of the most common precipitants of symptoms in IBS [55], and this leads many patients to conclude that they suffer from an allergy to certain foods. Despite this belief, most food-related IBS symptoms seem to represent food intolerance, a physiological reaction to food allergens not associated with an immune response [56], but most likely related to other mechanisms like stimulation of the gut by-products of the digestion, 5-HT and gut microbiota [14]. Thus, food intolerance tests commonly sought by our patients, based on immunoglobulin E or G antibodies, lack any evidence base [57].

Nevertheless, specialized diets may improve symptoms in individual IBS patients [57] and a food and symptom diary can help them determine which foods trigger symptoms [53]. A diet low in fermentable oligo-, di- and monosaccharide and polyol (FODMAPs) – slowly absorbed or indigestible short-chain carbohydrates – is one of the major options of treatment in IBS [14], with a symptomatic improvement in about 70% of the patients. This diet strategy effectively reduces functional GI symptoms such as bloating, abdominal pain, urgency, stool frequency and consistency [58], originated by the increase in intraluminal osmotic pressure and bacterial fermentation of the FODMAPs [34]. It is suggested that a low-FODMAP diet should be used as first-line treatment in combination with other methods. Still the safety of this diet needs to be monitored regarding long-term consequences, such as the possibility of malnutrition [59], and should preferably be delivered by a motivated and trained health professional [60].

Despite the absence of immunological, serological and histological markers of celiac disease, gluten ingestion can also be responsible for IBS symptoms in some patients, altering bowel barrier functions in patients with IBS-D [61]. However, wheat contains high levels of fructan, a polysaccharide, which might explain the benefits of a gluten-free diet that can also be achieved with a low-FODMAPs diet. In fact, a diet both low in FODMAPs and gluten-free did not have additional benefits compared with a low-FODMAPs diet alone, demonstrating that there is no benefit in avoiding gluten [62]. Also in dietary interventions, fibre and fibre-based supplements accelerate colon transit and facilitate stool passage, resulting in an increased stool frequency, which can be helpful in patients with IBS-C [8]. While soluble fibres (fruit, vegetables, psyllium) have symptomatic benefits in IBS, insoluble fibres (cereals, bran) may exacerbate IBS symptoms, including bloating, abdominal pain and distension [63].

Antispasmodic Drugs

In some patients with IBS, pain is mediated through colonic smooth muscle spasm [14]. Different studies have demonstrated that antispasmodic therapy improves IBS symptoms like abdominal pain and stool consistency. Butylscopolamine, due to its ability to antagonize the binding of acetylcholine to the muscarinic receptor at the neuromuscular junction, leads to smooth muscle relaxation [64–66]. However, due to anti-muscarinic adverse effects such as constipation, it should not be used in patients with IBS-C [57]. Pinaverium, a selective calcium channel blocker of GI smooth muscle cells, is one of the most commonly used IBS medications, with evidence proving that it reduces abdominal pain and improves stool consistency in 4 weeks [67]. Peppermint oil also inhibits smooth muscle contraction through calcium channel blockade and has been proven to reduce IBS symptoms, being a safe and effective treatment for IBS [68]. Mebeverine, a spasmolytic without atropine-like side effects, has high efficacy for abdominal pain and reduction in daily defecation frequency, as well as an improvement in global well-being, with good tolerability with minor complications [69, 70].

Laxatives and Motility Accelerants

In patients with constipation, simple laxatives are a suitable therapeutic option due to their relative safety, low cost and availability [71, 72]. However, lactulose is often poorly tolerated by IBS patients because of worsening of bloating and pain; therefore, it is not recommended [14].

Linaclotide and lubiprostone are novel drugs that increase fluid secretion into the GI tract and accelerate GI transit [73]. Linaclotide is a minimally absorbed peptide guanylate cyclase C receptor agonist that should be used as second-line therapy, in patients with IBS-C after the failure of laxatives [14]. Besides its laxative effect, linaclotide also reduces colonic nociception and abdominal

Table 1. Pharmacological therapies for IBS based on predominant symptoms, with dosage and level of evidence

Symptom	Therapy	Agent	Dose	Target	Type of study	Quality of evidence [57]	Results	Ref
Diarrhea	Opioid agonists	Loperamide	2–4 mg when necessary up to 16 mg/day	μ-opioid receptor	DBPCCT	Very low	Improvement of stool consistency, pain and urgency, decreasing frequency of defecation	[79, 80]
	Diet	Low FODMAPs	Not applicable	Lumen and gut microbiota	RCT	Very low	Improvement of bloating, abdominal pain, urgency, stool frequency and consistency	[58, 59]
	Bile acid sequestrants	Cholestyramine Colestipol*	4 g tid (up to 24 g/day) 2 g qd-bid	Bile acids	RCT	NA	Reduction of stool frequency	[88]
	Probiotics	Multiple products available		Gut microbiota	MA	Low	Improvement of bloating, abdominal pain and flatulence	[92, 92]
	Antibiotics	Rifaximin	400 mg tid, 14 days	Gut microbiota	DBPCCT	Moderate	Relief of bloating, abdominal pain and loose or watery stools	[90]
	5-HT_3 antagonists	Alosetron*, † Ondansetron	0.5–1 mg/day 4–8 mg tid	5-HT_3 receptor	RCT, MA	Moderate	Relief of loose stools, frequency and urgency	[84, 85]
	Mixed opioid agonists/ antagonists	Eluxadoline*, †	100 mg bid	μ-opioid, δ-opioid and κ-opioid receptors	RCT	NA	Delay of GI motility and reduction visceral hypersensitivity	[81]
Constipation	Soluble fiber	Psyllium	Up to 30 g/day in divided doses	Unclear	MA	Moderate	Improvement of global IBS-C symptoms, increasing stool frequency	[63]
	Motility accelerants	Polyethylene glycol	Up to 10 mg tid	Osmotic laxative	RCT	Very low	Improve stool frequency but not abdominal pain	[72]
		Linaclotide	290 μg qd	Guanylate cyclase C	DBPCCT, RCT	High	Laxative effect, reduction of colonic nociception and abdominal pain	[75, 76]
		Lubiprostone*	8 μg bid	Chloride channel	RCT	Moderate	Increased stool frequency and consistency, reduction of abdominal pain and bloating	[78]
Abdominal pain	Smooth muscle antispasmodics	Hyoscine butylbromide/ butylscopolamine	10–20 mg tid	Antimuscarinic	DBPCCT	Low	Reduces abdominal pain intensity	[66]
		Pinaverium	100 mg bid	Calcium channel	DBPCCT		Relief of abdominal pain and improvement of stool consistency	[67]
		Otilonium bromide	40 mg tid	Antimuscarinic + calcium channel blocker	DBPCCT		Reduction of abdominal pain and bloating	[65]
		Mebeverine	200 mg bid	Anticholinergic (unknown mechanism of action)	MA, RCT		Improvement of global wellbeing, with reduction of abdominal pain and defecation frequency	[69, 70]

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Table 1 (continued)

Symptom	Therapy	Agent	Dose	Target	Type of study	Quality of evidence [57]	Results	Ref
		Peppermint oil	Enteric-coated capsules, 250–750 mg, bid-tid	Calcium channel	MA	Moderate	Improvement of global IBS symptoms, especially abdominal pain	[68]
	Tricyclic antidepressants	Desipramine Amitriptyline	25–100 mg qhs 10–50 mg qhs	Mostly serotonin and noradrenaline transporters	MA	High	Improvement of global IBS symptoms, especially abdominal pain	[93]
	Selective serotonin reuptake inhibitors	Paroxetine Sertraline Citalopram	10–40 mg qd 25–100 mg qd 10–40 mg qd	Presynaptic serotonin receptor	MA	High	Improvement of global IBS symptoms, especially abdominal pain	[71]

DBPCCT, double-blind placebo-controlled clinical trial; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; MA, meta-analysis; NA, not available; RCT, randomized clinical trial. * Drug not available in Portugal. † Potential major side effects, refer to text.

pain [74–76]. Lubiprostone causes secretion of fluid and electrolytes in the small bowel through the activation of chloride channels [77]. Two randomized trials revealed the significant improvement of IBS-C symptoms with lubiprostone, without major side effects [78].

Antidiarrheals

Loperamide, a μ-opioid receptor agonist, frequently used as first-line therapy in IBS-D, slows peristalsis and increases fluid reabsorption, improving stool consistency, urgency and pain [79, 80]. Eluxadoline is a new oral agent with peripherally acting mixed μ-opioid receptor agonist-δ-opioid receptor antagonist and κ-opioid receptor agonist that slows GI motility and decreases visceral hypersensitivity [81]. Reports of severe pancreatitis and sphincter of Oddi dysfunction, particularly in patients without a gallbladder or those who abuse alcohol, led to the contraindication of eluxadoline in these groups of patients [82].

5-HT_3 receptor antagonists are effective in patients with IBS-D, both slowing colonic transit through the inhibition of peristaltic reflex [83] and modulating visceral nociception [30]. Alosetron significantly improved abnormal bowel function and relieved pain and discomfort on IBS-D but was withdrawn due to reports of severe constipation in around 25% of patients and ischemic colitis [84]. Ondansetron leads to significant improvements in stool consistency, though abdominal pain was not reduced. It has been used widely for over 25 years without a single report of ischaemic colitis [85].

In patients with IBS-D, an increased exposure of the ileal mucosa to bile acids leads to an excessive secretory response [86]. In fact, treatment with colestipol in these patients had a positive symptomatic response [87]. Additionally, there is evidence that colestyramine is effective in patients with functional chronic watery diarrhoea [88].

Manipulation of the Microbiota

Disruption of gut microbiota homeostasis has been proven to contribute to the pathophysiology of IBS. Thereby, antibiotics and probiotics may improve IBS symptoms by restoring balance to the gut microbiota [89].

The non-absorbable, non-systemic antibiotic, rifaximin, appears to play a role in modulation of the gut microbiota and in local micro-inflammation [14]. Rifaximin was associated with significant relief of IBS symptoms such as bloating, abdominal pain and loose or watery stools, in patients without constipation [90].

Probiotics are attenuated bacteria or bacterial products that are beneficial to the host. Although there are

some inconsistencies in different studies, there is enough evidence to suggest their efficacy in reducing IBS symptoms, such as bloating, abdominal pain and flatulence [91]. *Lactobacillus plantarum* had the most evidence in favour of their use [92].

Antidepressants

There is evidence to recommend the use of low-dose antidepressants, such as tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) for reducing abdominal pain in IBS, especially in patients who maintain symptoms after nutritional interventions and antispasmodic therapy [57]. In a recent meta-analysis, TCAs showed to improve the global symptoms of IBS [93]. However, TCAs have adverse effects that need to be considered, for instance, constipation, dry mouth, drowsiness and fatigue, which renders them particularly successful in patients with IBS-D, but less helpful in patients with IBS-C [14]. SSRIs may be considered in resistant IBS-C, although it is not currently recommended that SSRIs should be routinely prescribed for IBS in patients without comorbid psychiatric conditions [93, 94].

Psychotherapy

Patients who do not respond to pharmacological therapy after 12 months should be referred to cognitive behavioural therapy or other psychological therapies [14]. Gut-directed hypnotherapy seems to have a durable efficacy in reducing IBS symptoms [95]. Additionally, there is promising evidence of the feasibility and efficacy of a mindfulness intervention for reducing IBS symptom severity and symptoms of stress, lasting 6 months after the intervention [96]. Lastly, psycho-educational group intervention appears to be a cost-effective option in modulating IBS symptoms and improving the patients' quality of life [97].

New Therapies

In patients with IBS-C, plecanatide is a promising therapeutic option. It is a peptide guanylate cyclase C receptor agonist that, in a phase 3 clinical trial, led to a significant reduction of IBS symptoms [98]. Another novel agent is tenapanor, an inhibitor of the GI sodium/hydrogen exchanger NHE3. It increases intestinal fluid volume and transit, leading to an improvement of constipation, bloating and pain in a phase 2 clinical trial [99].

In patients with IBS-D, a bile acid sequestrant, colesevelam, has been evaluated. A clinical trial demonstrated that colesevelam increases the delivery of bile acids to stool, improving stool consistency, and increases hepatic bile acid synthesis, avoiding steatorrhoea in these patients [100]. Also, Farnesoid X-activated receptor agonists can reduce hepatic bile acid. Of these, obeticholic acid was shown to decrease bile acid synthesis and improve stool form and symptoms of diarrhoea in patients with bile acid diarrhoea [101], but trials in IBS are missing. Another drug also evaluated for IBS-D is ebastine, an antagonist of histamine receptor H1 [102].

Lastly, although faecal microbiota transplantation was thought to be a potential therapeutic option, current evidence suggests there is no improvement in global IBS symptoms after faecal microbiota transplantation [103].

Conclusion

Although IBS is an old disease with a humble clinical diagnosis, and largely considered a functional bowel disorder, efforts in identifying the different pathophysiological mechanisms involved in symptom generation have allowed the development of new symptom-based and target therapies, wishfully devoided of side effects and inexpensive. Hopefully, these new insights will bring a better quality of life to the patients as they contribute to a new understanding of this syndrome.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

The 3 authors contributed equally to the planning and organization of the article. A.I.F. was in charge of bibliographic research and first draft. M.G. and F.C.-P. were contributed to the improvement of the final draft and overall critical review.

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