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REVIEW

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Chronic constipation in adults: Contemporary perspectives and clinical challenges. 2: Conservative, behavioural, medical and surgical treatment

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Abbreviations: 5-HT, 5-hydroxytryptamine; ACE, anterograde continence enema; CC, chronic constipation; CI, confidence interval; CSBM, complete spontaneous bowel movements; FC, functional constipation; FMT, fecal microbiota transplantation; GC-C, guanylate cyclase-C; hERG, human ether-a-go-go-related gene; IBAT, ileal bile acid transporter; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; MDT, multidisciplinary team; NHE3, sodium-hydrogen exchanger 3; RCT, randomized controlled trials; SGLT1, sodium-glucose linked transporter 1; SMD, standardized mean difference; SNM, sacral neuromodulation; SRMA, systematic review and meta-analysis; STARR, stapled transanal rectal resection; TAI, transanal irrigation.

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Abstract

Background: Chronic constipation is a prevalent disorder that affects quality of life of patients and consumes resources in healthcare systems worldwide. In clinical practice, it is still considered a challenge as clinicians frequently are unsure as to which treatments to use and when. Over a decade ago, a Neurogastroenterology and Motility journal supplement devoted to the investigation and management of constipation was published (*Neurogastroenterol Motil* 2009;21(Suppl 2):1). In October 2018, the 3rd London Masterclass, entitled "Contemporary management of constipation" was held. The faculty members of this symposium were invited to write two reviews to present a collective synthesis of talks presented and discussions held during this meeting. The first review addresses epidemiology, diagnosis, clinical associations, pathophysiology, and investigation.

Purpose: The present is the second of these reviews, providing contemporary perspectives and clinical challenges regarding behavioral, conservative, medical, and surgical treatments for patients presenting with constipation. It includes a management algorithm to guide clinical practice.

KEYWORDS
algorithm, constipation, IBS-C, treatment

1 | INTRODUCTION

Chronic constipation (CC) remains a clinical challenge, with outcomes to a variety of interventions (behavioral, conservative, medical, and surgical) that are frequently suboptimal. Over a decade ago, a Neurogastroenterology and Motility journal supplement devoted to the investigation and management of constipation was published, disseminating all themes covered during a preceding two-day meeting held in London [1]. In October 2018, the 3rd London Masterclass, entitled "Contemporary management of constipation" was held, again over 2 days, and again boasting a world-renowned faculty. By way of dissemination, two side-by-side review articles have been produced, which represent a collective synthesis of talks presented and discussions held during this meeting. The authors were all invited faculty members. These reviews provide not only an update on topics addressed in the previous journal supplement, but also a state-of-the-art overview of the clinical management of this prevalent and often difficult-to-treat condition. Areas for future research are additionally highlighted. The first review article addresses epidemiology, diagnosis, clinical associations, pathophysiology, and investigation. This "sister" review addresses the contemporary perspectives and clinical challenges regarding behavioral, conservative, medical, and surgical treatments in patients presenting with constipation. It includes a management algorithm to guide clinical practice. As constipation can present as functional constipation (FC) or irritable bowel syndrome with constipation (IBS-C), where available, evidence for both is presented. When not specified, data should be assumed to relate to patients with CC and not to a specific subtype.

2 | BEHAVIORAL AND CONSERVATIVE INTERVENTIONS

2.1 | Behavioral management

Behavioral modification is a commonly recommended, but inconsistently applied, first-line treatment for patients with CC. It generally includes patient education about the nature of their condition, advice regarding lifestyle modification, toilet habit training, and instruction on defecation dynamics. The extent to which behavioral modification helps individual patients is difficult to quantify, perhaps inevitably given the nature of such a composite intervention; accordingly, clinical trials of the individual components that constitute behavioral modification therapy do not exist, though they are described below to help the reader understand the patient approach required.

Establishing rapport between patient and professional is a key component to any educational initiative. Empathic reassurance is also key to helping the patient recognize that they will be supported along their journey to improve compliance.

2.2 | Lifestyle advice

The average adult in the UK eats 60% (18 g) of the recommended daily fiber intake [2]. Irregular eating habits and low-fiber diets are considered risk factors for constipation [3,4].

Patients with CC are often told to increase dietary fiber; guidelines suggest supplementation with 25 g to 30 g per day [5, 6], but it is important to understand the mechanism of action since there

are some significant side effects, which may be reduced by gradual titration. Insoluble fibers, such as wheat bran, increase small bowel water content [7], and accelerate small bowel [8] and colonic transit [9], thereby increasing stool frequency [10, 11]. Bran contains substantial amounts of fermentable fiber, which may worsen some associated symptoms in CC, including abdominal pain, flatulence, and bloating [12]. Soluble fiber, such as psyllium, increases small bowel and colonic water content, but not colonic gas, with an increase in stool bulk and frequency [13]. When compared to psyllium in a RCT, a mixture of soluble and insoluble plum fiber appeared equally effective in patients with CC [14].

Despite this, support for the use of fiber in CC is not strong. A systematic review identified only six RCTs, four of which compared soluble fiber with placebo, and two insoluble fiber [15]. None was at low risk of bias. Compared with placebo, psyllium led to significant improvements in global symptoms, abdominal pain and discomfort, and straining in one RCT [16]. In another trial, psyllium led to a significant increase in stool frequency, from 2.9 stools per week at baseline to 3.8 after treatment; there was no improvement with placebo [17]. One RCT of wheat bran reported reduced straining, but this was no different than with placebo [18], and a trial of rye bread versus a low-fiber bread demonstrated a significantly higher number of stools per day with rye bread and softer stools [19]. A meta-analysis of seven placebo-controlled trials, published in 2015, reported that the relative risk of treatment success with fiber was significantly higher (1.71; 95% CI 1.20–2.42), stool frequency was significantly increased (SMD = 0.39; 95% CI 0.03–0.76), and stool consistency improved (SMD = 0.35; 95% CI 0.04–0.65), but again noted that the quality of evidence was low [20]. Both these systematic reviews identified a need for further large placebo-controlled trials of fiber in CC. With regard to effect of fiber supplementation in differing pathophysiological subgroups, it is worth noting that a study conducted in 149 patients with CC demonstrated that 80% of patients with slow transit and 63% of patients with a disorder of defecation did not respond to dietary fiber treatment [21]. The situation is similar in IBS-C. Although there is a meta-analysis of seven placebo-controlled trials of psyllium showing a benefit in IBS [22], none have formally evaluated the efficacy of fiber in any of the IBS symptom subgroups.

The laxative effect of various fruits in CC is well recognized. In one small crossover trial comparing dried plums with psyllium in 40 patients, the number of CSBMs was significantly higher, and stool consistency scores significantly improved, with dried plums [23]. However, effects on global symptoms and straining were no different between the two treatment arms, and there was no placebo. A placebo-controlled trial of fig paste in 80 patients with CC demonstrated reduced colonic transit time, and significant improvements in abdominal discomfort and stool form [24]. Finally, an RCT of kiwifruit extract reported that defecation frequency increased significantly, and painful defecation and abdominal pain were significantly lower, compared with placebo [25]. Stool softening and increased stool frequency in a small mechanistic trial of kiwifruit were associated with an increase in T1, a validated MRI marker of stool water content [26]. Thus, it appears that fibers that alleviate constipation act on both the small and large intestine to increase stool water, accelerate transit, and facilitate defecation.

Although a diet low in fermentable carbohydrates (FODMAPs) has been shown to improve symptoms of irritable bowel syndrome in several randomized controlled trials [27, 28], there is a lack of convincing evidence on its effectiveness in IBS-C specifically, and its impact in FC has not been investigated.

In dehydrated patients, increasing fluids will improve constipation, but it is important to recognize that patients with CC are not the same as patients with acute dehydration physiologically; an adequate fluid intake (up to 2 L/day) will increase the efficacy of a high-fiber diet [29]. Overhydration will not improve constipation as there is no association between fluid intake and constipation [29] Nevertheless, it is worth mentioning that four randomized, double-blind, placebo-controlled studies have demonstrated that magnesium sulfate-rich natural mineral waters improved stool consistency and number of bowel movements in patients with CC, in association with a very good safety profile. This effect is probably the result of an osmotic mechanism of action, and efficacy was more noticeable with a higher total concentration of magnesium and sulfate [30].

There is little evidence that increasing physical activity improves constipation. Physical activity can decrease colonic transit time and reduce symptoms of constipation in the elderly, but has not been shown to have any positive effect on constipation in young adults [31, 32]. The minor influence of physical activity on bowel function is highlighted by a recent North American survey [33]. Data from nearly 10,000 individuals suggested an odds ratio of less than two for physical activity reducing constipation, and these weak associations did not persist on multivariate analysis [33].

2.3 | Bowel (habit) retraining

Patients are often advised to defecate when the urge is felt, ideally in the morning and after meals to take advantage of the gastrocolic response, when colonic motor activity is at its highest. This is based on observations of people with normal bowel habits [34]. A recent survey found that bowel retraining was a widely employed therapeutic strategy, but often without formal training of practitioners and without standardized protocols [35]. The intervention was thought to be effective, but since habit retraining is often part of biofeedback therapy (see section below), there is no evidence of the benefit of such retraining in isolation.

2.4 | Biofeedback

Biofeedback is defined as a conditioning treatment where information about a physiological process is converted by dedicated devices to a simple signal to enable the patient to learn to control the disordered defecation process [36]. Biofeedback is considered

appropriate when the voluntary control of responses can be learned with the aid of systematic information about functions not usually monitored at a conscious level [36]. Initial open-label trials suggested that biofeedback was equally effective in slow-transit constipation and in evacuation disorders [37, 38]. However, a subsequent study demonstrated that biofeedback ameliorated symptoms and accelerated bowel transit in over 70% of slow-transit constipation due to dyssynergia, while patients with an isolated impairment of gut transit did not improve [39]. Three succeeding randomized controlled trials further addressed the specific therapeutic contribution of biofeedback therapy for dyssynergia and showed that biofeedback therapy was superior to other treatments for dyssynergic defecation including sham biofeedback, placebo pills, diazepam, and osmotic laxatives [40–42]. Improvements in measures of anorectal physiology correlated with successful outcomes, and no side effects occurred during 4 years of follow-up [40–43]. In these trials, a complex protocol addressing all specific mechanisms for defecation, including posture and pushing effort, was employed [40–42]. Other studies have shown that home-based and shorter biofeedback protocols appear to be effective in improving constipation due to functional defecation disorders [44, 45]. Factors that predict successful outcome of biofeedback therapy are harder stool consistency, digital maneuvers to facilitate defecation, shorter duration of laxative use, higher resting anal sphincter pressure, and failure to expel a rectal balloon during rectal balloon expulsion test [46]. The patient's willingness to participate and the therapist's skill and motivation are also relevant to a successful outcome [46]. No randomized studies have evaluated so far whether biofeedback has different effect in FC versus IBS-C.

2.5 | Transanal irrigation

Transanal irrigation (TAI) is a minimally invasive treatment option for patients with CC refractory to conservative therapy [47]. TAI is intended to assist the evacuation of stool from the rectum and distal colon by introducing tepid water via the anus. The method has been demonstrated to be superior to standard bowel care in patients with constipation secondary to a neurological disorder [48]. In these patients, the use of TAI improves quality of life [49], reduces time spent on bowel management compared with previous methods [49, 50], and reduces episodes of fecal incontinence [50]. More than one system is available, and the technology is well tolerated by most patients [47, 51]. Furthermore, TAI has been shown to result in a lower total cost to society than standard bowel management [48]. The exact mechanism of action is unclear, although there is likely to be a degree of "flushing" and/or stimulation of peristaltic contractions [52]. Regular use of TAI can aid emptying of the bowel and help to re-establish control of bowel function by choosing the time and place of evacuation, thus re-instating a more predictable evacuation. However, to date no studies have considered the cost-effectiveness, including prospectively collected health-related quality of life data, for long-term use of TAI in patients with CC [53].

2.6 | Psychological therapies

A recent meta-analysis reported that psychological therapies are efficacious for IBS, with CBT-based interventions and gut-directed hypnotherapy having the largest evidence base and greatest efficacy long-term [54]. However, whether these are effective in the specific subtype of IBS-C or in patients with FC has not been examined.

2.7 | Areas for future research

1. Lifestyle modifications are always reported as first-line treatment in patients with constipation, but the evidence regarding their efficacy is not strong.
2. Clinical investigation of the laxative effect of magnesium sulfate-rich natural mineral waters is a very recent field of research. Additional studies comparing efficacy and safety with that of other treatments, both in FC and in IBS-C, may be of interest.
3. It would be interesting to understand whether combining viscous fiber with agents with a prokinetic effect might improve tolerability and efficacy.
4. Biofeedback is a cumbersome procedure, and dedicated machinery is needed. Whether simple bowel retraining techniques could be non-inferior to instrumented biofeedback for functional defecation disorders remains to be evaluated.
5. We still do not know whether TAI has a long-term role in patients with CC; studies comparing TAI with biofeedback are lacking.
6. Whether psychological therapies are effective in the specific subgroup of IBS-C or in FC remains to be evaluated.

3 | MANIPULATING THE MICROBIOME

3.1 | Prebiotics

Prebiotics are defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit [55]. In another context, many of these substances are termed fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs). Compared with probiotics, which introduce exogenous bacteria into the human colon, prebiotics stimulate the preferential growth of a limited number of health-promoting commensal microbiota already residing in the colon and, especially, but not exclusively, lactobacilli and bifidobacteria [56]. Examples of prebiotics include the human milk oligosaccharides in breastmilk, the inulin-type fructans, which are linked by β (2–1) bonds that limit their digestion by enzymes in the small intestine, and galactooligosaccharides. Inulin-type fructans are present in many edible cereals, fruits, and vegetables, including wheat, onion, chicory, garlic, leeks, and artichokes, with galactooligosaccharides being present in legumes [57].

In a meta-analysis of 47 randomized controlled trials (RCTs), inulin-type fructan prebiotics were shown to increase stool frequency (+0.28 stools per day, $p < 0.001$), an effect seen particularly with

short-chain fructans (+0.36 stools per day, $p < 0.001$), although the trials were in mixed populations of healthy controls or patients [58]. Fewer clinical trials have been performed investigating prebiotics specifically in CC [58, 59]; a meta-analysis of five RCTs (involving a mere 199 patients) confirmed that prebiotics resulted in a small increase in stool frequency (+1.01 stools/week, 95% CI 0.04–1.99) [60]. Subgroup analysis suggested effects for galactooligosaccharides on stool frequency, stool consistency, ease of defecation, and abdominal pain [60]. However, in meta-analysis of fiber specifically in patients with constipation, two trials of prebiotics alone and two trials of prebiotics in conjunction with other fibers failed to show an impact on dichotomous response, stool frequency, or stool consistency [58]. No studies have evaluated the role of prebiotics specifically in IBS-C patients [61].

3.2 | Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [62]. Unfortunately, the interpretation of available data on many probiotic products is confounded by variability in strain selection, dose, delivery vehicle, and limited information regarding evaluation of viability and efficacy. Indeed, many "probiotic" products do not even meet the above-stated definition in that they: (a) do not contain live organisms or have not been adequately tested to ensure their viability in the conditions or for the length of time that is claimed, and/or (b) have not been confirmed to confer a health benefit in humans.

There are several animal and human studies suggesting that probiotics may regulate gut motility and improve constipation-related outcomes via their impact on the gut microbiota and their by-products, and on the nervous and immune system [63–65]. Systematic reviews have demonstrated variable results for different probiotic strains in both children [66, 67] and adults [68]. A systematic review of the use of probiotics among the elderly with constipation showed a modest benefit for probiotics [68]; however, the authors stressed that caution needs to be exercised in the interpretation of the available data. Another systematic review and meta-analysis (SRMA) of 14 RCTs demonstrated that *Bifidobacterium lactis* species significantly increased stool frequency (+1.5 stools/week, 95% confidence interval [CI] 0.7–2.3) and improved symptoms in people with CC, whereas *Lactobacillus casei Shirota* did not; this suggested a potential beneficial effect of probiotics in constipation in favor of *B. lactis*. However, RCTs published subsequent to this systematic review have shown no improvement in constipation symptoms following the administration of specific *B. lactis* strains, including *B. lactis* HN019 that had been previously shown to improve constipation in a smaller study [69, 70]. Such conflicting data may be attributed to study methodologies. Several studies are of low-quality and suffer from limitations in design and execution, including lack of adequate statistical power, use of inconsistent diagnostic criteria of CC, variable treatment duration, lack of consistency in outcomes, lack of validated assessment techniques, and selective outcome reporting. Similarly, SRMAs are burdened by high heterogeneity and risk of bias, rendering their interpretation and generalization difficult.

Therefore, the use of probiotics for the treatment of constipation should continue to be considered as investigational, and further high-quality RCTs are needed to confer confident conclusions regarding their effectiveness. Data collected in IBS patients do not allow us to conclude whether there is a particular IBS subtype that is more likely to benefit [61].

3.3 | Synbiotics

A synbiotic, the combined use of a probiotic and a prebiotic, aims to increase the survival and activity of proven probiotics *in vivo*, as well as stimulating indigenous bifidobacteria and lactobacilli. In an uncontrolled pilot study, Valerio and colleagues fed artichokes (containing inulin-type fructans) and *Lactobacillus paracasei* to healthy volunteers and noted a reduction in abdominal distension and the sensation of incomplete evacuation [69]. A more recent meta-analysis of eight RCTs involving a total of 825 people with CC concluded that synbiotics resulted in a small increase in stool frequency (+1.15 stools/week, 95% CI 0.58–1.71), improved stool consistency (standardized mean difference (SMD) 0.63, 95% CI 0.33–0.92), reduced whole gut transit time (−13.5 h, 95% CI −26.6 to −0.5), and also reduced straining and bloating [59]. However, it should be noted that only one trial was deemed to be at low risk of bias across all domains with a notable lack of intention-to-treat analysis. The interpretation of synbiotic RCTs is also hampered by the impossibility of defining the active agent(s)—prebiotic, probiotic, or both. There are insufficient data on the use of synbiotics in IBS-C [61, 71].

3.4 | Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) has also been investigated as a potential management strategy for CC. A RCT of 60 individuals with slow-transit constipation showed that a significantly higher proportion had 3 or more complete spontaneous bowel movements (CSBMs) per week following FMT compared with standard treatment (37% vs. 13%; $p = 0.04$), with improvements in stool consistency and gut transit time also demonstrated [72]. Additionally, there is emerging evidence to support a role for FMT in the management of IBS, including IBS-C [73]. Nevertheless, the use of FMT in CC or IBS-C is still investigational.

3.5 | Areas for future research

1. Characterization of the colonic microbiome in FC and IBS-C with control for confounding factors.

2. Does the baseline microbiome in a constipated individual predict response to various interventions?
3. High-quality studies of interventions that modulate the microbiome in FC and IBS-C.

4 | MEDICAL THERAPIES

4.1 | Laxatives

There are a range of laxatives available, both over the counter and prescribed. These are classified according to their primary mechanism of action: bulking agents (see lifestyle advice); stool softeners; stimulants; and osmotic agents. Nevertheless, despite being the mainstay of management of CC, high-quality clinical trials of laxatives are scarce. A recent meta-analysis [74] identified only four studies of laxatives of sufficient rigor and duration to be assessed.

A brief discussion on the challenges associated with laxative use in the setting of CC is worth bearing in mind. While laxatives can be very effective in the acute setting, long-term use can be associated with the development of tolerance and reduced response [75]. Poor adherence is often seen, and this is often related to the unpredictability of onset and offset of effect of these agents, which all depend on their contact time with the mucosa [76]. Development of side effects is also a frequent issue for patients; typically, stool looseness, urgency, and abdominal cramps are underlying symptoms that may be exacerbated by laxative use [76]. A final complication for the prescriber is that the clinical trials of laxatives are often of short duration and with endpoints that are not clinically meaningful for patients, such as bowel movement frequency and stool consistency [76]. Qualitative analyses have suggested that quality of life, predictability, and time taken in bowel management are of greater impact on patients' well-being [77].

Osmotic laxatives are cited in guidelines as the first-choice maintenance therapy for CC [75, 78]. Two of the four placebo-controlled studies identified in the above review used PEG with electrolytes as the osmotic agent [6] and demonstrated good efficacy for increasing stool frequency and good perceived safety. Accumulation of glycol derivatives was raised as a possibility in pediatric practice, but this has not been demonstrated when formally investigated [79]. When compared to other osmotic agents (specifically, lactulose), a meta-analysis demonstrated that PEG was superior to lactulose in terms of improving stool frequency, stool consistency, relief of abdominal pain, and reducing use of other laxatives [80]. A less-used osmotic agent is magnesium hydroxide; clinical trials have shown no difference between outcomes with PEG or such magnesium salts [81, 82]. In IBS-C, PEG has been found to improve constipation but not pain [83].

If symptoms persist, stimulant laxatives such as senna, bisacodyl, or sodium picosulfate are recommended in clinical guidelines [75, 78]. Use of the latter two is supported by placebo-controlled trial evidence [6]. They are both prodrugs, which need to be metabolized at the mucosal level to the active moiety, which acts to stimulate gut peristalsis. Both drugs showed significant advantage over placebo in both bowel symptoms and quality-of-life measures. However, side effects of abdominal pain and diarrhea were reported, and the number needed to treat, 3, was similar to the number needed to harm [6]. No large, randomized placebo-controlled studies have tested the efficacy of these laxatives in IBS-C.

The stool softener class of laxatives (docusate, liquid paraffin) has been compared with osmotic agents and found to be slightly less effective than the osmotic agents, and—especially with liquid paraffin—be associated with more adverse events [84, 85]. As such, they are more often used as adjuvant drugs when patients report hard stools despite use of other agents [84, 85]. Again, no large, randomized placebo-controlled studies have tested the efficacy of these laxatives either in FC or in IBS-C. Even though enemas are frequently used in patients with constipation, there are no controlled studies of their efficacy or safety. In contrast, three short-term (7–21 days) controlled studies have reported the benefit of potassium tartrate and sodium bicarbonate suppositories in improving "dyschezia" [86–88].

Clinical trials tend to be short for what is often a lifelong condition. A global survey identified that approximately half of all constipated patients remain dissatisfied with their current laxatives, related to poor efficacy and adverse effects [89]. This highlights the importance of tailoring laxatives to symptom response and monitoring the patient to confirm adequate response [90].

4.2 | Prokinetics

Serotonin (5-hydroxytryptamine; 5-HT) receptors are abundant in the gut and involved in both motility and sensation; of these, the 5-HT_4 receptor has been most closely associated with the promotion of intestinal motility and transit and a number of agonists have been developed. The first of these, cisapride, an upper gut prokinetic, was shown to have some efficacy in constipation [91], but lack of selectivity and interactions with the human ether-a-go-go-related gene (hERG) channel led to the worldwide withdrawal of the drug because of the occurrence of hERG channel-mediated cardiac arrhythmias [92]. Subsequently, tegaserod was developed to treat CC [93] and IBS-C [94] and was granted approval for these indications in some countries. Ultimately, it was withdrawn because of a small excess of cardiovascular ischemic events, the pathogenesis of which remains unclear [92]. Recently, tegaserod was reintroduced in the United States for the treatment of women with IBS-C.

In contrast to cisapride and tegaserod, prucalopride is a high-affinity, highly selective 5-HT_4 agonist with low affinity for the hERG-K^+ cardiac channels [95]. This 5-HT_4 receptor affinity and sensitivity confers greater efficacy for prucalopride and explains why it has not been shown to be arrhythmogenic [95]. Prucalopride promotes colonic motility and transit and has been studied in seven large (≥300 patients in each), multicenter, double-blind, placebo-controlled trials; all but one showed that

prucalopride significantly improved bowel function, reduced constipation-related symptoms, and improved patient satisfaction and constipation-related quality of life [96]. These studies enrolled patients not responsive to laxatives, with a therapeutic gain over placebo being around 20%. The most common adverse effects were headache (25%–30% prucalopride; 12%–17% placebo), nausea (12%–24%; 8%–14%), abdominal pain or cramps (16%–23%; 11%–19%), and diarrhea (12%–19%; 3%–5%) [90], all of which tend to occur early after treatment initiation. Prucalopride is currently approved in a number of countries for treatment of CC in women who have failed laxative treatment [96]. The current recommended dose is 2 mg once daily. It has also been used safely in the elderly where a lower dose of 1 mg per day is recommended. No studies have tested the efficacy and safety of prucalopride in IBS-C.

Velusetrag is another selective 5-HT_4 agonist that stimulates colonic motility and transit, and in a 4-week phase II dose-ranging study has been shown to increase spontaneous bowel movements in CC [97]. Naronapride has also been studied in a single randomized controlled phase II trial and shown to be effective in CC [98]; these results have been published in abstract form only. Side effects were generally minor, with headache being the most frequent problem [95].

4.3 | Prosecretory agents

The first of these agents was lubiprostone, a bicyclic fatty acid that activates a specific chloride channel (CLC-2) located on the apical membrane of the enterocyte. Activation leads to an indirect activation of Na^+-K^+-Cl^- cotransport, increasing water secretion into the intestinal lumen. Clinical studies on intestinal and colonic transit, and intestinal sensory function, have not been consistent [99]. However, phase III RCTs have demonstrated its efficacy in CC [99]. Used for up to 52 weeks, lubiprostone has demonstrated a good safety profile overall [100]. Nevertheless, given that lubiprostone is not systemically absorbed, it was surprising that nausea was the most common adverse effect followed by diarrhea [100]. The recommended dose for CC is 24 μg twice daily. Similar results have been obtained in IBS-C patients, and in this case, the recommended dosage is 8 μg twice daily [75]. At present, lubiprostone is only available in the United States, Canada, Switzerland, India, and Japan.

The other prosecretory agents are guanylate cyclase-C (GC-C) agonists. Linaclotide, a 14-amino acid peptide, and plecanatide (structurally highly similar to the physiological agonists of GC-C receptors, uroguanylin and guanylin) bind to and activate guanylate cyclase-C on the luminal surface of the intestinal epithelium. Activation of GC-C generates cyclic guanosine monophosphate, which, in turn, activates the cystic fibrosis transmembrane conductance regulator chloride channel, increasing the secretion of Cl- and HCO3 and the rate of plasma-lumen water flux; the net effect being an augmentation of stool volume [98].

Linaclotide has been shown to accelerate intestinal transit in man and reduce visceral afferent traffic in laboratory animals [101]. In phase III studies, linaclotide has been shown to be effective in CC and in IBS-C [75, 101]. Reflecting its negligible systemic absorption, the main adverse event experienced in these studies has been diarrhea [101]. The recommended dose for CC and IBS-C is respectively 145 and 290 μg once daily, but only the second dosage is available in Europe [75].

Plecanatide has also been shown to be effective in a phase III study in CC and in IBS-C [75, 102, 103]. Similar to linaclotide, the main adverse effect was diarrhea [102]. The recommended dose is 3 mg daily, but the drug is not available in Europe.

4.4 | Future therapies

It has been known for decades that deconjugated bile salts increase colonic motility and secretion and, if present in excessive amounts, lead to diarrhea [104]. With the description of the ileal bile acid transporter (IBAT), inhibitors of this molecule have been developed and one, elobixibat, has been subjected to phase II clinical trials in CC with encouraging results [104, 105]. Not only did this agent result in relief of constipation but also one of its "side effects" included a reduction in low-density lipoprotein cholesterol. At higher doses, abdominal cramping and diarrhea were, as would be predicted, problematic [104]. Akin to the prosecretory agents, systemic absorption is minimal. In a further randomized, double-blind, placebo-controlled 2-week phase III study in Japan, elobixibat was shown to be effective; a 52-week open-label extension found it to be well tolerated with diarrhea and abdominal pain being the most common side effects [105]. No studies have been conducted in IBS-C.

Tenapanor, a small molecule with minimal systemic availability, is a first-in-class sodium-hydrogen exchanger 3 (NHE3) inhibitor that acts in the gut to increase luminal sodium and water, and in a phase 2 study in patients with IBS-C (but not, as yet, in CC) demonstrated efficacy [106, 107]. Mizagliflozin is a sodium-glucose–linked transporter 1 (SGLT1) inhibitor that increases luminal glucose and water. This has also demonstrated efficacy in CC in a phase II study; diarrhea and abdominal distension were the most notable adverse effects [108].

4.5 | Areas for future research

1. While there are now a number of prescription drug options in FC and IBS-C, their relative efficacy is unknown and comparative studies between these medications and against more traditional and cheaper approaches (laxatives, fibers, etc.) are needed.
2. It is still not clear whether stimulant laxatives and prokinetics are equally effective in FC and IBS-C.
3. "Real-life" studies combining therapies (whether they are pharmacological, dietary, microbial, or behavioral) are needed.
4. Constipation sufferers frequently complain of developing tolerance to various medications—the true nature of this phenomenon and its management deserve further investigation.

5 | SURGICAL OPTIONS

The role of surgery is governed by establishing the dominant pathophysiology in terms of symptom generation. Surgery has a role in patients with refractory constipation associated with colonic inertia, when this is not part of a panenteric motility disorder. Surgery also has a role in the correction of pelvic floor prolapse where it is deemed to be causing symptoms. However, given the risk of potential harm and irreversibility of most procedures, surgery should only be considered when all conservative measures have failed [109].

5.1 | Colonic resection

Colectomy should only be considered for patients with refractory symptoms, proven generalized slow colonic transit, and an absence of a list of relative contraindications (see below). However, even in this well-selected group, before considering colectomy, a safe and potentially reversible option is a loop ileostomy. While little published evidence supports this approach, it is widely practiced due to concerns of potential for harm if the patient progresses directly to colectomy [109]. In addition, the procedure is potentially reversible if significant upper GI symptoms (suggestive of upper GI dysmotility) or significant abdominal pain and bloating (suggesting a diagnosis of IBS) persist or worsen (as they often do after colectomy). If a stoma provides relief of symptoms but there is a subsequent wish for restoration of bowel continuity, colectomy and ileorectal anastomosis is the procedure with the greatest supporting evidence (observational only, but >50 published series). Segmental colonic resection may be considered if there are concerns about diarrhea and incontinence; however, this will involve a trade-off with a higher risk of ongoing constipation [110].

Colonic resection is reported to improve constipation and quality of life in 50%–100% of patients [111], but may not improve other symptoms such as abdominal pain and bloating. However, in the majority of studies, outcomes have not been evaluated using validated questionnaires [111]. Complications occurred in approximately 24% of patients. Recurrent episodes of small bowel obstruction occurred in about 15% of patients in the long term, with significant burden of rehospitalization and frequent recourse to further surgery [111]. Patients may also experience diarrhea, urgency, and potentially fecal incontinence. In attempt to reduce postoperative diarrhea, total colectomy with an antiperistaltic cecorectal anastomosis has been proposed [112]. A recent prospective observational study of 42 patients found improved outcomes by shortening the length of the preserved ascending colon above the ileocecal junction [112].

Relative contraindications to colectomy include the following: major upper GI symptoms (proven dysmotility is an absolute contraindication) [111]; significant abdominal pain and bloating; and poor anal sphincter function. Such findings push more strongly toward ileostomy rather than resection. An untreated concomitant evacuation disorder [111] is more controversial, although there is agreement that management should initially focus on treating this rather than by resecting the colon.

5.2 | Sacral neuromodulation

Sacral neuromodulation (SNM) is an established treatment for patients with urinary retention, urinary incontinence, and fecal incontinence. Studies in the urological field have observed that some patients report improved bowel function. A prospective, multicenter study showed that patients with CC can benefit from SNM with increased episodes of successful defecation, reduction in sensation of incomplete evacuation, reduction in abdominal pain and bloating, and sustained improvement in patient visual analog scores being achieved in a cohort of patients with mixed pathophysiologies, that is, slow transit and/or evacuation disorders [113].

Two subsequent randomized, double-blinded, crossover studies have shown no significant difference between sham and active stimulation in patients with slow-transit constipation [114, 115]. Nevertheless, SNM has been reported to improve rectal sensitivity to balloon distension in patients with CC and rectal hyposensitivity [116], indicating that the clinical effects seen in some patients may thus be related to modulation of afferent pathways. Further studies are required to determine whether it is this patient group that is most likely to respond to therapy.

5.3 | Antegrade continence enema (ACE)

ACEs can be used to achieve antegrade colonic irrigation through either a tube caecostomy or appendicostomy (Malone procedure) [117]. Good clinical outcomes have been reported in children with spina bifida or slow-transit constipation [118]; however, adults and patients with colonic dysmotility have lower published success rates [118]. Stoma stenosis is common in adults and often requires surgical revision [118]. In patients with refractory slow-transit constipation, an (ACE) conduit is an alternative to loop ileostomy but best considered in non-obese patients with their appendix in situ.

5.4 | Stoma

Stoma creation for intractable constipation is generally considered a last resort. Sigmoid colostomy can be used when outlet obstruction cannot otherwise be managed; however, persisting pelvic discomfort coupled with diversion proctitis can give poor outcomes [119]. A loop ileostomy may be used as a temporary or long-term solution in patients with slow transit (see above). Patients should be aware that stoma complications are common and reintervention may be necessary; however, up to 70% of patients are satisfied with the intervention, despite a 20% reoperation rate [120].

5.5 | Rectal suspension

Rectopexy with or without mesh support of the middle compartment of the pelvis has become the preferred approach in Europe in treating rectal intussusception [121, 122]. A SRMA of 18 observational studies provided data on outcomes of laparoscopic rectopexy in 1238 patients (mostly high-grade rectal intussusception) with median follow-up of 25 months [123]. Improvement in constipation was achieved in 86% of patients [123]. Data on adverse outcomes were inconsistently reported with morbidity rates of 5%–15% and anatomical recurrence in about 2%–7% of the patients [123]. Further, 0.5% of patients experienced late complications due to mesh infection/erosion [123]. Most surgical experts would only consider this intervention in high-grade intussusception, that is, at least Oxford grade III (apex of the prolapse to the top of the anal canal). In some countries (e.g., UK), laparoscopic ventral mesh rectopexy requires enhanced consent (for mesh risk) and a mandatory registration on a national database [124].

5.6 | Rectal excisional procedures

Transanal resection of intussuscepting rectal wall with or without rectocele resection may be achieved by the STARR (stapled transanal rectal resection) procedures. A recent SRMA identified 47 studies (3 poor-quality RCTs and observational data) of outcomes in 8340 patients [125]. Mean follow-up was 1.9 years. Overall morbidity rate was 17%, with lower rates observed after the Trans-STARR procedure (9%). No mortality was reported, and while inconsistently reported, good or satisfactory outcome occurred in 73%–80% of patients, with a reduction of 53–91% in obstructive defecation score. The most common long-term adverse outcome was fecal urgency, occurring in up to 10% of patients, and long-term pain in about 2% of patients. These outcomes have reduced its former popularity. Recurrent prolapse occurred in 4.3% of patients.

5.7 | Recto-vaginal reinforcement procedures

These procedures are normally considered in patients with rectocele. A recent SRMA identified 43 articles (three RCTs and 40 observational studies) on outcomes of reinforcement of the rectal vaginal septum in 3346 patients [126]. Outcomes did not significantly vary between surgical approaches (vaginal, perineal, and anal). Seventy-eight percent of patients reported a satisfactory or good outcome, with 30%–50% experiencing reduced symptoms of straining, incomplete emptying, or reduced vaginal digitation. Complications were reported after 7%–17% of procedures. Postoperative bleeding was uncommon (0%–4%) as was hematoma or sepsis (0%–2%). Fistulation did not occur in most studies. Two procedure-related deaths were observed. Overall, 17% of patients developed anatomical recurrence. The use of mesh did not confer an outcome advantage and in vaginal repair was deleterious. There was insufficient evidence to prefer one type of procedure over another or relate outcome to size of rectocele.

5.8 | Areas for future research

1. The evidence base relating to surgical options for those with refractory constipation remains slim and suffers from many limitations. High-quality prospective studies are needed:

    a. To guide optimal patient selection for colectomy or pelvic floor/anorectal interventions
    b. To compare outcomes from various approaches to the management of the patient with dyssynergic defecation with or without rectal prolapse
    c. To define the role of surgical expertise/experience in outcomes
    d. To assess the additive value of a multidisciplinary approach to the patient with refractory constipation

6 | THE MANAGEMENT ALGORITHM

Figure 1 presents a pragmatic algorithm designed to guide the clinician in their practice. The management of patients with CC starts from a correct diagnosis. First step is the exclusion of organic disease and of relevant secondary causes, including opioid use (opioid-induced constipation is not included in this algorithm) as reported in Panel A.

The information collected during clinical evaluation then guides the selection of appropriate medications, with preference ideally given to those with proven efficacy in placebo-controlled clinical trials (Panel B). In this respect, it is important to consider the spectrum of symptom presentation and review the response to each treatment. It is indeed known that in IBS-C, some medications (e.g., PEG) can lead to improvement in constipation without improving abdominal pain [83]. In some countries, it is recommended to review treatment response after 4–8 weeks when using more expensive drugs such as prucalopride and linaclotide [127]. If there is no response to a single agent, combinations can be considered either before or after further investigations. Medications with complementary mechanisms of action (ie, osmotic laxative or secretagogue with a stimulant laxative or prokinetic) can be combined.

In the absence of an internationally recognized definition of refractory CC, in a recent publication, some of the authors of the present review suggested a practical definition [53]: “an inadequate improvement in constipation symptoms, as evaluated by an objective scale, despite adequate therapy (i.e., pharmacological or behavioral), for a minimum duration of 4 weeks for each drug, and 3 months for pelvic floor biofeedback therapy.” The 4-week criterion was chosen in recognition that most patients who respond to medications for CC generally do so within 4 weeks, and this is also reflected in NICE guidance [53]. In that publication, the use of a yet-to-be validated clinical decision-making tool was proposed [53]. However, the result of a recent study suggests that the modified version of the Patient Assessment of Constipation-Symptom could better capture the complex and multifactorial patient's response to treatment

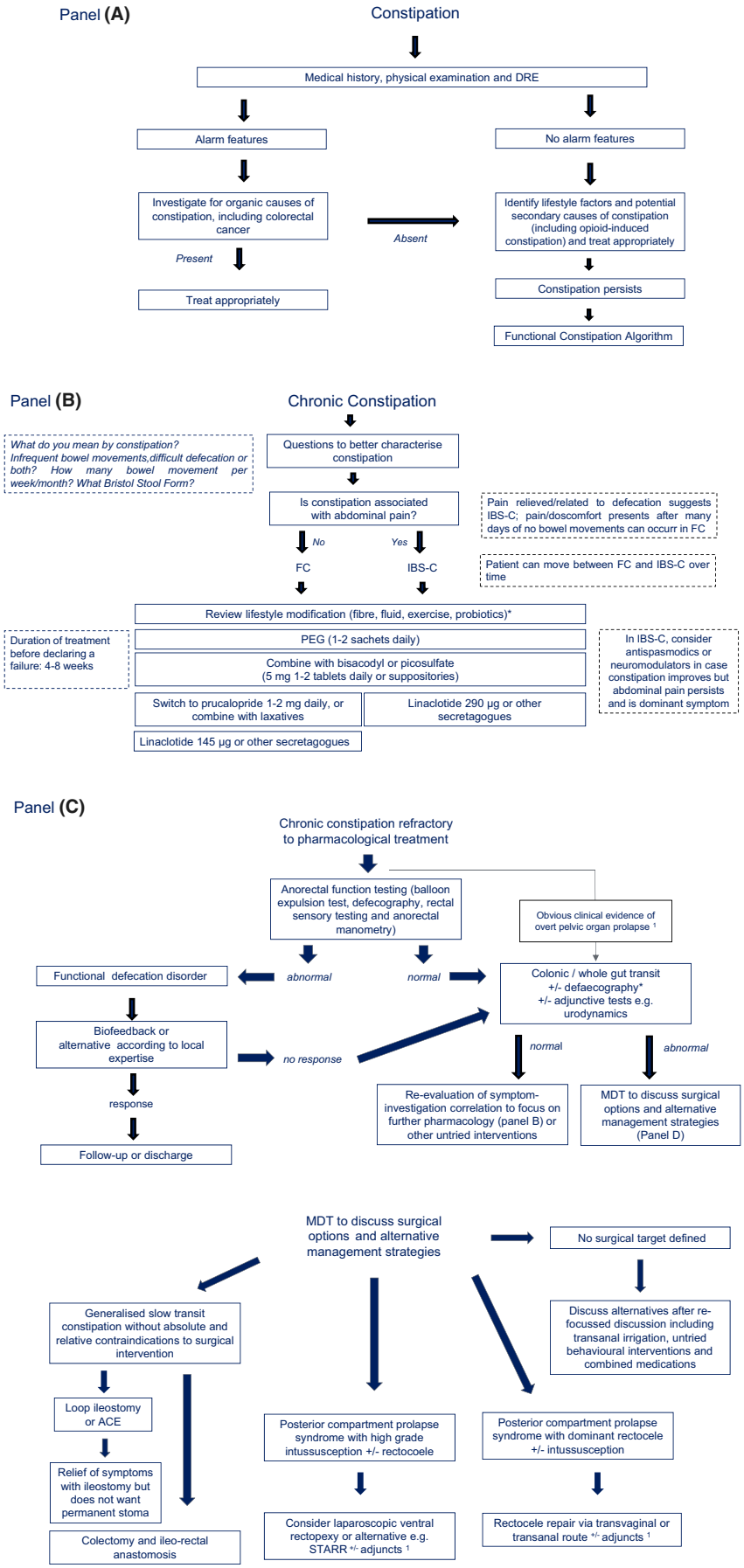

FIGURE 1 Algorithm for the management of patients with constipation. Panel A, evaluation to confirm the presence of a functional bowel disorder. Panel B, pharmacological and medical options. Panel C, management of patients not responding to pharmacological treatment. Panel D, when to consider surgical options

[128]. It should be remembered that in patients with CC, symptom improvement does not always equate to satisfaction with treatment [128, 129].

The next step (Panel C) in patients with persistent symptoms is to perform anorectal function testing, which may include defecography (a test that enables the dynamic evaluation of the process of defecation and of the possible presence of anatomical alterations) [130], the balloon expulsion test (a test that has been demonstrated to be predictive of response to biofeedback) [46], sensory response to rectal distension, and manometry to evaluate anorectal coordination and anal motor function. If these tests indicate the presence of a functional defecation disorder, the patient should be referred for biofeedback. A functional defecation disorder may reflect problems of coordination (addressed predominantly by classical biofeedback), muscle weakness (addressed mainly by pelvic floor muscle therapy), and rectal sensation (addressed in some centers by sensory forms of biofeedback) or combinations thereof. Although unsupported by RCT evidence, transanal irrigation is a further option [47]. The evaluation of anorectal function can also be considered earlier in the pathway in centers that have easy access to these investigations and biofeedback. Evaluation of colonic/whole gut transit can be used to further define underlying pathophysiology.

However, all investigations have some limitations as recently pointed out [131, 132]. It is therefore important that the results of diagnostic testing are considered in the context of the "holistic" clinical evaluation of the individual patient. It should also be remembered that psychological distress is common in patients with CC and, in particular, among patients with evacuation disorders [133].

If all test results are normal, medical therapy should be re-evaluated and alternative approaches to management may be required. If abnormal, further decisions on possible management options, including surgery, should be taken in the context of a multidisciplinary team (MDT) (Panel D). The composition of such MDT meetings varies internationally but should clearly include colorectal surgeon(s) with appropriate expertise. This approach will only be relevant in a minority of patients with constipation.

For patients considered for surgical intervention, all information from comprehensive assessment (symptoms, physical examination, and investigations) are synthesized, previous treatments reviewed, and all other factors that might influence surgical decision making considered. Multidisciplinary decision making is influenced by the composition of the team and by accuracy and thoroughness of presented information. While it certainly offers some reassurance of a balanced decision, whether this improves clinical outcome remains to be proven.

The MDT must distinguish patients with a modifiable surgical target from those in whom there is no detectable or surgically correctable anomaly, and those unsuitable for intervention for other reasons (e.g., high surgical risk). The presence of substantial underlying psychological or behavioral issues should also be assessed systematically, as these factors are a relative contraindication to surgery. In practice, two main patient groups may be considered for surgical intervention based on target pathophysiology, those with slow-transit constipation unresponsive to non-surgical interventions and those with significant posterior compartment prolapse.

6.1 | Areas for future research

1. Critically evaluate the feasibility of this algorithm in everyday clinical practice
2. Measure its implementation and resultant impact on patient outcomes.

7 | CONCLUSIONS

The literature accumulated over the last 10 years on CC management has certainly added important evidence to guide clinical practice. Biofeedback has been recognized as valuable treatment option for functional defecation disorders, some pharmacological treatments have been demonstrated to be more effective than placebo, and the surgical literature has been extensively reviewed to identify gaps in the current knowledge. In contrast, there are some areas where systematic review of the literature still reveals uncertainties, as reported in the areas for future research paragraphs.

CONFLICT OF INTEREST

MC acted as consultant for Allergan, Arena, Kyowa Kirin, and Sanofi. AE has served on advisory boards in the last 3 years for Kyowa Kirin, Shionogi, Takeda. MH has received research funding from MacGregor Healthcare Ltd. CK is a paid consultant and speaker for Medtronic Inc. He has consulted in the last 3 years for Coloplast, Enteromed, and Alimentary Health. He has received funding for research activities from Saluda medical, Cook Medical, Exero Medical, and Takeda. He is a member of committees that benefit from industry sponsorship including the Rome Foundation and The GI physiology International Working Group. GC acted as Consulter/Speaker for Kyowa Kirin, Shionogi, and is member of the Anorectal Committee of the Rome Foundation. MRF has acted as a paid consultant and has been paid for speaking and reimbursed for attending a symposiums by Medtronic, Reckitt Benckiser, and Shire Pharmaceuticals. MRF has received funding of research and support of staff by Medtronic, Mui Scientific, Reckitt Benckiser, and Nestle International. MRF has organized educational activities that have been supported by Medtronic, Sandhill Scientific Instruments, and Medical Measurement Systems. MS received unrestricted research grants from Danone Nutricia Research, Glycom, and Ferring Pharmaceuticals; acted as Consultant/Advisory Board member for Danone Nutricia Research, Nestlé, Menarini, Biocodex, Genetic Analysis AS, Glycom, Arena, and Shire; and was part of the speakers' bureau of Tillotts, Menarini, Kyowa Kirin, Takeda, Shire, Biocodex, Alimentary Health, AlfaSigma, and Falk Foundation. WW is a former member of the Rome Foundation. He oversaw development of the Rome IV Diagnostic Questionnaire and received a Rome Foundation Grant to validate the diagnostic criteria and design survey questions; these were adapted for the global survey. WW is also the recipient of a National Institute of Health Grant to compare treatments for severe forms of fecal incontinence (U01 DK115575). ED has received an education grant from Alpro, research funding from the British Dietetic Association, Almond Board

of California, International Nut and Dried Fruit Council, and Nestec Ltd and has served as a consultant for Puratos. EMMQ served as a consultant to 4D Pharma, Alimentary Health, Allergan, Biocodex, Ironwood, Menarini, Pharmasierra, Salix, and Vibrant; received research support from: 4D Pharma, Takeda, Vibrant, Zealand; and holds equity in Alimentary Health. RS has received research grants from Sanofi-Aventis and Zespri International and speaker fees from Alfa Wassermann. KW has received research funding from government bodies including National Institute of Health Research and Medical Research Council; from charities including Crohn's and Colitis UK, for Crohn's, the Leona M. and Harry B. Helmsley Charitable Trust, and Kenneth Rainin Foundation; and from industrial sources including Almond Board of California, Clasado Biosciences, Danone, and the International Dried Fruit and Nut Council. KW is the coinventor of a mobile application to support people following dietary restrictions (FoodMaestro). SMS has received honoraria for teaching for Laborie. The remaining authors have not conflict of interest.

AUTHOR CONTRIBUTIONS

MC and SMS wrote Introduction section. AE, GC, WW, and MH wrote Behavioral and conservative interventions section. ED, KW, and EMMQ wrote Manipulating the microbiome section. AE, AF, RS, EMMQ, MS, and MC wrote Medical therapies section. TD, PG, UG, PRO, and ABW wrote Surgical options section. MC, MF, CK, SB, SMS, MS, RS, and EMMQ wrote The management algorithm section. MC revised the initial manuscript. All authors performed the literature search, wrote Areas for future research section, critically revised subsequent versions of the manuscript, and approved the final version of the manuscript.

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