EUROPEAN SOCIETY OF NEUROGASTROENTEROLOGY AND MOTILITY GUIDELINES ON FUNCTIONAL CONSTIPATION IN ADULTS

Short title: Guidelines on functional constipation.

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15. A complete list of the Functional Constipation Guidelines Working Group appears on page 82

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KEY POINTS

- Chronic constipation is a common disorder with a reported prevalence ranging from 3-27% in the general population. Multiple management strategies, including diagnostic tests, empiric treatments and specific treatments are known to be used.
- The aim of the present manuscript was to create European guidelines for the clinical management of constipation, developed by experts in different fields related to constipation across Europe.
- After a full review of the literature, relevant statements, final recommendations and management algorithms were produced using a Delphi consensus process.

ABSTRACT

INTRODUCTION: Chronic constipation is a common disorder with a reported prevalence ranging from 3-27% in the general population. Several management strategies, including diagnostic tests, empiric treatments and specific treatments have been developed. Our aim was to develop European guidelines for the clinical management of constipation.

DESIGN: After a thorough review of the literature by experts in relevant fields, including gastroenterologists, surgeons, general practitioners, radiologists and experts in gastrointestinal motility testing from various European countries, a Delphi consensus process was used to produce statements and practical algorithms for the management of chronic constipation.

KEY RESULTS: Seventy-three final statements were agreed upon after the Delphi process. The level of evidence for most statements was low or very low. A high level of evidence was agreed only for anorectal manometry as a comprehensive evaluation of anorectal function and for treatment with osmotic laxatives, especially polyethylene glycol, the prokinetic drug prucalopride, secretagogues such as linaclotide and lubiprostone and PAMORAs for the treatment of opioid-induced constipation. However, the level of agreement between the authors was good for most statements (80% or more of the authors). The greatest disagreement was related to the surgical management of constipation.

CONCLUSIONS & INFERENCES: European guidelines on chronic constipation, with recommendations and algorithms, were developed by experts. Despite the high level of agreement between the different experts, the level of scientific evidence for most recommendations was low, highlighting the need for future research to increase the evidence and improve treatment outcomes in these patients.

92 KEY WORDS: Chronic constipation. Guidelines. Delphi process. Management of
93 constipation.
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INTRODUCTION

Chronic constipation is a common disorder with a reported prevalence ranging from 3-27% in the general population.[1, 2] Its prevalence increases with age,[3, 4] and consequently is expected to rise over the next few years,[5] in parallel with the predicted increase in longevity of the European population. Constipation is a symptom that may have diverse aetiologies, and for this reason, several diagnostic approaches and treatment options are available, ranging from simple lifestyle changes and general measures to sophisticated pharmacological treatments and surgical interventions.[6] In an attempt to unify the health care received by the population across Europe, the European Society of Neurogastroenterology and Motility (ESNM) decided to develop European guidelines to help physicians to take the best decisions to improve the quality of health in patients suffering from common functional and motor disorders. In this document, we present the ESNM guidelines for chronic constipation, which are intended to be a useful tool for the management of this condition in the general population in Europe. In order to produce comprehensive guidelines addressing the different aspects related with constipation, experts from European countries working in related fields developed relevant statements after a thorough review of the available literature, and final recommendations and management algorithms were produced following a Delphi consensus process.

METHODS

Participants

A chair (Jordi Serra) and co-chair (Daniel Pohl) were commissioned by the ESNM Steering Committee to develop the guidelines. A panel of 12 experts from different European countries, constituted by gastroenterologists, surgeons, general practitioners, radiologists and experts in gastrointestinal (GI) motility testing, was invited by the chairs to participate in the development of the guidelines. Each expert was assigned to develop a specific area of the document (see below), and to establish a team with one or two co-workers to complete the assigned task. The final ESNM guidelines working group was composed of 13 experts and 9 co-authors.

The Delphi consensus

Each expert and co-worker conducted a thorough review of the literature in their specific field of expertise. The following areas were covered by the different subgroups: 1. Definition. 2. Pathophysiology: causes and predisposing factors. 3. Diagnostic approach: clinical approach and basic investigations; functional studies; radiological studies. 4. Treatment: Lifestyle and general measures; bulking agents and osmotic laxatives; stimulant laxatives; prokinetics and secretagogues; biofeedback therapy; alternative treatments; probiotics; and surgical treatment. Based on the results of the search, several statements with specific recommendations were produced by each expert and rated according to the level of evidence. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to rate the level of evidence and recommendation. In parallel, an algorithm for the management of constipation was developed by the chair. When all the statements had been received from all the authors, a Delphi consensus process was initiated by sending all the statements and algorithms to all the experts for anonymous voting, with progressive refinement and re-voting of the re-formulated statements.

Finally, each expert wrote the final statements corresponding to the assigned section, including comments, unmet needs and the literature supporting the evidence of the recommendations, and three algorithms for the management of constipation were produced. The level of agreement between authors for each statement is shown in Figure 1.

RESULTS

DEFINITION

Statement 1: Constipation is defined as difficult, unsatisfactory or infrequent defecation.

a. Level of evidence: Not applicable
b. Recommendation: Not applicable
c. Level of agreement: 100% (**Figure 1**).

This definition is consistent with the definitions of chronic constipation used in recent guidelines and in the Rome consensus for functional constipation (FC).[7, 8] The term unsatisfactory evacuation has been chosen as a general and comprehensive term that includes, among others, feeling of incomplete evacuation. The term difficult evacuation includes straining, sensation of anorectal obstruction and need for manual manoeuvres to facilitate evacuation.

PATHOPHYSIOLOGY

CAUSES AND PREDISPOSING FACTORS

Statement 2: The prevalence of constipation is higher in women

a. Level of evidence: High
b. Recommendation: Not applicable
c. Level of agreement: 100%

Current evidence and literature:

The available evidence points towards a clear sex preponderance in women. Most of the studies in a systematic review[9] reported a predominance of females in the prevalence of constipation. The mean female/male ratio was 1.78 (median 1.58), but

differed according to the definition of constipation (1.7 for Rome I, 1.8 for Rome II and 2.3 for self-reporting of constipation).

Female predominance was also shown in a recent epidemiological study in FC patients based on Rome III Criteria, with a higher prevalence in female (17.4%) compared to male students (12.5%).[10] In univariate logistic regression analysis, FC was significantly associated with sex (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.06-2.06). In a different population of 7251 constipated patients and 7103 controls, Talley et al.[3] showed an OR of 1.62 (95% CI 1.49-1.76) in females. This predominance of females has been attributed to hormonal factors, such as a higher risk of constipation during the luteal phase of the menstrual cycle and the effect of progesterone, most notably in pregnancy, as well as damage to the pelvic floor muscles that may occur in women during childbirth or gynaecological surgery. This effect of additional progesterone on colonic transit could also be confirmed in a prospective study by Gonenne et al.[11] in 49 postmenopausal women. Additionally, premenopausal women (age 25-49) were shown to have longer transit times than older women (64.0 vs 59.5 hours; difference 4.6 hours, 95% CI 1.1-8.1 hours)[12]. This leads to less pronounced gender differences in constipation prevalence in the older population.

Future research/unmet needs:

Investigations on further pathophysiological differences except for the hormonal situation between men and women should be done.

Statement 3: The prevalence of constipation increases with age

a. Level of evidence: High
b. Recommendation: Not applicable
c. Level of agreement: 100%

Current evidence and literature:

It is generally perceived that the prevalence of constipation increases with age. In a postal health survey in 41 724 Australian women,[4] the prevalence of constipation was 14.1% (CI 13.5–14.7) in young women (18-23 years), 26.6% (CI 25.9–27.4) in middle-aged women (45-50 years) and 27.7% (CI 26.9–28.5) in older women (70-75 years). In data analyses from the General Practice Research Database (GPRD) in the United Kingdom, Talley et al.[3] showed a higher OR of constipation in patients >75 years compared to controls (OR 1.96, 95% CI 1.71-2.24).

Future research/unmet needs:

The effects of ageing on intestinal connective tissue, influence of hormonal status in relation to gut motility and age-related changes in the microbiome should be evaluated to analyse functional, intestinal and external structures as underlying causes of constipation and defecation disorders.

Statement 4: A positive family history of constipation predisposes the individual to constipation, including earlier age of onset, longer duration and higher rate of complications

a. Level of evidence: Low
b. Recommendation: Not applicable
c. Level of agreement: 100 %

Current evidence and literature:

Genetics and/or epigenetics may play a role in FC. Chan et al.[13] analysed the clinical characteristics of FC in 118 FC patients and 114 patients without FC according to the Rome II questionnaire. Patients with a positive family history of FC showed younger age at onset (median 11-20 years vs 21-30 years, $p<0.001$) and longer duration of

constipation (20±14 vs 15±13, p=0.016). Additionally, more complications, e.g. symptomatic haemorrhoids, anal fissure and rectal prolapse (54.2% vs 40.4%, p=0.034); fewer precipitating factors leading to the onset of constipation (35.6% vs 49.1%, p=0.037) and more frequent use of digital evacuation (27.1% vs 13.2%, p=0.008) were seen in patients with a positive family history of FC. Another study by Ostwani et al.[14] demonstrated significantly higher rates of constipation in siblings or parents of children with functional, habitual constipation than in controls (30% vs 7% and 42% vs 9%, respectively; p=0.001).

Future research/unmet needs:

Genetic and epigenetic studies are needed.

Statement 5: Lower social, economic and educational levels are associated with a higher prevalence of constipation

a. Level of evidence: Low
b. Recommendation: Not applicable
c. Level of agreement: 100 %

Current evidence and literature:

In general, individuals of lower social, economic and educational levels have a tendency towards higher constipation rates. Bytzer et al.[15] divided the sample of their questionnaire survey into five socioeconomic classes from 1st (highest) to 5th (lowest). They showed that the standardised prevalence rate (95% CI) for constipation symptoms was lowest in the 1st quintile (2.81 in males and 8.53 in females) compared to the 2nd to 5th quintile (4.03, 6.99, 5.68 and 5.15 in men, and 14.06, 13.35, 13.95 and 14.31 in women). Of interest, according to another study,[16] constipation correlated with a low maternal educational level (1.60; 1.08-2.35).

However, there may be a composite effect of socioeconomic class and a low fibre intake. In a systematic review including 75 different studies, Allen et al.[17] concluded that there was less consumption of fibre, fruit and vegetables in lower socioeconomic classes.

Future research/unmet needs:

Prospective behavioural studies are of interest, however will be unlikely to change practice.

Statement 6: After careful exclusion of a defecatory disorder with anorectal function testing including defecography, at least half of patients with functional constipation do not show signs of delayed colonic transit

a. Level of evidence: Low
b. Recommendation: Not applicable
c. Level of agreement: 82%

Current evidence and literature:

Different pathophysiological mechanisms may lead to FC. Constipation can be classified into three categories: functional defecatory disorders, normal colonic transit and slow colonic transit.[18] In a review of medical records, 1411 patients were analysed between 1994 and 2011 by a single gastroenterologist. The majority (960, 68%) of patients had normal transit constipation (NTC), 390 (28%) had dyssynergic defecation (DD) (abnormal balloon expulsion test and/or high anal sphincter pressure and/or failure of the anorectal angle to open) and 61 (1%) suffered from slow-transit constipation (STC) (diagnosed by colon transit scintigraphy).[19]

Future research/unmet needs:

There is still a lack of understanding how best to separate individual patient symptomatology from meaningful pathologic transit. Further research is needed in this area.

Statement 7: There is increased prevalence of rectal hyposensitivity in constipation

a. Level of evidence: Very low
b. Recommendation: Not applicable
c. Level of agreement: 100%

Current evidence and literature:

Shekar et al.[20] demonstrated anorectal hyposensitivity in FC (27%) compared to constipation-predominant irritable bowel syndrome (IBS-C) patients (4%) using 2.5th and 97.5th percentiles for pain threshold for healthy volunteers (18 mmHg and 42 mmHg, respectively). Hypersensitivity was seen in 30% IBS-C patients and no FC patients.

Another study by Gladman et al.[21] also showed a higher prevalence of rectal hyposensitivity in patients with constipation (23%) and incontinence associated with constipation (27%) compared to patients with faecal incontinence only (10%) and "others" (patients with anorectal physiologic investigations without constipation or faecal incontinence, 5%).

Future research/unmet needs:

Research should be conducted on the mechanisms/pathophysiology of the development of hyposensitivity (primary, secondary) in constipation.

Statement 8: The volume of interstitial cells of Cajal in the sigmoid colon and the neuronal structures within the colonic circular smooth muscle layer are decreased in patients with slow-transit constipation

a. Level of evidence: Low
b. Recommendation: Not applicable
c. Level of agreement: 100%

Current evidence and literature:

The pathophysiology of constipation, in particular STC, is not completely understood. Focusing on motility, He et al.[22] analysed the role of interstitial cells of Cajal (ICC) in STC patients. They found a significantly decreased volume of ICC in all layers of sigmoid colonic specimens in STC patients compared to controls. Neuronal structures within the colonic circular smooth muscle layer were also decreased.

Future research/unmet needs:

Research should be conducted on the mechanisms/pathophysiology of the development of hypo-/dysmotility in constipation. Current studies with histological data come from very select patients with more pronounced symptoms, that may not be representative of ordinary constipation. A way to move forward would make use of recent developments such as full thickness resection devices, that allow endoscopic retrieval of representative specimen[23]

Statement 9: Evacuation disorders represent an important underlying cause of constipation and should be excluded before diagnosing isolated slow-transit constipation

a. Level of evidence: Moderate
b. Recommendation: Strong

c. Level of agreement: 100%

Current evidence and literature:

Battaglia et al.[24] showed that, one year after biofeedback therapy, only 20% of patients with STC maintained a beneficial effect compared to 50% of patients with pelvic floor dyssynergia (PFD). In the short term (three-month assessment), both groups showed a significant improvement in abdominal pain, straining, number of evacuations/week and laxative use. The less effective biofeedback therapy in STC may be due to more complex pathophysiology and multiple involved factors like impairment of propulsive activity[25] as well as physiologic reflexes[26] not only in the most distal part of the bowel like in PFD. As not only therapy but also the underlying pathophysiology might be different in FC, PFD should be excluded.

Future research/unmet needs:

Pathophysiological studies that can discriminate/predict modifiable and innate factors of FC are needed.

DIAGNOSTIC APPROACH

CLINICAL APPROACH AND BASIC EXPLORATIONS

Statement 10: The diagnosis of constipation can be made mainly on symptoms alone. Objective testing can be performed if considered necessary to identify underlying pathophysiological mechanisms

a. Level of evidence: Very low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Despite very low evidence, most consensus guidelines agree that the diagnosis of constipation in the clinical setting is mainly made on the basis of symptoms alone.[5, 6, 27-30] A US survey showed that the most frequent symptoms of chronic constipation were straining, hard stools, abdominal discomfort, bloating, infrequent bowel movements and feeling of incomplete evacuation after bowel movement.[31] Hence, the guidelines underscore the importance of a careful history assessing the presence of these symptoms as well as their duration and progression. Specific validated questionnaires, like the Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire or the Bristol stool scale can be used for the clinical evaluation of the patient with constipation.[32] Objective testing is recommended when the physician considers it necessary to rule out organic disease, i.e. if alarm symptoms are present, or in refractory cases to identify underlying pathophysiology that may help guide treatment.

Statement 11: The most frequent symptoms of chronic constipation are straining and hard stools

a. Level of evidence: Moderate
b. Recommendation: Strong

c. Level of agreement: 100%

Current evidence and literature:

The prevalence of specific symptoms in chronic constipation has been addressed in systematic reviews and meta-analyses.[5, 6, 27-30, 33-38] These studies have agreed that straining and hard stools are the most frequent symptoms of chronic constipation.

Statement 12. For diagnosis of functional constipation, the Rome IV criteria are recommended.

a. Level of evidence: Not applicable
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

The Rome IV criteria include the following symptoms: a. Straining; b. Hard stools (Bristol 1-2); c. Sensation of incomplete evacuation; d. Sensation of anorectal obstruction; e. Need for manual manoeuvres to facilitate evacuation; and f. Less than 3 spontaneous bowel movements per week.[6] Despite differences in the prevalence of each individual symptom, the authors chose to maintain the 25% rule (symptom present in 25% of stool movements) for all symptoms to facilitate the use of the criteria in the clinical setting.[28, 30, 37, 39] However, in the clinical setting, especially in pragmatic primary care, patients can be diagnosed with FC with no awareness of formal criteria..

Statement 13: For the diagnosis of chronic constipation, patients must not fulfil criteria for IBS. This means not having abdominal pain as the primary symptom.

a. Level of evidence: Low

b. Recommendation: Weak

c. Level of agreement: 92 %

Current evidence and literature:

The differentiation between IBS-C and FC is an area of major controversy. Most authors consider that the presence of abdominal pain is the cornerstone for differentiating between both disorders. However, as recognised in the Rome IV criteria, functional bowel disorders are a spectrum of disorders with great overlap and no clear or definite borders that differentiate them in clinical practice. Hence, bloating and abdominal pain is often seen in patients with constipation. In line with recent recommendations, we believe that the diagnosis of IBS should be considered only when abdominal pain is the main symptom in a patient with constipation, but not when it is just a secondary accompanying symptom.[6, 27, 40-42]

Future research/unmet needs:

There is a lack of objective biological markers that can differentiate between FC and IBS-C.

Statement 14: In constipated patients on opioid medication, opioid-induced constipation (OIC) should be considered as a differential diagnosis

a. Level of evidence: Moderate

b. Recommendation: Strong

c. Level of agreement: 92%

Current evidence and literature:

Constipation is a common side effect of opioid use that can affect up to 81% of patients, even with the concomitant use of laxatives.[43] Due to the increasing use of

opioids in western countries, there is a strong need to rule out the use of opioids in patients with constipation, especially considering that opioid consumption is not always reported by patients.[6, 28, 37, 43-45]

However, in these patients, other aspects related to the illness requiring opiates such as anorexia, immobility and concomitant treatments have also to be considered. Owing to receptor downregulation the opiate effect on both pain and the bowel declines over time and finally, the best test of whether opiates are truly responsible is an improvement on discontinuing therapy or response to naloxegol.

Statement 15: A simple blood test should be performed in the evaluation of patients with constipation to identify secondary causes.

a. Level of evidence: Very low
b. Recommendation: Strong
c. Level of agreement: 100 %.

Current evidence and literature:

Observational studies have identified thyroid- and calcium-related disorders as potential causes of constipation. Consequently, several consensus reports[6, 28, 29, 33-36] emphasise the relevance of a simple blood test including glucose, calcium and thyroid-stimulating hormone (TSH) in the evaluation of patients with constipation.[46]

Future research/unmet needs

Cost effectiveness analysis on the value of blood test in patients without other symptoms suggestive of endocrine or metabolic disorders.

Statement 16: The Bristol Stool Form Scale (BSFS) can be used to record stool consistency in patients with constipation.

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100%

Current evidence and literature:

The usefulness of the BSFS in assessing constipation has been demonstrated in different studies. Lewis at al.[26] showed concordance between the whole gut transit time objectively measured with radiopaque markers and the stool form score. The BSFS has been proposed as a reliable indicator of FC that may be particularly useful in assessing patients with some discrepancy between the frequency of bowel movements and stool hardness.[32, 46, 47] Even though other aspects related to individual motor patterns or efficiency of water absorption could influence stool form, the authors agree that the BSFS is a useful but underused tool for clinical practice.

Statement 17: Physical examination in patients with FC should always include digital rectal examination (DRE)

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Digital rectal examination (DRE) is a very important physical examination in the diagnosis of a patient with constipation. DRE can detect stool in the rectal vault, anorectal masses, haemorrhoids, anal fissures, rectal prolapse, and rectoceles that may cause constipation. DRE should be performed at rest, and asking the patient to

strain, to identify alterations such as dyssynergic anal contraction, excessive or defective anal descent, or other structural abnormalities that are not apparent at rest.[48-53] However, due to the non-physiological conditions of the DRE, the final diagnosis of an evacuation disorder needs confirmation with functional studies.

FUNCTIONAL STUDIES

Statement 18: Functional testing in chronic constipation is recommended (where available) when first-line therapeutic measures have failed to improve symptoms.

a. Level of evidence: Very low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Patients consulting for constipation should initially be empirically managed with lifestyle and dietary modifications, withdrawal (or reduction) of constipating medications and fibre supplementation.[54] Most patients will respond adequately to these first-line therapeutic measures, and therefore specialised diagnostic evaluation should only be offered to patients in whom these measures fail to improve symptoms.[55] Advanced functional testing is not available in all settings; however, procedures such as the balloon expulsion test (BET) and whole gut transit evaluation using radiopaque markers may be performed even when resources are limited.[54]

Future research/unmet needs:

First-line measures are effective in most patients, but adherence is generally low. Increasing compliance to diet and laxatives is an area for improvement.

Statement 19**: **Aetiological factors to be evaluated in chronic constipation are: defecatory function (abdominal compression/anal relaxation), intrinsic innervation by rectoanal inhibitory reflex (minimal incidence of primary neuropathies and Hirschsprung's disease in adults, but increasing incidence of Chagas disease), colonic transit, and rectal sensation/compliance (in neurological diseases and severe cases).

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

The purpose of functional testing is to determine the pathophysiological mechanisms of constipation and subsequently guide therapeutic measures.[46] Tests evaluating defecatory function, specifically anorectal manometry (ARM) and BET should be the initial investigations, since evacuation disorders are highly prevalent and may be less likely to respond to first-line therapeutic measures.[56] Other dynamic tests, generally not as widely available as ARM and BET, but providing valuable complementary information on defecatory function, include defecography, electromyography and ultrasonography. None of the tests are individually sufficient to diagnose a defecation disorder, and therefore at least two abnormal evacuation tests are considered necessary to diagnose a functional defecation disorder (FDD).[57]

Other primary aetiological factors of chronic constipation to be evaluated are intrinsic innervation and colonic transit. In addition, functional testing is also useful to diagnose the consequences of chronic constipation: abnormal rectal compliance and perineal damage.

Future research/unmet needs:

Test protocols should be standardised, including instructions to the patient, which have been shown to significantly influence the outcome.[58] Studies evaluating ARM in healthy volunteers have shown dyssynergic patterns, which have been attributed to the non-physiological position during the test, embarrassment or fear of incontinence.[59]

Statement 20: Anorectal manometry evaluates defecatory function (coordination of abdominal compression and anal relaxation) and intrinsic innervation by the rectoanal inhibitory reflex (primary aetiologic factors) as well as sphincter function and rectal sensitivity/compliance.

a. Level of evidence: High
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Evaluation of the defecatory manoeuvre during ARM should demonstrate adequate coordination between the increase in intrarectal pressure and anal relaxation. Weak abdominal compression and inadequate relaxation of the anal canal are the physiological basis of DD, an important cause of functional constipation.[60]
The rectoanal inhibitory reflex (RAIR) depends on the intrinsic innervation of the gut. An abnormal RAIR is typically found in Hirschsprung's disease but may also be detected in other visceral neuropathies such as Chagas disease.[61] Technical aspects are important when evaluating the RAIR. A common pitfall is insufficient rectal distension in patients with megarectum, which may be overcome by using a barostat to obtain sufficient pressure.[62]

Future research/unmet needs:

There is significant discrepancy between methods in data acquisition, analysis and interpretation of ARM; there is a need for expert international cooperation to standardise ARM.[63]

Statement 21: High-resolution manometry is as useful as conventional manometry, and may be helpful in the interpretation of the defecatory manoeuvre

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

High-resolution manometry obtains circumferential pressure measurements of the anal canal and distal rectum. Unlike conventional manometry, it may detect asymmetry of the anal pressures at rest or during squeeze.[64] In addition, topographical colour-contour plots may facilitate interpretation of the defecatory manoeuvre compared to conventional manometry.[65] However, no significant differences in the diagnosis of DD have been detected when directly compared.[66-68]

Statement 22: An abnormal balloon expulsion test is indicative of an impaired defecatory manoeuvre and may predict a better response to biofeedback therapy.

a. Level of evidence: Moderate
b. Recommendation: Strong

c. Level of agreement: 100 %

Current evidence and literature:

The BET measures the capacity and time to evacuate an air- or water-filled balloon from the rectum. This test has been shown to be abnormal in a high proportion of patients with an evacuation disorder,[69] but as mentioned previously, is not diagnostic as a single test. In fact, agreement with disordered defecation measured with ARM is relatively low. Indeed, the BET may be normal in patients with DD who are able to compensate by excessive straining. The BET has been shown to predict response to biofeedback therapy,[70, 71] although this finding is not uniform in all studies.[72]

Future research/unmet needs:

There is considerable disagreement between the tests of evacuatory function; diagnostic criteria for impaired defecatory function should be established.[73]

Statement 23: Rectal compliance is evaluated by the pressure/volume relationship with an air-filled rectal bag. Patients with constipation may have higher rectal compliance than controls.

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Rectal compliance may be measured by evaluating the pressure/volume relationship during progressive rectal distension with a balloon. For this purpose, the use of a barostat is useful because it allows direct measurement of rectal capacity at fixed pressure levels.[74] Increased rectal compliance may be associated with chronic

constipation, particularly in children with megarectum.[75] Nevertheless, in paediatric constipation, increased rectal compliance has not been shown to increase treatment failure.[76, 77]

Statement 24: Oro-anal transit is most commonly measured by radiopaque markers; interpretation of slow colonic transit is not reliable in the case of functional or organic outlet obstruction.

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 91 %

Current evidence and literature:

The radiopaque marker (ROM) test is the current standard test for the evaluation of oro-anal transit, with the advantages of low cost, simplicity and wide availability. Unfortunately, protocols are not standardised, and the technique varies widely between centres. Alternatively, the Smart Pill test and scintigraphy may be used to evaluate colonic transit times, and have been shown to correlate well with the ROM test.[78]

STC is characterised by a delayed colonic transit time. However, transit time may also be delayed in patients with important faecal retention or with an evacuation disorder, so these must be excluded to identify patients with STC alone.[79-81] In patients with FC, transit times have been shown to correlate well with stool consistency/form but poorly with stool frequency and associated symptoms.[47, 82]

Future research/unmet needs:

The procedure should be standardised.

RADIOLOGICAL STUDIES

Statement 25: The recommended test name is 'defecography' (barium or magnetic resonance [MR])

a. Level of evidence: Very low
b. Recommendation: Strong
c. Level of agreement: 100 %.

Current evidence and literature:

The terminology is far from being universally accepted, given the numerous technical variations and the plethora of synonyms for defecography employed since its conception[83]: 'cineradiographic defecography',[84] 'cinedefecography',[85] 'evacuating'[86] or 'evacuation proctography',[21] 'defecation'[87] or 'defecating proctography'[88], 'videodefecography',[89] and 'videoproctography'.[90] However, the term 'defecography' has been most commonly reported (~60% of all published articles); it was initially proposed by Mahieu[91] to more clearly imply that the physiological act of defecation is examined in dynamic conditions analogous to the investigation of deglutition or micturition.

Future research/unmet needs:

One of the principle challenges will be to promote standardisation of the language and the technique so that results are transferrable between institutions.

Statement 26: Normative data for structural and functional parameters are available for both barium and MR defecography, but are limited in their scope, particularly for MR. There may be considerable overlap in findings between health and disease

a. Level of evidence: Moderate

b. Recommendation: Strong

c. Level of agreement: 100 %

Current evidence and literature:

A total of only four studies have been conducted in ≥40 healthy subjects, two using barium [X-ray] defecography (BD)[92, 93] and two using MR defecography (MRD).[94, 95] Regardless of the technique, a consistent criticism of defecography is the acknowledged overlap between health and disease,[92] hampered by a paucity of normative data, which challenges our ability to define 'true' (pathologic) abnormalities.

Future research/unmet needs;

The optimal technique for BD and MRD remains to be defined and should be subject to a Working Group initiative. Normative values are only applicable to specific protocols, and are mostly derived from female patients (for MRD, data existing for males are derived from a cohort of only 25 subjects in one study[94]).

Additional comments:

Normative data sets *have* provided evidence of truly pathologic findings (i.e. those *not* seen in health), such as large rectoceles, high-grade intussuscepta and enteroceles (whole gut or oro-anal).[96]

Statement 27: Adherence to standardised study protocols is necessary

a. Level of evidence: Low

b. Recommendation: Strong

c. Level of agreement: 100 %

Current evidence and literature:

The prevalence of structural and functional abnormalities detected by defecography is high, but varies considerably across studies, with high heterogeneity depending on technical protocol variations and diagnostic criteria used. For example, several different cut-offs have been used to define: a) dynamic perineal descent (ranging from 2 to 6 cm)[97, 98]; b) the magnitude of the infolding for rectal intussuscepta (any fold "more than a wrinkling of the mucosa"[99]; ≥3 mm[100]; >4 mm[85, 101]; or >1 cm[98, 102]); and c) severity of rectocele based on maximum depth: 2 cm[94, 100, 103-108]; 2.5 cm[109]; 3 cm[85, 90, 110, 111]; or 4 cm.[73, 112, 113]

Future research/unmet needs:

As above, standardisation of protocols is a prerequisite for obtaining results that are robust, reproducible and easily transferable between institutions.

Statement 28: Barium defecography is indicated in patients with refractory symptoms of an evacuation disorder, and can accurately delineate several rectal structural abnormalities that often co-exist

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

The prevalence of pathologic high-grade (i.e. Oxford III and IV) rectoanal intussusceptions and external rectal prolapse (i.e. Oxford grade V) on BD is 23.7% (95% CI, 16.8-31.4; based on 13 studies) and 5.3% (95% CI, 3.1-8.0; based on 16 studies), respectively. The prevalence of large (>4 cm) pathologic rectoceles is 15.9% (95% CI, 10.4-22.2; based on 9 studies). Enterocele and excessive perineal

descent are observed in 16.8% (12.7-21.4) and 44.4% (36.2-52.7) of patients, respectively[96] (numerous references omitted for the sake of brevity).

Future research/unmet needs:

As per the points listed above, optimum cut-offs to define true abnormalities (both in terms of anatomical features, and impaired evacuation) need to be refined, based on standardised protocols.

Statement 29: Amongst commonly performed investigations for symptoms of an evacuation disorder (e.g. ARM, BET, sonography), barium defecography can be considered the gold standard for assessment of structural rectal abnormalities

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

BD is considered the gold standard for the assessment of posterior compartment disorders, given its capability to dynamically evaluate the rectum during simulated defecation.[109] Its particular advantage over BET and manometry is that it enables characterization of structural abnormalities.[73, 92] BET and manometry are, *de facto*, unable to provide such information. A total of four studies (including ≥40 subjects) have used BD as the reference standard to assess the diagnostic yield of other imaging modalities (i.e. echodefecography[114, 115] and dynamic transperineal ultrasound[116, 117]) in diagnosing posterior pelvic floor compartment disorders.

Future research/unmet needs:

There is considerable disagreement between the results of various tests used to diagnose evacuation disorders. Diagnosis is test-dependent, which impacts upon patient management. This highlights the need for a reappraisal of both diagnostic criteria, and what represents the 'gold standard' investigation. There is also further scope for research in comparing the results of barium versus MR defecography.

Statement 30: ***There is no single gold standard investigation for diagnosis of a 'functional' evacuation disorder. Nevertheless, defecography can identify specific causes (e.g. ineffective expulsive force, non-relaxing puborectalis etc. [terminology inconsistently reported]) which may guide treatment***

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %.

Current evidence and literature:

In defecography, the diagnosis of a functional abnormality is made using three possible features, originally described by Mahieu et al.,[118] either combined or in isolation: a) poor opening of the anorectal angle (secondary to poor relaxation or indeed 'paradoxical' contraction of the puborectalis muscle); b) poor anal sphincter relaxation; and c) incomplete and/or prolonged evacuation based on percentage of contrast expelled and/or time taken, respectively. Diagnostic criteria and prevalence of functional abnormalities have been provided in 42 studies of ≥40 constipated patients, based on either 'a' (n = 22)[101, 103, 104, 116, 119-136]; 'b' (n = 2)[110, 137]; 'c' (n = 2)[138, 139]; 'a+b' (n = 4)[97, 112, 140, 141]; 'a+c' (n = 7)[85, 86, 114, 142-145]; 'b+c' (n = 1)[146]; or 'a+b+c' (n = 4).[115, 147-149] Quantitative meta-analysis of these studies, including four comparative (BD vs MRD) studies, shows a pooled prevalence of 24.1% (95% CI, 20.2-28.4) for BD and 25.9 (14.1-39.6) for MRD.[96]

Future research/unmet needs:

There is a need for prospective studies designed to evaluate the utility and cost-effectiveness of different diagnostic modalities to tailor management of constipation, as well as to determine predictors of response to biofeedback therapy.

Statement 31: Barium defecography is useful in evaluating the outcome of surgical interventions for structural rectal abnormalities, particularly in patients with ongoing or recurrent symptoms

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Three studies have used BD to assess outcomes of stapled transanal rectal resection (STARR).[150-152] One study compared the results of biofeedback retraining, botulinum toxin type A injection and partial division of puborectalis (PDPR) in a randomised study of 60 patients with anismus.[153]

Future research/unmet needs:

Defecography is widely used by the surgical community to direct surgical management in patients with constipation/evacuation disorder, where the operating procedure is directed to reversal of demonstrable posterior compartment abnormalities (e.g. rectocele, high grade intussusception) that are consistent with presentation of symptoms. However, no randomised controlled trials (RCT) or prospective stratified medicine studies are currently available. Such studies are

required now more than ever, given that litigation and intense media scrutiny have forced surgeons to rigidly objectify their motivation for offering surgery.

Statement 32: MR defecography is indicated in patients with refractory symptoms of an evacuation disorder and has the advantage of routinely evaluating all pelvic compartments in those with suspected multi-compartmental structural defects. However, comparative data with barium defecography is currently limited

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement 100 %

Current evidence and literature:

A multiplanar, diagnostic assessment of the anterior, middle and posterior compartments is possible with MRD. Five studies, comprising ≥40 study subjects, have compared BD to MRD.[105, 108, 109, 154, 155] BD represented the reference standard in all studies, except one that adopted the results obtained from the joint analysis of BD and MRD as reference.[109] None of these studies followed the Standards for Reporting Diagnostic Accuracy (STARD) guidelines.

Future research/unmet needs:

Well-designed diagnostic test accuracy studies following STARD criteria are needed.

Statement 33: MR and barium defecography are complementary and may provide additional diagnostic information when either one is equivocal or incomplete

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Compared to BD, MRD allows a thorough assessment of all pelvic floor organs. However, in centres where MRD is the standard test, patients who fail to evacuate should also undergo BD or significant pathology will be missed.[154]

Future research/unmet needs:

Further well-designed comparative studies are required.

Statement 34: Barium defecography is likely to be superior to MR defecography in detecting structural posterior pelvic compartment abnormalities leading to obstructed defecation

a. Level of evidence: Moderate
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Pooled results from the five studies (each comprising ≥40 study subjects) that have compared BD to MRD[105, 108, 109, 154, 155] show that BD is superior to MRD in the detection of intussusception (pooled prevalence: 57.8% vs. 37.8%; OR, 1.52 [95% CI 1.12-2.14, p=0.009]), although BD is associated with higher levels of embarrassment (qualitatively measured among patients), lower tolerance (54.3% vs. 30.0%; OR, 1.73 [95% CI 1.14-2.62, p=0.008])[96] and higher radiation exposure.

Future research/unmet needs:

Well-designed diagnostic test accuracy studies following STARD criteria are required to confirm these findings.

Additional comments:

Concerns over the impact of patient test position on diagnostic yield for MRD (supine in closed-magnet configurations, considered non-physiological, vs upright in open-magnet configurations) are yet to be adequately addressed.

TREATMENT

LIFESTYLE AND GENERAL MEASURES

Statement 35: Exercise has neither a positive nor a negative effect on constipation

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 92 %

Current evidence and literature:

The literature does not delineate between functional constipation, chronic constipation or constipation per se. The data are conflicting but largely against benefit from exercise alone for constipation. One study of secondary school pupils (hence, largely normal subjects), which used bowel evacuations less than every two days as the criterion, concluded that constipation was associated with “insufficient” exercise or sedentary behaviour, and that this was dose-related to the amount of exercise taken.[156] Similarly, in an education-led program in 35 women with chronic constipation, there was an improvement in their Bristol Stool scores and symptoms.[157] However, the intervention was multi-layered, consisting of advice on diet, fluids and counselling. Conversely, in a study of healthy men over 35 days, intervention with experimentally-controlled bed rest, stool consistency and bowel symptoms was not influenced by physical inactivity.[158] In another study conducted over six weeks in patients with idiopathic constipation, exercise levels and constipation were assessed. The level of exercise did not correlate with constipation indices and the conclusion was that physical activity to the extent considered “regular exercise” did not play a role in the management of idiopathic constipation.[159] While data do indicate that GI transit times may be accelerated by exercise, this does not translate into outcomes in constipation. Although subjects with the slowest resting

transit rates may show the largest exercise effects in mouth-to-caecum transit time, this is not necessarily reflected in constipation symptoms.[160, 161]

A review in 2011, which included two small randomised placebo-controlled trials and two cohort studies concluded that lifestyle modification to prevent or treat constipation was not substantiated by evidence.[162] No systematic reviews exist for exercise and constipation, but exercise appears to be associated with a range of health benefits for people of all ages.[159, 161, 163] A further review in 2011 confirmed conflicting evidence, again largely against the effect of exercise for constipation, with studies showing inconsistent effects.[164]. However, physical activity was noted to improve quality of life (QoL) in some subjects in some studies, and was associated with improved QoL and a decrease in symptom severity.[165]

<u>Future research/unmet needs:</u>

Evaluation of the level of exercise needed to maintain good general health and gastrointestinal health in individual people.

Statement 36: In patients who are not dehydrated, additional fluid intake alone does not have a positive effect on constipation

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

<u>Current evidence and literature:</u>

Medical advice frequently stresses the importance of “good” fluid intake for general health and, in particular, to manage constipation. There are no clear definitions of what constitutes an adequate or therapeutic level of fluid intake in people with constipation. Whilst there may be an association between “inadequate” fluid intake or

dehydration and constipation, there is a lack of evidence to support that increased fluids alone are of benefit.[157, 163, 165] In a study of 833 elderly patients with a mean age of 74 years, it was noted that 71% already drank six or more glasses of water daily, and that there was no difference between them in terms of bowel symptoms and the 29% who drank less fluids.[166] In a 2011 review, only one RCT and one observational study was noted, with the RCT showing benefit from fluids only in the presence of additional fibre.[162] Thus, the evidence in relation to increased fluid intake alone, as being positive for the management of constipation, is sparse.

Future research/unmet needs:

Larger, well-defined interventional studies should be done to provide data on appropriate intake for patients with constipation.

Statement 37. Dietary fibre alone within the normal (regular) diet helps functional constipation.

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement 92 %

Current evidence and literature:

This section relates to normal or regular intake of dietary components, essentially fibre, and does not relate to therapeutic supplements. However, much of the literature relates to fibre supplements and laxatives, and there is a paucity of data about lifestyle dietary measures geared to FC. A 2011 review concluded that, whilst increasing dietary fibre may help constipation caused by fibre deficiency, it should not be assumed that fibre deficiency is the main source of the problem.[157] Consuming a high fibre diet alone may not be as effective as combining it with

increased fluid intake. The overall evidence for increased dietary fibre (as opposed to recommended or prescribed fibre) is weak, although the effect may be enhanced if increased fluids are included.[157, 162, 165, 167]

Future research/unmet needs:

Interventional and observational studies in patients are needed.

Statement 38: Overall lifestyle measures may be of value in some patients to improve constipation, quality of life and contribute towards better health

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

With regard to overall lifestyle modification (combined factors), most studies consist of interventions or studies of fibre intake, fluids and exercise, but some also have additional factors such as counselling or individualised care. The effect of each of these is difficult to separate out. For example, an Egyptian study of 23 elderly patients with FC included group discussions about dietary patterns, fluid intake, physical activity and the use of laxatives.[168] There was no control group, but the lifestyle modification education significantly reduced the severity of the FC and recorded improvements in QoL. Combined with data from other studies, this suggests that there is overall benefit from a combination of lifestyle measures, both in constipation as well as in the QoL measures.[165, 167] To this can be added the benefits from a more active lifestyle in terms of general health. Whilst the data are not robust, this would seem a reasonable approach in the practical management of patients.

Future research/unmet needs:

More studies are needed on overall lifestyle and gastrointestinal health.

BULKING AGENTS & OSMOTIC LAXATIVES

Statement 39: Bulking agents, in particular soluble fibre, are effective in the management of chronic constipation

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Despite the fact that bulking agents, in the form of either soluble or insoluble fibre, have relatively little support from large RCTs in patients with chronic constipation, these agents are often recommended as first-line treatment options for patients with chronic constipation. This is influenced by the safety and low cost of this approach, as well as some efficacy data from trials, together with long-standing clinical experience with these agents. In a systematic review evaluating the effects of fibre in the management of chronic idiopathic constipation, only six RCTs were found to be eligible: four used soluble fibre (three psyllium, one inulin and maltodextrin) and two used insoluble fibre (one bran, and one fibre-rich rye bread). Soluble fibre led to improvements in global symptoms (86.5% vs. 47.4%), straining (55.6% vs. 28.6%), pain on defecation, and stool consistency, an increase in the mean number of stools per week (3.8 stools per week after therapy compared with 2.9 stools per week at baseline), and a reduction in the number of days between stools. In particular, the effect of psyllium was convincing with a Number-Needed-to-Treat (NNT) of 2 (95% CI 1.6 – 3), and with no statistically significant heterogeneity between the three

psyllium studies.[169] Evidence for any benefit of insoluble fibre was conflicting, mainly based on small patient numbers and few eligible studies. As a follow-up of this systematic review, the American College of Gastroenterology (ACG) recommended, based on these six trials, that fibre and soluble fibre in particular are effective in the management of chronic constipation.[8] Soluble and insoluble fibre are also frequently used in patients with IBS, but the status of fibre in general in IBS is far from straightforward.[169-175] Insoluble fibre may exacerbate symptoms and provide little relief in patients with IBS, but soluble fibre and psyllium, in particular, seem to provide relief in this condition.[176-178] These latter effects appear to relate to the relief of constipation, which further supports the use of soluble fibre in patients with constipation, either FC or IBS-C.

Future research/unmet needs:

Large, high-quality trials using modern clinical trial methodology are needed.

Statement 40: The usefulness of bulking agents, in particular insoluble fibre, in patients with chronic constipation is limited by adverse events, particularly bloating, distension, flatulence, and cramping

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Bulking agents, e.g. psyllium, bind water and prevent absorption of water from the lumen. This leads to increased small bowel water and increased colonic volumes.[179] These effects can explain both the positive effects of bulking

agents, i.e. increased stool frequency, and potential side effects. Adverse events, particularly bloating, distension, flatulence, and cramping may limit the use of insoluble fibre, especially if increases in fibre intake are not introduced gradually.[8, 169-178, 180]

Future research/unmet needs:

Strategies to use fibre to reduce side effects should be defined, as well as comparisons with other agents used to treat constipation.

Statement 41: Saline laxatives, especially polyethylene glycol (PEG), are effective in treating symptoms of constipation in patients with chronic constipation

a. Level of evidence: Strong
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

The evidence supporting the usefulness of saline laxatives, especially polyethylene glycol (PEG), is strong. There are several large, high quality trials supporting the fact that PEG is superior to placebo in improving symptoms in patients with chronic constipation, with a NNT of 3 (95% CI 2 – 4).[8, 181-189] Moreover, a Cochrane analysis also concluded that PEG is superior to lactulose in patients with chronic constipation, resulting in more frequent stools, looser stools, and less abdominal pain. PEG also increases the number of spontaneous complete bowel movements, improves stool consistency, and reduces severity of straining, without clearly affecting abdominal pain, in patients with IBS-C, further supporting its usefulness to treat constipation.

The most common side effects with PEG are diarrhoea and abdominal pain, but not all trials find these to be more common in patients treated with PEG compared to the placebo group.

Future research/unmet needs:

Direct head-to-head comparisons with newer agents treating constipation are needed.

Statement 42: Lactulose is efficacious in the treatment of patients with chronic constipation

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Clinical experience suggests that the osmotic properties of the unabsorbed mono/disaccharides and sugar alcohols lactulose, lactitol, mannitol and sorbitol benefit patients with chronic constipation, but evidence from high quality RCTs supporting this is largely absent. Few RCTs exist and these have a high risk of bias and moderate heterogeneity between studies, but suggest a positive effect of lactulose versus placebo in chronic constipation with a NNT of 4 (95% CI 2 – 7).[8, 181, 190, 191] Moreover, side effects such as abdominal cramping and bloating limit their clinical usefulness. Also dried plums, which contain sorbitol, but also dietary fibres and polyphenols, may be useful for constipation. This was demonstrated in a randomized controlled trial, where dried plums were found to be safe, palatable and more effective than psyllium for the treatment of mild to moderate constipation.[192] At

least part of the effect on constipation may be explained by the sorbitol content, which act as an osmotic laxative.

Future research/unmet needs:

High quality trials assessing the effects of the unabsorbed mono/disaccharides and sugar alcohols lactulose, lactitol, mannitol and sorbitol are needed, including comparisons with newer agents for the treatment of constipation.

STIMULANT LAXATIVES

Statement 43: Bisacodyl is effective in the management of chronic constipation.

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Bisacodyl is a diphenyl methane derivative hydrolysed by intestinal and bacterial enzymes to a deacetylated active metabolite that induces high amplitude propagative contractions of the colon and stimulates intestinal secretion.[193] It is usually given orally at a dose of 5-10 mg daily in a coated tablet that dissolves in the colon to ensure a local effect, or as a suppository given at a dose of 10 mg daily. In healthy volunteers, bisacodyl significantly accelerated emptying of the ascending colon, although overall transit was not modified.[194] In 2005, a systematic review of the literature found that stimulant laxatives, including bisacodyl, had a level III of evidence and were rated as a grade C recommendation,[195] while the American College of Gastroenterology Chronic Constipation Task Force underlined that high-quality data were lacking to make a recommendation about the efficacy of stimulant

laxatives for the management of chronic constipation.[196] Since then, only one randomized, double-blind placebo-controlled study comparing the efficacy of daily use of bisacodyl in chronic constipation has been conducted. In this study, performed in 368 patients with chronic constipation defined by Rome III criteria, oral bisacodyl at 10 mg once daily increased the frequency of both bowel movements and complete spontaneous bowel movements over a 4-week period.

Statement 44: The use of bisacodyl in patients with chronic constipation is often well tolerated

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Constipation-related QoL was also improved in the bisacodyl group compared with placebo.[197] Of note, six adverse events leading to drug discontinuation were recorded in the placebo-treated group, versus 44 in the bisacodyl-treated group, the most frequent being diarrhoea and abdominal pain. However, the occurrence of serious adverse events was similar (<2%) in both groups. A second randomised-double-blind placebo-controlled study showed the efficacy of bisacodyl (10 mg once daily for 3 days) to acutely relieve chronic constipation by increasing the frequency of bowel movements and softening stool consistency.[197] An open-label RCT conducted in two groups of patients with chronic constipation treated with either pyridostigmine or bisacodyl showed that both treatments achieved an increase in bowel movements per week compared to baseline, with greater efficacy with pyridostigmine compared to bisacodyl.[198]

Future research/unmet needs:

Controlled studies evaluating the efficacy of bisacodyl in FC over 4 weeks of treatment are lacking and should be conducted. Whether the association of bisacodyl with an osmotic laxative is superior to bisacodyl alone or an osmotic laxative alone has yet to be investigated.

Statement 45: Sodium picosulfate is effective in the management of chronic constipation, at least as a short-term treatment.

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Sodium picosulfate is a locally-acting stimulant laxative hydrolysed by the colonic microflora into the same active form as bisacodyl. It therefore has a similar mode of action to bisacodyl, including increased colon peristalsis and secretion. There is only one randomised, double-blind placebo-controlled study comparing the efficacy of sodium picosulfate in chronic constipation.[199] This study was conducted in 367 patients with Rome III-defined FC allocated 2:1 to receive either sodium picosulfate (10 mg/day) or placebo for 4 weeks. The number of complete spontaneous bowel movements (CSBMs) increased from 0.9 to 3.4 per week in the sodium picosulfate treated group compared with an increase from 1.1 to 1.7 per week in the placebo-treated group.

Future research/unmet needs:

Controlled studies evaluating the efficacy of sodium picosulfate in FC over a 4-week treatment period are lacking and should be conducted. Whether the association of

sodium picosulfate with an osmotic laxative is superior to sodium picosulfate alone or an osmotic laxative alone is yet to be investigated.

Statement 46: The use of sodium picosulfate in patients with chronic constipation is often well tolerated.

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Constipation-related QoL was also improved after treatment in the sodium picosulfate treated group compared with placebo. Comparable to bisacodyl, diarrhoea and abdominal pain were the most common adverse events reported compared with placebo. The efficacy of sodium picosulfate was compared with bisacodyl in an open-label RCT involving 144 patients with chronic constipation.[200] After 4 weeks of treatment, sodium picosulfate and bisacodyl both achieved a comparable number of bowel movements per week (3.2 in both groups).

Statement 47: Anthraquinones, and particularly senna, are effective in the management of chronic constipation

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

This class of laxatives includes mainly sennosides A and B and cascara. Sennosides are transformed by the colonic microbiota into active components[201] They cannot be

absorbed and are not excreted in breast milk. Clinical trials are sparse, and have often been conducted in the geriatric population or in patients with OIC. In these trials, the objective was often to demonstrate the additional benefit of combining senna to a bulk or osmotic laxative. The available trials prove their efficacy for increasing the number of stools or improving stool consistency. Senna provided more improvement than bulk or osmotic laxatives,[202-204] and obtained similar results to magnesium hydroxide,[205] sodium picosulfate,[206] and even lubiprostone.[207]

Future research/unmet needs:

Blinded controlled studies evaluating the efficacy of anthraquinones are still lacking and should be performed.

Statement 48: Anthraquinones, and particularly senna are often well tolerated in patients with chronic constipation.

a. Level of evidence: Moderate
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Anthraquinones have been linked with the development of melanosis coli, which is a brown pigmentation of the colonic mucosa due to collections of lipofuscin-containing macrophages.[208, 209] It is now established that this pigmentation has no clinical significance.[208] An increased risk of colorectal cancer has also been discussed. In a prospective study of 84 577 females, no association between laxative use and colorectal cancer was found.[210]

PROKINETICS & SECRETAGOGUES

Statement 49: The serotonin (5-HT)-4 agonist prucalopride has prokinetic action in the entire gut, and is effective in the management of chronic constipation, including conditions refractory to conventional laxatives.

a. Level of evidence: High
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

The serotonin (5-HT)-4 agonist prucalopride has been shown to be effective in severe chronic constipation refractory to laxatives, and has been approved in Europe for this indication for several years.[211-216] It is highly receptor-selective and has no cardiologic side effects. Other related substances play no practical role in the treatment of chronic constipation at this time; examples include cisapride, which is no longer available as it had been associated with QT prolongation, torsades de pointes and cardiac arrest, thought to be due to its binding and inactivation of a potassium channel encoded by the hERG gene; mosapride (established only for the upper GI tract); and molecules such as velusetrag (no current clinical trials available despite positive data from an earlier phase-2 study) and naronaprid (currently being evaluated); for review compare Prichard DO & Barucha AE, Recent advances in understanding and managing chronic constipation. F1000Res. 2018 Oct 15;7. pii: F1000 Faculty Rev-1640. doi: 10.12688/f1000research.15900.1. eCollection 2018. PMID: 30364088.

Future research/unmet needs:

Predictors of response are poorly defined. In particular, the relevance of different pathomechanism of constipation (e.g. slow vs. normal transit) has not been clarified.

The potential therapeutic role of prucalopride in other segments of the GI tract should be further elucidated.

Statement 50: Acetylcholinesterase inhibitors exert prokinetic effects in the intestine, but currently have no practical role in the management of chronic constipation

a. Level of evidence: Moderate
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Acetylcholinesterase inhibitors exert prokinetic action by inhibiting degradation of acetylcholine, thus amplifying its effects in the enteric nervous system (ENS) as well as in GI smooth muscle. Distigmine (and related substances) have their use in (often refractory, and usually acute or protracted) motility disturbances, such as colonic acute pseudoabstruction, postoperative ileus, etc.[217] On an individual basis they may be useful in selected cases of CC refractory to other established treatments. Indeed, a small trial reported similar efficacy as bisacodyl.[198] Overall, they have limited use in chronic constipation. This is also due to their low specificity, with effects on both muscarinic and nicotinic receptors, and because they have been associated with multiple systemic, secretory, and serious cardiologic side effects.[218, 219]
Acotiamide is a new acetylcholinesterase inhibitor with additional anti-muscarinic effects, available in Japan and currently being evaluated in Europe and the USA for functional dyspepsia[220]; there are no data for chronic constipation.

Future research/unmet needs:

Their therapeutic potential in defined subtypes of constipation disorders is not well defined and thus they are possibly under-utilized.

Statement 51: Peripherally Acting μ-Opioid Receptor Antagonists (PAMORA) have prokinetic properties by reversing the inhibitory effects of μ-opioid analgesics on GI motility, and are effective in the management of opioid-induced chronic constipation

a. Level of evidence: High
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Peripherally Acting μ-Opioid Receptor Antagonists (PAMORA) inhibit the peripheral effects of μ-opioid analgesics on bowel functions such as reduced GI motility and secretion, as well as increased fluid absorption.[221-223] True PAMORA (naloxegol, methylnaltrexone, alvimopan, naldemedine) do not pass the blood-brain barrier and are effective in the treatment of OIC without affecting the central analgesic effects.[224-234] The systemic opioid antagonist naloxone if administered as slow release formula may also inhibit intestinal opioid effects with little/no systemic action due the high first pass effect in the liver, it is available as a fixed combination tablet with oxycodone.[235, 236]

Future research/unmet needs:

Since there is limited data on combination treatments, further studies should be done.

Statement 52: Peripherally Acting μ-Opioid Receptor Antagonists (PAMORA) have prokinetic properties even in the absence of opioid therapy and may potentially be effective in constipation not caused by opioids

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

A high quality RCT[237] demonstrated that in healthy subjects the PAMORA alvimopan not only reversed opioid-induced inhibition of small-bowel and colon transit, but also significantly accelerated colonic transit in the absence of opioid co-treatment. These findings suggest that μ-opiate mechanisms participate in the physiologic regulation of colonic motility, independent of opioid-induced modulation.

Future research/unmet needs:

The therapeutic potential of PAMORA in chronic constipation subtypes not induced by opioids should be investigated.

Statement 53. The guanylate cyclase C receptor agonist linaclotide is effective and safe in the management of chronic constipation and IBS-C

a. Level of evidence: High
b. Recommendation: Strong
c. Level of agreement: 92 %

Current evidence and literature:

Linaclotide acts as an oral guanylate cyclase C receptor agonist, increases intracellular cyclic guanosine monophosphate (cGMP) levels, and thus fluid secretion into the intestinal lumen, which in turn accelerates gastrointestinal transit velocity. At a dose of 290µg/d it significantly improves chronic constipation with a RR of response to treatment of 1.95 [1.3-2.9] and a NNT of 7. In addition, it has been licensed as treatment for IBS-C as it also improves abdominal symptoms commonly associated with CC, such as bloating or pain[238, 239] due to decreasing effects on visceral hypersensitivity.[238, 239] Linaclotide may cause diarrhoea as its most frequent side effect, but has a very low risk of major systemic adverse responses due to its local action in the intestinal lumen and low bioavailability.[181, 240]

Statement 54: The chloride channel activator lubiprostone is effective in the management of chronic constipation and IBS-C, but has limited availability in the majority of European countries

a. Level of evidence: High
b. Recommendation: Strong
c. Level of agreement: 92 %

Current evidence and literature:

Lubiprostone is a chloride channel activator and induces intra-intestinal water and chloride secretion, and accelerates transit. In RCTs in patients with chronic constipation and IBS-C, Lubiprostone was associated with significantly improved symptoms[222, 241-245] with a therapeutic benefit of 7.8%, and a NNT of 12.8 .[246] Lubiprostone may cause nausea and has been suspected to promote abortion rates

in animal studies due to its prostaglandin properties.[222, 241-245] Hence, it is mostly used as reserve medication, and has not been approved in most European countries so far.

Future research/unmet needs:

The optimal target group and side effects should be defined more clearly. Limited or no availability in most European countries.

BIOFEEDBACK THERAPY

STATEMENT 55: Biofeedback is the preferred treatment for constipation due to functional defecation disorders whenever dedicated expertise is available, regardless of abnormal bowel transit

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Biofeedback is a conditioning treatment where information about a physiological process is converted to a simple signal to enable the patient to learn to control the disordered function.[247] Recently, instrumented biofeedback has been reported to ameliorate symptoms and accelerate bowel transit by improved defecation effort in over 70% of STC due to DD, while isolated STC did not benefit.[79] This study provided support for the specific therapeutic contribution of biofeedback therapy and heralded three pivotal RCTs addressing its effectiveness in FDDs.[248-250] These pivotal trials were adequately sized and included only severe, refractory constipation due to DD diagnosed by physiology testing, regardless of abnormal colon transit in most of them. Biofeedback therapy has been consistently reported to be superior to

controlled treatment modalities, including sham biofeedback, placebo pill, muscle relaxant drugs (diazepam), and osmotic laxatives.[248, 249] Improved anorectal physiology correlated with successful outcomes, supporting a specific mechanism of action of biofeedback that differed from psychotherapy interventions and simple education. Biofeedback was effective in the long term and devoid of side effects, as confirmed by a recent open-label trial with a follow-up interval extended up to 4 years.[248, 249, 251, 252] In the pivotal trials, a complex protocol addressing the defecation effort as a whole using dedicated instruments was employed[248-250]; this seems relevant to the successful outcome of biofeedback therapy, as simpler protocols were less effective than alternative treatments in FDDs.[153] In addition, constipation symptoms associated with isolated anatomical disruption of the pelvic floor seem to benefit little from retraining.[253] Factors that may predict successful outcome of biofeedback therapy are: baseline harder stool consistency, digital manoeuvres to facilitate defecation, shorter duration of laxative use, higher resting anal sphincter pressure, and failure to expel a rectal balloon.[70, 254] Comorbid slow colonic transit is not a contraindication to retraining, as it has been repeatedly shown that improved defecation effort is effective on normalizing bowel transit in the vast majority of DD patients.[79, 254] Finally, the patient's willingness to participate, motivation and therapist's skill are all considered relevant to a successful outcome, although these are generally not specifically addressed.[255]

<u>Future research/unmet needs:</u>

Other RCTs of biofeedback for constipation due to inadequate rectal propulsion with or without DD should be conducted. They should include both subjective and objective outcome measures, such as structural alterations of the pelvic floor. RCTs comparing simple bowel retraining measures to instrumented biofeedback for constipation due to FDDs are needed. RCTs for constipation due to FDDs aimed at standardizing biofeedback protocols for DD and inadequate rectal propulsion are

also required, as well as RCTs comparing biofeedback with conservative care for constipation due to structural alterations of the pelvic floor.

Statement 56: Habit training is an effective treatment option for chronic constipation non-responsive to standard care whenever dedicated expertise is available

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

<u>Current evidence and literature:</u>

Habit training, also called bowel retraining or pelvic floor retraining, has been developed to address constipation as a multifactorial disorder with a particular focus on the pelvic outlet. Habit training is generally not provided according to a standardised protocol, and is mostly a nurse-led treatment option.[256, 257] It involves dietary advice to improve stool consistency and to maximize the gastro-colic response in order to ease defecation.[256, 257] Patients can be given basic gut anatomy and function training to gain an appreciation of how psychological and social stresses may influence gut functioning, as well as advice about the frequency and length of toilet visits and posture. Simple pelvic floor exercises and abdominal muscular coordination training to improve the pushing effort are relevant treatment components in all protocols.[256, 257] However, habit training is not like biofeedback, where information about a physiological process is presented to enable mastering of a disordered function.[255] Some centres provide this treatment approach in all resistant chronic constipation, regardless of aetiology.[257] However, a pelvic floor retraining protocol was prescribed as sole treatment for 22% of constipated Italian patients consulting specialised care.[248] The recently published St Mark's experience has shed some light on habit training given to constipated patients non-responsive to conservative care.[2587] A retrospective analysis of data from 347 mostly female

constipated subjects (median age, 50 years) showed an improvement in symptoms in 62.5% and in the QoL score in 40.2% of the patients at the end of treatment. Multivariate analysis demonstrated that increasing age, the number of sessions attended, and non-irrigation constipation were independent predictors of treatment satisfaction.[257] No side effects were reported. The same group undertook an historical RCT comparing electromyography (EMG) on straining and rectal balloon biofeedback to abdomino-pelvic muscular coordination training and balloon feedback in a series of 60 adults with functional constipation unresponsive to conservative management.[259] After only two unsatisfactory sessions, patients who were judged unable to respond were switched to the alternative treatment, thus biasing the results. At the end of treatment, approximately 50% of patients in both groups rated their symptoms as significantly improved. The outcome did not correlate with colon transit time, the presence of FDD, or other functional and clinical variables.[259] No other RCTs have attempted to duplicate the results in the adult population.

In conclusion, habit training is an appealing treatment option for chronic constipation, regardless of aetiology. It is a safe and affordable treatment option. Dedicated expertise is essential to perform it, but costly pre-treatment testing is apparently not required. It comprises a non-drug, non-instrumental, holistic approach that is likely to appeal to patients with functional gastrointestinal disorders. However, it is not an evidence-based treatment and results from RCTs are pending before consistently endorsing it for all refractory constipation patients.[260]

<u>Future research/unmet needs:</u>

RCTs comparing habit training to instrumented biofeedback for constipation due to FDDs including both subjective and objective outcome measures should be conducted. RCTs comparing habit training to laxatives and different habit training protocols for chronic constipation are also needed, as well as RCTs comparing habit

training with biofeedback for constipation due to structural alterations of the pelvic floor.

ALTERNATIVE TREATMENTS

Statement 57: Chinese herbal medicine improves bowel function in functional constipation, but it is not known which formulation is best.

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

A large proportion of patients with constipation have tried alternative remedies,[261, 262] partly because of the misconception that laxatives damage the bowel in some way or make it lazy. In addition, many patients like to think that they are treating their constipation in a more 'natural' way and, therefore, food or plant extracts that are thought to have a laxative effect are very popular.

Alternative remedies are also often used by patients with IBS, and there are more studies for this condition than for FC.[263-265]

This raises the possibility of using data derived from IBS-C patients. However, the outcome measures used in these studies on alternative treatments in IBS tend to be more global, rather than reporting the actual effect on bowel function. Furthermore, even in those studies that divide patients into different bowel function subtypes, the outcomes are also usually global, rather than necessarily reporting specifically on change in stool form or frequency. Despite these drawbacks, where there is a lack of data with respect to the effect of alternative treatments in chronic constipation, it seems reasonable to consider extrapolating results from studies reporting results from IBS-C to chronic constipation.

In contrast to most other alternative approaches to treating constipation, Chinese herbal medicines have been the subject of more recent research in reasonably well-designed controlled trials. The results from these trials have shown consistently encouraging results.[266-271] However, the formulation of these products can vary, making it difficult to create specific recommendations on their use.

Future research/unmet needs:

Many of the alternative remedies for the treatment of constipation have been available for many years, but very few have been subjected to the scrutiny of a modern clinical trial. This situation is unlikely to change in the future, as it is doubtful that funding for research of these established, but largely unproven approaches, will be forthcoming. Many of these preparations contain multiple components and it would be useful to know whether all of the components are necessary for a clinical effect.

Statement 58: There is insufficient evidence to recommend acupuncture for the treatment of functional constipation

a. Level of evidence: Very low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Studies on acupuncture in any disorder are always criticised because of the difficulty in finding an appropriate control group. A systematic review of IBS acupuncture studies was inconclusive,[272] and there have been too few studies on constipation in the English literature to draw any firm conclusions.[267, 273] However, a systematic review of the Chinese literature suggests that acupuncture may be beneficial in

constipation, although the authors commented that the studies had methodological flaws.[274]

Future research/unmet needs:

Better designed trials are necessary before a final decision can be made about the utility of acupuncture in constipation.

Statement 59: There is insufficient evidence to recommend moxibustion for the treatment of functional constipation

a. Level of evidence: Very low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Moxibustion is a technique for applying heat to acupuncture points and is widely used in Asian countries. A systematic review of its use in constipation published in 2010 was inconclusive and a subsequent study was negative.[275, 276]

Future research/unmet needs:

Further trials are unlikely to provide enough new information to change practice.

Statement 60: There is insufficient evidence to recommend herbal remedies for the treatment of functional constipation

a. Level of evidence: Very low
b. Recommendation: Weak

c. Level of agreement: 100 %

Current evidence and literature:

It has been suggested that Iberogast (STW 5) may be beneficial in IBS,[277] but there are no data on its use in constipation. Other studies on herbal preparations are either conflicting, negative or of poor quality according to our understanding of medicine.[261, 278-282]

Future research/unmet needs:

Better designed trials are necessary and in particular emphasis should be placed on determining the relative contribution of the multiple constituents of these preparations to the clinical effect.

Statement 61: Abdominal massage may have an effect in functional constipation, but the way it is performed needs to be standardised before it can be recommended

a. Level of evidence: Very low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Abdominal massage would appear to be an attractive approach to managing constipation, as it should be a safe and cheap option in which the patient can engage. Trials show some effect, although the methodology of the older trials is questionable. In contrast, the more recent studies are better designed and still show an effect.[261, 283-286]

Future research/unmet needs:

More uniform and confirmatory studies using a standardised approach should be performed before abdominal massage can be recommended.

Statement 62: Behavioural approaches such as psychotherapy, cognitive behavioural therapy and hypnotherapy may improve quality of life and coping in functional constipation, but there is no research evidence to suggest that they directly improve bowel function in this disorder.

a. Level of evidence: Very low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Behavioural treatments such as psychotherapy, cognitive behavioural therapy and hypnotherapy have all been shown to be effective in IBS.[287] It therefore seems reasonable to assume that, at the very least, they might improve coping and QoL in patients with FC.

Future research/unmet needs:

The specific effect of behavioural treatments on constipation has not been investigated and there are no studies on the use of any these behavioural approaches in FC.

Statement 63: Despite a lack of good research evidence, rectal suppositories are frequently used to treat constipation and probably have some effect. They are not associated with any obvious risks.

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Glycerin or bisacodyl suppositories are frequently used as over-the-counter remedies for FC. However, there has been no good quality research on the subject, although studies that have been undertaken suggest an effect.[163, 288]

Future research/unmet needs:

Further trials on assessing the utility of these well used remedies would be welcome.

Statement 64: Rectal enemas are frequently used to aid evacuation of the distal colon and rectum, although there is no research evidence to support their use. However, a trial of enemas is probably justified in patients in whom all other measures have failed. They should be avoided in people at risk of fluid or electrolyte imbalance, such as those with cardiac or renal disease.

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

Enemas have been used for centuries to treat constipation, but unfortunately there have been no studies on their use in chronic constipation. They continue to be widely used and are available in ready-made delivery systems containing between 5 and

150 mL of fluid. The larger volume products should be avoided in the elderly or patients with renal or cardiac disease because of the potential for fluid overload or electrolyte problems, especially with phosphate enemas.[163, 288, 289]

Future research/unmet needs:

Further well designed trials on assessing the utility of enemas would be welcome.

Statement 65: Uncontrolled studies suggest that transanal irrigation improves constipation, especially where laxatives have failed. The risk of perforation is very low.

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Transanal irrigation using commercially available kits is being increasingly used for the management of bowel dysfunction, including FC. A systematic review and meta-analysis of the available uncontrolled studies in FC suggested a 50% response rate, which is comparable to that obtained with pharmacological agents.[290] Theoretically, this technique could lead to perforation, but a separate study addressing this possibility has suggested this risk is very low.[291] Active or suspected diverticulitis are contraindications and previous rectal or pelvic surgery increases the chances of perforation. Good instruction on how to use the technique is essential.[292] Colonic irrigation using large volumes of fluid is very popular as a private service but is not offered within healthcare systems. It is not recommended as there is no clinical or research evidence to support its use and it is potentially dangerous.

Future research/unmet needs:

Controlled trials of transanal irrigation in chronic constipation are needed.

MODULATION OF MICROBIOTA

Statement 66. There is insufficient evidence to recommend faecal microbiota transfer (FMT) for routine treatment of functional constipation.

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

A change in the faecal microbiota composition has been described in IBS patients. This has supported the assumption that faecal microbiota transfer (FMT) may be a therapeutic approach, particularly in patients with diarrhoea and IBS.

Only a few well-designed clinical studies have been performed in IBS patients. Johnsen et al.[293] reported on a double-blind, randomised, placebo-controlled, parallel-group, single-centre study in 90 patients with IBS with diarrhoea alone or with diarrhoea and constipation as defined by the Rome III criteria. Patients were randomly assigned (2:1) to receive either active or placebo FMT. The primary endpoint was symptom relief of more than 75 points assessed by the IBS Severity Scoring System (IBS-SSS) 3 months after FMT. Sixty-five percent of patients receiving active treatment versus 43% of patients receiving the placebo showed symptom relief 3 months after FMT (p=0.049); however, a separate analysis for the patients who also had constipation symptoms was not performed. Halkjaer et al.[294] performed a randomised, double-blind placebo-controlled trial to compare FMT versus placebo in 52 adult patients with moderate-to-severe IBS. The FMT was given

orally via capsules. The investigators found a significant improvement in the IBS-SSS score in the treatment group after 3 months (p=0.012) in favour of the placebo and not the FMT. This could indicate that the route of administration is crucial (colonoscopy versus oral administration). As patients with oral FMT also had persistent changes in their colonic microbiota composition, it may be concluded that altering the gut microbiota is not sufficient to obtain clinical improvement in IBS.[294] No subgroup analysis is available for IBS-C in this study.

Few studies with a number of methodological limitations have studied FMT in chronic constipation without IBS diagnosis. Ding et al. report an improvement in about a third of patients after three months.[295] However, patients were treated with vancomycin prior to FMT and used 2 liters of macrogol solution for bowel lavage. No sham control or placebo group was studied making it hard to conclude on the effectiveness of FMT. In a randomized trial Tian and colleagues provided evidence for superiority of FMT given by nasoduodenal tube for six consecutive days: The clinical improvement rate (ITT) was 53.3% vs. 20.0%, P = 0.009. The observation period was 12 weeks. The control group received no tube and no placebo transplant but only conventional treatment consisting of education, behavioural strategies, and oral laxatives, No long-term follow up data are available and the difference between the treatments makes it again hard to draw solid conclusions.[296] Zhang and coworkers performed another uncontrolled trial on FMT in 29 patients.[297] After 6 FMTs per patient they reported clinical remission at week 4 in 69.0% of patients. After one year 48.3% of the patients continued to have at least three complete spontaneous bowel movements per week. Again, the lack of a control group makes it hard to interpret these results.

Given the uncertainties in the definitive effect of FMT for the optimal route of administration, optimal choice of donor, optimal frequency of application, long-term outcome, and the lack of randomized, placebo/sham controlled trials, there is insufficient evidence to support such an approach in routine clinical practice.

Future research/unmet needs:

A number of different case reports and case series have been published; however, controlled trials are sparse. In patients with constipation, well-designed trials are lacking and should be performed.

Statement 67. There is some limited evidence for a positive effect of probiotic preparations on acceleration of intestinal transit time and improvements in stool frequency in both children and adults. However, studies are generally of high heterogeneity and the optimal species/strains are unknown. Therefore, there is no sufficient evidence to recommend a specific probiotic preparation/strain for the treatment of functional constipation.

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature:

Moreira et al. found no difference in an RCT comparing an intervention group receiving a probiotic fermented milk beverage with a control group receiving non-probiotic milk in 49 female patients with chronic constipation.[298] Interestingly, the consumption of milk resulted in an improvement in constipation symptoms, regardless of the probiotic culture.[298] In a well-designed RCT, Spiller et al. reported a positive effect of *Saccharomyces cerevisiae* in patients with IBS-C.[299] The study included 379 patients who received either 1000 mg of the probiotic or placebo for 12 weeks. While there was no overall benefit of *S. cerevisiae* on IBS symptoms and well-being in the total study population, a significant improvement was observed in the IBS-C subjects with respect to abdominal pain/discomfort and bloating.[299]

However, this subgroup analysis had not been planned initially. Mezzasalma et al., in a randomised, double-blind, three-arm parallel group trial in 150 IBS-C patients who received either a daily oral dose of two probiotic mixtures or placebo (for 60 days) found a higher response rate in the two treatment groups.[300] An increase in bowel movement frequency, improvement in stool consistency and reduction in abdominal bloating were reported in 70%, 60%, and 47% of patients in a study with the probiotic preparation VSL#3, which contains 8 different bacterial strains.[301]

Older studies have been summarised in a 2014 meta-analysis by Ford, Quigley and co-authors, who selected 43 RCTs.[302] In their analysis, probiotics had beneficial effects on abdominal pain, bloating, and flatulence scores in general.[302] In only two RCTs that focused on constipation, limited beneficial effects were described (mean increase in number of stools per week = 1.49; 95% CI=1.02-1.96).[303, 304]

The RCTs studied different bacterial preparations for different treatment periods, with or without PEG, with different endpoints. This obvious high heterogeneity of even the well-designed clinical trials prevents a recommendation on a specific probiotic preparation/strain for the treatment of FC.

<u>Future research/unmet needs:</u>

RCTs need to be performed for well characterised probiotic preparations that focus selectively either on IBS-C or FC patients. Too many post hoc subgroup analyses have been performed that had no primary focus on constipation. Additional microbiota analyses should be required to evaluate whether an impact on microbiota composition is associated with symptom relief.

SURGICAL TREATMENT

Statement 68. Surgical treatment options, both resecting and non-resecting, might be considered for selected patients if all other conservative treatments show no effect.

a. Level of evidence: Moderate

b. Recommendation: Strong

c. Level of agreement: 100 %

Current evidence and literature:

Surgical interventions for chronic constipation are, and should be, rare. If all other conservative treatment fails, there is a surgical option.[305, 306] Surgical interventions should be offered as a last resort and should be carefully considered.

Future research/unmet needs:

RCTs are lacking, there are few cases, and data in observational studies is inconsistent. RCTs should be performed and patient selection for procedures should be improved.

Additional comments:

If no other treatment achieves improvement and the patient is experiencing severe symptoms, then surgery can help to ease them **as a final option**. However, decision for surgical treatment option includes acceptance of any possible surgery related morbidity (wound infection, hernia formation, revision surgery) including even mortality. This has to be pointed out carefully to the patient during the informed consent discussion.

Statement 69: Surgical treatment should only be offered after performing physiological tests and only if the cause for the chronic constipation lies within the colon and/or rectum (slow-transit constipation, evacuation disorder)

a. Level of evidence: Low
b. Recommendation: Strong
c. Level of agreement: 100 %

Current evidence and literature:

We do not recommend performing any surgical intervention without a thorough physiological examination.[49, 307]

Future research/unmet needs:

RCTs are lacking, there are few cases, and data is inconsistent in observational studies. RCTs should be performed and patient selection for procedures should be improved.

Additional comments:

Surgery is always the last resort. With this statement we want to stress that before considering surgery, physiological testing is critical to plan for the right surgical treatment. And of course, ONLY after all other treatment options have failed.

Statement 70: PEC/Malone antegrade colonic enema is a non-resecting surgical treatment to flush the large intestine orthograde through an appendiceal stoma for highly selected patients suffering from slow transit constipation.

a. Level of evidence: Very low
b. Recommendation: Weak
c. Level of agreement: 100 %

Current evidence and literature

Only observational studies are available. Due to the low number of cases and lack of RCTs, there is no recommendation for this procedure. In rare cases, the procedure is successful. A recent study showed no improvement in QoL and the procedure also has a high complication rate.[308-311]

Future research/unmet needs

RCTs should be performed in adults. Very rarely performed procedure.

Additional comments:

The level of recommendation is “weak” because the literature mainly focuses on paediatric patients and the complication rate in adults is high; overall, the number of adult patients is low. Performing RCTs in this setting is not feasible. However, it is a procedure worth trying before performing more radical approaches such as a definitive stoma or colectomy. Therefore, we suggest this procedure before radical surgery.

Statement 71: Continuous direct nerve stimulation (SNS/SNM) can ease symptoms in patients suffering from chronic constipation (slow-transit constipation and/or evacuation disorder) and is the least invasive surgical option for patients after all conservative treatment has failed. The success rate might be low, but the low complication rate justifies the intervention.

a. Level of evidence: Low
b. Recommendation: Weak
c. Level of agreement: 75 %

Current evidence and literature

Three recent RCTs with n ~40-50 reported that SNS did not significantly improve (increase) the frequency of bowel movements.[312-315] However, SNS stimulates afferent and efferent nerves which might contribute to better awareness and consecutively ease complaints. Of all surgical therapy options SNS is the least invasive, and despite a low success rate, SNS also has a low complication rate which may justify its application in selected patients. Patients might choose SNS over colectomy or definitive stoma.

Future research/unmet needs

Three recent RCTs are available. Better patient selection seems to be the main goal for further studies.

Additional comments:

The evidence level is too “low for a strong recommendation”, but it may be worth trying before performing more invasive surgery.

Statement 72: Total or segmental colectomy can be an effective treatment in highly selected patients with normal upper GI function and slow-transit constipation who do not respond to medical treatment and have normal evacuatory function.

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 91 %

Current evidence and literature:

In segmental colonic resection, a targeted open or laparoscopic resection of the ineffective bowel segment is performed to improve transit time. Patients with an isolated megasigmoid profit most from segmental colonic resection. Total colectomy (open or laparoscopically performed) can be done by resecting or preserving the ileo-caecal valve (ileorectal anastomosis [IRA] vs. caecorectal anastomosis [CRA]). Complications occur in approximately 24% of cases, the most common being small bowel obstruction. However, reported patient satisfaction is high.[316] Significant psychological disorders seem to have a negative effect on the colectomy.

Future research/unmet needs:

In comparison to all other surgical procedures for constipation, colectomies are well studied.

Additional comments:

Worldwide, definitive stoma formation is probably the most frequently used surgical option for severe constipation (due to costs and lack of physiological testing).

Statement 73: Surgery can be an effective treatment for patients who suffer from an evacuation disorder due to structural causes (i.e. intussusception, rectocele, rectal prolapse, descending perineum syndrome) proven by imaging after failed conservative treatment.

a. Level of evidence: Moderate
b. Recommendation: Strong
c. Level of agreement: 92 %

Current evidence and literature

The surgical method is chosen depending on the pathology. In the case of intussusception, rectocele or prolapse, a STARR or internal Delorme procedure can be done. Patients show a decrease in the Longo's Obstructed defecation Score (ODS). There is virtually no evidence in the literature to support rectocele resection performed trans-anally, vaginally, or transperineally, with or without levatorplasty.[317-319]

Future research/unmet needs:

At present, there are mostly observational studies and the evidence level is low.

DISCUSSION

This document presents guidelines created by the ESNM for the management of chronic constipation. Following a careful Delphi process, 73 statements were produced and graded according to the level of evidence and the strength of recommendation using the GRADE method. Three algorithms were also developed for the management of constipation. The first algorithm is for first-line management of chronic constipation; the second for further investigation of patients with an unsatisfactory response to first-line management; and the third is for the treatment of constipation not caused by an evacuation disorder and which is refractory to first-line management. In addition to recommendations for the practical management of constipation, unmet needs were identified and future research lines proposed.

In order to develop these comprehensive guidelines that we hope will be useful across Europe, we included experts in different fields who manage constipation, including general practitioners, gastroenterologists, experts in neurophysiology and motility, radiologists and surgeons, originally from eight European countries. In general, the authors discovered only moderate or low levels of evidence for most of the evaluated items (Table 1). Among the diagnostic studies, only the usefulness of anorectal manometry for the comprehensive evaluation of anorectal function showed a high level of evidence.[60-62] Among the therapeutic alternatives, only treatment with saline laxatives, especially polyethylene glycol,[8, 181, 190, 191] the prokinetic drug prucalopride,[221-236] secretagogues like linaclotide and lubiprostone,[55, 70, 79, 247-260, 320-324] and PAMORAs for the treatment of opioid-induced constipation [181, 238-240] showed high levels of evidence. Despite the different backgrounds of the panel members and the lack of studies with high levels of evidence, an excellent level of agreement between the experts was obtained for most items, as observed in Figure 1. All but four statements were completely agreed/agreed upon by 70% or more of the authors (Figure 1). These four items were related to the surgical management of constipation, with the greatest disagreement on the use of continuous direct nerve

stimulation (SNS/SNM) for the treatment of this condition. Three newly published RCTs have shown no benefit for SNS/SNM on stool frequency in patients with chronic constipation,[312-315] and several of the panel considered that there was no place for this treatment modality. Nonetheless, other authors proposed a trial of SNS/SNM before more aggressive surgical treatment is considered, mainly due to the low rate of side effects of the technique.

In contrast to prokinetics and secretagogues, the evidence for the efficacy of alternative treatments and probiotics was “low” or “very low” in all cases. Consequently, the strength of the recommendation to use these treatments is generally “weak”. One exception was the use of suppositories and rectal enemas, which are strongly recommended despite the low scientific evidence in the literature, mainly because both treatments have been safely used for years worldwide.[163, 280-289] For the remaining treatment modalities, the authors found at least moderate evidence of their efficacy. However, the need for studies is great in most areas, and the final recommendations are the result of a mixture of tradition, personal experience and rational use of resources, as well as the available evidence. In this regard, in some cases the guideline is a compromise between what is traditionally used in different settings and the acceptance of different treatments in different regions. For example, rectal enemas or anal irrigation may have varying acceptance in different countries, and the choice of stimulant laxatives, prokinetics or secretagogues may depend on local tradition or on local costs and access to specific drugs.

Of note, and despite some minor differences, the present guidelines are largely consistent with previous publications.[8, 54, 55, 325, 326] The Guideline of the American College of Gastroenterology published in 2014[8] also recommends bulking agents, osmotic and stimulant laxatives, prokinetics and secretagogues, despite different levels of evidence between the treatments, but with a weak degree of

recommendation for non-pharmacological treatments like biofeedback therapy or probiotics. However, these European guidelines give a strong recommendation for biofeedback as the preferred treatment strategy for constipation in functional defecation disorders whenever dedicated expertise is available, regardless of abnormal bowel transit. The World Gastroenterology Organization Guideline published in 2010[54] differentiated between countries with high and low technical resources. For that reason, the colonic transit time test with radiopaque markers, which is cheap and easy to perform, was considered a first-line option. In the present guidelines, measurement of colonic transit time is suggested after an evacuation disorder has been excluded, as this may delay the colonic transit time and produce misleading results.[79-81] The American Gastroenterological Association (AGA) guidelines released 2013[55] considered that radiological examinations for evacuation disorders (defecography) should be performed when anorectal manometry and the balloon expulsion test are inconclusive. However, considering different levels of access to motility and sophisticated radiological explorations in European countries, we decided to put the various radiological and manometric investigations for evacuation disorders at the same level in the algorithm.

In the present guideline, the authors reached the consensus that when an evacuation disorder is suspected in patients non-responding to first line therapy with bulking agents/osmotic laxatives, evaluation of an evacuation disorder with functional studies could help to discriminate patients that could benefit from biofeedback therapy, before a costly chronic treatment with prokinetics and/or secretagogues is started. However, we acknowledge that this recommendation may be controversial, and treatment with secretagogues or prokinetics at this stage could also be considered before future studies comparing the cost-effectiveness of these strategies are available.

An important issue on which all authors agreed was the lack of consistent terminology in this area, resulting in considerable confusion in the medical community. Hence, the terms functional constipation, chronic constipation, defecation disorder, evacuation disorder, outlet obstructed evacuation, dyssynergic defecation, etc. have been used in the literature to describe sometimes the same and, at other times, completely different phenomena. After discussion, the authors of these guidelines reached the consensus that the term chronic constipation be used for all types of constipation with a duration greater than 3 months, and the terms slow-transit constipation or normal transit constipation only when objective evidence has been obtained from transit studies. In relation to evacuation disorders, the generic term “evacuation disorder”, which encompasses both structural and functional causes is used, and the specific terms “functional defecation disorder,” as defined by the Rome IV consensus, and “structural defecation disorder” are used to differentiate between both types of evacuation disorders.

The aim of the guidelines is to provide a practical tool for physicians all over Europe for the management of patients with chronic constipation. These guidelines have addressed mainly the general adult population with chronic idiopathic constipation. Specific groups such as those with constipation secondary to neurological disorders or to spinal cord injury, or constipation associated with special conditions like pregnancy have not been addressed in the present document. Likewise, the treatment of specific complications like faecaloma, disimpaction or incontinence secondary to constipation have not been covered here either.

In conclusion, these ESNM guidelines for the management of chronic constipation are presented as a practical tool for the management of adult patients with constipation. They provide sequential algorithms for a progressive diagnostic and management process. This starts with initial first-line assessment and management

using general measures and bulking or saline laxatives, followed by more comprehensive diagnostic procedures and more intensive treatment modalities in those patients who fail to respond to first-line treatments.

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TABLE 1. Level of evidence and strength of recommendation of the different statements related to diagnostic approaches and treatment groups (%).

	Level of evidence				Recommendation	
	High	**Moderate**	**Low**	**Very low**	**Strong**	**Weak**
Clinical approach	0	67	16,5	16,5	67	33
Functional studies	14	43	29	14	100	0
Radiological studies	0	30	60	10	67	33
General measures	0	50	50	0	75	25
Bulking/osmotics	25	50	25	0	75	25
Stimulant	0	83	17	0	67	33
Prokinetics/secretagoges	67	16.5	16.5	0	67	33
Biofeedback	0	50	50	0	50	50
Alternative treatments	0	0	44	56	22	78
Probiotics	0	0	100	0	0	100
Surgical treatment	0	50	33	17	83	17

FIGURE LEGENDS

Figure 1. Final agreement between the authors for each of the statements produced after the Delphi consensus process.

Figure 2. Algorithm 1. Management of constipation. First-line management of patients presenting with constipation at any level of the health-care system.

1. Defined as difficult, unsatisfactory or infrequent defecation for at least the previous 3 months.
2. Rescue therapy may include suppositories or rectal enemas, if accepted by the patient, or the use of fibre or osmotic laxatives on demand. Level of evidence very low. Recommendation strong.
3. Use of probiotics seems promising, however no strong evidence yet.
4. When available, anorectal function testing may be indicated at this stage when there is clinical suspicion of an evacuation disorder (manual manoeuvres, haemorrhoids, prolapse or rectocele, painful evacuation, etc.)
5. Alternatively, other treatments like prokinetics or secretagogues could be tried.

Figure 3. Algorithm 2. Further investigation of constipation.

1. Anorectal function testing with manometry should ideally include a balloon expulsion test. Depending on local availability and expertise, defecography could also be performed at this stage (either barium or magnetic resonance).
2. According to the Rome IV consensus, functional defecation disorder (FDD) is defined as:

I. The patient must satisfy diagnostic criteria for functional constipation and/or irritable bowel syndrome with constipation

II. During repeated attempts to defecate, there must be features of impaired evacuation, as demonstrated by 2 of the following 3 tests:

a. Abnormal balloon expulsion test

b. Abnormal anorectal evacuation pattern with manometry or anal surface EMG

c. Impaired rectal evacuation by imaging

Subcategories for FDD

a). Diagnostic Criteria for Inadequate Defecatory Propulsion

Inadequate propulsive forces as measured with manometry with or without inappropriate contraction of the anal sphincter and/or pelvic floor muscles[b]

b). Diagnostic Criteria for Dyssynergic Defecation

Inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defecation[b]

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

These criteria are defined by age- and sex-appropriate normal values for the technique.

3. Before considering any surgical correction, evaluate the feasibility of biofeedback treatment as the option with the least side effects.

4. Evaluation of colonic transit time can be useful in patients without evacuation disorders, as well as in patients with persistent constipation after treated evacuation disorders.

5. This means according to Rome IV: Chronic constipation due to "Disease-related", "Medication-induced" or "IBS-C“. At this stage

3068 further investigation or symptomatic treatment will be considered.

3069

3070 Figure 4. Algorithm 3. Treatment of constipation not caused by an evacuation
3071 disorder and refractory to first-line management.

3072 1. The first choice will depend on the patient's characteristics, like
3073 coexistence of abdominal pain or distension, cost/efficacy evaluation,
3074 and local preferences.
3075 2. As rescue therapy, stimulant laxatives may be used, as well as
3076 suppositories, rectal enemas or rectal irrigation.

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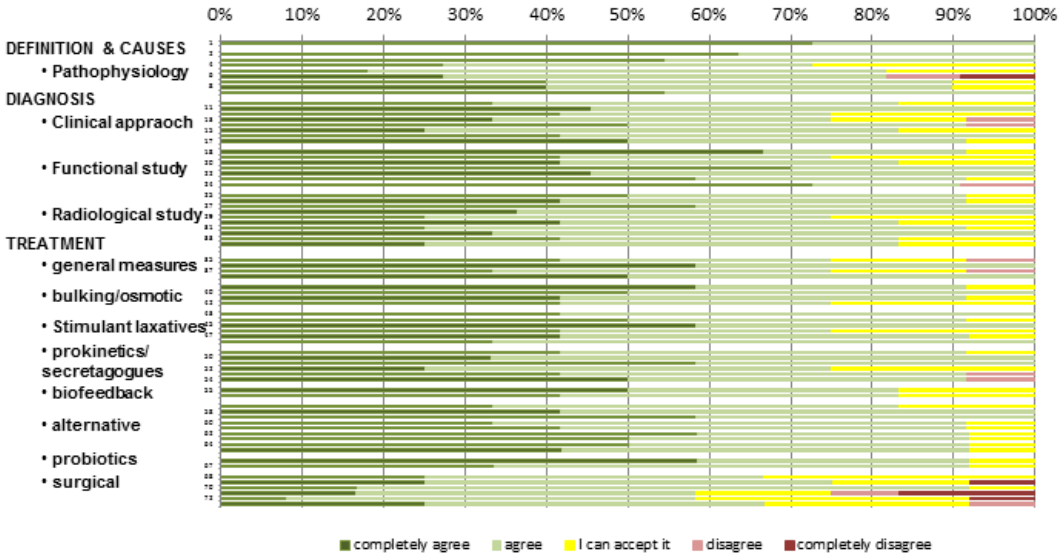
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• Stimulant laxatives
• prokinetics/ secretagogues
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Figure 2.

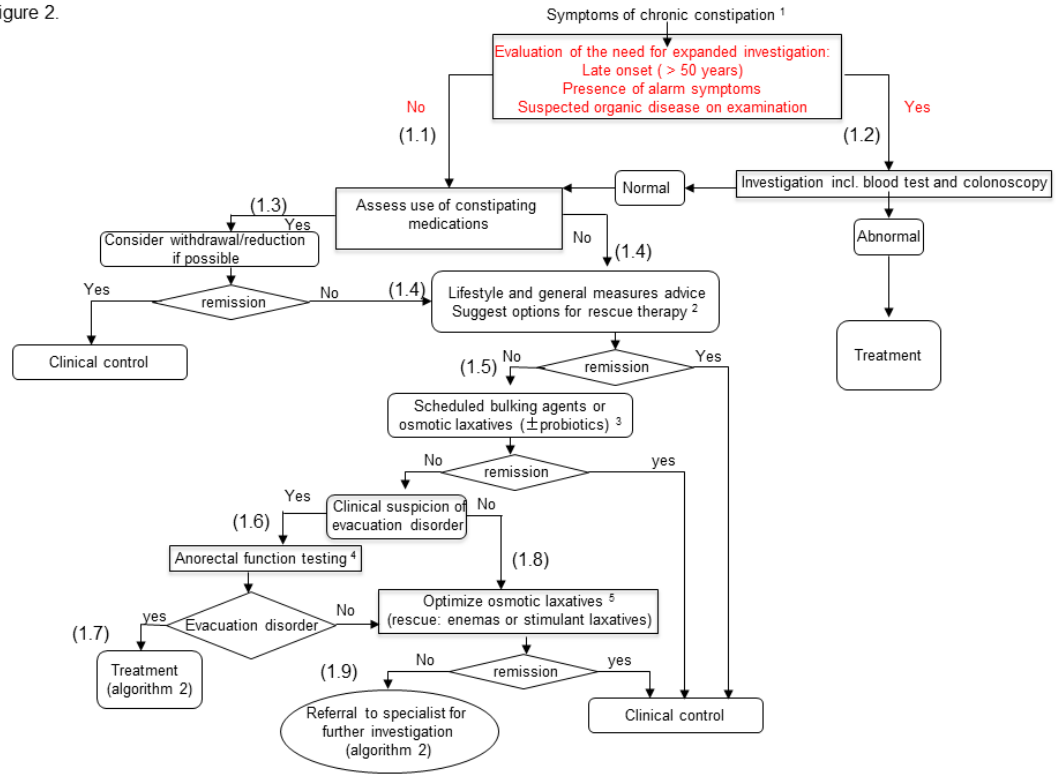

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Figure 3.

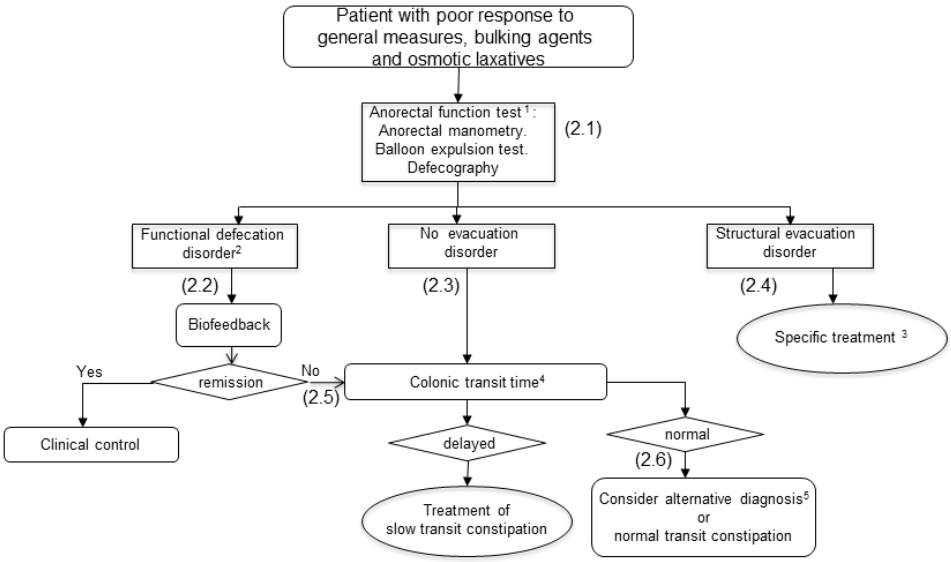

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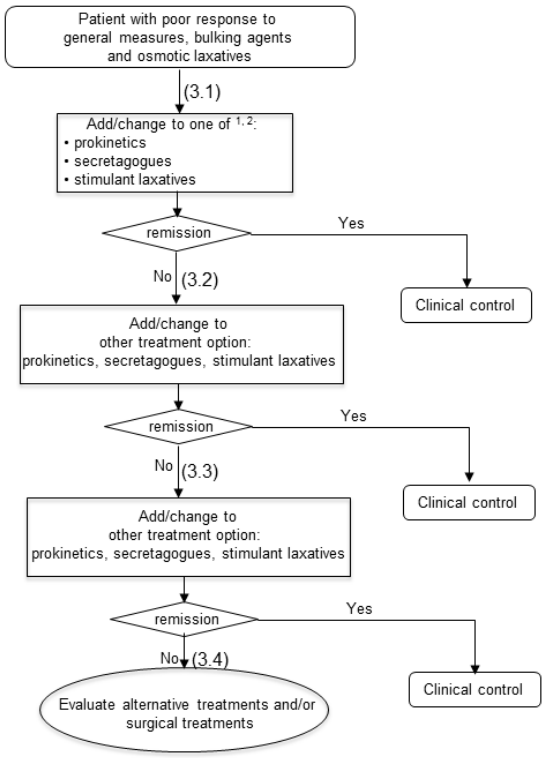
Figure 4.



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