

Guidelines for the Diagnosis and Treatment of Chronic Functional Constipation in Korea, 2015 Revised Edition

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The Korean Society of Neurogastroenterology and Motility first published guidelines for chronic constipation in 2005 and was updated in 2011. Although the guidelines were updated using evidence-based process, they lacked multidisciplinary participation and did not include a diagnostic approach for chronic constipation. This article includes guidelines for diagnosis and treatment of chronic constipation to realistically fit the situation in Korea and to be applicable to clinical practice. The guideline development was based upon the adaptation method because research evidence was limited in Korea, and an organized multidisciplinary group carried out systematical literature review and series of evidence-based evaluations. Six guidelines were selected using the Appraisal of Guidelines for Research & Evaluation (AGREE) II process. A total 37 recommendations were adopted, including 4 concerning the definition and risk factors of chronic constipation, 8 regarding diagnoses, and 25 regarding treatments. The guidelines are intended to help primary physicians and general health professionals in clinical practice in Korea, to provide the principles of medical treatment to medical students, residents, and other healthcare professionals, and to help patients for choosing medical services based on the information. These guidelines will be updated and revised periodically to reflect new diagnostic and therapeutic methods.

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Key Words

Adaptation; Constipation; Diagnosis; Guideline; Treatment

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Introduction

Background

Constipation is a common gastrointestinal disease that may result in chronic and disabling symptoms. Estimates of the prevalence of constipation range from 10% to 15% in North America.¹ In the survey administered to Asians, the prevalence of chronic constipation was reported as 15-23% of female respondents and 11% of male respondents^{2,3} and the prevalence of self-reported constipation was 16.5% in the general population and 9.2% of 'functional constipation' according to the Rome II criteria.⁴ Constipation substantially affects the quality of life in that 70% of respondents feel its disruption to their day-to-day activities.⁵ Chronic constipation can be primary or secondary to other medical conditions, including neurological, metabolic, or endocrine diseases. Functional constipation is a chronic condition and has various constipation-related symptoms; thus, its treatment is challenging and it has a high socioeconomic burden.⁶

In 2005, the Korean Society of Neurogastroenterology and Motility published guidelines for chronic constipation entitled "Review: evidence-based guidelines for diagnosis and treatment: diagnostic guidelines for constipation" and "Review: evidence-based guidelines for diagnosis and treatment: therapeutic guidelines for constipation", but these were based primarily on Western guidelines and were written in the form of a narrative review.^{7,8} In 2011, the "Guidelines for the treatment of constipation" were updated to fit a realistic medical environment in Korea using evidence-based development of guidelines.⁹

Since those guidelines were published, there have been several newly developed therapeutic tools, including pharmaceutical and non-pharmacologic modalities. Furthermore, the previous Korean guidelines lacked multidisciplinary participation and did not include a diagnostic approach for chronic constipation. Although the previous guidelines were introduced and promoted, a recent survey in Korea revealed that 25-48% of patients exhibited poor recognition of constipation¹⁰ and a European study reported that 28% of constipation patients were not satisfied with existing treatments.¹¹ As most laxatives, including stimulant laxatives, are currently purchased without prescriptions in Korea, there have been concerns about abuse. For these reasons, we sought to revise the clinical guidelines to realistically fit the situation in Korea and to be applicable to clinical practice. The Guideline Steering Committee under the Korean Society of Neurogastroenterology and Motility initiated this revision

in May 2013.

The attributes of this revision are as follows. First, systematic search and literature reviews were performed to examine the evidence in a scientific and objective manner. Second, the development of the revised guidelines used an adaptation process involving a methodology designed to maximize the use of existing evidence-based guidelines and to fit them into the clinical situation in Korea, where research evidence has been explored less extensively.¹² The development of evidence-based clinical guidelines has been increasingly recommended and recently, the ADAPTE Collaboration was organized; it has proposed principles and standardized processes to facilitate the consistent development of guidelines through this adaptation process. The development of the current guidelines used the ADAPTE process.^{13,14}

Target Population and Purpose of the Guidelines

Adults in need of diagnosis and treatment for chronic constipation are the primary targets, and patients who are suffering from the inconvenience associated with chronic constipation are included within the target population. The guidelines analyzed recent scientific evidence with the aim of assisting clinicians and patients in making decisions under conditions where diagnosis and treatments for chronic constipation are needed. The guidelines are also intended to help primary physicians and general health professionals to make management decisions in the fields of gastroenterology, digestive surgery, and radiology. The guidelines suggest a variety of alternatives for diagnoses and treatment methods, summarize the pros and cons of each method, and provide specific guidelines with regard to the choice of the methods and the corresponding clinical situations. Furthermore, they may be used as instructional materials and provide the principles of medical treatment to medical students, residents, and other healthcare professionals. Patients will benefit because they will have more accurate expectations of the services to be offered and will be able to choose medical services based on the information, indicating that these guidelines can educate and help them communicate regarding medical services and needs.

Scope of the Revised Guidelines

As standardized recommendations that address the diagnosis and treatment of chronic constipation in a comprehensive and practical manner, these guidelines targets adults and excludes children. Because it was not possible to address all methods associated with constipation in the guidelines, we included only commonly accepted or widely used methods, and briefly introduce new treatment modalities, including medicines, that have some clinical evidence. We

excluded controversial information that lacks scientific evidence and issues that are still embroiled in controversy from these newly revised guidelines. When necessary, experts achieved consensus using the Delphi method to settle issues lacking a clear scientific basis.

Process of Updating the Chronic Constipation Guidelines

Guideline Committee

The Steering Committee consisted of the President and executives of the Korean Society of Neurogastroenterology and Motility. The committee established guideline development strategies, appointed a committee chairperson, and appraised/approved budget related to the project. Furthermore, the committee reviewed the recommended revisions, approved/published the final version of the guidelines, and monitored the process to ensure the participation of interested parties and the independence of the editing.

The committee for constipation management guidelines included members of the clinical management guideline group under the Korean Society of Neurogastroenterology and Motility, the chairman (H.K.J.), the secretary (J.E.S.), 6 general members (Y.J.C., T.H.L., H.L., K.H.S., S.N.H., and H.C.I.), 1 methodology expert (E.S.S.), and a coordinator. In the process of guideline development, the Korean Society of Coloproctology (S.S.C.) and the Korean Society of Radiology (S.J.L.) facilitated multidisciplinary involvement. The Guideline Development and Writing Committee set detailed goals for the guidelines, carried out detailed procedures for adaptation development, and took on various tasks including searching the evidence, developing the proposed recommendations, drafting the guidelines, and revising them. At the first meeting in March 2013, the principles of guideline development, time schedules, and guideline scopes were agreed upon. There were several workshops for establishing methods for guideline development: “The use of adaptation development to establish guideline development” (May 10, 2013), “Quality evaluation of the literature according to the Appraisal of Guidelines for Research & Evaluation (AGREE) II” (June 21, 2013), “The practical evaluation of guidelines using AGREE II” (July 19, 2013), and “Method of data extraction/evidence inventory table” (August 31, 2013). During the development process of the guidelines, there were 12 meetings of the Guideline Development Committee.

Process of Adaptation Development

Characteristics

The guideline development was based upon the adaptation method because research evidence was limited in Korea; an organized multidisciplinary group involving the Korean Society of Coloproctology and the Korean Society of Radiology carried out systematic review and series of evidence-based evaluations. In contrast with the 2011 constipation treatment guidelines, the diagnosis of chronic constipation and new medicines were added. Following the findings of recent studies, we properly adjusted the grades of recommendation. An expert methodologist (E.S.S.) from the Korean Academy of Medical Science was involved in revising the guidelines to ensure the process in a scientific and standardized manner.

Clinical questions

To determine the clinical questions that should be included in the treatment guidelines, we designed an investigation table in accordance with the “PICO” principles: P (population) was defined as constipation patients or clinical characteristics of constipation, I (intervention) was defined as diagnostic or therapeutic intervention, C (comparison) was defined as the control group, and O (outcome) was defined as the effectiveness of the diagnosis or treatment. We tried to include these four principles into clinical questions. After collecting investigation tables that contained clinical questions, we prioritized them through structural debates.

Web search

In July 2013, we used the following electronic databases to search for relevant information and preexisting guidelines: MEDLINE, MEDLINE Systematic Review, MEDLINE Clinical Study, OVID MEDLINE, EMBASE, the Web of Science, SCOPUS, the Cochrane Library, the National Guideline Clearinghouse, Guidelines International Network, Google Scholar, KoreaMed, MEDRIC, KISS, and Korea National Assembly Electronic Library.

The search words were constipation-related index words (“constipation” OR “dyschezia” OR “anismus” OR “dyssynergic defecation” OR “obstructive defecation”) and guideline-related index words (“guideline” OR “guidelines as topic” OR “guideline adherences” OR “practice guideline” OR “practice guidelines as topic” OR “clinical guideline” OR “clinical practice guideline” OR “consensus” OR “recommendation” OR “workshop” OR their combination) (Appendix).

The criteria for selecting preexisting guidelines were as follows: (1) evidence-based, (2) written in Korean or English, (3) published between 2002 and 2013, (4) targeted at adults aged 19 or older, (5) latest revised versions, and (6) agreed upon by experts and external review.

Exclusion criteria were as follows: (1) guidelines not made in an evidence-based manner; (2) only targeted at inpatients, (3) outdated, and (4) addressed over-the-counter drugs (Fig. 1).

The first literature selection was performed by a medical librarian (E.A.J.), who is an expert in systematic literature reviews. She performed the search process as mentioned above, organized the findings with Endnote (Endnote X7; Thomson Reuters, New York, NY, USA) and Excel (Excel 2010; Microsoft, Redmond, WA, USA), and removed duplicate documents.

A second review was performed by reviewing the titles and abstracts from the first review to select articles that satisfied both

the inclusion and exclusion criteria. Then, 2 independent reviewers read selected full articles for content validity. When there was agreement between them and the article was suitable for this adaptation, the article was selected. If the 2 reviewers could not reach an agreement, a chairperson was engaged to reach consensus. Ultimately, six preexisting guidelines were selected as seed guidelines (Fig. 1).

Evaluation and selection of seed guidelines

We used AGREE II, which is an internationally recognized method for developing guidelines, to evaluate the quality of the seed guidelines for adaptation. Each seed guideline was evaluated by 2 reviewers; we provided lectures and workshops to minimize the variation in scores across reviewers and to enhance their understandings of AGREE II. For this process, we followed the Korean-AGREE II method, developed by the Steering Committee for Clinical Practice Guidelines of the Korean Academy of Medical

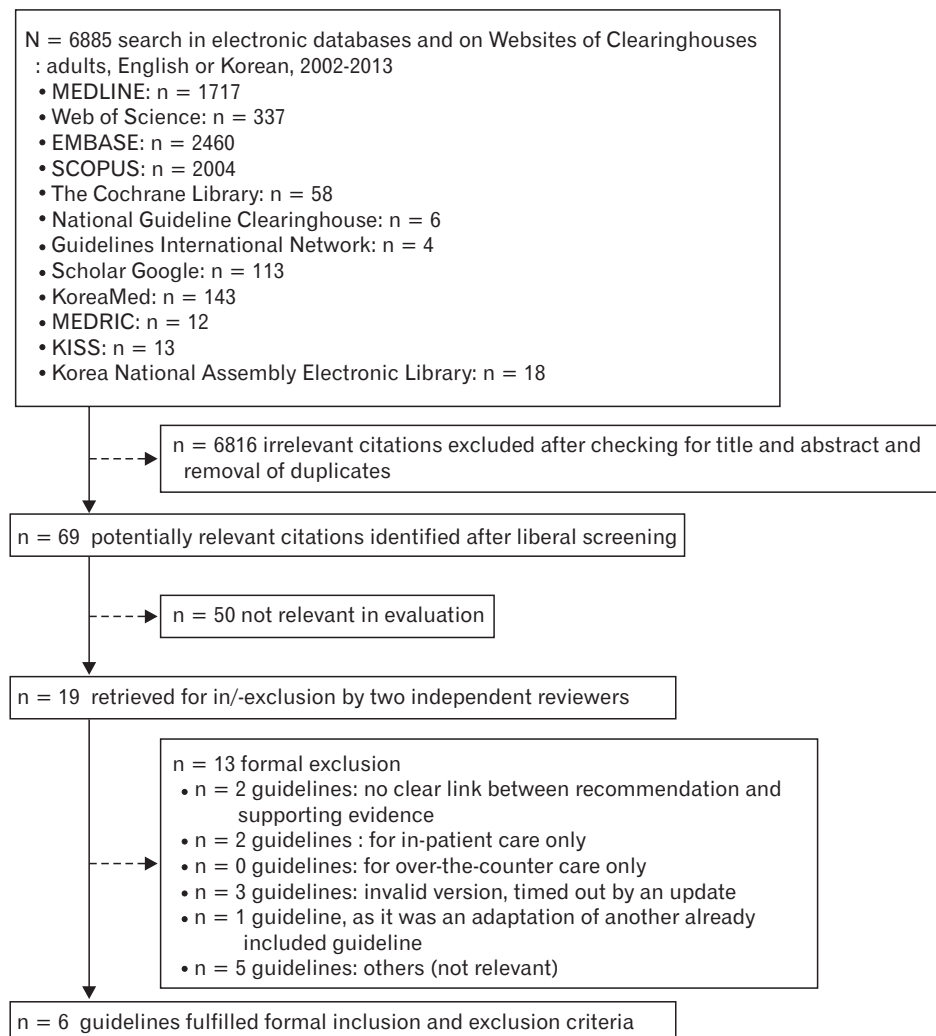


Figure 1. Flowchart of study selection.

Sciences. The Korean-AGREE II was tested for validity through official consensus, and was shown to be valid.¹⁵ In the workshops, we selected one guideline, and all reviewers evaluated it using

AGREE II, compared our findings with those of an experienced member for the Steering Committee for Clinical Practice Guidelines of the Korean Academy of Medical Sciences, and adjusted our

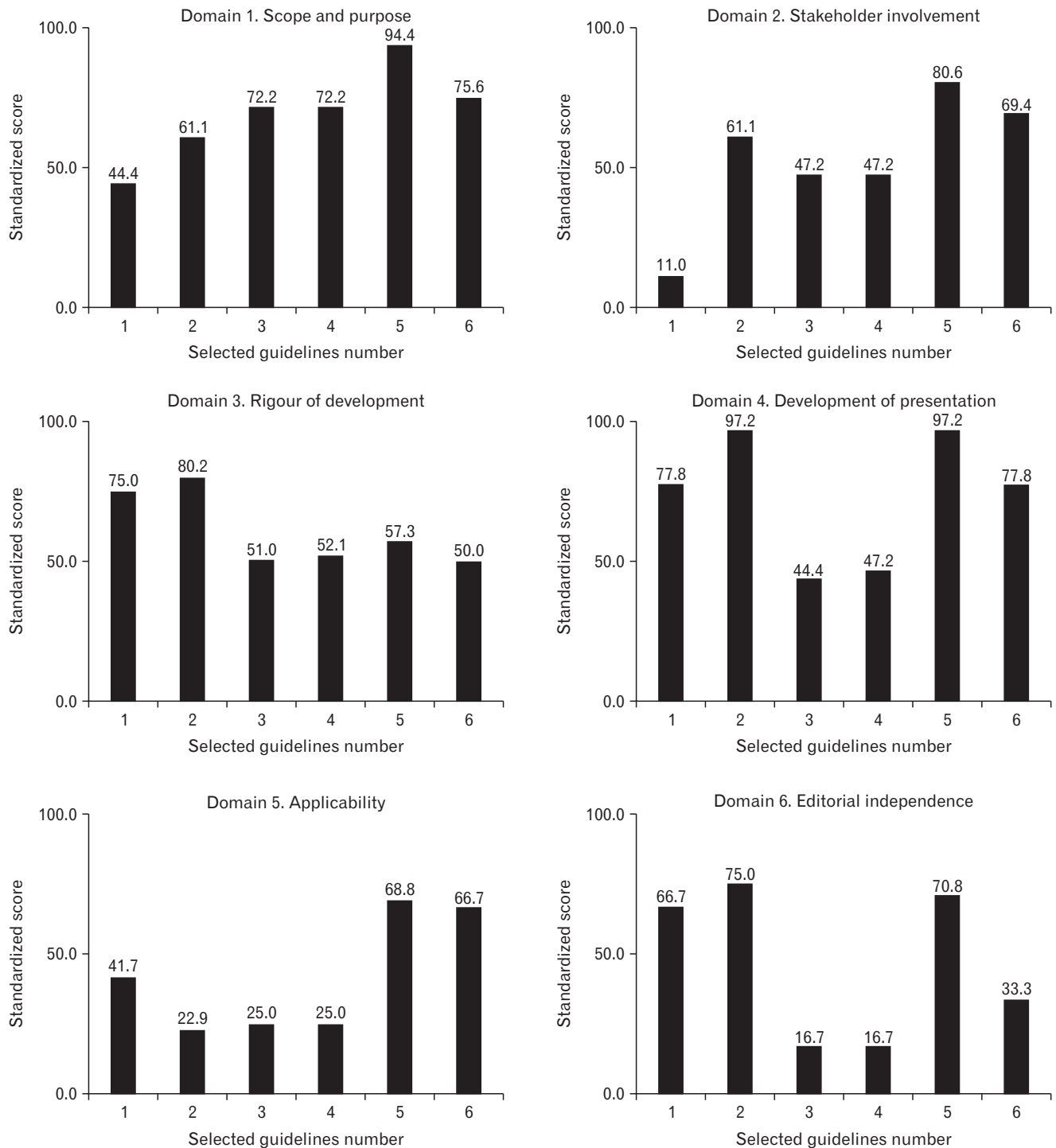


Figure 2. Appraisal results of candidate guidelines by the Appraisal of Guidelines for Research & Evaluation (AGREE) II. Selected guidelines number: 1, Canadian recommendation; 2, Korean guideline; 3, Italian consensus for diagnosis; 4, Italian consensus for treatment; 5, American Gastroenterological Association medical position statement on constipation; and 6, American Gastroenterological Association technical review on constipation.

findings based on the member’s feedback. Two reviewers assessed each guideline, and reevaluated any guidelines for which the difference in scores was 3 points or higher on any 5 items or more. We standardized scores for each domain, created a distribution chart, and then selected 6 seed guidelines by comparing the scores in each domain (Fig. 2). We prioritized rigor of development in the selection criteria, and only selected guidelines with a rigor score of at least 50 points.

Extraction of recommendations

After selecting seed guidelines, we prepared a recommendation

matrix for data extraction to extract recommendations for each subtitle based on the clinical question (PICO; Table 1). We extracted recommendations with references that best fitted the clinical questions from the selected guidelines, created a matrix based on commonly shared contents and referred articles, and developed a single set of proposed recommendations.

Level of evidence and grade of recommendation

To develop a rating system reflecting the level of evidence for each recommendation, we conducted a comprehensive quality evaluation that included the planning method, quality, and consistency

Table 1. Data Extraction Form/Evidence Inventory Form For the Effect of Bulking Agents in Chronic Constipation

Item	Guideline/Country/Synopsis of Recommendations	Supporting Evidence						
		SR/MA	NR	RCT	NRCS	OS	CS	G
Bulking agent	G1 (Canada) Psyllium is effective in the short-term treatment of chronic constipation. Studies of longer duration are lacking. (Level B; agreement a: 80%, b: 20%)	0	0	4	0	0	0	1
	G2 (Korea) Bulking agent is effective in the treatment of chronic constipation. (Grade 1A)	0	0	5	0	0	0	1
	G4 (Italy) The use of psyllium is supported by Level II evidence, Grade B recommendation	0	0	5	0	0	0	1
	G5, G6 (AGA): After discontinuing medications that can cause constipation and performing blood and other tests as guided by clinical features, a therapeutic trial (ie, fiber supplementation and/or osmotic or stimulant laxatives) is recommended before anorectal testing (strong recommendation, moderate-quality evidence)	1	0	0	0	1	0	1
	Fiber supplementation is a first step in patients with chronic constipation, particularly in primary care							

SR/MA, systemic review/meta-analysis; NR, nonsystematic, narrative review; RCT, randomized controlled trial; NRCS, non-randomized comparative study; OS, observational study; CS, case series study; G, guideline; AGA, American Gastroenterological Association.

Table 2. Level of Evidence and Grade of Recommendation^{16,17}

Item	Definition
Level of evidence	
A. High-quality evidence	Further research is unlikely to change our confidence in the estimate of effect. Consistent evidence from the RCTs without important limitations or exceptionally strong evidence from observational studies.
B. Moderate-quality evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.
C. Low-quality evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws, or indirect evidence, or expert’s consensus.
Strength of recommendation	
1. Strong recommendation	Recommendation can apply to most patients in most circumstances.
2. Weak recommendation	The best action may differ depending on circumstances or patient or society values. Other alternatives may be equally reasonable.

RCT, randomized controlled trial.

of the study based on Grading of Recommendations Assessments, Development, and Evaluation criteria for high overall quality of evidence across outcomes; this consisted of three levels (Table 2).^{16,17}

Recommendations were graded as either strong or weak. A strong recommendation was defined as a recommendation where positive effects are much greater than negative effects, expected effects were likely when users followed recommended instructions, and the research results were predicted not to change in the future. A weak recommendation was defined as a recommendation with inconsistent results that might not be reproducible in future studies.

Expert consensus process

For the adoption of recommendations, we structured a panel of experts that represented a group of users and specialists and used the Delphi method in the same way as for the development of updated gastroesophageal reflux disease guidelines.¹⁸

In total, 28 persons participated in the first round of Delphi consensus: 26 gastroenterologists, one surgeon from the Korean Society of Coloproctology and one expert from the Steering Committee for Clinical Practice Guidelines of the Korean Academy of Medical Sciences. The first draft included 41 recommendations: 4 concerning the definition and risk factors of chronic constipation, 8 regarding diagnoses, and 29 regarding treatments. Of the 41 draft recommendations, 37 were selected, whereas 4 were rejected. After the second Delphi round by e-mail voting, a final total of 37 recommendations were adopted.

Internal and external review methods

The editorial supervision committee consisted of 4 members. Three (H.K.J., J.E.S., and T.H.L.) edited and proofread the first draft of the guidelines. One external expert (S.J.M.) engaged in independent peer review for verification purposes, and to enhance the balance and completeness of the guidelines.

Limitations and Future Recommendations for Guideline Development

Limitations

Developing treatment guidelines in an objective and scientific manner is challenging because evidence-based research is insufficient in Korea. However, it is not realistic to simply accept guidelines developed in other countries because these may have different medical systems and epidemiological, clinical, and ethical settings. Considering these limitations, we used adaptation methods. These evidence based guidelines were developed to help clinicians en-

hance the quality of medical services and to allow patients to receive standardized and consistent clinical management. Therefore, this guideline may be different with the criteria for quality evaluation related to medical insurance.

Plans for dissemination, implementation, and revision

These revised guidelines will be accessible through the website of the Korean Society of Neurogastroenterology and Motility (<http://www.jnmjournal.org>). We plan to promote the guidelines using the information center for clinical treatment guidelines established by the Korean Academy of Medical Science and will continue to promulgate them at relevant academic conferences, seminars, and workshops. These guidelines will be revised every 3-5 years to reflect new data pertaining to the development of diagnostic and therapeutic methods and the accumulation of additional research findings.

Editorial independence

As confirmed by a written pledge by participants, the development of these guidelines was made without external financial support and there were no conflict of interest for the participants involved in this research process, and it was verified by written consents.

Recommended Guidelines for the Diagnosis and Treatment of Chronic Constipation

Definition of Chronic Constipation

1. Statement: *Chronic constipation is defined as the occurrence of bowel symptoms of infrequent bowel movements, hard stool, feeling of incomplete evacuation, straining at defecation, a sense of anorectal blockage during defecation, and use of digital maneuvers to assist defecation.*

- Grade of recommendation: not applicable.
- Level of evidence: C.
- Experts' opinions: completely agree (80.8%), mostly agree (19.2%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Constipation is a symptom-based disorder. Physicians often regard constipation as the occurrence of infrequent bowel movements, typically fewer than three times per week, but patients have

a broader set of symptoms, including hard stool, feeling of incomplete evacuation, and other symptoms (straining at defecation, a sense of anorectal blockage during defecation, and need for digital maneuvers to assist defecation).¹⁹ The latter symptoms suggest a defecatory disorder, even though symptoms alone do not appear to differentiate between subgroups of patients with constipation.^{20,21} Reduced stool frequency is poorly correlated with delayed colon transit time (CTT).²²

2. Statement: Functional constipation is classified into three categories: defecatory disorders, slow transit constipation, and normal transit constipation.

- Grade of recommendation: not applicable.
- Level of evidence: C.
- Experts' opinions: completely agree (61.5%), mostly agree (34.6%), partially agree (3.9%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Constipation can be primary or secondary to other medical conditions, including neurological, metabolic, and endocrine diseases. The criteria for primary functional constipation was developed by an international group of experts.²³ With respect to pathophysiology, primary functional constipation may be classified into defecatory disorders, slow transit constipation (STC), and normal transit constipation (NTC), a classification that facilitates its management.^{19,22}

Defecatory disorders are characterized by impaired rectal evacuation because of inadequate rectal propulsion and/or increased resistance to evacuation. Obstructed defecation includes increased anal resting pressure (anismus) or lack of coordination or dyssynergia of the defecatory muscles (pelvic floor dysfunction).²² The latter may be the most likely cause, and impaired rectal sensation may also be a significant pathogenesis.^{24,25} Rectal hyposensitivity may coexist with structural abnormalities, such as rectocele and rectal intussusceptions. Pelvic floor dysfunction may contribute to constipation with or without delayed transit.²⁶

STC is defined as prolonged delay in the passage of the stool through the colon. Slow transit is related to reduce colonic propulsive activity or increased uncoordinated motor activity of the colon. Motility changes in STC are occasionally related to abnormalities in the stomach and jejunum. Previous studies have demonstrated delayed gastric emptying and impaired gastric accommodation, which do not necessarily improve after colectomy for severe STC.^{27,28} These findings raised the possibility that STC may be a part of more global motor disorders in some cases.¹⁹

Generally, NTC is defined as a perception of constipation

on the patient's self-report; however, stool movement is actually normal through the colon. NTC is associated with constipation-predominant irritable bowel syndrome (IBS-C), although there is up to a 50% overlap between IBS-C and STC.²⁹ Abnormal results of barostat testing (reduced fasting, postprandial colonic tone or compliance) were detected in 40% of patients with NTC, 47% with STC, and 53% with defecatory disorders.³⁰ Thus, normal or slow colonic transit is not a perfect surrogate marker for normal or abnormal colonic motor function.

Risk Factors of Chronic Constipation

3. Statement: The physician should recommend discontinuing drugs that can cause constipation, if appropriate.

- Grade of recommendation: 1.
- Level of evidence: C.
- Experts' opinions: completely agree (74.1%), mostly agree (25.9%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Careful history taking pertaining to associated disease and medication is necessary for the differential diagnosis of constipation. Organic causes of constipation include metabolic diseases (hypothyroidism, diabetes mellitus, hypercalcemia, etc), myopathy (eg, amyloidosis), neurologic diseases (Parkinson's disease, multiple sclerosis, spinal cord disease, etc), and psychological problems, including depression. One of the most common causes of constipation is medication, including anticholinergics, opioid analgesics, calcium channel blockers, antidepressants, antihistamines, antispasmodics, anticonvulsants, aluminum antacids, and iron supplements.^{31,32} Thus, the physician should perform careful history taking related to drugs and recommend discontinuing them, if appropriate.

4. Statement: The prevalence of constipation in elderly populations increases because of multifactorial causes with co-morbid diseases, impaired mobility, reduced dietary fiber intake, and drugs contributing to constipation.

- Grade of recommendation: not applicable.
- Level of evidence: C.
- Experts' opinions: completely agree (51.9%), mostly agree (44.4%), partially agree (3.7%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

The prevalence of constipation increases with age and is especially frequent in women.^{33,34} In a study by Finland, the prevalence

of chronic constipation was 57% in elderly women and 64% in elderly men, and was more frequent in a nursing home setting: 79% in elderly women and 81% in elderly men.³⁵ Age-related intestinal intrinsic changes may lead to constipation, but multi-factorial causes often contribute in the elderly.^{33,36} These causes include increased use of various prescription medications, dietary changes (poor fluid intake, low dietary fiber, a diet proportionally higher in protein and fat, or small amounts of food), impaired morbidity, and co-morbid diseases (neurological or cognitive disorders, such as Parkinson's disease, stroke, spinal cord disease, dementia, depression, etc).³³

Diagnosis: When Should Tests Be Performed to Assess the Causes of Chronic Constipation and When Should It Be Applied?

Bristol Stool Form Scale

5. Statement: Stool form may be helpful in predicting colon transit time.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (17.9%), mostly agree (57.1%), partially agree (25.0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Stool form according to the Bristol Stool Form Scale (BSFS) is a useful visual aid (Fig. 3).³⁷ It uses simple visual illustration that is easily understood by patients, enabling them to recognize stool form and consistency. The BSFS is a reliable indicator of CTT³⁸ and particularly useful in patients reporting some discrepancy between the frequency of bowel movements and stool hardness.²⁶ Some patients

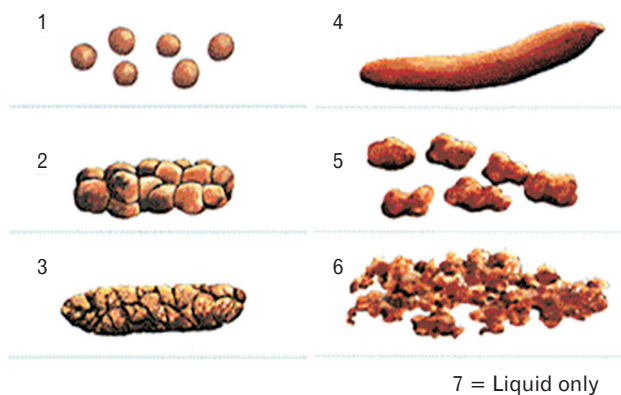


Figure 3. The Bristol Stool Form Scale.

complain of having constipation with a normal frequency of bowel movement and hard or lumpy stool, but in some cases, patients consider constipation to be having rare bowel movements with normal stool consistency. No correlation has been observed between stool frequency and measured transit in constipated or healthy adults.³⁸ In constipated adults, stool form correlated well with colon transit, but this correlation was not detected in healthy controls. Thus, history taking pertaining to stool form is a simple and useful way to estimate CTT in constipated patients.

Colonoscopy

6. Statement: Colonoscopy should be performed to exclude conditions of secondary constipation in patients with chronic constipation if the patients have alarm symptoms, such as blood in the stool, anemia, unexplained weight loss, new-onset constipation, or a family history of colon cancer.

- Grade of recommendation: 1.
- Level of evidence: C.
- Experts' opinions: completely agree (85.7%), mostly agree (10.7%), partially agree (3.6%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Basically, testing to rule out organic disease should be left to the judgment of the treating physician, based on the constipation symptoms, the impact on the patient's quality of life, and the presence of risk factors or alarm features obtained from the history and physical examination.¹⁹ Routine extensive diagnostic testing is not recommended for chronic constipation. A systematic review noted that no reported study has assessed routine blood tests or abdominal X-rays in patients with constipation.³⁹ A complete blood cell count can be performed.²² Although fasting serum glucose, thyroid-stimulating hormone, and calcium levels are often measured, the diagnostic utility and cost-effectiveness of these tests have not been rigorously evaluated and are probably very low.⁴⁰ However, colonoscopy should be performed in all patients with alarm symptoms.²² In subjects with no alarm symptoms, the rate of adenoma or colon cancer by colonoscopy has been found to be similar between groups reporting simple constipation and asymptomatic populations undergoing screening.³⁹

Economic analysis have suggested that screening tests for colon cancer is cost-effective,⁴¹ but no formal economic analysis of the evaluation of constipation has been reported. Because patients with constipation are at similar or higher risk (newly-onset constipation

or older age) for colon cancer; a colonoscopy is likely to also be cost-effective in patients with constipation.⁴²

7. Statement: Colonoscopy should be performed in patients with chronic constipation who have not undergone the appropriate colon cancer screening (patients ≥ 50 years of age).

- Grade of recommendation: 1.
- Level of evidence: C.
- Experts' opinions: completely agree (40.7%), mostly agree (55.6%), partially agree (3.7%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Testing for colon cancer with colonoscopy should be considered for patients aged 50 years or older who have not undergone an age-appropriate colon cancer screening procedure since the onset of constipation.^{19,22,26,43} However, routine colonoscopy is not warranted for most patients with chronic constipation, because the prevalence

of colonic neoplasms at colonoscopy is comparable to that in patients without chronic constipation.⁴⁴

Digital rectal examination

8. Statement: Digital rectal examination is useful for the differential diagnosis of secondary constipation (rectoanal mass, rectal prolapse, and rectocele) and predicting defecatory disorders.

- Grade of recommendation: 1.
- Level of evidence: B.
- Experts' opinions: completely agree (29.6%), mostly agree (63.0%), partially agree (3.7%), mostly disagree (3.7%), completely disagree (0%), and not sure (0%).

Digital rectal examination (DRE) is an important physical examination for the diagnosis of constipation. DRE can detect stool in the rectal vault, rectoanal masses, hemorrhoids, anal fissures,

Table 3. The Methodology of Digital Rectal Examination (Adapted from Talley⁴⁵ with Permission)

Techniques	Findings
1. Explain the need and method of digital rectal examination.	
2. Ask the patient to lie in the left lateral position, with both knees in flexion.	
3. Separate the buttocks and observe the anus and perianal area.	Evaluation of abnormalities such as anal cancer, rectal prolapse, external hemorrhoids, anal fissure or combined skin disease, etc.
4. Watch the perineum.	Leakage of stool, the presence of a patulous anus, prolapse of internal hemorrhoids and rectal prolapse on straining.
5. Check anocutaneous reflex by light scratch with cotton bud on perianal skin.	If the anocutaneous reflex notably decrease, consider abnormality of sacral nerve plexus and possibility of spinal cord disease.
6. Gently insert your index finger into the rectum through the anus.	If the patient feels pain on starting the examination, it strongly suggests anal fissure. Other causes of anal pain include ischiorectal abscess, active proctitis, or recently thrombosed external hemorrhoids.
7. Evaluate resting pressure of anal sphincter.	If the pressure is strongly high, it suggests defecatory disorders.
8. Rotate your finger and palpate rectal walls.	Evaluation of palpable mass, luminal narrowing, presence and consistency of stool in rectum, rectocele or rectal prolapse.
9. Test the presence of defecatory disorders.	
(1) Ask the patient to simulated defecation.	Normally, the anal sphincter and puborectalis muscle relax and the perineum descends by 1-3.5 cm. If the muscles tighten and perineum does not descend, it suggests defecatory disorders.
(2) Press on the posterior rectal wall.	If the patient feels pain when pressing on the posterior rectal wall, it suggests puborectalis muscle tenderness, which can occur in defecatory disorders.
(3) Ask to simulated squeezing effort.	Normally, puborectalis muscle contract and you feel as a "lift" that is finger lift toward the umbilicus by the muscle contraction.
(4) Place your other hand on the abdominal wall and ask to strain.	Evaluation of abdominal wall contraction.
10. During the finger removal, check blood, mucus, pus and feces color.	If there is persistent opening of the anal canal after finger removal, it suggests a possibility of external anal sphincter injury or neurological defect.

rectal prolapse, and rectoceles that cause secondary constipation.⁴² It is also useful for identifying defecatory disorders. DRE proceeds sequentially and precisely as shown in Table 3.⁴⁵ In short, if there is inappropriate perineal descent, absence of anal sphincter relaxation or paradoxical muscle contraction, it suggests the presence of defecatory disorders. For the diagnosis of dyssynergia, a carefully performed DRE has shown 75% sensitivity and 87% specificity when conventional anorectal manometry (ARM) was adopted as the reference.⁴⁶ DRE has also shown 93.2% sensitivity and 91.0% positive predictive value in detecting dyssynergia compared with high-resolution anorectal manometry (HRAM).⁴⁷ DRE can be used as a bedside screening test for the diagnosis of dyssynergia and is an effective diagnostic method that enhances decisions regarding additional anorectal function tests and treatment modalities in patients with constipation. However, a normal DRE does not exclude defecatory disorders.²²

Anorectal manometry and balloon expulsion test

9. Statement: Anorectal manometry is useful for diagnosing defecatory disorders in patients with constipation who fail to respond to laxatives.

- Grade of recommendation: 1.
- Level of evidence: B.
- Experts' opinions: completely agree (50.0%), mostly agree (50.0%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Anorectal physiologic tests are not routinely recommended for diagnosis of chronic constipation.²² ARM is performed in patients with constipation who fail to respond to laxatives for the diagnosis of defecatory disorders. However, it may be considered earlier in cases of strongly suspected defecatory disorders.^{22,48} ARM includes resting anal sphincter pressure, squeezing anal sphincter pressure, rectoanal inhibitory reflex, rectal and anal pressure during attempted defecation, rectal sensation, and rectal compliance. The main finding of a defecatory disorder is absent or inadequate relaxation or paradoxical contraction of the anal sphincter during straining, sometimes associated with absent or inadequate increase of rectal pressure. ARM results should be interpreted carefully because the methods of ARM have not yet been standardized, and the results may differ according to measuring methods and equipment in each center. HRAM is generally correlated with traditional ARM.⁴⁹ ARM is useful for diagnosing defecatory disorders in patients with constipation, but there is no gold standard for the diagnosis, and ab-

normal results may occur in the asymptomatic general population. Thus, a comprehensive evaluation with other anorectal physiological tests, including balloon expulsion test (BET), imaging techniques, and perhaps electromyography, is necessary for diagnosing defecatory disorders.²

10. Statement: Balloon expulsion tests may be helpful in predicting defecatory disorders, but other rectoanal physiological tests should be performed to confirm the diagnosis.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (24.1%), mostly agree (72.4%), partially agree (0%), mostly disagree (3.5%), completely disagree (0%), and not sure (0%).

The BET evaluates defecatory function during a simulated defecation and can identify patients with abnormal defecation. It is a simple and inexpensive test. However, it is not supported by placebo-controlled trials and has not yet been standardized. In recent studies, a "normal" result is defined as balloon expulsion within 1 minute after attempted defecation.⁴⁸ If the balloon is not expelled, it suggests the possibility of defecatory disorders. In one study, BET was 87.5% sensitive and 89% specific with positive and negative predictive values of 64% and 97% for the diagnosis of defecatory disorders, respectively.⁵⁰ It was concluded that a negative test was useful for identifying patients who do not have dyssynergia. However, Rao et al^{39,51} found that many patients with dyssynergia could expel the balloon, and they expressed the view that a normal test could not exclude the possibility of a defecatory disorder. BET can be helpful in predicting defecatory disorders, but other rectoanal function tests should be performed to confirm a diagnosis.⁴³

Defecography

11. Statement: Defecography is useful for detecting anatomical abnormalities and paradoxical contraction of the pelvic floor when defecatory disorders are suspected in patients with chronic constipation.

- Grade of recommendation: 1.
- Level of evidence: B.
- Experts' opinions: completely agree (42.9%), mostly agree (53.6%), partially agree (3.5%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Defecography is a type of radiological imaging in which the

mechanism of a patient's defecation is visualized in real time using a fluoroscope. The anatomy and function of the anorectum and pelvic floor are studied dynamically at various stages during defecation. Thus, defecography is considered after inconclusive results of ARM and rectal balloon expulsion in chronic constipation with an inadequate response of therapeutic trials.⁴² Defecography is particularly useful for identifying anatomical abnormalities, such as paradoxical contraction of the puborectalis muscle, a rectocele, rectoanal intussusception, and complete external rectal prolapse that may be amenable to surgical intervention.^{23,52-56}

Barium defecography is commonly used, although the test or technique is incompletely standardized and it has limited reproducibility in terms of anorectal angle measurements.⁵⁴ Internal consistency of defecographic parameters has been reported to be good ($\alpha = 0.78$), but agreements between each defecographic parameter and each test of ARM and electromyography have all been shown to be poor.⁵⁷ Magnetic resonance (MR) defecography avoids radiation exposure and is better for visualizing the bony landmarks that are necessary for measuring pelvic floor motion than barium defecography. Its measurements are reproducible among observers.^{58,59} However, MR defecography is an expensive test and is not commonly available at hospitals.

Endovaginal or endoanal sonography can be used to evaluate pelvic floor anatomy in patients with evacuation dysfunction.⁶⁰ Endovaginal sonography is recommended as an alternative to defecography or MR imaging.⁶¹ Endoanal 3-D reconstructed sonography can provide detailed abnormalities, such as anal sphincter defects, fistulous tracts, and submucosal invasion in early anorectal cancers.⁶⁰

Colon transit time

12. Statement: Colon transit time is useful for differentiating between the subtypes of defecatory disorders and slow transit constipation in patients with chronic constipation.

- Grade of recommendation: 1.
- Level of evidence: B.
- Experts' opinions: completely agree (20%), mostly agree (68%), partially agree (8%), mostly disagree (4%), completely disagree (0%), and not sure (0%).

Colonic transit is most commonly and inexpensively measured using radiopaque markers. Kolomark (M.I.Tech, Pyeongtaek, Korea)⁶² and Sitzmarks (a capsule containing 24 markers; Konsyl Pharmaceuticals, Texas, USA)⁶³ are commonly available markers

in Korea. Several methods have been suggested and the multiple capsules technique is one of the most popular methods to measure the CTT. This technique requires the ingestion of 1 capsule a day for 3 days, followed by abdominal X-rays on day 4 and 7; a normative value for total CTT in healthy Korean adults is 22.3 ± 16.1 hours in males and 30.1 ± 21.4 hours in females.⁶⁴ There are differences in CTTs by age, gender, race, and methodology. Western people and women have a longer transit time.⁶²⁻⁶⁴ Segmental CTT is believed to differentiate between STC and pelvic floor outlet obstruction.⁴³ CTT can be readily performed at an early stage in the diagnostic process of chronic constipation, because CTT is easily measured in many institutions, in contrast with other tests such as ARM, defecography, or electromyography.

However, lack of standardization in the procedure makes it difficult to compare results among hospitals,^{63,65} and the test is less reproducible in defecatory disorders and colonic inertia.⁶⁶ As more than 50% of patients with defecatory disorders show slow CTT, measurement of colon transit alone cannot exclude a defecatory disorder. Even if a defecatory disorder coexists with slow colonic transit, this finding does not alter a treatment modality such as biofeedback as the main approach for the patient. Some consider that colon transit should be performed when ARM, BET, or defecography show normal findings.⁴² Thus, the clinician should consider which tests are to be performed in patients with chronic constipation according to the main symptoms and the tests available at each institution.

Radiographic and scintigraphic methods correlate well, and scintigraphy requires scanning for 24 or 48 hours versus 5-7 days for completing a radiopaque marker study.⁶⁷ In patients with constipation, the correlation between colonic transit by using radiopaque markers and the wireless motility-pH capsule is reasonable (correlation coefficient = 0.7).⁶⁸

Management of Chronic Constipation

Physical activity

13. Statement: A low level of physical activity is associated with chronic constipation.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (7.1%), mostly agree (67.9%), partially agree (14.3%), mostly disagree (10.7%), completely disagree (0%), and not sure (0%).

Data regarding the effectiveness of physical activity in alleviating constipation have been variable. In a large survey conducted with 39,532 women, the odds ratio for constipation among women who reported lower to moderate physical activity was significantly lower than that among sedentary women in all three aged cohorts (young, middle aged, and older). Compared with sedentary young, middle aged, and older women, those with moderate physical activity showed significant odds ratios (0.70, 0.75, and 0.82, respectively).⁶⁹ Another survey showed that constipation in elderly patients was most clearly associated with poor mobility.⁷⁰ Elderly patients were thought to have an increased risk of constipation depending on their level of activity.³⁵ More frequent bowel movements may be caused by running.⁷¹ These findings suggest that low-to-moderate levels of exercise are associated with benefits for constipated patients. A study of colonic motility using a solid state manometric probe showed that colon phasic activity was decreased during exercise and propagated activity was enhanced after exercise.⁷² A Korean study showed that moderate or high levels of physical activity shortened CTT in females, but not in males.⁷³

However, the average of total physical activities was not significantly different in normally active subjects with and without constipation.⁷⁴ The effect of moderate physical exercise on bowel transit time has been questioned in healthy subjects.⁷⁵⁻⁷⁸ In a small group of chronically constipated patients who did an extra hour of exercise 5 days per week for 4 weeks, there was no improvement in the number or consistency of their bowel movements or the degree of straining required for defecation.⁷⁹ Increased physical activity might offer symptomatic improvement, especially in elderly constipated patients with low levels of physical activity. It is not clear that exercise helps younger constipated patients with normal activity. Recently, moderate-to-vigorous intensity physical activity (20-60 minutes, 3-5 days per week) has been shown to improve symptoms and quality of life in IBS.⁸⁰ Taken together, increased physical activity should still be recommended to patients because it improves quality of life and has other health benefits unrelated to chronic constipation.

Dietary fiber

14. Statement: Dietary fiber can increase stool frequency in patients with chronic constipation.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (27.6%), mostly agree (72.4%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Dietary fiber undergoes partial or total fermentation in the distal small bowel and colon, leading to the production of short-chain fatty acids and gas, thereby affecting gastrointestinal function and sensation.⁸¹ A prospective cohort study showed that higher daily fiber intake significantly reduced the likelihood of self-reported constipation.⁸² A recent meta-analysis concluded that dietary fiber intake can clearly increase stool frequency in patients with constipation.⁸³ Naturally occurring fiber types include soluble highly fermentable oligosaccharides (eg, fructo-oligosaccharides and galacto-oligosaccharides), soluble highly fermentable fiber (eg, resistant starch, pectin, guar gum), intermediate soluble fermentable fiber (eg, psyllium and oats), insoluble slowly fermentable fiber (eg, wheat bran, fruit, and vegetables), and insoluble non-fermentable fiber (eg, cellulose and sterculia).⁸¹ Good laxative effects were observed in intermediate soluble fermentable fibers, insoluble slowly fermentable fibers, and insoluble non-fermentable fibers.⁸¹ A recent study showed that treatment with dried plums resulted in a significant increase in the number of complete spontaneous bowel movements (CSBMs) and stool consistency, compared with treatment with psyllium.⁸⁴

However, it is not clear that dietary fiber improves stool consistency, treatment success, laxative use, or painful defecation.⁸³

15. Statement: Dietary fiber intake is an initial strategy in the management of chronic constipation because it has some benefits, is easy to implement, is low cost, and there is little risk of serious adverse events.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (35.7%), mostly agree (60.7%), partially agree (3.6%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Dietary fiber appears to be effective in relieving mild to moderate, but not severe constipation.⁸⁵ Two Korean studies reported that dietary fiber is effective in the management of constipation without adverse events.^{86,87} Increased dietary fiber intakes for adults with chronic constipation is associated with considerable cost savings, potentially exceeding \$12 billion in the US population.⁸⁸ There is a lack of evidence supporting the notion that dietary fiber is effective for individual constipation subtypes (obstructive, metabolic, neurological, diet-related, myogenic, drug-related, and pelvic floor dysfunction).⁸¹ Occasionally, patients will experience marked worsening of their constipation-related symptoms with fibers. When this occurs, severe STC or defecatory disorders should be strongly

considered.⁸⁹ It is reasonable to prescribe osmotic laxatives to avoid cramping abdominal pain before initiating an increase in dietary fiber, especially in patients with significant fecal stasis.⁸¹

Bulking agents

16. Statement: Bulking agents are effective in the treatment of chronic constipation.

- Grade of recommendation: 1.
- Level of evidence: A.
- Experts' opinions: completely agree (70.4%), mostly agree (29.6%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Bulking agents are fiber supplements including psyllium (ispaghula husks), calcium polycarbophil, methylcellulose, and bran. Among them, psyllium has the highest level of evidence with regard to the treatment of chronic constipation. Compared with placebo, bulking agents (especially psyllium) resulted in improvements in global symptoms, straining, pain on defecation, and stool consistency, an increase in the mean number of stools per week, and a reduction in the number of days between stools.⁹⁰ A randomized crossover study of 4 weeks treatment with psyllium showed that stool frequency, weight, consistency, and pain on defecation improved significantly on psyllium; however no effect was observed with respect to colon transit or ARM parameters.⁹¹ A single-blind, randomized, crossover study of 4 weeks treatment with psyllium improved gut transit time significantly in constipated patients with pelvic floor dysynergia, compared with a placebo group.⁹² However, there was no significant differences in stool frequency, consistency, or weight between the groups. In a randomized, double-blind, parallel study of 170 constipated patients, treatment with psyllium for 2 weeks significantly improved stool weight and frequency (in treatment week 2), compared with docusate.⁹³ Evidence from nine studies⁹¹⁻⁹⁹ of psyllium showed that it apparently improved stool frequency, but there were conflicting results regarding stool consistency and transit time. No significant difference in adverse events was observed between the psyllium group and the comparison group. However, the duration of treatment with psyllium in these studies was less than 8 weeks, although the therapeutic effect would be expected to be maintained for a long time.

Potential adverse effects of bulking agents include gas, bloating, esophageal obstruction, colonic obstruction, and calcium and iron malabsorption. There is a relative lack of data available for making a recommendation for calcium polycarbophil. Some patients tend to

prefer calcium polycarbophil to psyllium with respect to bloating.¹⁰⁰ Studies of methylcellulose and bran were lacking appropriate controls and were of low methodological quality.¹⁰⁰

17. Statement: Bulking agents can be effective in the treatment of constipated patients with inadequate fiber intake.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (15.4%), mostly agree (80.8%), partially agree (3.8%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Inadequate intake of dietary fiber is believed to contribute to constipation, and many guidelines recommend that increasing dietary fiber intake should be the first-line step in the management of constipation.^{9,22} Despite the limited evidence for the benefits of this approach in constipated patients with inadequate fiber intake, a bulking agent can be effective in their symptomatic improvement. However, psyllium is not effective in severe STC or defecatory disorders. The use of osmotic laxatives may be favored before initiating treatment of bulking agents to avoid abdominal discomfort, bloating, and pain in a subset of constipated patients.⁸¹

18. Statement: When bulking agents are used, adequate intake of fluid is recommended.

- Grade of recommendation: 1.
- Level of evidence: C.
- Experts' opinions: completely agree (37.0%), mostly agree (55.6%), partially agree (7.4%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Contraindications for bulking agents include hypersensitivity to any included components, fecal impaction, and bowel obstruction. When bulking agents are used, inadequate fluid intake can result in abdominal gas or bloating, which may then paradoxically predispose the patient to bowel obstruction.¹⁰¹ The elderly in particular may have insufficient fluid intake, which may predispose them to fecal impaction and bowel obstruction. Fluid intake alone has not been reported to be effective as a treatment for constipation,¹⁰² but it may benefit patients who are dehydrated.

Magnesium salts

19. Statement: Magnesium salts improve stool frequency and consistency in patients with normal renal function

- Grade of recommendation: 1.
- Level of evidence: C.
- Experts' opinions: completely agree (57.1%), mostly agree (39.3%), partially agree (3.6%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Magnesium salts have been widely used in mild-to-moderate constipation because of their low price and ready availability. Only one study of 64 institutionalized older patients (≥ 65 years) with chronic constipation showed that magnesium hydroxide resulted in significant improvements in bowel movements, stool consistency, and decreased use of additional laxatives, compared with a bulking agent (plantain rind) plus sorbitol.¹⁰³ Polyethylene glycol (PEG) solution plus magnesium hydroxide induced more significantly effective colonic preparation in constipated patients, compared with PEG solution alone.¹⁰⁴ In conclusion, few studies have examined the effect of magnesium hydroxide, but many clinicians believe that it improves stool frequency and consistency in patients with normal renal function.

20. Statement: Magnesium salts result in hypermagnesemia in patients with impaired renal function.

- Grade of recommendation: 1.
- Level of evidence: C.
- Experts' opinions: completely agree (44.4%), mostly agree (51.9%), partially agree (3.7%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

There are no contraindications but precautions are needed with disease-related concerns such as renal impairment or neuromuscular disease.¹⁰⁵ Hypermagnesemia is characterized by progressive loss of neuromuscular, respiratory, and cardiovascular function. Increased magnesium decreases impulse transmission across the neuromuscular junction, producing a curare-like effect.¹⁰⁶ Cardiovascular side effects of hypermagnesemia include hypotension, conduction defects, bradyarrhythmia, and even cardiac arrest.^{106,107} Because of the risk of hypermagnesemia, magnesium salts should not be used in patients with renal impairment.

Nonabsorbable carbohydrate

21. Statement: Nonabsorbable carbohydrates improve bowel frequency and stool consistency in patients with chronic constipation.

- Grade of recommendation: 1
- Level of evidence: B.
- Experts' opinions: completely agree (53.9%), mostly agree (46.1%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Nonabsorbable carbohydrates, such as sorbitol and lactulose, which are classified as hyperosmolar laxatives, pass unchanged into the colon to be metabolized by colonic bacteria into lactic, acetic, and formic acids, with the liberation of carbon dioxide. These low-molecular-weight organic acids increase intraluminal fluid osmotically. Lactulose is composed of galactose and fructose, which can be produced by the isomerization of lactose, and is a prebiotic carbohydrate that stimulates the growth of health-promoting bacteria in the human gastrointestinal tract.¹⁰⁸ The time of onset of lactulose's effect is between 24 and 72 hours.

Early studies that were methodologically limited showed the efficacy of lactulose in improving bowel frequency and stool consistency in patients with chronic constipation.^{109,110} In a very early randomized trial, the success rate for lactulose was 80% and for the placebo, 33%, showing a significantly different success rate.¹¹⁰ A 12-week, double-blind study of elderly constipated patients also revealed that reduction in the severity of symptoms, such as cramping, griping, flatulence, tenesmus, and bloating was greater with lactulose.¹⁰⁹ Additionally, results in comparison with other laxatives, such as psyllium, sorbitol, and psyllium plus senna have been reported.^{96,111} In a 4-week trial, the efficacy of lactulose and ispaghula was demonstrated, and effects were similar between the two groups. Differences were demonstrated with regard to acceptability in favor of lactulose.⁹⁶ When the efficacy of 4-week lactulose and 70% sorbitol were compared in a cross-over trial, there was no significant difference with regard to the percent of normal bowel movements, frequency or severity of symptoms such as bloating, cramping, and excessive flatulence, or overall health status.¹¹¹

An uncontrolled trial evaluating colon transit in Korean patients suffering with functional constipation demonstrated that patients with STC showed improvements in symptoms associated with acceleration of the proximal colonic transit via lactulose.¹¹²

Because lactulose is not absorbed systemically, it is not expected

to be associated with an increased risk of malformations in pregnant women.¹¹³ In particular, this strength can lead to the safe application of lactulose in other patients groups, including those with encephalopathy or diabetes.

22. Statement: Long-term administration of nonabsorbable carbohydrate is recommended because serious adverse reactions are rare.

- Grade of recommendation: 1.
- Level of evidence: A.
- Experts' opinions: completely agree (39.3%), mostly agree (60.7%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Nonabsorbable carbohydrates often cause gastrointestinal symptoms, including flatulence, intestinal cramps, nausea, and diarrhea. Although gastrointestinal side effects occur most often with lactulose due to its metabolism by colonic bacteria, these events are usually temporary.¹¹⁴ Considering that no potential serious side effects were found in patients treated with lactulose for more than 4 weeks, long-term treatment with this agent is generally regarded as safe and well tolerated.¹¹⁵

23. Statement: Nonabsorbable carbohydrates may be effective in improving bowel frequency and constipation-related symptoms in elderly patients with chronic constipation.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (10.7%), mostly agree (82.2%), partially agree (7.1%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Randomized controlled trials (RCTs) including elderly populations support the efficacy of lactulose for stool frequency and consistency, but many studies of the use of these nonabsorbable carbohydrates in the elderly are limited because of small sample sizes and problems with their methodologies.^{111,116,117}

Polyethylene glycol

24. Statement : Polyethylene glycol improves bowel frequency and stool consistency in patients with chronic constipation.

- Grade of recommendation: 1.
- Level of evidence: A.
- Experts' opinions: completely agree (73.1%), mostly agree (26.9%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

PEG is a nonabsorbable and nonmetabolized polymer that draws fluid into the intestinal lumen. There is reliable evidence for the use of PEG, with several well-designed placebo-controlled randomized trials demonstrating significant benefits of PEG in improving bowel frequency and stool consistency. Numerous trials have shown both electrolyte-enriched PEG and electrolyte-free PEG to be effective in patients with chronic constipation.^{115,118-127} A meta-analysis concluded that PEG treatment resulted in a highly significant increase in defecations per week over placebo.¹²⁸ In particular, a meta-analysis involving 10 RCTs found that PEG was better than lactulose with respect to the outcomes of stool frequency per week, form of stool, relief of abdominal pain, and the need for additional products.¹²⁹ PEG is poorly absorbed systemically, and does not appear to be associated with an increased risk of malformations in pregnant women.¹³⁰

25. Statement : Long-term administration of polyethylene glycol is recommended because serious adverse reactions are rare.

- Grade of recommendation: 1.
- Level of evidence: A.
- Experts' opinions: completely agree (50.0%), mostly agree (50.0%), partially agree (0%), mostly disagree (0%), completely disagree (0%), not sure (0%).

Long-term administration (for more than 6 months) of daily PEG was effective, and appeared to be safe, well tolerated, and devoid of significant adverse events.¹¹⁹ While osmotic laxatives can generally cause electrolyte disturbances, volume overload, or dehydration, and these medications should be used with caution in patients prone to renal insufficiency or cardiac abnormalities,¹³¹ PEG is considered relatively safe in these respects. Although there have been reports about common adverse events including diarrhea, ab-

dominal pain, nausea, and vomiting, no serious adverse events have been reported with long-term PEG treatment.¹²⁹

The majority of clinical guidelines, including Korean guidelines, have indicated the efficacy of PEG in patients with chronic constipation with high evidence and recommendations.^{9,19,42,132-134}

26. Statement: Polyethylene glycol may be effective in improving bowel frequency and constipation-related symptoms in elderly patients with chronic constipation.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (23.1%), mostly agree (69.2%), partially agree (7.7%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

An open-label study evaluating the safety and efficacy of PEG given in patients who were ≥ 65 years old supported the use of PEG in elderly patients.¹³⁵ In addition, a subgroup analysis of RCTs including geriatric patient groups demonstrated better efficacy of PEG than other laxatives in normalizing stool frequency and consistency.¹¹⁵ Although PEG can frequently cause nausea, flatulence, and diarrhea, no serious side effects were reported, and PEG was well tolerated in the elderly group.

Stimulant laxatives

27. Statement: Stimulant laxatives can be considered when bulk or osmotic laxatives are ineffective in improving bowel frequency and stool consistency in patients with chronic constipation.

- Grade of recommendation: 2.
- Level of evidence: B.
- Experts' opinions: completely agree (22.2%), mostly agree (70.4%), partially agree (7.4%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Stimulant laxatives represent a diverse class of agents derived primarily from anthraquinones (senna) and diphenylmethanes (bisacodyl and sodium picosulfate), and acting through direct contact with the submucosal plexus and the deeper myenteric plexus, resulting in predominantly motor but also secretory effects on the bowel. Medications including senna, cascara, bisacodyl, and sodium picosulfate are commonly used as stimulants.^{136,137} The onset of action of bisacodyl is 6-12 hours after oral administration and the onset of action of senna is usually 1-3 hours.

In randomized, placebo-controlled trials of sodium picosulfate and oral bisacodyl, it was reported that these agents increased the number of CSBMs per week, improved the stool consistency, and decreased the constipation-related symptoms.^{132,138,139} A senna-fiber combination was more effective than lactulose in treating constipation in geriatric long-stay patients.^{116,140} A meta-analysis found that stimulant laxatives provided superior efficacy for chronic idiopathic constipation (relative risk, 0.54; 95% confidence interval [CI], 0.42-0.69). The number needed to treat with stimulant laxatives was 3 (95% CI, 2.0-3.5).¹⁴¹ These agents are traditionally advocated for short-term use only, due to safety concerns with long-term use.

It has been reported that stimulant laxatives are associated with significant adverse events, including malabsorption, electrolyte disturbance, dose-dependent cramping, diarrhea, abuse, and development of melanosis coli.^{33,142-144} Cathartic colon is seen in some chronic users of stimulant laxatives, but it is unclear whether this is related to their prolonged use.^{145,146} Thus, stimulant laxatives may be used when patients fail to respond adequately to bulk or osmotic laxatives.^{131,144}

Docusate, a stool softener, acts as a surfactant, allowing water to penetrate the stool mass, and increases intestinal intraluminal water and sodium secretion. Although controversy has emerged regarding its effectiveness, docusate has been used to treat and prevent constipation in geriatric and institutionalized chronically ill patients.^{147,148}

Probiotics

28. Statement: Probiotics can be considered for use in conjunction with other drugs in the treatment of chronic constipation.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (14.8%), mostly agree (63.0%), partially agree (18.5%), mostly disagree (3.7%), completely disagree (0%), and not sure (0%).

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.¹⁴⁹ Previous studies have found that the intestinal microbiota in chronic constipation patients differed from that in healthy controls.^{150,151} A systematic review of RCTs to evaluate the efficacy and safety of probiotic supplementation for the treatment of constipation suggested a favorable effect of treatment with *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *Escherichia coli* Nissle 1917 on defecation frequency and stool consistency.¹⁵² How-

ever, to achieve the same health benefits seen in clinical trials, probiotics should be administered with specific strains, at a specific doses, in specific populations of people. Although the use of probiotics for the treatment of constipation may be beneficial, RCTs of probiotics in chronic constipation have potential limitations. Probiotics can be considered for use in conjunction with other drugs in the treatment of chronic constipation.¹³²

Prucalopride

29. Statement: Prucalopride improves stool frequency and consistency, and reduces the need for rescue medications.

- Grade of recommendation: 1.
- Level of evidence: A.
- Experts' opinions: completely agree (57.7%), mostly agree (42.3%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Prucalopride is a novel gastrointestinal prokinetic agent and acts as a high-affinity, highly selective 5-hydroxytryptamine type 4 agonist.¹³² Prucalopride accelerated gastrointestinal and colonic transit in constipation patients.¹⁵³ Prucalopride, 2 mg once-daily treatment over 12 weeks, was more efficacious than a placebo in improving stool frequency and stool consistency, decreasing the need for rescue medications, reducing the symptoms of constipation in Asian and non-Asian women, and was found to be safe and well-tolerated.¹⁵⁴⁻¹⁵⁸ In addition, in elderly patients, prucalopride has beneficial effects on bowel movements and constipation-associated symptoms.¹⁵⁹ Satisfaction with bowel function was maintained for up to 18 months of treatment with prucalopride.¹⁶⁰ Recently, prucalopride was more efficacious than placebo in improving stool frequency and life quality in men with chronic constipation, and was found to be safe and well-tolerated.¹⁶¹

Prucalopride is recommended at 2 mg once daily, however the dose for the elderly (> 65 years) and patients with severe renal impairment (glomerular filtration rate < 30 mL/min/m²) and severe hepatic impairment (Child-Pugh class C) should start at 1 mg once daily. Headache, nausea, abdominal pain, and diarrhea lead to discontinuation of prucalopride treatment in ~5% of patients. Prucalopride is contraindicated in patients with hypersensitivity, renal impairment requiring dialysis, intestinal perforation or obstruction, and severe inflammatory conditions of the intestinal tract.¹³² Previous nonselective 5-hydroxytryptamine type 4 agonists (cisapride and tegaserod) have been associated with significant interactions with other receptors, leading to adverse cardiovascular events and

resulting in the withdrawal of these drugs from the market.⁴² However, serious cardiac toxicity has not been reported in patients taking prucalopride.

Thus, when bowel symptoms are refractory to simple laxatives, prucalopride should be considered in patients with chronic constipation. If treatment with prucalopride is not effective after 4 weeks, patients should be re-examined and the benefits of continuing treatment should be reconsidered.

New agents

Lubiprostone

30. Statement: Lubiprostone improves stool frequency and stool consistency, and reduces straining.

- Grade of recommendation: not applicable.
- Level of evidence: A.
- Experts' opinions: completely agree (29.2%), mostly agree (58.3%), partially agree (4.2%), mostly disagree (0%), completely disagree (0%), and not sure (8.3%).

Lubiprostone is a chloride channel activator approved by the Food and Drug Administration for the treatment of chronic constipation, but is not yet available in Korea.¹³² Lubiprostone increases intestinal chloride secretion, accelerates transit, and facilitates ease of defecation.¹³² Two RCTs showed that lubiprostone, at 24 µg twice daily, significantly improved stool frequency and consistency, and reduced straining.^{162,163} During this 48-week open-label study, lubiprostone was well tolerated. Bowel symptoms improved consistently over 48 weeks in adult patients with chronic idiopathic constipation.¹⁶⁴ This study evaluating the efficacy of lubiprostone was, however, limited to Western subjects. Recently, lubiprostone produced a steady and effective improvement in the symptoms of chronic constipation with or without IBS in a dose-dependent manner with a good safety profile and tolerability in a Japanese population.¹⁶⁵ The most common adverse event was nausea, and the drug may be associated with diarrhea, headache, abdominal distention, abdominal pain, flatulence, and vomiting. Lubiprostone may be considered for NTC or STC patients refractory to simple laxatives.⁴²

Linacotide and bile acid transporter inhibitors

31. Statement: Linacotide, a newer intestinal secretagogue, may be effective in constipated patients who are refractory to conventional laxatives.

- Grade of recommendation: not applicable.
- Level of evidence: B.
- Experts' opinions: completely agree (7.2%), mostly agree (71.4%), partially agree (14.3%), mostly disagree (0%), completely disagree (0%), and not sure (7.1%).

Linacotide is a low-molecular-weight peptide having homology to the diarrhea-causing enterotoxins. Linacotide induces efflux of chloride ions and free water into the bowel lumen by activating the apical cystic fibrosis transmembrane regulator of enterocytes.¹⁶⁶ Linacotide increased CSBMs in constipated patients, as demonstrated consistently in 2 large RCTs.¹⁶⁷ The most common adverse event was diarrhea and most of the patients experienced the first episode of diarrhea during the initial 2 weeks of therapy.¹⁶⁷

The bile acid transporter inhibitor, elobixibat, is another new agent in phase 3 trials, and is not yet available in Korea. Almost all luminal bile acid is physiologically reabsorbed through bile acid transporters of ileal enterocyte. If the reabsorption of bile is blocked by ileal diseases or drugs, the remnant colonic luminal bile acid causes water secretion and facilitates bowel movement. Pharmacodynamic studies showed that bile acid transporter inhibitors accelerate colonic transit and relieve constipation-related symptoms in constipated patients.^{168,169} A bile acid transporter inhibitor may also offer an additional benefit of improving dyslipidemia through bile acid depletion and decreased lipid absorption.¹⁷⁰

Behavioral therapy – biofeedback therapy

32. Statement: Biofeedback therapy is effective for treating constipated patient with defecatory disorders.

- Grade of recommendation: 1.
- Level of evidence: A.
- Experts' opinions: completely agree (55.6%), mostly agree (44.4%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Biofeedback therapy is a retraining process for dyssynergic anorectal and pelvic floor muscles, which are used during defecation. This behavioral therapy employs auditory or visual presentation

of anorectal and pelvic floor muscular activity through electromyography and anal manometry. The patient can perceive abnormal straining during real-time sham defecation, becoming educated as to how to contract the abdominal wall and relax the pelvic floor and anal muscles. Repeated behavioral training processes can condition or retrain the patient. Eligible patients with dyssynergic patterns of defecation should be defined by ARM, or the diagnosis must be supported by one or more modalities including a BET, defecography, and CTT.¹⁷¹ This eligibility is supported by the fact that outcome of biofeedback therapy varies widely, depending on whether the type of constipation can be represented as isolated defecatory disorder, isolated STC, or combined type. Most (about 70%) defecatory disorder was adequately relieved by biofeedback therapy¹⁷²⁻¹⁷⁹ and this favorable effect lasted for 2 years or more, as observed in long-term follow-up data,^{173,174,178,179} whereas only 8% of isolated STC cases were treated effectively.¹⁸⁰ Regardless of concomitant STC, combined type patients reached satisfactory outcomes.¹⁷² Moreover, this concomitant slow transit can resolve in 65% of defecatory disorders. Thus, a detailed work-up on the type of constipation is essential before determining the indication for biofeedback therapy, and baseline diagnostic tests should define the presence of defecatory disorders, regardless of combined STC. Biofeedback therapy is believed to have little effect in isolated STC. Defecatory disorder can be treated with conventional laxatives, considering the poor availability of biofeedback therapy with respect to both experts and hardware. However, regardless of the response to conventional laxatives, it is reasonable to recommend that patients with defecatory disorders undergo biofeedback therapy.

Recently a systematic review has concluded that there is insufficient evidence to allow any firm conclusion favoring the efficacy of this behavioral therapy in the management of a chronically constipated patient.¹⁸¹ However, this review has also been criticized in terms of its inappropriate inclusion criteria.¹⁷¹ The review included constipated patients without defecatory disorder, who were therefore not actually eligible for biofeedback therapy, resulting in the inevitable dilution of the benefit of biofeedback therapy. Five RCTs have consistently concluded that biofeedback therapy is superior to controlled treatment modalities, including sham biofeedback therapy,¹⁸⁰ diet, exercise and conventional laxatives,^{174,180} PEG,¹⁸² diazepam, placebo medicine,¹⁸³ and balloon defecation therapy.¹⁸⁴

There are some reported factors that predict the outcome of biofeedback therapy. Harder stool consistency, shorter duration of laxative use, higher resting anal sphincter pressure, and more prolonged balloon expulsion time have been reported as predictors of a desirable outcome.^{185,186} Neither patient age nor gender significantly

affect the outcome.¹⁸⁶ The patient's willingness to participate or compliance is basically required for a behavioral therapy and seems to be one of the most important factors.

33. Statement: Biofeedback therapy may be applied repeatedly and safely, and can reduce the usage of laxatives.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (34.6%), mostly agree (65.4%), partially agree (0%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Biofeedback therapy theoretically has no harmful effect and can be applied repeatedly and safely even for aggravated patients after completion of previous sessions and for surgical candidates. The decreased use of laxatives may be one of the most important benefits that can be achieved. One controlled study showed that biofeedback therapy reduced laxative use.¹⁸⁷ Several reports concluded that biofeedback therapy was cost-effective.^{185,188}

Surgical treatment

34. Statement : Colectomy can be effective in patients with slow transit constipation and without a defecatory disorder who do not gain benefit from medical treatment.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (16.0%), mostly agree (64.0%), partially agree (16.0%), mostly disagree (4.0%), completely disagree (0%), and not sure (0%).

There are no controlled trials of surgery for patients with chronic constipation. However, surgical treatment for chronic constipation may improve constipation in patients who fail to achieve satisfaction through medical therapy. The overall rate of success documented in 39 studies involving 1423 patients was 86% (39-100%).¹⁸⁹ Total colectomy and ileorectal anastomosis are the most common surgical procedures for refractory constipation, and sigmoid colectomy, subtotal colectomy with ceco-rectal anastomosis, and left hemicolectomy have been used.¹⁸⁹ Recently, laparoscopic colectomy has showed similar success rates to open surgery.¹⁹⁰

A medical history, physical and laboratory examinations, colonoscopy, and barium enema are needed to rule out secondary causes of constipation, such as endocrine and metabolic disorders, neurological disorders, myogenic disorders, and medications. Barium

defecography and ARM studies are also required to evaluate evacuation disorders. CTT is necessary to diagnose STC for the decision of surgical treatment in constipation patients. Surgical interventions are less effective in patients who have constipation with upper gastrointestinal dysmotility, and studies including gastric emptying scan and small bowel transit time may be required.¹⁹¹ Surgical treatment, such as colectomy, has a limited role as a treatment option for a highly selected group of patients with STC and without defecatory disorder who have failed all non-surgical interventions, and in whom symptoms are sufficiently severe to contemplate major surgery due to serious complications and poor functional outcomes.¹⁹²

35. Statement : Surgical treatment can be effective in patients who have an outlet obstruction such as symptomatic rectocele and rectal prolapse.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (19.2%), mostly agree (61.6%), partially agree (19.2%), mostly disagree (0%), completely disagree (0%), and not sure (0%).

Obstructed defecation syndrome is associated with abnormalities of the pelvic organs including rectocele, rectal prolapse, and recto-anal intussusception. Surgical treatment can be an option for patients who have failed to achieve satisfaction through medical therapy, including biofeedback therapy.

Repair of the rectocele, transanal or transvaginal region, may improve obstructive defecation symptoms.⁵² Although surgery seems to correct anatomical defects, many side effects may occur (in approximately 50% of cases), such as constipation, fecal incontinence, incomplete bowel emptying, and sexual dysfunction.¹⁹³ Surgical treatment for internal rectal prolapse is controversial and is only considered when conservative treatments fail to alleviate the patient's symptoms.¹⁹⁴ Abdominal operations include techniques involving suspension of the prolapsed rectum with or without foreign materials, and sigmoid resection with or without rectopexy. A perineal approach and transabdominal repair (rectopexy and resection) can be used to treat rectal prolapse.¹⁹⁵ Perineal operations include rectosigmoidectomy, Delorme's operation, mucosal plication (Gant-Miwa procedure), and anal encirclement (Thiersch's operation).¹⁹⁶

The role of surgical treatment for rectal intussusception is controversial, and should be restricted to selected cases in which medical therapy has failed. Delorme's transrectal excision is an alternative procedure, and (laparoscopic) resection rectopexy is a new procedure that shows better results according to some researchers.

Local treatment – enema and suppositories

36. Statement : Enemas can be effective in a subset of patients with refractory defecatory disorders.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (21.4%), mostly agree (60.7%), partially agree (10.7%), mostly disagree (3.6%), completely disagree (0%), and not sure (3.6%).

An enema is a popular method of treatment for constipation and has been used for hundreds of years in a variety of forms, including water, soapsuds, phosphate, and sugar solutions. Despite this long history, there is only anecdotal evidence of its value in the management of chronic constipation. Routine use is typically discouraged but may be necessary. Whereas tap water enemas seem safe for more regular use, electrolyte imbalances are more common with phosphate enemas.

However, even in the absence of strong evidence for the efficacy of an enema, many clinicians and patients find them useful and effective, both for the treatment of acute and chronic constipation, and as a means of preparing or cleansing the distal colon for endoscopic or surgical procedures. By distending the rectum, all enemas stimulate the colon to contract and eliminate the stool. Enemas may be effective in a subset of patients with obstructed defecation, and in preventing fecal impaction when chronic constipation is not intractable to medical treatment, including biofeedback therapy.¹⁹⁷

37. Statement: An enema should be used carefully because there are no standardized guidelines, and because it may cause complications such as rectal mucosal injury or electrolyte imbalance.

- Grade of recommendation: 2.
- Level of evidence: C.
- Experts' opinions: completely agree (42.3%), mostly agree (38.4%), partially agree (15.4%), mostly disagree (0%), completely disagree (3.9%), and not sure (0%).

Enemas can be effective, but their routine use is typically discouraged due to serious adverse events, such as metabolic derangement or perforation. Hypertonic sodium phosphate enemas may cause severe phosphate nephropathy, especially in the elderly with chronic renal failure. Phosphate enemas should be used with caution in patients with impaired renal function, pre-existing electrolyte imbalances, risk of electrolyte disturbance (hypocalcemia,

hyperphosphatemia, or hypernatremia), and chronic inflammatory bowel disease.¹⁹⁸ The cause of perforation in patients who underwent enemas has been reported to be the device tip, related to localized weakness of the rectal wall and obstruction.¹⁹⁹ Because of their adverse irritating effects, resulting in rectal mucosa damage, soap enemas should be avoided.

Suppositories can help to initiate or facilitate rectal evacuation and have been used for many decades for chronic constipation in many forms, including the presumably inert but lubricating glycerin, and as stimulants, such as bisacodyl. Despite their inclusion in many 'bowel protocols' and personal testimonials of individuals, there is limited evidence to support their usefulness in the management of chronic constipation.

Other non-pharmacological treatment

Sacral nerve stimulation

Sacral nerve stimulation (SNS) may be effective in the treatment of chronic constipation when other approaches have failed.²⁰⁰ SNS is a surgical treatment option such that, following peripheral nerve evaluation, external electrical stimulation is delivered via a temporary lead inserted percutaneously through the third sacral foramen to the S3 sacral nerve. Thirteen published studies were found reporting the use of SNS for constipation.²⁰¹ Ten studies involved adult subjects, including two double-blind crossover studies and three were retrospective reviews. SNS appears to be an effective treatment for constipation; however, research to date has been predominantly confined to small, low-level evidence studies with most lacking a coherent definition of constipation and SNS. Thus, it remains unclear which patients are most likely to benefit from the therapy.

Extracorporeal magnetic stimulation therapy

Extracorporeal magnetic stimulation therapy (EMST) has been reported to offer the potential for therapeutic benefit for a subset of constipated patients.²⁰²⁻²⁰⁴ EMST, which uses current-changing magnetic fields, allows the induction of electrical stimulation in the desired deep tissue. The mechanism of EMST in the S2-S3 dermatomes for constipation is unclear. One study reported that EMST was clinically useful in STC, particularly among constipated patients with rectal hyposensitivity or the transit pattern of hindgut dysfunction.²⁰²

Electrical stimulation therapy

Electrical stimulation may be considered as an adjuvant thera-

peutic modality for the management of constipation with rectal hyposensitivity, or among some patients refractory to biofeedback therapy.²⁰⁵⁻²⁰⁷

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Appendix. Formulate Research Question

No	Keyword	Search results	Search category
1	Constipation	19 441	MeSH
2	Constipation	144 588	All Fields
3	Constipation	20 201	Title Word
4	Dyschezia	52 428	All Fields
5	Dyschezia	101	Title Word
6	Colonic Inertia	977	All Fields
7	Colonic Inertia	350	Title Word
8	Anismus	789	All Fields
9	Anismus	269	Title Word
10	Dyssynergic defecation	500	All Fields
11	Dyssynergic defecation	215	Title Word
12	Obstructive defecation	495	All Fields
13	Obstructive defecation	126	Title Word
14	OR/1-13	126 841	
15	Guideline	44 705	Pub Type
16	Guideline	890 174	All Fields
17	Guideline	91 945	Title Word
18	Guideline*	1 352 569	All Fields
19	Guideline*	212 119	Title Word
20	Guidelines as Topic	123 289	MeSH
21	Guidelines as Topic	430 912	All Fields
22	Guidelines as Topic	4	Title Word
23	Guideline Adherence	27 474	MeSH
24	Guideline Adherence	229 105	All Fields
25	Guideline Adherence	2078	Title Word
26	Practice Guideline	26 163	Pub Type
27	Practice Guideline	431 308	All Fields
28	Practice Guideline	13 998	Title Word
29	Practice Guidelines as Topic	96 644	MeSH
30	Practice Guidelines as Topic	365 202	All Fields
31	Practice Guidelines as Topic	3	Title Word
32	Clinical Guideline	62 502	All Fields
33	Clinical Guideline	7144	Title Word
34	Clinical Practice Guideline	35 330	All Fields
35	Clinical Practice Guideline	8173	Title Word
36	Consensus	10 580	MeSH
37	Consensus	440 518	All Fields
38	Consensus	63 878	Title Word
39	Recommendation*	718 933	All Fields
40	Recommendation*	102 557	Title Word
41	Workshop	727 098	All Fields
42	Workshop	51 211	Title Word
43	OR/15-42	2 746 585	
44	14 AND 43	8623	