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Mechanisms, Evaluation, and Management of Chronic Constipation

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Abstract

With a worldwide prevalence of 15%, chronic constipation is one of the most frequent gastrointestinal diagnoses made in ambulatory medicine clinics, and is a common source cause for referrals to gastroenterologists and colorectal surgeons in the United States. Symptoms vary among patients; straining, incomplete evacuation, and a sense of anorectal blockage are just as important as decreased stool frequency. Chronic constipation is either a primary disorder (such as normal transit, slow transit, or defecatory disorders) or a secondary one (due to medications or, in rare cases, anatomic alterations). Colonic sensorimotor disturbances and pelvic floor dysfunction (such as defecatory disorders) are the most widely recognized pathogenic mechanisms. Guided by efficacy and cost, management of constipation should begin with dietary fiber supplementation and stimulant and/or osmotic laxatives, as appropriate, followed, if necessary, by intestinal secretagogues and/or prokinetic agents. Peripherally acting μ-opiate antagonists are another option for opioid-induced constipation. Anorectal tests to evaluate for defecatory disorders should be performed in patients who do not respond to over-the-counter agents. Colonic transit, followed if necessary with assessment of colonic motility with manometry and/or a barostat, can identify colonic dysmotility. Defecatory disorders often respond to biofeedback therapy. For specific patients, slow-transit constipation may necessitate a colectomy. No studies have compared inexpensive laxatives with newer drugs with different mechanisms. We review the mechanisms, evaluation, and management of chronic constipation. We discuss the importance of meticulous analyses of patient history and physical examination, advantages and disadvantages of diagnostic testing, guidance for individualized treatment, and management of medically refractory patients.

The prevalence of chronic constipation (CC) among adults is approximately 15%, making it the sixth most common gastrointestinal symptom. CC often results in visits to ambulatory clinics and gastroenterology referrals.[1–3] Although the prevalence is greater in non-Caucasians than Caucasians, in women (median female to male ratio of 1.5:1), and in

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Supplementary Material

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Conflicts of interest

The authors disclose the following: Adil E. Bharucha: Intellectual property and royalties (Medspira, Medtronic). Brian Lacy: Scientific advisory boards (Salix, Ironwood, Takeda), consultant (Viver).

institutionalized rather than community-living elderly persons, symptoms can affect all ages, races, socioeconomic groups, and nationalities.

Definition and Classification

Chronic constipation is either primary or secondary (attributed to another disease), determined from patient history and results from examinations and laboratory tests (Table 1).[4] The Rome IV criteria for primary constipation are based on results from anorectal tests and categorize patients as having functional constipation (FC), constipation-predominant irritable bowel syndrome (IBS-C), or defecatory disorders (DDs) (Supplementary Figure 1).[5] FC and IBS-C are primarily defined by symptoms alone (Table 2). DDs are defined by symptoms (such as FC or IBS-C) and results from anorectal tests that indicate impaired rectal evacuation. Prior American Gastroenterological Association reviews and this update classify patients with constipation based on assessments of colonic transit and anorectal function; the classifications are normal transit constipation (NTC), slow transit constipation (STC), and pelvic floor dysfunction or DDs (Supplementary Figure 1).[4,6]

Patients with constipation have infrequent stools (fewer than 3 bowel movements per week) and, more importantly, straining at stool, a feeling of incomplete evacuation, a need for digital assistance to evacuate stool, bloating, and hard or lumpy stools.[7] The Rome IV criteria are predominantly symptom-based and as such require that patients with a diagnosis of FC have 2 or more of these symptoms, which affect >25% of bowel movements for at least 6 months and active symptoms for the past 3 months (Table 1). By contrast, IBS-C is defined by abdominal pain that is associated with 2 of 3 features: altered stool form, altered stool frequency, or relief of abdominal pain with defecation. Although patients with CC also have abdominal pain, the pain is not, in contrast to the definition for IBS-C, associated with the symptoms mentioned. In (real-world) clinical practice, it is more useful to conceptualize FC and IBS-C along a spectrum; it is sometimes difficult to distinguish FC from IBS-C and to determine which patients are true medication responders using the definitions used in clinical trials (see Table 2). IBS-C patients are more likely to predominantly have abdominal pain, heightened rectal sensation,[8] upper gastrointestinal symptoms (eg, heartburn, dyspepsia), anxiety and depression, and urinary symptoms.[9,10] However, blurring the distinction between FC and IBS-C, 1 study found that approximately 90% of patients with IBS-C also met criteria for FC and 44% of the FC patients also met criteria for IBS-C.[11] In approximately one-third of patients, symptoms shift over time between FC and IBS-C.[11] In individual patients, a diagnosis of either FC or IBS-C is possible only because the Rome criteria specify that patients with symptoms of IBS-C and FC be designated as IBS-C not FC.

This limitation can be overcome by classifying constipated patients, based on the presence or absence of moderate to severe abdominal pain, into 1 of 2 categories, such as painful or painless constipation (Supplementary Figure 2).[9,10] In contrast to the Rome IV criteria for IBS-C, these definitions do not specify the temporal relationship, or lack thereof, between abdominal pain and bowel habits. Similar to the differences for FC and IBS-C, compared to mild pain constipation, patients with painful constipation have more prominent bowel, upper gastrointestinal (such as dyspepsia), anorectal, urinary and sexual symptoms, anxiety and

depression, and slower rectosigmoid transit. The widespread symptoms in painful constipation could partly reflect increased perception of visceral sensations. Symptom-based criteria for discriminating between painful and mild-pain constipation have been proposed but require finalization.

Physiology of Colonic Motor Functions

The right colon is a reservoir that mixes and stores contents.[12–14] The left colon functions primarily as a conduit. The rectum and anal canal enable defecation and maintain fecal continence. Our understanding of motor activity, which is derived mostly from studies with non-high-resolution manometry catheters in which sensors were separated by 7.5 cm or more,[13] suggest that most colonic motor activity is irregular and nonpropagated and serves to segment and mix intraluminal contents. By comparison, newer high-resolution catheters have sensors separated by 1–2.5 cm and are more accurate for detecting propagated motor events (Supplementary Figure 3).[15] Colonic motor patterns are diverse, and include individual or rhythmic events, which may be simultaneous or propagated (antegrade or retrograde), and have low or high amplitude.[13] Of these patterns, the gastrocolonic response to a meal and high-amplitude propagated contractions are arguably the most physiologically important. The gastrocolonic response begins shortly, often within a few seconds, after eating and may last for up to 2½ hours.[16] Although a 1000-kcal meal invariably elicits a response, 600 kcal is probably equivalent.[17] Propagated contractions, categorized as low (5–40 mmHg) or high-amplitude propagated contractions (HAPCs, >75 mmHg), occur an average of 6 times per day, originate predominantly in the cecum or ascending colon, cause mass movement of colon contents, and often precede defecation.[18] HAPCs occur more frequently after awakening and after meals and can account for the urge to defecate in healthy subjects and in patients with IBS. HAPCs occur spontaneously, occasionally in response to luminal distention, or can be induced by glycerol, bisacodyl, oleic acid, and the cholinesterase inhibitor neostigmine.

Pathophysiology

Colonic sensorimotor disturbances and pelvic floor dysfunction are the most widely recognized causes. Other factors, such as reduced caloric intake, disturbances of the microbiome, anatomical issues, or medications, can also contribute.

Colonic Sensorimotor Dysfunctions and the Microbiome

Isolated slow-transit constipation (eg, no DD) is used as a marker of colonic motor dysfunction(s), perhaps due to reductions in colonic intrinsic nerves and interstitial cells of Cajal.[19,20] Manometry can reveal colonic motor disturbances, such as reduced propagated and nonpropagated activity and reduced phasic contractile responses to a meal and/or to bisacodyl or neostigmine, in patients with STC.[21–23] Manometry catheters only measure phasic pressure activity. A barostat balloon device also records colonic tone; fasting tone and tonic contractile responses to a meal and/or neostigmine are reduced in STC (Figure 1).[21–23] Colonic inertia, which represents profound motor dysfunction, can only be identified by manometry or a barostat and is defined by reduced or absent contractile response to a meal and to pharmacologic stimuli (such as bisacodyl or neostigmine).[23,24]

Unfortunately, NTC and STC are imperfect markers of normal and impaired colonic motor function, respectively. For example, fasting and/or postprandial colonic tone and/or compliance were reduced in 40% of patients with NTC, 47% in patients with STC, 53% in patients with DD and normal transit, and 42% in patients with DD and slow transit.[23] Similarly, 43% of patients with STC had normal fasting colonic motility and motor responses to a meal and bisacodyl.[25] Patients with NTC might have symptoms of FC or IBS-C; 23% of patients with FC or IBS-C had delayed colonic transit.[26,27] Some patients have increased perception of rapid distention and reduced perception of slow distention.[28] Increased rectal sensitivity is associated with abdominal pain and bloating, suggestive of IBS.[29–31]

Germ-free mice colonized with the fecal microbiome from patients with constipation developed slow colonic transit.[32,33] Slow colon transit correlates inversely with colonic serotonin content, associates with a decreased relative abundance of Firmicutes and increased Bacteroidetes, and associates with altered fecal content of short-chain fatty acids and bile acids.[32] In humans, CC is associated with alterations in colonic mucosal microbiota, especially more plentiful phylum Bacteroidetes, resulting from a greater abundance of Flavobacterium. [34] Adjusted for colonic transit, the colonic mucosal microbiome discriminated patients with constipation from controls with 94% accuracy, even after adjusting for diet and colonic transit. By contrast, fecal microbiomes were associated with colonic transit and increased methane in breath samples, but not with constipation.

Defecatory Disorders

DDs (also called functional outlet obstruction, anorectal dyssynergia, or pelvic floor dysfunction) are caused by reduced rectal propulsive forces and/or increased resistance to evacuation (Figure 2).[35] Increased resistance results from high anal resting pressure (anismus) or paradoxical contraction or incomplete relaxation[36] of the pelvic floor and external anal sphincters (dyssynergia).[37] These patterns are not associated with specific clinical patterns or the response to pelvic floor retraining.[38] DDs primarily develop via maladaptive pelvic floor contraction during defecation.[39] Other abnormalities, especially reduced rectal sensation and structural deformities (such as rectoceles and excessive perineal descent), can coexist and be primary or secondary to constipation.[14,40–44] Reduced rectal sensation could reduce desire to defecate[40,45]; as many as 50% of patients with constipation have delayed colonic transit.[23,37,46] Beside colonic motor dysfunction unrelated to DD,[22] retained stool can physically obstruct passage of contents or evoke rectocolonic inhibitory reflexes.[47] Over time, excessive straining can weaken the pelvic floor, increasing risk for excessive perineal descent, rectal intussusception, solitary rectal ulcer syndrome, and pudendal neuropathy. Pudendal neuropathy can weaken anal sphincters, increasing risk for fecal incontinence.[45,48–50]

The precise contribution of dyssynergia to impaired evacuation is unclear because dyssynergia has been reported in asymptomatic people as well as patients with rectal pain.[38,51,52] This might be because it is a challenge to simulate defecation in the laboratory. When dyssynergia and structural abnormalities (such as large rectoceles) overlap, it is difficult to determine the contributions of each to the symptoms (Figure 2). Some features

(such as delayed colonic transit) are consequences of DD and improve after biofeedback therapy.[53] Other factors, particularly stool form, affect development of symptoms in patients with DD.[54,55] The pathogenesis of DD is unclear. DDs are believed to result from maladaptive learning of sphincter contraction, possibly initiated by avoidance of pain, or trauma,[56] or even neglecting the call to defecate. One-third of children with constipation continued to have severe symptoms beyond puberty.[57] There is no evidence for an association between obstetric trauma and DD.[58]

Clinical Evaluation

The bowel symptom questionnaire is a quick and effective tool for evaluating symptoms of constipation (Table 1). Questionnaires provide a snapshot of symptoms, whereas a 2-week bowel diary provides a more refined assessment of day-to-day variations and the relationship between stool form and other symptoms.[54] Analyses of bowel diaries recorded by patients when they are off laxatives can help determine contribution of laxatives to symptoms (such as bloating). It is also important to collect information on prior bowel habits, when bowel habits changed, and what patients consider as normal, because perceptions, influenced by societal and cultural norms, influence symptom reporting. Some patients report constipation because they do not, perhaps in contrast to a spouse, pass a daily bowel movement. Other patients, in retrospect, have had mild and/or intermittent symptoms for longer than initially acknowledged (such as since childhood). Inadvertent withholding, perhaps secondary to an aversion to using public toilets, or constipation after recent surgery, medication changes, or coexistent urinary symptoms, are not uncommon. Addressing the most bothersome symptoms of constipation can increase patients' quality of life.[59]

Colonic transit affects fecal form, which is assessed using the Bristol Stool Form Scale and ranges from liquid, to semi-formed, to pellet-like stools.[60–62] Abdominal pain and its relationship to bowel movements can differentiate patients with CC from patients with IBS-C. Co-existing gastrointestinal symptoms should be identified; constipated patients frequently have bloating, which can be due to the underlying disorder and/or medications—especially fiber and osmotic laxatives. The presence of multiple other gastrointestinal symptoms (such as dyspepsia), especially in a younger patient without warning signs, supports a functional cause of symptoms.[63] However, distinct mechanisms can cause dyspepsia (such as impaired gastric accommodation) and constipation in the same patients.[64] In constipated patients, fecal impaction, perhaps compounded by laxative-induced overflow diarrhea, increases the risk for fecal incontinence.[65] It is important to ask patients about diet (for adequate fiber intake, intake of calories, and poorly absorbed carbohydrates that contribute to bloating),[66] lifestyle (such as level of activity), toileting habits, medical conditions, obstetric history, and surgery (Table 1). At the appropriate time, patients should be asked whether they have a history of abuse, which is common in patients with DD.[67] Medications and supplements should be reviewed (Supplementary Table 1). Warning signs, such as unintentional weight loss >10% of body weight, anemia, rectal bleeding, a family history of colorectal cancer, and polyposis syndromes should be identified, which have low predictive values in patients with CC.[68]

A meticulous and directed physical examination is essential for several reasons. Considered in isolation, symptoms (such as straining vs infrequent bowel movements) do not discriminate between DD and other causes of CC.[38,69] Examinations can identify an organic cause for constipation, such as an abdominal mass, whereas dry skin is associated with hypothyroidism. Examinations also reassure patients that their concerns are taken seriously.

Digital rectal examinations (DREs) identify not only structural disorders (such as anal fissures, hemorrhoids, fecal impactions, descending perineum syndrome, or anorectal cancer), but also pelvic floor dyssynergia, which is treated differently.[70] Although DREs are recommended by many different societies, many providers do not perform them for constipated patients.[71] DREs identified patients with dyssynergia with 75% sensitivity and 87% specificity when manometry was used as the reference standard.[70] Compared with the rectal balloon expulsion test (BET), the sensitivity and specificity of a DRE were 80% and 56%, respectively. For some people with normal pelvic floor function, it is a challenge to simulate defecation during a DRE. This might account for the lower specificity compared with a BET. A normal result from a DRE is more useful than an abnormal result from an examination.[70] Nonetheless, patients with persistent symptoms and a normal finding from DRE should be referred for anorectal testing to exclude DDs.

Thereafter, in the absence of warning signs, patients should receive a diagnosis of CC. A complete blood count is helpful in making a diagnosis, but other laboratory studies are unnecessary.[4,5,72] Colonoscopies are only necessary for patients with alarm symptoms, or as required for age-appropriate screening. Physicians and their patients should discuss the benign nature of CCs, treatment options, and their efficacy, safety, and cost; questions about special tests should be answered.

Diagnostic Tests

Anorectal testing with manometry and BET are recommended for patients who have not responded to a high-fiber diet and/or simple laxatives.[4,73,74] Because access to anorectal testing is not universal, some practitioners treat patients empirically with prescription laxatives before anorectal testing. However, <25% of patients with IBS-C report being very satisfied with prescription laxatives, perhaps partly because they have a DD. This observation supports the need for anorectal testing.[75]

During anorectal tests, maintenance of privacy will facilitate cooperation and reduce embarrassment, which can account for false-positive results from tests in asymptomatic and constipated patients.[52] Results should be interpreted along with clinical features. There is no criterion standard diagnostic test, or symptom, for a diagnosis of DD. Although different tests provide different information about individual patients,[14,44] overall, the results of anorectal high-resolution anorectal manometry (HRM), BET, and magnetic resonance (MR) imaging are significantly correlated with each other, which substantiates the criterion validity of these tests,[44] even though these tests are performed in different positions, with or without rectal filling. Therefore, the Rome IV criteria propose that a diagnosis of DD be confirmed by abnormal findings from 2 of 4 tests (such as manometry, rectal BET, surface electromyography, or barium or MR defecography). Taking all factors (such as diagnostic

utility, usability, availability, risk, and expense) into consideration, the rectal BET is the most useful test to make a diagnosis of DD.

Balloon Expulsion Test

The BET is a simple procedure generally performed in conjunction with anorectal manometry to evaluate the time required to evacuate a 50-mL water-filled balloon (warm tap water) in the seated position. The normal values depend on the type of rectal balloon used for the test.[76–78] Most centers use a party or commercial balloon, for which the upper limit of normal is 1 minute. For a Foley catheter inflated to 50 mL, which is above the manufacturer-recommended limit of 30 mL, the upper limit of normal is 2 minutes.[76] Even with the 2-minute cutoff, 25% of healthy people would be misclassified as abnormal because they require more than 2 minutes.[79]

Among 106 patients with FC and 24 patients with DD, the BET identified those with DD, documented with defecography, with 88% sensitivity and 89% specificity; positive and negative predictive values were 64% and 97% for diagnosis of DD, respectively.[80] However, this uncontrolled study excluded patients with secondary (such as medication-induced) CC. The rectal balloon was inflated not to a fixed volume but until patients experienced the desire to defecate, averaging 183 mL, which may compensate for reduced rectal sensation identified in some patients with DD.[41]

Anorectal Manometry

Conventional catheters that incorporate water-perfused, air-charged, or solid-state sensors, HRM, or high-definition manometry can be used.[81–83] HRM and high-definition anorectal manometry catheters have more closely spaced sensors that straddle the entire anal canal. They provide better spatial resolution, and allow pressures to be assessed without a pull-through maneuver (Figure 2). Although conventional and HRM catheters measure anal pressures with comparable levels of precision, pressures are much higher with HRM or high-definition anorectal manometry than conventional catheters.[84] Anorectal pressures vary among techniques, so they must be compared with normal values measured by the same technique. Compared with healthy individuals, patients with DD have lower rectoanal pressure gradients (rectal–anal pressure) during evacuation. The rectoanal pressure pattern can also indicate causes of DD, such as decreased propulsive force, paradoxical contraction, or both.[69] However, the rectoanal gradient measured by HRM is negative in many asymptomatic people, which limits the utility of this parameter for making a diagnosis of DD.[52,82,85] Anorectal manometry is best performed in a seated rather than a left lateral, recumbent position.[86] Other features of DD include a higher anal resting pressure (anismus) and/or reduced voluntary augmentation during pelvic floor contraction.

Barium and Magnetic Resonance Defecography

Some practitioners prefer defecography to the BET. Others use defecography as a backup method, when the other anorectal tests produce results that are inconsistent with clinical findings, to identify anatomic abnormalities, or for patients with persistent symptoms after biofeedback therapy.[87–90] Abnormalities include inadequate (such as a spastic disorder) or excessive (such as in descending perineum syndrome) widening of the anorectal angle

and/or perineal descent during defecation. Internal intussusception, solitary rectal ulcers, rectoceles, and rectal prolapse are also observed.[91] Enteroceles, bladder, and uterovaginal prolapse can be visualized when the vagina and small intestine are opacified.

The techniques for barium defecography are incompletely standardized; some radiologists have limited enthusiasm for the test.[88] Asymptomatic subjects have features of DD. Methodological limitations to barium defecography (such as limited reproducibility of anorectal angle measurements) can be minimized by using standardized techniques.[14,92] In contrast to barium defecography, MR defecography is performed in the supine position but avoids radiation exposure and can is better for visualizing pelvic organ prolapse and the bony landmarks, which are necessary to measure pelvic floor motion.[40,74,93,94] MR defecography is especially useful for patients who are believed to have DDs with a normal BET; this group includes >90% of patients with a large rectocele, enterocele, peritoneocele, and/or peritoneocele (Figure 2).[40,44] Average anal electromyographic activity is recorded by electrodes mounted on an acrylic anal plug or taped to the perianal skin, and is used to identify dyssynergia,[88] and to provide biofeedback training for DD.[95,96] Reduction of ≥20% in anal electromyographic activity during evacuation is considered normal. By contrast, impaired reduction is considered abnormal and is correlated with rectoanal dyssynergia, identified by manometry and abnormal results from a BET.[76]

Colon Transit and Intraluminal Measurements of Motor Activity

As many as 50% of patients with DD have slow colon transit, so slow transit does not preclude the need for anorectal testing. The algorithm recommends assessment of anorectal functions before colonic transit (Figure 3). DDs are treated with pelvic biofeedback regardless of colonic transit, so colonic transit should be assessed, using radiopaque markers, colon scintigraphy, colonic manometry, or the wireless motility capsule, only when indicated after anorectal testing, and after discontinuing medications that can affect colonic transit (Figures 2 and 3). Stool frequency is not, although stool form is, modestly correlated with colonic transit.[62] Radiopaque marker studies (Sitz-Mark, Konsyl Pharmaceuticals, Fort Worth, TX) are inexpensive, readily available, easy to perform, and entail modest radiation exposure.[97]

Of the techniques for assessing colonic transit, the simplest entails checking an abdominal x-ray image at 120 hours after 20 or 24 markers are ingested. Colonic transit is normal if >80% of markers have been passed. However, the actual transit time is not estimated. With the Metcalf method, a plain x-ray image is obtained on day 4 after ingesting 24 markers on each of 3 days; the maximum detectable colonic transit time is 72 hours. The number of markers provides the total colonic transit time; <62 hours is probably normal (personal communication, Michel Bouchoucha). The number of markers in each segment (right, left, and rectosigmoid colon) provides the segmental transit time. In patients with delayed colonic transit, the actual transit time can be more accurately quantified from a single x-ray image on day 7 after ingestion of 12 markers on days 1–6; the maximum detectable colonic transit time is 144 hours.[97]

Assessments of colonic transit are reproducible in patients with simple constipation,[61] but less so in patients with DD or STC.[98] Colonic transit should therefore be reevaluated to

confirm the diagnosis of STC before surgery. Contrary to older studies, a more recent multicenter study observed that the distribution of markers in the rectosigmoid colon is not associated with DD.[99] However, rectal gas volume, measured with computed tomography, is greater in patients with vs without a rectal evacuation disorder.[100]

Less widely used and more expensive approaches include radionuclide gamma scintigraphy [26,101] or a wireless pH-pressure capsule, which can concurrently measure gastric emptying and small intestinal transit.[102,103] Scintigraphy, performed only at a few select academic centers, requires 24 or 48 hours of measurement compared to 5–7 days for radiopaque marker tests (Figure 1).[104] Colonic transit measured using radiopaque markers correlates well with scintigraphy [61] and the wireless motility-pH capsule.[102] The capsule also measures colonic motor activity.[103] Bowel cleansing shortens colonic transit but is unnecessary because it does not affect the characterization of patients as having normal or slow colon transit.[105]

Although all 3 techniques are equally accurate for measuring colonic transit, only radio-opaque markers and scintigraphy assess regional colonic transit. Of these techniques, the radio-opaque marker method is the simplest and least expensive, and is therefore the best way to measure colonic transit. Scintigraphy or the motility pH capsule should be used when it is also necessary to measure gastric emptying and/or small intestinal transit. If patients can only discontinue medications for a few days, scintigraphy is preferred. The ability to distinguish normal from slow transit can aid in determining the need for colectomy.

Colonic phasic motor activity recorded with manometry varies even in healthy people. Few centers offer to assess colonic tone and phasic pressure activity with a barostat manometry assembly, for which extensive normal values are available.[23] For some patients with medically refractory STC, it is useful to evaluate colonic motility with colonic manometry or barostat manometry and document colonic motor dysfunction; findings can support the decision to proceed with subtotal colectomies for patients who do not have pelvic floor dysfunction (Figure 1).[21] This approach is more widely used in children than adults with STC.

Putting It All Together

At the conclusion of the initial clinical evaluation, it should be possible to tentatively classify patients with symptoms of constipation as NTC, STC when pelvic floor function is normal, DDs (anismus/dyssynergia-failure of relaxation; or descending perineal syndrome and other flaccid disorders), or a combination of these (see Figure 3). Patients could also have organic constipation (mechanical obstruction or drug side effect; see Table 1 and Supplementary Table 1). The severity of pain can be used to characterize patients as mild pain/painless constipation or painful constipation (see Supplementary Figure 1).

Management

Management options for patients differ in ease of use, availability, cost, mechanism, efficacy, and safety (Table 3). Some, but not all, have been studied in large, randomized, controlled trials. Others, although commonly used, have not been carefully scrutinized (such as cascara). The aim of treatment is to correct bowel disturbances in patients with CC or

IBS-C and reduce abdominal pain in patients with IBS-C. A treatment algorithm has been developed, based on factors that include efficacy, availability, ease of use, and cost, but not validated. Each patient requires an individual treatment plan; it is important to remember many patients in gastroenterology clinics have already been failed by over-the-counter agents, so prescription medications might be the logical first choice after DDs are excluded (for specific measures for opioid-induced constipation, see Luthra et al[106]).

It is important to educate patients about CC and its progression; patients' questions, concerns, and goals should all be addressed. Caloric intake should be estimated because caloric restriction might cause constipation.[107] Patients should be encouraged to consume 25–30 g fiber daily as fresh fruit, fresh vegetables, legumes, and whole grains, because fiber adds bulk to stool and stimulates intestinal transit.[108] Although exercise is generally beneficial, its effects on constipation are unclear.[109,110] Taking advantage of the gastrocolic reflex, bathroom time should be scheduled after meals. There is no evidence that drinking more water is beneficial for constipation.[109]

Fiber

Soluble (such as psyllium or ispaghula) but not insoluble dietary fiber (such as wheat bran) supplements improve symptoms in patients with CC[108] or IBS-C.[111] Of 4 trials of fiber, the largest enrolled 201 patients with CC[112] and 3 gave patients psyllium, but only for 4 weeks.[108] In a meta-analysis of 17 trials, soluble fiber improved symptoms in IBS-C but had variable effects on abdominal pain.[111] In a randomized trial of 275 primary care patients with IBS-C given psyllium (10 g, twice daily) or bran, only psyllium was more effective than placebo after 1 month.[113] At 3 months, bran was more effective placebo. More than 60% of patients given bran or psyllium reported adverse effects, primarily constipation or diarrhea. However, 29% and 40% of patients dropped out by 2 and 3 months of follow-up.

The potential therapeutic effects, low cost, safety profile, and other potential health benefits of dietary fiber justify increasing dietary fiber intake, either as a standardized supplement or with foods, as a first step for patients with CC—particularly those in primary care. In contrast to NTC, patients with drug-induced or STC are unlikely to respond to fiber supplementation.[114] Patients should be instructed to begin with 5 g fiber daily, divided in 2 doses, to be taken with fluids and/or meals and gradually increase at 1- to 2-week intervals up to 10–15 g daily. Unlike a purgative, the response may take several weeks to be evident. Fiber supplements may increase gaseousness but the symptoms often decrease after several days. Sometimes gaseousness can be reduced by switching to another fiber supplement.

Osmotic and Stimulant Laxatives

Osmotic agents include polyethylene glycol (PEG)-based solutions, magnesium citrate–based products, sodium phosphate–based products, and nonabsorbable carbohydrates. Through osmosis, these hypertonic products extract fluid into the intestinal lumen to soften stools and accelerate colon transit. By contrast, the PEG and electrolyte lavage solution used for colonic cleansing, typically not for CC, is iso-osmotic with plasma; bowel evacuation is by high-volume lavage.

The osmotic laxatives are consistently better than placebo for improving the symptoms of CC.[115] The strongest evidence exists for PEG, which has been evaluated in 19 trials, mostly compared to placebo, followed by lactulose and tegaserod.[115,116] In the largest study (304 patients treated for 6 months), patients given PEG had more bowel movements per week than patients given placebo.[117] One controlled trial with PEG was of 6 months' duration.[115] In a retrospective series study, its efficacy was maintained for up to 24 months, which is longer than the 7-day recommended trial.[117,118] Patients prefer PEG preparations without electrolyte supplements,[119] which are necessary when a large volume is used.[120]

Although magnesium hydroxide and other salts are sparingly absorbed and generally safe, these have not been tested in randomized controlled trials. Severe hypermagnesemia may occur in patients with renal impairment.[121] Sodium phosphate-based bowel cleansing preparations should be avoided because they are associated with hyperphosphatemia, hypocalcemia, and hypokalemia, and in fewer than 1 in 1000 individuals, with acute phosphate nephropathy.[121,122] A Cochrane review of 10 randomized trials concluded that PEG was superior to lactulose for improving stool frequency, stool consistency, and abdominal pain.[123] Among nonabsorbable carbohydrates, lactulose and sorbitol had similar laxative effects, but lactulose was associated with more nausea in a randomized crossover study of 30 men[124]; sorbitol is less sweet than lactulose and accelerates proximal colonic emptying.[125,126] Dosing of prescription laxatives varies from patient to patient and from agent to agent. The general goal is to improve predominant symptoms reported by patients. Bacterial metabolism of unabsorbed carbohydrate leads to gas production and abdominal cramping, which can limit long-term use. There have been no large studies of lactitol, mannitol, or sorbitol for treating constipation.

Stimulant Laxatives

Stimulant laxatives, which include diphenylmethane derivatives (bisacodyl and sodium picosulfate) and anthraquinone derivatives (senna, aloe, cascara sagrada), are often used on a rescue basis, such as for patients who have not defecated for 2–3 days. Bisacodyl and sodium picosulfate are converted, respectively, by mucosa deacetylase enzymes and desulfatases of the colonic microflora to the same active metabolite, bis-(p-hydroxyphenyl)-pyridyl-2-methane, which has anti-absorptive secretory effects and induces colonic HAPCs.[18,127] The anthraquinones also increase colonic motility, perhaps following epithelial damage, and alter colonic absorption and secretion.[128] Two 4-week double-blind, randomized controlled trials demonstrated that sodium picosulfate (10 mg/d) or bisacodyl (10 mg/d) were more effective than placebo in 367 and 247 patients, respectively, with FC.[129,130] However, there have been no long-term studies or comparisons with other drugs. Use is often limited by side effects of abdominal pain and diarrhea.

An ionic surfactant, docusate sodium, decreases the surface tension at the stool oil–water interface, allowing water to penetrate the stool. Although it is frequently recommended, there are few data to support its use. In a double-blind, randomized, controlled trial of 170 patients with constipation, docusate sodium (100 mg twice daily) was less effective than psyllium.[131]

Secretagogues

The US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency approved lubiprostone, linaclotide, and plecanatide for treatment of CC and IBS-C. The US FDA also approved tenapanor for treatment of IBS-C in September 2019. These secretagogues stimulate net efflux of ions and water into the intestinal lumen, likely accelerate transit, and facilitate ease of defecation.

By activating channels on the apical (luminal) enterocyte surface, these secretagogues increase intestinal chloride secretion. Other ion channels and transporters secrete sodium into the intestine to maintain electroneutrality; water secretion follows. Lubiprostone is a bicyclic fatty acid derived from prostaglandin E_1 that activates type 2 chloride channels on the apical membrane of epithelial cells. In a 4-week, randomized trial, lubiprostone was more effective than placebo in improving bowel symptoms in patients with CC.[132] Nausea, typically mild, was the most common adverse event. Linaclotide and plecanatide are guanylate cyclase C activators that induce fluid secretion into the gastrointestinal tract via an increase in cyclic guanosine monophosphate and subsequent activation of the cystic fibrosis transmembrane regulator. These drugs are similar to endogenous peptides, primarily expressed in the small (uroguanylin) or large (guanylin) intestine, that also activate guanylate cyclase C.[133] Fasting and/or postprandial levels of prouroguanylin and uroguanylin are reduced in patients with CC and IBS-C, which might impair fluid and electrolyte secretion to cause constipation. Increased cyclic guanosine monophosphate improved abdominal pain in an animal model of visceral pain.[134]

In two 12-week, double-blind, randomized controlled trials, comprising 1276 patients with CC, linaclotide (290 μg or 145 μg, once daily) reduced symptoms more effectively than placebo.[135] A lower dose (72 μg, once daily) was also more effective than placebo and has been approved by the FDA for treatment of CC.[135,136] Plecanatide (3- and 6-mg doses) was more effective than placebo in 2 phase 3 randomized trials comprising 2804 adults with CC; the 3-mg dose has been approved by the FDA.[137,138]

Diarrhea, the most common adverse event of linaclotide or plecanatide therapy, necessitated discontinuation of treatment in <5% of patients.[135–138] Linaclotide and plecanatide are of similar efficacy and tolerability for treatment of CC.[139] Tenapanor, a small-molecule inhibitor of the gastrointestinal sodium-hydrogen exchanger-3, was superior to placebo in improving constipation symptoms in a phase 2 study[140,141] and in 2 phase 3 trials. In these trials, 12 weeks (610 patients) and 26 weeks (593 patients) of tenapanor (50 mg, twice daily) were more effective than placebo in patients with IBS-C.[142]

Prokinetic and Other Agents

Prucalopride, a dihyrodrobenzofurancarboxamide derivative, is a selective agonist of serotonin 5-HT_4 receptors, which are found throughout the gastrointestinal tract, including the colon.[143] Multicenter, double-blind, randomized trials of prucalopride in patients with CC differed in sample size, study duration (4–24 weeks), and dose (1 mg, 2 mg, or 4 mg vs placebo).[143] In 6 of 7 studies, prucalopride was more effective than placebo. The only 24-week study did not find a statistically significant difference between effects of prucalopride

and placebo.[144] The most frequent, generally transient, side effects were headache, nausea, and diarrhea. There were no significant cardiovascular side effects. The European Medicines Agency and the FDA have approved prucalopride for treatment of CC. Based on 3 pivotal studies in 3199 patients, the 5-HT_4 agonist tegaserod was approved for treatment of IBS-C and then voluntarily withdrawn from the market in 2007 after a greater number of cardiovascular events were observed in a database of 18,000 patients given tegaserod (n = 13; 0. 11%) or placebo (n = 1; 0.01%).[145] In April 2019, the FDA reviewed extensive supplementary data and approved the use of tegaserod in women younger than 65 years of age who do not have a history of ischemic cardiovascular disease and who have no more than 1 risk factor for cardiovascular disease.

A systematic review found that probiotics (*Bifidobacterium lactis* DN173010, *Lactobacillus casei* Shirota, *Lactobacillus casei* YIT) can increase mean stool frequency.[146] However, the assessment was limited by a high risk of bias in these studies. Prunes (approximately 6 twice daily) might reduce symptoms of CC via their combination of fiber and fructose.[147] Hemp seed extract might also be effective in some patients.[148]

Comparison of Agents

In the absence of rigorous, direct comparisons of drugs,[117,149] the relative efficacy of these agents can be assessed by comparing the number needed to treat among trials or through network meta-analyses of CC [150,151] and IBS-C.[141] Although these comparisons are useful, they are limited by differences in patient populations, definitions of end points and adverse events, and durations of treatment. Nonetheless, lubiprostone, linaclotide, and prucalopride are all more effective than placebo and of comparable efficacy, with estimated numbers needed to treat of 4, 6, and 6, respectively, based on end points of complete spontaneous bowel movements and increases in complete spontaneous bowel movements compared with baseline.[150]

Plecanatide had not been rigorously evaluated when this analysis was performed. More recently, a network meta-analysis by Luthra et al[151] found that stimulant diphenyl methane laxatives were most effective at 4 weeks, although prucalopride (2 and 4 mg) and linaclotide (290 μg) had similar efficacies at 12 weeks. There have been no direct comparisons of the secretagogues or prucalopride vs over-the-counter laxatives. Little is known about the incremental effects, if any, of these agents vs more inexpensive laxatives.

Management of Defecatory Disorders

DDs should be managed with biofeedback-aided pelvic floor retraining.[152] Through visual or auditory feedback of anorectal and pelvic floor muscle activity, which is recorded with surface electromyographic sensors or manometry, patients learn to increase intra-abdominal pressure and relax the pelvic floor muscles during defecation. Subsequently, patients practice by expelling an air-filled balloon. Sensory retraining, in which patients learn to recognize weaker sensations of rectal filling, may also be provided to patients with reduced rectal sensation. Although therapy may also include Kegel exercises, the emphasis is on appropriately coordinating abdominal and pelvic floor motion during evacuation.

Regrettably, biofeedback therapy is underused, perhaps because its benefits are not widely recognized and the expertise is not widely available. Contrary to findings from a previous study,[153] pelvic floor retraining was found to be more effective for DD than in isolated STC.[53] Colonic transit normalized after biofeedback therapy in 65% of patients with DD, but in only 8% of patients with STC, indicating that delayed colonic transit could be secondary to pelvic floor dysfunction.[53] In controlled studies that provided 5–6 training sessions lasting 30–60 minutes at 2-week intervals, biofeedback therapy was more effective than PEG,[95] sham feedback,[154] or diazepam.[96] Alternatively, daily sessions can be provided. The skill and experience of therapists and patients' motivation affect responses to biofeedback therapy. Dietitians and behavioral psychologists should also be involved, as necessary. Third-party coverage for biofeedback therapy in DD has improved but is suboptimal.

Management of Chronic Constipation Refractive to Medical Therapy

Refractory symptoms, practically defined by a 4-week trial of pharmacologic therapy to each drug or a 3-month trial of pelvic floor behavioral therapy, are not uncommon.[155] A systematic review of colectomy for CC found that most studies were of ileorectal anastomosis.[156] Although the studies were limited by inconsistent reporting and heterogeneity, an average of 86% of patients benefited at 1 year or more after surgery. When the Cleveland Clinic Constipation scoring system was used, patients' scores decreased from a preoperative mean of 20 points or more, indicating severe constipation, to a low to normal range of 2–3. However, 18.2% of patients had persistent constipation after a colectomy. Others had diarrhea and fecal incontinence (5%–15% of patients), abdominal pain (30%–50% of patients), or bloating (10%–40%). When abdominal pain and/or bloating are predominant symptoms, the decision to perform a colectomy should be made carefully. If a colectomy is to be performed, it might be preceded by temporary loop ileostomy to determine whether symptoms emanate from the small intestine or colon. Outcomes after colectomy are poorer in patients with generalized intestinal, rather than isolated colonic, dysmotility and in some but not all patients with DD.

Patients with DD should therefore undergo biofeedback therapy before colectomy. Guided by regional measurements of colonic transit, segmental resection (such as left hemicolectomy) has been proposed but does not perform better than an ileorectal anastomosis. Approximately 20%–30% of patients have perioperative complications, primarily ileus and early or late small bowel obstruction. In some studies, these complications were less frequent after laparoscopic vs open surgery.

Therapeutic options for patients with DD refractory to biofeedback therapy are limited. Although enemas or suppositories are frequently used by patients, there have been no controlled studies of their utility or safety in patients with DD. The adrenergic α_1 receptor antagonist alfuzosin, which probably relaxes the internal anal sphincter, reduced anal pressures in healthy people and patients with DD, but did not improve symptoms of DD.[55,157] Sacral nerve stimulation increases pancolonic antegrade propagating sequence frequency in patients with STC.[158] Contrary to findings from uncontrolled studies,[159] findings from more rigorous studies[160–162] and from a double-blind study of 45 patients with constipation are less encouraging.[163] Sacral nerve stimulation is therefore not

recommended for treating refractory constipation. Poor-quality studies found that rectal suspension procedures, a form of rectopexy, might improve symptoms and also be accompanied by healing of prolapse-associated solitary rectal ulcer syndrome in patients with refractory constipation and rectal intussusception.[164] A systematic review of rectovaginal reinforcement procedures in patients with constipation and a large rectocele found limited evidence to support the efficacy of these procedures; most evidence was derived from observational studies and comparisons.[165]

Percutaneous endoscopic cecostomy is used for colonic irrigation in patients with sigmoid volvulus, chronic intestinal pseudo-obstruction, or CC.[155] Performed under local anesthesia and conscious sedation, it is a less-invasive alternative to surgery. Among 12 reports, the procedure was successful in 122 of 127 patients with medically refractory constipation, of which 56% had procedure-related complications (chronic pain [15%], granulation tissue at stoma site [12%], and local-site infections [10%]); only 1 patient developed peritonitis. Assessments of efficacy, albeit suboptimal, found symptoms to improve in >50% of patients. Further studies are necessary before this procedure can be recommended.

During transanal irrigation, a device is used to lavage the colon with water (volumes of 70–1000 mL). In 7 uncontrolled, mostly retrospective reports of transanal irrigation (comprising 254 patients with constipation), 30%–65% of patients reported a positive outcome.[166] A separate retrospective study analyzed outcome questionnaires given to 102 of 148 consecutive patients who used transanal irrigation for an average duration of 60.5 weeks.[167] Overall satisfaction was increased in 67% of patients; 39% reported being moderately better and 28% reported being very much better. Prospective controlled studies are underway[168] to evaluate different methods of irrigation and the cost-effectiveness of transanal irrigation.

Summary and Future Directions

An algorithm is useful for managing CC. Identifying the predominant symptom and a meticulous DRE are essential. Aside from a complete blood count, no tests are necessary in the absence of alarm symptoms; age-appropriate colonic structural evaluations should be performed. If feasible, medications that can cause constipation, especially opioids, should be discontinued. Thereafter, an empiric trial of fiber with osmotic and/or stimulant laxatives is advisable. Many patients obtain symptom relief with these measures, which are safe for long-term use. For patients who do not respond, anorectal testing is necessary; biofeedback therapy is the cornerstone for managing DD. Assessment of colonic transit will identify STC, which should be treated initially with laxatives and, if necessary, with secretagogues or prokinetic agents. Patients who do not respond to these treatments should be considered for surgery or other less-invasive options, although few will qualify after careful physiologic evaluation. Psychological conditions should be considered as contributing factors. Future trials of patients with IBS-C or FC should assess for and exclude patients with DD, compare newer therapeutic agents with over-the-counter laxatives, and evaluate the clinical effectiveness and cost-effectiveness of the management algorithm presented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

BET	balloon expulsion test
CC	chronic constipation
DD	defecatory disorder
DRE	digital rectal examination
FC	functional constipation
FDA	US Food and Drug Administration
HAPC	high-amplitude propagated contraction
HRM	high-resolution anorectal manometry
IBS	irritable bowel syndrome
IBS-C	constipation-predominant irritable bowel syndrome
MR	magnetic resonance
NTC	normal transit constipation
PEG	polyethylene glycol
STC	slow transit constipation

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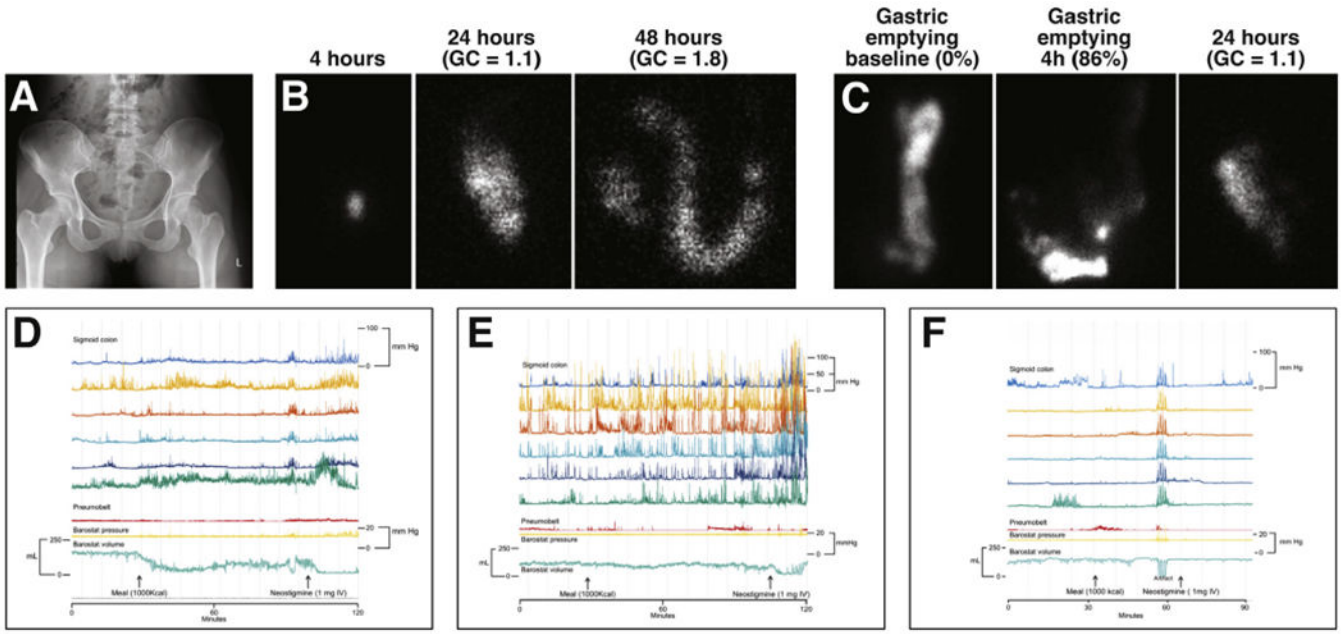

Figure 1.

Patterns of colonic motor dysfunctions in patients with CC. The pronounced reduction in sigmoid colonic balloon volume indicates a normal tonic response to a meal (*D*) in a patient with excess colonic stool burden (*A*). Anorectal tests (not shown) identified a DD. During scintigraphy, colonic transit is usually measured using an isotope^{111} coated with a pH-sensitive methacrylate that dissolves in the terminal ileum. In (*B*), the isotope is in an intact capsule (*left*) observed in the ascending colon at 24 hours (*center panel*) and then in the transverse colon at 48 hours (*right panel*). The geometric center (GC), which is the weighted distribution of the isotope throughout the colon, indicates slow colon transit; normal values are 1.4–3.6 at 24 hours and 2.1–4.9 at 48 hours. In this patient, the colonic manometry (*E*) depicts considerable phasic pressure activity during the fasting period, increased phasic activity after a meal, and more so after intravenous neostigmine. However, the tonic contractile response to the meal was reduced. (*C*) shows a patient with delayed colonic transit with normal gastric emptying. In this patient, the colonic manometry (*F*) reveals sparse phasic pressure activity and tonic or phasic contractile responses to a meal.

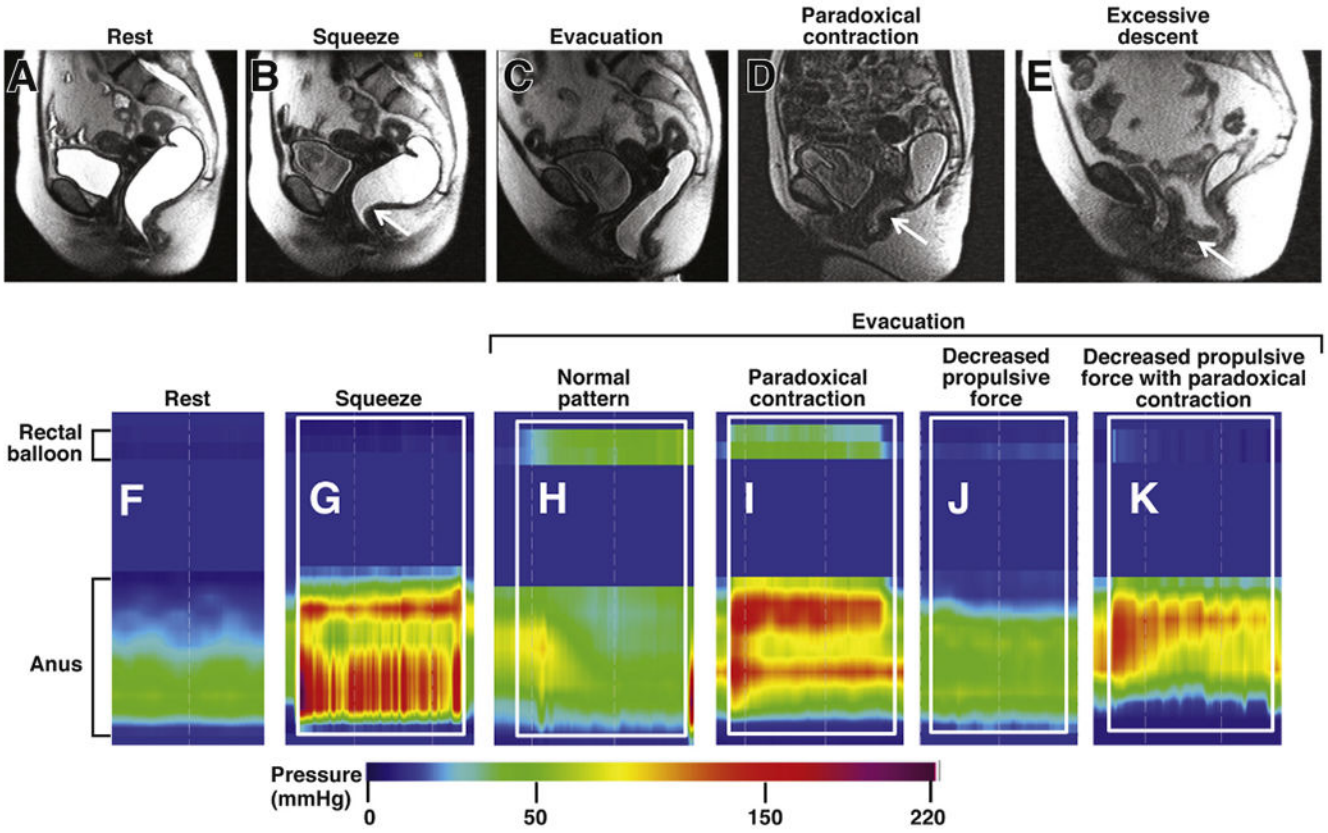

Figure 2.

Normal and abnormal anorectal evacuation. Evacuation was recorded by MR imaging (*top row*) and high-resolution manometry (*bottom row*). MR imaging shows anorectum filled with gel at rest (*A*), increased puborectalis indentation during squeeze (*B, arrow*) and normal relaxation of the puborectalis, perineal descent, opening of the anal canal, and evacuation of ultrasound gel during evacuation (*C*). In patients with constipation, during evacuation, there is paradoxical contraction of the puborectalis (*D, arrow*) and exaggerated perineal descent with an enterocele (*E, arrow*). High-resolution manometry shows anal pressure at rest (*F*) and increased anal pressure during squeeze (*G*) compared to rest (*F*). The *white rectangle* demarcates the duration of squeeze (*G*) and evacuation (*H–K*). Note the increased rectal pressure with anal relaxation during evacuation in a healthy person (*H*). By contrast during evacuation in constipated patients, note increased rectal pressure with paradoxical anal contraction (*I*), no change in rectal pressure vs rest (*J*), and no change in rectal pressure with paradoxical anal contraction (*K*). Reproduced from Bharucha and Wald,[72] with permission.

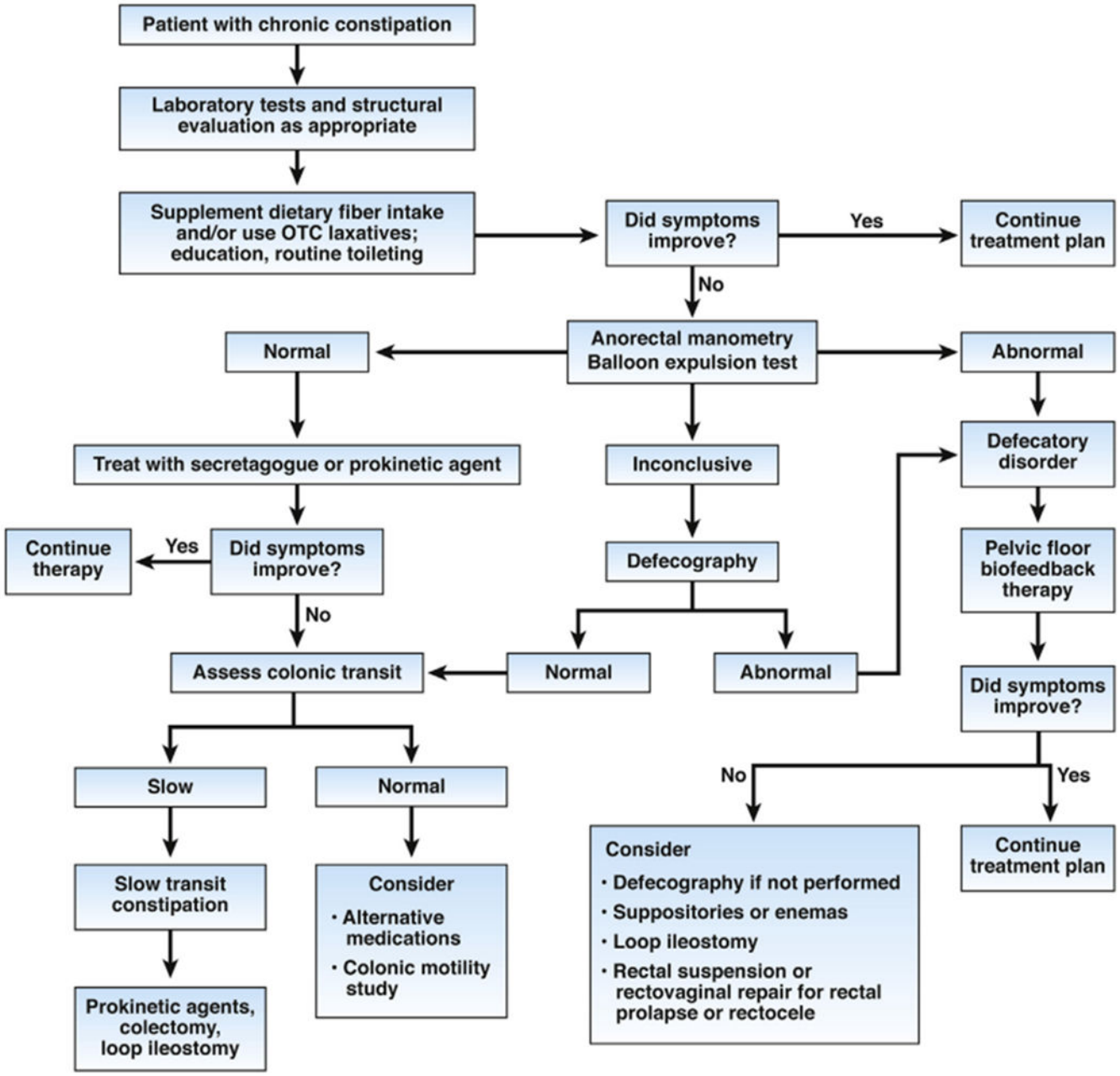

Figure 3.
Treatment algorithm for CC.

Table 1.

Common Medical Conditions Associated With Constipation

Cause	Comments
Drug effects	See Supplementary Table 1
Mechanical obstruction: colon cancer, external compression from malignant lesion, strictures (diverticular or post ischemic), rectocele (if large), megacolon, anal fissure	Often associated with alarm clinical features or laboratory tests, apparent on digital rectal examination (fissure) or x-ray image of the abdomen, or preceded by the primary event (diverticulitis)
Metabolic conditions: diabetes mellitus, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, uremia, heavy metal poisoning, uremia, heavy metal poisoning	All are associated with/can be diagnosed by abnormal results from laboratory tests, which should be performed only when there is a high index of suspicion (such as in patients on diuretics)
Myopathies: amyloidosis, scleroderma	Typically associated with other clinical features of these conditions
Neuropathies: Parkinson's disease, spinal cord injury or tumor, cerebrovascular disease, and multiple sclerosis	Constipation, either due to slow colon transit and/or DD, is common in patients with these disorders, which have many other features
Other conditions: depression, degenerative joint disease, autonomic neuropathy, cognitive impairment, immobility, cardiac disease	The disorder and/or medications may contribute to constipation

Table 2.

Definitions of Constipation

Rome IV criteria		Criteria used in studies of pharmacologic agents	
FC	**IBS-C**	**FC[169]**	**IBS-C[170]**
Symptoms for ≥6 mo and 2 or more of the following symptoms for >25% of defecations during past 3 mo: ◦ Straining ◦ Lumpy or hard stools ◦ Sensation of incomplete evacuation ◦ Sensation of anorectal obstruction/blockade ◦ Manual maneuvers to facilitate defecations; ◦ <3 defecations/wk ◦ Loose stools are not present, and there are insufficient criteria for IBS	Recurrent abdominal pain at least 1 d/wk in the past 3 mo associated with 2 or more of the following: ◦ Related to defecation ◦ Onset associated with change in frequency of stool ◦ Onset associated with change in form (appearance) of stool ◦ >25% of bowel movements were hard and <25% were loose stools	<3 SBMs/wk and 1 or more of the following symptoms for at least 12 wk during the preceding 12 mo ◦ Straining in >25% of defecations ◦ Lumpy or hard stools in >25% of defecations ◦ Sensation of incomplete evacuation in >25% of defecations ◦ No loose or watery SBMs (Bristol Stool Form Scale scores of 6 or 7)	Abdominal pain associated with 2 or more of the following: ◦ Related to defecation ◦ Onset associated with change in frequency of stool ◦ Onset associated with change in form and (appearance) of stool ◦ <3 SBMs and <3 CSBMs/wk; and at least 1 additional symptom ◦ Straining in ≥25% of defecations ◦ Lumpy or hard stools in ≥25% of defecations ◦ Sensation of incomplete evacuation in ≥25% of defecations

CSBM, complete spontaneous bowel movements; SBM, spontaneous bowel movement.

Table 3.

Medical Management of Chronic Constipation

Treatment and frequency	Dose	Number needed to treat for CC and IBS-C	Cost/mo, US $ (2019)	Comments
Bulking agents, psyllium, daily	CC: Variable dose IBS-C: Variable dose	CC: 2 (95% CI, 1–3)[79] IBS-C: 10 (95% CI, 6–33)[79]	8.34	Start with low dose and increase gradually.
PEG, daily	CC: 17 g IBS-C: 17 g	CC: 3 (95% CI, 2–4)[2] IBS-C: NA	30.90	More evidence from studies of CC than IBS-C. Improved bowel symptoms but not abdominal pain in patients with IBS-C.[80]
Lactulose, daily	20 g	NA	11.20	Can produce bloating and distension.
Bisacodyl, daily	CC: 10 mg IBS-C: 10 mg	CC: 4 (95% CI, NA)[81] IBS-C: NA	5.17	Available as suppository, preferably administered 30 min after breakfast.
Senna, daily	17.2–34.4 mg	—	5.90	Widely used anthraquinone laxative
Prucalopride, daily	CC: 2 mg IBS-C: NA	CC: 6 (95% CI, 5–9)[2] IBS-C: NA	395.67	Approved in the United States; available in Mexico, Canada, and Europe.
Linaclotide, daily	CC: 72 μg IBS-C: 290 μg	CC: 72 μg, 12 (95% CI, 6–29); 145 μg, 10 (95% CI, 6–19)[78] IBS-C: 290 μg, 6 (95% CI, 4–16)	395.41	Reduces abdominal pain, bloating, and overall symptoms of IBS in patients with IBS-C.
Lubiprostone, twice daily	CC: 24 μg IBS-C: 8 μg	CC: 24 μg, 4 (95% CI, 3–6)[79] IBS-C: 8 μg, 12 (95% CI, 8–25)	342.92	Also reduces abdominal bloating, discomfort, and severity of constipation in patients with opioid-induced constipation.[82]
Plecanatide, daily	CC: 3 mg or 6 mg IBS-C: 6 mg[a]	CC: 3 mg, 11 (95% CI, 8–19) 6 mg, 12 (95% CI, 8–23)[78] IBS-C: 3 mg, 9 (95% CI, 6–16) 6 mg, 9 (95% CI, 6–17)	384.36	Similar to linaclotide.
Tenapanor, twice daily	CC: NA IBS-C: 50 mg	IBS-C: NA	NA	Only studied in patients with IBS-C and only approved in the United States. Diarrhea is the most frequent side effect. Safety analysis underway in 2 phase 3 trials

NOTE. Modified from Bharucha and Wald,[72] with permission.

CI, confidence interval; NA, not available.

[a]FDA-approved dose for CC and IBS-C is 3 mg daily.