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Constipation

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Chronic constipation is a common disorder manifested by a variety of symptoms. Assessments of colonic transit and anorectal functions are used to categorize constipated patients into three groups, i.e., normal transit or irritable bowel syndrome, pelvic floor dysfunction (i.e., functional defaecatory disorders) and slow transit constipation. 'Slow transit' constipation is a clinical syndrome attributed to ineffective colonic propulsion and/or increased resistance to propagation of colonic contents. Defaecatory disorders are caused by insufficient relaxation of the pelvic floor muscles or a failure to generate adequate propulsive forces during defaecation. Colonic transit is often delayed in patients with functional defaecatory disorders. Normal and slow transit constipation are generally managed with medications; surgery is necessary for a minority of patients with slow transit constipation. Functional defaecatory disorders are primarily treated with pelvic floor retraining using biofeedback therapy.

Key words: constipation; anorectal; slow transit; pelvic floor; laxatives.

INTRODUCTION

Constipation is prevalent in Western societies and a common symptom in clinical practice. Constipation is often mild, intermittent, and self-treated with over the counter fibre supplements and laxatives. Only a small proportion of all people who perceive they are constipated seek health care.

The definition of constipation varies among physicians and laypersons. The Rome III criteria use symptoms to separate constipation into two syndromes, i.e., functional constipation and constipation-predominant IBS. Recognizing that patients refer to a variety of symptoms when they consider themselves to be constipated, the Rome III criteria

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define functional constipation by the presence of two or more of the following six symptoms, i.e., infrequent bowel habits (i.e., less than 3 stools/week), hard stools, excessive straining, a sense of anorectal blockage, or the use of manual manoeuvres during evacuation, and a sense of incomplete evacuation after defaecation.[1] Though patients with functional constipation may have abdominal discomfort, they do not have criteria for irritable bowel syndrome (IBS), i.e., abdominal discomfort associated with two or more of the following three symptoms, i.e., relief of discomfort passing a bowel movement, an association between discomfort and hard stools, and an association between discomfort and less frequent stools. Depending on the definition used, the prevalence of constipation in the community ranges from 2 to 25% and probably averages approximately 15%.[2]

In clinical practice, assessments of colonic transit and anorectal functions are used to categorize constipated patients into three groups, i.e., normal transit or irritable bowel syndrome, pelvic floor dysfunction and slow transit constipation (Figure 1).[3,4] In a study of more than 1000 patients with chronic constipation, normal transit through the colon was the most prevalent form (occurring in 59% of the patients), followed by defaecatory disorders (25%), slow transit (13%), and a combination of defaecatory disorders and slow transit (3%).[4] Beginning with the earliest report by Preston and Lennard-Jones, an overlap between slow transit constipation and pelvic floor dysfunction has been widely recognized.[5–7] They described a clinical syndrome characterized by intractable constipation poorly responsive to fibre and laxatives, abdominal pain, bloating, malaise, nausea, delayed colonic transit without megacolon and anorectal symptoms suggestive of difficult faecal expulsion.[7] Extragastrointestinal symptoms in this syndrome included painful and/or irregular menses, hesitancy in initiating micturition, and somatic symptoms such as cold hands or blackout. Since anorectal function tests are now more widely available, the term 'slow transit constipation' is reserved for patients who primarily complain of constipation and have delayed colonic transit but no underlying systemic disorder or pelvic floor dysfunction that explains these symptoms. Consistent with the theme of this book, this chapter will focus on 'idiopathic' slow transit constipation. Other causes of slow transit constipation (e.g., medications such as anticholinergic agents or opiates and neurological disorders) will not be discussed in detail.

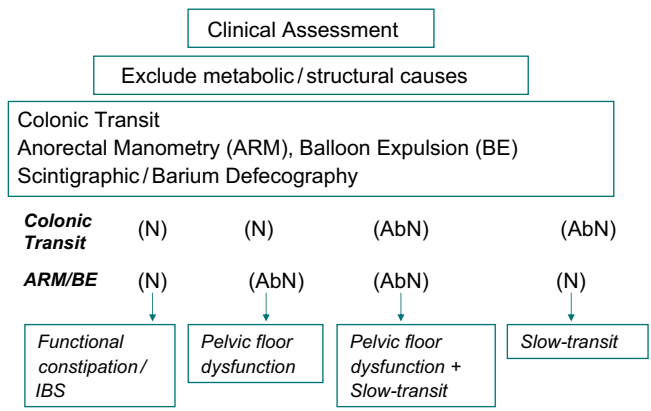

Figure 1. Diagnostic tests in management of constipated patients in clinical practice. Note these simple tests permit categorization of patients and choice of therapy. N, normal; AbN, abnormal. Reprinted with permission from Bharucha AE & Camilleri M. Physiology of the colon and its measurement. In Pemberton JH (ed.) Shackelford's Surgery of the Alimentary Tract. 6th ed. Vol. 4. The Colon. Philadelphia: Elsevier Saunders, 2007, pp 1871–1882.

PATHOPHYSIOLOGY

Colonic motor functions

In health, the right colon usually functions as a reservoir, mixing contents, while the left colon functions as a conduit. Colonic motor activity in humans is notoriously irregular and unpredictable; periods of activity may be interspersed with quiescence lasting for hours.[8] While intraluminal water-perfused or solid-state manometric sensors record phasic motor activity, a balloon controlled with a barostat can also record tonic motor activity since the balloon is continuously apposed to the colonic mucosa and haustrations, permitting identification of colonic contractions and relaxation (Figure 2).[9,10] Another advantage of a barostat compared to manometry is that it records not only phasic but also tonic or sustained contractions, which are a more prominent feature of colonic motor activity compared to other hollow viscera (i.e., stomach or small intestine). Both colonic tonic and phasic motor activity are increased after meals (Figure 3).

The relationship between colonic motor activity and transit in health is partly understood. Combined assessments of motor activity and transit in the cleansed colon of healthy subjects reveal that transit is associated with non-propagated and propagated contractions; propagated contractions propel contents over longer distances than non-propagated contractions.[11] However only one-third of propagated contractions are accompanied by propulsion of colonic contents. There is considerable interest in high-amplitude propagated contractions (HAPCs), which occur an average of five times daily, often shortly after awakening, are $\geq$75–90 mmHg amplitude, and perhaps more likely to induce mass migration of colonic contents (Figure 4). HAPCs generally occur during the day, often occur after meals, and may be accompanied by the urge to defaecate. Nonetheless even low amplitude propagated contractions (i.e., $<$40 mmHg amplitude), can induce mass migration of colonic contents.

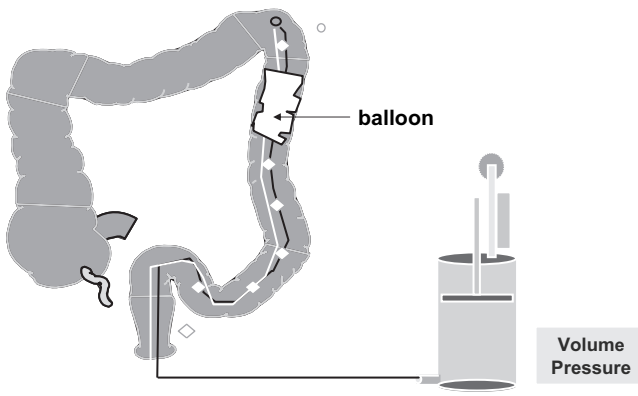

Figure 2. Barostat-manometric assembly positioned in the descending colon with polyethylene balloon in apposition with colonic mucosa connected by tubing to the barostat. The barostat is a rigid piston within a cylinder that can adjust either the pressure or volume within the bag using a servomechanism. When the balloon is inflated to a low constant pressure, colonic contraction is accompanied by expulsion of air from the balloon into the barostat. Conversely, when the colon relaxes, the balloon volume increases to maintain a constant pressure. Reprinted with permission from Bharucha AE & Camilleri M. Physiology of the colon and its measurement. In Pemberton JH (ed.) Shackelford's Surgery of the Alimentary Tract. 6th ed. Vol. 4. The Colon. Philadelphia: Elsevier Saunders, 2007, pp 1871–1882.

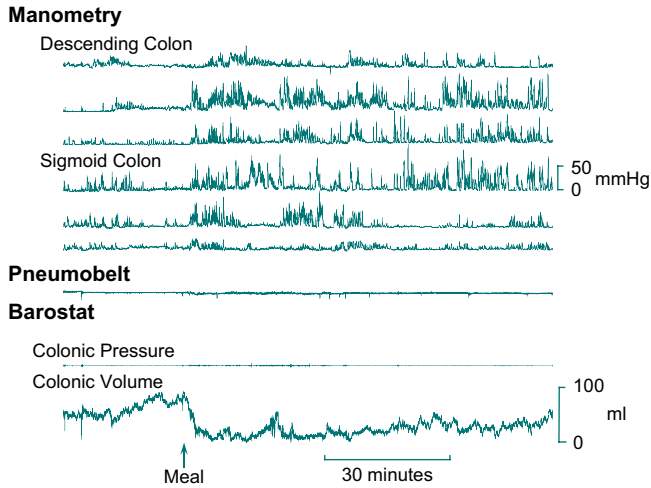

Figure 3. Colonic contractile response to a 1000 kcal meal. Note the increased phasic pressure activity recorded by manometric sensors and reduction in barostat balloon volume, reflecting increased tone. Reprinted with permission from Bharucha AE & Camilleri M. Physiology of the colon and its measurement. In Pemberton JH (ed.) Shackelford's Surgery of the Alimentary Tract. 6th ed. Vol. 4. The Colon. Philadelphia: Elsevier Saunders, 2007, pp 1871–1882.

Conceptually, the term 'slow transit' constipation refers to a clinical syndrome attributable to ineffective colonic propulsion. Although the syndrome may be associated with one or more of a variety of disturbances (e.g., reduced colonic contractile activity, disordered upper gut motility or altered psychological profiles), none of these abnormalities is pathognomonic for the disorder. Increased mucosal absorption may occur as a consequence of delayed transit, but does not cause slow transit constipation.[12]

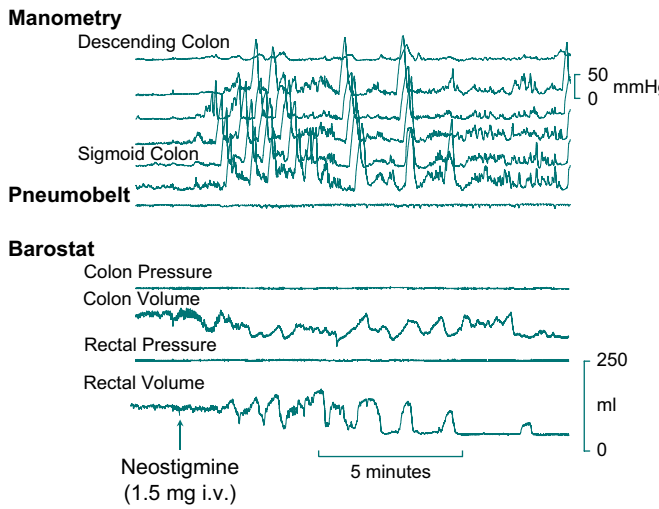

Figure 4. High-amplitude propagated contractions (HAPCs) induced by neostigmine. Reprinted with permission from Law et al. Am J Physiol 1997; 281: G1228–G1237.

In constipated patients, measurement of colonic transit may reveal segmental (i.e. right-sided, left-sided or rectosigmoid) or generalized delays in colonic transit.[13,14] Mass movements of colonic contents, which may occur after meals, are also impaired in slow transit constipation.[15,16] Impaired colonic transit has been attributed to ineffective colonic propulsion and/or increased resistance to propagation of colonic contents and/or pelvic floor dysfunction. Putative mechanisms of ineffective propulsion include fewer colonic HAPCs and impaired colonic contractile responses to physiological stimuli, e.g., a meal. Patients with idiopathic chronic constipation or constipation secondary to antidepressants have fewer HAPCs, on average 2/24 h, than healthy subjects who have approximately 6 HAPCs/24 h.[8,15–18] However, because the normal range for HAPCs in healthy subjects is wide (i.e., 1–15 HAPCs daily), only patients who have no HAPCs over a 24 h period are truly abnormal. In a large series, 17 of 40 patients (43%) with slow transit constipation had normal colonic motility as assessed by manometry during the fasting period, after a meal, and in response to bisacodyl.[18] While phasic motility was preserved, it is conceivable that the tonic contractile response to a meal was reduced in these patients. Indeed, the tonic and phasic components of the colonic contractile response to a meal are reduced in slow transit constipation (Figure 5) and normal in slow transit constipation.[5,19] However, the postprandial colonic contractile response is of limited diagnostic utility in distinguishing between slow transit constipation and pelvic floor dysfunction, since there is significant overlap in the meal response between these categories.[5] This is not surprising because colonic transit is often delayed in patients with pelvic floor dysfunction.

Connell raised the possibility of a sigmoid 'brake' by demonstrating that the duration but not the average amplitude of phasic motor activity in the sigmoid colon was greater in constipated subjects but lower in patients with functional diarrhoea compared to controls.[20] Similarly, Preston and Lennard-Jones suggested that phasic pressure activity in the sigmoid colon was higher in normal transit constipation than in controls or patients with slow transit constipation.[21] Subsequent studies have not

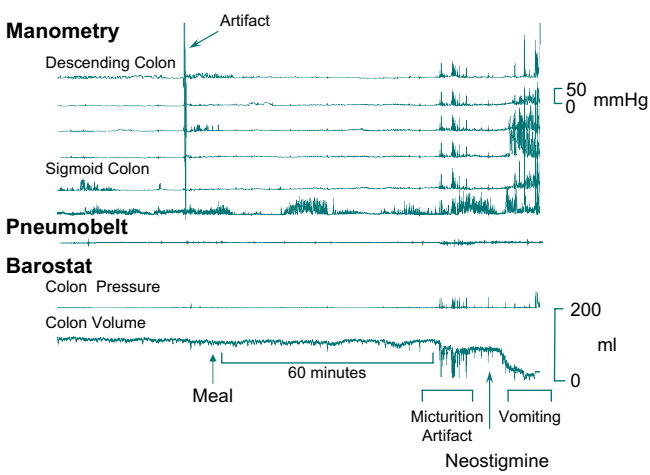

Figure 5. Impaired colonic contractile response to a meal in a patient with slow transit constipation. Barostat balloon volume and phasic activity did not increase after the meal, but did increase after neostigmine. Reprinted with permission from Bharucha AE & Phillips SF. Slow transit constipation. In Camilleri M (ed.) Gastroenterology Clinics of North America. Philadelphia: WB Saunders, 2001, pp 77–96.

demonstrated excessive sigmoid colonic phasic activity in constipated patients. Excessive periodic rectal motor activity may also impede colonic propulsion.[22]

Preston and Lennard-Jones compared the colonic motor response to topical bisacodyl in patients with normal and slow transit constipation; patients with slow transit constipation in that study also had features of pelvic floor dysfunction.[21] Nonetheless, bisacodyl induced a prominent, generally propagated colonic contractile response in all controls, but only some (11/18) patients with slow transit constipation. Others have confirmed that the colonic contractile response to bisacodyl[23–25] or to the cholinesterase inhibitors neostigmine or edrophonium[26] is impaired in some patients with slow transit constipation. Thus, in addition to severe constipation, delayed colonic transit, and absence of an evacuation disorder, the lack of a response to a meal and to a pharmacological stimulus such as bisacodyl or neostigmine are perhaps necessary to diagnose 'colonic inertia'.[27] Colonic inertia probably reflects a severe disorder of colonic motor function that will likely not respond to currently available laxatives and, in the absence of pelvic floor dysfunction, is an indication for colonic resection.

Chronic megacolon, not due to Hirschsprung's disease, generally represents the end stage of slow transit constipation, characterized by persistent colonic dilatation.[28] Although chronic megacolon suggests severe colonic dysfunction, intraluminal recordings may reveal a phasic colonic motor response to a meal,[29] and/or intravenous neostigmine (unpublished observations). However, the tonic contractile response to these stimuli is inevitably impaired.

By convention, symptoms such as abdominal bloating, discomfort and nausea are attributed to delayed colonic transit with 'back up' of contents and perhaps bowel distention. Alternatively, disturbances in visceral perception may be partly responsible for these symptoms, as is speculated to occur in IBS. Mertz et al observed a low threshold for discomfort during *rapid* rectal balloon distention, suggestive of 'visceral hypersensitivity' in ~66% patients with slow transit or normal transit constipation.[13] In contrast, the threshold for the sensation of stool during *slow* or ramp distention may be higher and associated with the symptomatic lack of the desire to defaecate.[30] These observations need to be confirmed in larger studies and suggest, as observed previously that different neural mechanisms are responsible for perception of rapid and slow balloon distention.[31]

Any of the disorders associated with autonomic neuropathy in Table 1 may cause slow transit constipation. Idiopathic slow transit constipation is infrequently associated with significant disturbances of autonomic function, when defined by stringent criteria.[32] The precise significance of disturbances of sweating identified by semi-quantitative methods, or orthostatic hypotension, which may result from dehydration,[33,34] or modest reductions in rectal mucosal blood flow in slow transit constipation are unclear.[35]

Table 1. Causes of constipation with delayed colonic transit.

Without pelvic floor dysfunction	Idiopathic slow transit constipation
	Intestinal pseudoobstruction
	Associated with autonomic neuropathies: diabetes, porphyria, multiple system atrophy*, paraneoplastic conditions, idiopathic Parkinson's disease*
With pelvic floor dysfunction	

*Conditions which may also be associated with pelvic floor dysfunction.

It has been suggested that slow transit constipation occasionally represents the presenting or primary feature of a more generalized dysmotility,[36,37] resulting from any cause of pseudoobstruction. While clinicians need to be cognisant to this unusual possibility, the disturbances of upper gastrointestinal motility described in patients with typical slow transit constipation are minor, hard to interpret, and may be secondary to rectal distention. These disturbances include relatively subtle abnormalities of oesophageal peristalsis, delayed gastric emptying or small intestinal transit. The methods used to assess gastric emptying and small bowel transit have been suboptimal. Other studies have described intestinal motor disturbances, i.e. non-propagated bursts or contractions, which are of doubtful significance, since they frequently occur during late phase 2 of the fasting migrating motor complex in normal subjects. Nonetheless gastric emptying may be delayed secondary to viscero-visceral inhibitory reflexes, activated by retained stool in the colon/rectum. Indeed rectal distention can inhibit colonic motor activity, reduce jejunal phasic contractility, and delay gastric emptying in healthy subjects.[38,39]

Defaecation

Normal defaecation is characterized by appropriate expulsion forces coordinated with relaxation of the puborectalis and the external anal sphincter. This can be demonstrated by simultaneously assessing intrarectal pressures and pelvic floor activity (by manometry, EMG, or imaging). In most healthy subjects, the pelvic floor muscles relax during defaecation (Figure 6). However, some chronically constipated patients either inappropriately contract or inadequately relax the pelvic floor muscles, indicative of dyssynergia, during defaecation. It is less widely appreciated that other patients cannot expel because they cannot generate adequate propulsive forces during defaecation.[6,40,41] Clinically, these patients are indistinguishable from patients with dyssynergic defaecation.

The mechanisms of slow colonic transit in patients with functional defaecatory disorders are not clearly understood. Similar to healthy subjects, rectal distention by retained stool may induce recto-colonic inhibitory reflexes, thereby retarding colonic transit.[42] Alternatively, retained stool may physically impede colonic transit

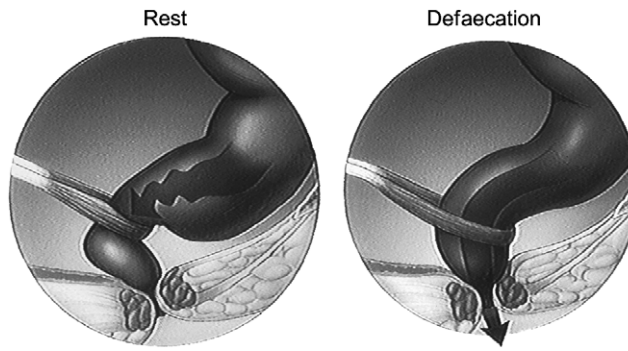

Figure 6. Anorectum and puborectalis muscle at rest (left panel) and during defaecation (right panel). The puborectalis and anal sphincters relax allowing opening of the anal canal and perineal descent during defaecation. Reprinted with permission from Bharucha AE & Wald A. Anorectal diseases. In Yamada T (ed.) Textbook of Gastroenterology. 5th ed. Lippincott Williams and Wilkins, 2007 (in press).

and/or delayed colonic transit may reflect coexistent colonic motor dysfunction. Indeed, one report on 11 patients suggested that patients with obstructed defaecation lack the normal predefaecatory augmentation in frequency and amplitude of propagating pressure waves and lack the normal stereotypic spatiotemporal patterning of colonic pressure waves that would normally culminate in effective expulsion of stool.[43] However, it is unclear if these patients had obstructed defaecation, because they all had normal anal manometry.

HISTOLOGY

Colonic histopathology in slow transit constipation is variable.[44] Except for melanosis coli, colonic nerves, interstitial cells of Cajal, and smooth muscle generally appear normal in specimens stained by haematoxylin/eosin and Masson's trichrome. Special stains may disclose fewer argyrophilic neurons in the colonic myenteric plexus,[45] decreased neurofilaments in enteric ganglia,[46] and variable alterations in nerves containing vasoactive intestinal peptide, substance P, PACAP, nitric oxide, or serotonin, as detailed elsewhere.[44] Antibodies directed against protein gene product 9.5 and c-kit which are expressed by nerve fibres and ICCs respectively reveal a marked reduction in the number of nerve fibres and interstitial cells of Cajal (ICCs) in the sigmoid colon in slow transit constipation, and more so in chronic megacolon.[47–49] Moreover, the remaining ICCs are frequently distorted and have lost their surface markings. The loss of ICCs may be of pathophysiological significance since ICCs are required for generating electrical slow waves in smooth muscle, and, for transducing/amplifying signals between nerves and smooth muscle.[50] The relative importance of loss of nerves versus ICCs needs to be clarified as does the aetiology of nerve/ICC loss. For example, it is unclear to what extent, if any, these findings are attributable to chronic laxatives.

Other pathologic findings in constipation are extremely rare. Hirschprung's disease, which is characterized by rectal aganglionosis, is a polygenic disorder characterized by mutations affecting a wide array of genes that control tyrosine kinase function and the neurotrophins that play a crucial role in neuronal differentiation, maturation, and binding to the tyrosine kinase receptor.[51] Hirschprung's disease is almost always diagnosed in infancy or in childhood. Mitochondrial neurogastrointestinal encephalopathy (MNGIE) are a heterogeneous group of autosomal recessive disorders that result from structural, biochemical or genetic derangements of mitochondria and are characterized by gastrointestinal dysmotility, ophthalmoplegia, and peripheral neuropathy. The diagnosis may be made by finding megamitochondria at a subsarcolemmal location on muscle biopsy, giving the appearance of ragged-red fibres. Enteric ganglionitis, which is often associated with anti-neuronal antibodies, may present with intestinal pseudoobstruction and/or rarely with constipation. These antibodies target a variety of molecules including the RNA binding protein Hu (anti-Hu or type-1 anti-neuronal nuclear antibodies, ANNA-1), the Purkinje cell protein Yo (anti-Yo, anti-Purkinje cell cytoplasmic antibodies), P/Q- and N-type Ca^{2+} channels, and ganglionic type nicotinic acetylcholine receptors. Anti-Hu antibodies are highly specific markers for a paraneoplastic syndrome, (e.g., due to small cell carcinoma of the lung).[52]

While histopathological studies have mainly focused on enteric nerve and ICC abnormalities, studies with smooth muscle markers and transmission electron microscopy have also revealed clusters of myocytes with noticeably decreased myofilaments and absent or focally reduced immunoreactivity for smooth muscle myosin heavy chain (SMMHC), histone deacetylase 8 (HDAC8), and/or smoothelin (SM) in Hirschsprung's

disease (80%), idiopathic megacolon (75%), and slow-transit constipation (70%).[53] In contrast, staining with antibodies against smooth muscle α-actin (α-SMA) was normal. Because SMMHC and SM expression is typical of differentiated smooth muscle cells, these changes suggest that smooth muscle cells switch from a contractile to a synthetic phenotype, consistent with the findings of reduced contractility and slow transit.

CLINICAL FEATURES

A majority of patients with the clinical syndrome of slow transit constipation are women. In the series of 64 patients reported by Preston and Lennard-Jones, the symptoms began insidiously, often before the age of 10 years. In 10 patients, symptoms reportedly began after an appendectomy, a hysterectomy or a fall with injury to the perineum. The symptom complex included infrequent defaecation together with symptoms that are consistent with irritable bowel syndrome (i.e., abdominal pain, bloating, and nausea), pelvic floor dysfunction (i.e., digital evacuation of stool from the rectum), rectal bleeding, rectal prolapse, urogynaecological symptoms (i.e., irregular menses, nocturia, and hesitancy), and systemic features (i.e. malaise). Most patients felt that the beneficial effect of laxatives declined over time.

Self-reported stool frequencies correlate poorly with colonic transit and cannot be used to distinguish between normal and slow transit constipation.[54] However carefully recorded stool diaries noting stool form and frequency correlate reasonably well with transit and can be used to facilitate that distinction on clinical grounds. In particular, stool consistencies at the extreme end of the scale, i.e. 'lumpy' stools on the 7-point Bristol stool consistency scale are suggestive of delayed colonic transit, and, are not confounded by indices of upper gastrointestinal transit in healthy subjects.[55]

Slow transit constipation may impair day to day functioning and account for absences from work in up to ~75% patients.[56] Kellow and colleagues compared psychological status using detailed psychometric measures in patients with functional gastrointestinal disorders associated with a variable degree of delayed transit.[56] The distinguishing features of patients with transit delays in two or more of three regions, i.e. stomach, small intestine and colon, were female gender, low levels of hypochondriasis, and high levels of depression and anger control. The low hypochondriasis scores runs counter to the notion that referral for illness is prompted by inappropriate illness concerns.

DIFFERENTIAL DIAGNOSIS

Having excluded organic disorders such as colonic obstruction, hypothyroidism, hypo- or hypercalcaemia or drug-induced constipation, the major differential diagnoses include functional defaecatory disorders, normal transit constipation, and chronic intestinal pseudoobstruction. The distinction of functional defaecatory disorders from isolated slow transit constipation is crucial since biofeedback therapy is the treatment of choice for the former condition. Symptoms which are suggestive of but not necessarily specific to functional defaecatory disorders include frequent straining, a sensation of incomplete evacuation, dyschezia, and digital evacuation of faeces. Unfortunately symptom assessment by questionnaire, psychological profiles, and rectosigmoid transit times are not sufficiently sensitive nor specific for distinguishing between functional defaecatory disorders and slow transit constipation.[57] Thus careful listening to the

patient's symptoms, a rectal examination with particular attention to pelvic floor motion and puborectalis relaxation during simulated defaecation, and tests to assess pelvic floor function are the keys to identifying pelvic floor dysfunction.

The symptoms of slow transit, also termed 'painless', and normal transit or 'painful' constipation overlap, blurring the distinction between these disorders. Patients with 'painful' constipation are more likely to experience abdominal distention and feeling of incomplete evacuation after defaecation.[58] In a community-based study of 2800 subjects, compared to painless constipation, patients with painful constipation reported worse general health (i.e., excellent or very good 37.5% versus 51.2%), more somatic symptoms (mean score 1.3 versus 0.9), and more urinary urgency (% often 58% versus 32%), and a higher prevalence of hysterectomy.[59]

Slow transit constipation can generally be distinguished from chronic intestinal pseudoobstruction. While patients with slow transit constipation may have nausea, abdominal bloating, distention, or delayed upper-gastrointestinal transit, patients with intestinal pseudoobstruction have more prominent abdominal distention and vomiting, and florid abnormalities on small bowel manometry.

DIAGNOSTIC TESTS

Assessment of colonic transit

Radiopaque marker methods

Since the original description by Hinton and colleagues, there have been several refinements to the radiopaque marker technique for measuring colonic transit.[60] In a widely used method, plain abdominal radiographs are taken 3 and 5 days after subjects ingest a capsule containing 20 radioactive markers on one day; the presence of $\geq$8 markers on day 3, or $\geq$5 markers day 5 is abnormal.[61] Alternatively, a plain X-ray is taken after subjects ingest 10 markers on each of six consecutive days. This technique provides a measure of overall colonic transit (upper limit of normal is 100 h) and regional colonic transit.

Scintigraphic techniques

To avoid dispersion of the radiolabel during passage through the gastrointestinal tract, the isotope is delivered into the colon by orocaecal intubation or a delayed-release capsule. The delayed-release capsule contains activated charcoal or polystyrene pellets radiolabelled with ^{99m}Tc or ^{111}In coated by a pH-sensitive polymer methacrylate, that dissolves at an alkaline pH within the distal ileum, releasing the radioisotope within the ascending colon (Figure 7). The colonic distribution of radioisotope on scans taken 24 and 48 h after administration of the capsule is highly sensitive and specific for identifying slow colonic transit.[62,63] Colonic transit measurements by radiopaque markers and scintigraphic techniques are correlated to each other,[64] are sensitive for identifying colonic transit delays in patients with slow-transit constipation, and involve similar total body radiation exposure, i.e. 0.08 rad for the radioactive capsule and for each abdominal radiograph.[65] The larger radiopaque particles (average size 6 mm) travel faster, and therefore provide a shorter absolute value for transit time through the ascending and transverse colon than the smaller radiolabelled pellets (average size 1 mm).

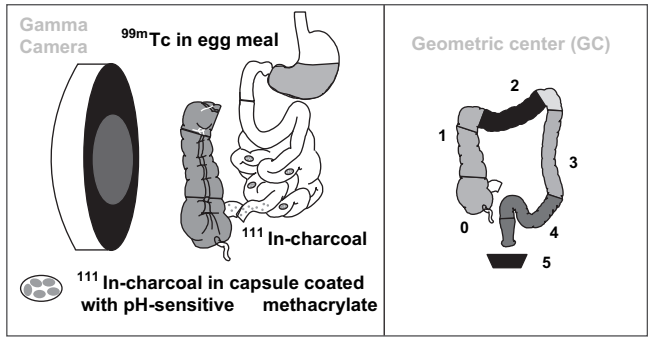

Figure 7. Scintigraphic assessment of gastrointestinal transit. Left panel: gastric emptying and small intestinal transit are assessed with ^{99m}Tc-labelled polystyrene pellets; ^{111}In-labelled charcoal in delayed-release capsules measures colonic transit. Right panel: proportion of ^{111}In counts in each of four colonic regions of interest and stool is multiplied by the appropriate weighting factor, ranging from 1 to 5. Reprinted with permission from Bharucha AE & Camilleri M. Physiology of the colon and its measurement. In Pemberton JH (ed.), Shackelford's Surgery of the Alimentary Tract. 6th ed. Vol. 4. The Colon. Philadelphia: Elsevier Saunders, 2007, pp 1871–1882.

Intraluminal assessments of colonic motility

Motor activity can be recorded by manometric sensors or by a barostat. The advantages of a barostat balloon over manometry are greater sensitivity for recording contractions which do not occlude the lumen, particularly when the colonic diameter is $>$5.6 cm.[29] In contrast to manometry, a barostat can also record changes in baseline balloon volume (i.e., tone), colonic relaxation, and colonic pressure–volume relationships. These intraluminal colonic recording devices can only be positioned using flexible colonoscopy, per-oral or per-nasal intubation techniques. Cleansing of the recto-sigmoid and occasionally the entire colon is necessary to facilitate placement and accurate recording. Cleansing can accelerate colonic transit, but does not, with the exception of more frequent high amplitude propagated contractions (HAPCs), fundamentally alter motor activity.[66] Recording myoelectrical activity with serosal, mucosal or intraluminal electrodes is fraught with technical difficulties and has fallen out of favour.

In slow transit constipation, intraluminal measurements may demonstrate fewer HAPCs over a 24-h period and/or a reduced colonic motor response to eating.[5] As indicated above, a subset of patients with slow transit constipation have colonic inertia. To emphasize, colonic inertia is not synonymous with slow transit constipation; the diagnosis of inertia, which implies a resistance to change, requires an impaired response to physiological and/or pharmacological stimulus.

Assessment of anorectal functions

In most patients, anorectal manometry and a rectal balloon expulsion test suffice to confirm or exclude a functional defaecatory disorder (Figure 8). Patients with a functional defaecatory disorder often have a high anal resting pressure (i.e., generally defined as a pressure higher than 90 mmHg), and/or a reduced recto-anal pressure gradient during simulated evacuation. The latter indicates that rectal propulsive forces are insufficient to overcome anal resistance during evacuation. Patients with defaecatory disorders require more time or more external traction to expel a rectal

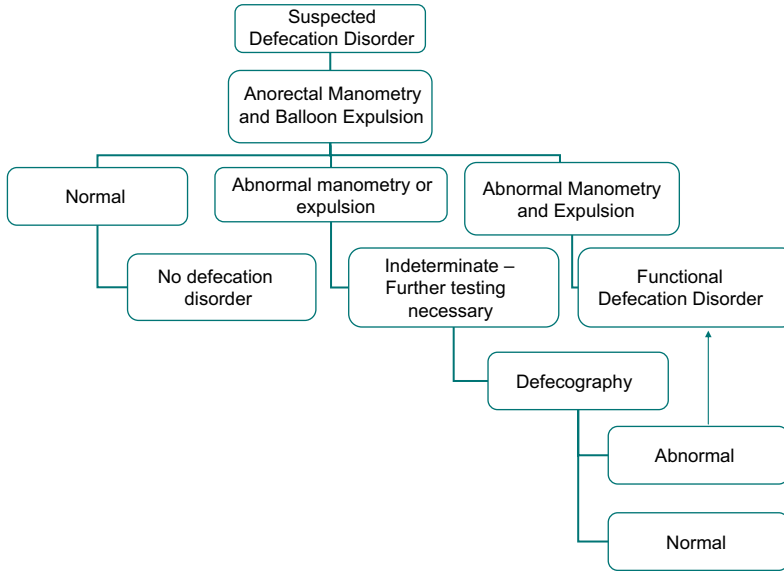

Figure 8. Algorithm for evaluating patients with symptoms of difficult defaecation. Reprinted with permission from Wald A & Bharucha AE. Functional anorectal disorders. In Drossman DA (senior ed.) The Functional Gastrointestinal Disorders. 3rd ed. McLean: Degnon Associates, Inc, 2006, pp 639–686.

balloon.[6,41,67] When these tests are inconclusive or inconsistent with the clinical impression, defaecography, either with barium or dynamic MRI is necessary and useful for confirming or excluding the diagnosis.[68,69] It is important to recognize that anorectal manometry may reveal an abnormal pattern, suggestive of dyssynergic defaecation, in up to 20% of asymptomatic subjects. Therefore, it is essential to integrate the clinical features with test results.

TREATMENT

A careful history, and if necessary formal evaluation, of caloric intake is mandatory since deficient caloric intake can cause, or, exacerbate constipation.[70] While this is recognized to occur in patients with formal eating disorders such as anorexia nervosa, other patients may have an 'atypical' eating disorder without overt criteria for anorexia nervosa or bulimia. Refeeding is accompanied by acceleration of colonic transit in these patients.[70] Likewise metabolic disorders (hypothyroidism, hypocalcaemia), drug-induced constipation, and colonic obstruction should be excluded.

It is important to educate patients regarding normal bowel habits and to emphasize that daily evacuations are not necessary to empty toxins from the body.[71] Though increased fluid intake may promote general health, there is no evidence that it improves bowel habits.[71] Some patients report the urge to defaecate while exercising. However, bowel habits did not improve after a 4-week exercise program in eight patients with chronic idiopathic constipation.[72] A systematic review of therapies of constipation observed there was moderate evidence to support the use of psyllium in constipation.[73] In a study of 149 patients treated with plantago for 6 weeks, symptoms improved in 85% patients with normal transit, but only 15% of patients with slow transit

constipation.[74] Therefore an empirical trial of fibre supplementation should be considered for patients with functional constipation at the initial presentation. Pelvic floor function and colonic transit should be assessed in patients unresponsive to dietary fibre, or, with clinical features suggestive of pelvic floor dysfunction. Bloating may be reduced by gradually titrating the dose of dietary fibre to the recommended dose, or by switching to a synthetic fibre preparation such as methylcellulose. The available fibre preparations and laxatives are summarized in Table 2.

Among osmotic laxatives, there is good evidence to support the use of polyethylene glycol and moderate evidence for lactulose in constipation.[73] In a trial of constipated men aged 65 years and older, sorbitol, administered as a 70% syrup (10.5 g/15 ml; 15–60 ml daily) was equivalent to lactulose in improving symptoms, but cheaper and better tolerated over a 4-week trial.[75] Sorbitol also accelerates colonic transit in healthy subjects,[76] Polyethylene glycol 3350 (PEG) is a large polymer that is not degraded by bacteria and serves as an osmotic laxative. In an 8-week, double-blind, placebo-controlled study, an isosmotic PEG electrolyte solution increased stool frequency and accelerated left colonic transit, without inducing abdominal cramps or bloating, in chronic constipation.[77]

Glycerol cannot be taken by mouth since it is absorbed by the small intestine. Glycerin suppositories induce colonic high-amplitude propagated contractions (HAPCs).[78] The 'stimulant laxatives' have effects on mucosal transport and motility and include surface active agents, diphenylmethane derivatives, ricinoleic acid and anthraquinones. Surface active agents such as docusates are relatively expensive and of little use as stool softeners in slow transit constipation. Of the diphenylmethane derivatives, phenolphthalein was withdrawn from the US market after animal studies suggested the compound may be carcinogenic; there is no epidemiologic evidence to support this claim. Bisacodyl produces defaecation, probably by inducing high-amplitude propagated contractions, within 6–8 h of taking the tablet or 15–30 min after the suppository. Bisacodyl is an effective rescue medication for chronic constipation. The anthraquinones, senna, cascara, sagrada, aloe and rhubarb are common constituents of herbal and over-the-counter laxatives. They pass unchanged to the colon where bacterial metabolism converts them to active forms. Therapeutic effects may also require absorption, hepatic conjugation and secondary excretion in bile (enterohepatic cycling); urinary excretion of metabolites may facilitate detection of laxative use. Side effects include allergic reactions, electrolyte depletion, melanosis coli and cathartic colon. Melanosis coli refers to brownish black colorectal pigmentation of unknown composition that is associated with apoptosis of colonic epithelial cells, reflecting cell death due to laxative action rather than programmed cell death. The term cathartic colon refers to alterations in colonic anatomy observed on barium enema associated with chronic stimulant laxative use, including colonic dilatation, loss of haustral folds, strictures, colonic redundancy and wide gaping of the ileocaecal valve.[79] Cathartic colon was initially attributed to destruction of myenteric plexus neurons by laxatives;[80] more recent studies do not confirm those findings.[81] The apparent decline in case reports of cathartic colon since the 1960s has been interpreted to suggest that the condition was secondary to other neurotoxic agents such as podophyllin,[82] which are no longer available, but not all agree.[83] Anthraquinones have also been proposed to have mutagenic effects, or to induce colorectal tumours in animal models. However, several cohort and a recent case–control study failed to find an association between anthraquinones and colon cancer,[84] a single case report[85] and a recent prospective study did.[86] Thus, the preponderance of evidence does not indicate a higher risk of colon cancer associated with long-term anthraquinone use.

Table 2. Summary of medications commonly used for constipation.

Type	Generic name	Trade name	Dosage	Side effects	Time to onset of action (h)	Mechanism of action
Fibre	Bran	—	1 cup/day	Bloating, flatulence, iron and calcium malabsorption	—	Stool bulk ↑, colonic transit time ↓, GI motility ↑
	Psyllium	Metamucil, Perdiem with fibre	1 tsp up to tid	Bloating, flatulence	—	
	Methylcellulose	Citrucel	1 tsp up to tid	Less bloating	—	
	Calcium polycarbophil	FiberCon	204 tabs qd	Bloating, flatulence	—	
Stool softener	Docusate sodium	Colace	100 mg bid	Ineffective for constipation	12–72	
Hyperosmolar agents	Sorbitol	—	15–30 ml qd or bid	Sweet tasting, transient abdominal cramps, flatulence	24–48	Non-absorbable disaccharides metabolized by colonic bacteria into acetic and other SCFA which accelerate colonic transit
	Lactulose	Chronulac	15–30 ml qd or bid	Same as sorbitol	24–48	
	Polyethylene glycol	Miralax	17 g/day	Incontinence due to potency	0.5–1	Osmotically ↑ intraluminal fluids
Suppository	Glycerin		Up to daily	Rectal irritation	0.25–1	Evacuation induced by local rectal stimulation
	Bisacodyl	Dulcolax	10 mg daily	Irritation	0.25–1	
Stimulants	Bisacodyl	Dulcolax	10 mg po up to 3 times/week	Incontinence, hypokalaemia, abdominal cramps	6–8 h	Similar to senna (see anthraquinones)
	Anthraquinones (senna, cascara)	Senokot	2 tabs qd to 4 tabs bid	Degeneration of Meissner's and Auerbach's plexus (unproven), malabsorption, abdominal cramps, dehydration, melanosis coli	8–12	Electrolyte transport altered by ↑ intraluminal fluids; myenteric plexus stimulated; motility ↑
		Perdiem (plain)	1–2 tsp qd		8–12	
		Peri-Colace	1–2 tsp qd		8–12	

	Tegaserod	Zelnorm	6 mg po bid	Headache, diarrhoea	Within 1 week	Facilitates peristalsis
	Lubiprostone	Amitiza	24 μg po bid	Nausea	Within 1 week	Intestinal secretion
Saline laxative	Magnesium	Milk of magnesia	15–30 ml qd or bid	Magnesium toxicity, dehydration, abdominal cramps, incontinence	1–3	Fluid osmotically drawn into small bowel lumen; CCK stimulated; colon transit time ↓
		Haley's M-O 0.25–1 (with mineral oil)	15–30 ml qd or bid	Avoid in renal failure	1–3	
Lubricant	Mineral oil	–	15–45 ml	Lipid pneumonia, malabsorption of fat-soluble vitamins, dehydration, incontinence	6–8	Stool lubricated
Enemas	Mineral oil retention enema	–	100–250 ml qd per rectum	Incontinence, mechanical trauma	6–8	Stool softened and lubricated
	Tap water enema	–	500 ml per rectum	Mechanical trauma	5–15 min	Evacuation induced by distended colon; mechanical lavage
	Phosphate enema	Fleet	1 unit per rectum	Accumulated damage to rectal mucosa, hyper-phosphataemia, mechanical trauma	5–15 min	
	Soapsuds enema	–	1500 ml per rectum	Accumulated damage to rectal mucosa, mechanical trauma	2–15 min	

With the advent of newer prokinetic agents, colchicine and misoprostol are not widely used for treating constipation.[87,88] Moreover, chronic use of colchicine may be associated with a neuromyopathy.[89] Misoprostol is expensive, may exacerbate abdominal bloating, and its beneficial effects appear to decline over time.

The serotonin 5-HT_4 receptor agonist tegaserod improves symptoms in patients with constipation-predominant IBS and in chronic constipation.[90,91] By stimulating 5-HT_4 receptors, tegaserod stimulates the peristaltic reflex in vitro. In pharmacodynamic studies, tegaserod increased canine intestinal and colonic motility and transit, reduced visceral afferent firing or sensation in response to distension in animals, accelerated gastric, small bowel, and colonic transit in healthy patients, and also accelerated small bowel transit in patients with constipation-predominant irritable bowel syndrome.[92] Large phase III randomized, double-blind, placebo-controlled trials, performed predominantly in females (approximately 85%) with constipation-predominant irritable bowel syndrome, support its efficacy as assessed by the subject's global assessment of relief and secondary endpoints (i.e., abdominal pain, bowel frequency and consistency).[92] Tegaserod also improves symptoms in women and men with chronic constipation.[93–98] However it is unclear whether tegaserod improves constipation in the elderly, who comprised only approximately 13% of patients in these trials. Moreover, the effect of tegaserod on symptoms and colonic transit in patients with slow transit constipation is unknown.

Lubiprostone belongs to a new class of bicyclic fatty acid compounds called prostones that are derived from a metabolite of prostaglandin E_1. Lubiprostone is a locally acting activator of type 2 chloride channels (CIC-2) which enhances intestinal secretion and thereby increases intestinal motility. In healthy subjects, lubiprostone accelerated small bowel and colonic transit, increased fasting gastric volume and delayed gastric emptying.[99] However, unlike prostaglandins, prostones have little or no effect on prostaglandin E or F receptors and do not stimulate smooth muscle contraction. In placebo-controlled clinical trials, over 1400 patients were exposed to 24 μg of lubiprostone (Amitiza) bid for up to 48 weeks.[100] Lubiprostone increased the frequency of weekly spontaneous bowel movements from a median of 1.5 at baseline to 5.0 in the first week (vs a change from 1.5 at baseline to 3.0 in 1 study and 3.5 in another study for the placebo group). Improvement in stool consistency, abdominal discomfort, and straining was also superior for lubiprostone compared to placebo. Similar results were observed in subpopulation analyses for gender, race, and elderly patients ($\geq$65 years of age). At the recommended dose of 24 μg bid, 30% of patients receiving lubiprostone reported nausea and 8.7% discontinued treatment due to nausea; 13.2% reported diarrhoea and 3.4% reported severe diarrhoea. The incidence of nausea may be reduced by taking lubiprostone with food or by reducing the dose to 24 μg once daily.

Neurotrophins such as recombinant brain derived neurotropic factor (r-metHuBDNF) and neurotrophin-3 (NT-3) promote survival and maturation of subpopulations of sensory neurons, and modulate synaptic transmission at developing neuromuscular junctions in *Xenopus* nerve muscle cultures. These agents administered subcutaneously increase stool frequency and accelerate overall colonic transit in healthy subjects and constipated patients.[101] However, their use is limited by pain at the injection site in one-third of patients[102] and they are not approved by the Food and Drug Administration for managing constipation.

Colonic resection should be considered for patients with medically refractory severe slow transit constipation or colonic inertia. The demonstration of impaired colonic contractile responses to a meal and/or provocative stimuli such as neostigmine

or bisacodyl may tilt the scales in favour of surgical therapy versus continued medical management. However, this concept has not been formally tested. Several surgical studies, beginning with Sir Arbuthnot Lane's experience, seem to prefer a subtotal colectomy with an ileorectal anastomosis;[103] there is little enthusiasm in the surgical community for a segmental or hemicolectomy.[104,105] A subtotal colectomy for constipation is safe with virtually no operative mortality. Patients may prefer the cosmetic benefit of a laparoscopic colectomy.[106] Minor post-operative complications include post-operative ileus and wound infections. Questionnaire-based assessments suggest that ~80–90% of patients are satisfied after a subtotal colectomy for constipation; up to 10% may need short-term treatment with antidiarrhoeal agents after the operation.[4] Less favourable success rates in other reports emphasize the importance of careful patient selection.[107] The importance of a careful clinical assessment and diagnostic studies for pelvic floor dysfunction cannot be overemphasized. Pelvic floor dysfunction is not an absolute contraindication for subtotal colectomy. While patients with pelvic floor dysfunction who undergo biofeedback therapy before the operation do well,[4] those who do not may continue to experience abdominal discomfort, bloating and difficult evacuation after surgery.[107]

Pelvic floor retraining by biofeedback therapy is the cornerstone of managing defaecatory disorders. A recent controlled trial demonstrates that 80% of patients treated with five weekly sessions of biofeedback therapy but only 22% of laxative-treated patients reported a major improvement at 6 months; improvement was sustained at 12 and 24 months.[108] Moreover, anorectal functions improved in patients treated with biofeedback therapy. An abnormal rectal balloon expulsion test predicted the response to biofeedback therapy.[109]

SPECIAL CIRCUMSTANCES

Colonic dysfunction after spinal cord injury

Urinary bladder dysfunction and intractable constipation are common manifestations of spinal cord injury. In a long-term follow up study, ~40% of patients with spinal cord injury complained of constipation.[109] In these patients, constipation may be due to delayed colonic transit, and/or inability to generate adequate abdominal pressure when the spinal lesion is between T_8–L_2 and/or pelvic floor dysfunction. Colonic motility studies reveal variable changes in resting motility, a reduced colonic contractile response to feeding, and a preserved response to neostigmine, suggesting that myogenic function is relatively preserved.[110] Therapy is directed toward maintaining soft, bulky stools and inducing reflex evacuation by digital stimulation and a rectal suppository after breakfast. Patients who are refractory to these measures may benefit from a colostomy, or, antegrade continence enemas delivered via a catheterizable appendicocecostomy.[111] Sacral nerve ($S_{2–4}$) stimulators may accelerate transit in the left colon, but have limited efficacy, and, studies with direct colonic stimulation in humans are awaited.[112–114]

SUMMARY

Assessments of colonic transit and anorectal functions allow constipation to be categorized into three groups, i.e., normal transit (and anorectal functions), isolated slow transit constipation, and pelvic floor dysfunctions (or functional defaecatory

disorders). A substantial proportion of women with pelvic floor dysfunctions also have slow colonic transit. Slow transit constipation spans a spectrum of variable severity ranging from patients who have relatively mild delays in transit, but are otherwise indistinguishable from IBS at one extreme, to patients with colonic inertia or chronic megacolon at the other extreme. Potential mechanisms for impaired colonic propulsion include fewer colonic HAPCs or a reduced colonic contractile response to a meal. The aetiology of the syndrome is unclear. The treatment is primarily medical; surgery is reserved for patients with severe disease or colonic inertia. Recognition and treatment of pelvic floor dysfunction is crucial for patients treated medically or surgically. Collaborative studies are necessary to determine the pathophysiology of this disorder and ascertain the efficacy of novel prokinetic agents.

Practice points

- assessments of colonic transit and anorectal functions are useful for categorizing constipated patients into three groups, i.e., normal transit or irritable bowel syndrome, pelvic floor dysfunction (i.e., functional defaecatory disorders), and slow transit constipation
- colonic transit is often delayed in patients with functional defaecatory disorders
- normal and slow transit constipation are generally managed with medications; surgery is necessary for a minority of patients with slow transit constipation; functional defaecatory disorders are primarily treated with pelvic floor retraining using biofeedback therapy

Research agenda

- understand the mechanisms of normal and disordered defaecation
- develop techniques to predict pathology (e.g., loss of interstitial cells of Cajal) without tissue in patients with slow transit constipation
- elucidate the mechanisms of delayed colonic transit in patients with functional defaecatory disorders

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