Suzanne Rose
Editor

Constipation

A Practical Approach to Diagnosis and Treatment

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To Kenny, my husband, for his love, support, and inspiration. He always reminds me what to do when "The Going Gets Tough…"

To Zach and Izzi, our children, for keeping me focused on the priorities in life and who both remind me to "Go with the Flow…"

Foreword

Constipation affects up to 20% of the US population. It is an indication for an estimated 5.7 million ambulatory visits a year and is the primary indication in 2.7 million of those visits [1]. For virtually all those who are affected, constipation has significant deleterious effects on quality of life, sense of wellness, and healthcare expenditures. Constipation also results in significant expenditures for over-the-counter remedies, herbal remedies, and dietary supplements. Millions more are spent on prescription medications and direct medical care. Physician expenses alone result in healthcare costs exceeding $235 million per year. While previously considered primarily as a nuisance disorder, for some patients, there is a substantial risk for serious and even life-threatening complications. These complications may result from acute dysfunction of the colon or from chronic, unrelenting dysfunctional motility of the colon and other organs. Complications vary from bloating, pain, and loss of appetite to moderately severe problems with weight loss, fecal incontinence, and absenteeism. As the condition worsens, however, serious complications from volvulus, bleeding, perforation, and impaired nutrition can result. Mild impairment of quality of life can become a serious issue if incontinence and isolationism become a consequence of this colonic disorder. Fortunately, advancing diagnostic capabilities have led to a greater understanding of the pathophysiology of this common disorder and clarification of subgroups of patients who will benefit from specific interventions. This has, in turn, led to major advances in available treatments. It is therefore incumbent upon all clinicians who encounter and treat constipation to gain a greater understanding of modern diagnostic options, pathophysiology, and treatments.

This text by Rose and her coauthors provides a valuable and authoritative resource for clinicians who are seeking such insights. This text is organized in logical and clinically relevant chapters. Nationally and internationally recognized experts have authored each section as they provide for the reader a well-balanced presentation of pathophysiology and treatment. Chapters have a generous distribution of endoscopic, radiographic, or motility figures. These summaries are followed

by illustrative cases to bring the science reviewed and recommendations of the experts to a practical application at the bedside. The first chapter's overview of the best way to approach this condition and its impact on cost and quality of life is an important starting point for all clinicians to appreciate how important this condition is.

Motility testing has emerged from the laboratory to become both essential and routine in the management of this common symptom. The authors of Chap. 2 have provided outstanding examples of how new diagnostic tests provide invaluable tools to help the busy clinician make the correct diagnosis and initiate effective therapy.

An especially valuable chapter that addresses new diagnostic and therapeutic assets for the reader is Chap. 6 on pelvic floor dysfunction and dyssynergic defecation. The authors clarify not only the pathophysiology but also outline how to approach these patients in a practical way. A clear review of the clinical presentations and utility of biofeedback and surgery is discussed. These practical strategies can be very beneficial to evaluating and managing these challenging patients.

The chapter by the editor is particularly useful. She addresses the problems diagnosing and treating constipation in specific clinical settings that pose a particular challenge to the clinicians. Most regrettably, many patients with constipation have experienced abuse in the past. Dealing with both the patient and the symptom requires special expertise and effectiveness to engender their respect and lead to a successful outcome. She also addresses the challenges of the symptom of constipation in children, pregnancy, spinal cord disorders, and systemic disease among others.

Taken together, this text will become an invaluable resource to the clinician who frequently faces the challenges of patients with constipation. While likely to be required reading for trainees, it will be equally valuable for the seasoned clinician who can take advantage of its many practical strategies, useful endoscopic photographs, and clear descriptions of the value of motility testing. I am quite certain that this symptom that presents so commonly to practicing clinicians will be better managed in the future through the application of the pathophysiological insights and the practical recommendations of the nationally recognized expert authors.

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Reference

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Preface

Constipation is a very common symptom and although it rarely leads to decreased quantity of life, constipation can have a major impact on the quality of one's life. Contrary to some common misperceptions, not all constipation can be attributed to the same etiology or pathophysiology. Sometimes individuals may experience constipation on a limited basis due to a lifestyle change (like a hike to the bottom of the Grand Canyon and back in 110° weather!) But for others, this symptom can be a problem that is chronic. While for some it may represent a lifestyle issue, for others constipation is a problem of motility or it is indicative of primary gastrointestinal issues. And in others still, constipation could be a manifestation of some medical problem, or quite commonly, it may result from therapy for another medical issue.

This text offers state-of-the-art information about the pathophysiologic basis of the symptom of constipation and outlines current approaches in diagnosis and management. The reader has the benefit of reading material from world-renowned experts in the area of neurogastroenterology and medical education. Figures and tables help to enhance your learning about this problem by providing visual information, helping to make sense of a very difficult and perplexing symptom. The final chapters include a compilation of cases based on the material presented; they can be used in settings for medical students, residents, fellows, allied health trainees, and continuing professional education for physicians and mid-level providers. Finally, there is a section entitled "Putting It All Together," which provides a summary in an FAQ format.

How to Use This Book for All Users

This book aspires to the highest level of sophistication with references to the state-of-the-art literature on a very complex and interesting topic. Therefore our primary target audience includes the training GI fellow or gastroenterologist. But we also

wanted to make this book accessible to students, other trainees, healthcare professionals, and the many physicians (Internists, Family Practitioners, OB/GYN doctors, surgeons, women's health specialists, etc.) who may have an interest in this area or are caring for patients with constipation. To facilitate learning, there are a few features of this book that are unique:

1. Learning objectives precede each chapter so that it is clear to the reader what is being covered in the chapter.
2. Each chapter has a special section that summarizes the key points reviewed in the chapter. These may be helpful in particular to non-gastroenterologists who may want to recognize the key points and then determine if they need to know more detail about that particular section.
3. The book includes a compendium of cases that can be applied in many settings: for medical or allied health students, at workshops, or at GI or Departmental conferences in academic centers or hospitals.

A caveat to patients and their families and friends: Although you or your loved one may be suffering from the symptom of constipation, this book is intended for those with a sophisticated background in medical information including pathophysiology, metabolism, pharmacology, and neurogastroenterology. It may be tempting to self-diagnose or consider a solution to your problem. The authors and editor ask that you seek care from your physician, sharing any concerns or symptoms.

We wish our readers a great learning experience and we hope this book helps you to promote improvements in bowel movements and quality of life for your patients!

Farmington, CT Suzanne Rose, M.D., M.S.Ed.

Acknowledgments

I would like to acknowledge the wonderful work of all of the contributing authors. This book was truly a team effort.

An extra special word of gratitude to my many mentors in Gastroenterology and in Medical Education. Your confidence and encouragement and the opportunities you provided have made for a very rich academic career. My thanks extends to the many incredible students, residents, and fellows who have touched my life and who continue to inspire me to greater heights of learning and teaching. And of course, the many patients I have had the privilege of caring for over the years have motivated me to think about how I can play a part in making the quality of life better for them and their loved ones.

I would like to thank Margaret Burns for her guidance and meticulous work and Richard Hruska for his vision for this book.

I express my thanks to my parents: Dr. Isadore Rose, of blessed memory, and Dr. Ryda Dwarys Rose along with my brothers, Lewis and Michael, and their families who have shown me that education is the highest priority along with family.

A very personal appreciation to Rabbi Kenneth A. Stern, my husband, and to Zachary and Isadora, our two grown children, with whom I have shared the most special moments in life and who always encourage and then endure my many projects: helping me, supporting me, and most importantly, leaving me alone so that I can do my work.

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Chapter 1
Overview of Constipation

Renée M. Marchioni Beery and Reena V. Chokshi

Chapter Objectives

At the conclusion of this chapter, the reader will be able to:

1. Review normal colonic physiology.
2. Describe epidemiology and quality of life issues related to constipation.
3. Distinguish primary from secondary constipation.
4. Recognize the elements of the history and physical examination that are important in the evaluation of this symptom.

Key Points

This chapter provides an overview of constipation. Normal colonic physiology is reviewed, and information about epidemiology, economic impact, and quality of life is included. Additionally, the chapter characterizes constipation subtypes and offers an approach to history and physical examination. Major points are as follows:

1. Constipation is a common digestive complaint with significant impact on economic and healthcare burden as well as patient quality of life.
2. Constipation can be a primary disorder or can be secondary to a variety of potential causes that must be considered as part of a thorough investigation.
3. Subtypes of primary constipation can be classified by transit time, pelvic floor dysfunction, and the presence or absence of abdominal pain, but significant overlap can exist.
4. History and physical examination are crucial in guiding diagnostic testing and tailoring management strategies.

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Normal Colonic Physiology

The primary functions of the human colon are absorption, propagation of contents, storage, and fecal expulsion (Fig. 1.1). Although some nutrients unabsorbed in the small intestine are reclaimed, the colon mainly absorbs water and electrolytes. On average, up to 2 L of fluid are resorbed daily, with generally only 100 mL of fecal fluid loss. In addition, hundreds of species of bacteria live in the colon; bacterial fermentation creates up to 10 L of mixed gas per day, the majority of which is absorbed versus expelled. Smooth muscle contractions propel ingested nutrients through the colonic conduit and determine the time available for digestion and absorption. Compartments created by haustra facilitate mixing, residue retention, and formation of solid stool, which is stored in the left colon until ready for elimination. The presence of stool in the rectum evokes the rectoanal inhibitory reflex that involuntarily relaxes the internal anal sphincter. Continence and defecation are a function of precise coordination between the various muscles of the pelvic floor.

Neural control of the colon arises through the autonomic and enteric nervous systems. Sympathetic motor activity is mediated by α2-adrenergic receptors and is generally excitatory to the sphincters and inhibitory to the non-sphincter musculature. Parasympathetic motor activity is usually excitatory to the smooth muscle and originates from the vagus nerve and sacral nerve plexus. The enteric nervous system is a complex and highly organized arrangement of neurons that involves two major ganglionic plexuses. The submucosal (Meissner's) plexus primarily regulates mucosal functions of the colon, whereas the myenteric (Auerbach's) plexus, located between the inner circular and outer longitudinal muscle layers, is responsible for motor activity (Fig. 1.2). The interstitial cells of Cajal reside throughout the gastrointestinal tract

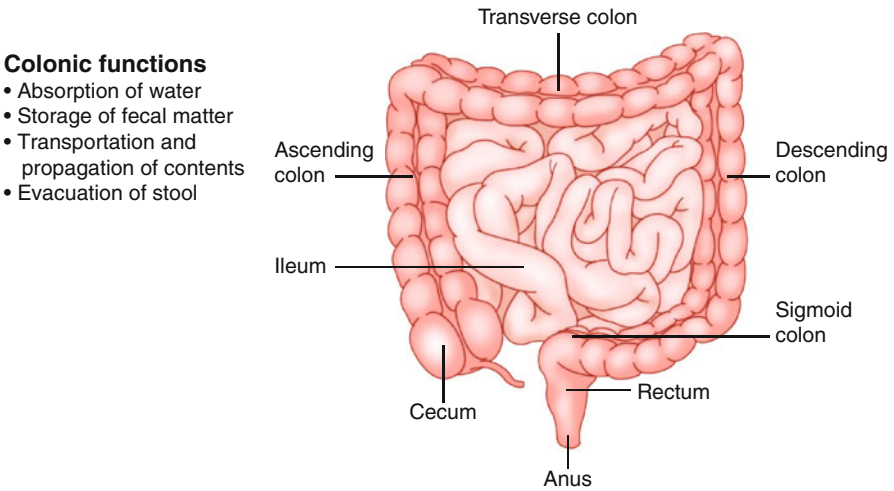

Fig. 1.1 Colonic structure and function. The basic segments and primary functions of the colon are described

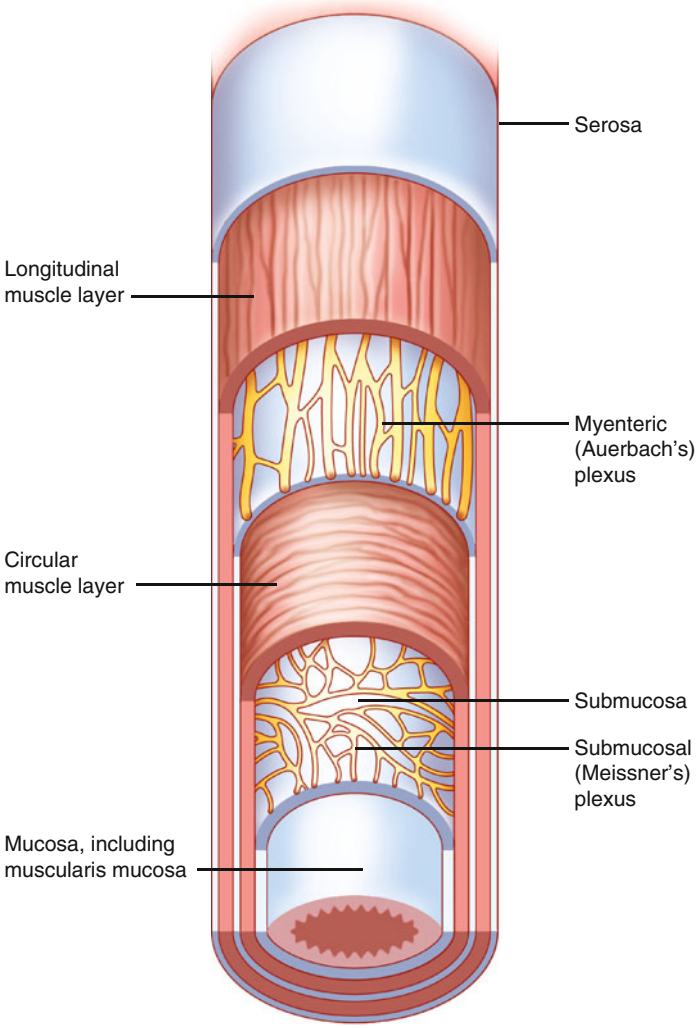

Fig. 1.2 Colonic layers and innervation. The layers of the colon starting from the luminal side are mucosa, submucosa, muscularis (consisting of the inner circular and outer longitudinal muscle layers), and serosa. Colonic function and motility are influenced by the enteric nervous system, which includes the submucosal (Meissner's) and myenteric (Auerbach's) plexuses as well as the interstitial cells of Cajal (not pictured)

from esophagus to internal anal sphincter and are located diffusely in the submucosal, intramuscular, and intermuscular layers. These cells are thought to function as intestinal pacemaker cells and play an important role in gastrointestinal motility. They generate slow wave activity and mediate signal transmission between the nerves and smooth muscle cells [1]. Dysfunction of the nerves, the muscle itself, or any of the chemical signals between them can lead to a motor disturbance.

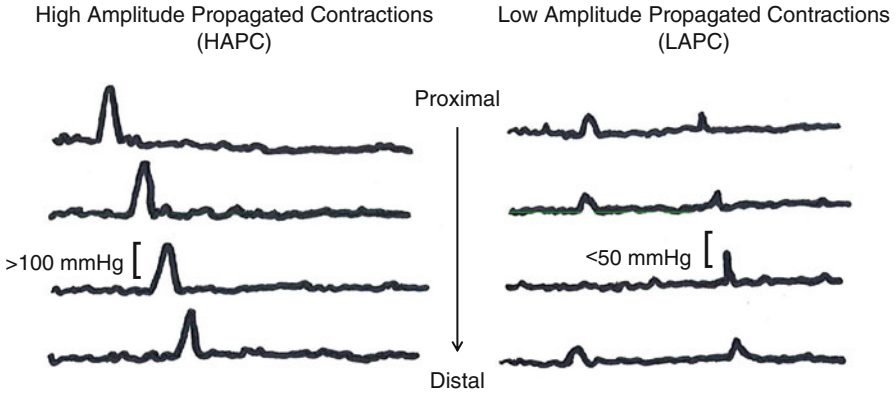

Fig. 1.3 Colonic propagated contractions. Propagated motor contractions in the colon are separated into high-amplitude and low-amplitude. High-amplitude contractions occur less frequently and are responsible for mass movement of colonic contents. Low-amplitude contractions occur with high frequency and can be associated with abdominal distension or flatus

Colonic motor activity is more irregular than that of the upper gastrointestinal tract; migrating motor complexes do not occur. Non-propagated, segmental activity can occur in isolation or short bursts, and propagated contractions can be of high- or low-amplitude. High-amplitude propagated contractions generally occur upon awakening and after meals and are responsible for the mass movement of contents through the colon, whereas low-amplitude contractions can be associated with abdominal distension or flatus (Fig. 1.3). Overall colonic transit time averages about 36 h, much longer than the average orocecal transit time of 6 h. Increased colonic motor activity is seen postprandially and is referred to by the somewhat misleading term, "gastrocolic reflex" [2].

Epidemiology and Risk Factors

Prevalence estimates of constipation vary due to heterogeneity in the definition of the disorder that subsequently affects study design and data collection. Additionally, only a percentage of patients with constipation actually seek medical care. Based on population studies conducted in North America, 1.9–27% of individuals experience constipation, with most accounts reporting a prevalence of 12–19%. This represents about 4–56 million people in the United States [3]. The worldwide prevalence in the general population is estimated to be from 0.7 to 79%, with a median of 16%. This range reflects variations in case definitions with a prevalence of self-reported constipation comprising 20.6%. Prevalence rates using the international Rome criteria are: 18% for Rome I, 12.7% for Rome II, and 11% for Rome III [4].

After a peak in young children, the prevalence of constipation increases gradually with age, becoming particularly pronounced between ages 60 and 65 and showing

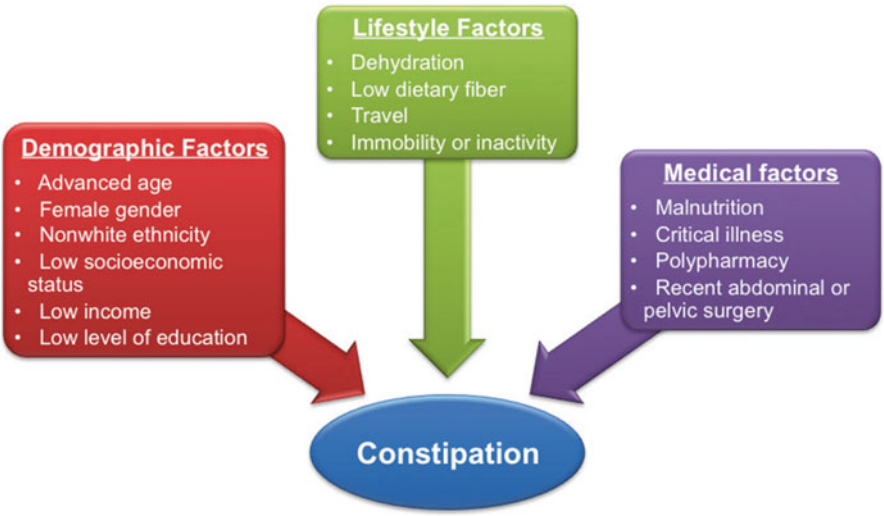

Fig. 1.4 Risk factors for constipation. Various demographic, lifestyle, and medical factors can lead to constipation

the largest increase after age 70 [3–6]. Many elderly people experience symptoms of constipation, with about one third of patients over age 70 dealing with such issues as straining, infrequency, or frequent laxative use [7, 8]. About 30% of patients over age 65 living at home self-report constipation [9]. In a cross-sectional study of 201 home-dwelling elderly patients, constipation was significantly associated with depression and limited mobility [10]. In a large community of independently living elderly subjects, the overall age- and gender-adjusted prevalence of constipation was 40.1% with a prevalence of 24.4% for functional constipation and 20.5% for outlet delay or difficulty [11]. Nearly 50% of women and 33% of men in this group had symptoms of constipation or used laxatives or enemas, and they reported more frequent straining, feelings of anal blockage, and digital manipulation versus middle-aged subjects [12]. Institutionalized elderly residents appear to be at increased risk for constipation and laxative use, with the highest frequency in geriatric hospitalized patients (79% and 76%, respectively) compared to those at old people's homes (59 and 60%), the day hospital (29 and 31%), and at home (12 and 5%) [13]. There appears to be no consistent or direct effect of aging on frequency of bowel movements [6, 9–11, 14, 15], and increased whole-gut transit time has not been particularly linked to the elderly population [8, 15]. Thus, the increase in constipation symptoms in the elderly may be linked to secondary factors acting upon gut motility such as comorbid conditions and medications.

In addition to advanced age, some other widely accepted risk factors for constipation in the United States are described in Fig. 1.4. Although gender differences in prevalence vary based on how constipation is defined, rates for women are reported higher overall. Female-to-male ratios range from 1.1 to 10 across studies worldwide

with a median of 1.5 and mean of 2.1 [4]. Data from the United States and North America report female-to-male ratios ranging from approximately 1.0 to 3.8 with a median of 2.2 [3, 16]. Female predominance has been supported in many studies [3, 4, 6, 16–19], particularly in the irritable bowel syndrome (IBS) population [20]. Self-reported constipation has been documented in about 16–20% of the US females versus 8–12% of men [6, 18]. Women are also more likely to seek medical care compared to men [21–23] and have significantly increased healthcare utilization and spending costs related to their condition [24].

Constipation has been reported to be 1.3 times more common in non-Caucasian patients [25]. Multiple studies in North America have confirmed this higher prevalence [3] with an increased risk in black patients worldwide [4]. The self-reported prevalence of constipation in African Americans versus Caucasians in the United States is 17.3% versus 12.8%, respectively [6]. There is no clear explanation for these racial variations [4].

In a pooled analysis assessing chronic idiopathic constipation, global prevalence appeared to be similar among all regions studied, although there was significant heterogeneity between studies. The highest prevalence was seen in South America (18%), while the lowest was seen in Southeast Asia (11%) [19]. A clear geographic distribution was observed in a study of Medicare beneficiaries in the United States, with hospital discharges for constipation more common in rural versus urban states. Additionally, similar geographic distributions were noted among women, men, whites, and non-whites in this population aged over 65 years, thus highlighting the role of environmental influences [26].

Patients with low socioeconomic status and low income experience higher rates of constipation [6, 17, 19, 26–28] than their counterparts. In a large population-based study of Australian adults, constipation was more frequently reported by subjects of greatest socioeconomic disadvantage in both males (prevalence rate ratio 1.83, 95% CI 1.16–2.51) and females (prevalence rate ratio 1.68, 95% CI 1.31–2.04) compared to those in the highest socioeconomic tier [26].

Certain dietary and lifestyle habits are also thought to play a role in the development and perpetuation of constipation. For example, low dietary fiber intake and dehydration are commonly thought to contribute. Higher intake of dietary fiber has been associated with a decreased prevalence of constipation [29]. Additionally, constipated persons, especially white men and women, report an increased daily intake of caffeinated beverages, including tea and coffee, and lower daily intake of products such as cheese, milk, fruits, and vegetables [6]. An inverse relationship has been demonstrated between smoking and alcohol consumption and constipation in the US women [29]. Regarding activity levels, the prevalence of self-reported constipation has been inversely correlated with amount of recreational exercise with a well-defined gradation from most to least active across all ages from 12 to 75 [6]. Increased large intestinal propulsions and endogenous hormonal changes associated with exercise are thought to play a role in this observation.

Constipation is associated with several malnutrition states such as cancer and critical illness. Gastrointestinal symptoms can influence weight loss and nutritional status in patients receiving chemotherapy for various malignancies, with constipation

commonly reported (31.9%) [30]. Constipation is also frequently seen in hospitalized patients receiving enteral nutrition therapy [31]. One study of critically ill patients receiving enteral nutrition documented constipation in 15.7% of patients [32].

Constipation rates in obese and overweight subjects range from 17.2 to 29.4%. Defecatory disorders are common and have been reported in up to 61% of morbidly obese patients with about one third of those patients experiencing constipation [33]. The etiology of constipation in obesity is multifactorial and may be related to increased body mass index and body habitus, insulin resistance, type 2 diabetes with subsequent autonomic dysfunction, and physical and dietary factors [29, 34]. Functional constipation by Rome III criteria has been reported with higher frequency in morbidly obese children (21%) compared to the childhood prevalence worldwide (8.1%) irrespective of dietary fat or fiber intake; alteration in colonic transit time in this group was less commonly observed [35, 36].

Finally, the presence of functional gastrointestinal disorders in general is very common in patients with eating disorders. In one sample, 98% of inpatients admitted to an eating disorders unit satisfied criteria for at least one upper or lower functional gastrointestinal disorder, with 52% experiencing at least three conditions simultaneously. IBS was seen in 52%, functional abdominal bloating in 31%, and functional constipation in 24% [37]. Functional abdominal bloating and distention very commonly occur in females with eating disorders, with bloating about twice as common; symptoms related to pelvic floor dysfunction seem to be predictive of both abdominal distention and bloating in this population, while IBS symptoms seem to be predictive of abdominal bloating alone [38]. Decreased consumption of calories, dehydration, and electrolyte disturbances such as hypokalemia from purging or laxative abuse may also contribute to constipation in this patient population [6, 39].

Economic and HealthCare Burden

Because an estimated 4–56 million American adults are affected by symptoms of constipation [3], a significant amount of time and revenue is spent evaluating and treating patients with this disorder. Previous data reported that constipation led to 2.5 million physician visits per year in the United States and was associated with significant medication costs [6]. More recent studies indicate this is a growing issue, suggesting constipation is involved in up to 5.7 million US ambulatory encounters. It is recognized as the primary diagnosis or reason for visit in approximately 47% of cases [40], and the highest rate of increase in ambulatory visits has been demonstrated in the pediatric population [41]. Although the majority of cases are treated in the outpatient setting, constipation has also been identified as the primary diagnosis in upwards of 38,300 inpatient visits [40]. The mean diagnostic tertiary care cost for constipation has been recorded at $2,752 per individual adult patient [42], and the cost of inpatient care is even more expensive [40]. The cost for one treated pediatric patient per year is about $3,362 due to higher emergency room, outpatient, and prescription costs. Treatment can also come at a significant price. The primary treatment

for constipation has moved from fiber supplements to osmotic laxatives [41], and hundreds of millions of dollars are spent on over-the-counter laxatives alone [6, 26].

Both the incidence and healthcare costs of constipation will almost certainly continue to rise with the expanding aging population. The economic burden of constipation is not only reflected in significant healthcare-related costs, but also extends to decreased work productivity and employer burden. In a Canadian survey of 1,000 adults with lower gastrointestinal symptoms including abdominal pain or discomfort, bloating, and constipation for greater than 3 months, almost 30% reported decreased productivity at school or work, with 13.2% of respondents missing working days and nearly 10% reporting being tardy or leaving work due to symptoms [43]. Patients with constipation-predominant IBS had less work productivity and greater activity impairment versus matched controls, along with a significantly increased number of provider and emergency room visits [44]. Estimated direct annual cost per patient with IBS of any type ranged from $348 to $8,750 in 2002, and annual indirect costs ranged from $355 to $3,344 [45]. Such conditions pose both direct (i.e., outpatient, hospital inpatient, physician, prescription, and ancillary services) and indirect (via sporadic work loss due to use of medical services and extended work loss due to disability) financial strain on employers and therefore contribute to public health impact [46].

Quality of Life

Constipation can impact an individual's physical, emotional, and social well-being. Although the disorder is often perceived as benign and easily treated, it can significantly interfere with daily activities and overall quality of life. Health-related quality of life (HRQOL) is a patient-based concept that incorporates physical and emotional status with sense of well-being in the setting of a chronic disease. Several studies have found that the diminished HRQOL in children [47] and adults with specific functional gastrointestinal disorders, including IBS and functional constipation [44, 48–50], contributes to increased healthcare utilization [50, 51]. Adverse impacts on general health perception, physical and social functioning, physical and emotional roles, vitality, and mental health have been documented [50]. These can, in turn, affect a patient's mood, drive, work and productivity, sleep, diet, relationships and intimacy, and recreational pursuits.

Both abdominal and psychological symptoms have been found to be independently associated with decreased HRQOL in patients with severe IBS [52]. A large study of patients with functional bowel disorders in primary care suggests that the presence and severity of both bowel and mental symptoms are contributing factors; such variables as total psychological symptom scores, abdominal distension, and abdominal pain greater than 12 weeks were shown to be independently and significantly associated with lower HRQOL in the primary care setting, regardless of whether patients met Rome criteria for IBS [53]. Furthermore, psychological distress can contribute to persistence of gastrointestinal complaints and related

repetitive healthcare seeking over 1 year [51]. Clinical trials suggest that patients with IBS-C compared to the general population have diminished HRQOL that can be improved with effective treatment of the disorder [54].

The physical and psychological effects of constipation are intricately linked. Constipation may be the manifestation of an emotional burden and may be exacerbated by stress. Investigations have demonstrated that patients with functional bowel disorders have higher rates of psychological anguish versus normal controls, and 40–50% have a diagnosable psychiatric disorder [51]. For example, patients with idiopathic constipation who seek tertiary medical care have an increased prevalence of depression, anxiety, and social dysfunction versus normal controls. Interestingly, impairments in general psychosocial functioning, somatization, depression, and anxiety are found in females with constipation and have been correlated to alteration in blood flow to the rectal mucosa, one measure of gut innervation [55]. This link underscores the importance of the relationship of the brain-gut pathway that appears to interact in a bidirectional fashion in functional gastrointestinal disorders [56].

Patients with functional constipation or IBS-C may have a fluctuation of symptoms over time. Healthcare-seeking behavior has been associated both with the degree of physical symptoms and with psychological distress [51]. Only a proportion of patients seek medical attention for constipation, and the majority turn to over-the-counter options in an attempt to relieve symptoms. While these medications can work in many cases, there are certain situations and patient populations in which they can be ineffective or even dangerous. Chronic constipation left inadequately treated can lead to serious unwanted consequences including fecal impaction or incontinence, stercoral ulcers, or even bowel perforation; such effects further impair quality of life and lead to greater healthcare costs.

Primary Versus Secondary Constipation

When constipation can be attributed to a structural abnormality, systemic disease (see Chap. 7), or other influencing factor, it is termed secondary constipation. Some causes of secondary constipation are outlined in Table 1.1 and include dietary and lifestyle factors, medications, and systemic disorders. For example, constipation is among the most common gastrointestinal complaints in patients with diabetes mellitus. In a small study, average colonic transit times in diabetic patients were prolonged compared to healthy controls with an average total transit time of 34.9 ± 29.6 h in diabetics compared to 20.4 ± 15.6 h in healthy controls. In particular, delayed colonic transit was noted in the left colon and rectosigmoid areas [57]. Potential mechanisms for such dysfunction in diabetes include enteric neuropathy or extrinsic denervation [58]. Constipation is also the most frequently reported gastrointestinal complaint in patients with hypothyroidism. Alterations in intestinal motor function and possible intestinal infiltration by myxedematous tissue can yield pathologic effects. Duodenal peristaltic wave amplitudes are decreased, and small bowel transit times are increased. Although rare, megacolon secondary to myxedematous

Table 1.1 Types of secondary constipation

Category	Subcategory	Examples
Dietary and lifestyle	Dehydration or inadequate fluid intake	
	Low fiber diet	
	Bed rest or inactivity	
	Poor bowel habits	Chronic suppression of defecatory urge
Medications	Analgesics	Opioids, nonsteroidal anti-inflammatories
	Diuretics	Thiazide diuretics, loop diuretics
	Antihypertensives	Calcium channel blockers, clonidine
	Anticholinergics	Antihistamines, antispasmodics, antidepressants, antipsychotics
	Bile acid resins	
	Cation-containing agents	Barium, iron supplements, calcium or aluminum (dietary supplements, antacids, sucralfate)
	Neurally active agents	Ganglionic blockers, serotonin antagonists, vinca alkaloids
	Antidiarrheals (overuse)	
Structural	Anorectal	Rectal prolapse, rectal intussusception, rectocele, anorectal stricture, perineal descent, anal sphincter spasm from anal fissure or painful hemorrhoids, solitary rectal ulcer, megarectum, neoplasm, fecal impaction
	Colonic stricture or obstruction	Neoplasm, ischemia, inflammation (diverticulitis, proctitis), post-radiation
	External compression	
Neurogenic	Peripheral neurologic dysfunction	Autonomic neuropathy, diabetes mellitus, Hirschsprung's disease, American trypanosomiasis
	Central neurologic dysfunction	Multiple sclerosis, Parkinson disease, spinal cord injury or tumor, cerebrovascular accident
	Colonic pseudoobstruction	Megacolon, Ogilvie syndrome
	Cerebral impairment leading to defecatory failure	Dementia, traumatic brain injury, stroke
Other systemic	Endocrine	Hypothyroidism, diabetes mellitus, hyperparathyroidism, panhypopituitarism, pheochromocytoma, pregnancy
	Metabolic	Chronic kidney disease, electrolyte abnormalities (hypercalcemia, hypokalemia, hypomagnesemia), heavy metal poisoning, porphyria
	Myopathic	Myotonic dystrophy, scleroderma, amyloidosis
	Psychiatric	Depression, anorexia nervosa, dementia, abuse
	Other	Sarcoidosis

infiltration of the colonic muscular layers can occur. Electrolyte disturbances, such as hypercalcemia, can also lead to constipation, as seen in patients with hyperparathyroidism, sarcoidosis, or malignancies involving bone. Neurological disease may predispose patients to constipation through multiple pathways. In general, autonomic and pelvic nerve dysfunction can lead to decreased colonic contractility and

Table 1.2 Rome III criteria for the diagnosis of functional constipation

Criteria must be present for at least 3 months with symptom onset at least 6 months prior to diagnosis:

1. Must include two or more of the following:
   - Less than three bowel movements per week
   - Straining occurring with ≥25% of defecations
   - Lumpy or hard stools occurring with ≥25% of defecations
   - Sensation of anorectal obstruction or blockage occurring with ≥25% of defecations
   - Sensation of incomplete evacuation occurring with ≥25% of defecations
   - Manual manipulation to allow for stool passage with ≥25% of defecations
2. Absence of loose stools without laxatives
3. Inadequate criteria to diagnose constipation-predominant irritable bowel syndrome (IBS-C)

Adapted from Thompson WG, Longstreth GF, Drossman DA, Heaton HW, Irvine EJ, Miller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; Suppl 2:II43-7, with permission

Table 1.3 Rome III criteria for the diagnosis of constipation-predominant irritable bowel syndrome (IBS-C)

Symptoms must be present for at least 3 months with symptom onset at least 6 months prior to diagnosis:

Recurrent abdominal pain or discomfort occurring at least 3 days per month with two or more of the following:

- Improvement with defecation
- Onset associated with change in stool frequency
- Onset associated with change in stool form or appearance

IBS is categorized into the constipation subtype (IBS-C) based on prominent stool features as outlined in the Bristol Stool Scale:

- Hard or lumpy stools (Bristol Scale 1–2: stool as separate hard lumps that are difficult to pass or lumpy and sausage-shaped) with ≥25% of defecations in the absence of use of laxatives or antidiarrheal medications
- Loose or watery stools (Bristol Scale 6–7: stool as fluffy mushy pieces with ragged edges or watery liquid without solid pieces) with ≤25% of defecations in the absence of use of laxatives or antidiarrheal medications

From Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006; 130(5):1480–91, with permission

attenuated voluntary motor function with altered anorectal sensation and reflexes. Constipation can also result from anorectal abnormalities that impair fecal flow, including strictures, rectal prolapse, or rectoceles. Finally, maladaptive cognition and emotions are thought to contribute to various types of GI distress including constipation [59].

Once secondary constipation is ruled out, patients with primary constipation can be classified even further. Subtypes of primary constipation are characterized by the presence or absence of abdominal pain, colonic transit time, and pelvic floor dysfunction. The Rome criteria distinguish between functional constipation and IBS-C, and the two definitions are mutually exclusive. The primary distinction is that patients with IBS-C complain predominantly of abdominal pain or discomfort. Tables 1.2 and 1.3 [60] list the criteria for functional constipation and IBS-C.

Table 1.4 Categorization of primary constipation by subtype[a]

Transit time
• Normal-transit constipation
• Slow-transit constipation
Pelvic floor disorders
• Also referred to as defecatory disorders, outlet dysfunction, obstructed defecation, anismus, dyschezia, and pelvic floor dyssynergia
Irritable bowel syndrome, constipation-predominant (IBS-C)

[a]Overlap can exist among subtypes

Controversy exists regarding use of the term "functional" to describe certain types of constipation, as there has been evidence suggesting a neuromuscular basis for the associated pathophysiology [61, 62]. For this reason, subtypes can be categorized as follows (Table 1.4): normal- or slow-transit constipation, pelvic floor disorders, and IBS-C. It is important to recognize that considerable overlap exists among these designations. For example, IBS-C patients can exhibit normal or slow transit [63], and approximately half of patients with pelvic floor dysfunction have slow-transit constipation [64, 65].

Although it may be intuitive to consider constipation a disorder of slowed peristalsis, the majority of patients have normal colonic transit times. In these patients, other abnormalities, such as ineffective propagation or increased distal segmental contractions, can contribute to symptoms [66]. True slow-transit constipation (see Chap. 5), however, may be associated with a deficiency of colonic interstitial cells of Cajal [61, 62]. These important cells have also been implicated in Hirschsprung's disease and megacolon [62].

Pelvic floor disorders (see Chap. 6), also called defecatory disorders, dyssynergic defecation, or anismus, are characterized by difficulty or inability to pass stool from the anorectum. The process of defecation requires appropriate coordination between the anal sphincters and pelvic floor musculature. In pelvic floor dyssynergia, the external anal sphincter and puborectalis muscles fail to relax or paradoxically contract when defecation is attempted, resulting in inability to expel stool at the anorectal level; colonic transit proximal to the rectum may be slow or normal. Each of these subtypes of primary constipation will be discussed in more detail in successive chapters.

History and Physical Examination

The evaluation of a patient with constipation begins with a thorough medical history (Table 1.5) and physical examination (Table 1.6). As discussions pertaining to bowel habits can create feelings of anxiety and embarrassment for the patient, it is crucial to maintain an open, trusting, and comfortable patient–clinician relationship to elucidate important, subjective historical accounts. Once the complaint of

Table 1.5 Pertinent history, review of symptoms, and alarm features in the assessment of constipation

History	• Frequency of bowel movements • Stool form and consistency • Feelings of incomplete evacuation • Presence of abdominal pain • Need for adjunctive maneuvers (straining, abdominal pressure, digital manipulation, manual disimpaction) • Diet and exercise habits • Use of laxatives
Review of systems	• Cold intolerance, weight gain, skin or hair changes • Vomiting or diuretic use • History of kidney stones, muscle weakness, or confusion • Neurologic or cognitive disturbances (tremors, memory loss) • Gastroesophageal reflux or dysphagia • Change or dose adjustment of home medications • Recent travel
Alarm features	• Sudden change in bowel habits or stool caliber • Age >50 years • Gastrointestinal bleeding (overt or occult) • Weight loss • Anemia • Nausea, vomiting, or obstructive symptoms

constipation is noted, it should be followed by a thorough defecation history, including frequency of bowel movements, stool form and consistency, feelings of incomplete evacuation, presence of abdominal pain, and the need for straining, digital manipulation, or manual disimpaction.

Categorization of stool form can be a useful aid in determining the passage rate of intestinal contents, with very hard or very loose stools representing the extremes of slow or rapid colonic transit, respectively. Intestinal transit time is an essential component of gastrointestinal physiology and can be an underlying factor predisposing to certain bowel symptoms. Although not widely utilized, stool form scales provide a simple and noninvasive measure of intestinal function and can predict whole-gut transit time better than stool frequency. One such scale is the Bristol Stool Scale (Fig. 1.5) that describes and graphically depicts seven stool types based on form and consistency. Patients can classify their individual stool types on a spectrum from the hardest, most formed stool (type 1) to the softest, most liquid stool (type 7) [67]. Stool form has been shown to correlate with both radio-opaque markers and scintigraphy in normal patients and in those with IBS [68, 69]. Stool types 1–3 correlate with slow intestinal transit while types 6 and 7 correlate with rapid transit. Clinically, stool form scales cannot only aid in initial evaluation but may also help to assess and monitor response to medical therapy. Changes in patient characterization of stool form by the Bristol scale have been significantly associated with alterations in bowel transit after administration of laxatives and constipating medications [67].

Table 1.6 Pertinent physical examination in the assessment of constipation

General systemic	Skin
	• Decreased turgor, fibrotic changes, rash, vitiligo, acanthosis nigricans
	Eyes
	• Extraocular movements, lid lag, iritis, dryness, icterus, pallor
	Mucous membranes
	• Dryness
	Neck
	• Thyroid nodules, goiter
	Heart
	• Murmur, bradycardia
	Lungs
	• Crackles, rales
	Extremities
	• Edema, peripheral pulses
	Neurologic
	• Tremors, muscle strength, sensation, deep tendon reflexes
Abdominal	Inspection
	• Scars, striae, vessels, masses, visible peristalsis
	Auscultation
	• Presence, pitch and frequency of bowel sounds in four quadrants; abdominal bruits
	Percussion
	• Tympany, ascites, organomegaly
	Palpation, light and deep
	• Distention, tenderness, guarding, rebound, masses, ascites, hernia, muscle spasm, retained stool
Perineal	Inspection
	• Scars, fistulae, ulcerations trauma, abscesses, skin tags, external hemorrhoids
	Dynamic observation
	• Perineal descent (view at rest and bearing down)
	Sensation
	• Anocutaneous reflex
Digital rectal examination	Palpation of rectal vault
	• Presence of stool, blood, hemorrhoids, fecal impaction, mass, anal stricture
	Pain assessment
	• Presence of ulcerations, fissures, pelvic floor muscle spasm
	Sphincter tone at rest and bearing down
	• Rectocele, rectal prolapse, paradoxical contraction

A thorough review of systems is central to establishing a focused differential diagnosis. For example, reported cold intolerance, weight gain, and changes in skin or hair may lead to consideration of hypothyroidism. Vomiting or diuretic use can cause electrolyte disturbances, such as hypokalemia, that predispose to ileus. Constipation in the setting of renal stones, fatigue, muscle weakness, and confusion may suggest hypercalcemia. Memory loss and intention tremors point toward a neurologic disorder such as Parkinson disease. In conjunction with esophageal

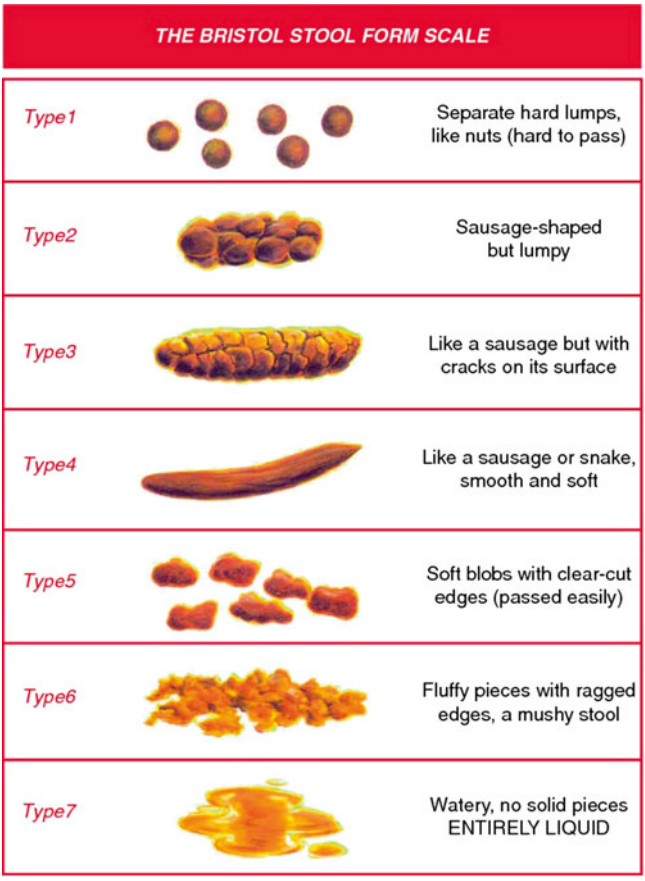

Fig. 1.5 Bristol Stool Form Scale. Seven stool types are graphically portrayed based on form and consistency. Patients can classify their individual stool types on a spectrum from the hardest, most formed stool (type 1) to the softest, most liquid stool (type 7) (From Taking the History from Moore K, *Urogynecology*: *Evidence-Based Clinical Practice*, London, Springer Science + Business Media, 2013, with kind permission of Springer Science + Business Media)

complaints such as gastroesophageal reflux or dysphagia, constipation can be suggestive of a systemic disorder such as scleroderma. Colon cancer presenting with obstructive symptoms is a late manifestation of the disease; thus certain screening questions deserve particular attention, including new onset or worsening of constipation, weight loss, overt rectal bleeding, fever, anorexia, nausea or vomiting, and family history of colorectal cancer or inflammatory bowel disease. Information regarding prior colonoscopic evaluations should be obtained and reviewed for procedural indication, exam findings, and biopsy results if applicable.

Practitioners must also obtain a complete list of medications, including prescription drugs and over-the-counter or herbal supplements. In some cases, the solution to constipation may be the simple discontinuation of an offending agent.

Some common culprits include opiate analgesics, tricyclic antidepressants, antipsychotics, anticholinergics, antihistamines, antiparkinsonian agents, antidiarrheals, bile acid-binding resins, calcium channel blockers, antacids, cation-containing agents (e.g., iron, bismuth), and diuretics. When possible, medications that may contribute to constipation should be discontinued before any further testing is initiated [17].

Physical examination can reveal gastrointestinal and systemic clues toward the etiology of constipation. Careful assessment of all organ systems including the skin (decreased turgor, fibrotic changes, rash, vitiligo, acanthosis nigricans), mucous membranes (dryness), eyes (extraocular motion abnormalities, lid lag, iritis, dryness, icterus, pallor), neck (thyroid nodules, goiter), heart (murmur, bradycardia), lungs (bibasilar rales, crackles/fibrosis), and extremities (tremors, edema, muscle weakness, delayed deep tendon reflexes) supplement the abdominal, perineal, and rectal examinations. Abdominal examination should include inspection for contour, symmetry, skin lesions including scars, striae, or dilated veins, masses, and visible peristalsis; auscultation for the presence, pitch, and frequency of bowel sounds (in four quadrants and prior to palpation) and for bruits; percussion to assess the amount and distribution of tympany and dullness suggestive of air, fluid, feces, or masses; and light and deep palpation for such features as distention, tenderness, masses, ascites, hernias, muscular spasm, rebound, or retained stool. The perineal and rectal examinations can also be very revealing. The perineal area should first be carefully inspected for scars, fissures, fistulae, trauma, abscesses, skin tags, or external hemorrhoids. The perineum should be observed both at rest and bearing down to assess the extent of pelvic floor descent (normal 1.0–3.5 cm). Excessive perineal descent over 3.5 cm or below the level of the ischial tuberosities suggests perineal laxity, often secondary to childbirth or prolonged defecatory straining. Perineal sensation should be assessed next, and the anocutaneous reflex (contraction of the external anal sphincter) should be evoked by stroking the perianal skin with a sharp object. This is followed by digital rectal examination, which begins with assessment of stool or blood in the rectal vault, internal hemorrhoids, fecal impaction, mass, or anal stricture. Anal sphincter tone can be assessed both at rest and while the patient squeezes as if to hold in a bowel movement. Next, dynamic neuromuscular function at the level of the anorectum can be assessed by asking the patient to bear down while feeling for rectocele, rectal prolapse, or paradoxical contraction. Pain on digital examination should heighten suspicion for such processes as anorectal ulceration, fissures, or even pelvic floor muscle spasm. A careful examination should be pursued before referral for other testing, such as anorectal manometry, although a normal examination does not necessarily exclude a defecatory disorder [17].

A definitive diagnosis of IBS with constipation or chronic constipation without alarm features does not require further testing (see Chaps. 3 and 4). As indicated, initial laboratory tests can include a complete blood count, basic chemistry panel including glucose, calcium, and electrolytes, thyroid function tests, and/or urinalysis. Stool should be checked for occult blood. More specific testing for endocrine, metabolic, or collagen vascular disorders should be pursued if suspected based on history and physical examination. Colonoscopy referral should be reserved for those with certain alarm symptoms (Table 1.5) including sudden change in bowel habits or

stool caliber in age >50 years, overt or occult gastrointestinal bleeding, weight loss, anemia, or family history of colorectal cancer [17]. Screening by definition pertains to asymptomatic individuals and should be considered separately. Current guidelines for individuals without risk factors for colorectal cancer are to begin screening at age 50 [70], and many experts suggest age 45 for African Americans [71].

As the diagnosis of constipation is frequently made based solely on patients' signs and symptoms, a careful history and physical examination are paramount. In certain patients, further testing may be warranted, as will be discussed in subsequent chapters. This testing allows for more precise categorization of primary constipation subtypes and can be used to guide management options and tailor therapy.

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Chapter 2
Overview of Testing of Motility and of the Anorectum

Vanessa C. Costilla and Amy E. Foxx-Orenstein

Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Recognize that routine testing is not indicated in the absence of alarm signs and symptoms.
2. Describe options for testing for the symptom of constipation.
3. Define what parameters are evaluated in each type of testing option.
4. Evaluate a patient presenting with constipation.

Key Points

Diagnostic testing is not routinely recommended in the initial evaluation of constipation in the absence of alarm signs. Testing should be targeted at symptoms or signs elicited in the history or physical that suggest an organic process.

1. Colonoscopy is indicated in all patients over 50 years of age (consider 45 years of age in African Americans and the obese) who have never had colorectal cancer screening and in those with alarm symptoms.
2. Anorectal manometry, along with the rectal balloon expulsion test, should be performed in patients who fail to respond to laxatives or empiric medical therapy for constipation.
3. Anorectal manometry systems quantify internal and external anal sphincter function at rest and during defecatory maneuvers, rectal sensation, and compliance.

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4. The balloon expulsion test can help identify, but does not exclude, a functional defecation disorder.
5. Colonic manometry may help identify colonic neuropathy, myopathy, or normal colonic function before consideration of colectomy in patients with severe constipation.
6. Standard defecography provides dynamic evaluation of the pelvic floor and can indicate the presence of rectal prolapse, enterocele, rectocele, intussusception, cystocele, and perineal descent.
7. Dynamic pelvic MRI is the only imaging modality that can evaluate global pelvic floor anatomy as well as the anal sphincter without radiation exposure.
8. Colonic transit studies are recommended if anorectal testing results do not show a defecatory disorder or if symptoms persist despite treatment of a defecatory disorder.

Introduction

Chronic constipation can be divided into two main categories: primary and secondary. Primary constipation is further divided into the following main types: normal transit constipation, slow transit constipation, and pelvic floor dysfunction. There can be overlap of primary types of constipation, as with slow transit and pelvic floor dysfunction, or pelvic floor dysfunction and normal transit [1]. Secondary constipation may be due to diet, medications, and underlying medical conditions (see Chap. 7).

Evaluation of constipation begins with a detailed history and physical examination, including an adequate visual and digital anal examination. This initial assessment will aid in determining primary and secondary causes of constipation, as well as the presence of alarm symptoms (Table 2.1). Diagnostic testing for constipation is not routinely recommended early on in the absence of alarm signs. Rather, a treat and test approach is practical and cost-effective, where testing can be pursued in

Table 2.1 Alarm symptoms in chronic constipation

Hematochezia
Heme-positive stools
Iron deficiency anemia
Rectal prolapse
Obstructive symptoms
Acute onset of constipation
Unintended weight loss
Family history of colon cancer
Change in stool caliber

From Gallegos-Orozco, J.F., Foxx-Orenstein AE, Sterler M, et al., *Chronic constipation in the elderly*. Am J Gastroenterol, 2012. 107(1): p. 18–25; quiz 26, with permission

patients refractory to conservative treatment. Diagnostic testing is often targeted at symptoms or signs elicited in the history or physical that suggest an organic process and should be employed if the information gained is apt to alter treatment. Not all patients require the same diagnostic approach. The objective of this chapter is to review diagnostic modalities key to assessing the anorectum, and their utility in the management of chronic constipation.

Colonoscopy

When alarm symptoms are present (Table 2.1), a dedicated evaluation of the colon with colonoscopy, or in selected cases, computed tomographic colonography or flexible sigmoidoscopy should be performed [1]. Colonoscopy is indicated in all patients over 50 years of age who have never had colorectal cancer screening and many experts recommend screening begin at age 45 for African Americans and for obese individuals due to the detection of pathology at a younger age in these populations. Endoscopic inspection of the colon, and the anorectum viewed in direct plus retroflex position, will identify lesions including inflammation, hemorrhoids, solitary rectal ulcer, or obstructing masses that may explain the etiology of the constipation. Flexible sigmoidoscopy with barium enema or CT colonography may replace colonoscopy in the identification of structural disease [2].

Anorectal Manometry

Anorectal manometry systems quantify internal and external anal sphincter function at rest and during defecatory maneuvers, rectal sensation, and compliance [3]. Anorectal manometry, along with the rectal balloon expulsion test, should be performed in patients who fail to respond to laxatives or empiric medical therapy for constipation [4]. Anorectal manometry can be used to diagnose and differentiate between the four patterns of dyssynergic defecation (Table 2.2). It may also aid in

Table 2.2 Patterns of dyssynergic defecation using anorectal manometry

Type I	Paradoxical increase in residual anal pressure in the presence of adequate propulsive pressure (increase in intrarectal pressure of ≥45 mmHg)
Type II	Inability to generate adequate expulsive forces (no increase in intrarectal pressure) together with a paradoxical increase in residual intraanal pressure
Type III	Generation of adequate expulsive forces, but absent or incomplete (<20%) reduction in intraanal pressure
Type IV	Inability to generate adequate expulsive forces (no increase in intrarectal pressure) and absence or incomplete reduction in residual intraanal pressure

assessing an objective response to biofeedback therapy or neuromuscular training in patients with dyssynergic defecation. Anorectal manometry also assesses for the presence of the rectoanal inhibitory reflex (RAIR). The RAIR is a decrease in anal resting pressure elicited by rectal distention and is mediated by the myenteric plexus.

The anorectal, manometry assembly consists of a probe, pressure recording device, device for displaying the recording, and a data storage facility [5]. Two types of probes are commonly available. The water-perfused probe is least expensive and traditionally used. Solid-state probes with closely spaced pressure sensors are becoming more common. High-resolution 3-D manometry with up to 256 sensors are now available to evaluate pressure profiles and topographic changes [6].

Anorectal manometry should be performed in experienced labs with experienced interpretive personnel. No fasting or discontinuation of medications is required prior to testing. Patients should evacuate their bowels prior to the testing if possible. If digital rectal examination reveals stool, a tap water enema may be administered. The lubricated manometry probe is inserted into the rectum while the patient lies in the left lateral position with knees flexed. A resting period of about 5 min is allowed for the patient to relax and for the sphincter tone to return to basal levels.

Anal pressures at rest and with squeeze are measured first. Patients are then instructed to squeeze as tight as possible for as long as possible. Next patients are asked to cough or blow up a balloon as hard as possible for as long as possible to increase intra-abdominal pressure, as would be done when bearing down. Each of these is repeated three times with a 1 min resting period between each attempt [3]. Figure 2.1 illustrates resting and squeeze pressures using high-resolution manometry. Patients are then instructed to attempt defecation of a liquid-filled balloon or fecal simulator while lying on the bed followed by simulated defecation on the commode. High-resolution anal manometry correlates well with traditional manometry and can more precisely define anal pressure profiles which might increase diagnostic yield [7].

Interpretation of anorectal manometry involves qualitative and quantitative analysis. Anal sphincter pressures, including maximum at rest, during squeeze, and sustained squeeze pressures with their duration, are compared to validated healthy adult results. Anorectal pressures during bearing down and defecatory maneuvers are also compared to healthy adults. Table 2.3 outlines the typical data collected and interpreted [3]. When evaluating patients with fecal incontinence, the functional anal canal length, maximum resting sphincter pressure and the duration of sustained squeeze pressures are helpful in determining the function of the internal and external anal sphincters.

Patients are assessed for patterns of dyssynergia when straining while lying down and while sitting on the commode. Dyssynergic defecation occurs when a patient is unable to coordinate an increase in the intrarectal pressure when bearing down and a volitional decrease in intraanal pressure (see Chap. 6) [8]. Paradoxical contraction or failure to relax the anal sphincters and puborectalis muscle occurs. Figure 2.2 compares a normal patient to one with dyssynergia using high-resolution anorectal manometry.

The RAIR reflex is tested by rapidly infusing the rectal balloon with 50 mL of air. Patients who lack a RAIR may have Chagas or Hirschsprung's disease (see Chap. 7) [3]. Figure 2.3 demonstrates a normal RAIR.

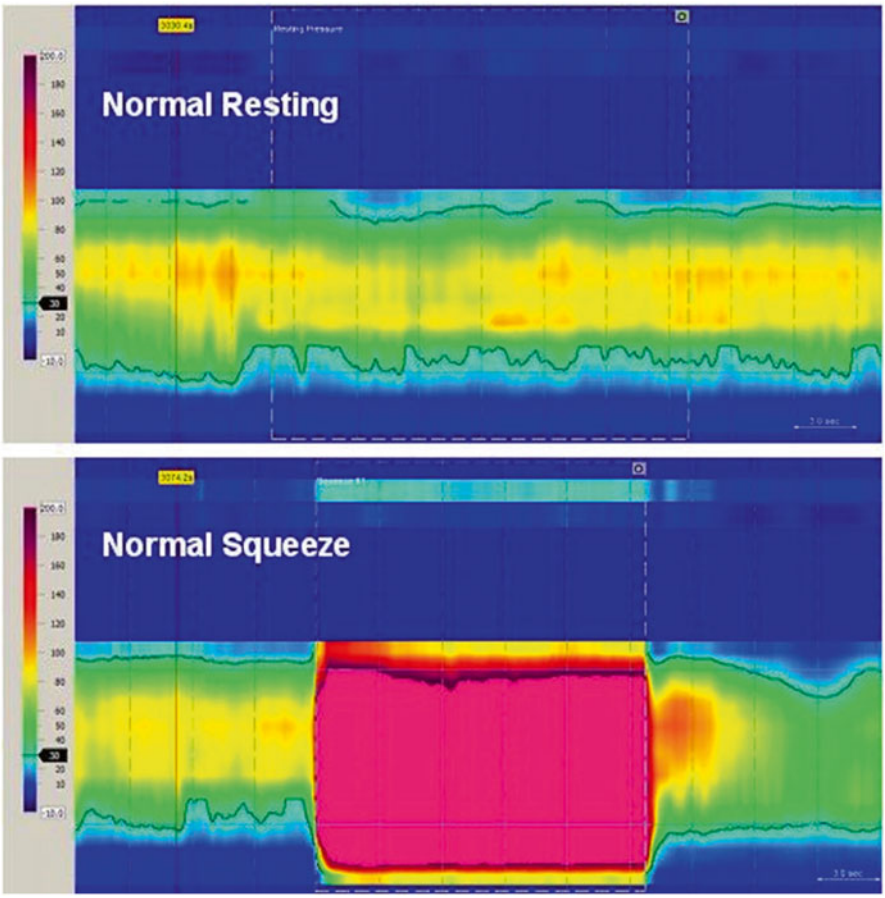

Fig. 2.1 High-resolution anorectal manometry: normal resting and squeeze. High-resolution topographic contour plot of resting anorectal motor function in a healthy control with normal resting internal anal sphincter tone (*top*). High-resolution topographic contour plot showing maximal squeeze pressures in a healthy control with normal external anal sphincter squeeze pressure and endurance (*bottom*). The resting and squeeze event windows are shown within the *dashed white lines*. Pressures in mmHg are calibrated to the color contour chart on the *left*. A *solid black contour line* delineates all pressures at 30 mmHg or above

The rectal balloon distention test measures rectal sensation and compliance by assessing sensory-motor responses to incremental volumes of air or water. The rectal balloon is inflated with air at a rate of 10 mL per second in 10 mL increments until the patient reports a first sensation. The balloon is then inflated with 30 mL of air incrementally to a maximum volume of 250 mL. The volume at which the patient feels the urge to defecate and the maximum tolerable volume are also recorded. There are no consensus thresholds for making the diagnosis of rectal hypo- or hypersensitivity. Thresholds for rectal hyposensitivity are center dependent, but typically 20 mL for first sensation, 100 mL for constant first urge to defecate,

Table 2.3 Anorectal manometry testing

Anal sphincter measurements	• Maximum resting pressure (mmHg) • Maximum squeeze pressure • Sustained squeeze pressure • Duration of sustained squeeze
Anorectal measurements while simulating defecation	• Maximal intrarectal pressure • Anal residual pressure • Presence/absence of dyssynergia while sitting or supine
Rectoanal inhibitory reflex (RAIR)	• Present or absent
Rectal sensation thresholds (mL)	• First sensation • Desire to defecate • Moderate desire to defecate • Maximum tolerable volume
Balloon expulsion test	• Able or unable to expel • Time to expel

150 mL for constant moderate urge, and greater than 200 mL for maximal tolerable volume are considered upper limits of normal.

The balloon expulsion test can help identify, but does not exclude, a functional defecation disorder [9]. A balloon is inflated with water to a fixed volume, usually 50 mL, inside the rectum. The patient is then seated on a commode and asked to expel the balloon. The test is normal if the patient expels it within 60 s. This test is often used in screening for dyssynergic defecation as it has an 88% sensitivity, 89% specificity for identifying dyssynergic defecation or pelvic floor dysfunction, and a negative predictive value of 97% for excluding pelvic floor dysfunction [10].

Colonic Manometry

Colonic manometry can be considered in adults with refractory constipation unresponsive to conventional treatment, although this test is generally available only in specialized motility centers [11]. Assessment of colonic transit using radio-opaque markers, scintigraphy, or wireless motility capsule does not provide the underlying pathophysiological basis of constipation and therefore cannot guide treatment. Colonic manometry measures the intraluminal pressure of the colon and rectum, providing information on the pattern of colonic motor activity, and if combined with barostat assembly will assess colonic tone, compliance, and sensation [3]. Colonic manometry may help identify colonic neuropathy, myopathy, or normal colonic function before consideration of colectomy in patients with severe constipation [3].

The colonic manometry assembly consists of four components: probe, pressure recording device, device for displaying the recording, and data storage facility [12]. Two types of probes are commonly available, solid-state and water-perfused. Probes have a variable number of measurement ports and can only measure pressure at 6–8 sites with the usual spacing between sensors ranging from 10 to 20 cm [3].

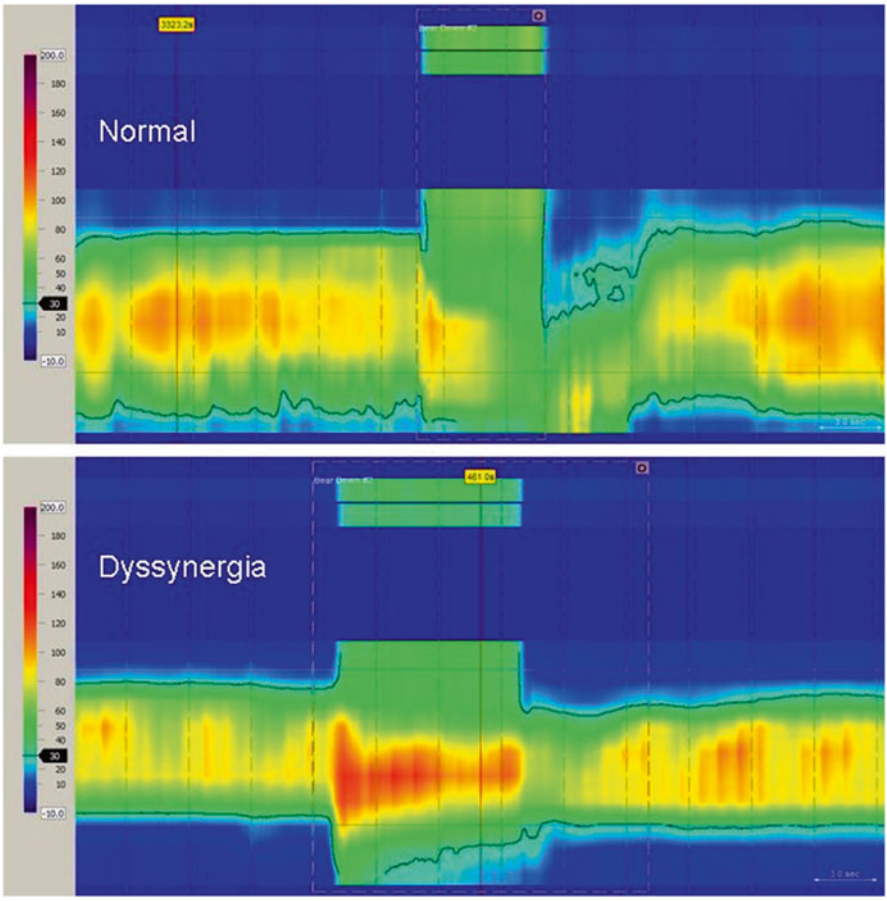

Fig. 2.2 High-resolution anorectal manometry: normal and dyssynergia. High-resolution topographic contour plot in a patient with a normal decrease in intraanal pressure when bearing down or attempted defecation (*top*). High-resolution topographic contour plot in a patient with dyssynergia (*bottom*). Note the paradoxical increase in intraanal pressure when bearing down or attempted defecation

High-resolution manometry with solid-state catheters is now available with a limited number of sensors as increasing sensors decrease flexibility of the device.

Colonic manometry can be done in the ambulatory setting with minimal sedation. An overnight fast is required and medications that affect gastrointestinal motility should be discontinued at least 48–96 h prior. Bowel cleansing is done through administration of polyethylene glycol colonic lavage or tap water enemas [12].

The colonic manometry catheter can be placed using one of the following methods: nasal intubation with migration of probe into the colon, guide wire-assisted probe placement, or retrograde direct probe placement [13]. Catheter placement should be verified with either fluoroscopy or abdominal X-ray.

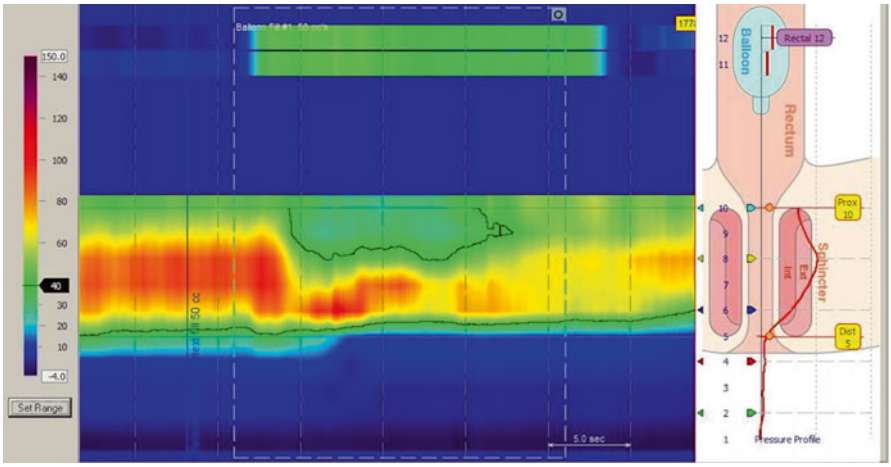

Fig. 2.3 High-resolution anorectal manometry: normal rectoanal inhibitory reflex (RAIR). High-resolution topographic contour plot in a patient with a normal RAIR. Note the decrease in resting anal pressure elicited by rectal distention

The duration of the study can be short or prolonged. Prolonged or physiological studies are typically 24 h in duration. During this period, patients are allowed to leave the lab, but are instructed to consume standardized meals, sleep and wake at specific times [13]. They also should keep an event diary for stool and symptoms. Short or provocation studies typically last less than 8 h and assess the effect of given stimuli, such as Bisacodyl or pyridostigmine, balloon distention, and a standardized meal [12] on motor activity. Colonic sensation and tone are also assessed during this time. Once the test is complete, the colonic probe is removed.

Analysis of the test has both qualitative and quantitative components. Qualitative analysis includes reviewing contractile patterns and the type of contractile activity [3]. Colonic motor activity is not rhythmic, but rather is composed of phasic or brief contractions and tonic or sustained contractions. Colonic motor activity is also divided into segmental and propagated activity. Segmental activity accounts for most of the colonic activity and consists of single contractions or bursts of rhythmic or arrhythmic contractions which are represented by waves ranging from 5 to 50 mmHg [3]. Segmental activity serves to slow colonic transit, allowing optimal absorption of contents and facilitating the propulsion of fecal contents over short distances. Propagated activity can be divided into low- or high-amplitude propagated contractions (LAPCs/HAPCs). LAPC are less than 50 mmHg and occur relatively frequently [14]. HAPCs are usually >50–100 mmHg and account for transport of contents over larger portions of the colon and play an important role in the defecatory process [13]. HAPCs occur about 4–6 times per day, usually upon awakening, after a large meal, or after a stimulant such as hot fluid or caffeine. The rectosigmoid colon experiences periodic rectal motor activity which includes discrete bursts of phasic and tonic pressure waves with a frequency and duration of greater than 3 min.

Table 2.4 Colonic neuropathy and myopathy using colonic manometry

Colonic neuropathy	Absence of two of the following three physiological responses • High-amplitude propagated contractions (HAPCs) • Meal-induced gastrocolonic response • Waking response
Colonic myopathy	Magnitude of response is less than two standard deviations of the normal range in two of the following three physiological responses • HAPCs • Meal-induced gastrocolonic response • Waking response

Quantitative analysis includes determining the number of contractions and the mean amplitude, duration, direction, and length of propagation and velocity of each contraction [3]. The number of HAPCs is reviewed and assessed for premature abortion. Patient event diaries are reviewed for waking-induced colonic motility response, meal-induced gastrocolonic response, and variations in motor activity secondary to stimuli. Symptoms from the diary are also compared to events and pressure waveforms.

Patients with slow transit constipation (see Chap. 5), also called colonoparesis, have abnormal phasic colonic motor activity with significantly decreased HAPCs which terminate prematurely and have decreased amplitude [14]. Patients with dyssynergic defecation lack pre-defecatory augmentation of frequency and amplitude of propagating pressure waves that would allow expulsion of stool [15]. Colonic neuropathy is diagnosed when two of the following three physiological responses are absent: (1) HAPCs, (2) meal-induced gastrocolonic response, and (3) waking response (Table 2.4) [16]. Colonic myopathy is diagnosed when two of the three previous responses are present, but with a magnitude of response that is less than two standard deviations of the normal range [16]. Distinguishing colonic neuropathy from myopathy is crucial in guiding treatment as those with neuropathy do not respond to aggressive medical management [16].

Colonic tone is essential for normal colonic motor activity. Lack of adequate increase in tone (<15%) following a meal indicates a colonic motility disorder [3]. However, alterations in tone can be found in all types of constipation and does not help differentiate the subtype of constipation [17].

Standard Defecography

Standard defecography provides dynamic evaluation of the pelvic floor and can indicate the presence of rectal prolapse, enterocele, rectocele, cystocele, pelvic floor descent, and effective evacuation. Defecography should be considered when results of anorectal manometry and rectal balloon expulsion are inconclusive for defecatory disorders [4].

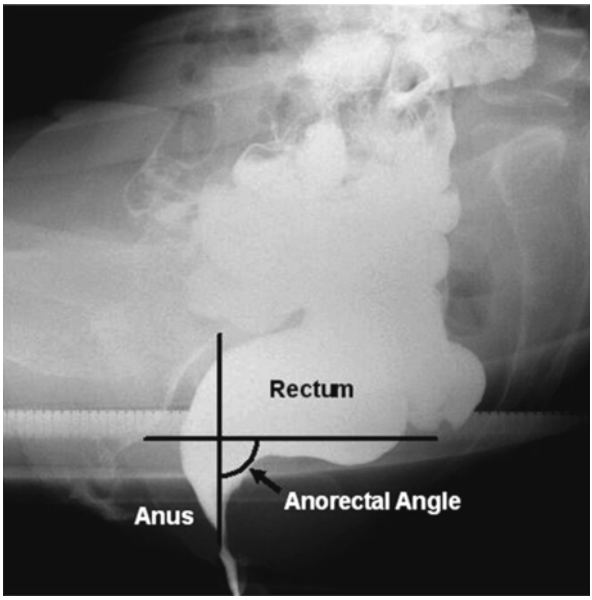

Fig. 2.4 Anorectal angle. The anorectal angle is measured between the anal canal longitudinal axis and the posterior rectum line that is parallel to the rectum longitudinal axis

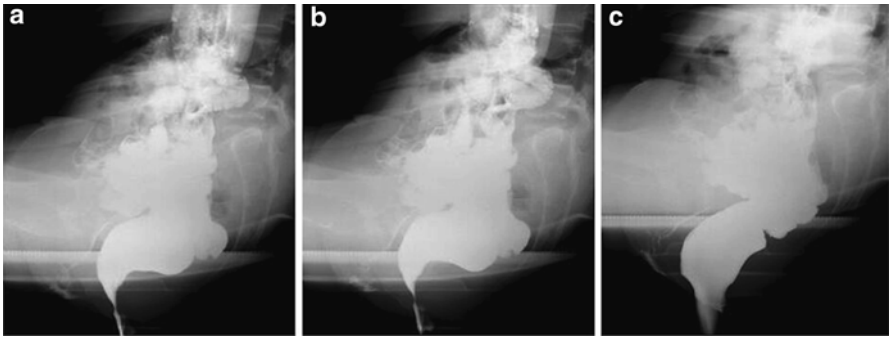

Fig. 2.5 Standard defecography. Standard defecography anorectal images at rest (**a**), squeeze (**b**), and evacuation (**c**). Note: a small amount of fecal leakage at present at rest and with squeeze

Oral liquid barium delineates the small intestine. Thick barium paste is inserted into the rectosigmoid, then dynamic anatomy and pelvic floor motion images are recorded with the patient at rest, coughing, squeezing, and straining to expel the barium [9]. Various parameters are measured to evaluate anorectal motion, including the anorectal angle, perineal descent, anal diameter, puborectalis indentation, and rectal contents [18].

Defecography is not standardized across institutions and is not widely available. There is significant variability in the measurements of the anorectal angle, which is considered vital in the interpretation of results. The anorectal angle is measured between the anal canal longitudinal axis and the posterior rectum line that is parallel to the rectum longitudinal axis (Fig. 2.4). An example of normal defecography study is shown in Fig. 2.5. Small rectocele, internal intussusception, and enterocele can occur

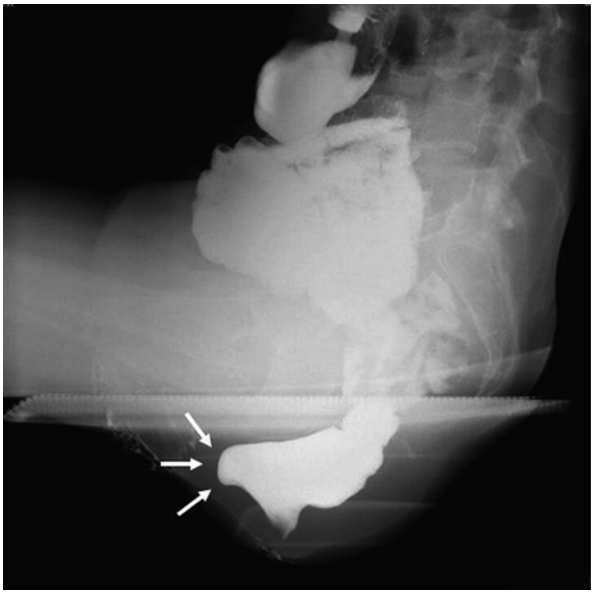

Fig. 2.6 Standard defecography: large anterior rectocele. Standard defecography anorectal image demonstrating a large anterior rectocele (*white arrows*) during defecation. Note excessive perineal descent

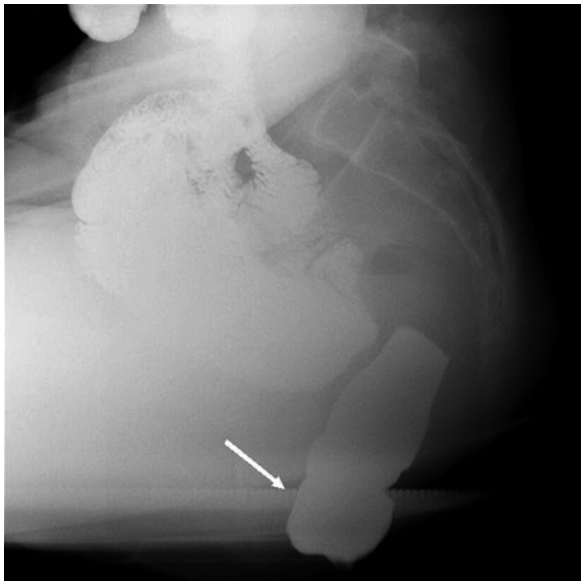

Fig. 2.7 Standard defecography: rectal prolapse. Standard defecography anorectal image demonstrating severe rectal prolapse (*white arrow*)

in asymptomatic patients and may not correlate with symptoms of infrequent or incomplete evacuation [19, 20]. Defecography can provide more detailed information about the anatomy of the pelvic floor and serve to reinforce the validity of prior testing, including anorectal manometry. Figure 2.6 demonstrates a large anterior rectocele, as well as excessive perineal descent. Figure 2.7 demonstrates severe rectal prolapse.

Dynamic Pelvic Magnetic Resonance Imaging

Dynamic pelvic magnetic resonance imaging (MRI) is the only imaging modality that can evaluate global pelvic floor anatomy as well as the anal sphincter without radiation exposure [21]. It allows visualization of the bladder, genital organs, and relationship of the colon to surrounding organs, thus providing a comprehensive view of pelvic floor structures and motion. Like standard defecography, it can indicate the presence of rectal prolapse, enterocele, rectocele, and cystocele. This modality has played a key role in identifying mechanisms of difficult or complex bowel function.

MRI of the anal sphincter provides superior spatial resolution of the internal and external sphincter compared to standard endoanal ultrasonography [21, 22]. The external sphincter can be distinguished from surrounding perirectal fat, allowing better diagnosis of external sphincter atrophy [21]. This is particularly useful in evaluation of patients with fecal incontinence.

Dynamic pelvic MRI can be performed with conventional, closed-configuration MR systems as there appears to be minimal difference in the detection of clinically relevant findings between supine MR and seated MR with open-configuration magnets [23]. Before the examination, patients are usually asked to empty their bladder but others prefer full bladder [24]. During the testing, patients will perform a variety of maneuvers, including straining and squeezing of the pelvic floor muscles, bearing down, and ultimately relaxation and rectal evacuation. Images are acquired in the axial, sagittal, and coronal planes angled to the pelvic floor muscles using a surface coil; however, an endoanal coil provides a detailed view of the sphincter [25]. Figure 2.8 demonstrates evacuation with dynamic pelvic MRI.

Dynamic pelvic MRI showed equivalent diagnostic performance compared to endoanal ultrasonography in the evaluation of patients with dyschezia in the identification of rectoceles, enteroceles, and perineal descent [26]. However, dynamic pelvic MRI was able to identify rectal intussusceptions when endoanal ultrasonography did not [26]. Figure 2.9 demonstrates multiple abnormalities, including a large anterior rectocele, rectal prolapse, and retention of contents. In a recent study, dynamic pelvic MRI and standard defecography showed no significant difference in the identification of rectocele, but did show differences in identification of a descending perineum [27].

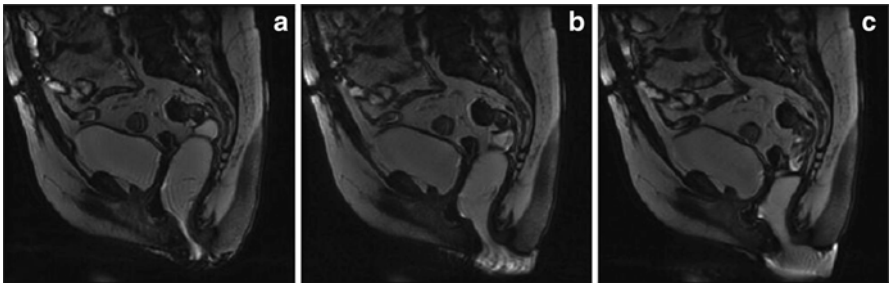

Fig. 2.8 Dynamic pelvic MRI: normal evacuation. Dynamic pelvic MRI demonstrating evacuation (**a**–**c**)

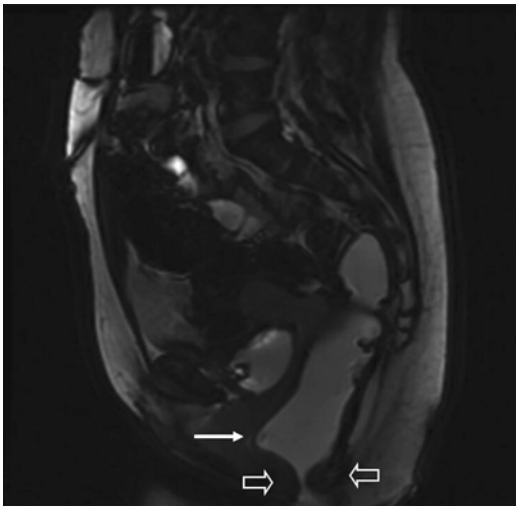

Fig. 2.9 Dynamic pelvic MRI. Dynamic pelvic MRI demonstrating anterior rectocele (*solid white arrow*), rectal prolapse (*hollow arrows*), and retention of rectal contents

Dynamic MRI has some advantages over conventional defecography, including avoidance of radiation exposure by the patient, better soft tissue resolution of all pelvic structures, and thus a more comprehensive picture that allows for better surgical planning [24, 28]. It is the preferred test for diagnosing rectal intussusception. However, MRI is costlier and not widely available.

Colonic Transit Studies

A colonic transit study objectively measures the speed of stool movement through the colon. Three methods to measure the speed of stool through the colon are available: radiopaque markers (Sitzmarks), colonic scintigraphy, and wireless motility capsule. These tests are useful for objectively confirming a patient's subjective complaint of constipation or decreased bowel frequency, confirming slow transit, and for documentation of regional delays in transit [19]. Colonic transit studies are recommended if anorectal testing results do not show a defecatory disorder or if symptoms persist despite treatment of a defecatory disorder [4].

Radiopaque Marker Test

The radiopaque marker or Sitzmarks technique is the most commonly used test for measuring colonic transit time [29]. It is not necessary to perform bowel cleansing prior to the study. The radiopaque marker test is performed by ingesting a single capsule containing 24 plastic markers on day 0 and obtaining a plain abdominal radiograph on day 5 or 120 h later. Retention of more than 20% or ≥6 markers on

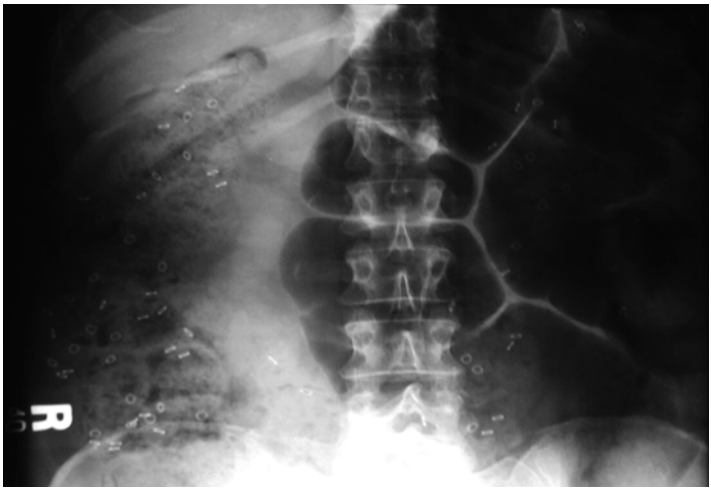

Fig. 2.10 Sitzmarks test. Multiple radiopaque markers are retained throughout the colon, suggesting abnormal colon transit time

day 5 is indicative of slow transit constipation [11, 30]. Alternatively, the multiple marker test involves ingestion of one capsule daily for 3 days. Plain abdominal radiographs are obtained on days 4 and 7. Retention of more than 20% of the makers on day 7 is indicative of slow transit constipation [31, 32]. Figure 2.10 demonstrates multiple retained radiopaque markers.

Patients with dyssynergic defecation may also retain excess markers, and therefore, dyssynergia should be excluded prior to diagnosing slow transit constipation. If colonic transit time is normal on two consecutive studies despite a patient's continued complaint of infrequent defecation, colonic function is likely normal and no further testing is required [19]. The radiopaque marker test has multiple drawbacks, including radiation exposure, multiple visits which may affect compliance, inability to assess regional gut transit, and lack of standardization protocols for the test and interpretation [33, 34].

Colonic Scintigraphy

Colonic scintigraphy involves the oral administration of radioisotopes such as 111Indium bound to diethylene triamine pentaacetic acid (DTPA) or 111Indium/activated charcoal slurry contained within a methacrylate-coated capsule which is designed to break down in the distal ileum [35–38]. Depending on the isotope ingested, gamma camera scans are taken at various intervals, until hour 48 or 96. A constructed time-activity curve can demonstrate the progression of the isotope through various regions of the colon. Diagnosis of slow or delayed transit is dependent on the percentage of isotope retention, but these values differ among centers and depend on the method used [37, 38].

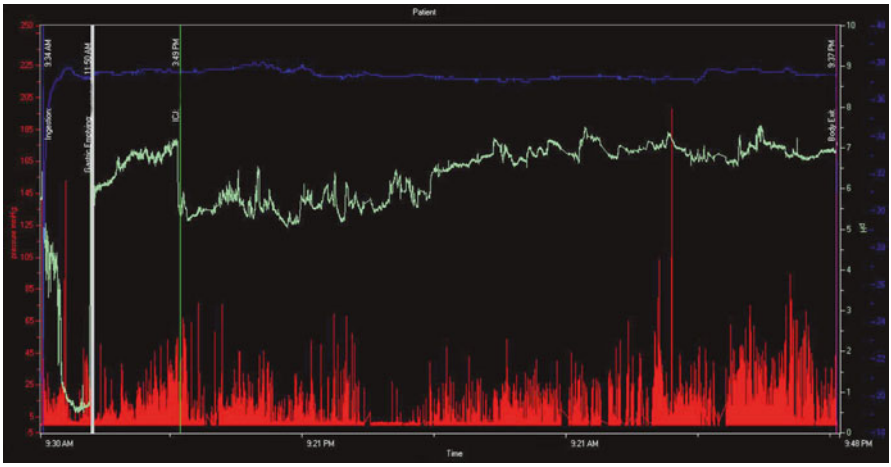

Fig. 2.11 Wireless capsule. The SmartPill system provides a noninvasive monitoring technique for characterizing disorders of GI motility. Segmental transit times can be assessed based on standardized changes in intraluminal pH (*green line*) from the stomach through the small intestine and the colon. The segmental motility index can be quantified using the intraluminal pressure sensor (*red line*). Temperature (*blue line*) should remain relatively constant under normal conditions

Wireless Motility Capsule

The wireless motility capsule or SmartPill™ is a data recording device that provides real-time measurements of temperature, pH, and pressure of its immediate surroundings [39] (see Fig. 2.11). It is a nonradioactive alternative for evaluating chronic constipation and can provide a quantitative assessment of colonic transit time [39]. In addition, it provides information on transit times of the stomach and small bowel and can help exclude a more global gastrointestinal transit disorder. It was approved for evaluation of colonic transit in patients with chronic idiopathic constipation by the Food and Drug Administration in 2009 [40].

The study may be done in a physician's office after an overnight fast and discontinuation of medications that could alter gastric pH and gastrointestinal motility. Proton pump inhibitors should be stopped 7 days prior to testing, histamine receptor antagonists 3 days prior to ingestion, and antacids 1 day prior to ingestion. Narcotics, antidiarrheal agents, prokinetics, laxatives, and anticholinergics should be stopped between at least 3 days prior to testing [39].

The wireless motility capsule is ingested immediately after consuming a standardized SmartBar™ and 50 mL of water. The patient wears a small external data recorder, which must be within 5 ft of the patients throughout the testing period. The patient records meals, sleep, and bowel movements by entering them into the data receiver. Exercise may alter the transit measurements so it should be avoided during the testing period. The data receiver is returned to the physician's office at the end of the study after 3 days. Passage of the capsule from the body can be confirmed by an abrupt drop in temperature or loss of recording signal [39].

Colonic transit time is defined from the time the wireless motility capsule enters the cecum to its passage from the body. The wireless motility capsule correlated well with radiopaque marker testing [29]. Delayed colonic transit using the wireless motility capsule is defined as a colonic transit time of greater than 59 h [39, 40]. Contraindications to wireless motility capsule include patients with a history of a gastric bezoar, swallowing disorders, dysphagia, suspected strictures or fistulae along the gastrointestinal tract, physiologic gastrointestinal obstruction, gastrointestinal surgery within the previous 3 months, Crohn's disease, diverticulitis or implanted or portal electromechanical medical device (e.g., cardiac pacemaker). The incidence of equipment failure was reported to be 0.8–0.9% [39]. Serious adverse events include inability to confirm passage of the capsule outside the body, capsule retention, and obstruction. Post-marketing, the retention rate was 0.33% [39].

Electromyography

Electromyography (EMG) can help identify myopathic, neurogenic, or a mixed injury through measurement of small or large polyphasic motor unit potentials [9]. Small polyphasic motor unit potentials are associated with myopathic damage, whereas large polyphasic motor unit potentials are associated with neurogenic damage. EMG of the pelvic floor may be done for the following reasons: (1) to identify areas of sphincter injury by mapping the sphincter, (2) to determine if the muscle contracts or relaxes, and (3) to identify denervation-reinnervation potentials indicative of nerve injury [19]. The 2013 American Gastroenterological Association (AGA) Technical review and position statement on constipation did not discuss the use of EMG in evaluating patients with chronic constipation, suggesting its role is limited in this population.

Both needle and surface electrodes are available. Though needle EMG allows mapping of the sphincter to identify defects, surface electrodes provide information about muscle behavior and can determine the presence of appropriate sphincter relaxation during defecation. Surface EMG also may be used during biofeedback pelvic floor retraining.

Pudendal Nerve Terminal Motor Latency Testing

Pudendal nerve terminal motor latency (PNTML) testing can help determine whether anal sphincter weakness is due to pudendal nerve injury, sphincter injury, or both. Patients with pudendal neuropathy do not fare as well as those without pudendal injury following surgical repair of sphincter defects. Patients previously underwent PNTML prior to undergoing surgical intervention to determine if surgical repair should be considered. However, subsequent studies questioned the utility of this test as 50% of patients with prolonged PNTML had normal anal canal squeeze pressures, and 27% of patients with chronic constipation had prolonged PNTMLs. In 1999 the AGA recommended that PNTML not be used in the evaluation of patients with fecal incontinence [19]. The role of PNTML testing has not been defined in patients with chronic constipation.

Summary

The evaluation of constipation with testing is not necessary in patients without alarm signs and symptoms and in those who have had a successful response to treatment. The most important first step is to obtain a detailed history and to do a thorough physical examination including an abdominal examination and rectal examination. Without alarm signs and symptoms (see Table 2.1), one can proceed with empiric treatment. The algorithms for testing have been changed recently [4]. The assessment of colonic transit is recommended to be done at a later stage and not initially but rather for patients who do not have a defecatory disorder or for those with defecatory dysfunction that has not responded to biofeedback. The algorithm presented as Fig. 5.3 shows one accepted approach to the patient with constipation. This shows the initial study as anorectal manometry with balloon expulsion. Other more detailed algorithms do include defecography if manometry and balloon expulsion are inconclusive.

There is great variability for what might be considered based on individual presentation and also the availability of testing. In unique tertiary and quaternary motility centers, there are often distinctive approaches. This author suggests that manometry and nuclear transit studies may be done at the same time in our center which serves as a quaternary referral center where refractory patients (many of whom have already undergone much testing) are seen and where combination constipation is a common presentation. This author begins the evaluation with a complete history and rectal exam including visual inspection and digital exam. The patient is then treated with high fiber, adequate hydration, and "bowel management techniques" (hot caffeinated beverage, breakfast, within 45 min of awakening). If there is no improvement, and if there are more than two bowel movements weekly, anorectal manometry and defecography are considered (Fig. 2.12). In situations where the patient notes symptoms of prolonged time between stools (<2 bowel movements weekly), the colon transit study with anorectal manometry may be performed. These strategies point out both the importance of an evidence-based

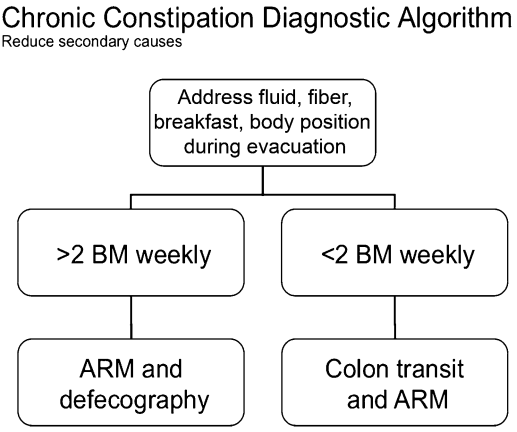

Fig. 2.12 Chronic constipation diagnostic algorithm

approach and also tailoring the evaluation to the patient's presentation and to the types of patients that may be seen in specialized centers. The chapters that follow further discuss the evaluation and management of constipation.

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Chapter 3
Chronic Constipation

Siddharth P. Sura and Jennifer Christie

Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Define chronic constipation
2. Distinguish chronic constipation from other primary causes of constipation
3. Evaluate and manage patients with chronic constipation

Key Points

This chapter covers the topic of chronic constipation. The symptom of constipation is common in adults. Patients may define the problem as difficulty defecating or straining in contrast to physicians and healthcare providers who usually define the problem by frequency of defecation. A few key points:

1. Constipation is a common and economically burdensome symptom.
2. Chronic constipation may be distinguished from irritable bowel syndrome with constipation as the latter has pain as the primary distinct symptom in association with altered bowel habits.
3. History and physical examination including a thorough rectal examination are key in the evaluation of the patient with constipation.
4. Patients with no alarm signs and symptoms may be treated without further evaluation and testing in many cases.

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5. A combination of treatment modalities may be necessary to improve the patient's quality of life.
6. Newly approved and experimental therapies may further improve outcomes in patients with chronic constipation.

Epidemiology

Determining the prevalence of chronic constipation requires a multi-perspective approach. Although recognized as a common problem among adults, identifying its true prevalence is complicated by differences in patient, provider, and criteria-based definitions of constipation. A patient who perceives himself/herself as suffering from constipation will not necessarily fulfill the Rome criteria for functional constipation or align with his/her provider's assessment of constipation. In a similar regard, an individual who meets Rome criteria for functional constipation may feel comfortable with his/her bowel habits.

Perceptions of constipation differ widely between patients and clinicians based on stool frequency and form [1]. Patient-defined constipation frequently involves straining during defecation and/or the passage of hard stools [2]. Conversely, clinicians often define constipation by stool frequency, in which normal bowel function is defined as ranging from three bowel movements per day to three bowel movements per week [3]. Finally, the Rome III criteria for functional constipation incorporate a combination of these definitions with a minimum duration of 6 months of symptoms (see Table 1.2 in Chapter 1) [4].

Discrepancies in perceptions regarding constipation are illustrated clearly in the primary care setting, where constipation is a common chief complaint. In an analysis of 56 individuals self-reporting constipation out of a total cohort of 201 women in an outpatient clinical setting, only eight met Rome III criteria for functional constipation. Conversely, of the remaining 145 women who did not report constipation, 13 met Rome III criteria [5]. Thus, attempts to understand constipation on a population-based level require its definition to be clearly identified.

Once the clinician has identified the presence of constipation, an attempt at differentiating occasional versus chronic constipation should be made. Occasional constipation is infrequent in contrast to chronic constipation which has been present for at least 3 months and may persist for many years [4]. In contrast to occasional constipation which may temporarily interrupt a routine or be bothersome, chronic constipation is long term and in some patients may dominate both personal and work life. Occasional constipation may have its onset related to a particular behavior: change in diet, exercise, medication, or illness. In chronically constipated patients these changes do not appear to be the only issues involved. The occasionally constipated patient may self-medicate or use dietary or even exercise to ameliorate symptoms whereas the patient with chronic constipation may require medical attention and prescription or even multimodal therapy.

A systematic review in 2004 found the prevalence of constipation, defined based on patient or provider perspective as well as the Rome criteria, to be approximately

14.8%, with a range of 1.9% to upwards of 25% of the North American population [6]. This finding is similar to that of other industrialized nations in Europe and Asia and higher than that of African indigenous populations based on stool weight and transit times [7, 8].

The morbidity associated with patient-perceived constipation argues for identifying constipation in the clinical setting based on patient perception. Unlike women with Crohn's disease, women with self-reported constipation have increased rates of anxiety, depression, and somatization than do otherwise healthy women [9]. Psychological distress is also increased in elderly Americans with self-identified chronic constipation [10]. However, morbidity extends beyond mental health disorders. Using the Short Form-36 Health Survey to assess quality of life factors, investigators in Canada found that adults with self-reported constipation scored lower than healthy Canadians in physical health as well [11]. The perception of poor health, both mental and physical, subsequently leads to increased healthcare utilization.

Healthcare resource utilization and spending associated with chronic constipation are significant. From 1997 to 2006, physician visits addressing constipation averaged greater than five million visits per year, with overall expenditures in the hundreds of millions of dollars per year [12, 13]. Additionally, as the population ages in the United States, the costs associated with constipation are likely to rise.

There are several well-established factors associated with an increased likelihood of constipation in industrialized countries which include:

- Female gender [6, 13–16]
- Older age [13, 14, 16, 17]
- Non-White race [6, 16, 17]
- Lower socioeconomic status [6, 16–18]

Inadequate fiber and water intake are often discussed in clinical practice as contributors to chronic constipation. However, dietary fiber is unlikely to be a significant contributor to bowel habits in individuals with slow transit constipation, and increasing dietary fiber in this subgroup may worsen symptoms [19, 20]. Additionally, inadequate water intake has not been shown to contribute to constipation in individuals without clinical evidence of dehydration [20].

Positioning during attempting defecation may also influence the likelihood of constipation. In particular, hip flexion at the time of defecation helps straighten the anorectal angle, facilitating the passage of stool [21]. In a study of 28 adult volunteers with normal bowel habits, subjective assessment of incomplete defecation and the degree of straining were significantly reduced in the squatting position compared to in the sitting position [22]. Similarly, in healthy volunteers, attempting defecation in the lying position has been associated with difficulty with stool expulsion compared to in the sitting position possibly due to increased dyssynergia [23]. These findings may partly explain the increased prevalence of constipation in the bedbound elderly.

Regardless of the definition used, chronic constipation is a common and economically burdensome disorder. Epidemiologic studies, both in urban and rural populations, identify particular subgroups with an increased predilection for constipation, and in turn shed light on the factors which may hinder normal bowel function.

Pathophysiology

Normal Colonic Transit and Defecation

The processes of colonic transit and defecation involve a series of complex and coordinated actions generated by both voluntary and involuntary triggers. Knowledge of colonic anatomy and physiology helps identify specific causes of constipation and select targeted therapies.

The embryologic origin of the colon explains its divided neurovascular anatomy. The cecum, ascending colon, and proximal two thirds of the transverse colon arise from the midgut and are supplied by the superior mesenteric artery, whereas the remainder of the colon is derived from the hindgut and is supplied by the inferior mesenteric artery [24]. Similarly, the parasympathetic innervation of the right and left portions of colon come from the vagus nerve and sacral nerves, respectively, and the sympathetic innervation from the thoracic splanchnic and lumbar splanchnic nerves, respectively.

Colonic motility is directed by the interstitial cells of Cajal, both independently and with extrinsic input from local and distant neurohormonal triggers [25, 26]. Neural input comes primarily through the autonomic and enteric nervous systems [27]. Within the autonomic nervous system, the parasympathetic fibers synapse in myenteric (Auerbach's) and submucosal (Meissner's) plexuses, and once activated, increase colonic motility and secretion. The sympathetic innervation of the autonomic nervous system, on the other hand, has an inhibitory effect.

The enteric nervous system is perhaps more complicated and less well understood than the autonomic nervous system. As opposed to the autonomic nervous system, the enteric nervous system regulates colonic motility primarily via local triggers (reflex behavior) rather than from signals derived from the central nervous system [27]. These local triggers can be mechanical or chemical and stimulate enteric sensory receptors, which in turn alter motility and secretion via communication with enteric motor neurons [27]. Enteric system neuronal bodies within Auerbach's plexuses help to control peristalsis, whereas cell bodies situated within Meissner's plexuses help regulate colonic secretion and absorption.

Colonic motility occurs as a result of coordinated contractions of the circular and longitudinal muscle layers of the colonic wall [28]. In addition to forward propagation, contractions are also important for mixing of luminal contents. Two distinct types of colonic contractions have been described [21, 26]:

1. Phasic contractions, which are further divided into segmental and propagated contractions [29].
2. Tonic contractions, which maintain sphincter tone [30].

Segmental contractions, which make up the majority of colonic motility, are low amplitude and help to enhance water as well as electrolyte absorption [29]. Propagated contractions can be of low- or high-amplitude. High-amplitude contractions are also called giant migrating contractions (GMCs) as they can propel intraluminal contents over long distances [31].

Coordination of these contractions is essential for forward propagation of luminal contents. With GMCs, the distal colon relaxes by inhibition of segmental and sphincter tonic contractions via inhibitory signals from the enteric nervous system; this is known as descending inhibition [30]. GMCs propagate luminal contents forward at approximately 1 cm/s, and colonic GMCs are associated with an urge to defecate [31–33].

Colonic GMCs occur on average six times per day in healthy subjects [33]. Particular triggers for GMCs include morning awakening, oral intake, and colonic distention [26, 32, 34, 35]. It has also been shown that the amplitude and frequency of propagated contractions is increased after exercise [36]. Prior studies suggest that dietary fats are potent stimulants for postprandial colonic activity, although more recent literature suggests a possible decrease in colonic transit with fatty foods [37, 38].

Paralleling their embryologic origins, the proximal and distal portions of the colon have different functions. The proximal colon is a reservoir for intraluminal contents, whereas the distal colon is a conduit for defecation [39].

The subconscious forward transit of stool in the colon is termed the basal phase of defecation [21]. During this stage, the puborectalis muscle is contracted, maintaining an acute angle between the rectum and anus. Further, the internal and external anal sphincters and anal cushions maintain resting anal tone [21]. Cyclic contractile activity in the rectum, in addition to contraction of the puborectalis muscle and anal sphincters, maintains continence. Approximately seven times per hour the internal anal sphincter relaxes to allow sampling of the intraluminal contents by the upper anal canal, thus invoking a conscious response to have a bowel movement, pass flatus, or maintain external anal sphincter tone [40].

The remainder of the defecatory process is defined by three additional phases: the pre-defecatory phase; the expulsive phase; and termination of defecation [21]. In the pre-defecatory phase, a defecatory urge is generated by distention in the rectum and stretch of perirectal structures. Additionally, the pelvic floor muscles and external anal sphincter are voluntarily contracted. In the expulsive phase, the internal anal sphincter relaxes involuntarily as a result of rectal wall tension. Subsequent voluntary relaxation of the pelvic floor muscles as well as the external anal sphincter lead to widening of the anorectal angle and perineal descent. With simultaneous voluntary increase in intraabdominal pressure, defecation occurs (Fig. 3.1). With passage of stool, termination of defecation is marked by a quick increase in external anal sphincter tone, slow closure of the internal anal sphincter, and increase in the acuity of the anorectal junction angle.

Subtypes and the Mechanisms of Chronic Constipation

Chronic constipation may be the result of a number of unrelated disturbances in colonic motility and defecation. Excluding constipation that is due to medications and systematic disorders that can slow gut motility, chronic constipation can be grouped into the following categories:

1. Normal transit constipation
2. Slow transit constipation

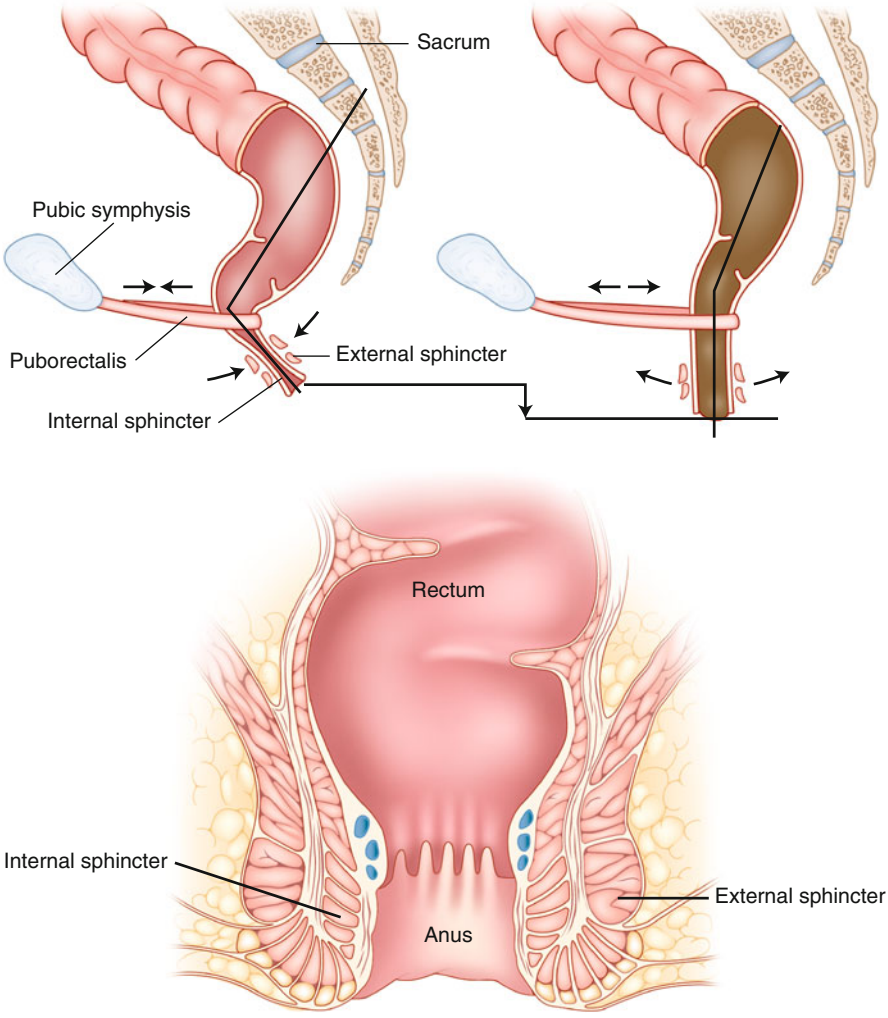

Fig. 3.1 Physiology of defecation

3. Pelvic floor dysfunction
4. Concurrent slow transit constipation and pelvic floor dysfunction (Table 3.1)

Chronic constipation is distinguished from irritable bowel syndrome with constipation (see Chap. 4) because of the primary symptom of pain in this latter disorder. Differentiating between these clinical categories is important given differences in management.

Normal transit constipation is the most common form of constipation presenting to the practitioner's office. In cases of severe constipation requiring specialty referral, normal transit constipation is seen less commonly. In a retrospective analysis of

Table 3.1 Constipation subtypes and associated pathophysiology

Subtype	Pathophysiology
Normal transit constipation	• Perceived difficulties with defecation
Slow transit constipation	• Decreased number, amplitude, and velocity of high-amplitude propagated contractions • Reduced gastrocolic and morning awakening colonic response • Loss of interstitial cells of Cajal • Loss of enteric and cholinergic neurons
Pelvic floor disorders	
Structural abnormalities	• Rectal prolapse • Rectal mucosal intussusception • Solitary rectal ulcer • Rectocele • Enterocele • Descending perineum syndrome
Dyssynergic defecation	• Reduced perception of rectal filling • Increased acuity of the anorectal angle • Failure of anal sphincter relaxation • Paradoxical contraction of the anal sphincters • Inadequate intraabdominal pressure • Lack of coordination between abdominal musculature, pelvic floor, and anorectal musculature
Concurrent slow transit constipation and pelvic floor disorder	• Combination of above mechanisms

Americans with intractable constipation undergoing anorectal and motility assessment, 42% had slow transit constipation, 12% had dyssynergic defecation (a subset of pelvic floor dysfunction), 25% had both, and 20% had neither [41]. In a separate retrospective analysis of individuals with constipation referred to a tertiary referral motility clinic, 37% had pelvic floor dysfunction and 27% had slow transit constipation, with an overlap of both pathologies in 55% of individuals [42].

Normal Transit Constipation

In normal transit constipation, patients have normal transit times through the colon but have the perception of constipation [43]. This perception may be due to evacuation difficulties or to hard stool that is difficult to pass. Additionally, patients may perceive gaseous distention of the bowel as constipation. Of note, among individuals with chronic constipation, those with normal transit have increased rates of depression in comparison to those with slow transit and/or pelvic floor dysfunction [44]. The reason for this association is not known.

Slow Transit Constipation (See Chap. 5 for Details)

In slow transit constipation, the propulsion of intraluminal contents can be delayed in portions of the colon or throughout the entire colon [45]. In affected portions of the colon, the number, amplitude, and propagated velocity of high-amplitude propagated contractions is decreased [46–48]. The gastrocolic and morning awakening colonic response are also reduced [46]. Furthermore, consecutive sequences of propagating contractions are also reduced in slow transit constipation [49]. Although less well understood, increased duration and amplitude of uncoordinated periodic rectal motor activity may also contribute to slow transit constipation [50].

With aging, the incidence of slow transit constipation increases. One acquired physiologic change that may underlie this finding is the progressive loss of colonic interstitial cells of Cajal with aging [51]. Other contributors may be the age-associated declines in enteric and cholinergic neurons, the latter of which are part of the parasympathetic innervation of the colon [52].

Pelvic Floor Disorders (See Chap. 6 for Details)

In pelvic floor disorders, the normal mechanism of fecal expulsion is interrupted. Several aberrations have been identified. Structural anorectal abnormalities which may lead to and be exacerbated by chronic constipation include rectal prolapse, rectal mucosal intussusception, solitary rectal ulcer, rectocele, enterocele, and descending perineum syndrome [53].

Functional disorders of defecation fall within the classification of dyssynergic defecation [53]. In dyssynergic defecation, one or more disruptions in the complex sequence of events in the pre-defecatory and expulsive phases can be identified. In the pre-defecatory phase, distention of the rectum normally leads to rectal contractions and a conscious recognition of the need to have a bowel movement; this ability to perceive rectal distension is often reduced in individuals with dyssynergic defecation [54–56]. In the expulsive phase, adequate pelvic floor relaxation may not be achieved due to increased acuity of the anorectal angle, failure of anal sphincters to relax, and/or paradoxical contraction of the anal sphincters [57–60]. Furthermore, adequate intraabdominal pressure necessary for expulsion or coordination of the abdominal musculature, pelvic floor, and anorectal muscle activity may be lacking [57, 60].

Clinical Presentation

Patients with chronic constipation seeking medical attention present with a wide range of symptoms. The symptoms may be related directly to defecation, such as excess straining, infrequency of bowel movements, and incomplete evacuation [61]. More generalized concerns, such as abdominal pain or bloating, nausea, or malaise, can also be due to chronic constipation [62].

Others may present with symptoms associated with complications of chronic constipation, such as diarrhea due to fecal overflow incontinence, and rectal pain and/or bleeding due to hemorrhoids or an anal fissure [63]. Less commonly, patients will present with pelvic organ prolapse, bowel obstruction, and bowel perforation with stercoral peritonitis from longstanding chronic constipation [63].

No single symptom is highly sensitive *and* specific for constipation or its pathophysiologic subtypes. Straining is seen in the majority of individuals with chronic constipation, but may be present in individuals with normal bowel habits as well [64, 65]. Among individuals with chronic constipation, Koch et al. found that infrequent defecation is sensitive for slow transit constipation. However, subsequent studies have failed to confirm this finding [64, 66]. On the other hand, the feeling of incomplete evacuation is sensitive and the use of digital maneuvers is specific for pelvic floor dysfunction [64].

Given the difficulty in identifying the subtypes of chronic constipation based on initial patient symptoms, patients who do not improve with conservative measures often need more specific investigation that will help direct therapy.

Diagnosis and Evaluation

As discussed above, diagnosing chronic constipation is complicated by a diversity of definitions among patients, physicians, and clinical researchers. Patients often define constipation based on straining and stool consistency whereas clinicians more often focus on stool frequency [2, 63]. The Rome III definition for functional constipation includes these and other specific defecation-related criteria and requires a minimum symptom duration of 6 months (see Table 1.2) [4]. Regardless of the definition used, diagnosing and evaluating chronic constipation require the clinician to perform an in-depth history and thorough physical examination.

History

Understanding patients' bowel habits requires detailed questioning. Specific questions to discuss with patients, based on and expanding beyond established definitions of constipation, are listed in Table 3.2.

The answers to these questions will help identify individuals with chronic constipation and those with alarm symptoms who require further diagnostic workup [67]. Further, for those with chronic constipation, this discussion will provide insight into its etiology and establish a baseline to assess the efficacy of various therapeutic interventions. A stool diary is useful for patients who are unable to answer the questions and/or identify the frequency of their symptoms.

Identifying stool consistency is particularly important because stool form has been found to correlate with colonic transit time [66, 68, 69]. Developed initially to assess the intestinal transit rate in individuals with irritable bowel syndrome, the Bristol Stool Scale identifies seven distinct stool forms based on stool "cohesion

Table 3.2 Suggested questions to identify and evaluate chronic constipation

• How many bowel movements do you have per week?
• Do you strain when attempting defecation?
• What is the consistency of your stools?
• Do you have to use your fingers or certain positions to help you to have a bowel movement?
• Following a bowel movement, do you feel that you have completely evacuated your bowels?
• How long have you had these symptoms? If symptoms started suddenly, was there a particular event that preceded symptom onset?
• What prescription, over-the-counter, and herbal medications have you tried to relieve the constipation?
• Do you have blood in your stools and/or have you had an unintentional weight loss of 10 lb or more?
• Do you have a family history of colon cancer or inflammatory bowel disease?

and surface cracking" (see Fig. 1.5) [70]. In adults with constipation, Bristol stool form types 1 or 2 have a sensitivity of 82% for delayed colonic transit [66].

Indeed, the sensation of incomplete evacuation following defecation is common among individuals with pelvic floor dysfunction [64]. Furthermore, the use of digital disimpaction is less common in but more specific for pelvic floor dysfunction [64].

Identifying disease duration also assists in understanding the etiology of a patient's symptoms and selecting appropriate treatments. In a survey study of young women with slow transit constipation, the majority had symptom onset in childhood, and particularly around the time of puberty [62]. However, symptom onset in childhood may also suggest undiagnosed Hirschsprung's disease (see Chap. 7, Constipation in Children section) or other familial motility disorders [71, 72].

Taking note of events and circumstances that coincide with the onset of constipation-related symptoms also helps to guide treatment. Examples include the initiation of anticholinergic or narcotic medications, or the presence of nongastrointestinal symptoms that suggest a systemic disorder, such as Parkinson's disease or scleroderma. Survey studies have identified pregnancy, the onset of mental illness, and a change in social circumstances as patient-perceived precipitants for dyssynergic defecation. Additionally, abdominal surgery, including appendectomy and hysterectomy, can trigger constipation in some women with slow transit constipation [61, 62]. Furthermore, although not always a triggering event, the prevalence of physical and/or sexual abuse is more common among individuals with constipation than in the general population [61].

Finally, alarm symptoms, such as rectal bleeding, weight loss, and/or a positive family history of colorectal cancer, are important to note as these factors may warrant timely evaluation for malignancy.

Physical Examination

After performing a thorough medical history, an abdominal examination should be performed. Inspection may identify abdominal distention, ventral or inguinal hernias, or prior surgical incisions. Auscultation may reveal hypoactive bowel sounds

Table 3.3 Components of a comprehensive rectal examination

Technique	Potential abnormalities
Inspection (at rest)	Thrombosed external hemorrhoids
	Anal fissure
Inspection (with Valsalva)	Patulous anus
	Rectal prolapse
	Internal hemorrhoids
Anal wink	Sacral nerve dysfunction
Palpation (anal canal)	Anal fissure
	Thrombosed external hemorrhoids
	Abscess
	Ulcer
	Increase sphincter tone
	Mass
	Stricture
Palpation (rectum)	Mass
	Rectocele
Palpation (rectum and abdomen, with Valsalva)	Incomplete anal sphincter relaxation
	Paradoxical anal sphincter contraction
	Absence of abdominal musculature contraction
	Incomplete perineal descent

or high-pitched bowel sounds suspicious for obstruction. If distention is present, percussion will help to differentiate between the presence of air or solid matter (e.g., stool, ascites). Finally, palpation may reveal masses or fecal loading.

Next, a thorough rectal examination, an important and often overlooked component in the evaluation of individuals with chronic constipation, should be performed. The approach to the rectal examination in gastroenterology has previously been outlined in the medical literature [73]. A summary of the rectal examination, as it pertains to the evaluation of chronic constipation, follows and is summarized in Table 3.3.

- With the patient in the left lateral position with hips flexed, spread the buttocks and inspect the perineum. Thrombosed external hemorrhoids or an anal fissure may be due to and can further exacerbate constipation.
- Ask the patient to strain. A patulous anus may suggest an underlying neurologic disorder, whereas rectal prolapse may be the cause for or the result of chronic constipation. Prolapsed internal hemorrhoids with straining may indicate long-standing constipation.
- To assess the integrity of sacral innervation to the anus, perform the anal wink maneuver. Specifically, with stimulation of all four quadrants around the anus with a cotton pad, a brisk contraction of the external anal sphincter should be seen.
- Palpate the anal canal. Painful palpation of the anus may be due to an anal fissure, thrombosed external hemorrhoids, ulceration, or an abscess.

- Assess the resting anal sphincter tone. An increased sphincter tone at rest may impede defecation.
- Advance the finger into the rectum. Palpate the anterior, posterior, and lateral rectal walls to identify masses or a rectocele which may obstruct stool passage.
- With the one finger in the patient's rectum and the other hand on the patient's abdomen, ask the patient to strain. Normally, the sphincter should relax and the perineum should descend 1–3.5 cm (Fig. 3.1). The abdominal musculature should contract and the rectum should push the finger distally. If the sphincter contracts with straining, pelvic floor dyssynergia is suggested, in which the external anal sphincter and puborectalis muscles paradoxically contract with attempted defecation.

In a study of individuals meeting Rome III criteria for functional constipation undergoing physiologic testing, the sensitivity and specificity of rectal examination for identifying dyssynergia were 75% and 87%, respectively [74].

Laboratory Testing

In the absence of alarm symptoms, the routine use of laboratory testing in the evaluation of constipation is not recommended [75]. A thorough history may suggest an underlying systemic etiology for chronic constipation, such as hypothyroidism, diabetes mellitus, or hypercalcemia. Laboratory evaluation may be warranted if such systemic disorders are suspected.

Endoscopy

As with laboratory testing, colonoscopy or flexible sigmoidoscopy are not necessary in the evaluation of chronic constipation in the absence of alarm symptoms [76, 77]. Exceptions include individuals 50 years of age or older who have not had prior colorectal screening (experts suggest starting screening at 45 years of age for African Americans due to diagnosis at a younger age) or individuals considering surgery due to prolonged, intractable constipation [76].

Physiologic Testing (See Chap. 2 for Details)

In individuals with functional constipation who lack alarm symptoms and who do not respond to fiber supplementation or laxatives, physiologic testing may be warranted. An algorithm for testing for functional constipation is outlined in Fig. 5.3 (see Chap. 5), and specific details regarding motility and anorectal testing are included in Chap. 2. To differentiate between slow transit constipation and pelvic

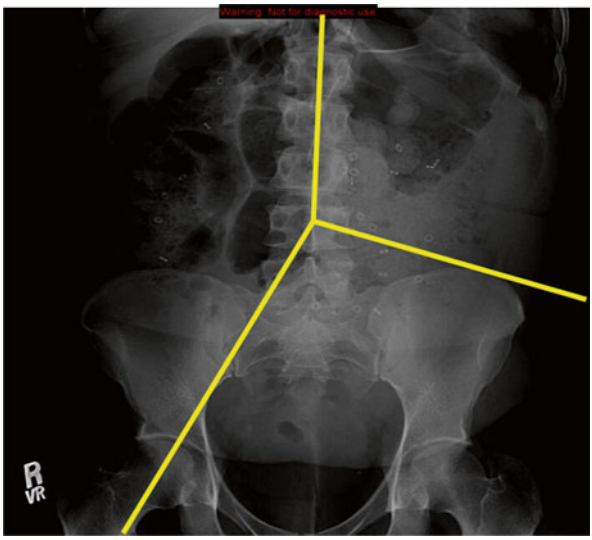

Fig. 3.2 Abnormal Sitzmarks test. Abnormal Sitzmarks test with greater than five markers remaining on day 5 after ingestion of Sitzmarks capsule. The equal distribution of markers in right, left, and rectosigmoid areas is suggestive of slow transit constipation. The absence of pooling of markers in the rectosigmoid area suggests the absence of pelvic floor dysfunction

floor dysfunction, the Sitzmarks test (Konsyl Pharmaceuticals, Inc.; Easton, Maryland) can be useful. There are several methods in which to conduct the Sitzmarks test. However, the most common used method is over 5 days. On day 5 after ingestion of the capsule, six or more radiopaque markers throughout the colon is suggestive of slow transit, whereas six or more markers in the rectosigmoid area suggests pelvic floor dysfunction (Fig. 3.2) [57].

In suspected slow transit constipation, three additional tests are helpful in further assessing colonic motility: scintigraphy, the SmartPill motility capsule (Given Imaging, Inc.; Duluth, Georgia), and colonic manometry. In scintigraphy, a large field view gamma camera assesses colonic transit of a long half-life radionuclide at 24 and 48 h. A prolonged geometric center, calculated based on isotope distribution throughout the colon, is suggestive of transit delay. Further, if slow transit is identified, scintigraphy may identify whether constipation is due to increased reservoir function of the ascending colon or impaired propulsion of the descending colon [45].

Given that approximately one half of individuals with chronic constipation also have upper gastrointestinal tract transit disorders, an assessment of whole motility may help identify abnormalities proximal to the colon [41]. The SmartPill motility capsule assesses gastric, small bowel, and colonic transit through a combination of pH, temperature, and pressure measurements. SmartPill transit time of greater than 59 h in the colon is associated with delayed colonic transit (Fig. 3.3) [78].

In assessing colonic motility, scintigraphy and the SmartPill motility capsule are preferred over manometry because they are noninvasive procedures. In colonic manometry, a water-perfused or solid-state catheter is placed via the anus or, less commonly, anterograde [79]. Colonic motor activity is assessed via recording ports or sensors spaced along the catheter. Among several potential aberrations in colonic motility, the presence of reduced GMCs and attenuated gastrocolic and morning awakening colonic responses are often seen in slow transit constipation [79].

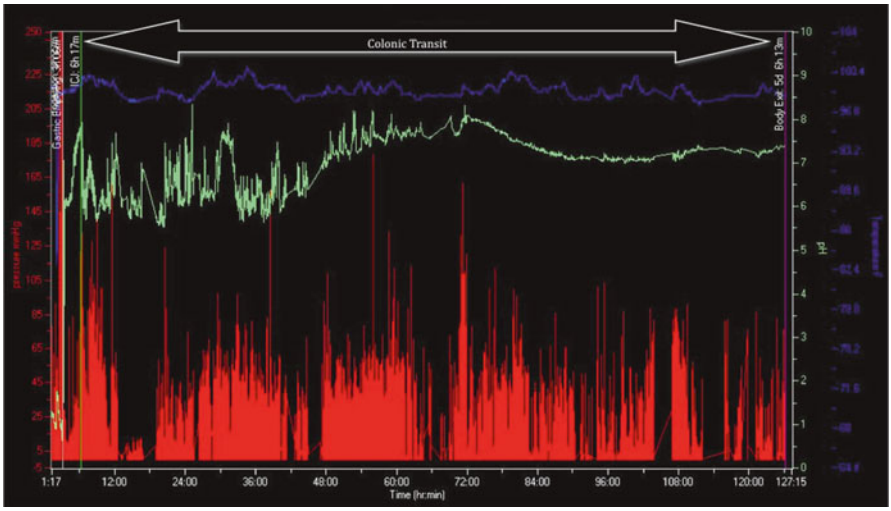

Fig. 3.3 Abnormal SmartPill motility capsule. Abnormal SmartPill motility capsule showing colonic transit time of >120 h. Normal colon transit time is less than 59 h. The *blue line* indicates temperature, with a decrease in temperature at the *right* side suggesting expulsion of the capsule outside of the body. The *green line* indicates pH; the drop in pH by >1 unit indicates passage of the capsule from the ileum to the colon. The *red* pressure spikes indicate peristalsis throughout the bowel

When the history, digital rectal examination, and/or the Sitzmarks test suggest pelvic floor dysfunction, anorectal function can be assessed with anorectal manometry, balloon expulsion, and defecography. In anorectal manometry, a failure in the coordinated increase in rectal pressure and relaxation of the anal sphincter is suggestive of dyssynergic defecation (Fig. 3.4a, b) [57]. The pathology may be due to impaired rectal contraction, impaired anal sphincter relaxation, or paradoxical anal contraction [57].

Rectal sensation is also assessed in anorectal manometry. Colonic hyposensitivity as evidenced by higher than expected pressures in the rectum to achieve first sensation and an urge to defecate may be due to colonic wall or sensory innervation abnormalities [80]. Importantly, a significant proportion of individuals with slow transit constipation may also have colonic hyposensitivity [80].

Anorectal manometry testing is often accompanied by a balloon expulsion test. An inability to expel a lubricated balloon from the rectum within 60 s was found to have an 89% specificity for dyssynergic defecation [81]. However, the test is thought not to be sensitive for dyssynergic defecation by some experts, as many individuals with this pathology will have a normal test [80].

If the results of anorectal manometry and balloon expulsion testing are not diagnostic for dyssynergic defecation, or a structural abnormality is suspected, magnetic resonance (MR) defecography should be pursued [77]. Through patient expulsion of a rectal contrast agent, MR defecography allows for identification of structural and functional abnormalities. Structural abnormalities include rectal prolapse,

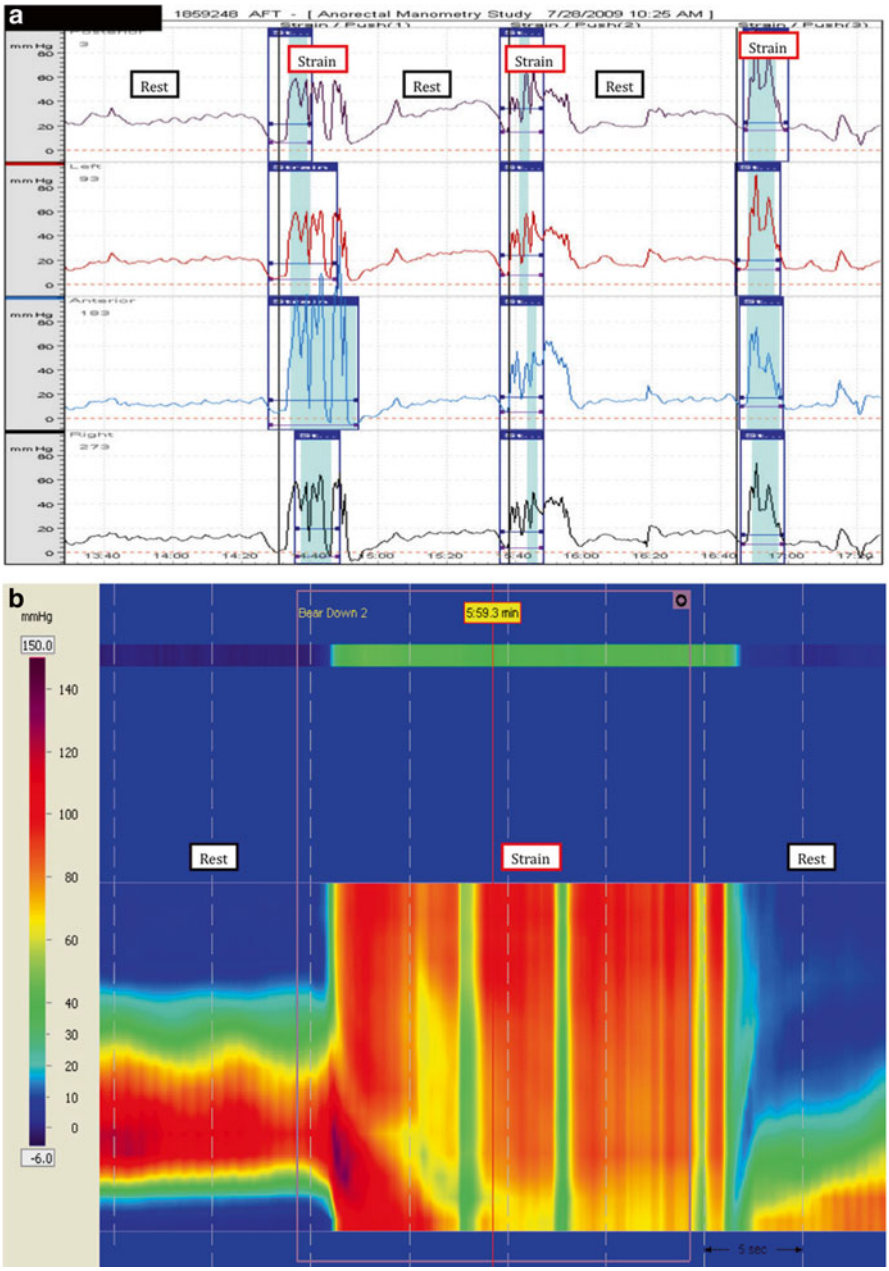

Fig. 3.4 (**a**) Abnormal anorectal manometry in a patient with constipation. Note the paradoxical increase in anal sphincter pressure with simulated defecation. This is exhibited by four pressure sensors located circumferentially around the manometry catheter on three separate strain attempts in this figure. (**b**) Abnormal high-resolution anorectal manometry in a patient with constipation. Note the paradoxical increase in anal sphincter pressure with simulated defecation, suggesting dyssynergic defecation

rectoceles, and enteroceles, and functional abnormalities include delayed time to evacuation, prolonged evaluation, increased acuity of anorectal angle with attempted defecation, and inadequate anal relaxation with defecation [77]. The sensitivity of this modality for dyssynergic defecation, as defined by abnormal anorectal angle change and paradoxical sphincter contraction, is 94% [82].

Management

Lifestyle and Diet Modification

In the absence of alarm symptoms, a conservative approach to chronic constipation is warranted. If possible, medications known to cause constipation, such as anticholinergics and narcotics, should be identified and eliminated. Recall that in the absence of obvious dehydration, increased water intake is unlikely to improve symptoms [20]. However, regular exercise is associated with a reduced perception of constipation, although a causative relationship is not certain [57].

The efficacy of dietary fiber in improving constipation may be determined by the underlying pathology. Fiber increases water content in stool and undergoes bacterial fermentation [83]. Many individuals with normal colonic transit and anorectal evaluations will respond to an increase in fiber. However, the response in individuals with slow transit constipation and pelvic floor dysfunction is only 20 and 37%, respectively [19]. Further, fiber intake may worsen symptoms of abdominal bloating in slow transit constipation [20].

Given the established role of fiber in normal transit constipation, increasing fiber intake remains a first-line intervention in individuals with constipation. Daily intake of 20–25 g of bran (an insoluble fiber) or 10 g of psyllium (a soluble fiber) are associated with increased stool frequency and stool weight [84, 85]. A gradual increase in fiber intake may help to minimize abdominal bloating.

Drug Therapy

Medications for the management of chronic constipation are outlined in Table 3.4. If fiber intake is not successful for relieving constipation, osmotic laxatives may be used. Osmotic laxatives are minimally absorbed, if at all, and draw water into the colon. Examples of osmotic laxatives include magnesium citrate, magnesium hydroxide, sodium phosphate, and poorly absorbed sugars, such as polyethylene glycol and lactulose. Osmotic laxatives typically take several days to take effect [43]. Caution should be taken in individuals with kidney disease or individuals at risk for dehydration.

Further therapy should be based on an understanding of the pathophysiologic subtype of constipation. Stimulant laxatives may improve slow transit constipation

Table 3.4 Pharmacologic management of chronic constipation

Category	Agent	Brand name (in USA)	Mechanism	When to use
Available in the United States				
Bulk laxatives	Psyllium	Metamucil	Increase fecal mass by retaining water in the lumen	First-line treatment of undifferentiated chronic constipation when increased dietary fiber is ineffective; take with plenty of water, and gradually increase dosing to minimize bloating
	Methylcellulose	Citrucel		
	Polycarbophil	FiberCon, Equalactin		
	Wheat dextrin	Benefiber		
Surfactant laxatives	Docusate	Colace	Lower stool surface tension to allow for increased water absorption	Use in mild constipation if bulk laxatives are not effective or not well tolerated
Osmotic laxatives	Polyethylene glycol without electrolytes	Miralax	Draw water into colon by osmotic gradient	Use if bulk laxatives are not effective or not well tolerated; avoid if abdominal bloating is a major concern
	Polyethylene glycol with electrolytes	GoLytely, CoLyte, NuLytely		
	Lactulose	Constilac, Constulose, Enulose, Generlac		
	Sorbitol			
	Magnesium hydroxide	Milk of Magnesia		
	Magnesium citrate	Citroma		
	Sodium phosphate	Fleet Phosphasoda		
		Fleet Enema		
Stimulant laxatives	Bisacodyl	Dulcolax	Increase intestinal peristalsis	Use if bulk laxatives are not effective or not well tolerated
	Anthraquinones (sennosides)	Senokot, Ex-Lax		
CIC-2 activator	Lubiprostone	Amitiza	Increase intestinal fluid secretion via activation of CIC-2 chloride channels on apical surface of intestinal epithelial cells	Use for moderate to severe constipation refractory to fiber and laxatives and in irritable bowel syndrome with constipation
GC-C agonist	Linaclotide	Linzess	Increase intestinal fluid secretion via GC-C activation on luminal surface of intestinal epithelial cells	Use for moderate to severe constipation refractory to fiber and laxatives and in irritable bowel syndrome with constipation

(continued)

Table 3.4 (continued)

Category	Agent	Brand name (in USA)	Mechanism	When to use
μ-opioid receptor antagonist	Methylnaltrexone	Relistor	Prevent opioid-induced decreased bowel motility via inhibition of opioid binding to peripheral μ receptors	Use for opioid-induced constipation refractory to fiber and laxative therapy
μ-opioid receptor antagonist	Alvimopan	Entereg	Prevent opioid-induced decreased bowel motility via inhibition of opioid binding to peripheral μ receptors	Use to accelerate the time to GI recovery after surgeries that involve partial bowel resection with primary anastomosis
Not available in United States				
5-HT4 agonist	Prucalopride		Stimulate peristalsis and intestinal secretion via 5-HT4 receptor activation in enteric nervous system	
	Tegaserod	Zelnorm		
	Mosapride			
	Cisapride	Propulsid		
Mixed 5-HT4 agonist and 5-HT3 antagonist	Renzapride		Stimulate peristalsis and intestinal secretion via 5-HT4 receptor activation in enteric nervous system	
GC-C agonist	Plecanatide		Increase intestinal fluid secretion via GC-C activation on luminal surface of intestinal epithelial cells	
Bile acid resorption inhibitor	Eloxibat		Increase bile acid content in colon via inhibition of ileal sodium-dependent bile acid transporter	

by stimulating colonic peristalsis. Examples of stimulant laxatives include anthraquinones (e.g., senna), diphenylmethane derivatives (e.g., bisacodyl), and mineral oil. Stimulant laxatives can take effect within hours of ingestion. Despite a long-held belief, stimulant laxatives do not cause tolerance or damage to the enteric nervous system [20]. However, melanosis coli is a benign manifestation of anthraquinone use.

Newer agents for slow transit constipation include serotonin receptor agonists (e.g., prucalopride) and chloride channel activators (e.g., linaclotide and lubiprostone).

Activation of 5-hydroxytrypamine receptor 4 (5-HT4) in the enteric nervous system increases acetylcholine release and thus stimulates small bowel and colonic motility [86]. In individuals with an unsatisfactory response to laxatives, a 3-month trial of prucalopride is associated with an increase in frequency of bowel movements and decrease in patient-reported constipation symptoms in comparison to individuals receiving placebo [87–89]. However, prucalopride is currently not available in the United States.

Tegaserod is another 5-HT4 agonist. However, due to concurrent affinity for non-5-HT [4] receptors which increases the risk for acute coronary syndrome and cerebrovascular events, tegaserod was removed by the United States Food and Drug Administration in 2007 [86].

Chloride release into the gut lumen occurs via the chloride channel protein 2 (CIC-2) and cystic fibrosis transmembrane regulator (CFTR) channels on the apical surface of enterocytes [90]. The negative charge of chloride ions allows for passive diffusion of sodium and water into the lumen. Lubiprostone directly activates CIC-2 channels to release chloride into the gastrointestinal lumen, whereas linaclotide and plecanatide stimulate guanylate cycle C receptors, which in turn increase chloride secretion via CFTR activation [90]. Chloride channel activators are known to be more efficacious than placebo in the treatment of chronic constipation, but head-to-head comparisons with laxatives are not available [91, 92].

Behavioral Therapy

When dyssynergic defecation is suspected, biofeedback therapy should be pursued. Biofeedback therapy helps to coordinate the abdominal, rectal, and anal musculature in defecation and can help to improve rectal sensation [53]. Through the use of anorectal manometry, biofeedback therapy provides real time assessments of rectal and anal pressures, allowing patients to practice coordination of anal sphincter relaxation with abdominal and rectal strain while attempting to expel air- or fluid-filled balloons [53]. Biofeedback therapy is known to provide prompt and sustained improved defecation patterns in individuals with dyssynergic defecation [93–95]. In comparison with standard therapy including dietary changes, exercise, and laxative use, Rao et al. found that biofeedback therapy increased the frequency of

weekly complete bowel movements (CBM) at 1 year from 1.91 to 4.85, whereas standard therapy did not change weekly CBM frequency [93]. Importantly, this study included individuals with dyssynergic defecation, as biofeedback therapy does not have a role in isolated slow transit constipation [96].

Outcomes and Future Directions

Satisfaction with biofeedback therapy in individuals with dyssynergic defecation is nearly 80%, yet individuals with normal transit and slow transit constipation are less likely to have adequate relief of symptoms with current therapies [97, 98]. Unfortunately, laxatives and lifestyle modification provide inadequate relief in one quarter to one half of individuals with chronic constipation [99, 100]. Of note, these estimates do not take into consideration the potential benefits of approved and investigational serotonin receptor agonists and chloride channel activators.

A wide array of experimental therapies may further improve outcomes in patients with normal and slow transit constipation.

Probiotics may also have a role in the management of chronic constipation. In particular, lactic acid bacteria have been shown to reduce colonic transit time and improve stool consistency and frequency [101]. Dietary supplementation with species within the Bifidobacterium genus has been shown to increase colonic motility in healthy women and those with constipation [102, 103]. In a separate randomized control trial of individuals with chronic constipation, consumption of a beverage with *Lactobacillus casei* Shirota improved self-reported severity of constipation [104]. Despite these positive findings, given limited data, the use of probiotics for chronic constipation is still considered investigational [105].

Other nonpharmacologic therapies targeting chronic constipation are also in the pipeline. Percutaneous tibial nerve stimulation and sacral nerve stimulation, currently approved in the United States for treatment of overactive bladder, may improve stool frequency in individuals with slow transit chronic constipation [106, 107]. Interferential therapy, which involves transcutaneous electrical stimulation, is also associated with improved constipation-related symptoms in adults with slow transit constipation [108]. Availability of these modalities will depend on additional studies to assess safety and efficacy.

In conclusion, as the US population ages, the incidence of chronic constipation and its associated healthcare-related costs are expected to increase. In patients with chronic constipation, a thorough history as well as physical examination will help to delineate the underlying abnormality. In patients not responding to the elimination of potential culprit medications and intervention with lifestyle and dietary modification and/or laxative use, physiologic testing to identify disorders with stool transit and rectal evacuation may help select targeted treatments. Ultimately, a combination of modalities may be needed to successfully resolve symptoms of chronic constipation and subsequently improve quality of life.

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Chapter 4
Irritable Bowel Syndrome with Constipation

Kelly K. Everhart and Brian E. Lacy

Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Describe the epidemiology and pathophysiology of IBS with constipation
2. Evaluate the patient with suspected IBS-C
3. Manage patients with IBS-C to improve quality of life and ameliorate symptoms

Key Points

This chapter covers the topic of irritable bowel syndrome with constipation. The high prevalence of this problem makes understanding the pathophysiology, evaluation, and management of patients with IBS-C all that more important. Gastroenterologists will not be the only healthcare providers seeing the IBS patient in the office. These patients will be evaluated by internists, family practitioners, gynecologists, physician assistants, nurse practitioners, and others. A few key points:

1. IBS is NOT a diagnosis of exclusion; you may be able to make a definitive diagnosis after careful history and physical examination.
2. Patients without any alarm signs and/or symptoms may be treated without further evaluation and testing in many cases.
3. Some patients will have a history of a recent infectious illness prior to the development of IBS.

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4. It is not uncommon for patients with IBS to switch subtypes (constipation, diarrhea, mixed).
5. Therapy should be targeted to the patient's main complaint.
6. There are promising therapies for the future based on novel mechanisms.
7. Education, good communication, and careful listening are the hallmarks of effective patient–physician or healthcare provider relationship.

Epidemiology

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that most clinicians have undoubtedly encountered—if not repeatedly—during the course of patient care. Worldwide, estimates propose that anywhere from 4 to 35% of the adult population is affected by IBS; in the United States, the prevalence demonstrates a narrower range, from 10 to 15% [1–3]. IBS appears to be slightly more prevalent in women than in men [1–3], although no cause has satisfactorily explained this gender discrepancy. Patients with symptoms that alternate between constipation and diarrhea are the largest cohort of the IBS patient population, followed closely by those who experience predominantly diarrhea (IBS-D), and then those who suffer most from constipation (IBS-C). Women are more likely than men to have symptoms of IBS-C. The incidence of IBS in the United States is estimated to be 200–400 cases per 100,000 people [4, 5]; typically, symptoms develop insidiously during the late teenaged years or early 20s, although there is usually a prolonged interval between symptom onset and diagnosis. The peak prevalence of IBS occurs in the third and fourth decades of life; thus, although IBS can be diagnosed at any age, a new diagnosis of IBS should be made cautiously in patients older than age 60, since other diseases (e.g., colon cancer or diverticulitis) may present with similar symptoms. Importantly, for most patients, IBS is a chronic disorder—nearly 75% of patients will still carry the diagnosis of IBS 5 years after its initial presentation [4, 6]. Fortunately, IBS does not predispose patients to more serious disorders (e.g., colon cancer), nor does it shorten life expectancy.

Pathophysiology

Our understanding of the pathophysiology underlying IBS is continually evolving. Fifty years ago, IBS was considered a somatic manifestation of neuroses or psychoses, nominally identified as "nervous colitis." Decades of technological and intellectual innovation have dramatically increased our appreciation for the complexity of the enteric nervous system (ENS) and its normal and diseased function. For instance, Almy and Mullin [7] demonstrated that emotion influences the gastrointestinal tract, experimentally observing changes in colonic motility in patients who had been given stressful information.

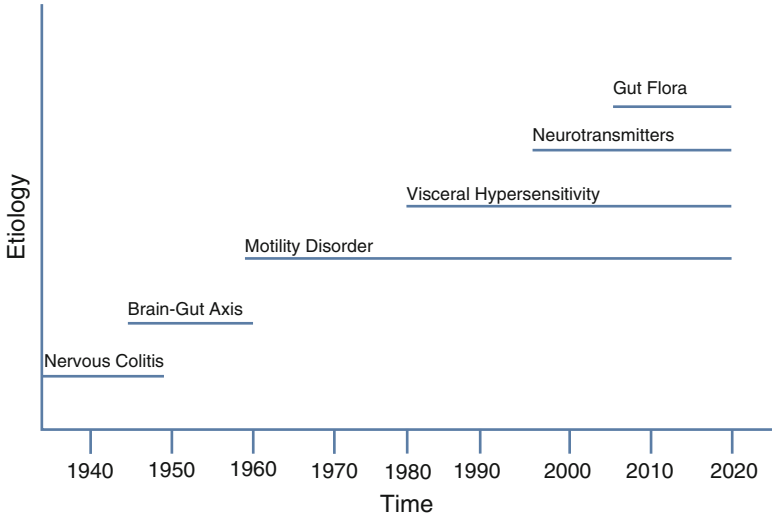

Fig. 4.1 Mechanistic evolution in the understanding of IBS pathophysiology

Subsequent research further elucidated the bidirectional information highway that connects the central nervous system (CNS) and ENS, labeling it the "brain-gut axis." In the 1970s, numerous research groups demonstrated that a subset of IBS patients experience alterations in GI motility; later research identified the importance of a panoply of neurotransmitters in both normal and abnormal GI physiology. Investigation then turned to the interface between the CNS and the ENS, revealing that IBS patients process sensory information from the GI tract differently than do healthy volunteers; today, this phenomenon is called "visceral hypersensitivity." Most recently, investigators have focused on the gut microbiome and its ability to mediate GI motility and sensation (Fig. 4.1).

Once thought to be the somatic manifestation of a nervous disorder, a synthesis of research in both the basic sciences and clinical wards has identified IBS as a complex disorder of multiple, overlapping pathophysiological processes that can include changes in CNS and ENS function. However, the precise etiology of IBS remains elusive. It is likely that IBS develops as a consequence of multiple etiological factors, especially given the complexity of its pathophysiology and the variety of its clinical course.

Currently, a widely accepted [8] theory suggests that some patients are genetically predisposed to develop IBS. In these susceptible individuals, an insult or injury to the GI tract disrupts normal GI homeostasis (Fig. 4.2), followed by the development of generally mild IBS symptoms. Such insults can involve anything from infection, inflammation, and medications to abdominal trauma or surgery. Resultant changes to the GI tract may include abnormalities in intestinal motility, alterations in visceral sensory function or CNS processing of sensory information, inflammation, alteration in the gut microbiome, or the development of food sensitivities. In some patients, mild IBS symptoms are intensified and exacerbated by poor coping

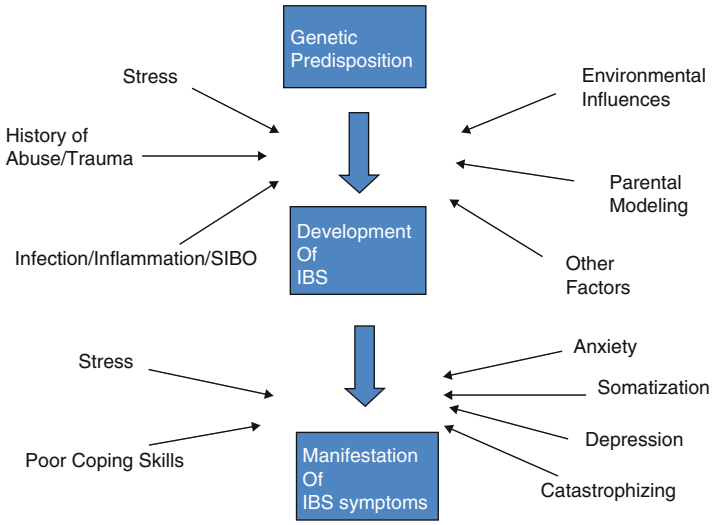

Fig. 4.2 Putative etiology of IBS

skills in the setting of concurrent and/or persistent stress, depression, anxiety, somatization, and catastrophizing behavior. These complex pathophysiological processes are described in further detail below.

IBS as a Motility Disorder

IBS is strongly associated with disorders of defecation (e.g., constipation or diarrhea); naturally, this relationship appears to identify abnormal GI motility as the underlying etiology of the disorder. Specialized gastric and small bowel motility studies (e.g., antroduodenal manometry) directly measure motor function in the upper GI tract. Although a number of different patterns of abnormal GI motility have been described in patients with IBS, no single pattern is pathognomonic for the disorder.

For example, discrete clustered contractions (DCCs) are bursts of rhythmic motility in the small intestine that are associated with episodes of abdominal pain in some IBS patients [9]. In others, the colon or small intestine experience prolonged and/or very high amplitude, propagating contractions, especially in the postprandial period; these also may be associated with episodes of abdominal pain [10]. Furthermore, alterations in the migratory motor complex (MMC), cyclical patterned waves of activity during interdigestive periods, may either delay (constipation) or accelerate (diarrhea) intestinal transit time [11]. In general, the underlying alterations in GI motility seen in some IBS patients appear to be concordant with the signs and symptoms of the disorder and may reflect an exaggeration of the normal patterns of GI motility rather than a unique process specific to IBS patients.

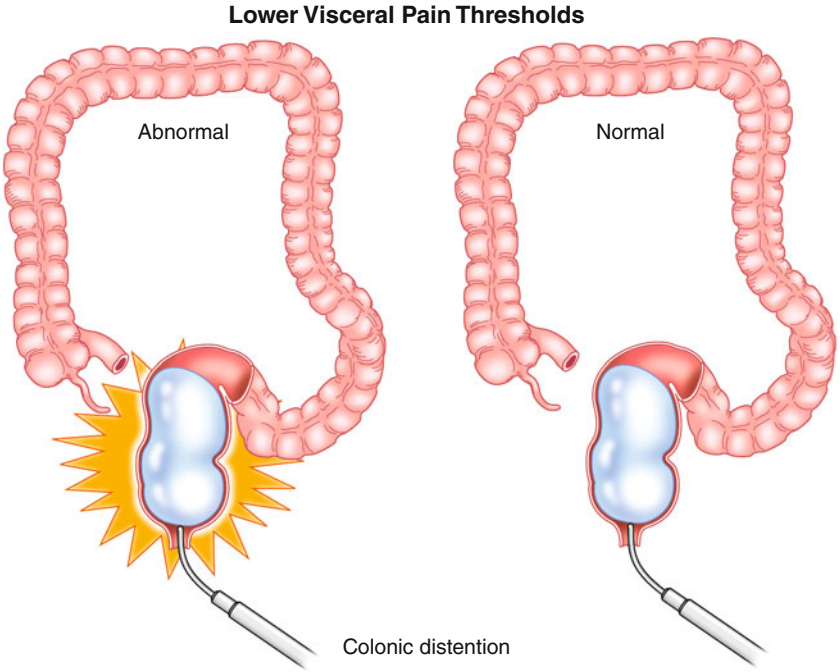

Fig. 4.3 Lower visceral pain thresholds are found in IBS patients. *Source*: Whitehead WE et al. *Gastroenterology*. 1990; 98:1187–1192

IBS as a Disorder of Visceral Hypersensitivity

Abdominal pain is intrinsic to the definition of IBS; its absence precludes diagnosis of the disorder. Historically, clinicians searched in vain for an organic cause of their patients' chronic abdominal pain. However, Thompson et al. [12, 13] seminally demonstrated that patients with IBS are more sensitive to pain within the GI tract. Many subsequent protocols used to assess visceral hypersensitivity in IBS patients involved balloon distention of the GI tract [14], with a balloon placed in the rectum, sigmoid colon, and/or the ileum which is gradually inflated. Notably, patients with IBS perceive balloon distention at much lower volumes of inflation than do normal subjects; they also describe the sensation of distention as more painful (Fig. 4.3) than do their healthy counterparts. In addition to visceral hypersensitivity, some patients with IBS also suffer from allodynia, mistakenly interpreting normal physiological events as painful.

IBS and CNS Processing

Abnormal sensory processing outside of the ENS is also a phenomenon seen in patients with IBS. A comparative study of CNS activation measured by positron

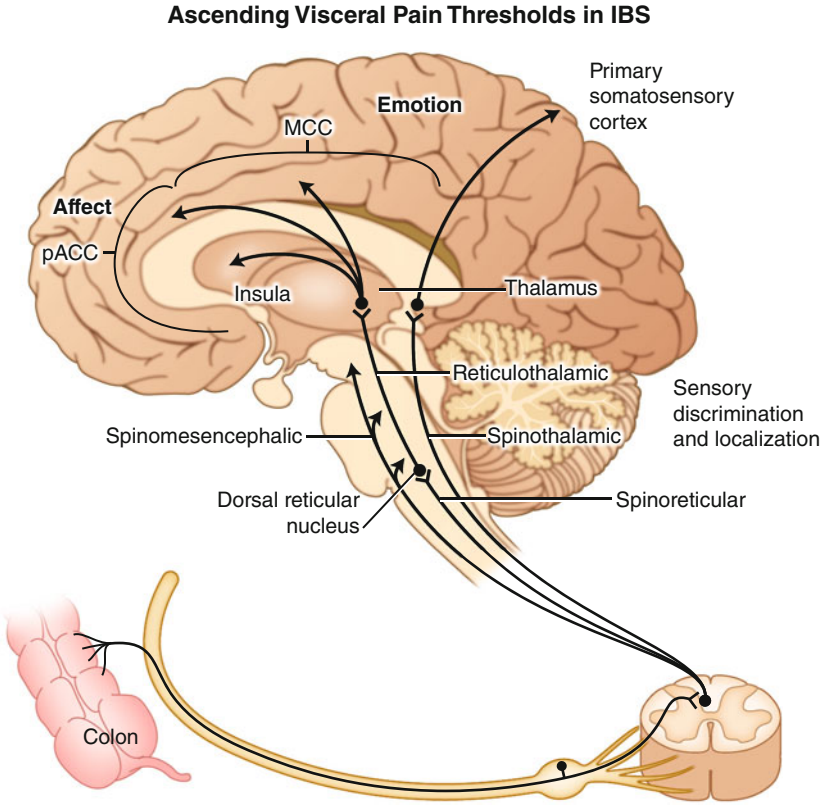

Fig. 4.4 Ascending visceral pain pathways in IBS. *Source*: Drossman DA. *Clin Gastroenterol Hepatol*. 2004; 2:353–365

emission tomography (PET) distinguished patients with IBS from their healthy controls during the inflation of a rectal balloon, recording an unusually increased level of activity in the prefrontal cortex—an area associated with anxiety and hypervigilance—and reduced activity in the anterior cingulate cortex—an area regulated by opioid activity—in the patient cohort compared to controls [15]. These findings may not surprise clinicians who are accustomed to the unique intensity with which many IBS patients monitor their symptoms. Similarly, Mertz et al. [16] used functional magnetic resonance imaging (fMRI) to characterize the differences in CNS activity that separate IBS patients from those without the disorder. Specifically, patients with IBS process sensory information from the GI tract in such a way that stimuli, such as stress, anxiety, and depression, may modulate and subsequently influence the perception of abdominal pain (Fig. 4.4).

These and other like findings have significant implications for the clinical course and treatment of IBS—therapy that is focused solely on the GI tract may not be nearly as successful as a multisystem approach that treats the GI tract, the CNS, and any psychosocial component of the disorder in parallel.

Infection as a Cause of IBS

Infection of the GI tract has been clearly linked to the development of IBS in some patients, yielding a diagnosis of "post-infectious IBS." For instance, a prior history of infectious gastroenteritis increases the likelihood that a patient will develop IBS later in life [17–19]. Clinically, many patients recall the persistence of bloating, abdominal pain, and altered bowel habits after an acute infectious illness (e.g., traveler's diarrhea). Although the precise mechanism underlying post-infectious IBS is unknown, several possibilities exist. An infectious process may transiently or permanently injure the ENS, impairing its ability to coordinate peristaltic activity within the GI tract. In the setting of recurrent exposure to a previously benign substance, a new immune hypersensitivity may induce inflammation in the GI tract and alter motility. Some experts also believe that an infectious agent can initiate a cycle of chronic mucosal inflammation that eventually alters gut motility. Although post-infectious IBS is more likely to be associated with IBS-D, a prior viral or bacterial infection can clearly predispose a patient to develop symptoms of any subtype of IBS.

Abuse and IBS

A history of physical, emotional, and/or sexual abuse may play a role in the development of IBS. In a retrospective analysis of etiological factors, Drossman et al. [20] found a higher prevalence of physical or sexual abuse in patients (primarily women) with IBS than in control groups without IBS. An abuse history is important to consider in all patients with functional bowel disorders; ideally, this issue should be raised during the initial evaluation. The timing of this discussion, however, is critical and depends on both the patient and the physician, who should have sufficient time and resources at hand to complete and then address what is undoubtedly a sensitive conversation.

Small Intestine Bacterial Overgrowth and IBS

Considerable energy has been directed towards characterizing the relationship between the gut microbiome and IBS. Small intestinal bacterial overgrowth (SIBO), a state of excessive bacteria in the upper GI tract, is frequently implicated as the cause of chronic diarrhea and malabsorption, and its symptoms (bloating, distention, abdominal cramps, and diarrhea) are frequently confused with those of IBS. In a landmark study, Pimentel et al. [21] found that 78% of 202 patients who met Rome I criteria for IBS had an abnormal lactulose breath test, suggestive of SIBO. These preliminary results generated a considerable amount of excitement in the field of IBS, since they raised the hope that IBS could be "cured" with antibiotics. Pimentel et al. [22] then more rigorously evaluated this relationship with a blinded,

randomized study, which found that 84% of IBS patients (Rome I) had an abnormal lactulose breath test consistent with SIBO, compared to 20% of healthy controls.

Although these promising results have been confirmed elsewhere [23], other research groups have failed to replicate the strong association between IBS and SIBO. Parisi et al. [24] evaluated a cohort of 85 consecutive IBS patients (Rome II)—none were positive for SIBO using glucose breath testing. Walters and Vanner [25] identified 10% of IBS patients (Rome II) as having SIBO using the lactulose breath test; similarly, Posserud et al. [26] found that the prevalence of SIBO measured with jejunal aspirates was no greater in IBS patients than in healthy volunteers—approximately 4%.

Given the uncertain role of SIBO in the development of IBS, Ford et al. [27] conducted a meta-analysis involving 12 studies and 1,921 subjects to estimate the prevalence of SIBO in patients with IBS. They found that the prevalence of SIBO depended upon the test and diagnostic criteria used to define a positive result, highest with lactulose or glucose hydrogen breath testing (54% and 31%, respectively), and lowest with a jejunal aspirate and culture (4%). Obviously, the role of SIBO in IBS remains unclear.

In summary, there is a small but significant subset of IBS patients who likely have an imbalance between species in their indigenous colonic flora, which could produce symptoms of gas, bloating, and distention. Given the association between SIBO and conditions like chronic diarrhea, an overgrowth or imbalance in the gut microbiome is more likely in patients with the diarrhea subtype of IBS.

Colonic Dysbiosis and IBS

Disruption of the normal intestinal microbiota has been connected to alterations in intestinal function and the development of functional GI disorders such as IBS. The natural flora of the colon, or the "gut microbiome," consists of approximately 1,000 species of bacteria in greater number than live cells present in the rest of the human body combined (approximately 10^{13}). It serves a variety of normal functions, including improvement in intestinal barrier function, modulation of the mucosal immune system, suppression of pathogenic bacteria, assistance with digestion and absorption of nutrients, vitamins, and minerals, and the synthesis of nutritional factors (e.g., short-chain fatty acids).

Comparative microbiological investigation indicates that the composition of the intestinal microbiota in IBS patients is different from that found in healthy people [28]. Furthermore, preliminary research appears to show that the intestinal microbiota may even be different in patients with IBS-C than patients with IBS-D, especially in those who have post-infectious IBS [29]. However, since most of the bacteria in the human intestine are still unknown, specific alterations in the composition of the gut microbiome between different disordered states are not yet well characterized; therefore, it is not yet clear whether these ecological differences are a cause of IBS symptomatology, or rather a secondary consequence of pathophysiologic factors related to IBS.

Celiac Disease and IBS

Symptoms of celiac disease can mimic those of IBS—bloating, abdominal distention, and diarrhea [30]. Although the prevalence of celiac disease in the United States is much lower than that of IBS (0.41–0.75% or 1 in 133 to 1 in 200) [31, 32], there was initially some speculation that celiac disease might be a causative disease state for IBS, given that there appeared to be an unusually elevated overlap between the two GI conditions. However, larger prospective studies have not identified any relationship between celiac disease and IBS [33, 34]. Rather than screening all patients with IBS for celiac disease, it is clinically appropriate to consider celiac disease in patients with IBS-D who experience persistent symptoms that are refractory to standard therapies. A more detailed discussion of the clinical approach to and management of IBS patients is included below.

Clinical Presentation

IBS is a syndrome, defined by a constellation of symptoms. Each patient may present with a unique collection of symptoms that vary in number and severity; however, two characteristic symptoms are prerequisite to the diagnosis of IBS-C: pain and disordered defecation. Abdominal pain or discomfort is the cardinal symptom of all subsets of IBS. Both "pain" and "discomfort" are important words in making this diagnosis, since some patients will insist that they do not have abdominal pain per se, just a sense of discomfort. The absence of pain makes the diagnosis of IBS untenable (Fig. 4.5).

Pain associated with IBS is typically located in the lower abdomen, but may vary from patient to patient; location is not specified in any definition of IBS. Patients

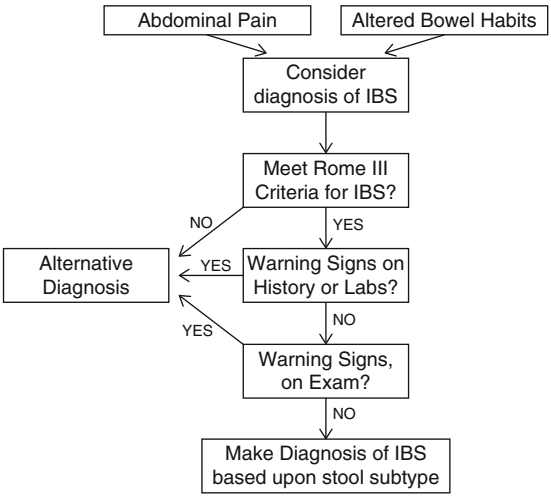

Fig. 4.5 Diagnostic algorithm for the diagnosis of IBS

Table 4.1 Common conditions associated with IBS

Migraine headaches
Fibromyalgia
Insomnia
TMJ syndrome
Functional dyspepsia
GERD
Pelvic floor dysfunction
Interstitial cystitis
Dyspareunia

often characterize IBS pain as "squeezing" or "crampy" or "twisting," finding it difficult to localize. Generally, IBS pain is episodic and unpredictable, although it is more likely to occur in the postprandial period (this is especially true in those patients with IBS-D, as they often have a heightened gastrocolic reflex). It is not solely related to urination, menstruation (although many women note a worsening of symptoms during their menstrual cycle), or physical activity, nor is it relieved by over-the-counter analgesics (e.g., acetaminophen, aspirin), or any type of anti-inflammatory agent. Unsurprisingly, abdominal pain is the primary reason patients with IBS see a healthcare provider.

In addition to abdominal pain, most patients with IBS will present with disordered defecation. Patients may describe symptoms of constipation (e.g., hard stool, straining at stool, feelings of incomplete evacuation, infrequent bowel movements), symptoms of diarrhea (loose stools, urgent bowel movements, more frequent stools) or both. Bowel habits can be unpredictable in IBS patients, which understandably add to their frustration. Although it was originally thought that IBS patients' bowel habits do not change, it is now widely recognized that they may experience multiple IBS subtypes (based on predominant bowel habit) over time. Variable bowel habits like these are not warning signs and should not elicit further diagnostic testing.

Patients with IBS often report a number of other gastrointestinal symptoms, notably including upper abdominal symptoms of burping, belching, reflux, and dyspepsia and lower abdominal symptoms of gas, bloating, distention, urgency, straining, and occasional episodes of fecal incontinence. IBS patients are also more likely to report chronic somatic symptoms, like chronic fatigue, jaw pain, chronic urinary issues, chronic muscle and joint pain, and migraine headaches [35] (Table 4.1).

Diagnosis and Evaluation

Diagnosing IBS need not be a difficult or prohibitively expensive process. However, when first evaluating a patient with multiple gastrointestinal symptoms, IBS is one of many options in a broad differential diagnosis (Table 4.2). A thorough and thoughtful interview, augmented by a careful physical examination, enables most providers to diagnose IBS at the first office visit. In some patients, simple laboratory

Table 4.2 Differential diagnosis of irritable bowel syndrome

Differential diagnosis	Clinical clues	Diagnostic tests
Small intestinal bacterial overgrowth (SIBO)	Previous abdominal surgery Bloating and diarrhea in diabetes mellitus or scleroderma	Lactulose breath test Glucose breath test Quantitative duodenal aspirate culture Trial of antibiotic therapy
Lactose intolerance	Diarrhea, abdominal pain, and flatulence after ingestion of milk or milk containing products	Trial of lactose-free diet Lactose breath test
Celiac disease	Diarrhea, weight loss, anemia, iron deficiency, gluten intolerance	Serology for celiac antibodies (tTG antibodies) Duodenal biopsy
Inflammatory bowel disease (Crohn's and ulcerative colitis)	Nocturnal symptoms, weight loss, blood and mucus in the stools, anemia	Colonoscopy Small bowel capsule study Laboratory tests
Infectious diarrhea (e.g., Giardia, parasites in endemic areas)	History of travel, history of exposure	Stool microscopy, culture; Laboratory tests
Colon cancer	Family history of colon cancer, rectal bleeding, weight loss, recent change in bowel habits in patients over >50 age	Colonoscopy

tests may be required to confirm the diagnosis; however, guidelines suggest that without alarm signs and symptoms, a definitive diagnosis may be made without further testing. When these simple guidelines are followed, the accuracy of a diagnosis of IBS is 97% [36].

IBS should not be a diagnosis of exclusion, nor should the patient be told, or led to believe, that "it is all in your head." Several steps in the clinical encounter ensure an accurate diagnosis of IBS: (1) take a careful history; (2) look for warning signs or "red flags"; (3) use the Rome III definition of IBS [37]; (4) perform a physical examination; and (5) consider targeted diagnostic studies.

Step 1. Take a History

IBS patients most commonly complain about abdominal pain and altered bowel habits, emphasizing whatever is most disturbing to them at the time of presentation. Symptom patterns vary considerably between affected individuals, but remain fairly consistent in a given patient, fluctuating only in intensity and frequency. IBS symptoms are typically intermittent, often absent for periods of days; however, some patients will experience symptoms daily without remission.

The presence of abdominal pain or discomfort is required for a diagnosis of IBS [37]. *If abdominal pain or discomfort is not present, the patient does not have IBS*. Timing is also an important component of an IBS history, given that IBS is a chronic disorder with an insidious onset (see definition for specific parameters below). Intervals of abdominal pain related to IBS should be associated with disordered defecation, and abdominal pain should be temporally related to defecation in some way. Pain related only to urination, menstruation, or exertion suggests an alternative diagnosis. The quality and location of abdominal pain varies between IBS patients, but remains relatively stable over time in individual patients. Some describe the pain as "crampy," whereas others describe it as sharp or burning. Common descriptions for pain in IBS include gurgling, churning, gnawing, stabbing, crampy, queasy, bloating, gassy, and urge to go but can't.

At this point the patient should be asked three key questions:

1. Is your abdominal pain (or discomfort) relieved by defecation?
2. At the onset of the abdominal pain or discomfort, are your stools looser or harder?
3. When the abdominal pain (or discomfort) begins, do you have more (or less) frequent stools?

An affirmative answer to two or more of these questions indicates that this patient likely fulfils the Rome III criteria for IBS. Although these criteria have yet to be validated, they appear to function perfectly well in practice.

Next, questions should focus on patients' bowel habits. Patients can find it difficult or even embarrassing to describe the appearance of stool. In practice the best way to obtain a consistent description of stool form is to use the Bristol Stool Chart (see Fig. 1.5). Questions can elicit information related to diarrhea-predominant, constipation-predominant, or mixed IBS based on the stool form. If patients do not reflect the characteristics of IBS-C, IBS-D, or IBS-M, a fourth category, labeled unsubtyped IBS, is now a recognized subtype of the disorder.

Normal patterns of defecation range from 3 bowel movements per week to 3 per day [38]. Many IBS patients prone to diarrhea find that the first stool in the morning is of normal consistency; however, subsequent bowel movements become increasingly loose and are associated with significant urgency, abdominal cramps, and flatulence. Fecal urgency and cramps are temporarily relieved by the passage of stool, but quickly return to precipitate repeated bowel movements. As bowel evacuation ends, the stools are primarily liquid or mostly mucus, and some patients are left feeling drained. By contrast, patients with IBS-C often report the passage of rocky hard, pellet-like stools (scybala) and may describe straining and the sensation of incomplete evacuation. Mucus may cover the stool or be passed without the presence of stool.

Fecal incontinence (usually slight staining of the undergarments) is more common in patients with IBS compared with the general population and may result from reflex relaxation of the sphincter muscles in association with repetitive colonic contractions. Although not well-studied, fecal incontinence is more likely to occur in patients with IBS-D or alternating constipation and diarrhea than in those with IBS-C.

IBS patients frequently report feelings of bloating and abdominal distention, which can be attributed either to increased amounts of abdominal gas, or more

Table 4.3 Common conditions that mimic IBS

Lactose intolerance
Fructose intolerance
Celiac disease
Small intestinal bacterial overgrowth (SIBO)
Colonic inertia (slow transit constipation)
Complicated diverticular disease
Pelvic floor dysfunction
Chronic intestinal pseudoobstruction (CIP)

likely, increased sensitivity to normal amounts of intestinal gas [39]. Lactose or fructose intolerances increase gas production, which can exacerbate underlying visceral hypersensitivity, as do large amounts of dietary fiber and legumes (e.g., beans) that contain stachyose or raffinose. As noted previously, SIBO has also been invoked as a cause of bloating in patients with IBS [20, 22, 40].

Finally, query the patient's past medical history, current medical conditions, and circumstances that might explain the etiology of the patient's discomfort. IBS patients often present with constitutional symptoms, such as fatigue, myalgia, arthralgia, insomnia, and headache; these symptoms are commonly caused by comorbid conditions like fibromyalgia, arthritis, or hypothyroidism, rather than IBS (Tables 4.2 and 4.3). Elicit a travel history for indications of a recent bacterial or parasitic infection, including giardiasis and amebiasis. Pay attention to the patient's family history, especially regarding GI malignancy and autoimmune conditions, and be sure to ask specific questions about food intolerances, anxiety and depression, sleep quality, medication use, alcohol consumption, and exercise, as these are all factors that can exacerbate or ameliorate IBS symptoms.

Step 2. Look for Warning Signs ("Red Flags")

The abdominal pain and altered bowel habits associated with IBS are frustrating and uncomfortable for patients, who often describe a significant decrease in their quality of life over the course of the disorder. Despite the apparent chronicity and severity of IBS, the disorder does not predispose patients to increased risk of malignancy or other life-threatening GI conditions. Therefore, it is important to distinguish IBS from other conditions, benign and serious, which can cause similar abdominal complaints (e.g., SIBO, lactose intolerance, celiac sprue, inflammatory bowel disease (IBD), and colorectal cancer).

To confirm the diagnosis of IBS, ask questions to investigate any alarm symptoms—all should be absent in the patient's history (Table 4.4). Standard questions evaluating alarm symptoms include:

– Do you know if you are anemic or have a history of anemia or iron deficiency?
– Have you had any gastrointestinal bleeding? (e.g., bloody bowel movements or vomiting of blood?)

Table 4.4 Alarm features that should alert you to the possibility of other diagnoses

Alarm features	Possible diagnosis	Tests recommended
Rectal bleeding	Colon cancer, inflammatory bowel disease	CBC, colonoscopy
Unintentional weight loss (>5–10% of body weight)	Colon cancer, celiac disease, other malabsorption syndromes	Upper endoscopy, duodenal biopsy, colonoscopy; Laboratory tests
Persistent nausea and vomiting	Bowel obstruction	Cross-sectional abdominal imaging; Laboratory tests
Anemia or iron deficiency	Celiac disease, colon cancer, inflammatory bowel disease	Upper endoscopy, duodenal biopsy, colonoscopy; Laboratory tests
Family history of other GI conditions	Colon cancer, inflammatory bowel disease, celiac disease	Upper endoscopy, duodenal biopsy, colonoscopy, celiac serology
Fever	Diverticulitis, abscess, inflammatory bowel disease	Abdominal CT scan; Laboratory tests
Abdominal mass	Colon cancer, Crohn's disease	Abdominal CT scan; Laboratory tests
Age >50	Colon cancer	Colonoscopy

- Do you have symptoms of recurrent nausea and vomiting?
- Have you had documented fevers with your symptoms of pain and altered bowel habits?
- Is there a family history of IBD, celiac disease, or any type of gastrointestinal cancer?
- Have you had symptoms consistent with a bowel obstruction?
- Any unintentional weight loss?
- Are you over the age of 50?

Weight loss (>10%), *occult blood in the stool*, *anemia*, *or other evidence of a GI bleed are not consistent with the diagnosis of IBS*. A positive answer to any query regarding alarm symptoms, or the presence of any alarm signs on physical examination (below), should prompt careful consideration of alternative diagnoses. Alarm symptoms ("red flags") raise the pretest probability that there is underlying structural disease; however, most patients with one alarm feature will not be found to have a serious organic explanation for their symptoms during subsequent evaluation [41]. The investigation of alarm features depends on the findings; usually blood work [e.g., complete blood cell count (CBC), erythrocyte sedimentation rate (ESR)] followed by a colonoscopy are the first tests considered. In the United States, preventive medicine guidelines recommend that all patients 50 years and older be offered a colonoscopy (if not previously performed) or an alternative test to screen for colon cancer. These screening tests should be performed 5 years earlier, at age 45 in African-Americans. In the setting of IBS, polyps or even an incidental cancer found on colonoscopy usually mean that the patient has the disorder plus the colonic pathology—*IBS symptoms are not sensitive markers of colorectal cancer*.

Table 4.5 Diagnostic criteria for IBS

Rome III

1. Symptom onset at least 6 months prior to diagnosis
2. Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:
   - Improvement with defecation
   - Onset associated with change in stool frequency
   - Onset associated with change in stool form (appearance)
3. One or more of the following symptoms on at least a quarter of occasions for subgroup identification
   - Abnormal stool frequency (<3/week)
   - Abnormal stool form (lumpy/hard)
   - Abnormal stool passage (straining, incomplete evacuation)
   - Bloating or feelings of abdominal distension
   - Passage of mucous
   - Frequent, loose stools

ACG definition of IBS

1. Abdominal discomfort associated with altered bowel habits
2. Symptoms of constipation include infrequent stools, straining, feelings of incomplete evacuation, difficult evacuation, passage of rocky, hard stools

From Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480–1491, with permission

When evaluating patients for suspected IBS, physicians can be inclined to routinely order a battery of investigative tests out of fear of missing a more serious condition before committing the patient to a diagnosis of IBS. This is neither economical nor clinically appropriate [36] and is a practice that should be reserved for only those patients who are identified by affirmative alarm features.

Step 3. Use the Rome III Definition of IBS

Clinically, IBS is currently defined using the latest iteration of the Rome criteria (Rome III). See Table 4.5 for a description of these criteria. What should be considered if the patient does *not* fulfil Rome criteria? These criteria are specific but not sensitive for the diagnosis of IBS; the absence of the criteria does *not* mean the patient does not have the disorder. Alternatively, clinicians can use The American College of Gastroenterology (ACG) IBS Task Force definition of IBS, which more broadly identifies the disorder as abdominal pain or discomfort associated with altered bowel habits over a period of at least 3 months, in the absence of warning signs or "red flags" suggestive of organic disease [42]. ACG criteria are sensitive, but not particularly specific; if a patient fails to fulfil Rome criteria, a more detailed clinical evaluation will exclude other potential etiologies before confirming the diagnosis of IBS (see Table 4.2).

Step 4. Perform a Physical Examination

A thorough physical examination serves a dual purpose in the diagnostic evaluation of IBS and should be performed during the initial clinical encounter: (1) a careful physical exam reassures patients that the clinician has listened to their complaints and takes their discomfort seriously. A physical exam is important for this reason even if the patient presents with classic symptoms of IBS that have been present for many years without alarm features or warning signs. (2) A physical exam might uncover comorbid, overlapping, or causal disease processes that exist in addition to or in place of the patient's IBS and is a helpful barrier to some physicians' tendency to prefer a single, unifying diagnosis for each patient. Suffice it to say—it is not uncommon for several disease processes to simultaneously shape a patient's illness experience.

Findings on physical examination are generally unremarkable in IBS patients, including vital signs, the head and neck, heart, lungs, skin, and cranial nerves. The abdominal examination may reveal some tenderness or firmness, especially in the left lower quadrant over the sigmoid colon. Don't confuse abdominal wall pain (which increases with tensing the abdominal wall muscles; a positive Carnett's sign) with deep tenderness sometimes found in IBS. The sigmoid colon often contains stool and can be palpated, regardless of whether the patient has IBS. Signs of rebound and guarding should be absent in IBS; their presence suggests alternative diagnoses. The physician also should look for evidence of masses in the abdomen, check for bruits, listen for a succussion splash (heard in patients with gastroparesis) prior to palpation, and the liver and spleen should be carefully examined.

A digital rectal examination should be considered in all patients. An anal fissure may explain a history of rectal bleeding, especially in patients with constipation and straining. A fistula or significant perianal disease raises the possibility of Crohn's disease. Some tenderness is often noted in the rectum of patients with IBS as a consequence of visceral hypersensitivity, rectal spasms, and muscular contractions; however, significant tenderness, evidence of a mass, or blood in the rectum warrants further investigation.

Step 5. Consider Targeted Diagnostic Studies

As with all diagnoses, the goals of testing in suspected IBS are to establish the diagnosis as early as possible, identify or rule out coexisting/alternative diagnoses, and avoid unnecessary studies. No further diagnostic evaluation is necessary in younger patients who meet system-based criteria for IBS, have normal findings on physical examination, and do not present with alarm signs or symptoms [36, 37, 42]. However, many IBS patients are reassured by results from an objective test that rule out serious organic disease [43], and many physicians cannot confidently diagnose IBS without the same objective tests, especially in an era of increasing medical malpractice suits [44, 45].

With these parameters in mind, we suggest consideration of a safe, cost-effective set of tests when indicated. Thyroid-stimulating hormone levels (TSH) may be

checked in patients with IBS-C. Tests might also include a CBC and an ESR or C-reactive protein (CRP) if they have not recently been performed (<6 months prior). The latter are especially useful in patients with IBS-D to exclude IBD. Test stool samples for fecal leukocytes in patients with diarrhea predominance, and if present, test for routine culture, ova and parasites, and *Clostridium difficile*. Reserve serologic tests for celiac disease for patients with persistent IBS symptoms (especially those with IBS-D); a cost-effective approach to celiac starts with serum tissue transglutaminase (TTg) antibody and serum immunoglobulin A, if indicated. Flexible sigmoidoscopy is usually recommended for patients younger than 40 years with a change in bowel habits or rectal discomfort, and colonoscopy is warranted in all patients 50 years of age or older (45 and older in African-Americans), and in those who are anemic or have a strong family history of IBD, or colorectal cancer (Fig. 4.5).

Management of IBS with Constipation

The management of patients with IBS and constipation does not follow a rigid algorithm. Rather, optimal treatment is tailored to each patient's symptom complex and is modified by symptom severity. For instance, lifestyle modifications and dietary changes may greatly improve very mild symptoms, whereas persistent or severe symptoms tend to benefit from additional therapeutic interventions (Table 4.6). In all cases, reassurance and education are the foundation of successful management of IBS.

Education

Patient education increases patient compliance with recommended treatment plans, enhances satisfaction with the healthcare system, and improves physician–patient interactions. Unfortunately, many patients with IBS report that they are insufficiently informed about their condition [46]. Healthcare providers should be educators at heart, and physicians offer their IBS patients great comfort and reassurance by making time each visit to answer questions, provide online and printed resources, and encourage patients to be honest about their confusion and fears. The latter is especially important—ideal patient education encompasses a bidirectional exchange of information, which accounts for each individual's understanding of IBS and its implications. Patient education should be specifically tailored to the level of education and most useful learning strategies that characterize each clinical relationship.

Reassurance

Many patients with IBS are needlessly fearful about their diagnosis. Nearly 20% are convinced that IBS will turn into cancer; another 30% believe that IBS increases the

Table 4.6 Treatment options for constipation symptoms in patients with IBS-C

Fiber supplements
Calcium polycarbophil (Equalactin, FiberCon)
Guar gum, partially hydrolyzed (Benefiber)
Coarse bran or ispaghula husk
Chloride channel activators
Lubiprostone (Amitiza)
Guanylate cyclase C activators
Linaclotide (Linzess)
Stool softeners
Docusate sodium (Colace)
Osmotic agents and unabsorbed sugars
Magnesium hydroxide (Phillips Milk of Magnesia, Freelax)
Magnesium citrate
Polyethylene glycol (Miralax)
Lactulose (Chronulac, Kristalose)
Sorbitol
Stimulant laxatives
Bisacodyl (Dulcolax, Gentlax)
Senna, sennosides (Senokot, Ex-Lax, Swiss-Kriss)
Aloe
Cascara
Combination agents
Docusate sodium and sennoside (Senokot-S)
Docusate sodium and casanthrol (Peri-Colace)
Herbal agents
Aloe vera (*Aloe barbadensis*)
Buckthorn (*Rhamnus catharticus*)
Cascara sagrada (*Rhamnus purshianus*)

likelihood of developing IBD (neither are true) [44]. For this reason, the importance of communication in the care of IBS patients cannot be overemphasized. Patients should be asked specifically about their fears and concerns at the start of the discussion regarding an individualized treatment plan. It would not be surprising for a patient to relate that he or she is concerned that he or she will develop colon cancer because of their IBS or that IBS can never be treated. All strategies should be employed to support patient honesty as an opportunity to eliminate future fear and distress. The provider's availability, good communication, and sufficient education can correct common misconceptions like these.

Lifestyle Modifications

Fortunately for patients with IBS-C, education, reassurance, and therapeutic lifestyle modifications can significantly alleviate their symptoms—patients with mild

IBS-C might find that this triad is all that is required. Patients should be queried about their diet, exercise plan, routines, and sleep, looking for small changes that can make a difference. For instance, although there is nothing magical about drinking eight glasses of water per day, and in fact no data to support that hydration is effective, nevertheless, some patients who drink very little liquid note some improvement in constipation symptoms when better hydrated. Patients should be counseled to consume foods with natural fiber (to a goal of approximately 25 g/day) if they are fiber deficient. However, if the patient is already ingesting 25 g of fiber per day, adding more fiber to the daily diet will not help constipation symptoms and likely will only worsen gas and bloating. Many IBS patients find that a daily routine improves their bowel habits, and an effective strategy includes timed toileting, meaning that a regular, convenient time be set aside for a bowel movement each day. Notably, many patients find that a daily morning regimen of fiber cereal along with fruit high in fiber and fructose and strong coffee or tea followed by routine scheduled bathroom time is all that is required to improve their symptoms. Finally, there is some evidence that exercise improves IBS symptoms [47]. Whether exercise directly affects the GI tract (e.g., change in motility), improves gas and abdominal distension, or simply increases patients' sense of well-being is unknown. Nonetheless, a daily or 4–5 times weekly exercise program will likely improve overall the general sense of well-being and IBS symptoms.

Medications

Fiber

Although fiber supplements are a safe, intuitive selection in the treatment of IBS-C, their therapeutic benefit is equivocal. Fiber supplements are categorized by their solubility in water (soluble fiber products include psyllium or ispaghula, calcium polycarbophil, and guar gum; insoluble fiber products include corn bran and wheat bran) and act as hydrophilic agents which bind water in the colon, preventing excessive dehydration of colonic contents. Over the course of three decades, only three studies have demonstrated that supplemental fiber significantly benefits IBS treatment plans—one for polycarbophil and two for ispaghula husk [48]. In a recent meta-analysis of 12 studies, Ford et al. [49] determined that IBS patients treated with fiber were only slightly less likely to have persistent IBS symptoms ($n = 591$; 52%), compared to those treated with placebo or a low-fiber diet (57%; $p = 0.05$), and estimated that 11 patients needed treatment with fiber to demonstrably improve symptoms. When treating patients with IBS-C, remember that fiber supplements are not effective if the patient is already taking in a normal fiber diet, that these products do not relieve abdominal pain, and that at least 30% of patients taking them experience significant bloating and abdominal distention.

Stool Softeners

Like fiber, stool softeners, such as docusate sodium, are historically significant agents in the treatment of IBS-C. Mechanistically, stool softeners are emollients that increase the water content of stool by 2–3%. Limited data available in the chronic constipation (CC) literature found that stool softeners are generally no better than placebo at improving constipation symptoms [50, 51]. No randomized, controlled studies have been performed in patients with IBS-C and thus, although safe, they cannot be recommended.

Stimulant Laxatives

Laxatives (e.g., bisacodyl) improve symptoms of constipation by stimulating the large intestine, thereby increasing intestinal transit. However, these agents generally worsen cramps, spasms, and pain in patients with IBS. No randomized, controlled studies have been performed in patients with IBS-C and thus cannot be recommended.

Osmotic Agents

Osmotic agents are widely available over-the-counter for the treatment of constipation. Lactulose, polyethylene glycol (PEG), and magnesium hydroxide or magnesium citrate are the most widely used agents in this class. Lactulose is a nonabsorbable, synthetic disaccharide composed of the sugars, D-galactose and D-fructose, which are fermented in the colon by bacteria to organic acids. These fermentation products (e.g., lactic acid and small-chain fatty acids) increase the osmotic load to the gut, thus stimulating peristalsis. Lactulose may improve symptoms of constipation, but will not help abdominal pain or discomfort and may worsen bloating (Fig. 4.6).

PEG is a nonabsorbable, non-metabolized osmotic agent that retains water in the stool, softening the stool and increasing the number of bowel movements (Fig. 4.7). It is approved for the treatment of transient constipation, but is not FDA approved for the treatment of IBS with constipation—no large prospective studies have been performed to evaluate the efficacy of PEG in IBS-C patients. Nevertheless, PEG appears to be widely used clinically to treat constipation symptoms in patients with IBS-C, even though it does not improve abdominal pain or bloating.

Magnesium hydroxide, in either liquid or pill form, is also an option for mild cases of constipation, but, once again, generally does not relieve abdominal pain and bloating. *The long-term use of magnesium hydroxide can be dangerous in patients with renal insufficiency or renal failure*.

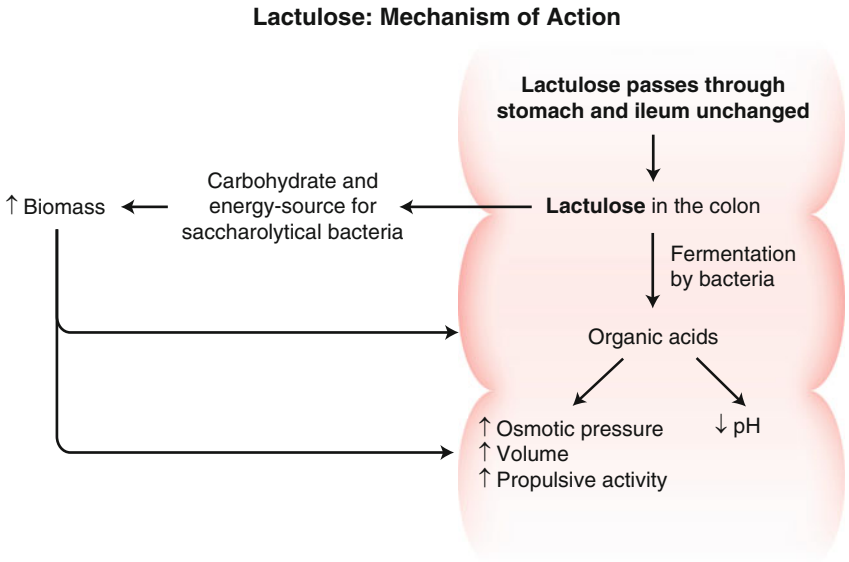

Fig. 4.6 Mechanism of action of lactulose

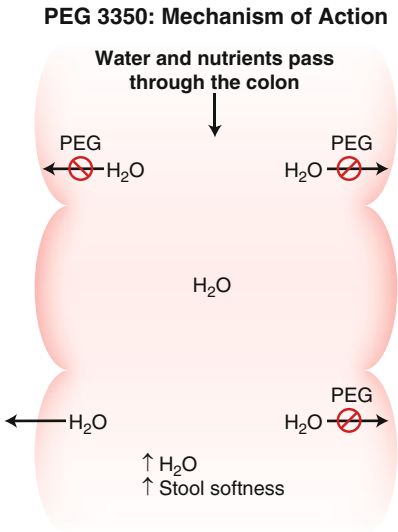

Fig. 4.7 Mechanism of action of PEG 3350 (glycolax)

Finally, magnesium citrate can be used on a p.r.n. basis to help with constipation, but it is not recommended for long-term use and will not help the abdominal pain that characterizes IBS.

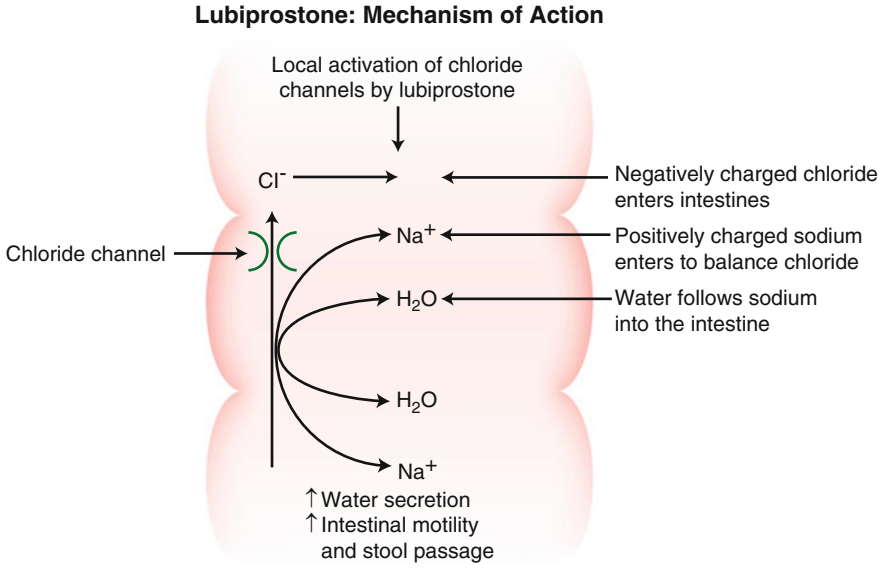

Fig. 4.8 Mechanism of action of lubiprostone

Lubiprostone

Lubiprostone, a bicyclic fatty-acid derivative that activates chloride channels within the lumen of the GI tract (Fig. 4.8), improves symptoms of chronic constipation in both men and women and was approved for the treatment of chronic constipation by the FDA in January 2006 [52]. These encouraging results naturally led researchers to evaluate the efficacy of lubiprostone in the treatment of IBS and constipation [53]. In a 2007 study, 1,171 adults diagnosed with IBS-C using the Rome II criteria were randomized to receive either 12 weeks of lubiprostone (8 μg) or placebo given twice daily [54]. Most patients were women (91.6%), and most were between the ages of 18 and 65 (91.7%). The primary efficacy variable was a global question rating overall IBS symptoms, while a 7-point balanced scale was used to rate changes in individual symptoms. The authors reported that patients receiving lubiprostone were nearly twice as likely as those receiving placebo to achieve overall response (17.9% vs. 10.1%; $p=0.001$). Secondary end points, including abdominal pain, bloating, straining, stool consistency, and constipation, all were significantly improved in the lubiprostone group compared with the placebo group ($p<0.05$ for all end points). Lubiprostone was generally well tolerated. The most common treatment-related side effects were nausea (8% vs. 4% in placebo) and diarrhea (6% vs. 4% in placebo).

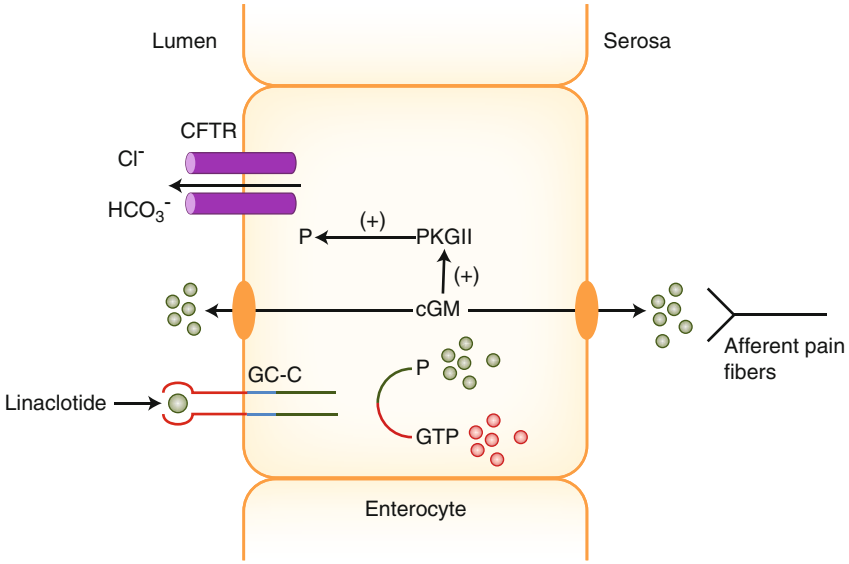

Fig. 4.9 Mechanism of action of linaclotide

Linaclotide

Linaclotide is an acid-stable, protease-resistant 14-amino acid peptide that stimulates intestinal guanylate cyclase type C (GC-C) receptors [55]. Linaclotide mimics the action of the endogenous intestinal peptides guanylin (15 amino acids) and uroguanylin (16 amino acids), activating cGMP-dependent protein kinase II pathways via the GC-C receptor on human colonic epithelial cells, which it binds with high affinity and independent of pH [56–59] (Fig. 4.9). Phosphorylation activates the cystic fibrosis transmembrane conductance regulator (CFTR), which increases the flow of electrolytes (HCO_3^- and Cl^-) and water into the lumen of the GI tract, accelerating the transit of its contents.

Linaclotide appears to be quite acid-stable [56]. Similar results were reported when linaclotide was exposed to pepsin [30]. The parent compound is broken down by removing the C-terminal tyrosine, leaving a 13 amino acid compound that appears to have full biologic activity; the metabolite appears to be completely broken down within several hours. In animal studies (mice), linaclotide has been shown to be minimally absorbed with bioavailability of approximately 0.10% [58]. Bioavailability in humans is also thought to be very low; in healthy volunteers linaclotide, at doses up to 1,000 μg, could not be detected in serum [60, 61]. Linaclotide is broken down within the lumen of the GI tract; a small amount may be recovered intact in feces.

The effects of linaclotide in women with IBS-C were first evaluated in a 5-day colonic transit study [62]. Thirty-six women with IBS-C (Rome II criteria; mean age = 39) were randomized to receive either placebo or one of two doses of daily linaclotide (100 or 1,000 μg) for 5 days. All study patients had documented slow colonic transit (defined by a geometric center ≤2.65 at 24 h or ≤3.0 at 24 h and ≤3.9 at 48 h). Patients with evacuation disorders were excluded. Analysis showed a significant effect of linaclotide on ascending and overall colonic transit at 48 h, but not 24 h, with the 1,000 μg dose, but not the 100 μg dose, compared to placebo (ascending $p=0.015$ and total $p=0.020$). Secondary outcomes that improved and were statistically significant compared with placebo include the time to the first bowel movement, stool frequency, stool consistency, and improved ease of stool passage. No serious adverse events were reported. These encouraging results led to two large prospective clinical trials which led to the FDA approval in August 2012 of linaclotide for the treatment of IBS-C.

Johnston et al. [63] conducted a phase IIb dose-ranging study to evaluate the efficacy and safety of linaclotide in patients with IBS-C. Men and women, age 18 and older, who met Rome II criteria for IBS with <3 spontaneous bowel movements (SBM) per week were eligible for the study. The primary efficacy endpoint was the change from the baseline period in weekly complete spontaneous bowel movements (CSBMs). Four hundred and twenty patients (92% women, mean age 44.4 years; 80% Caucasian) with IBS-C were randomized to receive either daily placebo or one of four doses of linaclotide (75, 150, 300, or 600 μg) for 12 weeks in a double-blind, multicenter study. Three hundred and thirty-seven patients completed the study (81%). The primary endpoint (mean change in CSBM compared to baseline) was met for all doses of linaclotide. CSBM rates for linaclotide (75, 150, 300, and 600 μg doses, respectively) were 2.90, 2.49, 3.61, and 2.68, compared to 1.01 for placebo ($p<0.01$ for all doses). SBM rates also improved for all doses of linaclotide compared to placebo ($p<0.001$), as did stool consistency and straining ($p<0.001$ for each). Abdominal pain was significantly better with 31.1–38.7% of linaclotide patients reporting improved abdominal pain compared to 22.7% for placebo ($p\leq0.01$ for 300 and 600 μg, $p\leq0.05$ for 75 μg). Abdominal pain returned to baseline levels after linaclotide was stopped and approached levels of pain found in the placebo group. Diarrhea was the most common AE and was the only dose-dependent AE, occurring in 11.4, 12.2, 16.5, and 18% of patients on 75, 150, 300, and 600 μg of daily linaclotide, respectively, compared to placebo (1.2%). The authors did not report any clinically significant differences in EKG recordings, electrolytes, vital signs, or physical examination for those patients on linaclotide compared to those on placebo.

Most recently, Rao et al. [64] conducted a phase III randomized, double-blind, placebo-controlled 12-week trial of linaclotide 290 μg in 800 IBS-C patients (mean age: 43.5 years; 90.5% women), followed by a 4-week randomized washout (RW) period. A significant number of linaclotide-treated patients reported clinical improvement of >30% in their abdominal pain (50.1% vs. 37.5% placebo, $p=0.0003$), and an increase in CSBM >1 from baseline (same week; 48.6% vs. 29.6% placebo, $p<0.0001$), consistent with FDA endpoint criteria for therapeutic drug approval. Patients were re-randomized following the 12-week trial; those

previously on linaclotide who were randomized to continue the therapy showed continued clinical improvement. Those randomized back to placebo returned to baseline symptoms, but without worsening of pretrial symptoms relative to baseline. Diarrhea was the most common adverse drug reaction (ADR).

Future Directions

Prucalopride

Prucalopride is an orally administered dihydrobenzofurancarboxamide derivative shown to be a potent, selective, high-affinity agonist at the 5-HT_4 receptor. The safety and efficacy of prucalopride for the treatment of chronic constipation has been evaluated in three large studies [65–67]. No large prospective studies have been performed in patients with IBS-C; however, given prucalopride's mechanism of action, and the prior success of both tegaserod and lubiprostone for the treatment of patients with both chronic constipation and IBS-C, it seems likely that prucalopride should improve constipation symptoms in patients with IBS-C. It should be noted that tegaserod, a 5-HT_4 agonist, was approved in 2002 for IBS-C, but removed from the market in 2007 related to concerns of cardiovascular side effects.

All three trials were similarly designed—12-weeks in duration, multicenter, randomized (2 vs. 4 mg vs. placebo), double-blind, placebo-controlled, and parallel group. Patients were defined as having chronic constipation if they had two or fewer CSBMs each week for a minimum of 6 months before the screening visit. Patients also had to have very hard or hard stools, or straining with at least 25% of bowel movements. The primary efficacy endpoint was the proportion of patients having three or more spontaneous, complete bowel movements per week, averaged over the 12-week period, using an intention-to-treat analysis. The main secondary endpoint was the percentage of study patients with an average increase of one or more CSBMs per week. Other secondary endpoints included the median time to the first CSBM, changes in stool consistency and straining at stool, and satisfaction with bowel habits.

Camilleri et al. [65] included 620 patients with chronic constipation (88% women; mean age = 48 year) in the study analysis. The primary endpoint (three or more CSBM/week) was reached by 31% of those on 2 mg of prucalopride, 28% of those on 4 mg, and 12% of those on placebo ($p<0.001$ for both study groups). During the 12-week study period, more patients treated with prucalopride had an increase of one or more CSBM/week when treated with either 2 mg (47%) or 4 mg of prucalopride (47%) compared to placebo (26%; $p<0.001$ for both doses).

Tack et al. [66] enrolled 720 chronic constipation patients, finding that most patients met the primary end point on treatment with prucalopride (both 2 and 4 mg daily) compared to placebo during the 12-week study period. Patients treated with prucalopride were more likely to rate their treatment as quite effective or extremely effective (35–36%), compared to placebo (19%; $p<0.001$).

Similar to the Camilleri et al. [65] and Tack et al. [66] studies, Quigley et al. [67] found that chronic constipation patients treated with prucalopride were more likely to rate their treatment as effective compared to those treated with placebo (37–39% vs. 20%; $p<0.001$) in a trial drawn from 41 US sites. No deaths were reported in any of these studies. Diarrhea was the most common adverse event.

Plecanatide

Plecanatide (SP-306) is an experimental 16 amino-acid GC-C agonist presently in Phase II/III trials for both chronic constipation (CC) and IBS-C. Structurally and functionally, it is nearly identical to the human hormone uroguanylin save for an extra methylene residue [68]. Binding of uroguanylin or plecanatide to transmembrane enteric receptors stimulates increased production of intracellular cyclic guanosine monophosphate (cGMP) which activates the CFTR and increases the secretion of fluid and ions into the gastrointestinal lumen. Data from a study involving patients with chronic constipation appears to support plecanatide's mechanism of action. In an unpublished study reported in January 2013, a 12-week randomized, double-blind, placebo-controlled, multicenter study involving 951 patients found that 3 mg of daily plecanatide was significantly more effective than placebo at improving symptoms of chronic constipation. A large multicenter trial is currently underway to evaluate the safety and efficacy of plecanitide in IBS-C patients.

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Chapter 5
Colonic Inertia and Megacolon

Arnold Wald

Chapter Objectives

At the conclusion of this chapter, the reader will be able to:

1. Define colonic inertia and megacolon
2. Describe the pathophysiology of these disorders
3. Discuss the evaluation and management of patients with slow transit constipation and chronic megacolon

Key Points

This chapter discusses two uncommon, but important etiologies of constipation. The pathophysiology of these problems is reviewed as well as the clinical presentation, evaluation strategies, and management options. Key points include:

1. Colonic inertia, also known as slow transit constipation, represents a primary cause of chronic constipation which is characterized by slow transit through the colon in the absence of a disorder of defecation or megacolon.
2. The diagnosis of colonic inertia should not be considered with a planned evaluation unless a constipated patient has not responded to fiber supplements and/or available laxatives because the pathophysiology of constipation is clinically unimportant in the vast majority of patients seen in clinical practice.
3. Chronic megacolon in the adult is an uncommon condition; two main types are recognized: (1) Hirschsprung's disease in which there is a congenital absence of myenteric and submucosal ganglia and (2) An acquired disorder either due to known causes such as Chagas disease, with neurologic disorders, diseases of intestinal smooth muscle, or an idiopathic form.

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Definition and Epidemiology of Colonic Inertia

Colonic inertia, also known as slow transit constipation, represents a subgroup of patients with chronic constipation which is characterized by slow transit through the colon in the absence of a disorder of defecation or megacolon. It is important to emphasize that this definition applies only to that relatively small group of patients who have chronic constipation which is poorly responsive to laxatives and other conservative measures and therefore requires diagnostic testing as described in Chap. 2. Even in tertiary referral centers in which sophisticated physiological testing is carried out, perhaps as few as 3% of constipated patients fall into this category; therefore, in the general population with constipation, only a miniscule number of patients will require treatment for this disorder. In patients with no obvious cause, the great majority of those with colonic inertia are young to middle-aged women who are presumed to have a disorder of colonic motility. Patients with chronic functional megacolon also have slow colonic transit but fall into a different category for purposes of management and will be discussed separately.

Pathophysiology of Colonic Inertia

In patients with slow colonic transit, it is important to first exclude potential causes or associated factors such as inadequate caloric intake [1], medications which are known to affect colonic transit [2], and defecatory disorders (see Chap. 6). The importance of the latter is the recognition that inadequate rectal expulsion is often associated with slow colonic transit which can be normalized with successful treatment of rectal evacuation [3]. It has also been shown that initiation of adequate caloric intake normalizes slow colonic transit within weeks, even before normal weight is restored [1].

In patients with idiopathic slow transit constipation with no defecation disorder, there is ample evidence of disordered colonic motor function in some patients. Several studies have demonstrated a marked reduction in colonic enteric nerves (Fig. 5.1) and interstitial cells of Cajal [4, 5] which act as the pacemakers of the colon neuroenteric system (Fig. 5.2). As these studies have been conducted in patients who have undergone colonic resection after failure to respond to pharmacologic agents, they are presumed to be the most advanced cases. It may be assumed that less advanced cases would show a milder reduction of enteric nerves, but this is not established. Indeed, manometric studies of patients with slow transit constipation show a spectrum of findings and there is (at present) an unclear relationship between colonic transit and motor activity [2] and even less so with neurohistochemical findings.

The classic manometric findings in colonic inertia include reduced numbers of high-amplitude peristaltic contractions (HAPCs) in response to a meal or to pharmacologic agents known to stimulate colonic motility such as bisacodyl and neostigmine [6–8]. Other findings include an increase in non-propagated or retrograde

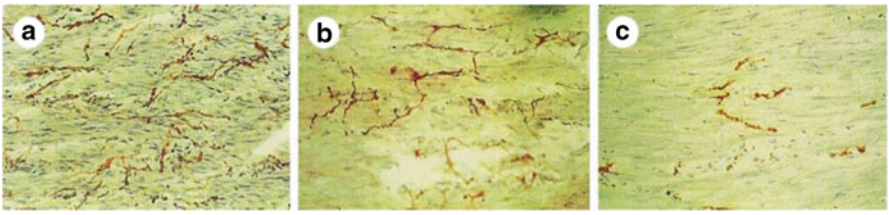

Fig. 5.1 Distribution of interstitial cells of Cajal (ICC) in the colon. (**a**) Control group: ICC are densely distributed within the muscularis propria. (**b**) Slow Transit Constipation: Compared with the control group, ICC are decreased in number. Although most ICC processes are readily discernible, some ICC exhibit blunted and shortened ramifications. (**c**) Megacolon: Both the number and the process length of ICC are remarkably decreased. However, the smooth muscle is not completely bare of pacemaker cells but contains ICC within all layers examined. C-kit immunohistochemistry, circular muscle layer; original magnifications 20× (From Wedel T, Spiegler J, Soellner S, Roblick UJ, Schiedeck TH, Bruch HP, Krammer HJ. Enteric nerves and ICC are altered in patients with slow-transit constipation and megacolon. Gastroenterology. 2002 Nov;123(5):1459–67, with permission)

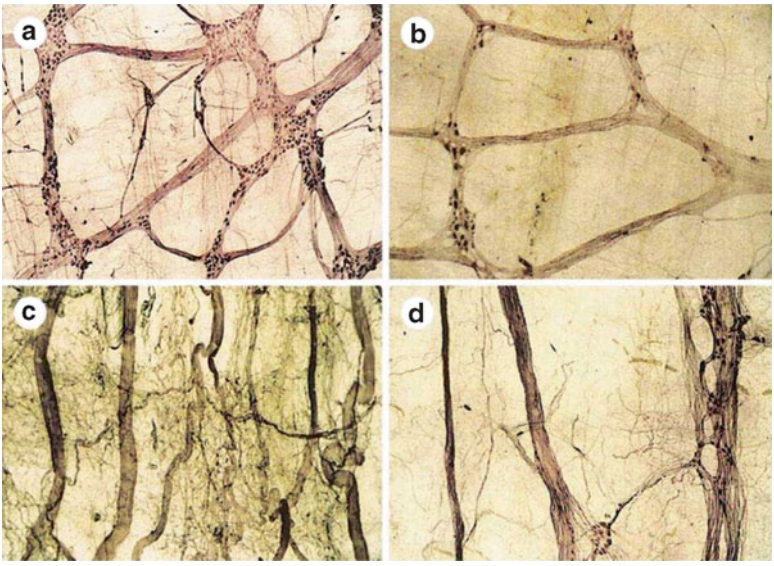

Fig. 5.2 Architecture of the colonic ENS (myenteric plexus). (**a**) Control group: The nerve network is composed of ganglia and interconnecting nerve fiber strands. Smaller branches (tertiary nerve fiber strands) ramify from primary and secondary nerve fiber strands and extend into the adjacent muscle layers. (**b**) Slow Transit Constipation: Compared with controls, the meshes of the nerve network are widened and the ganglia are reduced in size, containing a decreased amount of nerve cells. (**c**) Megacolon: Thickened nerve fiber strands run within the intermuscular plane. The bowel wall has no ganglia (aganglionosis). (**d**) Megacolon: Two of six patients with megacolon exhibited severe oligoneuronal hypoganglionosis. Few nerve cells are encountered within the hypertrophied nerve fiber strands and form small intrafascicular ganglia. However, the structural features are similar to those observed in specimens with complete aganglionosis (compare with **c**). PGP 9.5 immunohistochemistry applied to whole-mount preparations; original magnification 5× (From Wedel T, Spiegler J, Soellner S, Roblick UJ, Schiedeck TH, Bruch HP, Krammer HJ. Enteric nerves and ICC are altered in patients with slow-transit constipation and megacolon. Gastroenterology. 2002 Nov;123(5):1459–67, with permission)

propagated sigmoid or rectal phasic contractions which theoretically could impede colonic movement [9]. More recent studies using high-resolution colonic manometry in unprepared colons have demonstrated that there is less spatial overlap between adjacent propagated sequences [9]. It is unclear whether these patients will respond to pharmacologic stimuli. It is presumed that those with a poor or absent response to known stimuli will be refractory to medical therapy and will be candidates for surgical resection. However, there is no consensus that such tests are required for clinical decision-making [2].

Clinical Presentation

Most patients with slow transit constipation are women, and not uncommonly, they report having infrequent bowel movements, often with periods of 1–3 weeks without defecation. However, infrequent defecation alone is insufficient to make a diagnosis of chronic constipation [10]. The point to emphasize is that clinical presentation alone cannot distinguish the patient with slow transit constipation from one with a defecation disorder only, or a defecation disorder with slow colonic transit. Equally important is that patients are studied only after they have failed to respond to fiber supplements as well as over-the-counter laxatives and prescription drugs. Although some patients with constipation predominant irritable bowel syndrome (IBS-C) have slow colonic transit [11] and there is somewhat of an overlap between IBS-C and functional constipation, patients with symptoms of irritable bowel syndrome should be excluded from the category of colonic inertia because of management considerations (see Chap. 4).

Diagnosis and Evaluation

The diagnosis of colonic inertia should not be considered unless a constipated patient has not responded to fiber supplements and/or available laxatives. This is because the pathophysiology of constipation is clinically unimportant in the vast majority of patients seen in clinical practice. However, in medically refractory cases, pathogenesis hugely influences management and the primary concern is whether one is dealing with a defecation disorder, isolated slow transit constipation, or both.

Until recently, the algorithmic approach was to perform both colonic transit and defecation studies to classify constipated patients who respond poorly to conservative therapy. However, this approach has changed recently with the publication of the new American Gastroenterological Association guidelines on constipation [2]. These guidelines convincingly argue that such patients should be evaluated for a defecation disorder first; if none is present, one should proceed to colonic transit studies. If a defecation disorder is identified, appropriate treatment should be instituted. If treatment is successful and symptoms resolve, no further workup is necessary. If the defecation disorder is reversed and constipation persists, a colonic transit

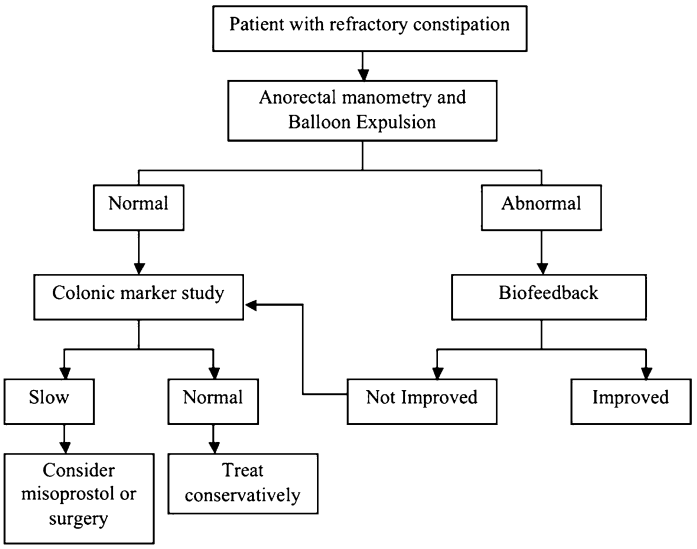

Fig. 5.3 Algorithm for the evaluation of a patient with intractable severe chronic constipation

study should be performed to determine if slow colonic transit is present and treatment should proceed on that basis (Fig. 5.3).

The reasons for this change are based upon recent studies and experience. Many patients will exhibit both slow colonic transit and a defecation disorder when tested, and most importantly, slow transit may normalize after successful treatment of the defecation disorder [3]. Another finding is that patterns of slow colonic transit (right-sided delay, left-sided delay) do not predict the presence or absence of a defecation disorder [12]. Even stasis of the markers in the rectosigmoid colon does not exclude willful withholding of defecation versus a true defecation disorder. Finally, defecation disorders are more prevalent in this population than is isolated slow colonic transit.

Once the diagnosis of colonic inertia is established, further tests should be considered only if surgery is contemplated. If a nonsurgical approach is attempted, there is little reason to perform additional studies in the absence of symptoms suggestive of upper gastrointestinal origin. However, if subtotal colectomy is a serious consideration, it is prudent to evaluate for a more generalized gastrointestinal dysmotility since the presence of this entity increases the risk of an unsuccessful outcome. Such tests may include esophageal manometry, gastric emptying, and perhaps small intestinal transit, although the latter is controversial in the absence of symptoms suggesting intestinal pseudoobstruction. One way to measure both gastric emptying and small intestinal transit is with the use of the wireless motility-pH capsule [13]. There is no consensus that adults with slow transit constipation require colon or small intestinal manometry, which are available only in a few highly specialized tertiary care centers. There may be a case for doing colonic manometry in children with severe constipation, although this is based upon evidence from a single, albeit influential, center [14].

Management

Medical

Since by definition, constipated patients who undergo diagnostic testing have been refractory to pharmacologic agents, they have already proven unresponsive to these agents. In addition, there are no published studies of any of the new intestinal secretogogues such as lubiprostone and linaclotide in this group of patients and it is difficult to conceive that they would respond to drugs which largely work by increasing intestinal water content. Not unexpectedly, these agents are often tried before referral to the gastroenterologist.

Although the literature is sparse, the prostaglandin E, analogue, misoprostol, may be effective in selected patients with colonic inertia [15]. Misoprostol stimulates intestinal smooth muscle and increases intestinal secretion and so may overcome the neuroenteric abnormalities in some patients with slow transit constipation. In this author's personal experience, the drug is effective in about 30–40% of patients in doses ranging from 400 to 1,000 μg daily given as a single dose. As misoprostol also increases uterine contractions and is a potential abortifacient agent, it is best used in men, postmenopausal women, women who have undergone a hysterectomy, or those who are sexually inactive. Abdominal cramps are often a dose-limiting side effect. Colchicine, despite a favorable published trial [16], should be avoided because it can cause neuromuscular complications, especially when renal function is impaired. In this author's limited experience, it has not proven effective.

Surgical

Abdominal colectomy with ileorectal anastomosis (IRA) should be considered in patients with refractory colonic inertia and in the absence of pelvic floor dysfunction [2, 17–19] as documented by appropriate testing (Chap. 2). Although not without morbidity [17–19], IRA is often effective in carefully selected patients with a number of important caveats. Firstly, it is optimal to exclude a more generalized disorder of gastrointestinal dysmotility with appropriate testing. Secondly, patients must be advised that IRA may not improve bloating and abdominal pain which indeed may increase after surgery. Thirdly, several studies document a significant incidence of postoperative problems including intestinal obstruction, bloating, and abdominal pain [17, 18]; if care is not taken to anastomose the small intestine to the upper third of the rectum and to not damage the presacral nerves, diarrhea and incontinence may result. Conversely, if a segment of sigmoid colon is retained, persistent constipation may result.

Several small studies have reported good results following segmental colectomy based upon segmental colonic transit time patterns [20, 21]. The literature does not support the use of segmental analysis to accurately predict which patient may benefit from segmental colectomy. This author's optimal approach is to use subtotal colectomy,

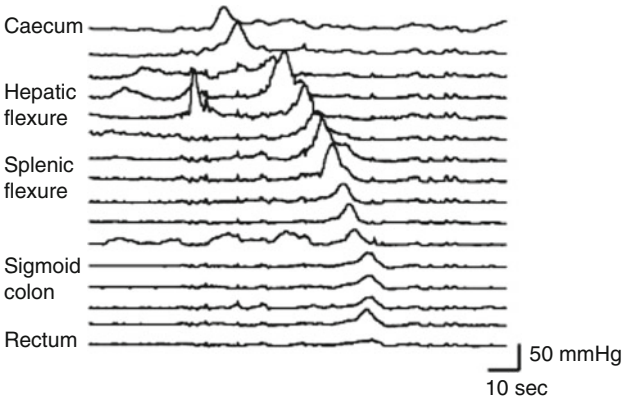

Fig. 5.4 Electrical stimulation of the sacral nerves resulted in a significant increase in the frequency of high-amplitude propagating sequences (HAPS). This HAPS was recorded during stimulation of the S3 sacral root at 14 Hz with a pulse width of 300 ls. Note that the HAPS originates in the caecum and extends the full length of the colon (From Dinning PG, Fuentealba SE, Kennedy ML et al. Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow transit constipation. Colorectal Dis 2007;9:123–32, with permission)

given the limitations of our current studies. Surgery can be performed either with laparoscopic or open techniques according to the skill and experience of the surgeon.

There are, at times, patients with slow colonic transit with complaints of abdominal pain and/or bloating in whom it is uncertain whether subtotal colectomy will abolish all symptoms. In such cases, a venting ileostomy may be performed [2]; if symptoms do not improve appreciably, one should be very reluctant to proceed with IRA. Such an approach may be useful in patients with slow transit constipation with suspected intestinal dysmotility and disabling obstipation.

Sacral Nerve Stimulation

A potential major advance in the treatment of slow transit constipation has been the use of sacral nerve stimulation, which was originally developed to treat patients with urinary or fecal incontinence [22]. This technique incorporates the temporary implantation of a stimulating wire in S_3 to evaluate efficacy during a 2–3-week period; if successful, a permanent electrode is placed and attached to a neurostimulator. In a large multicenter study of 62 patients with refractory chronic constipation, 45 proceeded to permanent stimulation of whom 39 reported improved symptoms [22]. Of 20 patients with documented slow colonic transit, 11 normalized their transit after treatment.

The biologic plausibility of this technique is derived from studies of pan-colonic motility [23]. Compared to basal activity, electrical stimulation of S_3 increased pan-colonic antegrade propagating sequences whereas stimulation at S_2 significantly increased retrograde-propagating sequences (Figs. 5.4 and 5.5). This finding was

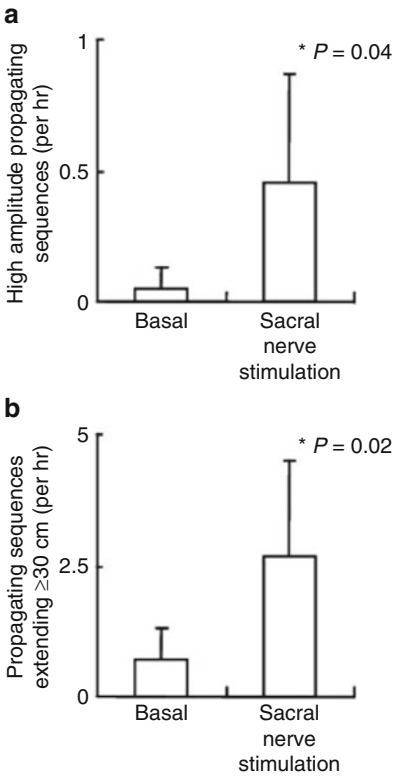

Fig. 5.5 Sacral nerve stimulation significantly increased the frequency of (**a**) HAPS, and (**b**) propagating sequences that extend ‡30 cm (From Dinning PG, Fuentealba SE, Kennedy ML et al. Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow transit constipation. Colorectal Dis 2007;9:123–32, with permission)

correlated by a 3-week trial in which 75% of patients reported increased bowel frequency and reduced usage of laxatives.

Although effective, a large review reported that more than 1/3 of 1,600 patients from 48 studies required surgical reintervention or discontinuation of treatment [24]. In addition, the investigators concluded that there has been significant underreporting of adverse events. The use of sacral nerve stimulation for treating severe constipation is not currently approved by the FDA for use in the United States.

Chronic Megacolon

Chronic megacolon in the adult is an uncommon condition which is often associated with constipation. Two main groups are recognized: (1) Hirschsprung's disease in which there is a congenital absence of myenteric and submucosal ganglia of varying portions of the distal colon (sometimes small intestine as well) and always affecting the internal anal sphincter (see Chap. 7); (2) An acquired disorder either due to known causes such as Chagas disease, with neurologic disorders, diseases of intestinal smooth muscle, or (most commonly) an idiopathic form. Studies of idiopathic

megacolon have demonstrated a severe disintegration of the enteric nerves in some cases [4, 25] (Fig. 5.2) whereas others have focused on atrophy of the collagenous connective tissue membrane of the myenteric plexus and muscularis propria which abolishes peristalsis and permits unlimited distension of the colon [26]. In either case, chronic megacolon is a decompensated colon and should not be managed as would chronic constipation alone.

Clinical Manifestations and Diagnostic Tests

Evaluation includes exclusion of a mechanical obstruction with colonoscopy or a water-soluble contrast enema. Medications which inhibit colonic motility should be stopped or replaced [27]. If there is significant exposure to traveling or living in South America, serologic screening for Chagas disease should be obtained.

Very uncommonly, Hirschsprung's disease will not be diagnosed until adulthood [27]. The diagnosis should be especially considered in a male with constipation since childhood and in the absence of fecal incontinence (see Chap. 7).

Treatment

Regardless of underlying etiology, management is symptomatic and palliative [27, 28]. For most patients with chronic megacolon, a nonsurgical approach is often effective. Stool retention is not uniformly seen in all patients with chronic megacolon. If large amounts of stool are present, the patient should undergo thorough cleansing of the colon with high colonic water enemas, water-soluble contrast enemas, and (if tolerated) large volumes of polyethylene glycol (PEG) electrolyte solutions. Once accomplished, a colonic maintenance regiment may be implemented.

Fiber supplements and osmotic agents such as lactulose and sorbitol should be avoided as they increase stool volume and gas production. Rather, fiber restriction with small amounts in PEG solutions (8.5 g/day) will reduce stool production and build-up. Periodic large volume warm water enemas or oral colonic lavage with PEG electrolyte solutions may be administered once or twice weekly to empty the colon regularly. Diets should be designed to avoid gas-producing foods which will increase distension and discomfort. Stimulant laxatives and enterokinetic agents are unlikely to be effective in view of failure of the enteric nervous system and colonic smooth muscle.

If conservative measures fail, there are several surgical options depending upon anorectal function (Table 5.1). These include ileostomy with colonic exclusion, subtotal colectomy with IRA (if anorectal function is preserved), or decompressive cecostomy with periodic antegrade enemas if distension is uncomfortable [29]. If subtotal colectomy with IRA is considered, exclusion of a more generalized intestinal pseudoobstruction predicts a more optimal outcome. In selected cases, segmental resection of isolated areas of dilated bowel may be appropriate.

Table 5.1 Surgical options for chronic megabowel

Condition	Surgical options
Isolated megacolon	Subtotal colectomy with ileorectal anastomosis[a]
	Diverting loop ileostomy[b]
Megacolon and megarectum	Colectomy with ileoanal anastomosis[a]
	Diverting loop ileostomy[b]
	Decompressive cecostomy with periodic antegrade enemas
Segmental megacolon	Segmental resection

[a]If anorectal function is normal
[b]If anorectal function is abnormal

Summary

Colonic inertia and chronic megacolon are two uncommon subtypes of chronic constipation. The etiology of the former should not be pursued without a trial of medications and laxatives. If refractory to treatment, the current recommended approach is to assess for the presence of defecatory dysfunction, and if present it should be appropriately treated first.

In the patient with chronic megacolon, exclusion of obstruction should be considered, medications that inhibit motility discontinued, and if there is a significant pertinent travel history, the diagnosis of Chagas disease may be entertained.

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Chapter 6
Pelvic Floor Dysfunction

Askin Erdogan and Satish S.C. Rao

Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Define disorders of pelvic floor dysfunction
2. Evaluate patients with suspected pelvic floor dysfunction
3. Recognize specific management strategies to treat patients with pelvic floor dysfunction

Key Points

This chapter covers the topic of pelvic floor dysfunction highlighting the epidemiology, clinical presentation, evaluation, and management of: dyssynergic defecation, fecal impaction, descending perineum syndrome and rectocele, enterocele, and cystocele. Patients with these disorders may present to many different types of specialists and clinicians; it is important to recognize these problems as strategies for treatment differ from those for other causes of constipation. A few key points:

1. Dyssynergic defecation is defined as inappropriate contraction of the pelvic floor or less than 20% relaxation of basal resting sphincter pressure with adequate propulsive forces during attempted defecation.
2. Fecal impaction is the abnormal accumulation of large amounts of hard stool in the rectum and distal colon with the inability of the individual to pass these stools.
3. Descending perineum syndrome is the excessive descent of the perineum, several centimeters below the bony outlet of the pelvis during a straining effort and can present with pain, straining, and/or difficulty defecating.

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4. Rectocele is a saccular protrusion of the rectal wall usually towards the vagina through the separations or tears of the fascia typically in the rectovaginal septum. Patients with a rectocele may suffer with incomplete evacuation, prolonged straining, vaginal splinting, and/or rectal pain.
5. Enterocele is the herniation of the peritoneum-lined sac usually filled with small intestine into the rectovaginal space. Symptoms may include pelvic pain and incomplete or obstructed defecation.

Pelvic Floor Dysfunction

Pelvic floor disorders are common and encompass many conditions that affect both defecation and continence. In this chapter, we discuss four common entities that affect defecation, notably dyssynergic defecation, fecal impaction, descending perineum syndrome (DPS) and rectocele, enterocele, and cystocele. Although there is a significant overlap among these conditions, and more than one problem may coexist or confound or cause a pelvic floor disorder, here we discuss each of these conditions separately. An algorithm for a clinical approach and management of pelvic floor disorders is presented in Fig. 6.1.

Dyssynergic Defecation

Epidemiology

Constipation affects 15–20% of the population in North America [1]. It increases with age, especially after age 65 with a higher female/male ratio 2.2/1. Twenty eight percent of nursing home residents have constipation; and many of them have difficulty with defecation. Constipation is more common in subjects with lower income and in non-Whites. Comorbidities like Diabetes mellitus, spinal cord injuries, neurologic disease, opioid usage for pain in noncancer patients, calcium channel blocker usage, and sexual abuse are also frequently associated with constipation (see Chap. 7).

Constipation composes of three pathophysiological subtypes, slow transit constipation (see Chap. 5), dyssynergic defecation, and irritable bowel syndrome with constipation (IBS-C) (see Chap. 4). The exact prevalence of dyssynergic defecation in the general population is not known, because unlike functional constipation which can be identified with symptoms alone, a diagnosis of dyssynergic defecation requires physiological tests that are only performed in a few centers.

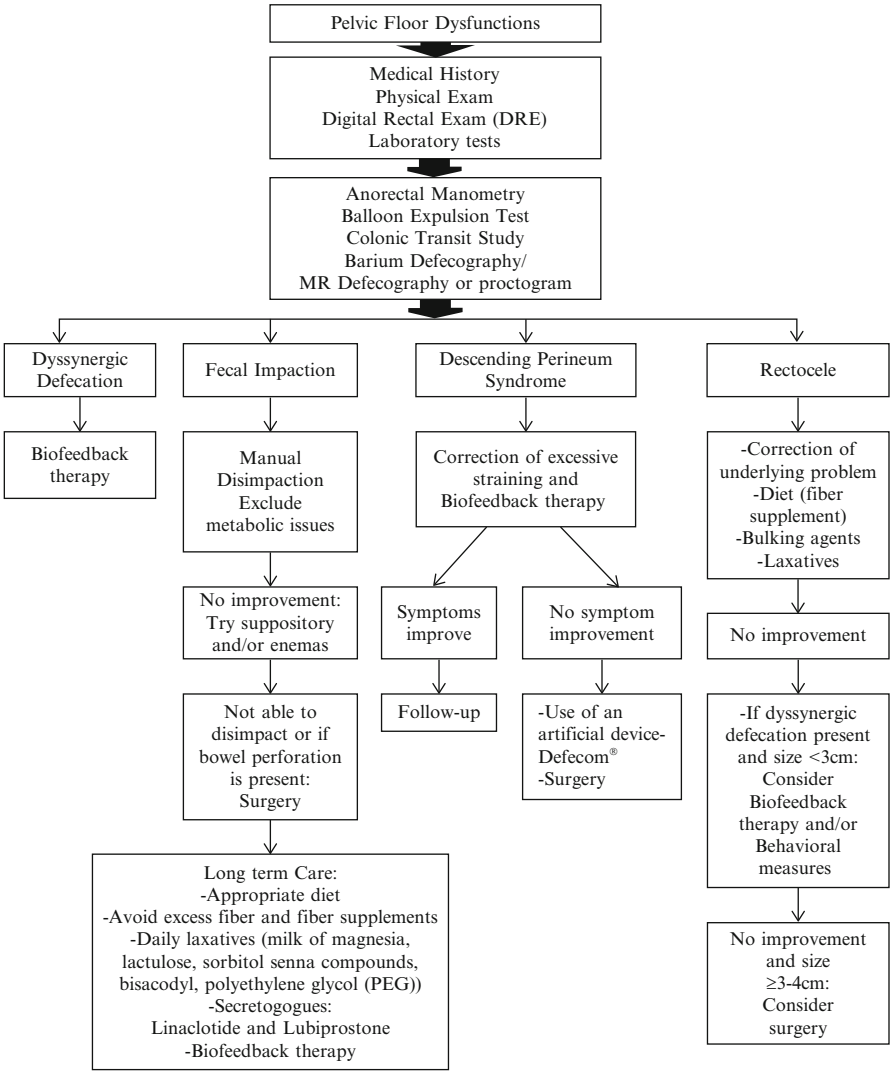

Fig. 6.1 Algorithmic approach for the evaluation and management of dyssynergic defecation, fecal impaction, descending perineum syndrome, and rectocele (Modified from: Schey R, Cromwell J, Rao SS. Medical and surgical management of pelvic floor disorders affecting defecation. Am J Gastroenterol. 2012 Nov;107(11):1624–33, with permission)

Pathophysiology

Dyssynergic defecation is defined as inappropriate contraction of the pelvic floor or less than 20% relaxation of basal resting sphincter pressure with adequate propulsive forces during attempted defecation by Rome Criteria (Rome III) (Table 6.1).

Table 6.1 Rome III criteria for dyssynergic defecation

A.	Fulfill the diagnostic criteria for functional chronic constipation (Rome III)
B.	Repeated demonstration of dyssynergic defecation pattern during anorectal manometry (type I–IV) or EMG recordings
C.	One or more of the following criteria during repeated defecation attempts
	1. Inability to expel an artificial stool or 50 cm^3 warm water-filled balloon within 1 min
	2. A prolonged colonic transit time (greater than five markers [>20% marker retention] on a plain abdominal radiograph taken 120 h after ingestion of one Sitzmark® capsule containing 24 radiopaque markers)
	3. Inability to evacuate or >50% retention of barium during defecography

Modified from Rao SS. Dyssynergic defecation and biofeedback therapy. Gastroenterol Clin North Am 2008; 37(3):569–86, with permission

Patients with dyssynergic defecation demonstrate impaired coordination of pelvic floor, including the abdominal and rectoanal sphincter muscles; manometrically this comprises failed anal relaxation or paradoxical increase in anal pressures or failure to increase intrarectal pressures to evacuate stools, i.e., impaired push effort. Impaired rectal sensation may also be seen in 50% of subjects with dyssynergic defecation [2, 3].

Dyssynergia is an acquired problem; approximately one third subjects describe this from childhood indicating that they may have never learnt the proper art of defecation, and the remaining two thirds develop this during adulthood [4]. Precipitating factors in adults include pregnancy and childbirth, surgeries, illnesses, excessive and prolonged straining, anorectal disorders, psychologic stress and anxiety, and physical abuse (32% in women) and sexual abuse (22% in men and women). In 40% of patients there was no identifiable cause for dyssynergic defecation.

Clinical Presentation

Patients with dyssynergic defecation present with several bowel symptoms. In a prospective study, excessive straining was reported as the most common symptom in 84% of patients while 76% reported a feeling of incomplete evacuation and 74% bloating [4]. Women reported excessive straining and incomplete evacuation more commonly than men. Digital maneuvers were more commonly reported by women (54%) than men (25%). Hard stools were another symptom reported more frequently by women (60%) than men (41%). In a retrospective study of 212 patients with intractable constipation, 25 (12%) had dyssynergic defecation, and of these 8 (32%) of patients were found to have upper gastrointestinal tract transit disorders (delayed gastric emptying) [5]. Also another prospective study revealed that patients with pelvic floor dysfunction demonstrated higher prevalence of backache (53%) and lower prevalence of normal stool frequency (19%), history of anorectal surgery (7%) and heartburn (12%) than controls with normal pelvic floor function [6].

Patients with dyssynergic defecation also exhibit significant psychological distress as evidenced by high scores for hostility and paranoid ideation when compared to

patients with slow transit constipation or healthy controls and demonstrate significant impairment of quality of life [7]. Many patients with anorexia nervosa and constipation and those with anorectal pain also show features of dyssynergic defecation [8].

Diagnosis and Evaluation

Dyssynergic defecation may be an isolated pathophysiological problem or may coexist with other structural abnormalities such as rectal prolapse, rectal mucosal intussusception, rectocele, enterocele, DPS, or solitary rectal ulcer syndrome (SRUS) [9] and needs to be differentiated in order to embark upon appropriate therapy [10]. After excluding pathologic and metabolic disorders that cause constipation, a diagnosis of dyssynergic defecation is based on fulfilling the symptomatic criteria of functional chronic constipation (Rome III), and the presence of dyssynergia, as demonstrated by manometry or EMG along with one or more of the following abnormal findings: Abnormal balloon expulsion test (BET), incomplete evacuation during defecography, or a delay in colonic transit time [3, 4]. An algorithmic approach for evaluation and management of dyssynergic defecation is shown in Fig. 6.1.

Digital Rectal Exam

Digital rectal examination (DRE) is an important diagnostic tool that can be performed at bedside. DRE may show presence of stricture, spasm, tenderness, mass, blood, or stool. If stool is present in rectum, patients should be asked about their awareness of stool. Failure of awareness may suggest rectal hyposensitivity. Resting anal sphincter tone is assessed as the next step followed by an assessment of squeeze tone. Next the patient is asked to push and bear down as if to defecate. Normally, the examiner should feel relaxation of the external anal sphincter and/or the puborectalis muscle, together with perineal descent. Failure of this normal finding should raise a suspicion of dyssynergic defecation or an evacuation disorder. The examiner must also place his/her hand on the patient's abdomen to assess the push effort. DRE has a sensitivity of 75% and specificity of 87% for detecting dyssynergia [11]. Unfortunately this examination is not performed by most physicians and trainees and merits emphasis during medical training [12].

Anorectal Manometry

Anorectal manometry is essential for a diagnosis of dyssynergic defecation. It is the most reliable way of detecting dyssynergic defecation especially when the patient is asked to attempt defecation on a commode [13, 14]. During a bearing down maneuver or defecation attempt, intrarectal pressure increases ($\geq$40 mmHg), accompanied

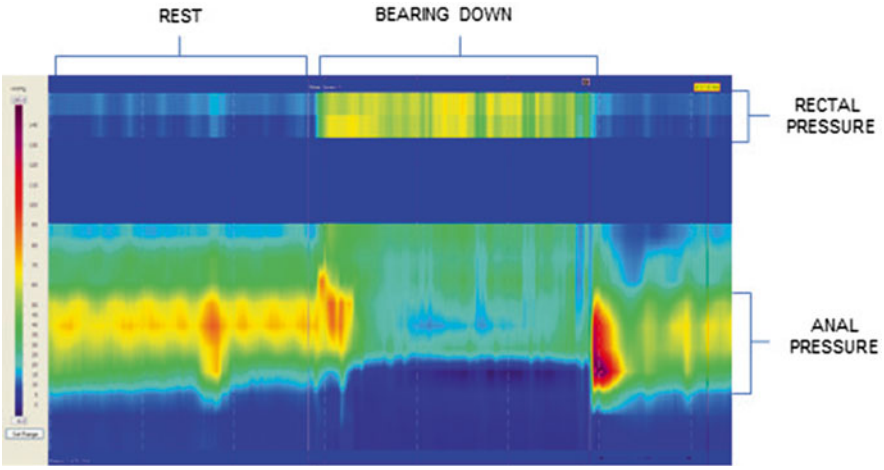

Fig. 6.2 Typical example of high-resolution manometry pattern showing normal defecation pattern

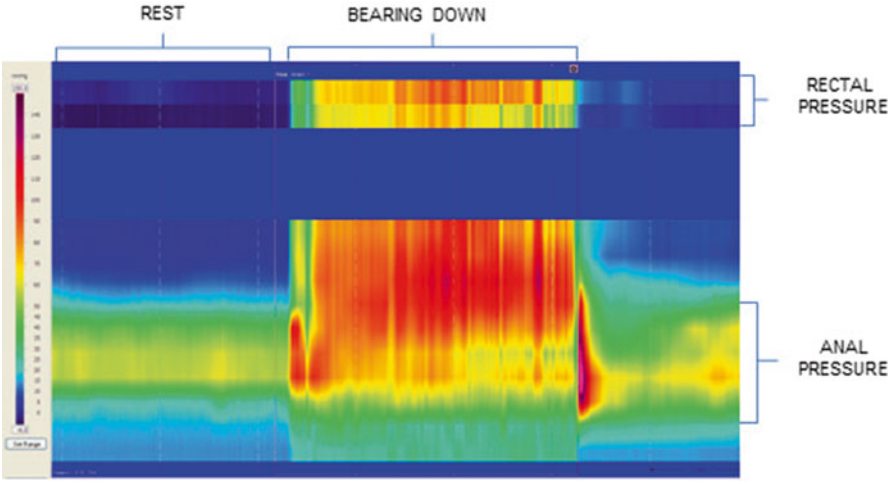

Fig. 6.3 Typical example of high-resolution manometry pattern showing Type I dyssynergia in a patient with dyssynergic defecation

by adequate decrease (>20%) in external anal sphincter pressure coinciding with the relaxation of external anal sphincter (Fig. 6.2). In dyssynergic defecation, this voluntary and learned response is impaired or uncoordinated; there is either inadequate increase in rectal pressure or impaired anal relaxation, or paradoxical anal sphincter contraction, or combination of these mechanisms. At least four types of dyssynergia patterns have been recognized by Rao et al. [14].

Type 1: There is adequate push effort (rise in rectal pressure) with paradoxical anal sphincter contraction and increase in anal sphincter pressure (Fig. 6.3).

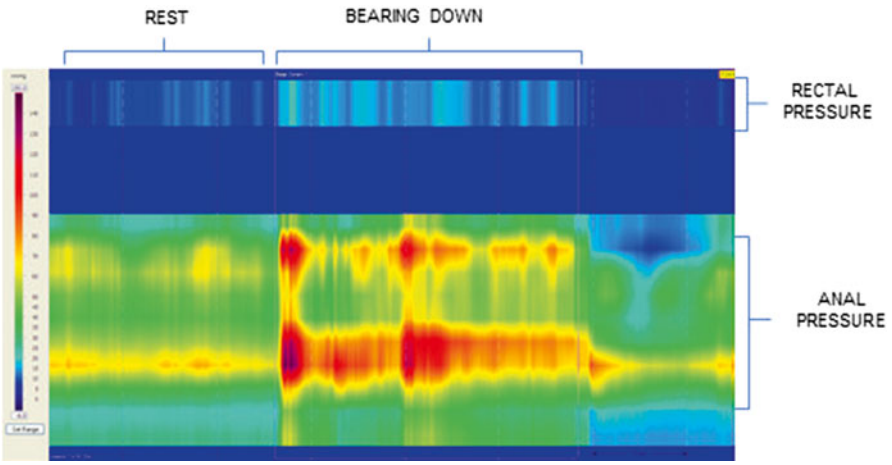

Fig. 6.4 Typical example of high-resolution manometry pattern showing Type II dyssynergia in a patient with dyssynergic defecation

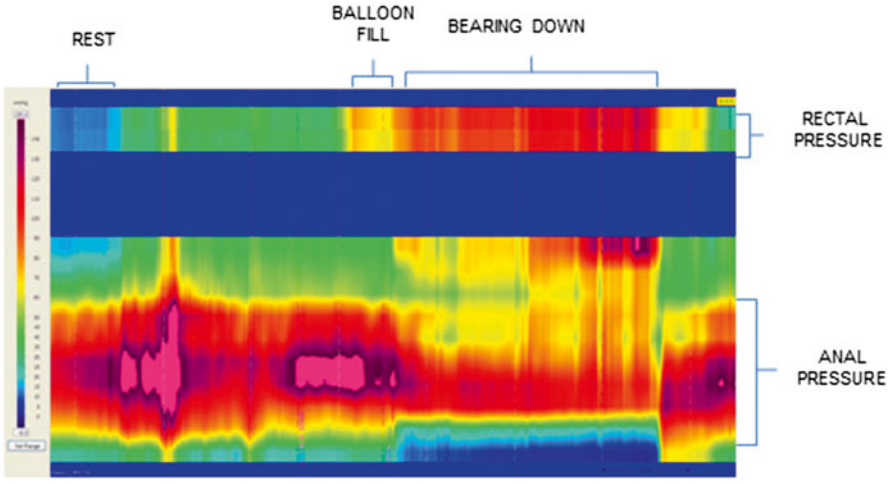

Fig. 6.5 Typical example of high-resolution manometry pattern showing Type III dyssynergia in a patient with dyssynergic defecation

Type 2: There is inadequate push effort (unable to generate rise in rectal pressure) with paradoxical anal sphincter contraction and increase in anal sphincter pressure (Fig. 6.4).

Type 3: There is an adequate push effort (rise in rectal pressure); however, there is incomplete (<20%) or absent anal sphincter relaxation (Fig. 6.5).

Type 4: There is inadequate push effort (unable to generate rise in rectal pressure) and there is incomplete (<20%) or absent anal sphincter relaxation (Fig. 6.6).

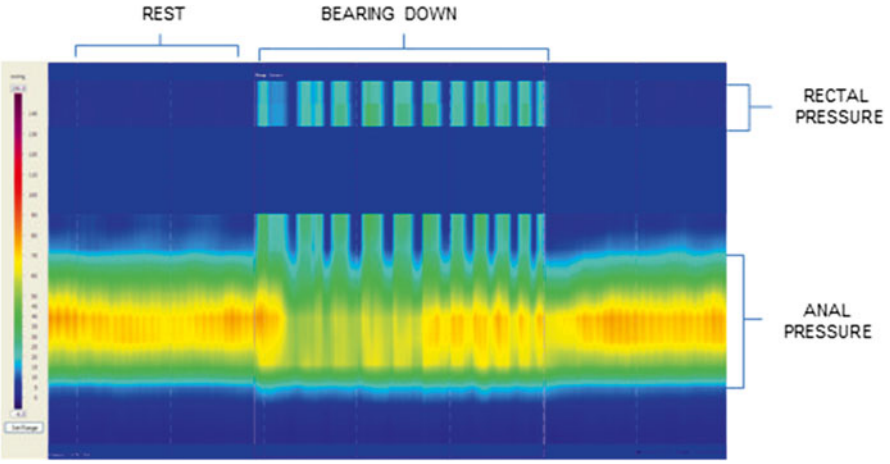

Fig. 6.6 Typical example of high-resolution manometry pattern showing Type IV dyssynergia in a patient with dyssynergic defecation

Balloon Expulsion Test

This is a useful screening test to identify patients with dyssynergic defecation. Although its specificity is high (80–90%), it has low sensitivity (50%). Test is performed by placing with a 4 cm long, balloon filled with 50 cm^3 of warm water or alternatively with a silicone-filled stool-like device fecom [15]. After placement in the rectum, the patient is given privacy and asked to bear down and expel the balloon/device. A stop watch is provided to assess the time required for expulsion. Normal healthy subjects can usually expel a balloon in less than 1 min [15].

Colonic Transit Study

Colonic transit study is considered positive if more than five (>20%) markers are retained in the colon on a plain X-ray film after 5 days (120 h) of ingestion of one capsule of Sitzmark® containing 24 radio-opaque markers [16]. Slow transit constipation may be present in two thirds of patients with dyssynergic defecation. Colonic transit study can differentiate patients who have isolated dyssynergic defecation and with slow transit constipation.

Wireless Motility Capsule Test (SmartPill®)

The Wireless Motility Capsule (WMC) (Smart Pill Corporation, Buffalo, NY) is a wireless pH, temperature, and pressure recording capsule. WMC significantly

correlates with colonic transit study and with radiopaque markers (ROM) [17]. This novel technique is ambulatory and can assess not only regional but also whole-gut transit time (gastric, small bowel, colonic) without radiation exposure. WMC is approved by FDA for the assessment of colonic transit in patients with suspected chronic constipation and in patients with suspected gastroparesis. This method is standardized and recommended as useful by the American Neurogastroenterology & Motility Society. However WMC cannot differentiate between slow transit constipation and dyssynergic defecation.

Defecography

Defecography is performed by asking a patient to sit on a special commode while undergoing video fluoroscopy. Prior to this, 150 mL of barium paste is placed in rectum, and the patient is asked to expel the barium. Although this test provides useful information about anatomic and dynamic changes of anorectum, because there is poor agreement between observers, and patients may be embarrassed during the test, defecography cannot be relied upon solely and often is used as an adjacent test for assessment of defecation disorders [18].

MR (Magnetic Resonance) Defecography

MR defecography is performed without radiation and with an open or closed system. This technique gives excellent details of all pelvic floor compartments, muscles, soft tissue, and supporting structures. In the open system the images are acquired when patient is in physiologic sitting position and thereby simulating true defecation, whereas in a closed system patient is lying or in a supine position [19, 20]. Recently dynamic MR defecography with an open-configuration and low-field tilting MR system was shown to detect pelvic floor disorders more accurately in orthostatic position than the supine position [20]. Although this technique gives useful information, it is not widely available.

Management

General Recommendations

Patients should avoid medications that cause constipation, such as calcium channel blockers, increase the exercise time, and increase the amount of water and fiber intake. Also patients should be encouraged to perform timed-toilet training. They should be advised to attempt a bowel movement two times a day preferably 30 min after meals or after waking up which are physiologic stimulants for the colon.

During every attempt they should push with a moderate effort (5–6 out of 10) for no more than 5 min. They should be discouraged from using digital maneuvers for stool. Additionally patients may require laxatives (magnesium, senna, prunes, bisacodyl), secretogogues (linaclotide, lubiprostone) or prokinetics such as prucalopride to facilitate stool delivery into the rectum as two thirds of patients with dyssynergic defecation have coexisting slow transit constipation. However, the mainstay of treatment is biofeedback therapy.

Biofeedback Therapy

The aim of biofeedback therapy is to correct dyssynergia and restore a normal pattern of defecation as well as improve rectal sensory perception. It is an instrument-based "operant conditioning" technique which is performed with the patient sitting on a commode and with a manometry or an EMG probe placed in the rectum. The goal is to develop a good push effort as demonstrated by an increased intrarectal pressure while simultaneously relaxing the pelvic floor, as evidenced by a decrease in anal pressures. After the patients' posture (keeping legs apart, leaning forward) and breathing effort (taking a good diaphragmatic breath) are corrected, the patient is asked to pay attention to the monitor. The monitor display gives the patient instant feedback on how the pressures are changing in the rectum and anal canal and thereby helps the patient to understand the physiological changes. This procedure is repeated 10–15 times in one session after filling the rectal balloon with 60 mL of air so that the patient has sensation of desire to defecate. The balloon is deflated and inflated between each attempt. At the end of session the balloon is deflated and the catheter is removed. Although typically 4–6 sessions, each 2 weeks apart, and 1 h in duration are performed, the duration, number of sessions, and the number of bearing down attempts during each session is usually customized for each patient based on individual needs. Reinforcement is usually performed at 6 weeks and at 3 and 6 months.

Simulated defecation training is performed with either an artificial stool such as fecom or a 50 mL water-filled balloon. The patient is asked to sit on a commode and expel the balloon, and assistance is provided on how to relax and coordinate the pelvic floor muscles.

Sensory training is performed to improve rectal hyposensitivity and promote better awareness of stool. Here the balloon is inflated until the patient feels an urge to defecate, and the threshold volume is noted. After the sensation is triggered with the same volume 2–3 times, the volume is gradually decreased by 5–10% with the hope of triggering the same sensation but with a lower volume. In case the patient fails to perceive the lower volume or reports a significant change in perception, the same or previously perceived higher volume is applied to help train the patient. The end goal is that through repeated inflations/deflations new sensory thresholds will be established. The balloon inflation can be performed either with a syringe or with a barostat, and a recent randomized study showed that barostat-assisted sensory training may be superior [21]. The biofeedback therapy may be performed by solid-state manometry catheter or with systems like EMG probes, or balloon defecation training or home biofeedback training devices [22].

Outcomes and Future Directions

The mechanism(s) through which biofeedback therapy improves bowel dysfunction is unclear. Early studies indicate that biofeedback therapy improves gut and brain interactions and thereby improves physiology and symptoms [23]. Biofeedback therapy has been shown to be more effective than sham therapy, laxatives, and standard therapy in patients with dyssynergic defecation [24–29]. Biofeedback therapy also improved bowel symptoms and anorectal sensation in the long term whereas standard therapy was ineffective [30]. The biofeedback therapy can also be performed at home. Therapy is performed by using a home device inserted into rectum and attached to a liquid crystal display (LCD) screen box which allows the patient to visualize their own performance. Home biofeedback therapy has been reported to be as effective as office biofeedback therapy but needs further validation [22].

Fecal Impaction

Epidemiology

Fecal impaction is the abnormal accumulation of large amounts of hard and compacted stool in the rectum/distal colon typically over several days to weeks together with the inability of the individual to pass these stools. The exact incidence and prevalence of fecal impaction is not known and the literature is very limited concerning its epidemiology. Fecal impaction is common in older patients and in one study was reported to occur in 40% of hospitalized older patients [31].

Pathophysiology

Chronic constipation is the main mechanism underlying fecal impaction and its pathophysiology is similar. Slow transit constipation together with dyssynergic defecation may predispose to this condition, particularly in elderly [32]. Also rectal hyposensitivity, either a primary problem or as a result of certain psychosocial and behavioral factors like decreased mobility, drugs, and others may lead to stool impaction [32]. In one study, abnormal rectal sensation with increased rectal compliance was described [33]. The factors contributing to fecal impaction are listed in Table 6.2.

Clinical Presentation

Fecal impaction usually presents with lower abdominal pain, distention, nausea, vomiting, and overflow incontinence, and in severe conditions; with colonic obstruction, stercoral ulceration, and bowel perforation, which can be life threatening [31]. Other presentations include anorexia, urinary frequency, urinary overflow incontinence, nausea and vomiting, gastroparesis, and megarectum [34, 35].

Table 6.2 Causes of constipation related to fecal impaction

Constipating medications	Neurological diseases	Other reasons
• Iron	• Cerebrovascular disease and stroke	• Dehydration
• Calcium channel blockers	• Parkinson's disease	• Immobility
• Antidepressants	• Multiple sclerosis	• Bed restraint
• Narcotics	• Autonomic neuropathy	• Mechanical obstruction
• Opioids	• Spinal cord lesions	• General weakness
• Anticholinergics	• Dementia	
• Antacids	Endocrine and metabolic diseases	
• Chronic laxative use	• Diabetes mellitus	
• Diuretics	• Hypothyroidism	
• Antihistamines	• Hyperparathyroidism	
• Anti-parkinsonian drugs	• Chronic renal disease	
	Myopathic diseases	
	• Amyloidosis	
	• Scleroderma	

Modified from Rao SS, Go JT. Update on the management of constipation in the elderly: new treatment options. Clin Interv Aging. 2010 Aug 9;5:163–71, with permission

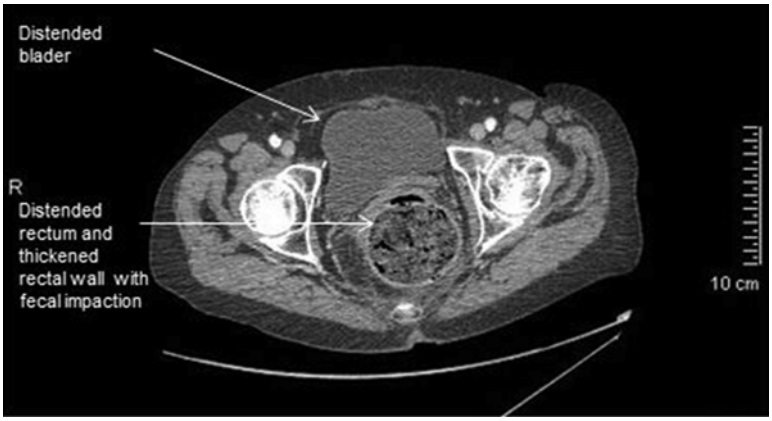

Fig. 6.7 This computed abdominal tomography scan image taken from a patient who presented to the emergency room with fecal impaction. The coronal image shows a distended rectum (8 cm) loaded with impacted stool, and thickened, edematous rectal wall

Diagnosis and Evaluation

On abdominal examination stool is usually palpable. Rectal examination may reveal impacted stool, but rarely the stool may be more proximal, if so a plain abdominal X-ray is required [34]. Sometimes a computerized abdominal tomography scan may be performed to evaluate abnormal pain and distention revealing fecal impaction (Fig. 6.7). The evaluation of fecal impaction is similar to that of patients with constipation, but evaluation should be deferred until disimpaction of stool has been achieved. Subsequently, appropriate colonic and anorectal function tests should be

performed to look for dyssynergic defecation [32]. Routine complete blood count, metabolic profile, calcium levels, and thyroid functions should be performed, along with a flexible sigmoidoscopy or colonoscopy. If no secondary cause is identified, colonic transit study, anorectal manometry, and BET should be performed to identify an underlying defecation disorder.

Management

An algorithmic approach for evaluation and management of fecal impaction is shown in Fig. 6.1. Fecal impaction should be removed and disimpacted manually. Stool softeners and enemas or suppositories may be needed if the impaction is located more proximally; however, stool softeners have limited efficacy [36]. Surgery may be needed if disimpaction cannot be managed manually or bowel perforation is present [37].

Once impaction is managed, patients should be placed on appropriate dietary regimen. Excess fiber and fiber supplements should be avoided. Patients must receive aggressive daily treatment with a laxative such as milk of magnesia, lactulose, sorbitol, senna compounds, bisacodyl, or polyethylene glycol (PEG). Similarly lubiprostone and linaclotide may be beneficial. However there are no studies of laxatives in patients with fecal impaction. In patients with dyssynergic defecation, biofeedback therapy is the treatment of choice. Biofeedback therapy was shown to be effective in dyssynergic defecation in randomized controlled trials [24–27]. However the efficacy of biofeedback has not established in elderly patients or in fecal impaction.

Outcomes and Future Directions

Further multicenter cooperative studies are needed to assess the epidemiology and pathophysiology of fecal impaction, in particular its etiology. There is also lack of information regarding outcomes of interventions and identification of a best clinical approach. Randomized controlled trials are needed for developing optimal approach to management.

Descending Perineum Syndrome

Epidemiology

DPS is the excessive descent of the perineum, several centimeters below the bony outlet of the pelvis during a straining effort [38]. The syndrome was first described by Parks et al. [39]. The exact prevalence of this syndrome is not known.

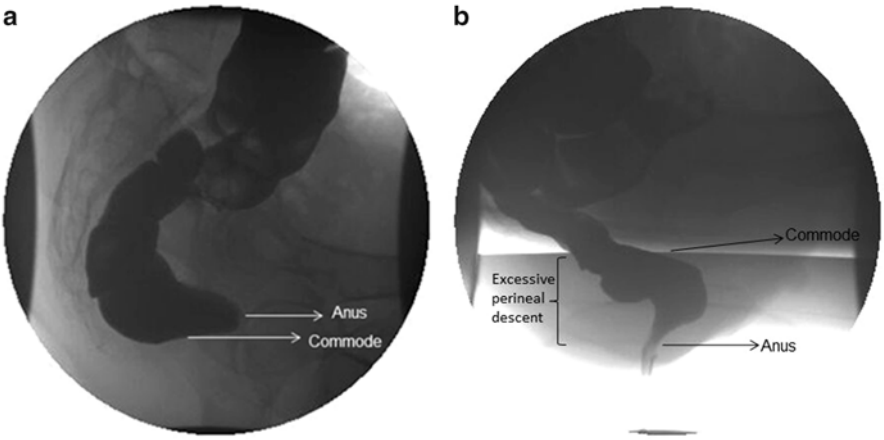

Fig. 6.8 Typical example of a defecography images showing the anorectal morphology at rest (**a**) and during a bearing down maneuver (**b**). When bearing down, it can be seen that there is excessive descent (>3 cm) of the perineum and anorectal junction

Pathophysiology

DPS is associated with pelvic floor weakness [40]. This condition is usually associated with other anorectal disorders such as rectocele, SRUS, enterocele, or rectal prolapse.

Clinical Presentation

The patient may present with rectal and perineal pain, prolonged and excessive straining, and feeling of incomplete evacuation and blockage during defecation and/or fecal incontinence [39, 41]. Passage of mucus and tenesmus are also common symptoms of DPS.

Diagnosis and Evaluation

This condition can be diagnosed with physical examination, 3-D high definition manometry, or with barium/MR defecography. A ≥3 cm descent of the perineum during straining or >4 cm descent at rest is diagnostic of DPS. On defecography, in healthy subjects the anorectal angle is approximately 90° and the angle increases with nearly complete loss of puborectalis impression during straining [42]. In patients with DPS, the anorectal angle is more than 130° at rest and increases to more than 155° during straining (Fig. 6.8a, b). A perineometer may also be useful

Fig. 6.9 Defecom®

for diagnosis as this can measure the length of perineal descent [43]. Open configuration MR systems provide valuable information about pelvic floor structure and the DPS; however, it is not widely available [44]. An algorithmic approach for evaluation and management of DPS is shown in Fig. 6.1.

Management

Treatment is mostly behavioral and consists of correcting excessive straining and dyssynergia. Pelvic floor retraining may be useful and the extent of perineal descent may be a good predictor of its efficacy [40]. Surgical options have been recently discussed for DPS. In one retrospective study, nine patients underwent "retro-anal levator plate myorrhaphy (RLPM)" [45]. There was a mean reduction of perineal descent of 1.08 cm, and surgery apparently improved stress urinary incontinence, urgency, dysuria, fecal incontinence, dyschezia, dyspareunia, perineodynia, cystocele, and rectocele. However randomized controlled trials are needed. Stapled Trans-Anal Rectal Resection (STARR) and Stapled Trans-Anal Prolapsectomy, associated with Perineal Levatorplasty (STAPL), are other surgical procedures performed. Both techniques were found to be safe and effective; however, STARR had caused less postoperative pain and better clinical outcomes upon reevaluation with postoperative defecography and manometry compared to STAPL [46]. Another study [47] also showed that STARR is safe and effective. An artificial device—defecom®—a polycarbonate plate with two separate holes for passing urine and stool as well as a built-in hump which supports the perineum when sitting on a commode may also be a good supportive approach (Fig. 6.9). The defecom® together with biofeedback therapy may improve symptoms in ~50% [48]. It is not FDA-approved and is not available in the USA.

Outcomes and Future Directions

At present, there is no standard or approved medical, behavioral, or surgical therapy for DPS. Future efforts should be directed towards a better understanding of the pathophysiology, a better characterization of the phenotype, prevalence and coexisting problems, and to perform well-designed prospective controlled therapeutic trials.

Rectocele

Epidemiology

Rectoceles are usually asymptomatic and hence its true prevalence is unknown [49]. Prevalence in the USA female population is reported to be 23.7% in a cross-sectional analysis among women participating in the National Health and Nutrition Examination Survey between 2005 and 2006. In a cohort study on young nulliparous women the prevalence was 12% and pouch size ranged from 10 to 25 mm [50]. Postmenopausal women also show rectoceles even in those who are nulliparous [51, 52]. According to an epidemiologic study, there is no difference in prevalence of rectocele between urban and rural females [53]. Increased age was found to be a risk factor for rectocele [54]. In one study, increased age (>50 years) was shown to be associated with a higher prevalence of significant rectocele; however, parity and type of delivery were not found to be correlated with the prevalence of rectocele [55]. Although age is a risk factor for the development of a significant rectocele, younger (18–24 year) nulliparous women also were found to have a rectocele [50].

Pathophysiology

Rectocele is the saccular protrusion of the rectal wall usually towards the vagina through the separations or tears of the fascia in the rectovaginal septum (anterior wall) and rarely towards the sacrum (posterior wall). Rectocele can be classified according to their anatomical position and size [56]. High rectoceles are associated with loss of support from the uterine body, mid rectoceles lack support of the pelvic floor, and low rectoceles result from weakness of the perineal body. Rectoceles can also be classified according to their size. Rectocele >2 cm is regarded as a cut-off value for a clinically significant problem.

Defects or weakness of the rectovaginal septum is believed to be the main cause [49]. Excessive straining and also vaginal delivery with instrument use (i.e., forceps) during delivery may cause weakness or defects in the rectovaginal fascia, weakness of the pelvic floor muscles, and damage to the pudendal nerve. As a result, the pelvic floor is weakened and the vaginal outlet becomes bigger. As vagina cannot close

during straining, the pressure gradient between the rectum (high pelvic pressure) and vagina (low atmospheric pressure) increases. The pressure gradient pushes the anterior rectal wall towards the vagina eventually causing rectocele.

Pelvic floor disorders were found to be more common in women, and associated with ageing, pregnancy, parity, and instrumental delivery [57]. Also factors like high body mass index, chronic obstructive pulmonary disease, and chronic constipation which causes increase in the intraabdominal pressure can also trigger rectocele formation [50]. A higher body mass index and a history of constipation were associated with rectocele; suggesting that the condition is multifactorial and that some rectovaginal defects might be congenital. A previous study showed no difference in physiological testing with regard to maximum resting and squeeze anal pressures in patients with or without rectocele. However in a more recent study, paradoxical anal sphincter contraction was found to be higher (60%) in patients with rectocele than patients without rectocele (24%) suggesting a correlation between rectocele and dyssynergic defecation [58]. Also, hysterectomy and intussusception have been found to be associated with rectoceles [52].

Clinical Presentation

Rectoceles that are <2 cm are usually clinically inconsequential; however, those that are >2 cm may be clinically significant. Small rectoceles are usually asymptomatic. However, rectocele size was not significantly related to demographic data, parity, or patient's symptoms [59]. The size or the position of the rectocele was also not correlated with the severity of symptoms. Only the emptying of rectoceles was found to correlate with the size, i.e., large rectoceles were associated with impaired emptying. Large rectoceles may be associated with symptoms of incomplete evacuation, prolonged straining, vaginal splinting, and rectal pain [56]. Dyspareunia, anorectal/vaginal pain, fecal soiling, and urologic symptoms are also reported by patients with rectocele [60].

Diagnosis and Evaluation

DRE performed during a straining maneuver may reveal out-bulging of the anterior rectal wall. A combined vaginal and DRE may also be more helpful in the diagnosis of rectocele. Posterior rectocele is usually difficult to detect but can be identified radiologically.

Defecography is considered as the gold standard for the diagnosis of rectocele (Fig. 6.10). It also reveals other pathologic findings such as excessive perineal descent and rectal mucosal intussusception. Because rectocele is commonly reported on a defecogram even in healthy women, a clinical diagnose should be based both on symptoms and defecography [61]. However, defecography findings cannot predict the clinical outcome of surgery [62]. MR not only detects rectocele, but can also

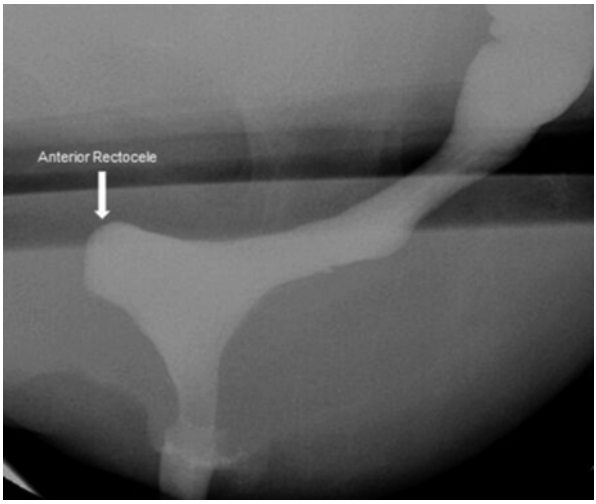

Fig. 6.10 Typical example of a defecography image showing an anterior rectocele during a bearing down maneuver

provide dynamic multicompartment evaluation of the pelvis when both the dynamic and static sequences are used together [63, 64]. A real-time continuous imaging with a dynamic true fast imaging with steady-state precession (FISP) sequence is suggested to be included in MR studies to evaluate pelvic floor dysfunction [65]. A recent study comparing dynamic anal endosonography and MR defecography in pelvic floor disorders revealed that the two techniques were similar with regard to the sensitivity, specificity, or positive and negative predictive values for detecting these disorders [66]. However, more internal anal sphincter defects were detected by dynamic anal endosonography, and this technique was reported to be better tolerated by patients when compared to dynamic MR or conventional defecography. In one study rectocele <2.5 cm was found in 55% of patient with dyssynergic defecation diagnosed by anorectal manometry [60, 67]. An algorithmic approach for evaluation and management of rectocele is shown in Fig. 6.1.

Management

The first approach is the correction of any underlying problem. Diet with fiber supplement, bulking agents, laxatives, behavioral therapy, and timed-toilet training may be helpful. If dyssynergic defecation is an underlying problem, biofeedback therapy is indicated before surgery. The underlying occult disorders like psychological distress, anismus, and rectal hyposensitivity should be corrected before considering surgery since this can affect the outcome of surgery [60, 68]. Patients who are symptomatic and who do not respond to conservative treatment and have a large rectocele (>3 or 4 cm) or have coexisting vaginal prolapse may be suitable candidates for surgery [69]. Posterior colporrhaphy is the standard surgical procedure which can provide cure rates of up to 95% [70]. Both transanal and transvaginal techniques

have been found to be effective in rectocele repair and may avoid postoperative dyspareunia; however, the transanal technique was associated with greater recurrence of rectocele [71]. The use of native tissue or a mesh seems to have similar outcomes when repairing a rectocele, but native tissue is generally regarded as the gold standard [72]. A recent study showed that transperineal repair of rectocele is superior to transanal repair [73]. Transperineal repair was also found to improve the functional outcomes and sensory thresholds such as urge to defecate. When a levatorplasty was added to the transperineal approach, the overall bowel function score increased significantly, but there were unwanted side effects such as dyspareunia.

Enterocele and Cystocele

Enterocele is the herniation of the peritoneum-lined sac usually filled with small intestine into the rectovaginal space. Sometimes sigmoid colon may also herniate into this space. It may present alone but often occurs along with rectocele, excessive perineal descent, or rectal prolapse [74, 75]. Associated risk factors include previous hysterectomy and pelvic surgery [75]. Symptoms are pelvic pain and incomplete or obstructed defecation. Although physical examination may reveal an enterocele, defecography is the best method for diagnosis often with oral contrast. Defecography reveals a barium-filled ileal loop between rectum and vagina [42]. Dynamic MR is more sensitive but not widely available.

Conservative treatment and biofeedback should be considered as the first treatment option although data is lacking. Surgery may be needed if the patient has persistent and intractable symptoms, and rectal or vaginal ulceration is present. There are transvaginal and transabdominal surgical approaches, both seem to be somewhat effective [76, 77]. In one study correction of pelvic support defects with abdominal approach was found to be more effective than a vaginal approach [78].

Cystocele is the prolapse of bladder into perivaginal space as a result of weakness of structures supporting the anterior vaginal wall [79]. Factors that contribute to cystocele formation include congenital defects in fascia, increase in intraabdominal pressure, and childbirth or obstetric injury. Anterior colporraphy is the preferred procedure for repairing a cystocele in symptomatic patients, but lacks randomized controlled trials [80].

Outcomes and Future Directions

Although common, there is a significant dearth of information regarding the origin and pathogenesis of rectocele, enterocele, and cystocele. Demographics and phenotypes remain unclear and likewise who needs a rectocele, enterocele, or cystocele surgically repaired, and when, and through which means, remains to be defined through prospective controlled studies.

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Chapter 7
Constipation and Special Considerations: The Elderly, Children, Pregnancy, Spinal Cord Injury, Metabolic Disorders and Systemic Diseases, Opioid-Induced, and History of Abuse

Suzanne Rose

Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Describe situations where the diagnosis and management of constipation have unique features.
2. Differentiate secondary causes of constipation from primary causes.
3. Evaluate patients in light of special circumstances related to their current health or psychosocial situation.

Key Points

1. There are many causes of secondary constipation with either comorbid illnesses, external circumstances, or medications that impact the gastrointestinal tract resulting in the symptom of constipation.
2. The symptom of constipation occurs commonly in the elderly, adversely affecting quality of life.
3. The etiology of constipation in children may be anatomic/developmental, neurologic, obstructive, endocrinologic/metabolic, or functional.
4. Hormonal factors appear to be the key influences related to constipation in pregnancy.
5. Constipation is a significant complaint experienced by patients with spinal cord injury.
6. Patients with some systemic diseases may experience constipation as a symptom, and in some cases patients may present initially with constipation as a manifestation of another problem.

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7. Although tolerance to pain alleviation occurs with long-term use of opioid drugs, there is no development of tolerance to the GI side effects, including constipation.
8. Prevalence of abuse history is higher in patients with the most severe symptoms and who are evaluated in tertiary centers.

Introduction

This chapter reviews the presentation, evaluation, and management of constipation in special populations: the elderly, children, and pregnant women, and explores secondary causes of constipation. Prior chapters have addressed the primary causes of constipation: functional constipation, irritable bowel syndrome with constipation, colonic inertia, and pelvic floor dysfunction. A primary etiology indicates that the issue or problem relates directly to the gastrointestinal tract, although perhaps in a complicated relationship with the brain-gut access and other organ systems. There are many secondary causes of constipation whereby an illness or external circumstance (e.g., recent surgery) can result in the symptom of constipation. A section on psychosocial influences with a focus on a history of abuse is also included. This chapter is intended as an overview of selected issues that have been prioritized because the special populations involved have a high prevalence, and their special circumstances have a great impact on the well-being of patients.

Constipation in the Elderly

Epidemiologic data show that constipation is a common symptom of the elderly. Physiologic alterations that occur with advancing age affect the colon, including changes in mucosal cell growth, differentiation, metabolism, and immunity [1]. It should be noted, however, that changes in motility due to aging have not been supported by all studies; nevertheless, there are data suggesting that colonic motility may slow with aging *in women* [2].

Older patients, similar to younger ones, may experience different etiologies for the symptom of constipation. Because of comorbid disease and the highly prevalent use of many prescribed and over-the-counter medications, secondary causes of constipation related to medications should be considered (Table 7.1). Diseases such as diabetes mellitus and neurologic problems may also occur in the elderly; therefore, the symptom of constipation secondary to an illness or a metabolic problem should be considered via the history and physical examination. As with the younger cohorts, red flag symptoms (Table 7.2) should always prompt further evaluation.

Although IBS often presents in younger patients, the prevalence of diagnosis of IBS in older cohorts may in fact be similar [3]. Other primary causes of constipation are: chronic constipation, dyssynergia, or pelvic floor dysfunction (see Chap. 6 for details). Terminal reservoir syndrome or megarectum related to impaired sensation

Table 7.1 Common classes of medications causing constipation in the elderly

Pain medications	Opiates
	NSAIDS
	Tramadol
Antihypertensives	Calcium channel blockers
	Diuretics (furosemide and hydrochlorothiazide)
Psychiatric medications	Tricyclic antidepressants
	Antipsychotics (phenothiazines)
Antacids	Calcium-containing
	Aluminum-containing
Anti-Parkinsonian	Dopaminergic agents
Supplements and OTC	Calcium
	Iron
	Anti-histamines
Other	Bile acid resins
	Anticholinergic drugs
	Anti-convulsants

Table 7.2 Red flags and alarm symptoms in the evaluation of constipation

Alarm signs and symptoms
• Unexplained weight loss
• Anorexia
• Bleeding
• Family history of colon cancer
• Family or personal history of IBD
• Lack of improvement with therapy
• Unexplained change in bowel pattern
Risk factors for secondary constipation
• Comorbidities/illnesses
• Age >50
• Medications
• Female sex
• History of abuse
• Prior pelvic surgeries

can lead to fecal impaction as well as overflow incontinence, making this a distressing problem affecting quality of life. Patients with megarectum have high compliance of the rectum allowing stool to accumulate. Patients may require disimpaction. Although fiber is often considered a standard recommendation for patients with constipation, in those patients with megarectum, the goal should be to keep the rectum clear. This may require a low residue diet and a combination of laxatives and rectal therapies (suppositories and/or enemas). The symptom of incontinence, which can occur with overflow in this situation, can be particularly difficult for patients with mobility problems with the inability to maneuver to a bathroom; also the leakage of stool can affect the peri-anal skin, particularly in bed-bound patients.

Hospitalized elderly patients with constipation require special attention. One study showed via multivariate analysis that the use of laxatives at home was the only risk

factor for constipation while hospitalized [4]. Therefore hospitalists and admitting physicians should be aware of home bowel regimens for all hospitalized patients.

The symptom of constipation can affect the quality of life in the elderly. In a study of 126 community-dwelling elderly, those with constipation had lower scores for a variety of areas assessed on the Short-Form 36 quality of life instrument including functioning, mental health, and general health perception [5]. In another study it was found that treating constipation resulted in improved quality of life measures in patients with constipation and lower urinary tract symptoms [6].

Treatment of constipation in the elderly deserves similar consideration as in younger cohorts. As noted above, it is first important to assess if impaction is present. In general, increasing fluid intake has not been shown to affect bowel habits in non-dehydrated patients; however, because of medications, less food consumption, and even mobility or access issues, the fluid status of the elderly should be assessed and adjusted as necessary. Timed toileting may be of benefit. It is generally recommended to take advantage of the gastro-colic reflex by encouraging the patient to attempt a bowel movement 30 min after a meal. An algorithm suggested for the treatment of constipation in the elderly can be found in Fig. 7.1 [7].

Constipation in Children

Constipation in children is a very common complaint. Studies have shown a prevalence in the general population from 0.7 to 79% [8, 9]. The latter figure of 79% comes from a systematic review of 19 studies which, overall, found the median value to be 16% [9]. The symptom of constipation accounts for 5% of all pediatric out-patient visits and more than one quarter of the referrals to Pediatric gastroenterology [10]. The etiology of constipation in children may be anatomic/developmental (anorectal malformations), neurologic (spina bifida, Hirschsprung's), obstructive, endocrinologic/metabolic, or functional. Each of these etiologies will be examined in the sections that follow along with additional topics including: constipation in neonates, encopresis, slow transit constipation, syndromes associated with constipation, and surgical management of constipation in children.

Anatomic/Developmental Causes of Constipation in Children: Anorectal Malformations

Anorectal malformations occur in 1 out of every 4–5,000 live births, and they appear to be more common in boys than girls. Defects of embryological development can include anorectal stenosis, imperforate anus, or cutaneous or perineal fistula. These defects are usually diagnosed shortly after birth and the presentation may be constipation. The absence of the anus is usually noted when attempting to take a rectal

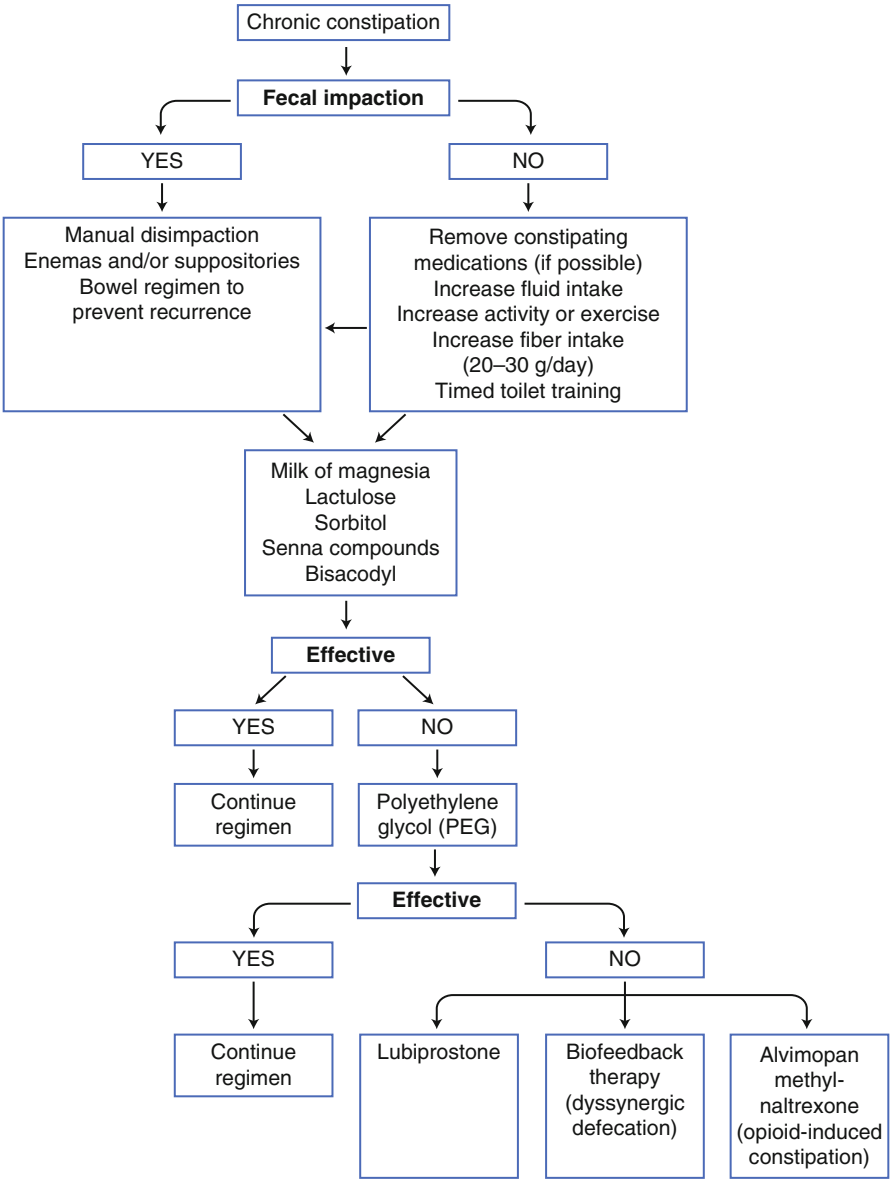

Fig. 7.1 Algorithm for the treatment of constipation in the elderly (Republished with permission of Dove Medical Press, Rao SS, Go JT. Update on the management of constipation in the elderly: New treatment options. Clin Interv Aging. 2010;5:163–171; permission conveyed through Copyright Clearance Center, Inc.)

temperature in the neonate with imperforate anus [11]. The treatment of these defects is surgical, but postsurgery medical management is complex and may be difficult. In some patients with imperforate anus, other anomalies may be present affecting multiple organ systems.

Neurologic Causes of Constipation in Children: Spina Bifida

Myelomeningocele or spina bifida is the result of a neural tube defect. This can lead to motor and sensory deficits in the lower extremities and can affect bowel and bladder function. Unlike Hirschsprung's disease (see below), the rectoanal inhibitory reflex (RAIR) is intact with a relaxation of the anal sphincter with rectal distention, but there is a lack of urge to defecate and therefore fecal incontinence may ensue [11]. Because of motor limitation in general, patients with spina bifida may be less active and there may be weak abdominal musculature; both of these factors can exacerbate constipation. These complex symptoms related to bowel dysfunction may lead to both fecal incontinence and constipation, and these dual symptoms make treatment considerations challenging.

Neurologic Causes of Constipation in Children: Hirschsprung's Disease

Hirschsprung's disease deserves special attention as an etiology of constipation in children. Although relatively rare, with an incidence of about 1 in 5,000, if recognized, it can be a treatable problem. Hirschsprung's disease represents a lack of ganglion cells in both the myenteric and submucosal plexuses of the distal colon. In fact, 80% of cases are limited to the rectosigmoid [11]. The bowel that is proximal to the aganglionic segment becomes dilated due the functional obstruction that follows.

The majority (>90%) of newborns with Hirschsprung's disease do not pass meconium within 24 h of birth. Children can present with symptoms of obstruction including abdominal distention, discomfort, vomiting, and refusing to eat. Those with short-segment Hirschsprung's may fail to be diagnosed until late childhood or even early adulthood; however, in most cases this disorder is diagnosed within the first 3 months of life. Diagnosis is made by rectal biopsy and manometry. On biopsy there will be a notable absence of ganglion cells, and cholinesterase staining will show hypertrophied nerves. The pathognomic finding on manometry is failure of the internal anal sphincter to relax after air insufflation into the rectum. This reflex is known as the RAIR and the RAIR is absent in Hirschsprung's disease.

Enterocolitis is a serious complication of undiagnosed Hirschsprung's disease [12]. The presentation may include fever, abdominal distention, explosive and foul-smelling stool, sometimes with bloody diarrhea. Enterocolitis is most commonly seen in the second or third month of life and carries a 20% mortality rate. It can also occur in the postoperative state [13].

Treatment for Hirshsprung's disease is surgical, with resection of the aganglionic segment and anastomosis of healthy colon with ganglion cells directly to the anal canal. Following surgery, constipation and/or fecal incontinence may follow in up to 50% of patients [11]. Anorectal stenosis may be a problem, but other considerations must be evaluated as some patients may have remaining aganglionic colon. Some patients are also thought to have functional megacolon.

Obstructive Constipation in Children

Obstructive causes of constipation can be related to developmental embryologic abnormalities or may be due to other conditions such as cystic fibrosis, cancer, pelvic mass, or postsurgical adhesions [10, 14]. Further details are beyond the scope of this chapter, but it is important to consider this etiology in children.

Endocrinologic/Metabolic Causes of Constipation in Children

There are many endocrinologic or metabolic causes of constipation in children. Some of these conditions will be considered later in this chapter, but it is worth mentioning visceral myopathy, diabetes, hypothyroidism, and porphyria [10].

Functional Constipation in Children

By definition, in the absence of structural problems or genetic or endocrinologic/metabolic disorders, the passage of less than two well-formed stools per week, with or without posturing behaviors of retention, is considered functional constipation in children [10]. There is a cyclical process of factors interacting to sustain the problem.

A three-phase treatment strategy for the treatment of constipation should be considered in children:

1. Complete evacuation if impaction present.
2. Sustained evacuation.
3. Weaning from interventions to promote bowel movements [14].

Family education is a key component of the treatment of constipation in children. Explanation of the problem and engaging the family in the treatment approach is most important. Three areas should be reviewed in particular with families: normal toileting, physical and psychological factors associated with constipation in children, and dietary factors [10].

Constipation in childhood often responds to stool softeners and/or stimulant laxatives coupled with behavioral therapies and education [15]. PEG 3350 has been shown to be significantly better than placebo in both producing improved bowel movement frequency and in decreasing fecal incontinence [16]. Children who have refractory symptoms, despite high dose PEG 3350 therapy and behavioral therapy, may benefit from stimulant laxatives. There is no definitive data to support the concerns of an earlier era that chronic use of stimulant laxatives leads to neuromuscular injury to the colon [15].

A systematic review of non-pharmacologic treatments for childhood constipation failed to find any advantage to water intake increases or prebiotics and probiotics. This same review found some evidence that fiber is more effective than placebo,

and it did not find that behavioral therapy with laxatives is be more effective than laxatives alone. The authors of this review noted the lack of any well-designed, randomized-controlled trials for the study of non-pharmacologic treatments in children with functional constipation. In fact there were no randomized studies for physical movement, multidisciplinary treatment, or alternative medicine [17].

In terms of overall prognosis for children with functional constipation, over 60% of children are found to be free of symptoms after 6–12 months. No factors have been identified for those children who have a poorer prognosis with persistent symptoms [18].

Constipation in Neonates

Bowel movement frequency can be variable for the young infant and baby. There are many factors, particularly dietary (breast-fed vs. formula), that may impact this. If constipation is evident early, it is important to evaluate for structural or developmental problems. Other diagnoses that must be considered in a baby include Hirschsprung's disease (as outlined above), neuronal intestinal dysplasia, pseudo-obstruction, and cystic fibrosis [10]. Upon exclusion of all of these causes, the next step would be to use a glycerin suppository which may soften the stool and facilitate passage of a bowel movement. This should be done under medical supervision and not for longer than 3 days. Another option is rectal stimulation, but routine manipulation is not recommended [14]. If the stool is found to be hard, barley cereal and vegetables with high fiber content and non-digestible sugars can be implemented in babies over 6 months of age. Due to toxicity, mineral oil, stimulant laxatives, and phosphate enemas should not be used in neonates and babies [19, 20].

Encopresis

Encopresis deserves special attention as it relates to constipation. By definition encopresis is repeated involuntary soiling unassociated with a structural defect or illness. Children should be continent of stool by age 4 and therefore the definition of encopresis by psychologists notes normal-size bowel movements passed in inappropriate places after 4 years of age [21]. Encopresis is a complex symptom with changes in anorectal function associated with psychological influences. Although this symptom relates to loss of stool, it is included in the discussion of constipation as this condition occurs in children with a history of withholding defecation that results in the stretching of the rectal wall and poor sensation. The development of encopresis may occur after an event of painful defecation, and in some cases, non-retentive encopresis is the result of a behavioral problem. There are also organic causes of encopresis related to anatomic, neurologic, metabolic, or iatrogenic etiologies. The treatment for encopresis may include disimpaction manually, with enemas or with PEG 3350 osmotic laxatives. Maintenance therapy combines both behavioral modification techniques and counseling along with medical therapy [21].

It should be noted that adults with developmental disabilities, as well as children, are more likely than the general population to have encopresis, constipation, and soiling. This can bring added stress to treatment and limit options for independent living for these individuals [22].

Slow Transit Constipation in Children

Slow transit constipation in children, first described in 1996, appears to occur similarly in boys and in girls. Laparoscopic biopsies in more than 200 children with slow transit constipation revealed that approximately one third of the patients had a deficiency of Substance P [23]. Treatment of slow transit constipation in children includes medical therapy, dietary advice, including the fact that a high fiber diet is not required and, in fact, may exacerbate symptoms. In patients with intractable constipation, an appendiceal stoma for antegrade enemas (see below) might be considered. Transcutaneous electrical stimulation may be a promising therapy [23].

Children with autism, with and without neurodevelopmental psychiatric diagnoses, appear to have earlier onset of constipation symptoms, a longer history of symptoms, and some have signs suggestive of slow transit constipation suggesting an inborn etiology. It has been proposed that perhaps there is a common genetic link of gut and behavioral abnormalities that might be of value for evaluation and treatment [24].

Syndromes Associated with Constipation in Children

There are a number of syndromes associated with the symptom of constipation in children. There have been some interesting studies of fingerprint patterns or dermatoglyphics in children with constipation. One study found an increased percentage of simple arches on fingers of children with early onset constipation [25]. A number of autonomic nervous system disorders, innervation disorders, muscular diseases, metabolic problems, connective tissue diseases, coordination disorders, water and electrolyte imbalance disorders, malformations, and chromosome translocations are associated with constipation in children [26]. Because syndromic forms of constipation are known to occur, this should be taken under consideration in young patients presenting with constipation. It appears as if genetic factors may play a significant role in some children with constipation. Nevertheless, it should be noted that less than 5% of children with constipation appear to have an underlying disease [27].

Surgical Management of Constipation in Children

The majority of children with constipation can be treated medically with laxatives, diet, and behavioral therapy. There are, however, instances where surgery is required.

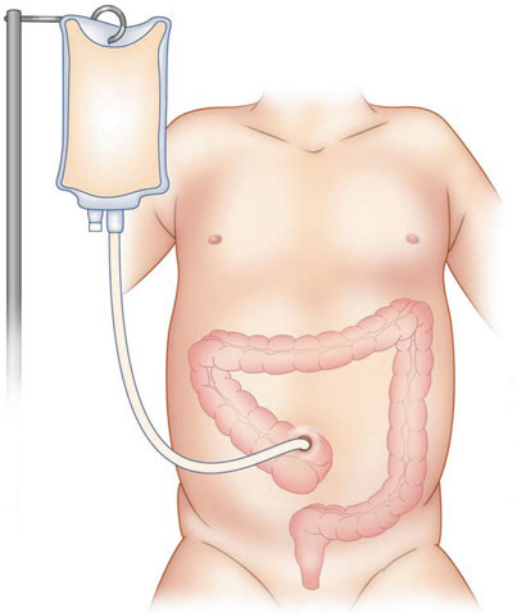

Fig. 7.2 Configuration of the Malone appendicostomy for antegrade enemas

As already noted above, certain developmental abnormalities of the anus as well as Hirschsrung's disease require a surgical remedy.

A unique option for children who require a daily enema is the creation of a continent appendicostomy (Malone procedure), and in some cases, where the antegrade continence enema (ACE) does not work, a permanent stoma. The creation of this continent appendicostomy involves a procedure whereby the appendix is connected to the umbilicus, and through this opening an enema can be administered (Fig. 7.2). Complications may occur and include strictures and leakage [28]. In one long-term follow-up study of ACE patients, success was seen in 69% of patients; 63% had a stoma complication and 33% required a surgical revision [29].

It should be noted that this Malone procedure allows for a different route to administer an enema. The key to success remains with the enema and bowel regimen. In highly selected cases, where the sigmoid is massively dilated and large quantities of enema are required, a segmental resection of the colon may be indicated [28]. These patients require careful follow-up as dilation of the remaining colon may occur.

Constipation and Pregnancy

Symptoms related to the gastrointestinal tract are common in pregnancy. Although nausea is the number one GI complaint during pregnancy, constipation is the second most common complaint. In a study of 103 pregnant women, it was found that

Table 7.3 Factors affecting constipation in pregnancy

Hormones
• Sex hormones affect gastrointestinal transit times
• Sex hormones affect gastrointestinal motility
• Sex hormones affect smooth muscle
Mechanical factors
• History of gynecologic surgery with adhesions
• Intestinal malrotation later in gestation
• Levator ani damage
Diet, supplements, water
• Iron
• Calcium
Activity
• Reduced in pregnancy

constipation prevalence was 24%, 26%, 16%, and 24% in the first, second, third trimesters, and 3 months postpartum, respectively. This study also looked at the diagnosis of IBS and found the prevalence to be: 19%, 13%, 13%, and 5% at the same time intervals. Using multivariate longitudinal analysis, it was determined that iron supplementation and a history of past treatment for constipation were the two primary factors associated with constipation in pregnancy [30]. This study also noted that the symptom of constipation was less associated with infrequency and more related to straining, hard stools, and incomplete evacuation. Other studies confirm the high prevalence of constipation in pregnancy with some reporting over 40% of pregnant women experiencing this symptom, and even higher percentages reporting straining with defecation [31, 32].

The factors that may impact this symptom in pregnancy are outlined in Table 7.3. It is generally accepted that hormonal factors are the key influences related to constipation in pregnancy [33]. There have been studies that have evaluated the effect of the menstrual cycle on colonic transit times [34, 35]. Although no differences were found between the luteal and follicular phases or with male controls, the studies were of small sample size and are therefore limited value. It should also be noted that the progesterone rise in pregnancy is much greater than that seen in the luteal phase. In another study looking at sex hormone levels in constipated patients, it was found that constipated patients had reduced levels of steroid hormones. The authors of this study hypothesized that the reason may be related to delayed transit with altered enterohepatic circulation and breakdown of these hormones, rather than a primary cause [36].

It appears that hypomotility may occur due to intestinal smooth muscle relaxation related to progesterone. How this is facilitated at the physiologic level is not entirely clear, but there is suggestive evidence that hypomotility may result from increased release of nitric oxide, down-regulation of stimulatory G-protein expression, and/or up-regulation of G-protein inhibition [37, 38]. Utilizing the lactulose hydrogen breath test as a measure of transit time to the colon, Wald et al. found an increase in small bowel transit time when progesterone is increased, compared to

Table 7.4 Classification of laxatives used in pregnancy[a]

FDA pregnancy category	Definition of that category	Laxatives
Category A	No demonstrated risk by adequate, well-controlled studies in first trimester, no evidence of risk in later trimesters	Epsom salts
Category B	Animal studies failed to demonstrate risk to fetus; no adequate studies in pregnant women	Lactulose Magnesium citrate Psyllium Sorbitol
Category C	Animal studies have shown an adverse effect on fetus; no adequate studies in women; potential benefits may warrant use	Bisacodyl PEG 3350 Senna Polycarbophil Lubiprostone Docusate Kaopectate Mineral oil
Category D	Positive evidence of human fetal risk on adverse reaction data or marketing experiences; potential benefits may warrant use	
Category X	Animal or human studies have shown fetal abnormalities and/or positive evidence of human fetal risk based on adverse reaction data or marketing experiences; risks *clearly* outweigh potential benefits	Misoprostol Bismuth subsalicylate Cascara
No category		Methylcellulose

[a]The reader must not employ this list for clinical decisions and must check the status of any drug as there may be revisions by the FDA

the postpartum period. This study also found that the transit times and progesterone in the first trimester were similar to those of the puerperium [39]. It is difficult to explain these findings in light of patients generally reporting higher symptoms of constipation earlier in their pregnancy.

Treatment of constipation in pregnancy must proceed cautiously. Table 7.4 outlines the Pregnancy Classification of commonly used laxatives; most laxatives are category B or C; the reader must check any current classification for any medication, but the current list is provided to demonstrate the need for caution [40]. In addition to these FDA designations, it should be noted that castor oil may initiate premature contractions (and in patients with prior Cesarean section, rupture), mineral oil may impair absorption of fat-soluble vitamins, and some laxatives could affect the neonate with resulting diarrhea [33, 41].

In a clinical evidence review, it was found that there is no evidence that bulk-forming laxatives are better than no treatment in pregnant women with constipation. There was low quality evidence that bulk-forming laxatives may be less effective than stimulant laxatives [42]. There is a small pilot study showing that defecation frequency increased and other symptoms of constipation decreased in 20 pregnant patients with functional constipation who used a combination of six probiotics [43].

There is a growing literature on the effect of pregnancy on the anal sphincters and pelvic floor [44]. Although muscle disruption and pudendal nerve damage may lead to fecal incontinence either postpartum or many years after delivery, changes in pelvic floor physiology could result in rectoceles, enteroceles, and perineal descent which could lead to constipation. Although there may be other factors associated with these problems, it appears that trauma at the time of delivery can lead independently to pelvic floor descent and difficulty defecating [44].

Spinal Cord Injury and Constipation

Traumatic spinal cord injury (SCI) affects 11,000 individuals annually in the United States. SCI is associated with a mortality rate of 27.4 per million individuals [45]. SCI patients may have chronic pain, urinary and sexual dysfunction, and spinal cord trauma may affect colon motility, anorectal sensation, anal sphincter function and result in neurogenic constipation. Bowel problems are reported in 27–62% of SCI patients with constipation being a significant complaint [46]. Predictors of severe neurogenic bowel dysfunction relate to the level of the injury, with cervical or thoracic injury patients more likely to have severe bowel problems than those with lumbar injuries. It appears as if bowel dysfunction and management impacts more on the quality of life of these patients compared with other SCI-related impairments and problems [47].

In a study of long-term colorectal function in SCI patients, it was found that at 10-year follow-up, the frequency and severity of symptoms related to constipation worsened while those related to fecal incontinence decreased [48]. It was hypothesized by the authors that this may be due to changes in colonic motility over time, but more studies would be needed to confirm this.

The management of SCI is complex and may involve: manual evacuation, oral laxative therapy, abdominal massage, and rectal suppositories and enemas. Sixty-eight percent of SCI patients will experience abnormal defection, with digital stimulation required by 20%, enemas by 28%, and suppositories by 10% [45].

Other options include sacral neuromodulation, dorsal penile/clitoral nerve neuromodulation, and magnetic stimulation. Less commonly employed strategies include colostomy, ileostomy, anterograde continence enema, or sacral anterior root stimulator implantation. In one study of 23 SCI patients undergoing sacral neuromodulation, the median number of bowel movements per week improved from 1.65 to 4.98 with associated improvement in quality of life scores [49].

Studies of transanal irrigation have shown this strategy to be highly effective. This procedure is done by placing a catheter into the anal canal with a balloon inflated to keep the catheter in place. A tepid tap water enema is then administered. This procedure is usually done daily, but must be individualized as necessary [50]. The average volume of irrigation is 961 mL and the time for the enema to be completed averages 34 min [51]. In one study of 32 SCI patients with poorly treated bowel function, 28.6% were able to reduce or eliminate drug therapies and 24 of the patients reported

less dependency on caregivers. Sixty-three percent of the patients with constipation reported an overall successful outcome [52]. In a review of 23 studies using transanal irrigation, it was found that this technique had significant benefits for managing constipation, reducing symptoms, and improving quality of life [53].

In contrast to the transanal irrigation studies, a systematic review of 2,956 studies, of which 57 met inclusion criteria related to pharmacologic vs. non-pharmacologic treatment of SCI neurogenic bowel, found that transanal irrigation was promising, but when conservative management is not effective, pharmacologic agents are supported by evidence for the treatment of constipation in SCI. The authors did concede that effective bowel routines may be a multimodal effort [54].

Constipation in Metabolic Disorders and Systemic Disease

Many systemic diseases may involve constipation as a symptom, and in some cases patients may present with constipation as the main complaint as a manifestation of another problem. Therefore a careful history and physical examination is in order to consider any alarm signs or symptoms (Table 7.2), and to elicit any symptoms in the review of systems that might suggest a disease state or problem.

Table 7.5 provides a list of systemic problems that may be associated with constipation. This section of the chapter will highlight only a few of the most common problems including hypothyroidism, hyperparathyroidism, diabetes mellitus, multiple sclerosis (MS), Parkinson's disease (PD), and scleroderma. Issues related to opioid-induced constipation will be covered later in this chapter.

Endocrine and Metabolic Disorders: A Focus on Hypothyroidism, Hyperparathyroidism, and Diabetes Mellitus

Although hypothyroidism is mentioned in the differential diagnosis of constipation, it is in fact a rare cause of constipation. In one pediatric study of 873 patients on whom thyroid testing was performed, with 56 patients having documented hypothyroidism, only nine patients had constipation and clinically significant hypothyroidism. Of these nine, only one child presented with constipation [55]. Hypothyroidism has a prevalence of approximately 1.4%. Orocecal transit time in adults as determined by lactulose hydrogen breath testing appears to be normal, but diminished motility may be seen in myxedema which is reversible with thyroid replacement. Hypothyroidism in adults has been associated with decreased stool frequency, ileus, megacolon, and pseudo-obstruction [56]. Thickened haustrations may be secondary to submucosal myxedema.

Parathyroid hormone is the regulator of calcium in the body, and constipation may be related to bowel atony. High calcium levels may cause a reduction in neuromuscular excitability [57].

Table 7.5 Constipation and systemic diseases

Endocrine and metabolic disorders	Diabetes mellitus
	Addison's
	Hypopituitarism
	Phaeochromocytoma
	Hormones
	Progesterone
	Pregnancy
	Hypercalcemia
	Hyperparathyroid
	Malignancy
	Hypocalcemia
	Hyperuremia
	Porphyria
	Toxins
	Lead
	Mercury
	Arsenic
Neurologic diseases	Brain lesions
	Bilateral putamen lesions
	Frontal lobe damage
	Stroke
	Dementia
	Tumors
	Spinal cord injury
	Paraplegia
	Cauda equina tumor
	Lumbosacral cord disruption
	Tabes dorsalis
	Neurologic diseases
	Guillain–Barré
	Diabetes
	Dysautonomia
	Multiple sclerosis
	Parkinson's
	Enteric nervous system issues
	Hirschsprung's disease
	Chagas' disease
	Gangliomatosis
	Primary
	Reclinghausen's
	Multiple endocrine neoplasia II
Myopathic disorders	Scleroderma
	Amyloid
Other	Cancer

In general the treatment of constipation in the presence of these metabolic problems is to treat the underlying problem. Although these types of problems are rare, checking the levels of thyroid-stimulating hormone and/or calcium should be prompted by the history and the patient's presentation. As described in other chapters, in the absence of alarm signs and symptoms, it is not routinely recommended

to check these levels, but to make a definitive diagnosis of chronic constipation or irritable bowel syndrome with constipation as is appropriate.

Diabetes mellitus is a complex disorder with many different gastrointestinal manifestations that appear to be of multifactorial etiology [58, 59]. Autonomic neuropathy, sympathetic nerve damage, vagal dysfunction, and electrolyte abnormalities may all contribute to motility problems of the upper and lower gastrointestinal tract. The role of glycemic control is not completely understood, but likely plays a role in hormone regulation, GI motility, and motor dysfunction. There are many factors that may impact motility and neuroenteric structures and function in the GI tract including changes in neurons number and size, alterations in chemical coding of neurons, loss of inhibitory neurons, increase in excitatory neurons, reduction in sensory neuropeptides, apoptosis, and oxidative stress [60].

Constipation appears to be the most common GI complaint of diabetic patients; it may be intermittent and associated with alternating diarrhea. In one study of community-dwelling diabetics, up to 44% reported symptoms of constipation and/or laxative use [61]. The etiology of the symptom is not completely understood. In patients with peripheral neuropathy, the colonic motor response to a meal appears to be impaired; however, the response to cholinergic stimulation with neostigmine in terms of smooth muscle contractility appears to be intact. Furthermore there may be an impairment of rectal sensation due to neuropathy which can result in impaired response to distention [58]. If pelvic floor dysfunction or rectal sensory abnormalities are present, biofeedback is the first line of therapy. If these are absent, use of osmotic or bulk laxatives may be tried [62]. For those patients with impaired motility, stimulant agents, or even rectal suppositories, may influence high amplitude colonic contractions.

Neurologic Diseases: A Focus on Multiple Sclerosis and Parkinson's Disease

Bowel dysfunction is common in multiple sclerosis (MS) and is reported by over half of the patients with this disorder; [63] in one study 68% of MS patients noted constipation and/or fecal incontinence [64]. A systemic analysis reported several studies wherein defecatory dysfunction was more likely in those with progressive disease and in disease of longer duration [65].

The etiology may be related to visceral neuropathy, muscle atrophy, and in some cases fibrosis, but exact mechanisms are not clearly elucidated. MS patients with bowel complaints appear to have delayed somatosensory-evoked potentials recorded from the brain, with normal potentials recorded at the lumbar spine, suggestive of higher spinal or cerebral involvement in these patients; there also appears to be involvement of motor spinal pathways. Many of these studies are older and limited by lack of control groups [66]. Impaired external anal sphincter function and/or decreased volumes of rectal distention to inhibit the internal anal sphincter may contribute to fecal incontinence in multiple sclerosis patients [67].

There are not many studies on quality of life related to this symptom in MS, but in one study, nearly half of patients reported changing their routines to

accommodate their bowel regimen [68]. MS presents unique challenges particularly related to treatment, as treating the constipated patient with MS may in turn lead to fecal incontinence. Achieving the optimal bowel regimen may be difficult and may require frequent adjustment and trials. A study from 1990 has shown that laxative use is more common with more severe MS disease and correlates with worsening disability and duration of the disease [69].

Parkinson's Disease

Constipation may be a preceding symptom in patients who are later diagnosed to have Parkinson's disease (PD) [70]. Decreased defecation (less than three bowel movements per week) may be seen in up to half of the patients with Parkinson's disease [71]. Colon transit time has been found to be prolonged in Parkinson's disease patients [72], but defecatory dysfunction may also be problematic in up to 67% of PD patients [71]. This defecatory dysfunction may result from the intricate muscle movements that must take place in defecation of both the sphincter complex and the abdominal musculature. Paradoxical contraction of the puborectalis muscle and of the external anal sphincter, similar to what may be seen in dyssynergic defecation, has been described in PD patients [73, 74].

Myopathic Disorders: A Focus on Scleroderma

Systemic sclerosis or scleroderma is a chronic systemic disease involving the connective tissue, and gastrointestinal involvement affects over 80% of patients suffering with this disease [75]. In terms of symptoms of colorectal function, patients may suffer from diarrhea, constipation, fecal impaction, rectal prolapse, megacolon, and/or fecal incontinence [76]. Patients who have scleroderma and have symptoms of constipation may have prolonged colonic transit compared to those with the disease but no constipation [77]. Patients may have wide-mouthed diverticula, which in contrast to idiopathic diverticula, involve all layers. This phenomenon may be the result of the uneven distribution of atrophic changes in the muscularis propria throughout the colon, in addition to focal muscle fibrosis. Although a dilated colon is not uncommon in scleroderma, development of true megacolon is rare [76].

The usual postprandial colonic spike activity may be reduced or absent early in the course of scleroderma. With the administration of anticholinesterase drugs, this response is restored in about half of patients. In advanced cases, as smooth muscle atrophy worsens, initiation of colonic spike activity may not occur at all, even with pharmacologic stimulation [78].

Treatment of constipation in scleroderma patients may be challenging. Surgery is generally contraindicated, as this is a systemic disorder with multiple organ involvement; this is not an isolated colonic motility problem [79].

Opioid-Induced Constipation

Opioids are commonly prescribed to treat severe pain syndromes, and it is estimated that 90% of those presenting to chronic pain centers are on a treatment regimen including opioids [80] The side effects of opiates can result in many different types of symptoms related to the gastrointestinal tract including nausea, vomiting, reflux, dry mouth, bloating, abdominal pain, anorexia, constipation, hard stool, and a sense of incomplete evacuation. In addition to the underlying pain, these side effects can alter the sense of well-being and impact quality of life. Although tolerance to pain alleviation occurs with long-term use, there is no development of tolerance to the GI side effects.

There are several subtypes of opioid receptors, three of which have effects on the human GI tract: δ, κ, and μ. These three receptors inhibit adenylate cyclase and belong to the G-protein-coupled receptor family [81]. The μ-receptor appears to be the major mediator of analgesia in the CNS and these receptors are present in the gastrointestinal tract, localized on myenteric and submucosal neurons and on immune cells in the lamina propria (Fig. 7.3) [80]. It appears that opioid drugs inhibit the release of neurotransmitters that have a direct effect on gastrointestinal motility resulting in dysmotility or abnormal coordination of motility.

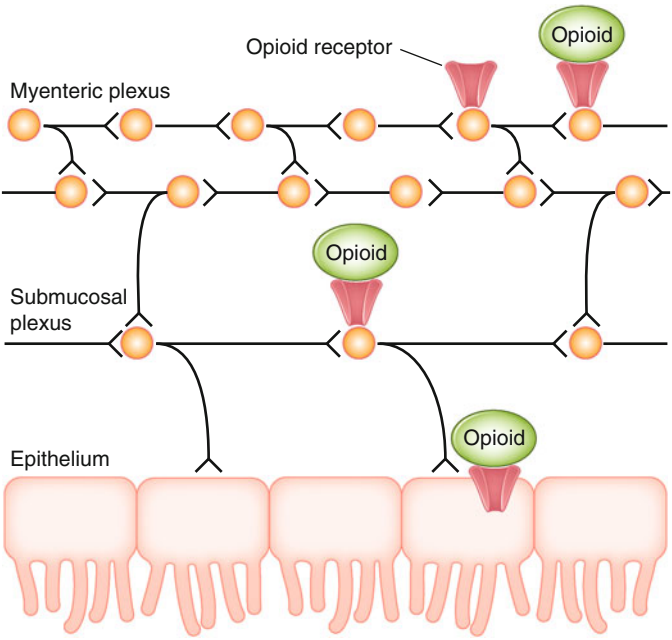

Fig. 7.3 Neural control of the gut (Adapted from Brock C, Olesen SS, Olesen AE, Frokjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: Pathophysiology and management. *Drugs*. 2012;72(14):1847–1865, with kind permission from Springer Science + Business Media)

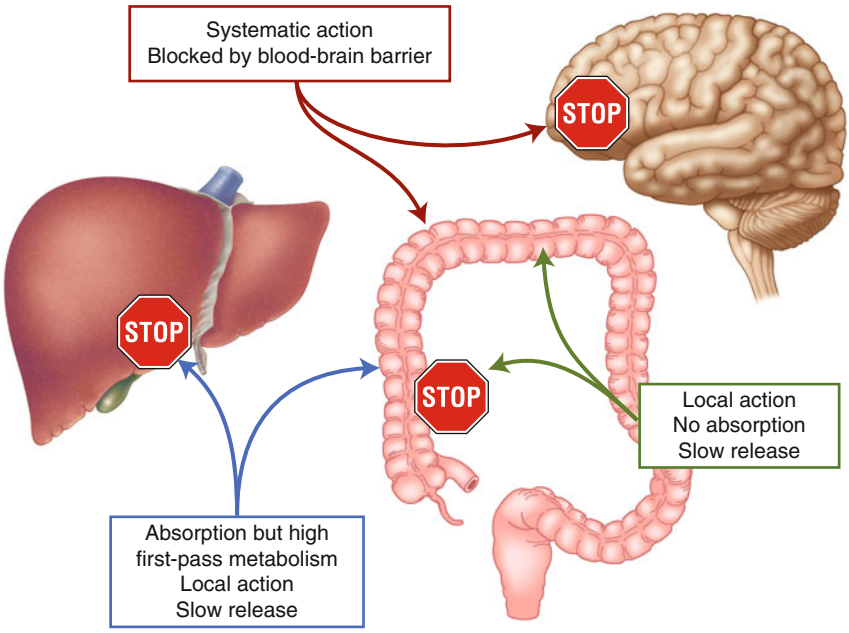

Fig. 7.4 Potential sites to antagonize opioid effects on the gut without affecting pain control (Adapted from Mueller-Lissner S. Fixed combination of oxycodone with naloxone: A new way to prevent and treat opioid-induced constipation. Adv Ther. 2010;27(9):581–590, with kind permission from Springer Science + Business Media)

There are very likely multifactorial causes of constipation in patients using opiate drugs: delayed transit, nonpropulsive motility, and effects on sphincters [81]. In addition, chronic pain patients may have decreased mobility, anorexia, and poor diet and may be on other medications that can affect motility. Figure 7.4 indicates possible pathways to antagonize the opioid effects on gut receptors while still maintaining effective pain control without interfering with the CNS actions of the drugs [82]. There are many strategies for the treatment of opioid-induced constipation including: (1) Discontinuing the opiate and instituting another agent including the possibility of tapentadol a μ-opioid agonist, (2) Using μ-receptor antagonists to reverse the effect of the opioid, and (3) Treating the symptom of constipation with a prokinetic agent such as the 5-HT4 receptor agonist, prucalopride, or with a secretagogue such as lubiprostone (see Table 7.6 for a list of emerging drug options to treat opioid-induced constipation). Lubiprostone recently received FDA approval (April 2013) for the treatment of opioid-induced constipation in adults with chronic noncancer pain. This approval was based on results from three Phase III placebo-controlled trials in patients taking opioids (among them, morphine, oxycodone, and fentanyl) for chronic noncancer pain. Two of the three studies met the primary efficacy endpoint. In addition there was a long-term, open-label safety study providing additional support for use in patients with noncancer pain.

Table 7.6 Emerging treatment options for opiate-induced constipation

Pharmacologic agent	Class of drug
Lubiprostone	Chloride channel activator
Naloxone	Non-selective opioid antagonist
Methylnaltrexone	Selective μ-opioid antagonist
Alvimopan	Peripherally restricted μ-opioid receptor antagonist
Tapentadol	μ-Opioid agonist (also norepinephrine reuptake inhibitor)
NKTR-118	Peripherally restricted μ-opioid receptor antagonist (oral PEGylated naloxol conjugate)
TD-1211	Peripherally restricted μ-opioid receptor antagonist

Specific Treatment Review in Opioid-Induced Constipation

There have been several randomized-controlled trials of the use of stimulant laxatives in patients receiving palliative care, but only one showing any significance between treatment options [83]. The authors of a therapeutic review suggest that, in the palliative care setting, a reasonable approach could include optimizing a stimulant laxative before considering a surface-acting agent or osmotic laxative. These authors pointed out the expense and the requirement for subcutaneous administration of methylnaltrexone as a barrier to its consideration [83].

The National Comprehensive Cancer Network recommends the routine assessment of the symptom of constipation in cancer patients. It appears that opioid analgesics are the primary therapy for moderate to severe pain in patients with cancer. Constipation as a side effect is very common, and in many cases, may affect adversely the quality of life to the extent that the discontinuation of pain therapy is considered. Although preventative strategies and routine therapies may be employed at first, methylnaltrexone has been studied and has served as the recommended therapy for this symptom in cancer patients. This seems to be a well-tolerated treatment with effective relief up to 4 months. With the advent of new therapies, this general clinical approach may require further evaluation [84]. One retrospective analysis of methylnaltrexone in critical care patients showed promising results for this therapy, albeit in a small number of patients [85]. Currently, when response to laxatives is insufficient for patients who are receiving palliative care, methylnaltrexone bromide (in the United States) is the indicated treatment of opioid-induced constipation in patients with advanced illness. It has not been approved for chronic, noncancer pain.

Alvimopan has been shown to produce a bowel movement within 8 h in a 21-day trial of 168 patients with noncancer pain [86]. The treatment was well-tolerated and did not affect analgesia efficacy. Weekly bowel movements and patient satisfaction improved on this therapy. The current FDA approval is for prevention of postoperative ileus following partial bowel resection with primary anastomosis.

The development of novel therapies and approaches to the treatment of opioid-induced constipation must focus on providing relief of constipation while not interfering with the analgesic therapy that is required for the adequate relief of pain. This is a challenging pharmacologic and clinical issue that requires an evidence-based approach to the evaluation of efficacy of current and future options.

History of Abuse and Functional Bowel Disorders

There is an evolving literature on history of abuse and trauma associated with gastrointestinal symptoms. It has been observed that the prevalence of abuse history is higher in those with the most severe symptoms and who are evaluated in tertiary centers [87]. Furthermore, a history of more severe abuse appears to be present in patients with functional gastrointestinal disorders. The exact mechanism has not been elucidated, but one proposal is that stress-associated brain-gut interactions may stem from altered stress-induced mucosal immune function or impaired coordination of the central nervous system to down-regulate either visceral or somatic afferent information.

In a study of 1,781 women with pelvic floor disorders, 12% reported a history of sexual abuse or assault. Abused women had higher symptom severity and poorer quality of life. These authors suggested that a history of sexual abuse or assault changes disease or symptom perception in patients with pelvic floor disorders without evidence of physiologic changes. Therefore treatment options might be targeted with this in mind [88]. In yet another study of patients with dyssynergic defecation, sexual abuse was reported by 22% and physical abuse by 32% [89].

Not all of the literature confirms the association of abuse and functional gastrointestinal disorders. In a study of constipated patients who were compared with matched groups of IBS patients, Crohn's disease patients, and non-patient controls, no significant differences were found between all four groups related to abuse or distress. The study, however, did find that patients with past history of abuse do demonstrate higher levels of distress, suggesting abuse history may be related to psychopathology [90].

It is important to recognize when the clinician might consider asking about a history of abuse in a clinical encounter. Clinical features suggesting further investigation would include psychologic factors, chronic pain, severe constipation, pelvic pain, narcotic bowel, morbid obesity, unexplained vomiting, sexual dysfunction, or symptoms suggestive of somatic etiologies. There are also illness behaviors that might prompt the clinician to pursue an abuse history including denial of psychologic factors, disability seeking, overutilization of the healthcare system, multiple tests and surgical procedures, and anxiety with components of the physical exam (vaginal or rectal exam) or with endoscopic procedures [87]. The inquiry into this history has to be done in a comfortable setting, in a relationship of trust, with the availability of time, and with readily available support from mental health services.

Treatment may include antidepressants, behavioral interventions, and psychotherapy and often requires a multidisciplinary approach.

Summary

Constipation is a common and debilitating symptom. This chapter has covered special circumstances where the etiology of constipation prompts unique considerations in the evaluation and management of the symptom. Although constipation rarely

will result in mortality, the symptom can have a major impact on the patient's quality of life, and therefore a comprehensive understanding of associated issues and special considerations is essential in leading to effective treatment and improvement.

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Chapter 8
Cases

Brijen Shah

Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Integrate information from the book and apply it to clinical situations.
2. Evaluate clinical presentations of constipation and develop an evaluation and management strategy.
3. Differentiate between the different etiologies of constipation and create a management plan.

Introduction

These cases are provided to be used for application of the concepts presented in this book. These cases can be read through for self-assessment of knowledge or can be used with learners as part of a problem-based or case-based discussion. The cases are presented in an unfolding format with questions suggested for discussion. References to other sections in the book are also provided.

Case 1

S.C. is a 56-year-old man with a chief complaint of constipation referred to you by his primary care physician. He has three bowel movements a week for the last 1 year. Prior to this, he was having one bowel movement most days of the week.

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Table 8.1 Suggested questions to evaluate for and the etiology of chronic constipation

• How many bowel movements do you have per week?
• Do you strain when attempting defecation?
• What is the consistency of your stools?
• Do you have to use your fingers or certain positions to help you to have a bowel movement?
• Following a bowel movement, do you feel that you have completely evacuated your bowels?
• How long have you had these symptoms? If symptoms started suddenly, was there a particular event that preceded symptom onset?
• What prescription, over-the-counter, and herbal medications have you tried to relieve the constipation?
• Do you have blood in your stools and/or have you had an unintentional weight loss of ten pounds or more?
• Do you have a family history of colon cancer or inflammatory bowel disease?

When he has a bowel movement, he describes it as something "squeezing through" his left side. He denies blood in his stool. Other symptoms include left-sided back pain and neck pain, related to a work injury several years ago. His weight has increased and his appetite is unchanged. He was prescribed docusate with little relief. He has never had a colonoscopy.

What Additional Questions Should Be Part of the History?
A complete history is crucial to determining the etiology of constipation and differentiating it from other disorders such as IBS. In addition to stool frequency, clinicians should ask about frequency of straining, stool form, and sensation of incomplete evacuation. The Bristol Stool chart can help to facilitate this conversation.

Facilitator's note: *Encourage learners to phrase the questions how they would ask a patient* (Table 8.1).

Additional history: He describes straining with most bowel movement and does not feel empty most times he has a bowel movement, i.e., a sensation of incomplete evacuation.

PMH: hypertension, hypercholesterolemia, asthma, depression, BPH, chronic renal insufficiency, stage III, lumbar spondylolisthesis.

PSH: laminectomy, cervical region.

Meds: albuterol inhaler as needed, tizanadine 4 mg daily, zolpidem 10 mg daily, HCTZ 25 mg daily, lisinopril 20 mg daily, nifedipine 30 mg daily, atenolol 100 mg daily, simvastatin 20 mg daily, lactobacillus ten billion units daily.

SH: current smoker, no alcohol, former heroin use.

FH: father with prostate cancer (age 80), mother with colon cancer at age 85.

Based on this information does S.C. have chronic constipation or IBS-C?
S.C. lacks abdominal pain or discomfort which is the main characteristic associated with IBS-C. However, he does have few loose stools and has had these symptoms for more than a few months, similar to IBS-C.

Which items from S.C.'s medical history are contributing to his constipation?
Lumbar back problem, medications (beta blocker and calcium channel blockers), and depression are associated with constipation. Although he is not in renal failure, his renal disease does increase his blood urea nitrogen and may contribute to his constipation.

Physical Examination
A physical exam reveals a well-developed, well-nourished male.
HR 65 and BP 110/70.
Oropharynx is clear, there is no cervical lymphadenopathy and no thyroid enlargement.
Heart and lung exam are unremarkable.
Abdomen is soft with bowel sounds in all four quadrants. There is some abdominal distention on the left side and no tenderness.
Rectal exam showed hard occult blood negative stool with a normal anal wink, appropriate anal sphincter relaxation, and abdominal muscle contraction.

At this point, how would you manage S.C.? Would you offer testing or treatment for his problem?
Although constipation is generally managed with a trial of high-fiber diet and over-the-counter laxatives, this should only be done after organic disorders have been evaluated. Given S.C.'s age, a colonoscopy is warranted as part of colon cancer screening and to ensure there is not a mass causing his symptoms. In addition, he requires a more formal rectal exam to rule out pelvic floor dysfunction.

If the patient was a 26-year-old female with similar symptoms how would you manage her differently?
Given her age, she has normal transit constipation related to low dietary fiber. The clinician should ensure there are no alarm signs (weight loss, GI blood loss, abdominal pain, family history of a colon cancer syndrome) and then treat with over-the-counter laxatives and fiber. A colonoscopy was performed (Fig. 8.1).

Explain the mechanism for the colonoscopy findings
Diverticulosis is an out pouching of colonic mucosa which is not a true diverticulum. It does not contain all the layers of colonic mucosa. They occur at areas where the vasa recta penetrates the serosa, and with higher colonic pressures, results in the development of diverticulosis. Diverticulosis is thought to be the result of constipation and not causative.

Does S.C. have normal or slow transit constipation? What are the differences between the two? How can you test for this?
S. C. likely has slow transit constipation due to his medications and his lumbar back disease. Slow transit constipation refers to colonic motor dysfunction with fewer high-amplitude propagated contractions and reduced response to meals. This has been correlated with a decrease in the interstitial cells of Cajal. Tests to assess for slow transit constipation include Sitz marker study or a wireless motility capsule.

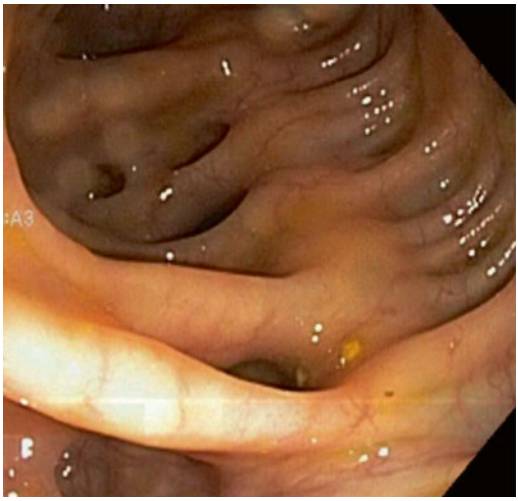

Fig. 8.1 Diverticulosis as seen on colonoscopy

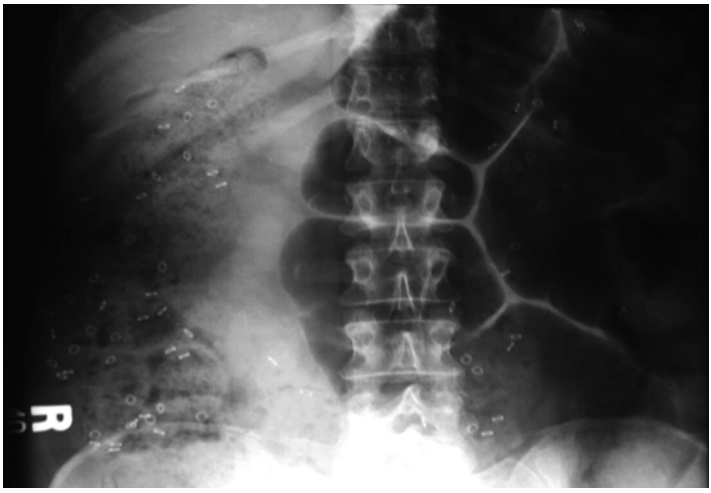

Fig. 8.2 Sitzmarks test: multiple radiopaque markers are retained throughout the colon, suggesting abnormal colon transit time

Facilitator's note: *For advanced learners or those focusing on pathophysiology*, *this question could be broadened for a larger discussion on colonic motility*, *review of histopathology as it correlated with function* (*roles of circular and longitudinal muscles*), *and the GI neuroanatomy related to colonic motility* (*see Chap. 3*). *It should be noted also that the newer algorithm from the AGA recommends ruling out pelvic floor dysfunction prior to the evaluation of colonic transit. See Fig. 8.2*, *Sitz marker study example*.

How do you interpret the Sitz marker study? How is this performed?

The patient ingests 24 markers and takes an abdominal X-ray at day 0 and day 5. If greater than 20% or six markers are still seen, the test suggests slow transit

constipation. In the study shown a different protocol was used using a capsule of 24 markers taken on days 1, 2, and 3 with an X-ray on days 4 and 7. Retention of 20% of the markers on day 7 is indicative of slow transit.

Facilitators note: *Ask the learners to describe how they read the study. For students or residents*, *consider reviewing how to read an abdominal radiograph*.

Why did docusate not work for him in the past? What treatment options can you begin with?
Colace acts as a stool softener, but has no effect on increasing colonic transit. S.C. has documented slow colonic transit and requires an osmotic agent to increase his stool frequency. A PEG-based product, such as PEG-3350, could be used a few times a week to increase his bowel movements. Sodium phosphate and magnesium citrate-based products should be avoided given his renal insufficiency. A plan for treatment should also include a "rescue" agent in the form of a stimulant laxative such as bisacodyl. Non-pharmacologic adjuncts may include increased physical activity and soluble fiber; however, these alone will not be sufficient.

Facilitator's note: *Have learners model how they would educate the patient*, *including use of visual aids and the "teach back" technique*. "*Teach back*" *is a communication tool which asks the learner to repeat back the major point of the conversation. For example*, *when teaching a patient about new medications*, *the provider asks the patient to explain in his/her own words what was said. Practicing "Teach Back" can be added to a small group discussion for skill practice. This can be done through role play where the instructor plays the patient or one learner acts the role of the patient while the other is a provider counseling using "Teach Back."*

Case 2: IBS-C

M.W. is a 38-year-old woman who is referred for a chief complaint of left-sided abdominal pain and weight loss. Her pain has been present for almost a year and she describes it as a "bulge and a pressure" in the left lower part of her abdomen. She also relates a 40 lb unintentional weight loss. She has an appetite but continues to lose weight. The only dietary change she has made is to cut down on alcohol. She has one bowel movement per week for the last 8–9 months.

PMH: migraine headaches, ovarian cyst (removed 5 years prior), major depressive disorder (age 22, treated at that time with medication), GERD.

PSH: laparoscopic ovarian cyst removal, G_1P_1, cesarean section.

SH: Lives with her daughter. Single mother, works as a clinic secretary; which is very stressful for her. Current 0.5 pack per day smoker, 1–2 glasses of wine/week.

FMH: breast cancer in maternal aunt and mother (both in their sixties), sister with diabetes, brother with hypertension. No family history of GI malignancies.

Table 8.2 Differential diagnosis for constipation

Common diagnoses	Must not miss	Non-GI diagnoses
Chronic constipation	Colon cancer	Endometriosis
Diverticulitis	IBD colitides	Kidney stones
Irritable bowel syndrome	Ectopic pregnancy	Salpingitis
Pain from adhesions		Ovarian cyst
		Depression/anxiety
		Physical abuse

Medications: Acetominophen 500 mg as needed for headaches, ibuprofen 400 mg during periods.

What is in the differential diagnosis for M.W.'s left-sided abdominal pain?
M.W.'s differential should include common and must not miss diagnoses for her left-sided abdominal pain and weight loss, which may be unrelated (Table 8.2).

What additional history questions will be helpful to obtain?
Clinicians should focus questions to gather data on the items in the differential listed above. In young patients with pain and constipation, it is helpful to ask questions to determine if there are alarm features suggestive of structural diseases such as cancer, which would require further evaluation. The following set of questions will determine the status of alarm signs and symptoms:

Is there blood in the stool?
Is the pain relieved with defecation?
What is the stool consistency?
When the abdominal pain (or discomfort) begins, do you have more (or less) frequent stools?
At the onset of your abdominal pain, is your stool loose or hard?
What other associated GI symptoms are present (bloating, dissention)?
Do you strain while having a bowel movement?
Is the pain different with your menstrual cycle? Do you have heavy menstruation?
Perform an assessment of mood for depression, anxiety, and other disorders.

Additional history: M.W.'s pain improves after a bowel movement, but within a few days the pain returns. She sees some blood on the toilet paper after a bowel movement. She strains with every bowel movement and does not feel completely empty most times. Her stool is hard and pellet-like. She has tried milk of magnesia with rare relief. M.W. has associated nausea and bloating with her symptoms. Her menses have been regular and her pain is the same before and after her cycle.

Physical Examination
BP 104/66, Pulse 95, Ht 5′ 7″, Wt 75.297 kg (166 lb), BMI 26.00 kg/m^2.

Constitutional: no acute distress and well developed/well nourished.

Eyes: anicteric.

Ears/Nose/Mouth/Throat: oropharynx pink and moist.

Cardiovascular: normal s1, s2, no murmurs, and regular rhythm.

Respiratory: clear to auscultation bilaterally, no wheezing, and no rales.

Back: no costo-vertebral angle tenderness (CVAT).

Gastrointestinal: normal bowel sounds, tender to deep palpation in LLQ, no hepatosplenomegaly and no masses.

Rectal: hemoccult: negative, negative for fistula, negative for fissure, external hemorrhoids present, sphincter tone: normal, and squeeze pressure: normal.

Musculoskeletal: normal gait.

Extremity: no peripheral edema and no swelling/erythema/tenderness.

Neurological: alert, awake, and oriented times three (AA&0 ×3).

Lymphatic: no cervical nodes palpated.

Psychiatric: poor sleep, difficulty concentrating, describes mood as "down."

Skin: no rash.

Labs: basic metabolic panel normal, TSH normal, CBC: hgb 10.9, hct 33, platelets and WBC normal; iron 130, ferritin 11, TIBC normal.

What testing should be pursued next?
Given the weight loss and anemia associated with pain and recent change in bowel habits, a colonoscopy and EGD is warranted as part of her work-up. M.W. has several "red flags" (weight loss, anemia, change in bowel habits) which require investigation. A plain film may also be useful to assess stool burden. M.W.'s exam was notable for some features suggestive of depression, and given her prior depression history, a further psychiatric evaluation is important to obtain.

A colonoscopy and EGD were performed which were normal. She gets in touch with her psychiatrist who diagnoses her with depression and places her on 10 mg citalopram. She is diagnosed with IBS-C.

Review the criteria for IBS-C.
The Rome III criteria define IBS-C as recurring abdominal pain for at least 3 days per month associated with two of the following: improvement with defecation; onset associated with change in frequency of stool; onset with change in appearance of stool; <25% of bowel movements are loose.

Facilitator's note: *Can compare this to chronic constipation diagnostic guidelines and chronic abdominal pain*.

What other conditions or symptoms might be associated with M.W. condition that you might want to ask about?
She has migraine headaches and GERD. Table 8.3 lists other associated diseases clinicians may inquire about including interstitial cystitis, dyspareunia, and fibromyalgia symptoms.

Table 8.3 Common conditions associated with IBS

Migraine headaches
Fibromyalgia
Insomnia
TMJ syndrome
Functional dyspepsia
GERD
Pelvic floor dysfunction
Interstitial cystitis
Dyspareunia

What treatment will you recommend for M.W.?
Diet history and supplemental psyllium with or without osmotic laxative or milk of magnesia. Alternatively, she could be counseled to take 25 g of natural fiber a day.

As part of a therapeutic plan, how will you counsel M.W.?
Patient education is a corner stone of IBS treatment and should include reassurance, diet education, and counseling about exercise.

What is the significance of M.W.'s depression and her IBS-C? How should this be addressed as part of her treatment plan?
Patients with IBS experience a greater amount of stress and associated symptoms of depression or anxiety compared to patients without IBS. Psychological counseling, stress reduction, and medical therapy for anxiety and depression may help to alleviate some of the GI symptoms. Lower doses of serotonin reuptake inhibitors have been proven to help reduce pain and global symptoms. Increased physical activity, which can help with depression, will also reduce intestinal gas and bloating, which can increase quality of life in IBS.

M.W.'s symptoms are slightly improved at your 6-week follow-up. She is slowly gaining some weight. Her stress level has reduced while taking a leave from her job and her citalopram has been increased by her psychiatrist.

What other treatment options can be offered to M.W.? How do these work?
Linaclotide (guanylate cyclate C) and lubiprostone (chloride channel activator) are other pharmacologic options.

Case 3: Pelvic Floor Dysfunction

Thirty-two-year-old woman, L.P. is referred to you by her primary care doctor for consultation for her constipation which at times is also mixed with diarrhea. The patient had regular bowel habits, prior to a few years ago when she started to have period of constipation, with no bowel movement for 7–10 days. She would occasionally have some loose watery stool. She often seeks care at urgent care facilities and has been given PEG-3350, suppositories, and at times, enemas with little relief.

She has no nausea or vomiting, but some lower abdominal pressure. Her weight and appetite are stable. Her primary care doctor calls you to give you a heads up that she has an appointment to see you tomorrow. A CBC, TSH, and chemistries were checked at the primary care office and were normal.

Based on this information, what are your initial thoughts about the case that you can covey to the primary care doctor? What types of items or questions will you focus on during the visit?
At this point, one must consider chronic constipation versus IBS as the etiology. Based on the above history there are no red flags. History taking should focus on getting a more accurate description of the bowel habit frequency, stool consistency using the Bristol stool chart, and asking other symptoms related to pelvic floor dysfunction.

You confirm the above history and the patient describes the periods of diarrhea as "liquid moving around the stool." She describes her stools as rabbit pellets at times and other times as if the stools were "at the bottom" and it will not come out. Enemas have provided some relief and can be associated with some blood on the stool. Other associated symptoms include pain with vaginal intercourse with her boyfriend and some urinary leakage.

How do you explain the diarrhea?
This may be overflow diarrhea in the setting of severe constipation.

What are your next steps in evaluation?
A rectal exam should be performed. Although there is a component of constipation, pelvic floor dysfunction has not been assessed.

Physical Examination
PE: 111/65, 98, afebrile.
Well nourished, well developed.
Cardiovascular, respiratory, neurologic, and skin exam are normal.
Abdominal exam: non-tender, non-distended abdomen with normal bowel sounds.
Rectal exam: no external lesions, no evidence of prolapse, normal tone and normal descent, increase in pressure on examining finger with valsalva. Hard stool palpated on tip of examining finger. Guaiac negative.

What does the rectal exam suggest? What should normally occur?
Normally the EAS should relax with simulation of defecation. Instead, the patient increased her EAS tone suggestive of dyssynergic defecation. It should be noted that this is suggestive but not necessarily diagnostic as the patient may feel inhibited during the examination.

What testing should be done next?
Anorectal manometry with balloon expulsion or high-resolution anorectal manometry should be done as she has not adequately responded to laxatives.

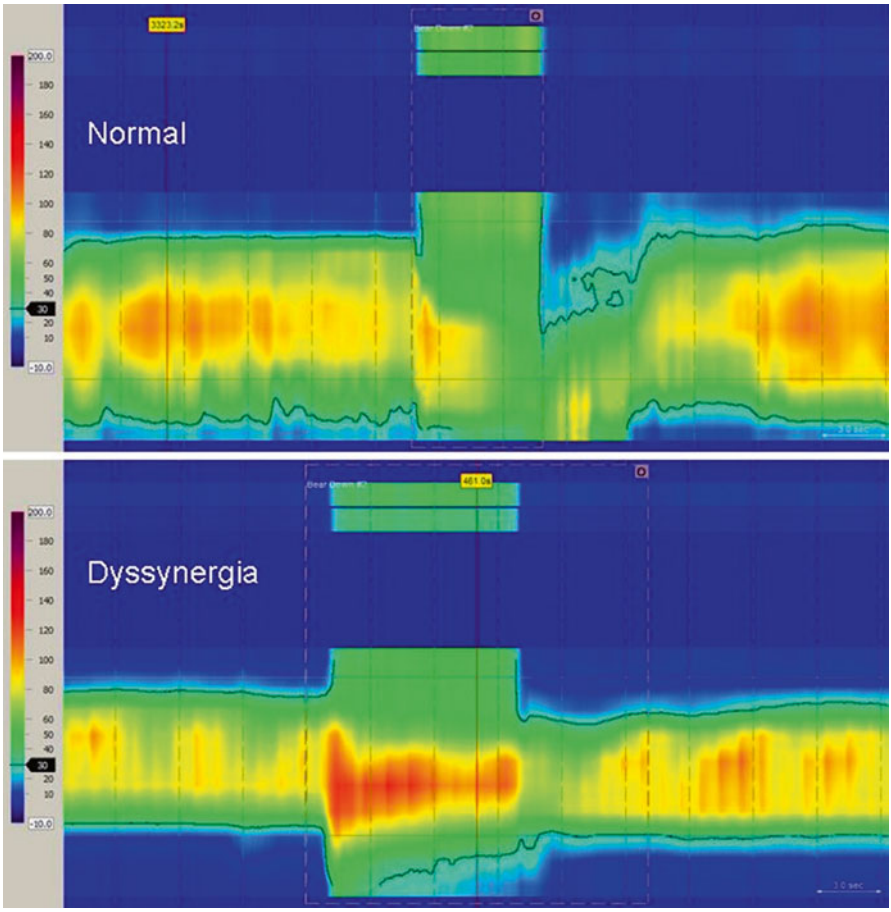

Fig. 8.3 High-resolution anorectal manometry: normal and dyssynergia. High-resolution topographic contour plot in a patient with a normal decrease in intraanal pressure when bearing down or attempted defecation (*top*). High-resolution topographic contour plot in a patient with dyssynergia (*bottom*). Note the paradoxical increase in intraanal pressure when bearing down or attempted defecation

Facilitator's note: *Would mention the importance of what is locally available*.

Interpret what is seen in Fig. 8.3.

What conditions can predispose to this condition?
Pregnancies, childbirth, trauma, prolonged straining, and psychological stress and anxiety can lead to this problem; however, in 40% of women no cause is found.

What treatments and counseling can be offered?
Biofeedback is an option in this patient as well as providing a laxative regimen for her constipation. Patients should attempt to defecate 30 min after meals or upon waking and attempt a moderate push. Digitalization should be avoided.

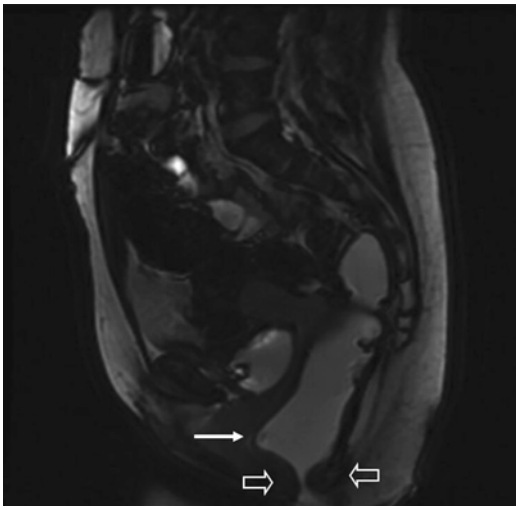

Fig. 8.4 Dynamic pelvic MRI demonstrating anterior rectocele (*solid white arrow*), rectal prolapse (*hollow arrows*), and retention of rectal contents

Facilitator's note: *This is an opportunity for the student to role practice counseling with a patient*.

What other structural problems can be associated with pelvic floor dysfunction?

Rectocele, cystocele, solitary rectal ulcer, rectal prolapse, and excessive perineal descent can be associated with this problem. If a patient does not improve, pelvic MRI or defecography should be considered.

Due to her continued symptoms, a pelvic MRI is performed and shows a small cystocele, 2.3 cm below the pubococcygeal line. Mild/moderate middle compartment descent 3.1 cm below the pubococcygeal line. 3.2 cm anterior rectocele (Fig. 8.4).

Case 4: Constipation, Elderly Impaction

J.L. is an 87-year-old World War II veteran who resides at a long-term care home for Veteran's at the local VA campus. As the physician covering the long-term care unit, you are asked to come evaluate him for confusion. The nurse notes he is talkative, cooperative, but has poor short-term memory at baseline. He is able to feed himself and engages in activities of daily living with some assistance, but has been more confused and somnolent over the last few days. He has limited ambulation and uses a walker. You review the nursing chart which showed stable vital signs, no fever, and no change in oral intake over the last few days. The nursing chart shows he has had small volume diarrhea for the past 5 days. He provides very little history and only mentions that his abdomen and belly hurt.

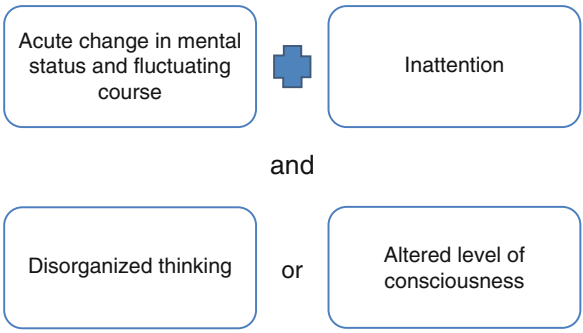

Fig. 8.5 Confusion assessment method for evaluating delerium

His past medical history includes dementia, hypertension, gout, chronic lower back pain from spinal cord injury from a motor vehicle accident, and BPH. He has had an appendectomy and surgery for internal hemorrhoid repair.

Medications include hydrochlorothiazide, donepezil, *Ginkgo biloba*, nifedipine, aspirin, and oxycodone.

At this point, what is your approach to evaluating his presentation?

This is an elderly patient presenting with delirium (acute change in mental status) in the setting of dementia. The evaluation should focus on looking for causes of delirium which can be reversed including medication side effects, metabolic disturbances, infection, liver failure, renal failure, and myocardial infarction.

In the nursing home setting and in an elderly man with BPH, the clinician must consider urinary retention and fecal impaction as causes of delirium. A physical exam including mental status assessment and a rectal exam should be performed as part of the work-up (Fig. 8.5).

Facilitator's note: *For primary care or medical student learners*, *consider discussing the Confusion Assessment Model* (*CAM*) *to evaluate delirium. Also*, *highlight the importance of establishing a mental status baseline and obtaining supporting history from other care givers when patients are cognitively impaired.*

Physical Examination

Thin elderly man, eyes open, edentulous, lying in bed, cooperative with the exam.
His oropharynx is dry.
Cardiovascular and lung exam are unremarkable.
Abdomen is slightly distended, normal bowel sounds, dull to percussion on the left side. No rebound, guarding, or pain.
Rectal exam shows a weak tone, hard stool felt at the end of the examining finger.
You ask the patient if he has the urge to go to bathroom and he is unaware he needs to have a bowel movement.

Why is this patient constipated? Is this a primary or secondary cause of constipation?
The contradiction between a history of diarrhea and a physical exam with hard stool in the rectal vault raises the concern for fecal impaction. The diarrhea is an example of overflow diarrhea where loose watery fecal matter seeps around hard inspissated stool.

While there are many etiologies for constipation, a case for each type of constipation could be made at this point. He has poor dentition and an institutional meal plan which is low in fiber. He takes several medications, including opiates which create slow transit. Finally, his BPH, back pain, and prior anorectal surgery impact normal functioning of his pelvic floor. At this point, it is not possible to determine the cause of his constipation. Most elderly patients have multifactorial causes for such a presentation.

Facilitator's note: *This is an opportunity to review the approach to classifying constipation and to remind learners that pelvic floor causes may coexist with other slow and normal transit etiologies*.

What tests should be part of your work-up?
Metabolic tests such as chemistries, thyroid function, and calcium should be considered in addition to other tests to evaluate causes of delirium. An abdominal X-ray or CT scan in patients with severe pain, nausea/vomiting, or other obstructive symptoms may be indicated. In this patient, no further imaging is required at this point.

If he was younger and without cognitive impairment, what testing would you start with? What might you find?
Anorectal manometry and balloon expulsion test could be offered. Manometry might reveal a type IV pattern with inability to generate adequate expulsive forces (no increase in intrarectal pressure) and absence or incomplete reduction in residual intraanal pressure. A balloon expulsion test would show little to no sensation to defecate until high volumes (150 mL or greater is reached).

What risk factors does this patient have for fecal impaction?
Institutionalization, impaired ambulation, decrease cognition/dementia, opiate use.

How should you approach his treatment?
Manual disimpaction may be needed. The key to treatment is an effective bowel regimen that includes oral laxatives and enema/suppositories. In patients with dementia, creating a toileting schedule which includes laxatives and timed toileting can be effective. This includes utilizing the physiologic gastro-colic reflex with toileting within 30 min after a meal.

Chapter 9
Putting It All Together

Suzanne Rose

Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Define the different types of constipation.
2. Describe approaches to the evaluation of constipation.
3. Identify new paradigms and strategies for evaluation.
4. Assess situations where algorithms may or may not apply.
5. Evaluate best practices and approaches to the symptom of constipation.

Key Points

1. Constipation is a common symptom.
2. Evaluation begins with a detailed history and physical examination.
3. In the absence of alarm signs and symptoms patients can be treated without extensive testing.
4. Remember that in considering colonoscopy in patients with this symptom, it is important to separate screening for colon cancer vs. testing for the symptom due to the presence of alarm symptoms.
5. Pelvic floor dysfunction is an under-recognized cause of constipation and there are unique approaches to its evaluation and management.

The chapters of this book have presented the epidemiology and impact of constipation on quality of life and economic factors. The authors present approaches to testing and have reviewed the presentation, evaluation, and management of: chronic

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constipation, irritable bowel syndrome with constipation, slow transit constipation, and pelvic floor dysfunction. And there is also a chapter related to special considerations related to this symptom.

The authors have been very careful to provide state-of-the-art and evidence-based information. This brief chapter is being presented as a series of Frequently Asked Questions (FAQs) in order to summarize the information provided and to synthesize it. The reader will note that there is some opinion included in this section. The chapters have been written by the world's experts on this topic, and although they have presented all the information with detailed references, often authored by these contributors, there are situations that may require the clinician/diagnostician to consider deviating from published protocols. This is the art of medicine—individualizing and personalizing one's approach for a particular patient, perhaps in a particular setting and with specific available resources. The authors caution that this book is intended for those with a sophisticated background in medical information including pathophysiology, metabolism, pharmacology, and neurogastroenterology. It may be tempting to self-diagnose or to consider a solution if you are suffering with constipation. However, the authors and editor ask that you seek care from your physician, sharing any concerns or symptoms.

FAQs

What are the different types of constipation?
First of all, one must consider primary vs. secondary constipation. The latter is due to a comorbid condition or perhaps medications that influence bowel movements and causes the symptom. Many of these issues are reviewed in Chap. 7.

In contrast, primary constipation relates to the problem arising within the GI tract, and there are several main types: normal transit or functional constipation which may be chronic idiopathic constipation (see Chap. 3), irritable bowel syndrome with constipation (see Chap. 4), slow transit constipation (see Chap. 5), or pelvic floor dysfunction or dyssynergic defecation (see Chap. 6). Many patients will suffer from "combination constipation" which can be slow transit with pelvic floor dysfunction or normal transit constipation with pelvic floor dysfunction.

What is normal stool consistency?
The first chapter includes the Bristol Stool Form Scale (see Fig. 1.5). This scale identifies seven distinct stool forms that can correlate with transit. In general, stool should be soft, but formed. The passage of stool should be easy and with regular frequency it is described to patients as analogous to toothpaste flowing from a tube.

How often should one move one's bowels?
Interestingly enough, physicians often define constipation by frequency, but patients are much more concerned by associated symptoms: pain, difficulty defecating, straining, etc. There is a range of normal from three bowel movements per day to

as few as three bowel movements per week. The important issue is whether a patient is comfortable with his or her current frequency and that it conforms to a fairly consistent pattern.

What are the strategies for the evaluation of constipation?
Chapter 2 reviews the many options for testing. The most important first step is to obtain a detailed history and to do a thorough physical examination, including an abdominal examination and a rectal examination. Without alarm signs and symptoms (see Table 2.1), one can proceed with empiric treatment. The algorithms for testing have been changed recently [1]. It is recommended that the assessment of colonic transit be done at a later stage and not initially and reserved for patients who do not have a defecatory disorder or for those with defecatory dysfunction that has not responded to biofeedback. The algorithm presented as Fig. 5.3 shows one accepted approach to the patient with intractable severe chronic constipation. The initial study is anorectal manometry with balloon expulsion. Other, more detailed algorithms do include defecography if manometry and balloon expulsion are inconclusive.

There is great variability for what approaches might be considered based on individual presentation and also the availability of testing. In unique tertiary and quaternary motility centers, there are often distinctive approaches. Chapter 2's author, Dr. Foxx-Orenstein, notes that manometry and nuclear transit studies may be done at the same time in her center which serves as a quaternary referral center where refractory patients (many of whom have already undergone much testing) are seen and where combination constipation is a common presentation. Dr. Foxx-Orenstein further notes that she begins her evaluation with a complete history and rectal exam including visual inspection and digital exam. The patient is then treated with high fiber, adequate hydration, and "bowel management techniques" (hot caffeinated beverage, breakfast, within 45 min of awakening). If there is no improvement, anorectal manometry, colonic transit, and/or defecography are considered. In situations where the patient notes symptoms of prolonged time between stools (>3 days), the colon transit study with anorectal manometry may be performed. These strategies point out the importance of an evidence-based approach as well as tailoring the evaluation to the patient's presentation and to the types of patients that may be seen in specialized centers.

What about the need for colonoscopy?
In general a colonoscopy is not necessary if there are no alarm signs or symptoms. The physician, physician's assistant, nurse practitioner, or trainee MUST always consider screening for colon cancer as a separate issue. Current guidelines call for screening in average-risk patients beginning at age 50, but in African American patients or obese patients some experts suggest that screening begin at age 45 because of the advanced lesions found in these patients.

How do you determine the best treatment option for the symptom of constipation?
Treatment must be individualized depending on the patient's etiology of the symptom. It is important to address pelvic floor dysfunction with biofeedback. This is a unique

form of therapy that addresses the underlying issue and has support for success in the literature (see Chap. 6). Other Chaps. 3–5 review the different options for treatment.

Can using laxatives chronically hurt or lead to addiction?
It is a myth that chronic laxative use leads to harm or to addiction. There were long-held beliefs that the use of chronic stimulant laxatives could cause tolerance or damage to the enteric nervous system, but there is no evidence to support this.

When is surgery the best option?
In general the symptom of constipation can be treated medically. There are certain situations—pertaining to a group of highly selected patients, with slow transit constipation (Chap. 5), some patients with pelvic floor dysfunction (Chap. 6), and specific conditions, e.g., Hirschsprung's disease (Chap. 7), who may require consideration of surgery.

What's new in improvements for bowel movements and what can we look forward to in the future?
There are many drugs in development with novel mechanisms that are being studied for efficacy in the treatment of constipation. Other modalities such as sacral nerve stimulation and colonic pacing are also under study and in development. The gut microbiome and its relationship to disease and symptoms is also an area of high interest. There appear to be promising options for the future.

Summary

Constipation is a problem affecting the quality of life of many. The authors of this book believe that with a deliberate and evidence-based approach, healthcare practitioners across many fields of medicine and serving in many capacities can help patients suffering with this symptom. When "the going gets tough," we recommend a practical approach to diagnosis and treatment in an effort to help the many patients suffering with this symptom.

Reference

1. American Gastroenterological Association, Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. Gastroenterology. 2013;144(1):211–7.

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