bowel syndrome and an ostomy usually require parenteral nutrition and hydration. Those with extensive ileal resection should be tested and treated for vitamin B_{12} deficiency. Adjunctive therapies include antimotility and antisecretory drugs. Glucagon-like peptide 2 and its analog, teduglutide, are new pharmacologic agents for treatment of short bowel syndrome. Both have been evaluated in randomized trials and found to increase intestinal wet weight absorption and decrease parenteral fluid support in patients with short bowel syndrome.

Carbohydrate Malabsorption

Carbohydrates can be classified as monosaccharides (glucose, fructose), disaccharides (lactose, sucrose), oligosaccharides (maltodextrose), or polyols (sorbitol, mannitol). These short-chain carbohydrates are osmotically active and can lead to increased luminal water retention and gas production through colonic fermentation. These two actions can cause gastrointestinal symptoms, including gas, bloating, and diarrhea.

Lactose malabsorption is commonly due to loss of the brush border lactase enzyme in adulthood. Fructose malabsorption can also lead to gastrointestinal symptoms such as bloating and diarrhea. Although both lactose and fructose breath tests are available, testing is often not required, as symptoms subside with exclusion of the sugar from the diet and recur with ingestion.

KEY POINTS

- Small intestinal bacterial overgrowth is caused by various conditions, including impaired motility, strictures, or blind loops, and is treated with antibiotic therapy.
- Short bowel syndrome is defined by a small-intestine length of less than 200 cm, resulting in maldigestion, malabsorption, and malnutrition.
- Lactose malabsorption is common, with symptoms occurring when lactose is ingested and subsiding with exclusion of lactose from the diet.

Inflammatory Bowel Disease

IBD is an idiopathic chronic inflammatory condition of the gut that includes ulcerative colitis and Crohn disease. In addition, microscopic colitis is considered a type of IBD with distinct clinical and pathologic features. The pathogenesis of IBD likely involves host genetic predisposition and abnormal immunologic responses to endogenous gut bacteria.

Risk Factors

The primary risk factor for development of IBD is family history, with a risk of approximately 10% for first-degree relatives of affected patients. Individuals of Ashkenazi Jewish descent have increased risk for IBD. Tobacco smoking increases the risk for Crohn disease and is protective for ulcerative colitis.

IBD has a bimodal age presentation, with an initial peak incidence in the second to fourth decades of life followed by a less prominent second peak in the seventh and eighth decades.

Clinical Manifestations

Ulcerative Colitis

The major symptoms of ulcerative colitis include diarrhea, abdominal discomfort, rectal bleeding, and tenesmus, with symptoms varying depending on the extent and severity of disease. Symptoms typically have a slow, insidious onset and often have been present for weeks or months by the time the patient seeks care, although ulcerative colitis may present acutely, mimicking infectious colitis.

Rectal inflammation (proctitis) causes frequent defecatory urges and passage of small liquid stools containing mucus and blood. Although bloody diarrhea is considered the hallmark presentation of ulcerative colitis, diarrhea is not always present. Patients with proctitis or proctosigmoiditis may have constipation. Abdominal pain is usually not a prominent symptom of ulcerative colitis; however, most patients with active disease experience vague lower-abdominal discomfort relieved with defecation. Physical examination in patients with mild or moderate ulcerative colitis is usually normal but may reveal mild lower-abdominal discomfort over the affected colonic segment. The presence of fever, nausea, vomiting, or severe abdominal pain indicates a severe attack or complication such as superimposed infection or toxic megacolon.

Crohn Disease

The clinical presentation of Crohn disease may be subtle and varies depending on the location and severity of inflammation along the gut axis as well as the presence of intestinal complications such as abscess, stricture, or fistula. Compared with ulcerative colitis, abdominal pain is a more common symptom of Crohn disease. The ileocecal area is the most common bowel segment affected by Crohn disease, and it often presents insidiously with mild diarrhea and abdominal cramping. Abdominal examination may reveal fullness or a tender mass in the right hypogastrium. Some patients present initially with a small-bowel obstruction caused by impaction of indigestible vegetables or fruit. Occasionally, the main presenting symptom is acute pain in the right lower quadrant, mimicking appendicitis. In patients with Crohn colitis, tenesmus is less common than in patients with ulcerative colitis because the rectum is often less inflamed than other colonic segments. Perianal disease is a common presentation of Crohn disease with anal fissures, ulcers, and stenosis.

Fistulae are a frequent manifestation of the transmural nature of Crohn disease and consist of abnormal connections between two epithelial surfaces (perianal, enteroenteric, enterocutaneous, rectovaginal, enterovesical). Drainage of fecal material from fistulae leads to symptoms such as passage of feces through the vagina (rectovaginal fistula). Intra-abdominal

abscesses may form; the classic presentation is spiking fevers and focal abdominal tenderness, which may be masked by the use of glucocorticoids. Strictures represent long-standing inflammation and may occur in any segment of the gastrointestinal tract, although the terminal ileum is the most common site. Strictures may be secondary to fibrosis or severe inflammatory luminal narrowing. Patients with intestinal strictures often initially present with colicky postprandial abdominal pain and bloating that may progress to complete intestinal obstruction.

Table 20 summarizes the features of ulcerative colitis and Crohn disease.

Extraintestinal Manifestations

Inflammatory conditions involving extraintestinal structures, including the joints, eyes, liver, and skin, may occur in patients with IBD. These extraintestinal manifestations are categorized as either associated with active bowel disease or independent of bowel inflammation. Up to 30% of patients with IBD experience an extraintestinal manifestation at some time during the course of their disease; peripheral arthritis is the most common. See MKSAP 18 Rheumatology for discussion of IBD-related arthritis.

The two most common dermatologic extraintestinal manifestations are erythema nodosum and pyoderma gangrenosum. Erythema nodosum most commonly presents as single or multiple tender nodules on extensor surfaces of the lower extremities (**Figure 16**). Pyoderma gangrenosum typically presents as a papule that rapidly develops into an ulcer with undermined and violaceous borders (**Figure 17**). Both manifestations usually correspond to underlying IBD activity. See MKSAP 18 Dermatology for discussion of cutaneous manifestations of IBD.

Ocular extraintestinal manifestations of IBD include episcleritis and uveitis. Episcleritis is more common and consists of injection of the sclera and conjunctiva. It does not affect visual acuity and occurs in association with active bowel disease. Uveitis presents with headache, blurred vision, and

TABLE 20. Features of Ulcerative Colitis and Crohn Disease

Feature	Ulcerative Colitis	Crohn Disease
Depth of inflammation	Mucosal	Transmural
Pattern of disease	Contiguous and symmetric	Skips areas and asymmetric
Location	Colorectum	Mouth to anus
Rectal involvement	Nearly 100%	Less common
Ileal disease	Backwash ileitis (15%)	Common
Fistulas, abscess, and strictures	Rare	Common
Perianal disease	Rare	Common
Granulomas	Unlikely	In approximately 30%
Overt rectal bleeding	Common	Less common
Tobacco use	Protective	Exacerbates

FIGURE 16. Erythema nodosum, a manifestation of inflammatory bowel disease, typically appears as ill-defined erythema overlying subcutaneous, tender nodules most commonly symmetrically located on the anterior shins.

FIGURE 17. Pyoderma gangrenosum, a manifestation of inflammatory bowel disease, typically begins as a small pustule or red nodule that rapidly expands with an edematous, infiltrated, actively inflamed border and a painful, exudative wet ulcer. The border is characteristically violaceous with an edge that overhangs the ulcer.

photophobia. Uveitis is an ocular emergency requiring prompt referral to an ophthalmologist. See MKSAP 18 General Internal Medicine for discussion of episcleritis and uveitis.

Primary sclerosing cholangitis is a major liver manifestation of IBD, occurring in 5% of patients. Patients most often present with isolated elevations in the serum alkaline phosphatase level. The liver disease is typically progressive and independent of the outcome of the IBD. See Disorders of the Liver for discussion of primary sclerosing cholangitis.

Diagnosis

The diagnosis of IBD relies on the integration of the clinical presentation, exclusion of infectious enteropathogens, endoscopic appearance, histologic assessment of mucosal biopsies, and radiologic features. IBD should be considered in any patient with chronic or bloody diarrhea. It is paramount to exclude infection, particularly with *C. difficile* and Shiga toxin-producing *E. coli*, by stool tests, especially in patients with acute onset of symptoms. Fecal calprotectin should be considered to help differentiate IBD from irritable bowel syndrome. Laboratory testing helps to assess disease activity. Common findings include anemia and hypoalbuminemia. Many patients develop iron deficiency anemia from chronic blood loss. Hematologic changes, such as thrombocytosis and leukocytosis, reflect active inflammatory disease. Persistently abnormal serum alkaline phosphatase levels should prompt further investigation for primary sclerosing cholangitis.

Endoscopy (either sigmoidoscopy or colonoscopy) with biopsy is needed to help make the diagnosis of IBD. Colonoscopy is most commonly used to assess the extent and severity of disease. At presentation, 50% of patients with ulcerative colitis have disease limited to the rectum and sigmoid (proctosigmoiditis), 20% have left-sided disease (to the splenic flexure), and 30% present with pancolitis (to the cecum). Endoscopic findings range from decreased vascular pattern with erythema and edema in mild disease to large and deep ulcerations in severe disease. Histopathology characteristically shows features of chronic colitis with distorted and branching colonic crypts along with crypt abscesses.

Crohn disease has a different pattern of distribution from ulcerative colitis: 50% of patients have ileocolonic disease, 30% have isolated small bowel disease, and 20% have colonic disease. A minority of patients have isolated upper gastrointestinal tract or perianal disease in the absence of inflammation in the small bowel or colon. The earliest endoscopic findings of Crohn disease include aphthous ulcers, which can coalesce to form stellate ulcers, and a "cobblestone" mucosal appearance. A characteristic mucosal feature of Crohn disease is the so-called "skip lesion," consisting of affected areas separated by normal mucosa. Granulomatous inflammation is characteristic of Crohn disease but uncommonly found on mucosal biopsies. Histopathology in small-intestinal Crohn disease will show chronic jejunitis or ileitis, and Crohn colitis will have histology similar to that in ulcerative colitis, with exception of granulomas.

Radiographic studies establish the location, extent, and severity of IBD. Patients with a severe attack of IBD require a plain abdominal radiograph to assess for a dilated colon (indicative of evolving toxic megacolon) or small-bowel obstruction (**Figure 18**). CT or MR enterography provides information about the location and severity of small bowel disease and the presence of complicating fistula, abscess, or stricture. Video capsule endoscopy is a highly sensitive modality for detection of small inflammatory lesions of the intestine, although it is not commonly required.

Treatment

The goals of therapy for IBD are to induce and maintain remission, and to prevent disease- and treatment-related complications. Four categories of drugs are used to treat IBD: 5-aminosalicylates, glucocorticoids, immunomodulators, and biologics. Stratification based on clinical severity is important in guiding IBD management. Currently, there are no validated or consensus definitions of mild, moderate, or severe IBD. However, three domains are relevant to the evaluation of disease severity in IBD: impact of the disease on the patient (clinical symptoms, quality of life, and disability); inflammatory burden (extent, location, and severity of bowel involvement); and disease course, including structural

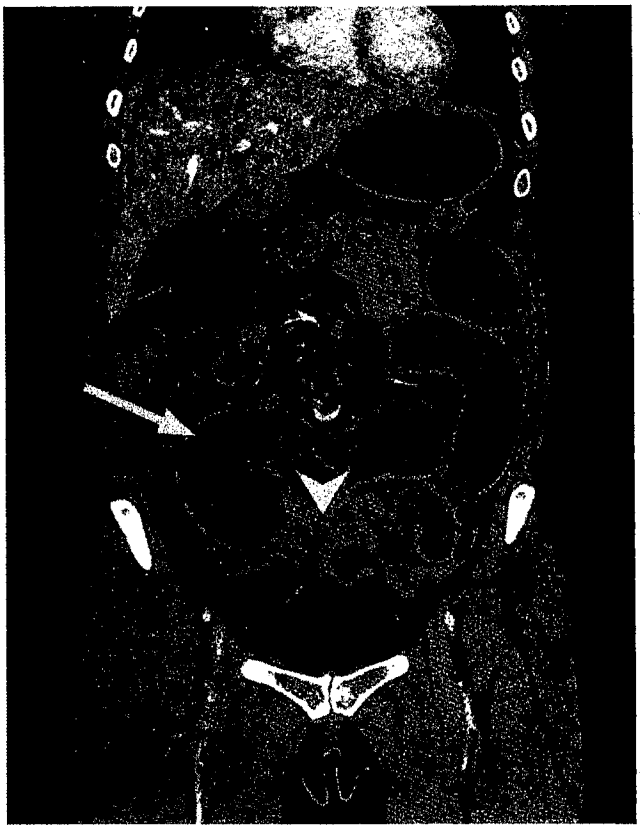

FIGURE 18. CT scan of the abdomen and pelvis in a patient with Crohn disease, showing small-bowel obstruction with dilated loops of small intestine (*arrow*) and matted loops of bowel (*arrowhead*) in the pelvis.

damage. Surgery is reserved for refractory symptoms and complications.

Patients with IBD are at markedly increased risk for venous thromboembolism. The cause of thromboembolism is multifactorial and related to severity of disease, immobilization, and hospitalization. It is important that all hospitalized patients with IBD be given venous thromboembolism prophylaxis with subcutaneous heparin. Only in cases of massive gastrointestinal bleeding with severe anemia, tachycardia, and hypotension should nonpharmacologic prophylaxis with intermittent pneumatic compression of the lower extremities be used.

Pharmacotherapy

5-Aminosalicylates

5-Aminosalicylates (5-ASAs) are believed to have an anti-inflammatory mechanism of action. Various formulations and controlled-release systems are available, with some preparations purported to deliver 5-ASAs to the small bowel.

5-ASAs are the mainstay of treatment of mild to moderate ulcerative colitis, with a dose-dependent response when used to induce disease remission. Three major factors need to be considered when choosing therapy for ulcerative colitis (**Figure 19**). Patients with proctitis or left-sided disease should receive topical therapy with 5-ASA suppositories and enemas. In mild to moderate ulcerative colitis, combined 5-ASA therapy (oral and topical) is superior for induction of remission compared with oral or topical therapies alone. Once remission is achieved, 5-ASAs are effective in maintaining it. Of the available agents, sulfasalazine has the most adverse effects, including fever, rash, nausea, vomiting, and headache. In addition, sulfasalazine may cause reversible sperm abnormalities and impair folate absorption.

Despite the availability of several formulations designed to deliver the drug to the small bowel, 5-ASAs have not proved to be efficacious in small-bowel Crohn disease.

Glucocorticoids

Oral and intravenous glucocorticoids are commonly used to treat moderate to severe flares of IBD and are effective in inducing remission. However, glucocorticoids are not effective for maintenance therapy and have significant adverse effects. One formulation of oral budesonide is a controlled-release glucocorticoid with high first-pass metabolism in the liver and minimal systemic adverse effects. It is effective in inducing remission in mild to moderate ileocolonic Crohn disease. Another oral formulation is multimatrix (MMX) budesonide, designed to release the drug throughout the colon. It is effective in inducing remission in mild to moderate ulcerative colitis.

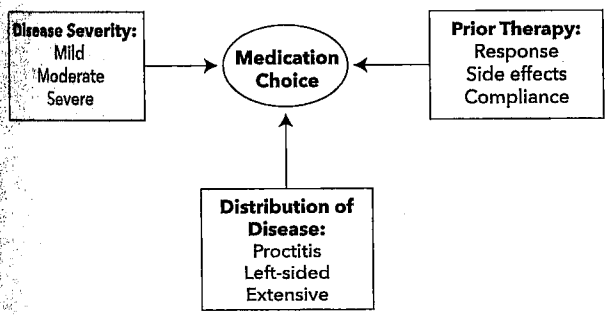

FIGURE 19. Factors to consider when choosing medical therapy for ulcerative colitis.

Immunomodulators

Thiopurines (azathioprine and mercaptopurine [6-MP]) are immunomodulators used as glucocorticoid-sparing agents. They have a slow onset of action (2-3 months) and patients require a tapering glucocorticoid regimen to bridge the time interval until the thiopurines take effect. Thiopurine methyltransferase, a key enzyme involved in the metabolism of azathioprine and 6-MP, exhibits a population polymorphism that greatly increases the risk for bone marrow toxicity with use of these agents. Therefore, before initiation of thiopurine therapy, testing for the *TPMT* genotype or phenotype (enzyme activity) is recommended to help prevent toxicity by identifying individuals with low or absent *TPMT* enzyme activity. However, regardless of *TPMT* status, all patients require monitoring with complete blood counts and liver chemistry testing because 70% of patients who develop leukopenia while using these agents do not have *TPMT* mutations. Azathioprine and 6-MP are reported to cause the rare hepatosplenic T-cell lymphoma. Azathioprine and 6-MP are effective in maintaining remission in patients with ulcerative colitis and should be considered in glucocorticoid-dependent patients. This includes patients who require two courses of glucocorticoids for induction of remission within 1 year, or patients who require intravenous glucocorticoids for acute disease flare.

Methotrexate is an immunomodulator that is beneficial in inducing and maintaining remission in Crohn disease but not in ulcerative colitis. Side effects of methotrexate include hepatotoxicity and interstitial pneumonitis, which can manifest with cough and dyspnea of insidious onset.

Biologic Agents

Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that plays a critical role in the pathogenesis of both Crohn disease and ulcerative colitis. The anti-TNF agents infliximab, adalimumab, and certolizumab are used to treat moderate to severe Crohn disease. Infliximab is administered by intravenous infusion; adalimumab and certolizumab are given subcutaneously. Combination therapy with infliximab and azathioprine is more efficacious than monotherapy with either agent alone in achieving glucocorticoid-free remission and mucosal healing. There is increasing evidence for the use of biologic agents early in the course of disease. Before initiation of anti-TNF agents, patients should undergo testing for latent tuberculosis because of an increased risk for reactivation of tuberculosis during therapy. If latent tuberculosis is present,

treatment with isoniazid should occur for at least 2 months before initiation of anti-TNF therapy. Patients should also be assessed for chronic hepatitis B viral infection before starting anti-TNF therapy and receive treatment if needed.

The anti-TNF agents infliximab, adalimumab, and golimumab are used to treat moderate to severe ulcerative colitis. Combination therapy with infliximab and azathioprine is more effective than monotherapy with either agent in achieving glucocorticoid-free remission and mucosal healing.

The anti-adhesion agents natalizumab and vedolizumab are effective in inducing and maintaining remission for moderate to severe Crohn disease. Ustekinumab, a monoclonal antibody that blocks the biologic activity of interleukin-12 and -23 by inhibiting receptors for these cytokines on T-cells, is efficacious in severe Crohn disease. These agents are typically used after anti-TNF therapies prove ineffective.

Surgery

Indications for surgery in patients with Crohn disease include medically refractory fistula, fibrotic stricture with obstructive symptoms, symptoms refractory to medical therapy, and cancer. The guiding principle of surgery in Crohn disease is the preservation of bowel length and function, as the rate of disease recurrence after segmental resection is high. Patients with Crohn disease who undergo surgery require aggressive pharmacologic treatment with anti-TNF agents and/or immunomodulators to decrease the rate of postoperative recurrence of Crohn disease.

In patients with ulcerative colitis, total proctocolectomy with end-ileostomy or ileal pouch-anal anastomosis is performed for medically refractory disease, toxic megacolon, or carcinoma.

Health Care Considerations

Patients with IBD are at increased risk for vaccine-preventable illnesses, and vaccines are underutilized in this patient population. Inactivated vaccines can be safely administered to all patients with IBD, regardless of immunosuppression. Patients with IBD should receive a seasonal influenza vaccine as well as the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine. Ideally, pneumococcal vaccination should occur before beginning immunosuppressive therapy. Live vaccines such as measles, mumps, rubella; varicella; and herpes zoster are contraindicated in immunosuppressed patients with IBD. See MKSAP 18 General Internal Medicine for discussion of vaccination strategies.

Women with IBD are at increased risk for developing cervical dysplasia; this risk is greater in women with Crohn disease than in those with ulcerative colitis, and is also greater in women using immunosuppressive therapy. Women with IBD should undergo Pap testing annually, and human papillomavirus vaccination is recommended.

All patients with IBD should be encouraged to stop smoking. Smoking increases Crohn disease activity and the risk for extraintestinal manifestations. Patients with IBD are at increased risk for metabolic bone disease due to use of glucocorticoids and diminished vitamin D and calcium absorption. Patients with Crohn disease are at greater risk than those with ulcerative colitis. Screening for osteoporosis should be considered in patients at increased risk.

Patients with IBD are at increased risk for developing cancers of the colorectum, cervix, and skin. Longstanding inflammation of the colorectum increases the risk for cancer. In patients with IBD (ulcerative colitis with disease proximal to the sigmoid colon and Crohn disease with more than one third of the colon involved), surveillance colonoscopy should begin 8 years after diagnosis and recur every 1 to 2 years thereafter. Primary sclerosing cholangitis increases the risk for colorectal cancer, and surveillance colonoscopy should begin at the time of diagnosis and recur yearly thereafter.

Patients with IBD are at increased risk for both melanoma and nonmelanoma skin cancers. Most of the risk has been associated with specific treatments; however, there is some evidence that IBD is associated with an increased risk for melanoma, independent of treatment. All patients with IBD should be advised to use sunscreen, wear protective clothing, avoid tanning beds, and have a yearly skin examination.

Microscopic Colitis

Microscopic colitis is a distinct type of IBD characterized by macroscopically normal mucosa with inflammatory changes seen only on histopathology of colon biopsies. It is subclassified into lymphocytic colitis and collagenous colitis (**Figure 20**) based on predominating histologic features. It predominantly affects middle-aged women and is associated with other autoimmune conditions, particularly celiac disease. It presents with abrupt or gradual onset of watery diarrhea that has a relapsing and remitting course over months to years, sometimes accompanied by mild weight loss.

Several classes of medications, including NSAIDs, selective serotonin reuptake inhibitors, and proton pump inhibitors

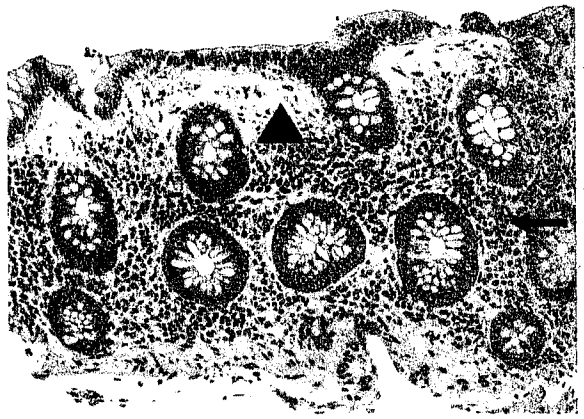

FIGURE 20. Collagenous colitis: colon mucosal biopsy showing a pink, abnormal subepithelial collagen band (*arrowhead*) and lamina propria expanded by inflammatory cells (*arrow*).

have been associated with development of microscopic colitis. The first step in management is to discontinue any potentially causative medication. First-line treatments include supportive treatment with antidiarrheal agents such loperamide or bismuth subsalicylate. The next step is oral budesonide, which is efficacious but has a high rate of recurrent symptoms when discontinued. Unlike Crohn disease and ulcerative colitis, there is no long-term increased risk for colorectal cancer in patients with microscopic colitis.

KEY POINTS

- The major symptoms of ulcerative colitis include diarrhea, abdominal discomfort, rectal bleeding, and tenesmus, with a slow onset of symptoms.
- Fistula, abscess, and stricture are characteristic complications of Crohn disease.
- Endoscopy with biopsy is needed to help make the diagnosis of inflammatory bowel disease.
- The goals of therapy are to induce and maintain remission of inflammatory bowel disease, and to prevent disease- and treatment-related complications.
- Unlike patients with Crohn disease or ulcerative colitis, patients with microscopic colitis are not at increased risk for colorectal cancer.

Constipation

Constipation is one of the most common gastrointestinal symptoms, affecting 20% of the general population. Constipation can present with symptoms including infrequent, difficult, or incomplete defecation. It can be acute or chronic, and either secondary or idiopathic in nature. Medications are the most common cause of secondary constipation; other causes include mechanical obstruction, systemic illnesses, altered physiologic states, and psychosocial conditions (**Table 21**).

Once secondary causes have been excluded, chronic constipation is considered to be functional (idiopathic). The definition of functional constipation has been refined by the fourth Rome working group for functional gastrointestinal disorders. Functional constipation is subtyped into categories of slow transit, normal transit, or dyssynergic defecation. Slow transit constipation is defined as the delayed passage of fecal contents through the colon based on objective transit testing (radiopaque marker study, scintigraphy, or the wireless motility capsule). Normal transit constipation is idiopathic constipation in which colonic transit times are adequate based on objective transit testing. Dyssynergic defecation (also termed pelvic floor dyssynergia, obstructed defecation, or outlet obstruction) refers to difficulty with or inability to expel stool as a result of some combination of abnormalities in contraction and/or relaxation of the muscles of the pelvic floor during defecation. In some cases, functional constipation can be the result of slow transit constipation and coexistent dyssynergic defecation.

TABLE 21. Secondary Causes of Constipation

Medications
Opioids
Antidiarrheals
Anticholinergics (antispasmodics, antiparkinsonian drugs, tricyclic antidepressants, antipsychotics)
Antihistamines
NSAIDs
Iron supplements
Calcium supplements
Bismuth
Antihypertensives (calcium channel blockers, diuretics, clonidine)
Serotonergic antagonists (ondansetron)
Mechanical Causes
Colorectal cancer
Rectocele
Rectal intussusception
Rectal prolapse
Sigmoidocele
Enterocele
Anastomotic stricture
Anal stenosis/stricture
Extrinsic compression from pelvic/abdominal process
Systemic Illnesses
Endocrinologic
Diabetes mellitus
Hypothyroidism
Panhypopituitarism
Pheochromocytoma
Glucagonoma
Neuropathy/myopathy
Altered Physiologic State
Hypercalcemia
Hypokalemia
Pregnancy
Porphyria
Heavy-metal poisoning (arsenic, lead, mercury)
Psychosocial
Depression
Cognitive impairment
Immobility