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Chapter 54: Diarrhea, Constipation, and Irritable Bowel Syndrome

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UPDATE SUMMARY

Update Summary

February 17, 2023

The following sections, tables, and figures were updated:

- Irritable Bowel Syndrome, Epidemiology: revisions made to entire section
- Figure 54-4: loperamide and low-dose tricyclic antidepressants added for diarrhea-predominant disease
- Irritable Bowel Syndrome, Treatment, Constipation Predominant Disease: new paragraph added on tenapanor
- Self-Assessment Questions: questions 13, 14, and 15 updated, along with the answers for 13 and 15

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 22, Constipation and Chapter 23, Diarrhea.

KEY CONCEPTS

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KEY CONCEPTS

1. Diarrhea is caused by many viral and bacterial organisms. It is most often a minor discomfort, not life-threatening, and usually self-limited.
2. The four pathophysiologic mechanisms of diarrhea have been linked to the four broad diarrheal groups, which are secretory, osmotic, exudative, and altered intestinal transit. The three mechanisms by which absorption occurs from the intestines are active transport, diffusion, and solvent drag.
3. Management of diarrhea focuses on preventing excessive water and electrolyte losses, dietary care, relieving symptoms, treating curable causes, and treating secondary disorders.
4. Bismuth subsalicylate is marketed for indigestion, relieving abdominal cramps, and controlling diarrhea, including traveler's diarrhea, but may cause interactions with several components if given excessively.
5. Constipation is defined as difficult or infrequent passage of stool, at times associated with straining or a feeling of incomplete defecation.
6. Underlying causes of constipation should be identified when possible and corrective measures taken (eg, alteration of diet or treatment of diseases such as hypothyroidism).
7. The foundation of treatment of constipation is dietary fiber or bulk-forming laxatives that provide 20 to 25 g/day of raw fiber.
8. Irritable bowel syndrome (IBS) is one of the most common GI disorders characterized by lower abdominal pain, disturbed defecation, and bloating. Many non-GI manifestations also exist with IBS. Visceral hypersensitivity is a major culprit in the pathophysiology of the disease.
9. Diarrhea-predominant IBS should be managed by dietary modification and drugs such as rifaximin or eluxadoline when diet changes alone are insufficient to promote control of symptoms.
10. Several drug classes are involved in the treatment of the pain associated with IBS including tricyclic compounds and the gut-selective calcium channel blockers.

BEYOND THE BOOK

Go to www.loperamidesafety.org/resources and review the fact sheets for healthcare providers aimed at helping identify potential loperamide misuse. Reflecting on your role on the healthcare team, what can you do to ensure safe and appropriate loperamide use?

DIARRHEA

Diarrhea is a troublesome discomfort that affects most individuals in the United States at some point in their lives and can be thought of as both a symptom and a sign. Usually diarrheal episodes begin abruptly and subside within 1 or 2 days without treatment. This chapter focuses primarily on noninfectious diarrhea, with only minor reference to infectious diarrhea (see Chapter 136 for a discussion of gastrointestinal infections). Diarrhea is often a symptom of a systemic disease, and not all possible causes of diarrhea are discussed in this chapter. Acute diarrhea is commonly defined as less than 14-day duration, persistent diarrhea as more than 14-day duration, and chronic diarrhea as more than 30-day duration.

To understand diarrhea, one must have a reasonable definition of the condition; unfortunately, the literature is extremely variable on this. Simply put, diarrhea is an increased frequency and decreased consistency of fecal discharge as compared with an individual's normal bowel pattern. Frequency and consistency are variable within and between individuals. For example, some individuals defecate as often as three times per day, whereas others defecate only two or three times per week. A Western diet usually produces a daily stool weighing between 100 and 300 g, depending on the amount of

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nonabsorbable materials (mainly carbohydrates) consumed. Patients with serious diarrhea may have a daily stool weight in excess of 300 g; however, a subset of patients experience frequent small, watery passages. Additionally, vegetable fiber-rich diets, such as those consumed in some Eastern cultures (eg, those in Africa), produce stools weighing more than 300 g/day.

Diarrhea may be associated with a specific disease of the intestines or secondary to a disease outside the intestines. For instance, bacillary dysentery directly affects the gut, whereas diabetes mellitus causes neuropathic diarrheal episodes. Furthermore, diarrhea can be considered as acute or chronic disease. Infectious diarrhea is often acute; diarrhea secondary to diabetes is chronic. Congenital disorders in GI ion transport mechanisms are another cause of chronic diarrhea.[1] Whether acute or chronic, diarrhea has the same pathophysiologic causes that help in identification of specific treatments.

Epidemiology

The epidemiology of diarrhea varies in developed versus developing countries.[2] In the United States, diarrheal illnesses are usually not reported to the Centers for Disease Control and Prevention (CDC) unless associated with an outbreak or an unusual organism or condition. For example, the acquired immune deficiency syndrome (AIDS) has been identified with protracted diarrheal illness. Diarrhea is a major problem in daycare centers and nursing homes, probably because early childhood and senescence plus environmental conditions are risk factors. Although an exact epidemiologic profile in the United States is not available through the CDC or published literature, 25% of individuals in the United States experience an episode of acute diarrhea annually with increased incidence in children and older adults.[3] In developing countries, diarrhea is a leading cause of illness and death in children, creating a tremendous economic strain on healthcare costs.

1 Most cases of acute diarrhea are self-limiting infections caused by food or waterborne organisms, such as viruses, bacteria, or protozoa.[4] Although viruses are more commonly associated with acute gastroenteritis, bacteria are responsible for more cases of acute diarrhea. Evaluation of a noninfectious cause is considered if diarrhea persists and no infectious organism can be identified, or if the patient falls into a high-risk category for metabolic complications with persistent diarrhea. Common causative bacterial organisms include *Shigella*, *Salmonella*, *Campylobacter*, *Staphylococcus*, and *Escherichia coli*. Foodborne bacterial infection is a major concern, as several major food poisoning episodes have occurred that were traced to poor sanitary conditions in meat processing plants. Acute viral infections are attributed mostly to the Norwalk and rotavirus groups.

Physiology

In the fasting state, 9 L of fluid enters the proximal small intestine each day. Of this fluid, 2 L is ingested through diet, while the remainder consists of internal secretions. Because of meal content, duodenal chyme is usually hypertonic. When chyme reaches the ileum, the osmolality adjusts to that of plasma, with most dietary fat, carbohydrate, and protein being absorbed. The volume of ileal chyme decreases to about 1 L/day on entering the colon, which is further reduced by colonic absorption to 100 mL daily. If the small intestine water absorption capacity is exceeded, chyme overloads the colon, resulting in diarrhea. In humans, the colon absorptive capacity is about 5 L daily. Colonic fluid transport is critical to water and electrolyte balance.

Absorption of fluid from the intestines back into the blood occurs by three mechanisms: active transport, diffusion, and solvent drag. Active transport and diffusion are the mechanisms of sodium transport. Because of the high luminal sodium concentration (142 mEq/L [mmol/L]), sodium diffuses from the sodium-rich gut into epithelial cells, where it is actively pumped into the blood and exchanged with chloride to maintain an isoelectric condition across the epithelial membrane. Hydrogen ions are transported by an indirect mechanism in the upper small intestine. As sodium is absorbed, hydrogen ions are secreted into the gut. Hydrogen ions then combine with bicarbonate ions to form carbonic acid, which then dissociates into carbon dioxide and water. Carbon dioxide readily diffuses into the blood for expiration through the lung. The water remains in the chyme.

Paracellular pathways are major routes of ion movement. As ions, monosaccharides, and amino acids are actively transported, an osmotic pressure is created, drawing water and electrolytes across the intestinal wall. This pathway accounts for significant amounts of ion transport, especially sodium. Sodium plays an important role in stimulating glucose absorption. Glucose and amino acids are actively transported into the blood via a sodium-dependent cotransport mechanism. Cotransport absorption mechanisms of glucose–sodium and amino acid–sodium are extremely important for treating diarrhea.

Gut motility influences absorption and secretion. The amount of time in which luminal content is in contact with the epithelium is under neural and hormonal control. Neurohormonal substances, such as angiotensin, vasopressin, glucocorticoid, aldosterone, and neurotransmitters, also regulate ion transport.

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Pathophysiology

Four general pathophysiologic mechanisms disrupt water and electrolyte balance, leading to diarrhea, and are the basis of diagnosis and therapy. These are (a) a change in active ion transport by either decreased sodium absorption or increased chloride secretion; (b) change in intestinal motility; (c) increase in luminal osmolarity; and (d) increase in tissue hydrostatic pressure. These mechanisms have been related to four broad clinical diarrheal groups: secretory, osmotic, exudative, and altered intestinal transit.

Secretory diarrhea occurs when a stimulating substance either increases secretion or decreases absorption of large amounts of water and electrolytes. Substances that cause excess secretion include vasoactive intestinal peptide (VIP) from a pancreatic tumor, unabsorbed dietary fat in steatorrhea, laxatives, hormones (such as secretion), bacterial toxins, and excessive bile salts. Many of these agents stimulate intracellular cyclic adenosine monophosphate and inhibit Na^+/K^+-adenosine triphosphatase (ATPase), leading to increased secretion. Also, many of these mediators inhibit ion absorption simultaneously. Secretory diarrhea is recognized by large stool volumes (more than 1 L/day) with normal ionic contents and osmolality approximately equal to plasma. Fasting does not alter the stool volume in these patients.

Poorly absorbed substances retain intestinal fluids, resulting in osmotic diarrhea. This process occurs with malabsorption syndromes, lactose intolerance, administration of divalent ions (eg, magnesium-containing antacids), or consumption of poorly soluble carbohydrate (eg, lactulose). As a poorly soluble solute is transported, the gut adjusts the osmolality to that of plasma; in so doing, water and electrolytes flux into the lumen. Clinically, osmotic diarrhea is distinguishable from other types, as it ceases if the patient resorts to a fasting state.

Inflammatory diseases of the GI tract discharge mucus, serum proteins, and blood into the gut. Sometimes bowel movements consist only of mucus, exudate, and blood. Exudative diarrhea affects other absorptive, secretory, or motility functions to account for the large stool volume associated with this disorder.

Altered intestinal motility produces diarrhea by three mechanisms: (1) reduction of contact time in the small intestine, (2) premature emptying of the colon, and (3) bacterial overgrowth. Chyme must be exposed to intestinal epithelium for a sufficient time period to enable normal absorption and secretion processes to occur. If this contact time decreases, diarrhea results. Intestinal resection or bypass surgery and drugs (such as metoclopramide) cause this type of diarrhea. On the other hand, an increased time of exposure allows fecal bacteria overgrowth. A characteristic small intestine diarrheal pattern is rapid, small, coupling bursts of waves. These waves are inefficient, do not allow absorption, and rapidly dump chyme into the colon. Once in the colon, chyme exceeds the colonic capability to absorb water.

Examination of the Stool

Stool characteristics are important in assessing the etiology of diarrhea. A description of the frequency, volume, consistency, and color provides diagnostic clues. For instance, diarrhea starting in the small intestine produces a copious, watery or fatty (greasy), and foul-smelling stool; contains undigested food particles; and is usually free from gross blood. Colonic diarrhea appears as small, pasty, and sometimes bloody or mucoid movements. Rectal tenesmus with flatus accompanies large intestinal diarrhea.

Clinical Presentation

Table 54-1 outlines the clinical presentation of diarrhea, and Table 54-2 shows common drug-induced causes of diarrhea. A medication history is extremely important in identifying drug-induced diarrhea. Many agents, including antibiotics and other drugs, cause diarrhea or, less commonly, pseudomembranous colitis. Self-inflicted laxative abuse for weight loss is common.

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TABLE 54-1

Clinical Presentation of Diarrhea

General

- Usually, acute diarrheal episodes subside within 72 hours of onset, whereas chronic diarrhea involves frequent attacks over extended time periods.

Signs and symptoms

- Abrupt onset of nausea, vomiting, abdominal pain, headache, fever, chills, and malaise.
- Bowel movements are frequent and never bloody, and diarrhea lasts 12-60 hours.
- Intermittent periumbilical or lower right quadrant pain with cramps and audible bowel sounds is characteristic of small intestinal disease.
- When pain is present in large intestinal diarrhea, it is a gripping, aching sensation with tenesmus (straining, ineffective, and painful stooling). Pain localizes to the hypogastric region, right or left lower quadrant, or sacral region.
- In chronic diarrhea, a history of previous bouts, weight loss, anorexia, and chronic weakness are important findings.

Physical examination

- Typically demonstrates hyperperistalsis with borborygmi and generalized or local tenderness.

Laboratory tests

- Stool analysis studies include examination for microorganisms, blood, mucus, fat, osmolality, pH, electrolyte and mineral concentration, and cultures.
- Stool test kits are useful for detecting GI viruses, particularly rotavirus.
- Antibody serologic testing shows rising titers over a 3- to 6-day period, but this test is not practical and is nonspecific.
- Occasionally, total daily stool volume is also determined.
- Direct endoscopic visualization and biopsy of the colon may be undertaken to assess for the presence of conditions such as colitis or cancer.
- Radiographic studies are helpful in neoplastic and inflammatory conditions.

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TABLE 54-2

Drugs Causing Diarrhea

- Laxatives
  - Antacids containing magnesium
- Antineoplastics
- Auranofin (gold salt)
- Antibiotics
  - Clindamycin
  - Tetracyclines
  - Sulfonamides
  - Any broad-spectrum antibiotic
- Antihypertensives
  - Reserpine
  - Guanethidine
  - Methyldopa
  - Guanabenz
  - Guanadrel
  - Angiotensin-converting enzyme inhibitors
- Cholinergics
  - Bethanechol
  - Neostigmine
- Cardiac agents
  - Quinidine
  - Digitalis
  - Digoxin
- Nonsteroidal anti-inflammatory drugs
- Misoprostol
- Colchicine
- Proton pump inhibitors
- H_2-receptor blockers

Most acute diarrhea is self-limiting, subsiding within 72 hours. However, infants, young children, older patients, and debilitated persons are at risk for morbid and mortal events in prolonged or voluminous diarrhea. These groups are at risk for water, electrolyte, and acid-base disturbances, and potentially cardiovascular collapse and death. The prognosis for chronic diarrhea depends on the cause; for example, diarrhea secondary to diabetes mellitus waxes and wanes throughout life.

Patient Care Process for Diarrhea

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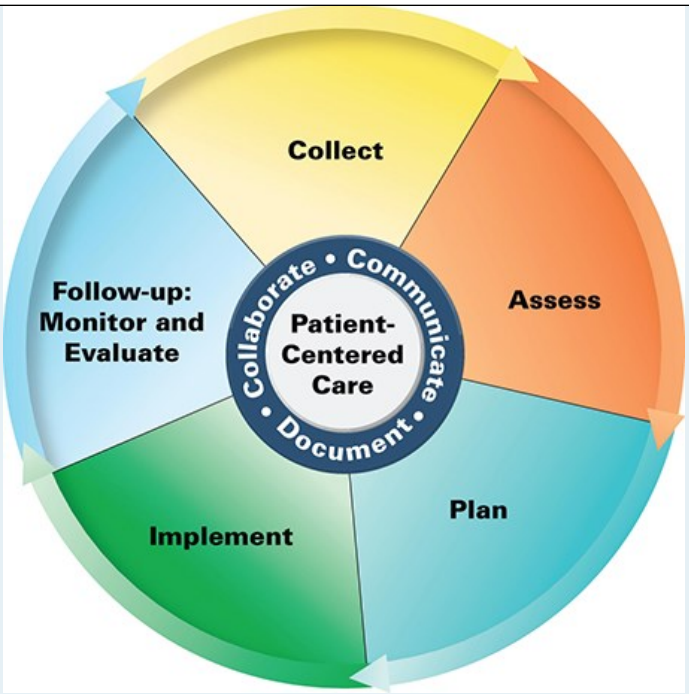

Collect

- Patient characteristics
- Patient medical, family, social history, and dietary habits
- Current medications, including nonprescription
- Vital signs and weight
- Laboratory tests depending upon medical history and other presenting symptoms
    - Thyroid function tests, complete blood count, glucose, serum electrolytes

Assess

- Underlying causes of diarrhea (see Tables 54-1 and 54-2)
- Severity and duration of symptoms
- Patient preference for symptom resolution
- Ability/willingness to pay for treatment options

Plan*

- Treat specific cause of diarrhea (ie, diabetes, infectious)
- Increase fluid intake using oral rehydration solutions (ORS) (Table 54-3)
- Antidiarrheal medication (Table 54-4)
- Monitor symptom resolution for efficacy, and pronounced constipation for safety
- Patient education regarding importance of prevention dehydration

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- Referral to other providers when appropriate

Implement

- Educate the patient on all aspects of the treatment plan
- Schedule follow-up to monitor safety and efficacy of treatment plan

Follow-up: Monitor and Evaluate

- Determine resolution of diarrhea and related symptoms
- Evaluate for signs and symptoms of dehydration
- Assess for presence of adverse effects (eg, abdominal pain, constipation)
- Assess patient adherence to treatment plan
- Reevaluate periodically until resolution

**Collaborate with patient, caregivers, and other healthcare professionals.*

Treatment and Prevention

Acute viral diarrheal illness often occurs in daycare centers and nursing homes. Because person-to-person contact is the mechanism by which viral disease spreads, isolation techniques must be initiated. For bacterial, parasitic, and protozoal infections, strict food handling, sanitation, water, and other environmental hygiene practices can prevent transmission. If diarrhea is secondary to another illness, controlling the primary condition is necessary. Antibiotics and bismuth subsalicylate are advocated to prevent traveler's diarrhea, in conjunction with treatment of drinking water and caution with consumption of fresh vegetables.[5,6]

Desired Outcome

If prevention is unsuccessful and diarrhea occurs, therapeutic goals are to (a) manage the diet; (b) prevent excessive water, electrolyte, and acid-base disturbances; (c) provide symptomatic relief; (d) treat curable causes; and (e) manage secondary disorders causing diarrhea (Figs. 54-1 and 54-2).

FIGURE 54-1

Recommendations for treating acute diarrhea. Follow the following steps: (a) Perform a complete history and physical examination. (b) Is the diarrhea acute or chronic? If chronic diarrhea, go to Fig. 54-2. (c) If acute diarrhea, check for fever and/or systemic signs and symptoms (ie, toxic patient). If systemic illness (fever, anorexia, or volume depletion), check for an infectious source. If positive for infectious diarrhea, use appropriate antibiotic/anthelmintic drug and symptomatic therapy. If negative for infectious cause, use only symptomatic treatment. (d) If no systemic findings, then use symptomatic therapy based on severity of volume depletion, oral or parenteral fluid/electrolytes, antidiarrheal agents (see Table 54-4), and diet. (RBC, red blood cells; WBC, white blood cells.)

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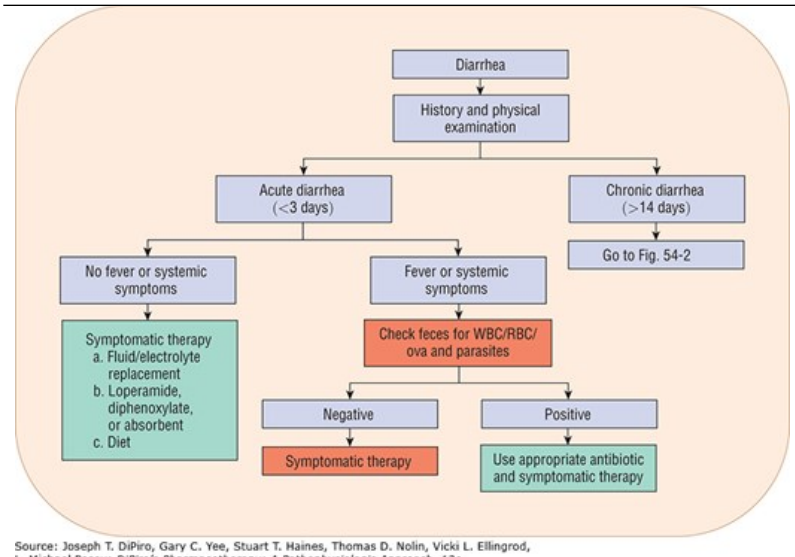

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FIGURE 54-2

Recommendations for treating chronic diarrhea. Follow the following steps: (a) Perform a careful history and physical examination. (b) The possible causes of chronic diarrhea are many. These can be classified into intestinal infections (bacterial or protozoal), inflammatory disease (Crohn's disease or ulcerative colitis), malabsorption (lactose intolerance), secretory hormonal tumor (intestinal carcinoid tumor or vasoactive intestinal peptide-secreting tumor [VIPoma]), drug (antacid), factitious (laxative abuse), or motility disturbance (diabetes mellitus, irritable bowel syndrome, or hyperthyroidism). (c) If the diagnosis is uncertain, selected appropriate diagnostic studies should be ordered. (d) Once diagnosed, treatment is planned for the underlying cause with symptomatic antidiarrheal therapy. (e) If no specific cause can be identified, symptomatic therapy is prescribed. (RBC, red blood cells; WBC, white blood cells.)

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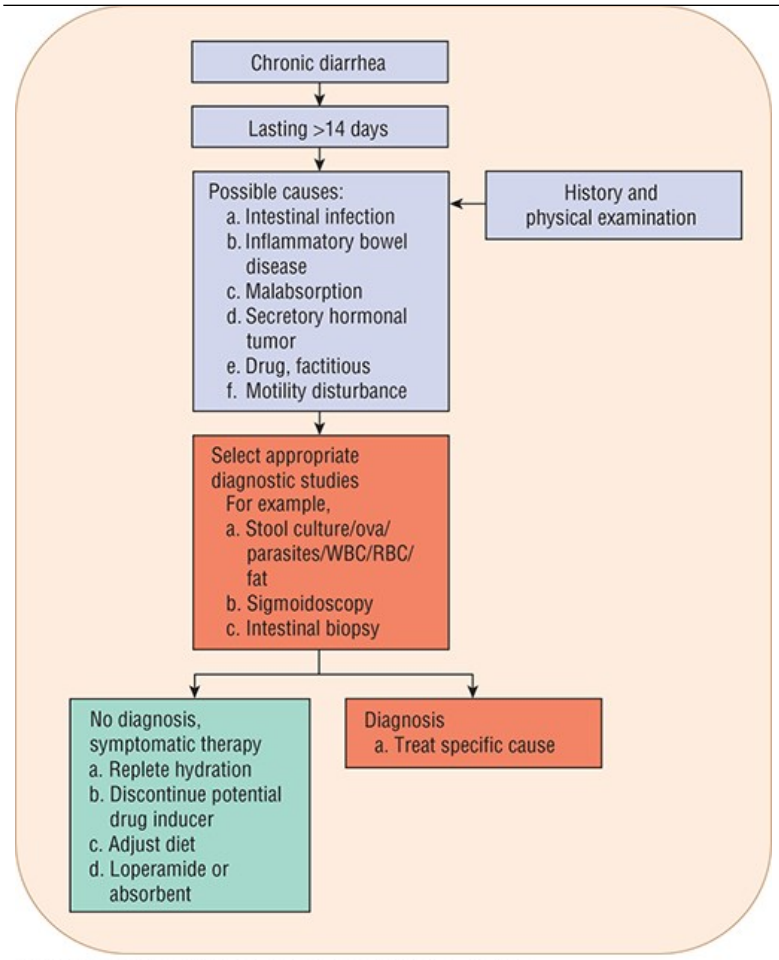

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Clinicians must clearly understand that diarrhea, like a cough, may be a body defense mechanism for ridding itself of harmful substances or pathogens. The correct therapeutic response is not necessarily to stop diarrhea at all costs.

Nonpharmacologic Management

Dietary management is a first priority in the treatment of diarrhea. Feeding should continue in children with acute bacterial diarrhea. Fed children have less morbidity and mortality, whether or not they receive oral rehydration fluids. Studies are not available in older patients or in other high-risk groups to determine the value of continued feeding in bacterial diarrhea.

Water and Electrolytes

Rehydration and maintenance of water and electrolytes are primary treatment goals until the diarrheal episode ends. If the patient is volume depleted, rehydration should be directed at replacing water and electrolytes to normal body composition. Then water and electrolyte composition are maintained by replacing losses. Many patients will not develop volume depletion and therefore will only require maintenance fluid and electrolyte therapy. Parenteral and enteral routes may be used for supplying water and electrolytes. If vomiting and dehydration are not severe, the enteral route is the less costly and preferred. In the United States, many commercial oral rehydration preparations are available (Table 54-3).

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TABLE 54-3

Oral Rehydration Solutions

	WHO-ORS[a]	Pedialyte[b] (Ross)	CeraLyte (Cera Products)	Enfalyte (Mead Johnson)
Osmolality (mOsm/kg or mmol/kg)	245	250	220	167
Carbohydrates[b] (g/L)	13.5	25	40[c]	30[c]
Calories (cal/L [J/L])	65 (272)	100 (418)	160 (670)	126 (527)
Electrolytes (mEq/L; mmol/L)				
Sodium	75	45	50-90	50
Potassium	20	20	20	25
Chloride	65	35	40-80	45
Citrate	—	30	30	34
Bicarbonate	30	—	—	—
Calcium	—	—	—	—
Magnesium	—	—	—	—
Sulfate	—	—	—	—
Phosphate	—	—	—	—

[a]The World Health Organization (WHO) reduced osmolarity oral rehydration solution.

[b]Carbohydrate is glucose.

[c]Rice syrup solids are carbohydrate source.

Because of concerns about hypernatremia, physicians continue to hospitalize patients and use IV fluids to correct fluid and electrolyte deficits in severe dehydration. Oral solutions are strongly recommended when tolerated to limit side effects, reduce costs, and improve recovery.[7] In developing countries, the WHO oral rehydration solution (WHO-ORS) saves the lives of millions of children annually.

During diarrhea, the small intestine retains its ability to actively transport monosaccharides such as glucose. Glucose actively carries sodium with water and other electrolytes. The WHO recommends an ORS with a lower osmolarity, sodium content, and glucose load (see Table 54-3).[8] A separate oral supplement of zinc 20 mg daily for 10 days in addition to ORS significantly reduces the severity and duration of acute diarrhea in developing countries.[2] ORS is a lifesaving treatment for millions afflicted in developing countries. Acceptance in developed countries is less enthusiastic; however, the advantage of this product in reducing hospitalizations may prove its use as a cost-effective alternative, saving millions of dollars in healthcare expenditures.

Pharmacologic Therapy

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Various drugs have been used to treat diarrheal attacks (Table 54-4), including antimotility agents, adsorbents, antisecretory compounds, antibiotics, enzymes, and intestinal microflora. Usually these drugs are not curative but palliative.

TABLE 54-4

Selected Antidiarrheal Preparations

	Dose Form	Adult Dose
Antimotility		
Diphenoxylate	2.5 mg/tablet 2.5 mg/5 mL	5 mg four times daily; do not exceed 20 mg/day
Loperamide	2 mg/capsule	Initially 4 mg, and then 2 mg after each loose stool; do not exceed 16 mg/day
Paregoric	2 mg/5 mL (morphine)	5-10 mL one to four times daily
Opium tincture	10 mg/mL (morphine)	0.6 mL four times daily
Difenoxin	1 mg/tablet	Two tablets, and then one tablet after each loose stool; up to eight tablets per day
Adsorbents		
Kaolin-pectin mixture	5.7 g kaolin + 130.2 mg pectin/30 mL	30-120 mL after each loose stool
Polycarbophil	500 mg/tablet	Chew 2 tablets four times daily or after each loose stool; do not exceed 12 tablets per day
Attapulgite	750 mg/15 mL 300 mg/7.5 mL 750 mg/tablet 600 mg/tablet 300 mg/tablet	1,200-1,500 mg after each loose bowel movement or every 2 hours; up to 9,000 mg/day
Antisecretory		
Bismuth subsalicylate	1,050 mg/30 mL 262 mg/15 mL 524 mg/15 mL 262 mg/tablet	Two tablets or 30 mL every 30 minutes to 1 hour as needed up to eight doses per day
Enzymes		
lactase	1,250 neutral lactase units/4 drops	Three to four drops taken with milk or dairy product
	3,300 FCC lactase units per tablet	

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Bacterial replacement (*Lactobacillus acidophilus*, *Lactobacillus bulgaricus*)		Two tablets or one granule packet three to four times daily; give with milk, juice, or water
Octreotide	0.05 mg/mL 0.1 mg/mL 0.5 mg/mL	Initial: 50 mcg subcutaneously One to two times per day and titrate dose based on indication up to 600 mcg/day in two to four divided doses

Opiates and Their Derivatives

Opiates and opioid derivatives (a) delay the transit of intraluminal contents or (b) increase gut capacity, prolonging contact and absorption. Enkephalins, which are endogenous opioid substances, regulate fluid movement across the mucosa by stimulating absorptive processes. Limitations to the use of opiates include an addiction potential (a real concern with long-term use) and potential for worsening of diarrhea in selected infectious diarrhea.

Most opiates act through peripheral and central mechanisms with the exception of loperamide, which acts only peripherally. Loperamide is antisecretory; it inhibits the calcium-binding protein calmodulin, controlling chloride secretion. Loperamide, available as 2 mg capsules or 1 mg/5 mL solution (both are nonprescription products), is suggested for managing acute and chronic diarrhea. The usual adult dose for acute diarrhea is initially 4 mg orally, followed by 2 mg after each loose stool, up to 16 mg/day. Used correctly, this agent has rare side effects, such as dizziness and constipation. If the diarrhea is concurrent with a high fever or bloody stool, the patient should be referred to a physician. Also, diarrhea lasting 48 hours beyond initiating loperamide warrants medical attention. Loperamide can also be used in traveler's diarrhea. It is comparable to bismuth subsalicylate for treatment of this disorder.[5] The Food and Drug Administration (FDA) has released a warning about using high doses of loperamide for euphoria as it can lead to serious side effects including cardiovascular problems.[9] The packaging of loperamide has been reduced to minimize abuse.[10]

Diphenoxylate is available as a 2.5-mg tablet and as a 2.5 mg/5 mL solution. A small amount of atropine (0.025 mg) is included in the product to discourage abuse. In adults, when taken as 2.5 to 5 mg three or four times daily, not to exceed a 20 mg total daily dose, diphenoxylate is rarely toxic. Some patients may complain of atropinism (blurred vision, dry mouth, and urinary hesitancy). Like loperamide, it should not be used in patients who are at risk of bacterial enteritis with *E. coli*, *Shigella*, or *Salmonella*.

Difenoxin, a diphenoxylate derivative also chemically related to meperidine, is also combined with atropine and has the same uses, precautions, and side effects. Marketed as a 1-mg tablet, the adult dosage is 2 mg initially, followed by 1 mg after each loose stool, not to exceed 8 mg/day.

Paregoric, camphorated tincture of opium, is marketed as a 2 mg/5 mL solution and is indicated for managing both acute and chronic diarrhea. It is not widely prescribed today because of its abuse potential.

Adsorbents

Adsorbents are used for symptomatic relief. These products, many not requiring a prescription, are nontoxic, but their effectiveness remains unproven. Adsorbents are nonspecific in their action; they adsorb nutrients, toxins, drugs, and digestive juices. Polycarbophil absorbs 60 times its weight in water and can be used to treat both diarrhea and constipation. It is a nonprescription product and is sold as a 500-mg chewable tablet. This hydrophilic, nonabsorbable product is safe and may be taken four times daily, up to 6 g/day in adults. See Table 54-4 for selected antidiarrheal preparations.

Antisecretory Agents

Bismuth subsalicylate have antisecretory, anti-inflammatory, and antibacterial effects. As a nonprescription product, it is marketed for indigestion, relieving abdominal cramps, and controlling diarrhea, including traveler's diarrhea. Bismuth subsalicylate dosage strengths are a 262-mg chewable tablet, 262-mg/5 mL liquid, and 524-mg/15 mL liquid. The usual adult dose is two tablets or 30 mL every 30 minutes to 1 hour up to eight doses per day.

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Bismuth subsalicylate contains multiple components that might be toxic if given in excess to prevent or treat diarrhea. For instance, an active ingredient is salicylate, which may interact with anticoagulants or may produce salicylism (tinnitus, nausea, and vomiting). Bismuth reduces tetracycline absorption and may interfere with select GI radiographic studies. Patients may complain of a darkening of the tongue and stools with repeat administration. Salicylate can induce gout attacks in susceptible individuals.

Bismuth subsalicylate suspension is useful in the treatment of secretory diarrhea of infectious etiology as well. With a dose of 30 mL every 30 minutes for eight doses, unformed stools decrease in the first 24 hours. Bismuth subsalicylate may also be effective in preventing traveler's diarrhea.

Octreotide, a synthetic octapeptide analog of endogenous somatostatin, is effective for the symptomatic treatment of carcinoid tumors and other peptide-secreting tumors, dumping syndrome, and chemotherapy-induced diarrhea.[11] It has had limited success in patients with AIDS-associated diarrhea and short-bowel syndrome, does not appear to have an advantage over various opiate derivatives in the treatment of chronic idiopathic diarrhea, and has the disadvantage of being administered by injection.[4] Metastatic intestinal carcinoid tumors secrete excessive amounts of vasoactive substances, including histamine, bradykinin, serotonin (5-hydroxytryptamine, 5-HT), and prostaglandins. Primary carcinoid tumors occur throughout the GI tract, with most in the ileum. Predominant signs and symptoms experienced by patients with these tumors are attributable to excessive concentrations of 5-hydroxytryptophan and 5-HT. The totality of their clinical effects is termed the carcinoid syndrome. Some patients have a violent, watery diarrhea with abdominal cramping. Initially, diarrhea might be managed with various agents such as codeine, diphenoxylate, cyproheptadine, methysergide, phenoxybenzamine, or methyldopa, but octreotide is now considered first-line therapy for carcinoid syndrome.

Octreotide blocks the release of 5-HT and many other active peptides and has been effective in controlling diarrhea and flushing. It is reported to have direct inhibitory effects on intestinal secretion and stimulatory effects on intestinal absorption. Non–gastrin-secreting adenomas of the pancreas are tumors associated with profuse watery diarrhea. This condition has been referred to as Verner–Morrison syndrome, watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome, pancreatic cholera, watery diarrhea syndrome, and vasoactive intestinal peptide-secreting tumor (VIPoma). Excessive secretion of VIP from a retroperitoneal or pancreatic tumor produces most of the clinical features. Surgical tumor dissection is the treatment of choice. In nonsurgical candidates, the profuse watery diarrhea and other symptoms commonly encountered are managed with octreotide.

The dose of octreotide varies with the indication, disease severity, and patient response.[11] For managing diarrhea and flushing associated with carcinoid tumors in adults, the initial dosage range is 100 to 600 mcg/day in two to four divided doses subcutaneously for 2 weeks. For controlling secretory diarrhea of VIPomas, the dosage range is 200 to 300 mcg/day in two to four divided doses for 2 weeks. Some patients may require higher doses for symptomatic control. Patients responding to these initial doses may be switched to Sandostatin LAR Depot, a long-acting octreotide formulation. Initial doses consist of 20 mg given intramuscularly intragluteally at 4-week intervals for 2 months. During the first 2 weeks of therapy the short-acting formulation should be administered subcutaneously. At the end of 2 months, patients with good symptom control may have the dose reduced to 10 mg every 4 weeks, while those without sufficient symptom control may have the dose increased to 30 mg every 4 weeks. For patients experiencing recurrence of symptoms on the 10 mg dose, dosage adjustment to 20 mg should be made. Patients with carcinoid tumors or VIPomas may experience periodic exacerbation of symptoms. Subcutaneous octreotide for several days should be reinstituted in these individuals. In so-called carcinoid crisis, octreotide is given as an IV infusion at 50 mcg/hr for 8 to 24 hours.

Because octreotide inhibits many other GI hormones, it has a variety of intestinal side effects. With prolonged use, gallbladder and biliary tract complications such as cholelithiasis may occur. Approximately 5% to 10% of patients complain of nausea, diarrhea, and abdominal pain. Local injection pain occurs with about an 8% incidence. With high doses, octreotide may reduce dietary fat absorption, leading to steatorrhea.

Two other somatostatin analogs, lanreotide and vapreotide, have been studied.[4] Lanreotide is approved for use in the United States for acromegaly. The starting dose is 90 mg subcutaneously every 4 weeks for 3 months, and then the dose is adjusted based on growth hormone and insulin-like growth factor levels.[12] Vapreotide is an orphan drug that is indicated for pancreatic and GI fistulas as well as esophageal variceal bleeding.

Miscellaneous Products

Probiotics are microorganisms given to reestablish normal colonic microflora. This supposedly restores normal intestinal function and suppresses the growth of pathogenic microorganisms. There is conflicting evidence on whether *Saccharomyces boulardii*, *Lactobacillus* GG, and *Lactobacillus acidophilus* decrease the duration of infectious and antibiotic-induced diarrhea in adults and children.[13] Probiotics may prevent antibiotic-associated diarrhea (AAD).[14] However, a randomized control trial in hospitalized patients over the age of 65 years found no difference in cases of AAD between a

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probiotic preparation (two strains of lactobacillus acidophilus and Bifidobacterium) and placebo.[15] The dosage of probiotic preparations varies depending on the brand used. Intestinal flatus is the primary patient complaint experienced with this modality.

Anticholinergic drugs such as atropine block vagal tone and prolong gut transit time. Drugs with anticholinergic properties are present in many nonprescription products. Their value in controlling diarrhea is questionable and limited because of side effects. Angle-closure glaucoma, selected heart diseases, and obstructive uropathies are relative contraindications to the use of anticholinergic agents.

Lactase enzyme products are helpful for patients who are experiencing diarrhea secondary to lactose intolerance. Lactase is required for carbohydrate digestion. When a patient lacks this enzyme, eating dairy products causes an osmotic diarrhea. Several products are available for use each time a dairy product, especially milk or ice cream, is consumed.

Vaccines

Vaccines are a new therapeutic frontier in controlling infectious diarrheas, especially in developing countries.[16] An oral vaccine for cholera (Vaxchora®) is licensed for use in the United States. The Advisory Committee for Immunization Practices (ACIP) recommends the vaccine for adults aged 18 to 64 years old who are traveling to an endemic area.[17] Studies in the United States suggest the vaccine can reduce the risk of severe diarrhea by about 90%, but data in endemic areas is lacking.[18]

Oral *Shigella* vaccine, although effective under field conditions, requires five weekly oral doses and repeat booster doses, thereby limiting its practicality for use in developing nations. With about 1,500 serotypes for *Salmonella*, a vaccine is not available for humans. There are two newer typhoid vaccine formulations, one a parenteral inactivated whole-cell vaccine and the other an oral live-attenuated (Ty21a) vaccine that is administered in four doses on days 1, 3, 5, and 7, to be completed at least 1 week before exposure. Two rotavirus vaccines prevent gastroenteritis due to rotavirus infection in infants and children in the United States.[19] The pentavalent human-bovine reassortant vaccine (RotaTeq from Merck) is administered as a three-oral-dose sequence, and the monovalent human vaccine (Rotarix from GlaxoSmithKline) is administered as a two-oral-dose sequence. Two additional vaccines were prequalified by the WHO in 2018 and are being utilized in India (Rotavac from Bharat Biotech and ROTASIL from Serum Institute of India Pvt. Ltd.).[20]

Evaluation of Therapeutic Outcomes

Therapeutic outcomes are directed toward key symptoms, signs, and laboratory studies. Constitutional symptoms usually improve within 24 to 72 hours. Monitoring for changes in the frequency and character of bowel movements on a daily basis in conjunction with vital signs and improvement in appetite are of utmost importance. Also, the clinician needs to monitor body weight, serum osmolality, serum electrolytes, complete blood cell counts, urinalysis, and culture results (if appropriate).

Acute Diarrhea

Most patients with acute diarrhea experience mild-to-moderate distress. In the absence of moderate-to-severe dehydration, high fever, and blood or mucus in the stool, this illness is usually self-limiting within 3 to 7 days. Mild-to-moderate acute diarrhea is usually managed on an outpatient basis with oral rehydration, symptomatic treatment, and diet. Older patients with chronic illness as well as infants may require hospitalization for parenteral rehydration and close monitoring.

Severe Diarrhea

In the urgent/emergent situation, restoration of the patient's volume status is the most important outcome. Toxic patients (fever dehydration, hematochezia, or hypotension) require hospitalization, IV fluids and electrolyte administration, and empiric antibiotic therapy while awaiting culture and sensitivity results. With timely management, these patients usually recover within a few days.

CONSTIPATION

5 Constipation is a common complaint among the general population and accounts for many medical visits each year in the United States.[21] It is generally defined by the American Gastroenterology Association (AGA) as difficult or infrequent passage of stool, at times associated with straining or a

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feeling of incomplete defecation.[22]

Constipation may be further defined by quantitative or qualitative measures. For instance, physicians often use stool frequency to define constipation (most commonly fewer than three bowel movements per week); however, the “normal” frequency of bowel movement is not well established and can vary from person to person. Patients more often describe constipation in terms of symptoms or a combination of quantitative and qualitative descriptors that are difficult to quantify: bowel movement frequency, stool size or consistency (hard or lumpy stools), straining on defecation, inability to defecate at will, and symptoms such as sensation of incomplete evacuation. The condition is considered chronic if symptoms last for at least 3 months. Many people believe that daily bowel movements are required for normal health or that accumulation of toxic substances will occur with infrequent defecation. Inappropriate laxative use by the general public may result from these misconceptions.

Though often considered more of a minor uncomfortable or unpleasant problem, constipation can have serious consequences and be costly to the healthcare system. Patients with constipation spend approximately $8,700 more in overall medical costs compared to patients without constipation.[21]

Epidemiology

The prevalence of constipation depends on the definition used and whether the condition is self-reported or provider-diagnosed. The prevalence of chronic constipation in adults (older than or equal to 15 years old) worldwide is estimated to be 15%.[23]

Constipation is more common in women (2.4-fold more likely) and older patients.[23] Other factors associated with constipation in some reports include inactivity, resource limited populations, lower income, non-White race, symptoms of depression, and history of physical or sexual abuse.

Pathophysiology

Constipation may be primary or secondary. Primary, or idiopathic, constipation occurs without an identifiable underlying cause, whereas secondary constipation may be the result of constipating drugs, lifestyle factors, or medical disorders (Table 54-5).[23] Primary constipation can be further divided into three categories—normal transit, slow transit, and pelvic floor dysfunction, or disordered defecation.[23,24] Normal transit constipation, often referred to as functional, is the most common type. These patients have normal GI motility and stool frequency but may experience difficulty evacuating, passage of hard stools, or bloating and abdominal discomfort. Slow transit constipation represents an abnormality of GI transit time that leads to infrequent defecation. Dysfunction of the pelvic floor muscles and/or anal sphincter is the most frequently encountered reason for disordered defecation. In patients with defecatory disorders, these muscles or sphincter contract during defecation instead of relax and impede evacuation of stool. It is common for patients to have and present with more than one type of constipation.

TABLE 54-5

Possible Causes of Constipation

Conditions	Possible Causes
GI disorders	Irritable bowel syndrome
	Diverticulitis
	Upper GI tract diseases
	Anal and rectal diseases
	Hemorrhoids
	Anal fissures
	Ulcerative proctitis

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	Tumors
	Hernia
	Volvulus of the bowel
	Syphilis
	Tuberculosis
	Helminthic infections
	Lymphogranuloma venereum
	Hirschsprung's disease
Metabolic and endocrine disorders	Diabetes mellitus with neuropathy
	Hypothyroidism
	Panhypopituitarism
	Pheochromocytoma
	Hypercalcemia
	Enteric glucagon excess
Cardiac disorders	Heart failure
Pregnancy	Depressed gut motility
	Increased fluid absorption from colon
	Use of iron salts
Lifestyle factors	Dietary changes
	Inadequate fluid intake
	Low dietary fiber
	Decreased physical activity
Neurogenic causes	CNS diseases
	Trauma to the brain (particularly the medulla)
	Spinal cord injury
	CNS tumors

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	Cerebrovascular accidents
	Parkinson's disease
Psychogenic causes	Ignoring or postponing urge to defecate
	Psychiatric diseases
Drug induced	See Table 54-6

Factors associated with the increased prevalence of constipation in older patients include a higher number of daily medications, particularly anticholinergic agents, increased incidence of chronic comorbidities, and changes in mobility status.[25] Changes in diet such as decreased fluid and/or fiber intake, diminished physical activity, and institutionalization can lead to constipation. Physiologic changes such as mesenteric dysfunction and changes in anorectal function, including loss of rectal wall elasticity, are also thought to predispose older patients to constipation.

Drug-Induced Constipation

Use of drugs that inhibit the neurologic or muscular function of the GI tract, particularly the colon, may result in secondary constipation.[23] Medications that are commonly associated with causing constipation include opiates, anticholinergic agents, and certain antacids.[23] With most of the agents listed in Table 54-6, the inhibitory effects on bowel function may be dose dependent, with larger doses causing constipation more frequently.

TABLE 54-6

Drugs Causing Constipation

Analgesics
Inhibitors of prostaglandin synthesis
Opiates
Nonsteroidal anti-inflammatory agents
Anticholinergics
Antihistamines
Antiparkinsonian agents (eg, benztropine or trihexyphenidyl)
Phenothiazines
Tricyclic antidepressants
Antacids containing calcium carbonate or aluminum hydroxide
Barium sulfate
Calcium channel antagonists
Clonidine
Diuretics (non–potassium-sparing)
Ganglionic blockers
Iron preparations
Muscle blockers (d-tubocurarine, succinylcholine)
Polystyrene sodium sulfonate

Opiates have effects on all segments of the bowel, but effects are most pronounced on the colon. The major mechanism by which opiates produce constipation has been proposed to be prolongation of intestinal transit time by causing spastic, nonpropulsive contractions. Additionally, anal sphincter tone may be increased with an accompanying decrease in reflex relaxation leading to difficult rectal evacuation.[26]

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While all opiate derivatives are associated with constipation, the degree of intestinal inhibitory effects seems to differ between agents. Orally administered opiates appear to have greater inhibitory effects than parenterally administered products.

Other medications may increase the risk of constipation by a variety of mechanisms. Anticholinergic agents decrease contractility of intestinal muscle while calcium channel blockers are thought to cause rectosigmoid dysfunction, leading to constipation. Nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to constipation due to their inhibition of prostaglandin synthesis.[27]

Clinical Presentation

A symptom-based system for classifying functional constipation (and other functional GI disorders) is often used to define constipation in clinical trials. The Rome criteria encompass both quantitative (frequency) and qualitative (stool consistency, etc.) symptoms associated with constipation.[28] Table 54-7 outlines general clinical presentation of patients with constipation. According to the Rome IV criteria, patients should have at least two of the signs and symptoms listed in Table 54-7 apply to a minimum of 25% of bowel movements.

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TABLE 54-7

Clinical Presentation of Constipation

Signs and symptoms

- Infrequent bowel movements (<3 per week)
- Stools that are hard, small, or dry
- Straining
- Feeling of incomplete evacuation
  - Feeling of anorectal obstruction or blockage
  - Physical tactics needed for defecation
  - Loose stools rarely occur without laxative use

Alarm signs and symptoms

- Hematochezia
- Melena
- Family history of colon cancer
- Family history of inflammatory bowel disease
- Anemia
- Unintentional weight loss >10% body weight
- Anorexia
- Nausea and vomiting
- Severe, persistent constipation that is refractory to treatment
- New-onset or worsening constipation in elderly without evidence of primary cause

Physical examination

- Perform rectal exam for presence of anatomical abnormalities (such as fistulas, fissures, hemorrhoids, rectal prolapse) or abnormalities of perianal descent
- Digital examination of rectum to check for fecal impaction, anal stricture, or rectal mass

Laboratory and other diagnostic tests

- No routine recommendations for lab testing—as indicated by clinical discretion
- In patients with signs and symptoms suggestive of organic disorder, specific testing may be performed (ie, thyroid function tests, electrolytes, glucose, complete blood count) based on clinical presentation
- In patients with alarm signs and symptoms or when structural disease is a possibility, select appropriate diagnostic studies:
  1. Rectal Balloon Expulsion Test (BET)
  2. Anorectal manometry
  3. Colonoscopy
  4. Barium defecography

Evaluation of constipation should attempt to clarify the patient's specific symptoms (ie, exactly what the patient means by constipation).[23] A complete and thorough history should be obtained from the patient, including frequency of bowel movements and duration of symptoms. Constipation occurring abruptly in an adult may indicate significant colon pathology such as malignancy. Constipation present since early infancy may be indicative of neurologic disorders. The patient should also be carefully questioned about usual diet and laxative regimens. Does the patient have a diet consistently deficient in high-fiber items and containing mainly high refined foods? What laxatives or cathartics has the patient used to attempt relief of constipation? The patient should be questioned about other concurrent medications, with interest focused on agents that might cause constipation.

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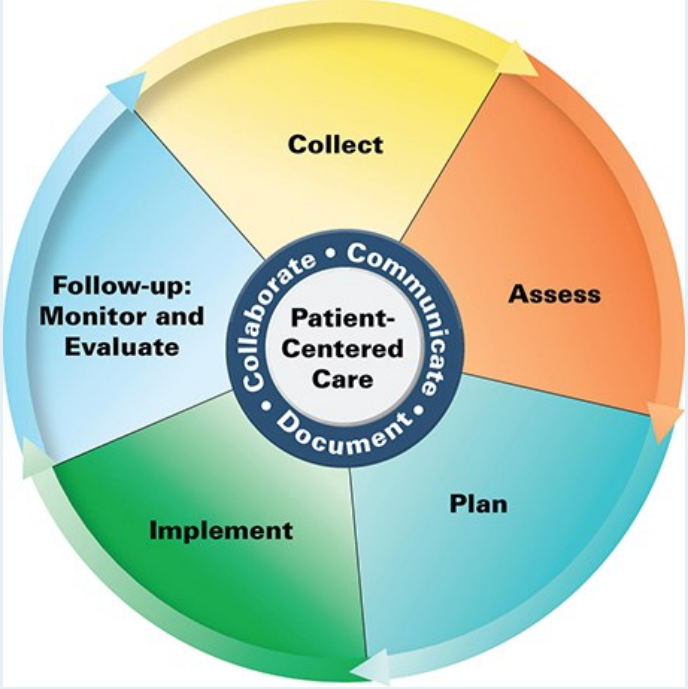
Evaluation should also include perianal and anal examinations to identify fecal impaction or other anatomical obstructions that may be contributing to or causing constipation. General health status, signs of underlying medical illness (ie, hypothyroidism), and psychological status (eg, depression or other psychological illness) should also be assessed. Laboratory tests may be performed, particularly if the patient is presumed to suffer from secondary causes and is still experiencing symptoms after a trial of fiber supplementation or other nonprescription therapies.[23]

Specific attention should be given to identify any "alarm symptoms" that would warrant further diagnostic workup (see Table 54-7).[23] Patients with alarm symptoms, a family history of colon cancer, or those more than 50 years old with new symptoms may need further diagnostic evaluation.

Patient Care Process for Constipation



Collect

- Patient characteristics
- Patient medical, social, and family history including dietary habits
- Current medications, including nonprescription
- Vital signs and weight
- Laboratory tests depending upon medical history and other presenting symptoms
    - Thyroid function tests, complete blood count, glucose, serum electrolytes

Assess

- Underlying causes of constipation (see Tables 54-5 and 54-6)
- Presence of alarm symptoms (Table 54-7)
- Severity of symptoms
- Patient preference for symptom resolution

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- Ability/willingness to pay for treatment options

Plan*

- Treat specific cause of constipation (ie, thyroid dysfunction)
- Dietary modification to increase fiber (Fig. 54-3)
- Laxative or cathartic option if quick resolution desired and no contraindications (Fig. 54-3; Table 54-8)
- Other pharmacologic therapy (Fig. 54-3; Table 54-8)
- Monitor symptom resolution for efficacy, and pronounced diarrhea for safety
- Patient education regarding lifestyle and dietary modifications, drug-specific information, etc.
- Referral to other providers when appropriate (unresolved symptoms or alarm symptoms present)

Implement

- Educate the patient on all aspects of the treatment plan
- Schedule follow-up to monitor safety and efficacy of treatment plan

Follow-up: Monitor and Evaluate

- Determine resolution of constipation and related symptoms
- Assess for presence of adverse effects (eg, abdominal pain, diarrhea)
- Assess patient adherence to treatment plan
- Reevaluate periodically until resolution

****Collaborate with patient, caregivers, and other healthcare professionals.***

Treatment

Desired Outcome

The major goals of treatment are to (a) relieve symptoms, (b) reestablish normal bowel habits, and (c) improve quality of life by minimizing adverse effects of treatment.

General Approach to Treatment

Figure 54-3 presents a general treatment algorithm for the management of constipation.

FIGURE 54-3

A general treatment algorithm for constipation.

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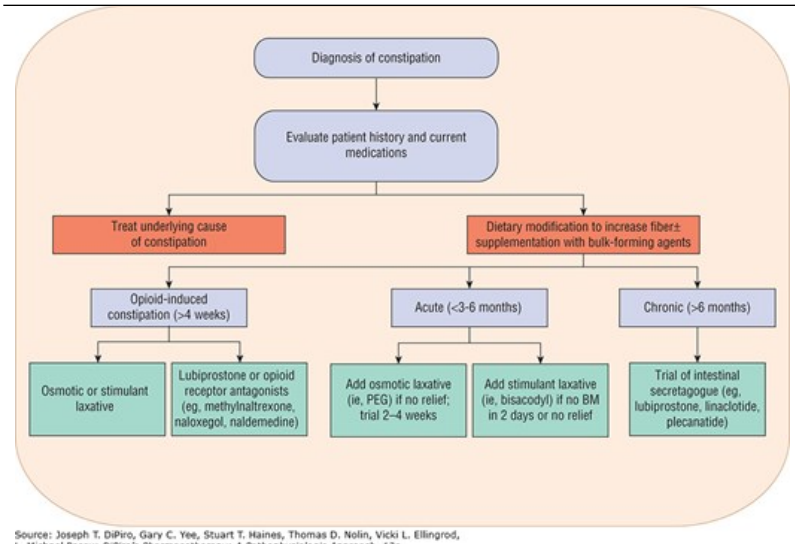

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6 Approaches to the treatment of constipation should begin with attempts to determine its cause. If an underlying disease is recognized as the cause of constipation, attempts should be made to correct it. Malignancies may be removed via surgical resection. Endocrine and metabolic derangements should be corrected by the appropriate methods. For example, when hypothyroidism is the cause of constipation, cautious institution of thyroid replacement therapy is the most important treatment measure. If a patient is consuming medications known to cause constipation, consideration should be given to alternative agents. If a patient must remain on constipating medications, then more attention must be given to general measures for prevention of constipation, as discussed in the next section. Also, patients with opioid-induced constipation (OIC) may require the routine use of pharmacologic agents, also discussed below.

The proper management of constipation will require a combination of nonpharmacologic and pharmacologic therapies. Osmotic laxative therapy is considered the preferred first line for the treatment of constipation, in addition to increasing dietary fiber or using fiber supplementation.[28,29] Patients are often encouraged to increase daily fluid intake and physical activity as well dedicate time to respond to the urge to defecate, although efficacy data are conflicting for these measures.[23]

Nonpharmacologic Therapy

Dietary Modification

The most important aspect of therapy for constipation for the majority of patients is dietary modification to increase the amount of fiber consumed. Fiber, the portion of vegetable matter not digested in the human GI tract, increases stool bulk, retention of stool water, and rate of transit of stool through the intestine. The result of fiber therapy is an increased frequency of defecation. Also, fiber decreases intraluminal pressures in the colon and rectum, which is thought to be beneficial for diverticular disease and for irritable bowel syndrome (IBS).

7 The specific physiologic effects of fiber are not well understood. Patients should be advised to gradually increase daily fiber intake to 20 to 30 g, through either dietary changes or fiber supplement products (see section "Bulk-Forming Agents" below), a strong recommendation from the American College of Gastroenterology.[30] Fruits, vegetables, and cereals typically have the highest fiber content. Bran, a by-product of milling of wheat, is often added to foods to increase fiber content and contains a high amount of soluble fiber, which may be extremely constipating in larger doses. Raw bran is generally 40% fiber.

A trial of dietary modification with high-fiber content should be continued for at least 1 month before effects on bowel function are determined. Most patients begin to notice effects on bowel function 3 to 5 days after beginning a high-fiber diet, but some patients may require a considerably longer period of time. Patients should be cautioned that abdominal distension and flatulence may be particularly troublesome in the first few weeks of fiber therapy, especially with high bran consumption. Gradually increasing dietary fiber over a few weeks to the goal of 20 to 30 g may help reduce some of the adverse abdominal effects, as well as ensuring adequate fluid intake. In most cases these problems resolve with continued use.

Surgery

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In a small percentage of patients who present with complaints of constipation, surgical procedures are necessary because of the presence of colonic malignancies or GI obstruction from a number of other causes. Patients who have slow-transit-type primary constipation that is refractory to treatment are also surgical candidates.[23,29] Surgery may be required in some endocrine disorders that cause constipation, such as pheochromocytoma, which requires removal of a tumor. In each case, the involved segment of intestine may be resected or revised.

Biofeedback

Patients with constipation due to pelvic floor dysfunction/disordered defecation may have a less favorable response to fiber therapy than other constipation subtypes.[30] Many adult patients with functional defecatory disorders appear to benefit from pelvic floor retraining with biofeedback therapy. The goals of biofeedback are to improve pelvic floor relaxation to facilitate the passage of stool and the procedure is typically performed over 4- to 6-hour-long sessions. Success rates of 65% to 80% have been reported in controlled and uncontrolled studies, and improvement has been sustained for up to 1 year. The value of biofeedback in children with chronic constipation has not been well demonstrated.

Electrical Stimulation

Sacral nerve stimulation is a minimally invasive technique that has been used for treatment of fecal incontinence and there are some reports of its use in severe refractory chronic constipation.[31] However, clinical data supporting the use of electrical stimulation for this purpose are limited and there are no recommendations for general practice.

Pharmacologic Therapy

Three general classes of laxatives are discussed in this section: (a) those causing softening of feces in 1 to 3 days; (b) those that result in soft or semifluid stool in 6 to 12 hours; and (c) those causing watery evacuation in 1 to 6 hours (Table 54-8). Other pharmacologic agents available for the treatment of constipation include a calcium channel activator, guanylate cyclase C agonist, and serotonergic agents.

TABLE 54-8

Dosage Recommendations for Pharmacologic Therapy

Agent	Recommended Dose
Agents That Cause Softening of Feces in 1-3 Days	
Bulk-forming agents	
Methylcellulose Polycarbophil Psyllium	Varies with product 4-6 g/day Varies with product
Emollients	
Docusate sodium Docusate calcium Docusate potassium	50-360 mg/day 50-360 mg/day 100-300 mg/day
Osmotic Laxatives	
Polyethylene glycol 3350 Lactulose Lacitol	17 g/dose 15-30 mL orally 20 g/day orally

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Sorbitol	30-50 g/day orally
Agents That Result in Soft or Semifluid Stool in 6-12 Hours	
Bisacodyl (oral) Senna Magnesium sulfate (low dose)	5-15 mg orally Dose varies with formulation <10 g orally
Agents That Cause Watery Evacuation in 1-6 Hours	
Magnesium citrate Magnesium hydroxide Magnesium sulfate (high dose) Sodium phosphates Bisacodyl Polyethylene glycol-electrolyte preparations	18 g 300 mL water 2.4-4.8 g orally 10-30 g orally Varies with salt used 10 mg rectally 4 L
Intestinal Secretagogues	
Lubiprostone Linaclotide Plecanatide	24 mcg orally twice daily 145 mcg orally daily 3 mg orally daily
Opioid Antagonists	
Methylnaltrexone Naloxegol Naldemedine	450 mg orally daily or 12 mg subcutaneously daily 25 mg daily 0.2 mg daily
Prokinetics	
Prucalopride	2 mg daily

Bulk-Forming Agents

Medicinal products, often called “bulk-forming agents,” such as psyllium hydrophilic colloids, methylcellulose, or polycarbophil, have properties similar to those of dietary fiber and may be taken as tablets, powders, or granules.[25] These agents increase the water content of stool to increase stool bulk and weight and relieve the symptoms of constipation within 3 days of initiating therapy.

Bulk-forming laxatives have few adverse effects. The most common effects include flatulence, abdominal bloating, and distention. Rarely, these agents may lead to bowel obstruction. Patients should also be cautioned to consume sufficient fluid while supplementing with bulk-forming agents to avoid obstruction of the esophagus, stomach, small intestine, and colon.

Emollient Laxatives

Emollient laxatives, including docusate in its various salts, are surfactant agents that work by facilitating mixing of aqueous and fatty materials within the intestinal tract; these are commonly referred to as stool softeners.[23,25,32] Increased stool moisture content should lead to a softer, easier-to-pass stool. These products are generally given orally, although docusate potassium has also been used rectally. With these products, softening of stools occurs within 1 to 3 days of therapy. Docusate has little evidence to support efficacy in treating constipation.[23] Although docusates are generally safe, a

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few adverse drug reactions have been noted.

Hyperosmolar Agents

Nonabsorbable Carbohydrates

Lactulose is a nonabsorbable disaccharide that is metabolized by colonic bacteria to low-molecular-weight acids, resulting in an osmotic effect whereby fluid is retained in the colon.[33] The fluid retained in the colon lowers the pH and increases colonic peristalsis within 2 to 3 days of use. Lactulose increases stool frequency and consistency in patients with chronic constipation (vs placebo) and may be more effective than fiber alone. In comparison to polyethylene glycol (PEG), lactulose is slightly less effective in increasing stool frequency per week and patients are more likely to need additional products for constipation relief. The most common adverse effects include flatulence, nausea, and abdominal discomfort or bloating—although lactulose can be useful in some patients. It may be justified as an alternative for acute constipation or in patients with an inadequate response to increased dietary fiber and bulking agents. In addition to the adverse abdominal effects associated with lactulose, diarrhea and electrolyte imbalances can occasionally occur. Sorbitol, a monosaccharide, also exerts its effect by osmotic action and has been recommended as a cost-effective alternative to lactulose. It is as effective as lactulose but may cause less nausea and is much less expensive.

Lactitol is a monosaccharide sugar alcohol that is approved for the treatment of chronic idiopathic constipation. The oral powder should be dissolved in four to eight ounces of a liquid beverage and taken with a meal daily. The most common adverse drug reactions are flatulence and diarrhea.[34]

Polyethylene Glycol

PEG is FDA-approved for treatment of constipation at low doses and is expected to produce a bowel movement in 1 to 3 days.[23,33] For this indication, PEG is administered in smaller volumes (10-30 or 17-34 g per 120-240 mL) usually once (or twice) daily. PEG is not absorbed systemically or metabolized by colonic bacteria, and therefore has a lower incidence of adverse effects compared with other osmotic laxatives. Daily use in low dose (17 g) may be safe and effective for up to 6 months, even in children.[35] PEG has a strong recommendation from the American College of Gastroenterology for the treatment of chronic constipation and is available as a nonprescription drug.[28] It is also preferred by the AGA if fiber supplementation is insufficient due to high efficacy based on high quality of evidence available.[29,30] The most common adverse effects are GI-related and include nausea, vomiting, flatulence, and abdominal cramping.[23] PEG solutions with electrolytes are used as bowl cleansing regimens prior to GI-related procedures, and should not be used routinely for treatment of constipation.

Magnesium Salts

Magnesium salts, including hydroxide, phosphate, and citrate, and sodium phosphate, are frequently used as bowel preparations prior to diagnostic procedures such as colonoscopy.[23,32] Milk of magnesia (an 8% suspension of magnesium hydroxide), though, may be used occasionally to treat constipation in otherwise healthy adults, but efficacy data are limited. These agents should not be used on a routine basis as they may cause fluid and electrolyte depletion. Also, magnesium or sodium accumulation may occur in patients with renal dysfunction or congestive heart failure. These risks increase with long-term use.

Glycerin

Glycerin is usually administered as a suppository and exerts its effect by osmotic action in the rectum. As with most agents given as suppositories, the onset of action is usually less than 30 minutes. Glycerin is considered a safe laxative, although it may occasionally cause rectal irritation. Its use is acceptable on an intermittent basis for constipation or fecal impaction, particularly in children.[35]

Stimulant Laxatives

Stimulant laxatives such as diphenylmethane (bisacodyl) and anthraquinone (senna and others) derivates primarily affect the colon.[23] These agents stimulate the mucosal nerve plexus of the colon and may also affect intestinal fluid secretion by altering fluid and electrolyte transport, and are expected to cause a bowel movement within 8 to 12 hours of administration. Stimulant laxatives may cause severe abdominal cramping and electrolyte imbalances, particularly with chronic use. Compared with placebo, bisacodyl is effective in treatment of constipation.[30] These agents are typically

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reserved for intermittent use or in patients who fail to respond adequately to bulking and osmotic laxatives. Some patients, though, with severe chronic constipation and nonmodifiable risk factors may use these agents on a more regular basis.[24]

Intestinal Secretagogues

Lubiprostone

Lubiprostone is a chloride channel activator that acts locally in the gut to open chloride channels on the GI luminal epithelium, which, in turn, stimulates chloride-rich fluid secretion into the intestinal lumen. Increased intraluminal fluid secretion helps to soften stool and accelerate GI transit time.[24] Lubiprostone is FDA-approved for adults with chronic idiopathic constipation as well as treatment of patients with OIC at a recommended dose of one 24-mcg capsule twice daily with food.[24] Patients treated with lubiprostone have a significant increase in spontaneous bowel movements versus placebo as well as improvement in straining, stool consistency, and overall constipation severity.[30] For most patients, bowel movements occur within 24 to 48 hours of lubiprostone administration. Common adverse effects include nausea, headache, and diarrhea and may be dose dependent.[32] Because of its high cost (especially relative to other available laxative agents) and lack of comparative data with other laxative therapies, lubiprostone is reserved for patients with chronic constipation who fail conventional first-line agents such as osmotic laxatives and fiber supplementation, or for those with OIC.

Linaclotide

Linaclotide is approved for the treatment of constipation and constipation-predominant irritable bowel syndrome (IBS-C).[23] It is a synthetic 14-amino-acid peptide that binds to and activates the guanylate cyclase C receptor found on the intestinal epithelium. This increases intestinal fluid secretion and quickens intestinal motility. Doses of 72 mcg and 145 mcg are approved for treatment of constipation, and patients should be instructed to take linaclotide on an empty stomach at least 30 minutes before the first meal of the day. Diarrhea was the most commonly reported adverse event in clinical trials, followed by flatulence and abdominal pain. Linaclotide should not be used in patients under the age of 18.[36]

Plecanatide

Plecanatide is approved for the treatment of adults with chronic idiopathic constipation.[37] It activates the guanylate cyclase C receptor that increases intestinal fluid secretion and motility similarly to linaclotide. Plecanatide is given once daily without regard to food at a dose of 3 mg. The most common side effect is diarrhea. Plecanatide is contraindicated in patients less than 6 years of age or those with mechanical gastrointestinal obstruction, and should not be used in patients under the age of 18.

Opioid Receptor Antagonists

Alvimopan is an oral GI-specific μ-opioid antagonist approved for short-term use in hospitalized patients to accelerate recovery of bowel function after large or small bowel resection.[38] It antagonizes the GI (peripheral) effects of opioids without affecting analgesia because it does not cross the blood–brain barrier. Alvimopan is only available through a special use program (ENTEREG access support and education [EASE]), which requires hospitals to register and meet all requirements before the drug can be administered. Additionally, alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than seven consecutive days prior to surgery as they may be more sensitive to the drug's effects. Dosing for alvimopan is as follows: 12-mg capsule administered 30 minutes to 5 hours before surgery and then 12 mg twice daily for up to 7 days or until discharge (maximum of 15 doses).

Methylnaltrexone is μ-receptor antagonist approved for OIC in patients with advanced disease receiving palliative care or when response to laxative therapy has been insufficient for patients with OIC with chronic noncancer pain.[26,38] This agent does not cross the blood–brain barrier or antagonize analgesia; it acts on peripheral μ-receptors to block unwanted opioid side effects such as constipation. It is administered at a weight-based dose as a subcutaneous injection in patients with advanced illness, usually every other day (no more than once daily). For patients with noncancer pain, methlynaltrexone can be given as a 12-mg subcutaneous injection or 450-mg oral dose daily. Laxative use should be discontinued upon initiation of methlnaltrexone, and its use is contraindicated in patients with known or suspected GI obstruction. Patients with reduced creatinine clearance (<60 mL/min [1 mL/s]) or moderate-to-severe hepatic impairment should receive reduced dosing of methlnaltrexone (ie, 150 mg orally or 6 mg subcutaneously).

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Naloxegol is approved by the FDA for the treatment of OIC in adult patients with noncancer pain.[39] It is an oral pegylated naloxone molecule and antagonizes the μ-receptor. Pegylation reduces naloxegol's passive permeability of the blood–brain barrier. The recommended dose is 25 mg by mouth once daily, 1 hour before or 2 hours after a meal. The dose should be reduced by half in patients with diminished renal function (CrCl <60 mL/min [1 mL/s]) or in those unable to tolerate 25 mg. The most common side effects are abdominal pain, diarrhea, and nausea. In clinical trials, naloxegol significantly increased the number and frequency of bowel movements compared to placebo at 12 weeks.[38]

Naldemedine is a peripherally acting opioid antagonist approved for treatment of OIC in patients with chronic noncancer pain.[26] The recommended dose is 0.2 mg by mouth once daily, and there are no dose adjustments for renal or hepatic impairment. However, patients with severe hepatic impairment (ie, Child-Pugh class C) should not use naldemedine. The most common adverse effects are abdominal pain and diarrhea. Naldemedine increased the frequency of bowel movements compared to placebo in clinical trials.[26]

Other Agents

Prucalopride is a selective 5-hydroxytryptamine-4 (5-HT_4) receptor agonist approved for treatment of chronic constipation in the United States and Europe.[40] It demonstrates proenterokinetic effects (increased colonic motility and transit), specifically in the GI tract. Prucalopride is more selective than the previously available serotonergic agonists cisapride and tegaserod with higher affinity for the 5-HT_4 receptor. Receptor selectivity is thought to improve the safety profile of prucalopride over cisapride and tegaserod, which were removed from the market due to concerns for adverse cardiovascular events. In clinical trials, prucalopride significantly increased the number of complete, spontaneous bowel movements in adults with chronic constipation. Constipation symptoms and quality of life were also improved with prucalopride. This agent has been safely tolerated in clinical trials with no adverse cardiovascular effects versus placebo (although data are limited).

Probiotics may be useful in the treatment of constipation. Several randomized controlled trials conducted in children and adults revealed that certain strains of probiotics increased weekly stool frequency.[30] However, these trials were small (370 patients total) and only slight improvement was realized (one additional stool per week). More studies are needed to strengthen evidence involving probiotics, but these may be an option for patients seeking alternative treatment.[23]

Prevention

For patients recovering from myocardial infarction (MI) or rectal surgery, straining at defecation should be avoided. The basis of preventive therapy in these patients should be bulk-forming laxatives or PEG. Additionally, the use of docusate is popular, although its effectiveness is debated. In pregnant patients, constipation may result because of alterations in hormones or iron supplementation.

Evaluation of Therapeutic Outcomes

The ultimate goal of treatment for constipation is to prevent further episodes of constipation. Short-term goals include alleviation of acute constipation with relief from symptoms. For patients with chronic constipation, the goals include use of proper diet and decreased reliance on laxatives in addition to relief of symptoms for the patient so that quality of life is not diminished. Effective treatment of constipation requires the patient to become more knowledgeable about the causes of constipation, proper diet, and appropriate use of laxatives.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is a GI syndrome that is the most commonly diagnosed GI condition, and is characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause.

Epidemiology

The prevalence of IBS is approximately 10% worldwide among adults.[41] IBS affects all ages, genders, and ethnicities, however is more predominant in younger patients and women. In addition, IBS results in reduced quality of life.[41,42]

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Pathophysiology

Although the exact pathophysiologic abnormalities with IBS are still being actively investigated, IBS likely results from altered somatovisceral and motor dysfunction of the intestine from a variety of causes. Abnormal CNS processing of afferent signals may lead to visceral hypersensitivity, with the specific nerve pathway affected determining the exact symptomatology expressed. This visceral hypersensitivity is a neuroenteric phenomenon that is independent of motility and psychological disturbances.[43] Factors known to contribute to these alterations include genetics, motility factors, inflammation, colonic infections, mechanical irritation to local nerves, stress, and other psychological factors.

The enteric nervous system contains a significant percentage of the body's 5-HT receptors.[44] Two types of 5-HT receptors exist within the gut: serotonin type 3 (HT_3) and serotonin type 4 (HT_4), which are responsible for secretion, sensitization, and motility. There is an increase in the postprandial levels of 5-HT in the GI tract in those diagnosed with diarrhea-predominant IBS compared to those who are not.[44] Therefore, stimulation and antagonism of these 5-HT receptors have become a focused area for research on new drug therapies for both diarrhea- and constipation-predominant diseases.

Clinical Presentation

Irritable bowel syndrome presents as either diarrhea- or constipation-predominant disease and can be defined as lower abdominal pain, disturbed defecation (constipation, diarrhea, or an alternating pattern of both), and bloating in the absence of structural or biochemical factors that might explain these symptoms (Table 54-9). Table 54-10 provides the diagnostic criteria for the Rome IV symptom-based criteria.[42]

TABLE 54-9

Clinical Presentation of Irritable Bowel Syndrome

Signs and symptoms • Lower abdominal pain • Abdominal bloating and distension • Diarrhea symptoms, >3 stools/day • Extreme urgency • Passage of mucus • Constipation symptoms, <3 stools/week, straining, incomplete evacuation • Psychological symptoms such as depression and anxiety
Non-GI symptoms • Urinary symptoms • Fatigue • Dyspareunia
Other concurrent conditions • Fibromyalgia • Functional dyspepsia • Chronic fatigue syndrome • Reduced health-related quality of life

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TABLE 54-10

Rome IV Diagnostic Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:

1. Relieved with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Data from Reference 42.

Additional diagnostic steps that can be taken include testing for fecal lactoferrin and C-reactive protein to rule out inflammatory bowel disease and serologic testing to rule out celiac disease.[42] Routine colonoscopy, examination of the stool for occult blood and ova and parasites, or testing for food allergies are not recommended.

Treatment

General Approach to Treatment

The treatment approach to IBS is based on the predominant symptoms and their severity (Fig. 54-4). Exercise and a limited trial of a diet with reduced fermentable oligosaccharides, disaccharides, and monosaccharides, and polyols (FODMAPs) are recommended for overall symptom improvement.[42] More persistent disease may require pharmacologic agents, such as secretagogues, rifaximin, or eluxadoline.

FIGURE 54-4

A general stepwise approach to the management of both constipation- and diarrhea-predominant irritable bowel syndrome. [a]Consider manufacturer-sponsored patient access program.

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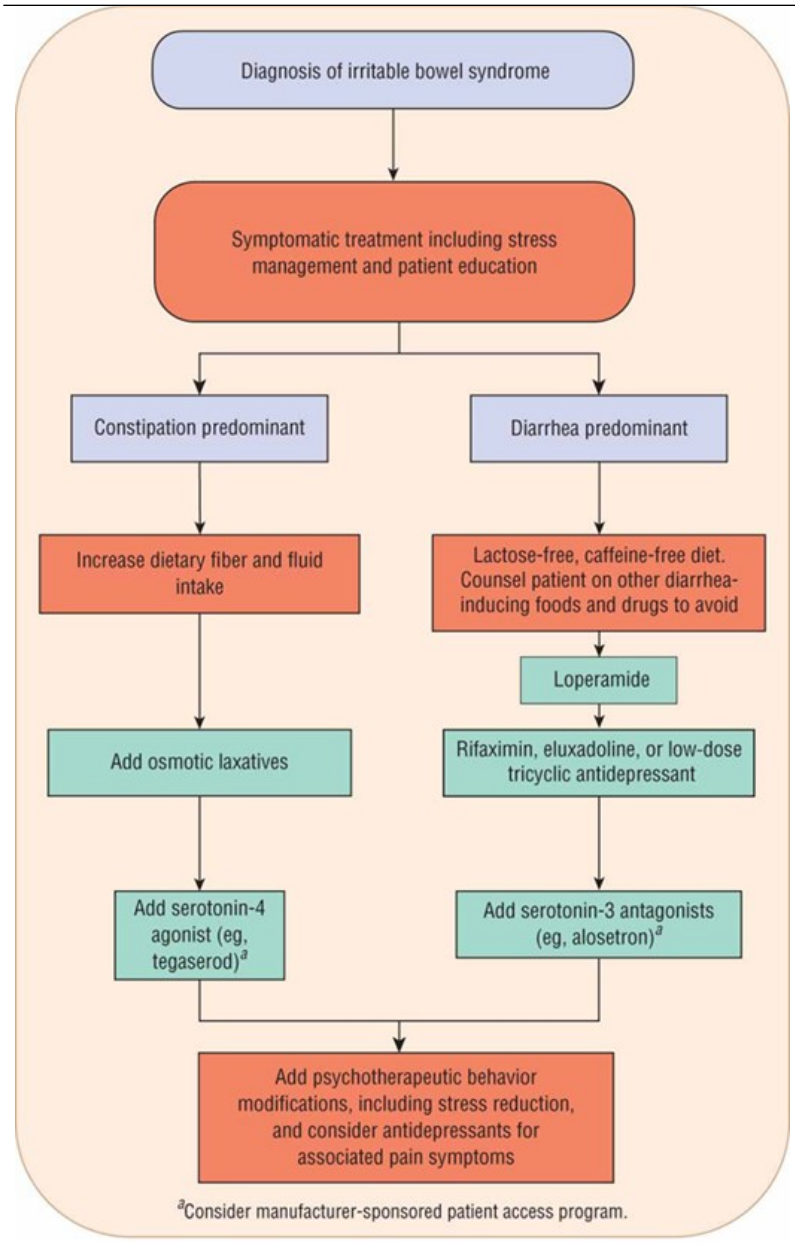

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Constipation-Predominant Disease

In the constipation-predominant patient, dietary fiber may be beneficial. Patients should be instructed to begin with one tablespoonful of fiber with one meal daily and gradually increase the dose to include fiber with two and three meals a day until the desired outcome is achieved. End points that the patient should aim for include bulkier and more easily passed stools. For patients unable to tolerate dietary bran, bulking agents such as psyllium may be substituted.[45] PEG laxatives may be used, especially for mild symptoms; however, the use of PEG may not improve abdominal pain.[41,42] When lifestyle modifications alone do not control symptoms, intestinal secretagogues such as linaclotide (290 mcg daily), plecanatide (6 mg daily), tenapanor (50 mg twice daily), and lubiprostone (8 mcg twice daily) should be recommended.[41]

Tenapanor is a sodium/hydrogen exchanger 3 (NHE3) inhibitor, and is approved for use in adults with IBS with constipation.[46] The inhibition of NHE3 decreases sodium absorption from the gut, which increases intestinal fluid secretion and motility. Tenapanor should not be used in patients less than 12 years of age and does not require any dose adjustments for renal or hepatic function. Patients should be instructed to take tenapanor immediately

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before meals twice daily. The most common adverse effect is diarrhea. In clinical trials, tenapanor was most effective at improving abdominal pain, and more patients treated with tenapanor experienced greater overall symptom relief compared to placebo.[41]

The 5-HT_4 partial agonist tegaserod is approved specifically for short-term, intermittent treatment of IBS-C in women.[42] Tegaserod is available in the United States through a restricted-access program due to a small, yet significant, increase in ischemia events (MI, cerebrovascular accident [CVA], and unstable angina) in patients with preexisting cardiovascular disease and/or cardiovascular risk factors. It is given as 2- or 6-mg doses given twice daily 30 minutes prior to a meal with water for up to 12 weeks. Stimulation of the 5-HT_4 receptors by tegaserod increases gastric secretions and promotes motility, with improvement in symptoms generally occurring within the first week of therapy. Diarrhea was the most common adverse effect, resulting in drug discontinuation in 1.6% of study subjects.

Diarrhea-Predominant Disease

9 For patients in whom diarrhea is the primary complaint, avoidance of certain food products may be necessary. Caffeine, alcohol, and artificial sweeteners (sorbitol, fructose, and mannitol) are known to irritate the gut and produce a laxative effect. Lactose intolerance should be considered in certain patients; however, the prevalence of this condition may be exaggerated.

Herbal medicines or teas often contain senna, which may produce diarrhea. In patients with disease persistence following dietary modification, loperamide may be used for episodic management of urgent diarrhea, or in situations in which the patient wishes to avoid the possibility of an acute onset of symptoms.[47] Loperamide decreases intestinal transit, enhances water and electrolyte absorption, and strengthens rectal sphincter tone. However, loperamide is not likely to address other symptoms of IBS such as abdominal pain.[42]

Diarrhea-predominant IBS caused by excessive stimulation of the 5-HT_3 receptor can be relieved by the drug alosetron, a 5-HT3-receptor antagonist. Its use is limited to an FDA-approved restricted-use program, and requires extensive postmarketing surveillance due to association with serious adverse effects, including severe constipation and ischemic colitis.[47] Additional information can be found at http://www.lotronex.com. It is indicated for women with severe diarrhea-predominant symptoms that are not relieved by other conventional therapy at a recommended starting dose of 0.5 mg twice daily.

Other agents, eluxadoline and rifaximin, are approved and recommended for use in IBS-D, especially for more moderate symptoms.[42] Rifaximin is a rifamycin antibacterial indicated for the treatment of travelers' diarrhea that is indicated for the treatment of IBS-D in adults based on several randomized control trials demonstrating improvement in abdominal pain, stool consistency, and bloating.[47,48] The recommended dose is 550 mg orally three times a day for 2 weeks. Recurrences may be retreated up to two times; however, there is no evidence to support repeating the regimen. Eluxadoline is a μ-opioid receptor agonist indicated for adults with IBS-D. The recommended dose is 100 mg orally twice a day with food. A lower dose of 75 mg twice daily is recommended for patients who cannot tolerate the 100 mg dose and if they have hepatic impairment; eluxadoline should be avoided in patients without a gallbladder, and patients who consume more than 3 alcoholic beverages per day.[49] Its main benefits are improvement in abdominal pain and stool consistency. The main side effect seen is constipation.

Use of Antidepressants in Irritable Bowel Syndrome

Tricyclic antidepressants have some benefit in treatment of diarrhea-predominant IBS associated with moderate-to-severe abdominal pain, by modulating perception of visceral pain, altering GI transit time, and treating underlying comorbidities.[50,51] Selective 5-HT reuptake inhibitors (SSRI), fluoxetine, citalopram, and paroxetine have been studied, but the results are conflicting. The AGA does not recommend SSRIs for use in IBS based on available evidence.[47] Large randomized control trials lasting longer than 3 months are needed to determine the place of SSRIs in therapy.[52]

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been used in the management of IBS with comorbid generalized anxiety disorder and major depressive disorder. Although the effect was gradual over 12 weeks, both symptom severity and quality of life significantly improved.[53,54]

Pain in Irritable Bowel Syndrome

10 Some patients with IBS suffer significant pain associated with their disease. Data supporting the use of antispasmodic agents in these patients are

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conflicting. While not recommended to treat global IBS symptoms, antispasdmodic agents may be used for abdominal pain.[42,47] A trial of low-dose antidepressant therapy is indicated, especially if pain is associated with eating. Preprandial doses of drugs containing anticholinergic properties may suppress pain (and/or diarrhea) associated with an overactive postprandial gastrocolonic response. Tricyclic antidepressants should be avoided in patients with pain and constipation. In addition, psychotherapy, including cognitive behavioral therapy, relaxation therapy, and hypnotherapy, decreases IBS symptoms.[41,47]

Evaluation of Therapeutic Outcomes

Irritable bowel syndrome is usually classified as constipation-predominant, diarrhea-predominant, or IBS with mixed symptoms, or unclassified. Therapeutic goals in IBS should focus on the patient's primary complaint. Additionally, global symptoms may be treated with antidepressants, relaxation/stress management, cognitive behavior treatment, and/or hypnosis aimed at specific affective disorders.[41,47] Lastly, the 5-HT receptor agonists and antagonists can be used in carefully selected patients whose symptoms are not adequately controlled with other agents.

ABBREVIATIONS

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AAD	antibiotic-associated diarrhea
AGA	American Gastroenterology Association
AIDS	acquired immune deficiency syndrome
ATPase	adenosine triphosphatase
CDC	Centers for Disease Control and Prevention
CVA	cerebrovascular accident
EASE	ENTEREG access support and education
5-HT	serotonin
HT_3	serotonin type 3
HT_4	serotonin type 4
$5\text{-}HT_4$	5-hydroxytryptamine-4
IBS	irritable bowel syndrome
IBS-C	constipation-predominant irritable bowel syndrome
MI	myocardial infarction
NSAID	nonsteroidal anti-inflammatory drug
OIC	opioid-induced constipation
ORS	oral rehydration solution
PEG	polyethylene glycol
VIP	vasoactive intestinal peptide
VIPoma	vasoactive intestinal peptide-secreting tumor
WDHA	watery diarrhea, hypokalemia, and achlorhydria
WHO	World Health Organization
WHO-ORS	World Health Organization oral rehydration solution

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SELF-ASSESSMENT QUESTIONS

1. Most cases of acute diarrhea in the United States are due to:

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A. Diabetes.

B. Food and waterborne organisms.

C. AIDS.

D. Prescription medications.

2. This type of diarrhea occurs when a stimulating substance either increases secretion or decreases absorption of water and electrolytes:

A. Osmotic

B. Exudative

C. Secretory

D. Transitory

3. Which statement about acute diarrhea is TRUE?

A. It is self-limiting, usually subsiding within 72 hours.

B. It is secondary to diseases such as diabetes.

C. It is treatable with bulk-forming laxatives.

D. It is a chronic condition that waxes and wanes throughout life.

4. Which of the following is advocated for prevention of traveler's diarrhea?

A. Drinking water and eating fresh vegetables as much as possible while traveling

B. Use of Bismuth subsalicylate (BSS) as needed

C. Avoidance of meat products

D. Taking loperamide around the clock for 48 hours prior to travel

5. If diarrhea occurs, an appropriate treatment approach is to:

A. Increase fluid intake.

B. Stop prescription medications.

C. Withhold food.

D. Administer antibiotics until symptoms resolve.

6. This antisecretory agent used to treat diarrhea may interact with anticoagulants, interfere with tetracycline absorption, and interfere with some GI radiographic studies:

A. Polycarbophil

B. Bismuth subsalicylate

C. Loperamide

D. Diphenoxylate with atropine

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7. Which of the following statements about constipation is TRUE?

   A. Patients often describe constipation in measures that are easily quantified.

   B. Daily bowel movements are required for health and well-being.

   C. Decreased fiber intake can lead to constipation.

   D. Normal healthy subjects pass at least six stools per week.

8. Possible medical causes of constipation include:

   A. Osteoporosis.

   B. Hypothyroidism.

   C. Inflammatory bowel syndrome.

   D. Hypertension.

9. The cornerstone of therapy in the treatment of constipation should include:

   A. Decrease in fluid intake.

   B. Increase in dietary fiber.

   C. Biofeedback therapy.

   D. Stimulant laxatives.

10. Which laxative is preferred first line for treatment of constipation in most patients?

    A. Cascara sagrada

    B. Bisacodyl

    C. Polyethylene glycol

    D. Glycerin

11. To prevent constipation, patients should be advised to include this amount of fiber in their daily diet:

    A. 10 to 15 g

    B. 20 to 25 g

    C. 50 to 55 g

    D. 100 to 110 g

12. For patients with opioid-induced constipation, which of the following medications can only be administered in the hospital for short-term use?

    A. Alvimopan

    B. Lubiprostone

    C. Methylnaltrexone

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D. Naloxegol

13. Which of the following treatment measures is recommended in constipation-predominant IBS for mild symptoms?

    A. Saline cathartics

    B. Loperamide

    C. Mineral oil

    D. Polyethylene gylcol

14. In addition to avoidance of certain food products, which of the following treatments is recommended in diarrhea-predominant IBS for moderate symptoms?

    A. Saline cathartics

    B. Rifaximin

    C. Loperamide

    D. Dietary fiber

15. Which of the following medications may be used for their analgesic effects in patients suffering from IBS-associated pain?

    A. Amitriptyline

    B. Bupropion

    C. Sertraline

    D. Loperamide

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Common causes of acute diarrhea in the United States are food and waterborne organisms. The specific bacterial organisms are listed under the epidemiology section of diarrhea.

2. **C.** Secretory diarrhea occurs when a stimulating substance either increases secretion or decreases absorption of large amounts of water and electrolytes. See pathophysiology of "Diarrhea" section.

3. **A.** Most acute diarrhea is self-limiting, subsiding within 72 hours. The prognosis for chronic diarrhea depends on the cause; for example, diarrhea secondary to diabetes mellitus waxes and wanes throughout life. Bulk-forming laxatives are a treatment option for constipation, not diarrhea. See clinical presentation of "Diarrhea" section.

4. **B.** Antibiotics and bismuth subsalicylate are advocated to prevent traveler's diarrhea, in conjunction with treatment of drinking water and caution with consumption of fresh vegetables. It is not recommended to withhold food during acute episodes of diarrhea. Loperamide may be used to treat traveler's diarrhea; however, there is no data to support its use prophylactically. See treatment of "Diarrhea" section.

5. **A.** If prevention is unsuccessful and diarrhea occurs, the primary therapeutic goal is to prevent excessive water, electrolyte, and acid–base disturbances by increasing fluid intake. Withholding food, giving antibiotics, or stopping prescription medications are not appropriate recommendations. See treatment of "Diarrhea" section.

6. **B.** Bismuth can potentiate the effects of anticoagulants, can reduce tetracycline absorption, and may interfere with select GI radiographic studies.

7. **C.** A healthy number of stools per week can vary person to person, and measures used to describe constipation may be difficult to quantify. A lack

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of fiber in the diet can lead to constipation, and castor oil should be avoided due to risks. See "Constipation" section of text, and treatment algorithm.

8. **B.** Hypothyroidism is associated with constipation. See Tables 54-5.

9. **B.** Increasing fiber should be the first step in treating constipation. See treatment algorithm.

10. **C.** Due to its efficacy and fewer adverse effects, polyethylene glycol is the preferred laxative for most patients. See treatment algorithm and pharmacologic treatment in text.

11. **B.** The American College of Gastroenterology recommends increasing dietary fiber to 20 to 30 g/day. See treatment text.

12. **A.** Alvimopan is only for short-term use in the inpatient setting. See pharmacologic text.

13. **D.** In the constipation-predominant patient, polyethylene glycol (PEG) may be beneficial for mild symptoms. Patients should be instructed to begin with one tablespoonful of fiber with one meal daily and gradually increase the dose to include fiber with two and three meals a day until the desired outcome is achieved

14. **B.** In diarrhea-predominant IBS, rifaximin is recommended because it can improve abdominal pain, stool consistency, and bloating, whereas loperamide may be used for episodic management of urgent diarrhea. Loperamide is unlikely to improve other symptoms.

15. **A.** A trial of low-dose antidepressant therapy is indicated, especially if pain is associated with eating. Tricylic antidepressants produce analgesia and may relieve depressive symptoms if present. 5-HT reuptake inhibitors are not recommended by the AGA based on current evidence. Preprandial doses of drugs containing anticholinergic properties may suppress pain (and/or diarrhea) associated with an overactive postprandial gastrocolonic response.

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