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Managing Chronic Diarrhea With Colorectal Cancer

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Chronic diarrhea is a frequent symptom among colorectal cancer patients, both during and after treatment for the disease. Chronic diarrhea is the frequent passage of loose stools (>3 unformed stools and/or a volume of stool >200 g in 24 hours) with urgency and duration of more than 4 weeks. Chronic diarrhea can result in metabolic disturbances and poor quality of life. There are many causes, both related and unrelated to the physiological changes with colorectal cancer and its treatment. Patients should be assessed for the underlying cause and adverse outcomes of the chronic diarrhea, including dehydration and electrolyte abnormalities. It is managed with fluid resuscitation, electrolyte repletion, diet modification, and a variety of nonpharmacological and pharmacological interventions. Patients should be referred to gastrointestinal specialists and dietitians for collaborative management. A case study is used to illustrate assessment and management of this symptom.

KEY WORDS

cancer patients, chronic diarrhea, colorectal cancer, fecal incontinence, quality of life

While the actual number of cancer patients who are affected by chronic diarrhea cannot be calculated, it is known that chronic gastrointestinal (GI) adverse effects are a common cause of morbidity in cancer patients. The number of patients experiencing chronic GI symptoms after treatment for cancer who report a moderate or severe impact on quality of life is similar to the annual number of patients newly diagnosed with irritable bowel disease, up to 70 000 patients per year.[1] However, most cancer patients with adverse GI effects are not referred for specialized GI assessment.[2]

Chronic diarrhea is a common consequence of cancer or cancer treatment. It is especially prevalent among colorectal patients, both during treatment and in survivorship. Colorectal cancer is the third most common cause of cancer in the United States, with almost 137 000 new cases of colorectal cancer forecast for 2014. More than 50 000 deaths will be attributed to colorectal cancer in 2014. Five-year survival rates from 2003 to 2009 were 65%.[3] Chronic diarrhea may be a long-term problem, as 1 study on patient-reported symptoms 4 years after diagnosis with colorectal cancer found that 13% of survivors experienced diarrhea fairly often or very often and 24% of patients who had received radiation therapy reported diarrhea.[4]

Clinical situations causing chronic diarrhea have not been well described, and there are few comparative experimental studies for treatments of chronic diarrhea.[5] Clinical practice guidelines have been developed through consensus groups based on the limited evidence and expert clinical opinion, and these have been used as sources for describing the investigation and management of chronic diarrhea.[2,5-10] The most recent update of these guidelines was in 2008. Moreover, there is little evidence to support treatment pathways for cancer patients with chronic diarrhea.[5]

DEFINITION OF SYMPTOM

Diarrhea is the frequent passage of loose stools (>3 unformed stools and/or a volume of stool >200 g in 24 hours) with urgency.[10] The American Gastroenterological Association defines chronic diarrhea as diarrhea with duration of more than 4 weeks.[8] The National Cancer Institute has developed common toxicity criteria for reporting diarrhea in patients without colostomy.[11] (See Table 1.)

Diarrhea can be classified as watery, fatty (steatorrhea), or inflammatory (bloody) (Table 2). Watery or secretory diarrhea is frequently nocturnal and is unrelated to food intake. Steatorrhea is often accompanied by bloating; is greasy, foul smelling, or bulky; and is often difficult to flush. It is typically associated with malabsorption and may contain undigested food particles. Inflammatory diarrhea presents with an elevated fecal white blood count or occult or frank blood or pus.[12] Bloody diarrhea likely represents inflammation and disruption of the intestinal mucosa.[13]

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TABLE 1 Toxicity Criteria for Diarrhea in Patients Without Colostomy

Grade	Description
1	Increase of <4 stools/d over baseline
2	Increase of 4-6 stools/d over baseline
3	Increase of ≥7 stools/d over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death

Adapted from the National Cancer Institute toxicity criteria.[11]

The presence of water-insoluble fecal solids is an objective criterion for the evaluation of diarrhea.[8] The patient's definition of diarrhea is subjective and often includes increased liquidity in addition to increased frequency. Patients commonly associate fecal incontinence (FI) with diarrhea. Fecal incontinence is the involuntary loss of solid or liquid feces or mucus.[14] Although FI may be associated with loose stool, the problem may be with mechanisms of continence without alterations in intestinal fluid and liquid absorption. The presence of FI may not be elicited without targeted questioning because of patients' embarrassment about this condition.[15]

INCIDENCE AND PREVALENCE

Chronic diarrhea among the adult population in general is poorly studied, and the existing data are more than 10 years old.[7,9] Fine and Schiller[8] estimate the overall prevalence of adults with chronic diarrhea and an absence of abdominal pain in all populations at approximately 5%, whereas 13% of colorectal cancer survivors experienced diarrhea fairly often or very often in a 4-week period.[4] Chronic diarrhea is a strong risk factor for FI. The estimated prevalence of FI in noninstitutionalized US adults is 8.3%, with 75% reporting liquid stool.[14] A recent study demonstrated that 12% of patients admitted to FI when directly questioned about it, as compared with 2.4% in the control group.[16]

There is much literature that investigates diarrhea as an adverse effect of cancer treatments in all cancer patients, but the incidence and duration of diarrhea as an adverse effect are not quantified.[2] Patients may not report their symptoms because they want to please the provider by appearing to be a "good" patient or have the desire to think positively and to deny complications.[2,17,18]

CLINICAL SIGNIFICANCE

Severe diarrhea can cause dehydration, renal insufficiency, and acid-base and electrolyte disturbances.[7] Over time, it can contribute to poor nutritional status, resulting in impaired immunity and skin breakdown, including the formation of pressure ulcers.[8] Dose reductions or discontinuation of cancer treatment therapies can adversely affect clinical outcomes.[19] Chronic diarrhea can mask symptoms of recurrent or new cancers.[6]

The conditions of chronic diarrhea and FI are distressing and have a significant adverse impact on quality of life, often causing patients to become homebound or to withdraw from work and society for fear of having embarrassing "accidents." Ramsey et al[20] found that quality of life was negatively and significantly correlated with reported diarrhea problems among colorectal cancer survivors, and Alsheik et al[16] reported the lowest quality of life among patients with FI. Bruheim et al[21] also found a negative impact on quality of life with FI and reported that patients with a remote history of radiation therapy have worse social function. Caravati-Jouvenceaux et al[22] demonstrated lower scores in social function 5 years after diagnosis. Gastrointestinal cancer survivors have a higher relative risk (1.44) for unemployment than healthy adults.[23] The psychological stress associated with chronic diarrhea can in turn exacerbate existing or precipitate new GI symptoms.[2]

TABLE 2 Common Causes and Types of Diarrhea

Watery Diarrhea	Steatorrhea
Bile acid malabsorption	Bile acid malabsorption
Carbohydrate malabsorption	Free fatty acid malabsorption
Constipation with overflow	Intestinal lymphangiectasia
Dietary/alcohol problems	Pancreatic insufficiency
Medication or alcohol ingestion, including chemotherapy	Small bowel bacterial overgrowth
Endocrine abnormalities, including hyperthyroidism	Celiac disease
Infection	Short bowel syndrome
New/recurrent neoplasia	**Inflammatory diarrhea**
New onset primary inflammatory bowel disease	Radiation colitis
Rapid transit	Neoplasia
Short bowel syndrome	Colon cancer
Small bowel bacterial overgrowth	Lymphoma
Stricture formation	
Idiopathic	

Chronic diarrhea can continue long after cancer treatments have stopped, but the symptom may be overlooked during posttreatment follow-up if not specifically queried.

Nurses should anticipate and identify symptoms and implement care plans based on evidence or best practice. Symptoms must be palliated/managed throughout all phases of the disease course, including during survivorship. Knowledge of the patient's prior treatment plan can help the clinician anticipate the types of symptoms that may occur.[24]

Jefford et al[25] describe a nurse-led pilot intervention that provides patients and their primary care providers with information that describes the physical consequences of treatments, a personalized care plan, a face-to-face nursing session at the end of treatment, and 3 follow-up phone calls at 1, 3, and 7 weeks after the completion of treatment for colorectal cancer. Study participants reported satisfaction with the opportunity to ask questions and to preempt issues before they became problematic.[25]

CAUSES AND PATHOPHYSIOLOGY OF CHRONIC DIARRHEA

Chronic diarrhea can arise for numerous reasons, including causes that are unrelated to the cancer or cancer treatment.[5] It is important to determine the underlying cause of the diarrhea in order to minimize the potential of harming the patient. Chronic diarrhea must also be distinguished from irritable bowel syndrome (IBS), which is the combination of abdominal pain and abnormal bowel habits that include constipation, diarrhea, or variable bowel movements.

The most common underlying causes of chronic treatment-related diarrhea are chemotherapy, radiation, and bowel resection. Table 2 summarizes the common physical causes of chronic diarrhea after cancer treatment by category. The cytotoxic effect of chemotherapy and radiation triggers mucositis that affects the entire GI tract.[26,27] Common chemotherapeutic drugs that induce mucositis are fluoropyrimidines, capecitabine, and irinotecan. Lactose intolerance, bile acid malabsorption, and pancreatic insufficiency are common after chemotherapy. Possible hepatic adverse effects include reactivation of viral hepatitis, sinusoidal obstruction syndrome, steatosis, and steatohepatitis.[2] Small bowel bacterial overgrowth is thought to be a frequent source of chronic diarrhea. Increased bowel permeability among immunosuppressed individuals can result in GI transmural infection that in turn can lead to sepsis, shock, and secondary mucosal ischemia.[2]

Radiation therapy of the abdomen or pelvis also damages intestinal mucosa. Acute radiation enteritis usually resolves within 2 to 6 months but can create permanent changes that result in altered intestinal transit, reduced bile acid absorption, increased intestinal impermeability, bacterial overgrowth, and lactose malabsorption.[8]

Surgical resection causes significant disruption of normal GI physiology due to decreased absorptive surface area and transit time. Colectomy reduces the capacity of the colon to absorb water, possibly resulting in diarrhea. Distal resection of the ileum impairs bile acid recovery, absorption of vitamin B_{12}, and absorption of sodium chloride. Resections of the liver and pancreas create a risk of biliary structures secondary to fibrosis at the anastomoses or to disease recurrence.[2]

The possibility that chronic diarrhea is unrelated to cancer must also be considered. Fecal impaction or partial bowel obstruction can allow fluid to leak past the area of blockage. This condition can also be associated with FI. Patients may also have comorbid irritable bowel disease or hyperthyroidism as underlying causes of diarrhea. Preexisting illnesses or lifestyles can predispose patients to chronic diarrhea.

Poor nutritional status as evidenced by hypoalbuminemia can cause decreased osmotic pressure and edema in the intestinal mucosa that lead to diarrhea.[8] Dietary factors such as excess fiber or the intake of nutritional supplements should be investigated. Excessive use of laxatives or antacids containing magnesium can also trigger diarrhea.

ASSESSMENT

Careful evaluation of the underlying cause of chronic diarrhea must be conducted in addition to managing associated symptoms. Although history and physical examination can determine the severity of the diarrhea and underlying disease, it rarely points to a specific cause, which should be determined for effective treatment. It is most important to also evaluate for adverse outcomes of diarrhea, dehydration, and electrolyte depletion and to include repletion in treatment plans.[8,13] Table 3 summarizes important steps in the history, physical examination, and data collection process.

Onset of diarrhea soon after eating and/or relief from fasting suggests possible malabsorption. Pain that is worse after meals can occur with pancreatitis and chronic intestinal ischemia. The pain can be so severe that patients are afraid to eat (sitophobia). Pain can also be associated with IBS, celiac disease, and lactose intolerance. A sense of urgency with straining and incomplete emptying is associated with IBS, as are upper GI symptoms such as heartburn and dyspepsia.[13] Weight loss or wasting indicates a severe underlying disease and malnutrition. Orthostasis can suggest autonomic dysfunction as well as dehydration. The patient's general appearance and mental status can indicate toxicity or chronic debility.

Review records from previous provider encounters and treatments. Abdominal x-rays evaluate obstruction or impaction. Radiographic studies of the stomach and colon can detect fistulas and strictures. Computed tomography imaging evaluation can identify the presence of neutropenic enterocolitis, and ultrasound can assess bowel wall thickness.[13] Colonoscopy may be appropriate to evaluate for recurrent

TABLE 3 History, Physical Examination, and Data

Topic	Data
History	
Characteristics	Obtain description and frequency, and ask the following questions:
	Are you woken from sleep with the urge to defecate?
	Do you have troublesome urgency to defecate and/or fecal leaking, soiling, or incontinence?
	Do you have any gastrointestinal symptoms preventing you from leading a full life?[2]
Medications	Review all current medications, especially new medicine, antibiotics in the last 6-8 wk, and medicines containing magnesium
	Include over-the-counter medications, nutritional supplements, illicit drugs, alcohol, and caffeine
Diet	Obtain a detailed record of dietary habits. Ask about recent changes to diet, special diets, consumption of sugar-free foods, ingestion of raw seafood or shellfish
Weight loss	Quantify recent weight loss, intentional or unintentional
Family history	Ask about congenital absorptive defects, celiac sprue, irritable bowel syndrome, cancer
Social history	Ask about sexual history, as HIV is a frequent cause of chronic diarrhea
Physical examination	
Vital signs	Include weight
Abdominal examination	Important but generally nonspecific
Perianal/rectal	Skin changes, gaping anus, and weak sphincter tone are signs of fecal incontinence[9]
Diagnostic studies	
Laboratory tests	Complete metabolic panel, albumin, vitamin B_{12} level, thyroid function, celiac screen[8]
Stool analysis	Test for blood, pus, fat, microbes, pH, electrolyte and mineral concentrations, laxatives[8]
Breath tests	Glucose, lactulose, C-xylose, C-glycocholate to detect bacterial overgrowth[8]

or new neoplasms. Sigmoidoscopy requires less preparation, but it cannot evaluate the proximal colon or terminal ileum.

MANAGEMENT

Initial treatment should focus on restoring and maintaining fluid and electrolyte balance, then treating the underlying cause of the diarrhea. Other management focuses on minimizing additional irritation to the bowels.

Nonpharmacological

Adequate hydration or rehydration is critically important. Patients should drink enough clear liquids to make up for the volume lost by diarrhea. This is best assessed by the restoration of normal urine output and may require the intake of 3 to 4 L of fluid per day. Oral fluid intake should include broth, gelatin desserts, and beverages that contain some salt and sugar. Schiller[5] recommends rehydration solutions such as the World Health Organization oral rehydration solution, Ricelyte, Rehydralyte, and Pedialyte. Replacement of fluid with water alone can result in hyponatremia and hypokalemia.

Symptoms can be improved with dietary modifications and, initially, bowel rest. Smaller, more frequent meals reduce the rate of nutrient exposure to the gut and may be easier to digest. The BRAT (bananas, rice, applesauce, toast) diet may be indicated for management of acute exacerbations of chronic diarrhea. Easily digestible foods such as plain pasta, white-meat skinless chicken, and scrambled eggs should be encouraged.[17]

Avoid indigestible sugars such as sorbitol and mannitol. Gas production is decreased with reduced carbohydrate intake. Cruciferous vegetables such as cabbage, Brussels sprouts, and broccoli produce gas and can cause increased abdominal cramping and bloating. Gas retention and bloating are decreased with reduced fat intake. Avoid milk products because mucosal injury to the gut can cause a transient lactase deficiency, resulting in lactose malabsorption. Patients can be advised to reduce caffeine intake on a trial basis because it may speed transit through the small bowel and colon.[5]

It is important to address weight loss and malnutrition because they can complicate chronic diarrhea. Refer patients to a registered dietitian for assessment of malabsorption and for management of dietary changes. Monitor the patient's nutritional status, including weight, anthropometry, and the levels of vitamin and trace elements. Undergarment pads can reduce the anxiety and embarrassment related to incontinence. Use skin barriers to minimize the risk of pressure ulcer formation for patients with FI or poor protein status.

Pharmacological

Electrolyte repletion should be a priority after evaluation of the metabolic panel. Intravenous fluids should be administered if the patient is unable to tolerate recommended oral

intake as discussed above. Consider hospitalizing patients with grade 3 or 4 diarrheas as measured by the National Cancer Institute toxicity criteria. Planned chemotherapy treatments should be delayed for patients presenting with diarrhea above pretreatment baselines to minimize the risk of further metabolic disturbances.[17]

Opioids are the criterion standard of treatment for diarrhea. The agonist effect on opioid receptors in the GI tract slows peristalsis and enhances absorption.[18] Imodium (loperamide) and Lomotil (diphenoxylate and atropine) are the most frequently used opioids in diarrhea management. More potent opioids should be used in refractory cases, most frequently codeine, tincture of opium, or morphine sulfate. Opiates are most effective if prescribed on a scheduled rather than "as needed" basis.

The somatostatin analog octreotide has been shown to be effective in managing chemotherapy-induced diarrhea. Clonidine can be effective as an antidiarrheal agent, but its utility is limited because of its antihypertensive effects.[5] Table 4 summarizes recommended dosages and mechanisms of actions for these drugs.

Other medications may be appropriate, depending on the underlying pathophysiology. Bile acid binders such as cholestyramine may be effective if bile acid is suspected as the cause of diarrhea. Pancreatic enzyme supplementation is reasonable for suspected pancreatic insufficiency. Antimicrobials can be used for chronic infection or small intestinal bacterial overgrowth. There is a lack of good evidence to support the use of bulking agents such as psyllium or adsorbents such as charcoal or kaolin plus pectin.[13] A recently published guideline suggests that probiotic treatment containing *Lactobacillus* species may be helpful in preventing chemotherapy and radiation-induced diarrhea in patients with pelvic cancers. More research is needed in order to recommend specific dosing regimens.[27]

CASE STUDY

A.M. was a 67-year-old white woman who had a diagnosis of cecal adenocarcinoma following routine colonoscopy in January 2013. Her weight at the time was 164 lb. A positron emission tomography scan revealed extensive metastases to the lungs and liver. She received 4 cycles of chemotherapy that included capecitabine before undergoing right hemicolectomy and liver resection in May. Following the surgery, she continued chemotherapy treatments. In September, she began to report intermittent diarrhea.

TABLE 4 Dosages and Mechanisms of Action for Commonly Used Antidiarrheal Agents

Drug	Administration	Comments
Loperamide	Oral, initial dose of 4 mg, 2 mg every 2-4 h or after every unformed stool, up to 16 mg/d[7]	Reduces fecal weight, frequency, urgency, and incontinence by slowing peristalsis. Action is localized to the gut; available over the counter; 97%-99% respond within 48 to 72 h
Lomotil (diphenoxylate-atropine)	Oral, dispensed as 2.5 mg diphenoxylate and 25 μg atropine. Titrate upward until central nervous system (CNS) tolerance is reached[15]	Mechanism of action similar to loperamide but does affect the CNS. Atropine is anticholinergic and is used to minimize overuse. Clinical improvement is usually achieved within 48 h
Codeine, tincture of opium, morphine	Oral, start codeine at 30 mg 4 times daily; titrate up to 120 mg 4 times daily. Others should be started at dose equivalent of 1-2 mg of morphine 4 times daily and titrated up to equivalent of 60 mg morphine 4 times daily[5]	Same action as other opioids and affects the CNS. May cause excessive sedation when combined with other sedative drugs. Patients may become habituated and may experience withdrawal symptoms if stopped abruptly. Avoid use of combination drugs with acetaminophen to avoid administering potentially toxic amounts of acetaminophen
Clonidine	Oral and transdermal; initial dose is 0.1 mg 2 times daily up to a maximum dose of 0.6 mg 2 times daily[5]	Inhibits motility and increases net rate of absorption by the intestine. May cause excessive sedation when combined with other sedative drugs. May cause hypotension if combined with other antihypertensive drugs
Octreotide	Subcutaneous or intravenous, 100-150 μg titrated up to 500 μg 3 times daily, or continuous infusion at 25-50 μg/h[7]	Increases absorption of water, electrolytes, and nutrients from the gut by suppressing hormone production and increasing gastrointestinal transit time. Effective in controlling hormonal diarrheal syndromes due to serotonin production from carcinoid tumors

Mrs A.M.'s diarrhea worsened, and in November, she began treatment with loperamide. Capecitabine therapy was stopped, but the diarrhea persisted, increasing to multiple times a day. She was started on pancrelipase therapy empirically but did not have any significant improvement in symptoms. The diarrhea progressed to FI and interfered with her ability to leave the house. Octreotide therapy was introduced in April 2014 and reduced the frequency of diarrhea. The patient reported occasional formed stool, so the octreotide treatment was stopped, even though the patient continued to experience diarrhea and FI.

In May Mrs A.M. presented to the emergency department with an acute change in mental status. She was discovered to have metabolic alkalosis with pH of 7.43 and HCO_3 of 30.5. Her weight had declined to 112 lb. Her ammonia level was high at 62 μmol/L. White blood count was slightly elevated at 13.3 thousand/μL. Her low levels of albumin (3.2 g/dL) and vitamin B_{12} (275 pg/mL) were probably secondary to poor intake and malabsorption. Alanine aminotransferase was normal at 34 IU/L, aspartate aminotransferase slightly elevated at 57 U/L, and alkaline phosphatase significantly elevated at 401 IU/L. Bilirubin, prothrombin time, and international normalized ratio were within normal limits, but partial thromboplastin time was 100.7 seconds. The significantly elevated alkaline phosphatase level indicated possible biliary obstruction or cholestasis. Her metabolic alkalosis could have been related to contraction alkalosis. Elevated blood ammonia may have been the primary cause of her altered mental status, but vitamin B_{12} deficiency may also have been a contributing factor.

Mrs A.M.'s case illustrates the consequences of chronic diarrhea and illuminates several missed opportunities to manage the metabolic and quality-of-life issues that she experienced. The treatments that were offered for the management of her chronic diarrhea did not result from a thorough assessment of its underlying causes. She did not disclose her FI until she became increasingly housebound and socially isolated. Early referral to gastroenterology may have resulted in proactive and better management of her symptoms. Ongoing involvement of a dietitian could have prevented her low protein status, vitamin B_{12} deficiency, and significant weight loss.

SUMMARY

Chronic diarrhea is an underreported symptom that has important consequences to colorectal cancer patients' health and quality of life. Left untreated, chronic diarrhea can result in severe metabolic disturbances and adverse effects on quality of life. Nurses are in a good position to identify the presence of chronic diarrhea and to advocate for appropriate diagnosis and treatment on behalf of their patients. Patients with chronic diarrhea should be referred to GI specialists and dietitians before a crisis occurs. Intensive follow-up with these specialists should be continued even after active treatment for the cancer ends.

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