CLINICAL CHALLENGES

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Chemotherapy-Induced Diarrhea

Case Study

L.M. is a 61-year-old man who presented to his oncologist with complaints of uncontrollable diarrhea with associated fever and progressive weakness for one week. These symptoms started a day after he received his fourth cycle of 5-fluorouracil (5-FU) and leucovorin, the chemotherapy regimen that he was receiving to treat his colon cancer.

L.M. reported for work a day after receiving 5-FU and started having bouts of watery diarrhea every one to two hours that prompted him to end his workday around noon. The diarrhea persisted for the next two days and was refractory to loperamide and diphenoxylate. His wife asked him to see his oncologist after noticing that he was getting progressively weaker with accompanying loss of appetite and abdominal cramping. L.M. denied nausea or vomiting but reported an approximately 10 lb weight loss in the past month. He denied having fevers, chills, or sweats at home, but his oral temperature was 101.3°F on presentation.

The patient's medical and surgical history included a right upper lobectomy three years prior to this episode for poorly differentiated non-small cell lung cancer and a right hemicolectomy two years prior for a moderately differentiated adenocarcinoma of the ascending colon. L.M.'s medical history was significant for gastrointestinal reflux disorder and hyperlipidemia treated with rabeprazole sodium and simvastatin. Social history included a history of alcohol (quit 14 years ago) and current tobacco use (25 pack per year smoking history).

Review of systems revealed poor appetite, lethargy, fatigue, and weight loss. L.M. reported dry skin, taste alterations (salty), and a history of oral thrush. Other pertinent findings included dyspnea on exertion and occasional upper respiratory infections (four to five times per year).

On physical examination, L.M. appeared ill and frail but was in no acute distress. He was alert and oriented to name, place, and time; communicated effectively; and had an appropriate affect. His skin was dry and cool to touch with fair turgor. Mucous membranes were moist and pink. Oral examination revealed thrush with no erythema or signs of inflammation of the glands or tonsils. No lymphadenopathies were appreciated. Bilateral bronchovesicular breath sounds that cleared with coughing were auscultated, and cardiac examination was unremarkable. The abdomen was flat and soft but tender to palpation; no rebound tenderness, guarding, or apparent organomegaly or mass was found on palpation. External rectal examination showed erythema around the anus without skin breakdown.

His vital signs were temperature 101.3°F, blood pressure 92/50 mmHg, pulse 60 beats per minute, and respirations 18 breaths per minute. His blood chemistries were sodium 134 mEq/l, potassium 3.2 mEq/l, chloride 102 mEq/l, carbon dioxide 26 mEq/l, blood urea nitrogen 14 mg, creatinine 0.9 mg, glucose 171 mg, magnesium 2.3 mEq/l, phosphorus 1.6 mg, and calcium 7.7 mg.

Blood counts revealed a white blood cell count of 2.7 (neutrophils 22, bands 25), hemoglobin 10.6 g, hematocrit 30.6%, and platelets 193,000 mm^3. Stool cultures for *C. difficile* toxin and ova and parasites were negative. L.M.'s inpatient medication profile included fluconazole 200 mg daily, metronidazole 500 mg IV every eight hours, octreotide acetate 500 mcg subcutaneously every eight hours, levofloxacin 500 mg IV daily, docusate sodium 100 mg daily, famotidine 20 mg IV every 12 hours, hydromorphone 1 mg every three hours as needed, diphenoxylate 2.5 mg every two hours as needed, and prochlorperazine 5–10 mg IV every four hours as needed.

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Clinical Problem Solving

Responding to this clinical interview by Associate Editor Nancy Jo Bush, RN, MN, MA, AOCN®, is Marlon Garzo Saria, RN, MSN, OCN®, an oncology clinical nurse specialist at the University of California, San Diego.

When did chemotherapy-induced diarrhea (CID) become a focus of clinical assessment and treatment for nurses?

Acute diarrhea, although not commonly encountered in the general population of patients with cancer, is a symptom that can cause severe distress, negatively affect quality of life, and be life threatening. However, it was not recognized as such until the mid-1990s, when several oncology nurses met to discuss the care of a patient with CID. This gathering led to the formation of the Working Group on Cancer-Related Diarrhea during the 1995 Oncology Nursing Society Congress in Anaheim, CA (Rutledge & Engelking, 1998). Then, an expert multidisciplinary panel of physicians, nurses, and pharmacists developed recommendations for the treatment of CID in 1998 (Wadler et al., 1998), and these standards remain the most widely referenced in current literature and practice.

Diarrhea is a side effect of many cancer treatments. What population of patients is most at risk for CID?

In the case study, a 61-year-old man with colon cancer presented with acute diarrhea and fever. The accompanying elevation in body temperature sets this case apart from the typical presentation of diarrhea in patients with colon cancer.

CID is a significant cause of morbidity and mortality in a subgroup of patients with cancer and may be more devastating to adults with cancer as they advance in age. Some of the most common sequelae associated with CID, such as electrolyte imbalances, malnutrition, and dehydration (Hogan, 1998), may not be as well tolerated by older adults when compared to their younger counterparts. Because most malignancies occur in older adults, the case study points out this population's inherent clinical risk of developing CID.

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In what clinical scenario is CID most likely to occur?

CID is a common occurrence in patients with colorectal cancer being treated with 5-FU (Cascinu et al., 2000). The addition of leucovorin increases the incidence and severity of diarrhea, which is estimated to affect 25%–40% of the patients receiving the combination (Hogan, 1998; Petrelli, Rodriguez-Bigas, Rustum, Herrera, & Creaven, 1993; Wadler et al., 1998). The clinical manifestations of CID (i.e., frequent watery stools occurring 24–96 hours postchemotherapy [Cascinu, 1995]) were observed in the case study; however, L.M. had not experienced the same symptoms with prior chemotherapy treatments. In addition, the concurrent febrile episode suggests a coexisting condition or an entirely different pathology.

L.M. presented with CID and fever. What differential diagnoses must be considered in the case of CID and fever?

The differential diagnoses to consider for CID, although limited, encompass complex mechanisms and multiple etiologies. Inflammatory processes, cancer therapies, malabsorption disorders, motility disturbances, intestinal resection, medications, stress, and diet are some of the causes that may be considered when investigating the etiology of CID. The process of identifying the etiology of CID was made straightforward when Cascinu (1995) classified CID into six types, each involving different pathophysiologic mechanisms and unique clinical presentations (see Table 1).

What specific etiologies were considered in the case of L.M. and why?

Acute infectious diarrhea was a consideration in the case of L.M. The differential diagnoses for infectious diarrhea may be narrowed when a practitioner is aware of the incubation period for common offending organisms, which are grouped into less than 6 hours, 6–24 hours, and 16–72 hours (Thielman & Guerrant, 2004). Diagnosing infectious diarrhea may not be necessary in immunocompetent individuals because most intestinal infections are self-limiting (Casburn-Jones & Farthing, 2004). However, diagnosis is imperative in patients such as L.M. who are receiving cancer treatment. Waiting for the symptoms to subside may become life threatening.

Viral gastroenteritis, characterized by abrupt onset of nausea and abdominal cramps followed by vomiting or diarrhea with low-grade fever, occurs in about half of patients with CID (Manatsathit et al., 2002). Initially considered in L.M.'s case in addition to the possibility of bacterial toxin-induced food poisoning, gastroenteritis was ruled out because the major clinical manifestation associated with these infectious etiologies, vomiting, was not present in his chief complaint and history. The index of suspicion for other pathogen-induced diarrhea was low because no link was identified between the onset of L.M.'s diarrhea and the ingestion of a particular food or meal. More importantly, the stool cultures were negative for bacteria and protozoa.

In patients with cancer, the widespread use of broad-spectrum antibiotics has demonstrated the clinical significance of antibiotic-associated diarrhea commonly attributed to opportunistic infection with *C. difficile* (Farthing, 2000). *C. difficile*-induced diarrhea, spread nosocomially, often is associated with antibiotic use with accompanying leukocytosis (Thielman & Guerrant, 2004). This diagnosis was eliminated when the *C. difficile* stool culture was negative.

This case highlights the importance of a differential diagnosis in CID not only to determine appropriate medical management but also to provide symptom management and comfort for the patient. How does the case of L.M. instruct professionals in the management of CID?

L.M. developed diarrhea with an associated fever of 101.3°F on a single occasion less than 24 hours after receiving his fourth cycle of high-dose 5-FU and leucovorin. His presentation raised the suspicion of CID. The episode of fever, however, suggested a coexisting condition, with the probability of a superimposed viral or bacterial etiology that eventually was ruled out when stool microscopy and cultures yielded negative results. Manatsathit et al. (2002) noted that fever may be present with watery diarrhea but often is mild and does not last longer than two days. Wadler et al. (1998) suggested that although fever in a patient with CID may indicate an infectious cause, practitioners should recall that the fever may be indicative of high risk for sepsis, especially because the potential for neutropenia leading to a septic condition is increased in patients who receive 5-FU. L.M.'s white blood cell count of 2.7 with absolute neutrophil count calculated at a safe but lower normal range of 1,269 indicated that the transient febrile episode was related to the continued drop in neutrophils. Healthcare professionals could safely expect a sustained drop in neutrophils with L.M.'s weekly dose schedule of 5-FU, with the nadir for granulocytes anticipated at 9–14 days (Cleri & Haywood, 2002). Blood cultures never were obtained, and the fever did not recur and remained an isolated event. One question that also remained unanswered was why CID developed after the fourth cycle of chemotherapy when the first three cycles were well tolerated.

Severe diarrhea adversely affects quality of life and may have life-threatening consequences, especially in patients who are vulnerable to its associated complications. In addition, according to Anthony (1993), who revealed the survival advantage of full-dose adjuvant therapy, the occurrence of CID is one of the dose-limiting toxicities of colorectal cancer treatment that may negatively affect treatment outcomes. Therefore, prompt recognition, treatment, reduction, and prevention of CID are essential for the management of patients undergoing treatment for colon cancer and all malignancies.

What assessment criteria and standards of practice would you recommend for professionals in the management of CID?

Diarrhea, regardless of its etiology, should be managed with a three-point approach: (a) supportive therapy (i.e., fluid and electrolyte replacement, nutritional support, relief of abdominal cramping), (b) the use of antidiarrheal agents (i.e., antimotility and antisecretory agents), and (c) initiation of antimicrobial therapy, if warranted (Casburn-Jones & Farthing, 2004; Manatsathit et al., 2002; Stern & Ippoliti, 2003). All therapies, with the exception of supportive therapy, require pharmacologic intervention. A fourth approach, reduction and prevention of diarrhea through nonpharmacologic interventions, has been documented in nursing literature and was discussed in Wadler et al.'s (1998) guidelines.

Priority should be given to correcting fluid and electrolyte imbalances, the major cause of morbidity and mortality associated with CID. Dehydration should be corrected properly, regardless of the etiology of CID (Manatsathit et al., 2002). Casburn-Jones and Farthing (2004) stressed the importance of fluid and electrolyte replacement and defined this intervention as the cornerstone of treatment. For patients with mild dehydration and minimal or no vomiting, oral rehydration salt solution should be given at approximately 1.5 times the volume of stool loss in 24 hours (Manatsathit et al.). A simpler way to guarantee adequate fluid intake is to recommend intake of approximately 3 l of fluid daily (Hogan, 1998). IV fluid replacement is indicated for patients with severe dehydration, those who are in hypovolemic shock, or those who have mild to moderate dehydration but are unable to tolerate oral fluids (Manatsathit et al.)

The use of antimotility agents has been advocated and recommended as part of the management of CID. Common pharmacologic therapies for CID include opioids (e.g., loperamide, diphenoxylate, codeine, tincture of opium, paregoric) and anticholinergics (e.g., atropine, scopolamine). Guidelines for pharmacologic management and recommended doses have been published (see Rutledge & Engelking, 1998; Stern & Ippoliti, 2003; Wadler et al., 1998). The use of antimicrobial therapy in uncomplicated CID is not routinely indicated and although its use in noncancer-related infectious diarrhea has remained controversial, it is a mandatory treatment modality for patients who have cancer or are immunosuppressed with documented infectious diarrhea (Casburn-Jones

Table 1. Types, Descriptions, Etiologies, and Clinical Manifestations of Cancer-Induced Diarrhea

Type	Description	Etiologies	Clinical Manifestations
Chemotherapy induced	Combined mechanical and biochemical disturbances stimulated by chemotherapeutic effects on bowel mucosa	Gut wall toxicity; most frequent offending agents include fluoropyrimidines (e.g., 5-fluorouracil) and topoisomerase inhibitors (e.g., irinotecan).	Frequent watery to semisolid stools with onset occurring within 24–96 hours postchemotherapy administration
Dysmotility associated	Mechanical disturbance characterized by deranged intestinal motility resulting in rapid transit of stool through the small or large intestine	Clinical problems such as irritable bowel syndrome and narcotic withdrawal syndrome and external factors including ingestion of peristaltic stimulants (food, fluid, or medications) or psychoneuroimmunologic effects of stress, anxiety, and fear	Frequent small semisolid or liquid stools of variable volume and frequency
Exudative	Resulting from excess blood, serum proteins, and mucus in the intestinal lumen	Radiation to bowel mucosa (dose dependent)	Variable volume (< 1,000 ml per day), but high-frequency stools (> 6 stools per day) are associated with hypoalbuminemia, anemia from cumulative protein, and blood loss.
Malabsorptive	Secondary to factors that alter luminal and mucosal integrity and nature	Enzyme deficiencies that prevent complete digestion of fats (e.g., lactose intolerance and pancreatic insufficiency secondary to obstruction by cancer or pancreatectomy); morphologic or structural changes resulting in decreased absorptive capacity (e.g., surgical resection of intestine); mucosal changes that alter membrane permeability	Large-volume, foul-smelling steatorrhea-type stools
Osmotic	Mechanical disturbance characterized by large-volume influx of fluid and electrolytes into intestinal lumen that overwhelms absorptive capacity of bowel	Ingestion of hyperosmolar preparations and substances that include nonabsorbable solutes (e.g., sorbitol, magnesium-based antacids) and enteral-feeding solutions; intestinal hemorrhage where intraluminal blood acts as osmotic substance	Large-volume, watery stools that resolve with withdrawal of causative agent
Secretory	Characterized by intestinal hypersecretion stimulated by an array of endogenous mediators that exert primary effect on intestinal transport of water and electrolytes, resulting in accumulation of intestinal fluids	Endocrine tumors producing excessive quantities of peptide secretagogues (vasoactive intestinal peptide tumors, carcinoid gastrinoma, insulinoma, glucagonoma); enterotoxin-producing pathogens irritate bowel wall stimulating intestinal secretion, and an antibiotic-induced change in microbial flora permits growth of *C. difficile.*	Large-volume watery stools (> 1,000 ml per day) that persist despite fasting; osmolality equals plasma concentration.

Note. From "Cancer-Related Diarrhea: Selected Findings of a National Survey of Oncology Nurse Experiences" by D. Rutledge and C. Engelking, 1998, *Oncology Nursing Forum, 25,* p. 862. Copyright 1998 by the Oncology Nursing Society. Adapted with permission.

& Farthing, 2004). Stern and Ippoliti discussed the benefits of prophylactic probiotics such as *Lactobacillus acidophilus* in reducing diarrhea.

Prevention of CID in high-risk patients does not only reduce mortality and morbidity but also allows for the continuation of full-dose chemotherapy or radiotherapy (Anthony, 1993). Octreotide, an agent that inhibits the secretion of gastrointestinal hormones, does not always prevent CID in patients with weekly 5-FU and leucovorin (Meropol, Blumenson, & Creaven, 1998). The possible role of the long-acting formulation of octreotide (octreotide long-acting repeatable depot) in the prevention of CID has been proposed (Anthony), although several trial results are pending.

CID may be minimized with appropriate dietary modifications. Small, frequent, bland meals that are rich in protein and high in potassium are recommended (Hogan, 1998; Stern & Ippoliti, 2003). In certain instances, depending on the clinical situation, bowel rest may be necessary. Foods and beverages that are considered to promote diarrhea should be avoided. These include cabbage and onions, which produce gas; caffeine; spices (e.g., curry, chili powder, pepper sauce); alcohol, which irritates the gut; and hyperosmotic supplements (e.g., Ensure®, Abbott Laboratories, Abbott Park, IL; Boost®, Novartis Medical Nutrition, Minneapolis, MN) that contribute to the production of loose, high-volume stools (Hogan; Stern & Ippoliti).

Self-management of CID is possible with over-the-counter medications. Loperamide, the most accessible diarrhea medication, is mildly cost prohibitive. Tincture of opium, the least expensive among the antidiarrheal agents, is a controlled substance; therefore, obtaining a prescription may be an inconvenience for patients or caregivers. Finally, the importance of preventing dehydration associated with diarrhea cannot be overemphasized. By preventing dehydration associated with CID, mortality and morbidity are reduced greatly.

Effective management of CID relies on initial assessment and continuous evaluation of patients undergoing treatment. Appropriate pharmacologic and nonpharmacologic techniques must be used to maximize therapeutic benefits to reduce the morbidity associated with CID.

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References

Anthony, L. (1993). New strategies for the prevention and reduction of cancer treatment-induced diarrhea. *Seminars in Oncology Nursing, 19*(4, Suppl. 3), 17–21.

Casburn-Jones, A., & Farthing, M. (2004). Management of infectious diarrhea. *Gut, 53,* 296–305.

Cascinu, S. (1995). Drug therapy in diarrheal diseases in oncology/hematology patients. *Critical Reviews in Oncology/Hematology, 18,* 37–50.

Cascinu, S., Bichisao, E., Amadori, D., Silingardi, V., Giordani, P., Sansoni, E., et al. (2000). High-dose loperamide in the treatment of 5-fluorouracil-induced diarrhea in colorectal cancer patients. *Supportive Care in Cancer, 8,* 65–67.

Cleri, L., & Haywood, R. (2002). *Oncology pocket guide to chemotherapy*. Philadelphia: Mosby.

Farthing, M. (2000). Diarrhoea: A significant worldwide problem. *International Journal of Antimicrobial Agents, 14,* 65–69.

Hogan, C. (1998). The nurse's role in diarrhea management. *Oncology Nursing Forum, 25,* 879–886.

Manatsathit, S., Dupont, H., Farthing, M., Kositchaiwat, C., Leelakusolvong, S., Ramakrishna, B., et al. (2002). Guideline for the management of acute diarrhea in adults. *Journal of Gastroenterology and Hepatology, 17,* 54–71.

Meropol, N., Blumenson, L., & Creaven, P. (1998). Octreotide does not prevent diarrhea in patients treated with weekly 5-fluorouracil plus high-dose leucovorin. *American Journal of Clinical Oncology, 21,* 135–138.

Petrelli, N., Rodriguez-Bigas, M., Rustum, Y., Herrera, L., & Creaven, P. (1993). Bowel rest, intravenous hydration, and continuous high-dose infusion of octreotide acetate for the treatment of chemotherapy-induced diarrhea in patients with colorectal carcinoma. *Cancer, 72,* 1543–1546.

Rutledge, D., & Engelking, C. (1998). Cancer-related diarrhea: Selected findings of a national survey of oncology nurse experiences. *Oncology Nursing Forum, 25,* 861–873.

Stern, J., & Ippoliti, C. (2003). Management of acute cancer treatment-induced diarrhea. *Seminars in Oncology Nursing, 19*(4, Suppl. 3), 11–16.

Thielman, N., & Guerrant, R. (2004). Acute infectious diarrhea. *New England Journal of Medicine, 350,* 38–47.

Wadler, S., Benson, A., Engelking, C., Catalano, R., Field, M., Kornblau, M., et al. (1998). Recommended guidelines for the treatment of chemotherapy-induced diarrhea. *Journal of Clinical Oncology, 16,* 3169–3178.

Clinical Highlights: Chemotherapy-Induced Diarrhea

Definition: Chemotherapy-induced diarrhea (CID) is a risk for all patients receiving cancer treatment, but patients receiving regimens that include fluoropyrimidines and irinotecan have a significantly higher risk. The morbidity and mortality related to CID result from fluid and electrolyte imbalances that can lead to life-threatening dehydration, renal insufficiency, and cardiovascular morbidity.

Pathophysiology: The exact pathophysiologic mechanism underlying CID is not clearly understood; however, researchers believe it is caused by an imbalance between the absorptive and secretory cells of the small intestine resulting from damage by chemotherapeutic agents to the intestinal epithelium that, in turn, causes superficial necrosis and inflammation of the bowel lining.

Risk factors: Previous episodes of CID and the use of fluoropyrimidines (e.g., 5-fluorouracil and prodrugs of this compound, including capecitabine), topoisomerase I inhibitors (e.g., irinotecan, topotecan), and other agents (e.g., cisplatin with or without docetaxel, oxaliplatin, cytarabine) can increase risk.

Clinical findings: Frequent loose and watery stools, abdominal cramping, dehydration, generalized weakness, and loss of appetite are present. Patients complaining of blood in the stool, fever, or dehydration necessitate immediate assessment and intervention to prevent life-threatening ileus, opportunistic infection or sepsis, and cardiac compromise.

Differential diagnosis: Chemotherapeutic toxicity, inflammatory conditions, malabsorption disorders, motility disturbances, ileus, comorbid conditions or medications, stress, and diet all must be considered.

Treatment: Patients are treated with dietary management, fluid and electrolyte support, bowel rest, antidiarrheal medications, intestinal transit inhibitors, and patient education for self-management. Treatment should be matched to symptom severity.

Prevention: Prevention includes the identification of high-risk patients, dietary and nutritional education for high-risk patients, and astute assessment and intervention at initial symptomatology.