Putting Evidence Into Practice:
Evidence-Based Interventions to Prevent, Manage, and Treat Chemotherapy- and Radiotherapy-Induced Diarrhea

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Diarrhea is a common side effect of chemotherapy regimens, particularly fluorouracil- and irinotecan-based therapies and abdominal and pelvic radiation regimens. Diarrhea can cause depletion of fluids and electrolytes, malnutrition, dehydration, and hospitalization, all of which can lead to cardiovascular compromise and death. Therefore, diarrhea can interfere with and detract from cancer treatment by causing dosing delays or reductions. Evidence supports pharmacologic interventions such as loperamide and octreotide as recommendations for practice. Emerging evidence suggests that probiotics are likely to be effective, but more extensive research is warranted as the field evolves. Soluble fiber supplements are likely to be effective for treating chemotherapy- or radiotherapy-induced diarrhea; however, additional research is needed because the type and dose of soluble fiber most effective in treating and preventing these types of diarrhea are unknown. This article is limited to recommendations for chemotherapy- and radiotherapy-induced diarrhea. The chemotherapy regimens included in most of the studies reviewed were the commonly used regimens containing drugs such as fluorouracil, cisplatin, adriamycin, and irinotecan.

Diarrhea is a common side effect of chemotherapy regimens, particularly fluorouracil- and irinotecan-based therapies and abdominal and pelvic radiation regimens. Chemotherapy-induced diarrhea (CID) can occur as often as 50%–80% of the time depending on the chemotherapy regimen (Benson et al., 2004; O'Brien, Kaklamani, & Benson, 2005). Patients undergoing pelvic or abdominal radiotherapy experience diarrhea at a rate of 50%, with an even higher incidence when concurrent chemotherapy is administered (Benson et al.). Diarrhea can cause depletion of fluids and electrolytes, malnutrition, dehydration, and hospitalization, all of which can lead to cardiovascular compromise and death. Therefore, diarrhea can interfere with and detract from cancer treatment by causing dosing delays or reductions. Ultimately, the delays and reductions may have an impact on survival (Ippoliti, 1998).

Because of numerous significant clinical implications, the management and treatment of diarrhea is receiving increased attention. Appropriate management requires interdisciplinary interventions. Currently, the National Comprehensive Cancer Network (NCCN) does not have guidelines available regarding cancer treatment–induced diarrhea. The purpose of this article is to present an interdisciplinary review of evidence-based interventions for the management of CID and radiotherapy-induced diarrhea (RID), as detailed in the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) diarrhea resource (www.ons.org/outcomes/volume4/diarrhea/pdf/ShortCard_Diarrhea.pdf). The findings address the ONS PEP question: What interventions

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At a Glance

- Diarrhea is a common side effect of certain chemotherapy regimens and abdominal and pelvic radiation.
- Pharmacologic interventions have the highest level of evidence for managing cancer treatment-induced diarrhea.
- Dietary modifications, provided by a registered dietitian, are consistent with clinical guidelines for management of cancer treatment-induced diarrhea.

are effective in preventing and treating diarrhea in adults with cancer receiving chemotherapy or radiation therapy?

Healthcare professionals from multiple disciplines, including nursing, palliative care, nutrition, and medicine, collaborated for this review. Because of the vast scope of the problem of diarrhea in patients with cancer, the review was focused. Specifically, the ONS PEP resource does not address diarrhea induced by graft-versus-host disease (GVHD) because of its extensive and unique etiology. In addition, the resource does not address diarrhea related to biologic therapies, such as interferon, interleukin-2, or monoclonal antibodies, or targeted therapies, such as epidermal growth factor receptor (EGFR) inhibitors or multikinase receptor inhibitors, because of the paucity of clinical trials related to diarrhea management for the therapies. Diarrhea management for tumor-induced diarrhea also was not included. The recommendations in this article are appropriate for the adult population. Application to the pediatric population is limited and was not addressed in this study.

Methods

Articulating an accurate definition of diarrhea was a challenge because a universally accepted definition does not exist. Most sources refer to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (see Table 1). For the purposes of this review, diarrhea is defined as an abnormal increase in stool liquidity, stool frequency (four to six stools or more per day over baseline), with or without nocturnal bowel movements and/or moderate abdominal cramping (Eastern Cooperative Oncology Group, 2007; NCI, 2006; Sabol & Carlson, 2007; U.S. Food and Drug Administration, n.d.). The definition was chosen to capture a broader picture of diarrhea than the CTCAE guidelines, which primarily focus on the number of stools. However, the CTCAE toxicity grading system is referenced throughout this article when referring to grades of diarrhea.

An extensive literature search of multiple databases, including CINAHL®, PubMed®, MEDLINE®, EMBASE™, Cochrane Database of Systematic Reviews, and UpToDate® with the search terms listed in Figure 1 was performed. Originally, the search was conducted on published reports from 2002–2007, but it was extended to 1997 because of older medications commonly used to manage diarrhea (i.e., tincture of opium).

Critical Review of the Evidence

Each member of the team, which included advanced practice nurses, staff nurses, a nurse scientist, and a registered dietitian (RD), analyzed the articles specific to their discipline using standardized guidelines to promote a systematic and consistent approach to study analysis. Each study was organized into a level of evidence (LOE) table according to the following information.

- Author and year of publication
- Characteristics of the intervention (e.g., treatment drug, diet intervention)
- Sample characteristics (e.g., age, sex, diagnosis)
- Setting characteristics (e.g., inpatient versus outpatient)
- Study design and conceptual model
- Measures assessed during the study (e.g., definition of diarrhea used to assess effectiveness of treatment)
- Results and conclusions of study and limitations, flaws, cautions, and/or contraindications of study.

Based on the previous information, each study was assigned a LOE rating according to criteria recommended by the ONS Research Team. The criteria were expanded upon by the review team to include more precise delineation and guidance for each LOE (see Figure 2). To further refine the process and provide guidance for the review team in evaluating each of the studies, an additional rating system based on Melnyk and Fineout-Overholt's (2005) hierarchy of evidence was developed to facilitate the critique process as each study was reviewed for strengths and weaknesses in the various levels of design. This was done for the edification of the team members for this review to assist in assigning LOE and is not a part of the ONS LOE rating system.

Table 1. Common Terminology Criteria for Adverse Events Version 3.0: Diarrhea Definition

ADVERSE EVENT	GRADE 1	2	3	4	5
Diarrhea	Increase of four stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of four to six stools per day over baseline; IV fluids indicated less than 24 hours; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of seven or more stools per day over baseline; incontinence; IV fluids 24 hours or more; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)	Death

Note. From "Common Terminology Criteria for Adverse Events [v3.0]," by National Cancer Institute, 2006. Retrieved November 13, 2007, from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

After reviewing all of the available studies, team members participated in a series of conference calls to combine all pertinent studies into one LOE table, which was used as the basis for the ONS PEP resource. This article discusses only the interventions that have sufficient evidence to warrant recommendation for practice or are likely to be effective. Many of the commonly used interventions require further research, and the details regarding those interventions can be found on the ONS PEP resource and online in the supporting documentation.

Effective Interventions for Prevention and Treatment

Interventions with the best evidence to prevent and treat CID or RID primarily are pharmacologic, which are discussed in detail in the section on interventions recommended for practice. The section, as well as the ensuing sections for recommendations likely to be effective or expert opinion, are divided into treatment for CID and RID. The information also can be found more expediently in the ONS PEP resource.

Recommended for Practice

Chemotherapy-induced diarrhea: A loading dose of 4 mg of loperamide, an oral opiate, followed by 2 mg orally every four hours is the standard first-line therapy for CID (Benson et al., 2004; Halmos, 2007). High-dose loperamide has shown moderate effectiveness in controlling CID associated with irinotecan. High-dose loperamide is 2 mg orally every two hours (4 mg every four hours at night), but the dose should not be given for more than 48 hours (Benson et al.; Janssen Pharmaceutica, 1998).

Another agent that has shown good efficacy is octreotide acetate, a somatostatin analog administered subcutaneously at a standard dose of 100–150 mcg three times daily (Benson et al., 2004; Zidan et al., 2001).

Radiotherapy-induced diarrhea: No recent studies specifically addressing RID reached the LOE needed to be recommended for practice; however, based on a review of current clinical practice guidelines, the use of loperamide and diphenoxylate continue to be recommended as the standard of practice for patients with mild symptoms (Benson et al., 2004). Mild symptoms generally are classified as grade 1 or 2 with no added risk factors like cramping, nausea and vomiting, impaired performance status, fever, sepsis, neutropenia, dehydration, or frank bleeding (Benson et al.).

Likely to Be Effective

Chemotherapy-induced diarrhea: One study examined long-acting repeatable (LAR) octreotide (Sandostatin LAR® Depot, Novartis Pharmaceuticals Corporation) as an intramuscular injection. LAR octreotide was given as a 20–30 mg monthly injection as secondary prophylaxis after patients failed loperamide with or without Lomotil® (Pfizer, Inc.). Even higher doses of octreotide (i.e., 30 mg–40 mg) have been suggested to be effective, but no specific recommendations exist at this time (Rosenoff, 2004; Rosenoff et al., 2006).

Chemotherapy and diarrhea
Radiotherapy and diarrhea
Cancer and diarrhea
Cancer surgery and diarrhea
Constipation related to diarrhea
Immunosuppression and diarrhea
Infectious diarrhea in cancer patients
Dietary interventions for cancer diarrhea
Probiotics and diarrhea
Glutamine and diarrhea
Selenium and diarrhea
Psyllium and diarrhea
Fiber and diarrhea
Nutrition and diarrhea and radiation
Nutrition and diarrhea and chemotherapy

Figure 1. Search Terms of Computerized Databases
Note. This wide variety of search terms was used to help narrow the focus of the review.

Octreotide may be titrated upward from 150 mcg–500 mcg subcutaneously administered three times daily until symptoms are controlled. The dose may be more effective than standard doses in patients with CID who fail loperamide. No optimal dose of loperamide has been determined (Benson et al., 2004).

Expert Opinion

Clinicians must be highly vigilant when monitoring gastrointestinal toxicity in patients receiving irinotecan-based therapies and other intensive combination therapies (Benson et al., 2004). Assessment should include baseline bowel habits, duration of symptoms, constellation of signs and symptoms (i.e., gas, bloating, and abdominal pain), and severity of symptoms. A tool such as the NCI (2006) CTCAE can help with the assessment. However, as previously noted, the tool does not include volume of stool, which is an important consideration when assessing the presence and severity of diarrhea. Other assessment strategies are outlined in the ONS PEP resource.

When treating CID and RID, clinicians also should include an evaluation of dietary intake to identify foods or fluids that may contribute to or exacerbate diarrhea (American Institute for Cancer Research, 2009; Benson et al., 2004; Kornblau et al., 2000; Maroun et al., 2007; McCallum & Polisena, 2000). General diet strategies and recommendations are included in the PEP resource. An RD should be consulted at the onset of diarrhea to assist with nutritional management.

Older medications, such as tincture of opium, commonly are used to manage cancer treatment–induced diarrhea, and expert opinion considers the practice useful. However, because of a lack of randomized controlled trials, the treatment cannot be unequivocally recommended for practice. Two different preparations of tincture of opium are available but the morphine content is different, so careful dosing is essential.

Radiotherapy-Induced Diarrhea

Prevention

Probiotic supplementation is a rapidly growing area of interest in the treatment of bowel disorders. Several studies have investigated the potential use of probiotics for patients with cancer with treatment-related diarrhea. Probiotics, as defined in a joint report

by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) are, "live microorganisms, which when administered in adequate amounts, confer a health benefit on the host" (FAO and WHO, 2002, p. 8). The use of probiotics shows promise in prevention of RID in high-risk patients undergoing radiation to the lower abdomen and pelvis. Specifically, supplementation with the VSL#3® (VSL Pharmaceuticals, Inc) strain, beginning on the first day of radiation and continuing until the end of the radiation treatment period, was shown to lead to a significant difference in the number of bowel movements and toxicity of diarrhea among 490 patients receiving pelvic radiation following surgery for sigmoid, rectal, or cervical cancers (Delia et al., 2007). In another study, *Lactobacillus acidophilus* NDCO 1748 significantly reduced diarrhea when given to patients during radiation to the pelvis (Marteau, de Vrese, Cellier, & Schrezenmeir, 2001). Another strain of *Lactobacillus*, given two weeks after radiation therapy, known as *Lactobacillus rhamnosus* reduced the need for diarrhea medication and the mean number of daily bowel movements among patients who had been experiencing diarrhea for more than two weeks, although the difference was not significant when compared with the control group (Urbancsek, Kazar, Mezes, & Neumann, 2001). Before definitive recommendations can be made, further research is needed to determine the probiotic strain(s), dosage(s), and timing of administration that is most effective for the prevention and treatment of RID.

Psyllium fiber supplementation also has been recommended for prevention and treatment of RID and continues to be recommended by clinical experts and in clinical guidelines (Singh, 2007). One study using psyllium fiber during pelvic radiation for prostate or gynecologic cancer found that 1–2 tsp daily was effective in reducing the incidence and severity of diarrhea (Murphy, Stacey, Crook, Thompson, & Panetta, 2000).

Octreotide also has been studied as an intervention for RID. In a study of patients receiving concomitant fluorouracil with pelvic radiation therapy for rectal carcinoma, patients with grades 2 or 3 diarrhea who were refractory to loperamide received 150 mcg of octreotide subcutaneously three times a day with nearly complete resolution of their symptoms (Topkan & Karaoglu, 2006). In a similar study of patients who were receiving radiation therapy only, the researchers found that subcutaneous administration of 100 mcg three times a day produced better results than diphenoxylate 10 mg per day in patients with grade 2 or 3 diarrhea (Yavuz, Yavuz, Aydin, Can, & Kavgaci, 2002).

Issues raised for discussion during the literature review for octreotide and the treatment of RID included significant concerns about the cost of the drug and difficulties in obtaining insurance authorization for its use for this purpose because the research is still in the early stages.

Implications for Practice

Patient assessment should include baseline bowel habits; change in bowel habits; consistency of stool; presence of abdominal pain, gas, or cramping; and signs and symptoms of dehydration. Assessment must be ongoing throughout the treatment trajectory. Medications such as loperamide and tincture of opium are opiate derivatives, so a change in the patient's abdominal status, especially the onset of nausea, pain, or bloating or a decrease in bowel movements, should alert the practitioner to evaluate for other potential underlying issues such as an ileus.

Level I: Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials (RCTs) or evidence-based clinical practice guidelines based on systematic reviews of RCTs

Level II: Evidence obtained from at least one well-designed RCT

Level III: Evidence obtained from well-designed controlled trials without randomization

Level IV: Evidence from well-designed case-control and cohort studies

Level V: Evidence from systematic reviews of descriptive and qualitative studies

Level VI: Evidence from a single descriptive or qualitative study

Level VII: Evidence from the opinion of authorities or reports of expert committees

Figure 2. Level of Evidence Criteria

Note. Based on information from Melnyk & Fineout-Overholt, 2005; Michelle & Friese, n.d.

Currently, strong empiric evidence supports pharmacologic interventions as recommendations for practice. Emerging evidence suggests that probiotics are likely to be effective, but this field continues to evolve, so more extensive research is warranted. Soluble fiber supplements are likely to be effective for treating CID or RID, but further research is needed because the type and dose of soluble fiber most effective in treating or preventing these types of diarrhea is unknown.

Octreotide has been studied in various methods of administration (Benson et al., 2004; Rosenoff et al., 2006), but more research is needed to support administration of intramuscular LAR octreotide. Larger clinical trials using LAR octreotide versus short-acting octreotide are needed and would be beneficial to patients. LAR octreotide would allow fewer injections, thus increasing patient comfort. A significant issue with octreotide is cost, considering the amount needed to treat diarrhea and the current limitations regarding insurance coverage.

The value of an RD on the team cannot be overstated. An RD can make recommendations that could help alleviate diarrhea, decrease dehydration, and maintain nutritional status. Nurses should be encouraged to consult with an RD at the onset of diarrhea and as needed during or after treatment to improve patient outcomes. However, if this is not possible, the recommendations described in the ONS PEP resource provide a guide for nurses in assisting patients with food choices and meal planning. Interventions as simple as eliminating sorbitol-containing substances, such as sugar-free gums and sugar-free candy, may help diminish diarrhea. Encouraging intake of oral rehydration solutions, such as sports drinks, also will assist with rehydration and electrolyte repletion.

Conclusion

This article is limited to recommendations for CID and RID. The chemotherapy regimens included in most of the studies

reviewed were the commonly used regimens containing drugs such as fluorouracil, cisplatin, adriamycin, and irinotecan. The review did not include biologic therapies, such as interferon, interleukin-2, or monoclonal antibodies, or targeted therapies, such as EGFR inhibitors or multikinase inhibitors. Additional clinical trials and more clinical experience are needed to provide the best recommendations for patients receiving these biologic and targeted therapies. GVHD in particular was excluded from the review because of the wide scope of the problem with GVHD-induced diarrhea. Clinical experience and expert opinion may suggest that treatment approaches for diarrhea for these therapies are similar to the approaches outlined in the review, but the evidence base established in the review can reliably be applied only to standard chemotherapies, as cited in the literature studied, and to pelvic and abdominal radiation therapy.

The challenge in developing evidence-based practice is to expect the evidence to be in peer-reviewed literature to support practice. Evidence-based guidelines can help direct the clinician in assessing and managing patients with specific problems, in this case with CID and RID. Care should be evidence-based when the evidence exists, but because research is a necessarily slow process, clinicians still have to rely on clinical experience and good judgment to provide expert care and ensure good patient outcomes.

In light of the aforementioned limitations, the authors of the review conclude that diarrhea continues to be a problem for patients undergoing some chemotherapy regimens and pelvic or abdominal radiotherapy. Diarrhea can adversely impact quality of life, integrity of cancer treatment, and patient survival, and therefore, it needs to be vigorously managed to avoid complications, hospitalization, or serious harm. A multidisciplinary approach will best address and control cancer treatment–induced diarrhea.

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