

EPEEC-O

Education in Palliative and End-of-life Care - Oncology

Participant's Handbook

Module 3i:

Symptoms –

Diarrhea

Emanuel LL, Ferris FD, von Gunten CF, Von Roenn J.
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Contact EPEC by E-mail at info@epec.net, or

The EPEC Project™
750 N. Lake Shore Drive, Suite 601
Chicago, IL 60611
USA

Phone: +1 (312) 503-EPEC (3732)

Fax: +1 (312) 503-4355

Case*

S.D. is a 79-year-old tax attorney with advanced colon cancer. He has been receiving chemotherapy with oxaliplatin, irinotecan, and fluorouracil. Approximately 7 days after receiving chemotherapy, he reports frequent watery stools. His daughter reports he is unusually unsteady on his feet when he gets up to walk. He has been incontinent once, and slipped and fell. He says he is exhausted.

* This case is not on an EPEC-O Curriculum trigger tape.

Introduction

Diarrhea is *stools that are looser than normal and may be increased in frequency*. It may be acute (< 14 days), persistent (>14 days), or chronic (> 30 days). Diarrhea can lead to dehydration, malabsorption, fatigue, hemorrhoids, and perianal skin breakdown. Secondarily, it can lead to electrolyte abnormalities. In the setting of chemotherapy, unrecognized and/or untreated diarrhea can be fatal.

Most cases of acute diarrhea are viral and self-limited. Those that are serious (watery diarrhea with signs of hypovolemia, stools containing blood and mucus, fever, >6 unformed stools in 24 hours, severe abdominal pain, recent antibiotic use or hospitalization) are likely bacterial.

Prevalence

The prevalence of chronic diarrhea in the general population in developed nations has not been well established, but seems to be around 5%.¹ As a general rule, the principal causes of diarrhea depend upon the socioeconomic status of the population and the setting in which they are seen. In developing countries, chronic diarrhea is often due to infections, although functional disorders, malabsorption, and inflammatory bowel disease are also found. In developed countries, the commonest causes are irritable bowel syndrome, inflammatory bowel disease, and malabsorption syndromes.

Diarrhea can be the dose-limiting adverse effect of a fluoropyrimidine, eg, 5-fluorouracil and capecitabine, and/or irinotecan chemotherapy. In combination, diarrhea occurs in 30-90% of patients.² As an adverse effect, diarrhea is also associated with methotrexate and cisplatin.

Prognosis

Diarrhea itself has no definite prognostic implications. Sequelae from diarrhea, ie, dehydration, can limit prognosis.

Pathophysiology

The pathophysiology of the gastrointestinal tract leading to diarrhea is complex. Normal gastrointestinal function is mediated through endocrine, paracrine, autocrine, and

neuronal forms of cellular communication. The gastrointestinal tract has its own intrinsic nervous system in the form of the myenteric and submucosal plexi. Additionally, there is extrinsic input from the central nervous system via the autonomic nervous system. These inputs mediate fight or flight responses and other emotional factors that are known to affect bowel function. Furthermore, the gastrointestinal tract has its own pacemaker cells, the interstitial cells of Cajal, which generate rhythmic electrical activity. Complex communication and coordination is required to produce segmental contractions that serve to mix luminal contents in place or produce peristaltic contractions that move luminal contents forward. Many agents mediate this communication including peptides like vasoactive intestinal peptide, small molecules like nitric oxide, and modified amino acids such as serotonin. Over 80% of the body's serotonin (5-HT) resides in the GI tract and over 21 serotonin receptor subtypes subserves its function. The 5-HT₄ receptor subtype is known to play a key role in intestinal motility. Finally, acetylcholine is the neurotransmitter ultimately responsible for smooth muscle cell contraction.

With normal gut function, approximately 2 liters per day of fluid is ingested. In addition, 5-7 liters or more of fluid are secreted into the gut lumen from the stomach, small intestine, and from exocrine sources such as the pancreas. This fluid is reabsorbed in the large intestine. Loose stools can occur when as little as 100 ml of fluid is not absorbed in the large intestine. Disruption of the complex orchestration of communication at the level of pacemaker cells, nerves, muscle, or transmitters can lead to diarrhea.

Chemotherapy-associated diarrhea

Both 5-fluorouracil and irinotecan cause acute damage to the intestinal mucosa leading to loss of epithelium. The increased volume of fluid that leaves the small bowel exceeds the absorptive capacity of the colon, leading to clinically significant diarrhea. In addition, irinotecan has a direct cholinergic effect causing diarrhea during, or within a few hours of infusion in 45-50% of patients.³ The diarrhea from desquamation begins between 6 and 11 days after administration. When severe dehydration, renal failure, and electrolyte abnormalities occur, they may be life-threatening.

Assessment

A thorough medical history can guide appropriate evaluation. Important components of the history include:

- Establish the patient's normal bowel habit.
- Elicit a description of the stool that is different from normal, ie, consistency or frequency, urgency, fecal soiling, greasy stools that float, presence of blood, color, volume, etc.
- Duration
- Nature of onset (sudden or gradual)

- Travel history
- Risk factors for human immunodeficiency virus infection
- Weight loss
- Diarrhea with fasting or at night (suggests secretory)
- Family history of irritable bowel disease
- Systemic symptoms, eg, fever, joint pain, mouth ulcers, eye redness
- Chemotherapy and over-the-counter medications and supplements
- Dietary history, including sorbitol-containing candies, specific food associations such as dairy products

On physical examination, look for fever, signs of dehydration, ie, poor skin turgor, dry/cracking mucous membranes, orthostatic hypotension.⁴

Rule out overflow incontinence, ie, leakage of liquid stool around obstructing feces.

Management

This module focuses on symptomatic management of diarrhea. It will not detail the treatment of underlying causes, as these can be found in many textbooks and journal articles.^{5,6,7}

General approaches

- Establish normal bowel habits (there is wide variation).
- Assure adequate hydration. Oral rehydration solutions that contain sodium chloride, eg, soups, red juices with salt and sport drinks may be adequate. Subcutaneous hypodermoclysis or intravenous rehydration is sometimes needed.
- Avoid gas-forming foods, particularly lactose. Acute diarrhea is frequently associated with transient lactose intolerance.
- Increase bulk, eg, psyllium, bran, pectin.

Specific approaches

For the transient or mild diarrhea consider:

- Attapulgate, 30 ml or 2 tablets PO PRN. This forms a gel in the bowel without affecting the overall volume of diarrhea. However, for some patients, passing formed stools will help skin integrity and decrease the frequency of bowel movements.
- Bismuth subsalicylate, 30 ml or 2 tablets PO every 30 minutes PRN up to a maximum of eight doses. This has both antiinflammatory and antibacterial actions.

For persistent and bothersome diarrhea, to slow peristalsis, consider:

- Codeine, 15 – 30 mg PO q 4 h PRN
- Diphenoxylate/atropine, 5.0 mg (2 tablets) PO q 6 h. Maximum 20 mg/24h. Diphenoxylate is a central opiate. Atropine is an anticholinergic agent which dries the bowel and decreases peristalsis.
- Loperamide, 4 mg (2 tablets) initially, then 2–4 mg PO q 6 h to a maximum of 16 mg/24h. This is a peripheral acting opioid. It may be used with acute diarrhea even if there is a low grade fever, as long as there is not blood in the stool.
- Paregoric, 5 ml PO q 4 h. This camphorated tincture of opium is less concentrated than tincture of opium at 0.4 mg/ml.
- Tincture of opium, 0.7 ml PO q 4 h and titrate to effect. This is alcoholized morphine at approximately 10 mg/ml; very bitter tasting; and more potent than loperamide and diphenoxylate.

For persistent, severe secretory diarrhea provide parenteral fluid support, as needed and appropriate to treat or prevent dehydration and consider octreotide, a synthetic congener of somatostatin. Octreotide blocks secretion at the level of the epithelium of the small and large bowel as well as the secretory organs like the pancreas. For a more detailed explanation of octreotide action (see EPEC-O Module 3e: Symptoms - Bowel Obstruction).

- Octreotide, 50 µg SC q 8–12 h, then titrate up to 500 µg q 8 h SC, or higher, or 10–80 µg q 1 h by continuous SC, IV infusion.

Two long-acting preparations of octreotide are available:

- Octreotide long-acting, 20 mg IM once a month
- Lanreotide SR, 20 – 30 mg IM every 10 days

Management of chemotherapy-associated diarrhea

Assess patients treated with combination irinotecan, fluorouracil, and leucovorin weekly, at least during the first cycle. Consider abdominal cramping to be equivalent to diarrhea. Mucosal injury leads to a temporary lactase deficiency, so limit milk-containing foods.

Aggressively orally rehydrate patients with fluids that contain water, salt, and sugar such as broth/soups, red vegetable juices with added salt, or sports drinks.

- Loperamide, 4 mg PO followed by 2 mg PO q 2–4 h or after every formed stool to start. Titrate until diarrhea-free for 12 hours.

Administer intravenous or subcutaneous fluids if there is evidence of dehydration.

Octreotide can be used as a second-line therapy if the diarrhea is refractory to

loperamide.⁸ If there is severe diarrhea, nausea, vomiting, fever, sepsis, neutropenia, or bleeding, admit to hospital for close observation and management.

Management of carcinoid-associated diarrhea

Patients with carcinoid syndrome frequently develop an associated secretory diarrhea. Mild diarrhea may respond to an opiate. Cholestyramine may ameliorate the diarrhea if the patient has had a distal ileal resection to remove the primary tumor causing a bile acid diarrhea.

Octreotide, a synthetic somatostatin, is usually well tolerated. It has some adverse effects including nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption. These adverse effects usually subside after the first several weeks of therapy. Long-term octreotide therapy reduces postprandial gallbladder contractility and delays gallbladder emptying that predisposes the patient to gallstones or sludge.⁹

Pancreatic insufficiency-associated diarrhea

Patients treated with total pancreatectomy, ie, Whipple Procedure, frequently experience diarrhea due to maldigestion and steatorrhea due to exocrine pancreatic insufficiency. This is treated with a low fat diet and administration of exogenous pancreatic enzymes. Several commercial preparations are microencapsulated so that they are stomach acid-resistant to avoid enzyme inactivation. As a general rule, 30,000 IU of pancreatic lipase, swallowed during each meal, should suffice in reducing steatorrhea and preventing weight loss. Nonencapsulated formulations may be more successful in patients who are achlorhydric or who have dyssynchronous gastric emptying, eg, Billroth II anatomy, since there is no need to protect the enzymes from acid. Microencapsulation will only delay the release of the enzymes.¹⁰

Summary

After managing underlying pathophysiology, symptomatic management of diarrhea involves measures that either thickens the stool, slow peristalsis to permit more time for water absorption, or agents to decrease secretion of fluid into the gut.

Key take-home points

1. Diarrhea can be a serious symptom—even life-threatening. It is an expected adverse effect of fluorouracil and irinotecan chemotherapy. If it is managed aggressively and expectantly, outcomes are better.
2. Management of serious diarrhea begins with an opiate to slow peristalsis. Titrate to effect.

Pearls

1. Ask for specific details to ascertain the impact of the diarrhea.
2. Titrate medications to effect—don't be dissuaded by over-the-counter labels of maximum doses.

Pitfall

1. If diarrhea isn't managed, patients can die of dehydration or falls or skin breakdown associated infections.

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