EPECTM-O

Education In Palliative And End-Of-Life Care For Oncology

Self-Study Module 3i:

Diarrhea

Module 3i: Diarrhea

Abstract	3
Introduction	3
Case	4
Pathophysiology	4
Assessment	
Management	6
Summary	8
Key Take-Home Points	8
Appendix: Diarrhea Medication Table	10
References	1
Self-Assessment	1

Abstract

Many symptoms and syndromes are commonly encountered in patients with cancer. This module first presents general approaches to symptom management, followed by management of the specific symptoms and syndromes, including: anorexia/cachexia, anxiety, constipation, depression, diarrhea, fatigue, insomnia, menopausal symptoms and sexual health, mucositis, nausea and vomiting, and skin problems.

Any symptom can be debilitating and prevent the patient and family from achieving goals that are important to them. As with other aspects of medicine, tailored management is based on the underlying etiology and pathophysiology. When several symptoms occur together, they can be interrelated and management can be complex.

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. Serious cases of diarrhea, characterized by watery diarrhea, signs of hypovolemia, stools containing blood and mucus, fever, >6 unformed stools in 24 hours, severe abdominal pain, especially if the diarrhea occurs in the setting of a patient who has recently been on antibiotics or in a patient who is requiring hospitalization, are likely bacterial in origin.

Prevalence

The prevalence of chronic diarrhea in the general population in developed nations has not been well established, but seems to be around 5%. (Ref. 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 most common causes are irritable bowel syndrome, inflammatory bowel disease, and malabsorption syndromes.

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

Prognosis

Diarrhea itself has no definite prognostic implications. Sequelae from diarrhea (i.e., dehydration) can limit prognosis.

Case

Review the case below, and keep it in mind as you progress through the module. How would you approach the assessment of this patient? What interventions might be appropriate?

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 having 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 has slipped and fallen. He says he is exhausted.

Pathophysiology

The diarrhea-related pathophysiology of the gastrointestinal tract 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 are 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 subserve 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.

Approximately 2 liters per day of fluid are ingested. In addition, 5-7 liters or more of fluid are secreted into the gut lumen from the stomach, small intestine, and 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 reabsorbed 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-flurouracil 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. (Ref. 3) Diarrhea from desquamation begins between 6 and 11 days after administration. When severe dehydration, renal failure, and electrolyte abnormalities occur, they can be life-threatening.

Assessment

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

- The patient's normal bowel habits
- A description of how the stool is different from normal (i.e., consistency or frequency, urgency, fecal soiling, greasy stools that float, presence of blood, color, volume, etc.)
- The duration of symptoms
- The nature of onset of the symptoms (sudden or gradual)
- The patient's travel history
- The presence of risk factors for human immunodeficiency virus infection
- Weight loss
- Diarrhea occurring with fasting or at night (suggests secretory)
- A family history of irritable bowel disease
- Presence of systemic symptoms (e.g., fever, joint pain, mouth ulcers, eye redness)
- Chemotherapy administration and use of over-the-counter medications and supplements
- Dietary history, including sorbitol-containing candies, and specific food associations such as dairy products

On physical examination, look for fever, signs of dehydration (i.e., poor skin turgor, dry/cracking mucous membranes, orthostatic hypotension). (Ref. 4)

Rule out overflow incontinence (i.e., 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. (Ref. 5) (Ref. 6) (Ref. 7)

General approaches

- Identify the patient's normal bowel habits (there is wide variation).
- Assure adequate hydration. Oral rehydration solutions that contain sodium chloride (e.g., 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 (e.g., psyllium, bran, pectin).

Specific approaches

For transient or mild diarrhea, consider:

- Attapulgite, 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 8 doses. This has both anti-inflammatory and antibacterial action.

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 peripherally acting opioid. It may be used with acute diarrhea even if there is a low-grade fever, as long as there is no 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. Also consider administration of 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 mg SC q 8-12 h, then titrate up to 500 mg q 8 h SC, or higher, or 10-80 mg 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 rehydrate patients by the oral route with fluids that contain water, salt, and sugar (e.g., broth or 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 loose 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. (Ref. 8) If there is severe diarrhea, nausea, vomiting, fever, sepsis, neutropenia, or bleeding, admit to the 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. Patients who undergo distal ileal resection to remove a tumor may experience a bile acid diarrhea as a result of the surgery. Cholestyramine use may ameliorate this 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. (Ref. 9)

Pancreatic insufficiency-associated diarrhea

Patients treated with total pancreatectomy (i.e., the 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 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. Non-encapsulated formulations may be more successful in patients who are achlorhydric or who have dyssynchronous gastric emptying (e.g., due to Billroth II anatomy), since there is no need to protect the enzymes from acid. Microencapsulation will only delay the release of the enzymes. (Ref. 10)

Summary

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

Key Take-Home Points

- 1. Diarrhea can be a serious, even life-threatening, symptom. It is an expected adverse effect of fluorouracil and irinotecan chemotherapy. If it is managed aggressively and expectantly, the outcome for the patient is 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.
- Titrate medications to effect-don't be dissuaded by over-the-counter labels of maximum doses.
- 3. Make a partnership with your patient and the family caregiver; draw them into the interdisciplinary team and foster their active participation in the care plan.
- 4. Additional material can be found in Module 3: Patient Resources.

Pitfall

1. Failing to manage diarrhea, as patients can die from dehydration, falls, or infections associated with skin breakdown.

Appendix: Diarrhea Medication Table

Diarrhea Medication Table

Diarrhea (ant	Diarrhea (antidiarrheals)							
Generic Name	Trade Name(s)	Dosage Forms/ Time C _{max}	Elimination t _{1/2}	Route of Elimination	Adult Doses	Pediatric Doses	Adverse Effects	Common Interactions
Attapulgite Antidiarrheal	Kaopectate®: tabs: 300 mg/chewable tab 600 mg/regular strength tab 750 mg/extra strength tab suspension: 600 mg/15 ml in children's 600 mg/15 ml in regular 750 mg/15 ml in extra strength	Not absorbed	NA	NA	30 ml or 2 tabs PRN (max 6 doses = 12 tabs/24h)	suspension: 3-6 y: 7.5 ml 6-12 y: 15 ml >12 y: 30 ml	none significant	none significant
Bismuth subsalicylate Antidiarrheal	Various; Pepto- Bismol® is an example: liquid: 17.6 mg/ml tab: 262 mg	PO: (salicylate): 1.8-5 hr	Bismuth: 21-72 days Salicylic acid: 2-5 hr	Intestinal wall, extent unknown Renal excretion: Bismuth, 0.003%; Salicylate 95% Feces: Bismuth, 99%	30 ml or 2 tabs PO q ½ h PRN (max 8 doses = 240 ml or 16 tabs/24h)	<2 y: ③ 2-4 y: 5 ml PO q ½ h PRN 5-9 y: 7.5 ml or ½ tab PO q ½ h PRN 10-14 y: 15 ml or 1 tab PO q ½ h PRN	 blackens tongue & feces constipation 	direct binding or altered gastric pH may alter drug absorption; see antacids, Al or Mg hydroxide antacids

Diarrhea (anti	-							
Generic Name	Trade Name(s)	Dosage Forms/ Time C _{max}	Elimination t _{1/2}	Route of Elimination	Adult Doses	Pediatric Doses	Adverse Effects	Common Interactions
Diphenoxylate Synthetic opioid, related to meperidine Inhibits excessive gastric motility	Various in combination with atropine; Lomotil® is an example: tabs: 2.5 mg with atropine 0.025 mg liquid: 2.5 mg/5 ml	PO: 2 hr	2.5 hr	Liver metabolism: extensive Renal excretion: 14% Feces: 49%	2.5-5 mg PO daily, qid (max 20 mg/24h) (avoid in hepatic failure)	0.3-0.4 mg/kg/24h PO ÷ bid-qid	• uncommon	may potentiate the effect of phenothiazines, barbiturates, TCAs
Loperamide Synthetic opioid, related to meperidine	Various; Imodium® is an example: caplets: 2 mg caps: 2 mg liquid: 1 mg/5 ml	PO cap: 5 hr PO liquid: 2.5 hr	7-15 hr	Liver metabolism: significant first pass Renal excretion: 1% Feces: 25%-40%	4 mg PO first dose, then 2-4 mg after each unformed stool (max daily dose 16 mg/24h)	2 y or older: ≈ 0.2 mg/kg/24h PO ÷ bid-tid	 abdominal pain constipation dizziness dry mouth nausea/vomiting hypersensitivity 	cholestyramine
Octreotide Synthetic octapeptide analogue of somatostatin. Inhibits secretion of gastroenteropan -creatic endocrine system, reducing volume of intestinal secretions	Sandostatin®: inj: 50, 100, 200, 500, 1000 µg LAR: 10, 20, 30 mg	SC: 15-30 minutes	1.5 hr	Liver metabolism: extensive Renal excretion: 32%	100 μg SC q 8 h for 48 h or 10 μg/h continuous SC, IV infusion and titrate	1-10 mcg/kg bid- tid	generally well tolerated	cimetidine cyclosporine

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Module 3i: Diarrhea

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Self-Assessment

Module 3i: Diarrhea

	7.	Which of the following	g antidiarrhea	l agents acts	through opioid	I receptors?
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a). diphenoxylate

b). atropine

c). bismuth

d). octreotide

Self-Assessment Answers

Question 7. The correct answer is: a)

This question is aimed at understanding how to symptomatically treat diarrhea, especially treatment-related diarrhea. Diphenoxylate is a synthetic opiate commonly available in combination with atropine, an anticholinergic. Octreotide is a synthetic analog of somatostatin.