EPEC-O

Education in **P**alliative and **E**nd-of-life **C**are - **O**ncology

Participant's Handbook

Module 3f:

Symptoms – Constipation

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Case*

M.R. is 28-year-old woman with pseudomyxoma peritonei developed subacute onset of increased abdominal pain described as difficult to localize, sharp, 10/10 with intermittent nausea. She had been on long-acting morphine 60 mg PO q 12 h and ondansetron 4 mg PO q 8 h PRN nausea. She had been eating, had flatus, and had been having a daily soft bowel movement. She denied fevers or chills. There was no other significant past medical history and review of systems was otherwise negative. On exam, bowel sounds were present but diminished. There was gross abdominal distention that is dull to percussion. There was no shifting dullness. There is diffuse abdominal tenderness to palpation without rebound. Rectal exam revealed normal sphincter tone and soft, claylike stool in the vault. To symptomatically treat her pain, morphine was given parenterally and incrementally titrated to 18 mg/hour (equivalent to approximately morphine 1,300 mg PO per day) with only moderate control of her pain. A radiograph of the abdomen showed stool throughout her colon. After aggressive bisacodyl suppositories, sodium phosphate enemas, and oral polyethylene glycol, the patient had multiple bowel movements and her pain became controlled on her previous baseline oral opioid regimen.

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

Introduction

Constipation refers to *stools that are decreased in frequency and may be difficult to evacuate.*

There are a number of possible causes of constipation: congenital, myopathic, mechanical, endocrine, metabolic, neurological, psychological, and medication related. There are rare causes such as congenital aganglionosis, myopathy, or anal dyssynergia where pelvic floor muscles contract rather than relax with defecation. However, acquired causes of constipation are much more common. Endocrine/metabolic causes include diabetes, hypothyroidism, and hypercalcemia. As psychologic conditions such as depression have been linked to an increased incidence of constipation, a comprehensive assessment is required.[1] Nerve function can be perturbed by diseases such as Parkinson's, direct invasion by tumor, or from paraneoplastic syndromes. Intrinsic or extrinsic luminal compression from masses can mechanically lead to constipation. Finally, medications such as calcium channel blockers, anticholinergic agents, antiserotonergic agents, and opioids are prime mediators of constipation.

At its least, constipation is uncomfortable and detracts from quality of life. At its worst, it can be a primary source of considerable suffering. It can cause nausea, emesis, abdominal pain, delirium, and urinary retention. The volume of gas and stool may synergize with other space occupying processes such as ascites or tumor to worsen pain. In fact, the pain of luminal distention can be one of the worst pains people experience and is highly opioid resistant. Constipation's synergism with other abdominal processes can limit

diaphragmatic excursion worsening dyspnea. Furthermore, constipation can evolve into impaction. At its worst, it can lead to bowel obstruction.

Prevalence

In the general population, the baseline prevalence of constipation is high and increases with age. In advanced medical illness, such as cancer, the combination of underlying disease and medication often lead to a dramatic increase in occurrence. For example, when opioids are used for pain and/or dyspnea, prevalence of constipation approaches 90%.[2]

Prognosis

Constipation itself has no definite prognostic implications. Sequelae from constipation, ie, aspiration pneumonia from emesis or impaction, can limit prognosis. Management is virtually always possible.

Pathophysiology

The pathophysiology of the gastrointestinal tract leading to constipation is complex and is still being elucidated. 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 gastrointestinal tract and over 21 serotonin receptor subtypes subserve its function. The 5-HT_4 receptor subtype is known to play a key role in intestinal motility. Finally, acetylcholine is the neurotransmitter ultimately responsible for smooth muscle cell contraction.

The gastrocolic reflex is an example of the integration of this complex communication. Food contents trigger the release of transmitters such as cholecystokinin that result in a wave of communication inducing forward colonic peristalsis. Local stimulation of the colon can trigger peristalsis as well. Luminal distention causes enterochromaffin cells lining the gastrointestinal tract to release serotonin that in turn leads to a cascade of messengers ending in forward peristalsis. In most patients this predictably occurs one to two hours after they wake and eat breakfast.

Opioids interact with the gastrointestinal tract via receptors (mu and kappa subtypes) that are located throughout its length.[3] Immunohistochemical studies in animals identify their location on enteric nerves and interstitial pacemaker cells. Clinically used opioids are predominantly mu agonists and contribute to constipation in two ways: 1) gastrointestinal secretions are diminished, and 2) productive forward peristalsis is reduced.[4]

Disruption of this complex orchestration of communication at the level of pacemaker cells, nerves, muscle, or transmitters can lead to constipation.

Assessment

Most importantly, ask about bowel function. Patients may not initiate discussion on this topic. Establish what is normal for the patient; there is a range. Then put current function in context of what is normal for the patient.

The Rome II criteria represent a definition of constipation originally derived for research purposes. They are:

- Straining with defecation

- Hard stool

- A sensation of incomplete evacuation

- A sensation of anorectal obstruction

- Fewer than 3 bowel movements/week

A diagnosis of constipation is made when there are ≥ 2 of the above symptoms for 12 weeks (may be noncontiguous, but in one year). These criteria highlight physical characteristics of stool, frequency of bowel movements, and subjective perceptions of distress as important to the definition, as well as a component of chronicity.

Patients with advanced medical illness may define themselves as being constipated without formally meeting this definition, especially the chronicity component. A patient may feel constipated even after having a bowel movement because of the burden of stool remaining in the gastrointestinal tract. Therefore, in advanced medical illness, the definition needs to be individualized.

A presentation of diarrhea may lead to a diagnosis of fecal impaction. Liquid stool from the right colon or stool that has been reliquified by bacterial action may leak around the hard stool of fecal impaction and mimic the presentation of diarrhea (particularly if bowel tone is decreased secondary to over-distention with hard stool). A careful history may reveal that such a patient had been experiencing constipation before the onset of loose stools.

After a careful history, perform a physical exam. Assess for stigmata of hypothyroidism. During the abdominal exam assess for bowel sounds, tympanitic distention, ascites, and masses that could be tumors or stool. A rectal exam will provide neurologic information

by assessing sphincter tone. Moreover, if stool is present, information about consistency can be gleaned and a low impaction that requires manual disimpaction can be detected.

Laboratory assessment may be useful to look for hypothyroidism, diabetes, dehydration, hypercalcemia, or other electrolyte abnormalities. A flat plate of the abdomen may help to assess for obstruction or colonic stool load. Be sure to specifically query the radiologist for an estimation of stool content and look at the films yourself.

Management

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

Toileting strategies

It is useful to synergize pharmacologic interventions with normal physiologic processes. To improve outcomes, time interventions with a patient's normal toileting schedule and take advantage of the gastrocolic reflex after meals (usually 8-9 AM).

Fiber/fluids

In general, a greater volume of stool in the lumen stretches the colon and luminal stretch triggers peristalsis. Hydration and high dietary fiber content are usually advantageous. Consider a dosing regimen of:

- Psyllium, 15 ml daily, mix with at least 240 ml of water

In patients with advanced medical illness, when hydration is often suboptimal, avoid added dietary fiber as it may actually worsen constipation.

Activity

Activity has been shown to correlate with an improvement in constipation.[8]

Stool softeners

Stool softeners, eg, docusate sodium, are detergents that break up the fat content of stool, allowing water to penetrate more effectively. As a result, stool stays moister and softer. Stool softeners may also increase luminal fluid secretion.[9] They do not affect peristalsis. A standard dosing regimen is:

- Sodium or calcium docusate 100-200 mg PO daily to tid

Stimulant laxatives

Stimulant laxatives such as prune juice, senna, and bisacodyl predominantly increase intestinal propulsive activity through unknown mechanisms. Senna is a prodrug and

becomes active only upon reaching the colon where bacteria metabolize it. Bisacodyl is activated in the small intestine and may cause more cramping. Dosing options include:

- Prune juice 120-240 ml PO daily to bid. To reduce the sweetness, mix with a little lemon juice.

- Senna 1-3 tablets PO daily to tid. Also available as a tea.

- Bisacodyl, 5-10 mg PO, PR daily to tid

Osmotic agents

Osmotic agents, eg, magnesium salts, lactulose, sorbitol, and polyethylene glycol, pull water into the bowel lumen along with other luminal contents. This helps keep the stool softer and more voluminous. Extensive use of magnesium containing osmotics can lead to magnesium toxicity. Some patients find the disaccharide osmotics such as lactulose and sorbitol to be unpalatable. Moreover, when they reach the colon, bacteria can metabolize them leading to gas production and bloating. Studies have shown lactulose and sorbitol to be equally efficacious; however, sorbitol is cheaper.[10]

Polyethylene glycol exists both as an oral liquid and a tasteless, odorless powder. The powder can be mixed with foods or liquids increasing palatability. It is not metabolized by colonic flora and therefore there may be less gas bloating. Compared to lactulose, studies have shown polyethylene glycol to be more effective and better tolerated.[11,12] However, it is more expensive. Dosing options include:

- Magnesium hydroxide, 15-30 ml PO daily to qid routinely or PRN

- Polyethylene glycol, 15-30 ml PO daily to bid routinely or PRN

- Lactulose, 15-60 ml PO daily to tid routinely or PRN

- Sorbitol, 15-60 ml PO daily to tid routinely or PRN

- Magnesium citrate, 50-150 ml PO daily to tid PRN

Lubricants

Lubricating suppositories and enemas work mechanically to soften the leading edge of hard, dry stool. Examples include glycerin suppositories, oil enemas, and sodium phosphate small volume enemas. Large volume enemas, in addition to lubricating and softening the distal leading edge, can cause luminal distention and trigger peristalsis and defecation. Dosing options include:

- Glycerin suppository, 1 PR daily to bid PRN

- Phosphate enema, 1 PR daily to bid PRN

- Oil enema, mineral oil 15-30 ml PR, retain for as long as possible; followed by 500-1,000 ml tap water as tolerated daily to bid PRN

- Tap water enema, 500-1,000 ml tap water as tolerated daily to bid PRN

Anal topical anesthetics

Patients experiencing significant anal/rectal pain from hemorrhoids, muscle spasm, fissures or impaction may benefit from a topical antiinflammatory and/or anesthetic applied to the involved areas routinely or before each bowel movement to reduce inflammation, pain and pruritus. A standard dosing regimen is:

- Lidocaine, 2-5% spray or jelly PRN. Maximum 200 mg/24 hour

Miscellaneous agents

Given acetylcholine's key role in smooth muscle contraction, neostigmine, an acetylcholinesterase inhibitor, has been used in acute colonic pseudo-obstruction, ie, Ogilvie's syndrome.[13] Results were impressive but systemic adverse effects of bradycardia and increased respiratory secretions are a concern. Given serotonin's role in gastrointestinal tract modulation and our increasing understanding of the multiple subtypes of serotonin receptors, several serotonergic agents are being studied. The 5-HT4 agonist tegaserod has been approved by the Federal Drug Administration for constipation-predominant irritable bowel syndrome.[14] Another 5-HT4 agonist, prucalopride, has been studied in Europe and found to be effective for constipation.[15] The role these agents may play in a population with advanced medical illness remains to be seen.

Constipation from opioids

All opioids cause constipation as discussed above. Whereas pharmacological tolerance develops to many of opioids' adverse effects, it never seems to develop to the constipating effects. Dietary interventions alone, eg, fiber and fluids, are usually not sufficient. Bulk-forming agents, eg, psyllium, may cause worsened constipation in a patient who cannot drink sufficient fluid. Most experts recommend a combination of a stimulant laxative, eg, senna, and a softener, eg, docusate, to manage the condition. Prokinetic medications, such as metoclopramide, have been advocated for refractory cases. A standard dosing option is:

- Metoclopramide, 5-20 mg PO, SC, IV q 6 h

Systemically active opioid antagonists such as naltrexone and naloxone have been shown to be useful but they reverse opioids' analgesic effects as well. Therefore, peripherally acting opioid antagonists that do not cross the blood-brain barrier would be ideal. Two such agents, alvimopan and methylnaltrexone, are undergoing clinical trials with encouraging preliminary results.[16,17,18] Both are predominantly mu-receptor antagonists.

In lieu of the availability of these agents, prevention and early detection is much easier than management of opioid-induced constipation. When an opioid is initially prescribed,

start every patient on a combination of a stool softener and stimulant laxative at the same time. Titrate doses to effect. Add osmotic laxatives, and use enemas as needed.

Summary

Constipation is a common condition that causes significant morbidity. Reversible causes can be removed if identified. The complex control of laxation is being elucidated and new agents are being developed based on this knowledge. Currently, there are multiple categories of pharmacologic agents that work in different ways that can be successfully synergized to control constipation. Using these agents in concert with physiological processes such as the gastrocolic reflex and daily patterns of bowel movement can further enhance success. It remains true that the easiest and the best treatment for constipation is prevention in the first place.

Key take-home points

1. Assess what is normal for the patient before deciding on a treatment plan.

2. Titrate agents to effect before adding other agents.

3. Combine agents with different mechanisms of action.

Pearls

1. Titrate senna to effect – do not be limited by over-the-counter label warnings on maximum dose.

2. Don't wait for the patient to bring up the symptom – ask about it.

Pitfall

1. Forgetting proactive management of constipation for patients on opioids will be disastrous.

References

[1] Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. *Palliat Med.* 1998;12(5):375-382. Full Text

A prospective study of 498 hospice inpatients with advanced cancer showed that laxatives were required by 87% of patients taking oral strong opioids, 74% of those on weak opioids and 64% of those not receiving opioid analgesia. Opioids account for about a quarter of the constipation found in terminally ill cancer patients in a hospice.

[2] Derby S, Portenoy RK. Assessment and management of opioid-induced constipation. In: Portenoy RK, Bruera E, ed. *Topics in Palliative Care*. New York, NY: Oxford University Press; 1997:95-112.

[3] Portenoy RK. Constipation in the cancer patient: causes and management. *Med Clin North Am.* 1987;71:303-311. PMID: 3029525.

Therapy of constipation is based on identification and management of underlying causes combined with symptomatic treatment. A working knowledge of bowel physiology and laxative pharmacology forms the foundation for this approach.

4   Mercadante S. Diarrhea, malabsorption, and constipation. In: Berger A, Portenoy RK, Weissman DE, eds. *Principles and Practice of Supportive Oncology*. Philadelphia, PA:Lippincott–Raven, 1998:203-2004. ISBN: 0397515596.

5   Levy MH, Catalano RB. Control of common physical symptoms other than pain in patients with terminal disease. *Semin Oncol*. 1985;12(4):411-430. PMID: 3909412.

6   Fallon M, O'Neill B. ABC of palliative care. Constipation and diarrhoea. *BMJ*. 1997;315(7118):1293-1296. PMID: 9390060. Full Text

A review of the assessment and management of constipation and diarrhea.

7   Sykes N. Palliation of abdominal symptoms. In: von Gunten CF, ed. *Palliative Care and Rehabilitation of Cancer Patients*. Norwell, MA:Kluwer Academic Press,1999:43-57. ISBN: 079238525X.

8   Bagnol D, Mansour A, Akil H, Watson SJ. Cellular localization and distribution of the cloned mu and kappa opioid receptors in rat gastrointestinal tract. *Neuroscience.* 1997;81(2):579-591. PMID: 9300443. Full Text

Numerous neurons expressing mu receptor-like proteins were found in the submucosal plexus with comparatively few in the myenteric plexus. In contrast, a higher number of neurons expressing kappa receptor-like immunoreactivity were visualized in the myenteric plexus with a small number in the submucosal plexus.

9   De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. Pharmacol Ther. 1996;69(2):103-115. PMID: 8984506. Full Text

In recent years, opioid mechanism and sites of action in exerting their antidiarrheal effect have been studied intensely. Attempts have been made to propose their general mode of action. Whilst there are numerous similarities in their general effects on motility, fluid secretion, and neuroeffector transmission, the differences between species, in some cases, can be remarkable.

10 Garvey M, Noyes R, Jr., Yates W. Frequency of constipation in major depression: relationship to other clinical variables. *Psychosomatics.* 1990;31(2):204-206. PMID: 2330403.

A semistructured interview that evaluates 70 clinical variables, including constipation, was administered to 170 patients with major depression. Twenty-seven percent of the patients had depression-associated constipation. Constipation was not associated with any other clinical variable.

11 Holdstock DJ, Misiewicz JJ, Smith T, Rowlands EN. Propulsion (mass movements) in the human colon and its relationship to meals and somatic activity. *Gut.* 1970;11(2):91-99. PMID: 5441889.

12 Moriarty KJ, Kelly MJ, Beetham R, Clark ML. Studies on the mechanism of action of dioctyl sodium sulphosuccinate in the human jejunum. *Gut.* 1985;26(10):1008-1013. PMID: 2414161.

An intestinal perfusion technique has been used to investigate the mechanism of action of the laxative, dioctyl sodium sulphosuccinate, in the human jejunum. Dioctyl sodium sulphosuccinate stimulated net secretion of water, sodium, chloride and potassium and inhibited net absorption of glucose and bicarbonate.

13 Lederle FA, Busch DL, Mattox KM, West MJ, Aske DM. Cost-effective treatment of constipation in the elderly: a randomized double-blind comparison of sorbitol and lactulose. *Am J Med.* 1990;89(5):597-601. PMID: 2122724.

Thirty men aged 65 to 86 with chronic constipation were studied in a randomized, double-blind, cross-over trial The average number of bowel movements per week was 6.71 with sorbitol and 7.02 with lactulose. There were no significant differences between sorbitol and lactulose in any outcome measured except nausea, which was increased with lactulose (p less than 0.05).

[14] Attar A, Lemann M, Ferguson A, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut.* 1999;44(2):226-230. PMID: 9895382. Full Text

A total of 115 patients with chronic constipation entered a multicentre, randomised, comparative trial. Low dose polyethylene glycol was more effective than lactulose and better tolerated.

[15] Freedman MD, Schwartz HJ, Roby R, Fleisher S. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: a double-blinded placebo-controlled trial. *J Clin Pharmacol.* 1997;37(10):904-907. PMID: 9505981. Full Text.

57 patients with opioid-induced constipation participated in a randomized, triple cross-over after control run-in (no treatment) study conducted at a methadone maintenance program. Polyethylene glycol produced the loosest stool ($P < 0.0001$) compared with the control, whereas lactulose had the most adverse effects.

[16] Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med.* 1999;341(3):137-141. PMID: 10403850. Full Text

21 patients with acute colonic pseudo-obstruction had abdominal distention and radiographic evidence of colonic dilation, with a cecal diameter of at least 10 cm, and had had no response to at least 24 hours of conservative treatment. Ten of the 11 patients who received neostigmine had prompt colonic decompression, as compared with none of the 10 patients who received placebo ($P<0.001$). The median time to response was 4 minutes (range, 3 to 30). Adverse effects of neostigmine included abdominal pain, excess salivation, and vomiting. Symptomatic bradycardia developed in two patients and was treated with atropine.

[17] Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther.* 2002;16(11):1877-1888. PMID: 12390096. Full Text

In a randomized, double-blind, multicentre study, 1519 women received either tegaserod, 6 mg bid (n = 767), or placebo (n = 752) for 12 weeks. Tegaserod produced significant ($P < 0.05$) improvements in the Subject's Global Assessment of Relief and other efficacy variables. Diarrhea was the most frequent adverse event.

[18] Schmidt WK. Alvimopan* (ADL 8-2698) is a novel peripheral opioid antagonist. Am J Surg. 2001;182(5A Suppl):27S-38S. PMID: 11755894. Full Text

In the treatment of opioid naive patients who underwent surgery and received opioids for acute pain, oral alvimopan (6.0 mg) improved the management of postoperative ileus (POI) by shortening the time to achieve normal bowel function and, ultimately, hospital stay, without compromising opioid analgesia or inducing central nervous system symptoms of withdrawal.