Emergent Management of Constipation in Cancer Patients

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Constipation is a common disorder and a frequent cause of ED visits in cancer patients. As illustrated by the case described below, substantial morbidity can result from constipation. If left untreated, the condition can be fatal. Causes, evaluation, and pharmacologic treatment are discussed herein, and an algorithm for treatment is provided.

Constipation affects more than 50% of cancer patients in palliative care and is a common and distressing symptom[1] and a major cause of ED visits for cancer patients.[2] In academic year 2010, there were 20,538 visits to the Emergency Center at MD Anderson Cancer Center in Houston, Texas, and 3.3% of visits were related to constipation (unpublished data). Constipation can lead to complications such as nausea, emesis, urinary retention, abdominal pain, delirium, hemorrhoids, anal fissures, spurious diarrhea, fecal impaction, bowel obstruction, and perforation.[3] Constipation can also reduce diaphragmatic excursion and trigger dyspnea.[4] The following case illustrates some of these features.

CASE

A 43-year-old white man with recently diagnosed metastatic sigmoid carcinoma and diffuse bilobar liver metastases who is undergoing FOLFOX systemic therapy (folinic acid, 5-fluorouracil, oxaliplatin) has chronic pain, for which he has been taking high-dose narcotics. He has developed significant constipation and presents to the emergency center with nausea, progressive abdominal distention, worsening colicky abdominal pain, and dyspnea secondary to abdominal distention. An abdominal plain film shows a large amount of stool (Figure 1). The patient is given magnesium citrate and a milk molasses enema. The follow-up abdominal radiographs (Figure 2) show findings consistent with impending colon perforation secondary to a large bowel obstruction with minimal small bowel dilatation and a significant amount of stool within markedly dilated colon. He is taken to the operating room immediately for diverting colostomy.

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CAUSES OF CONSTIPATION

Many neurotransmitters and modulators, such as vasoactive intestinal peptide, nitric oxide, serotonin, and acetylcholine, are involved in regulating bowel movement. Any disruption in neurotransmission or mechanical movement in this process can lead to constipation. Opioids disrupt intestinal function by reducing motility, reducing the amount of secretions, and increasing fluid absorption.[4] Indeed, constipation is especially common in cancer patients taking opioids, for whom the prevalence can be as high as 90%.[2] Common causes of constipation in cancer patients are listed in the Table.[4,5]

DIAGNOSIS OF CONSTIPATION

History and Evaluation

The normal frequency of bowel movements is highly

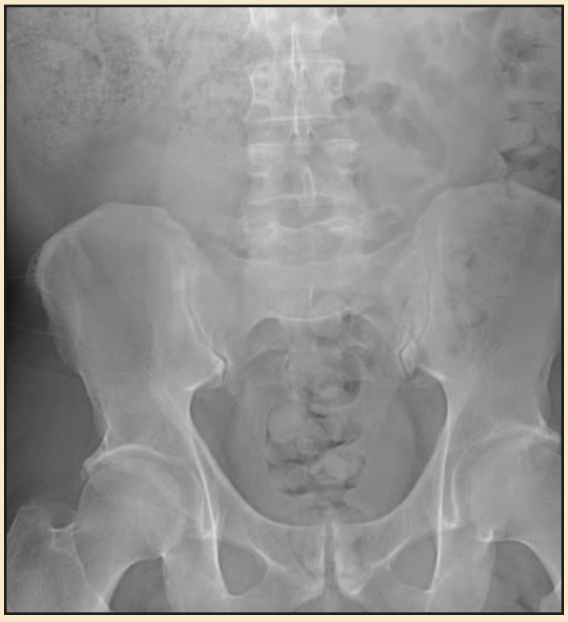
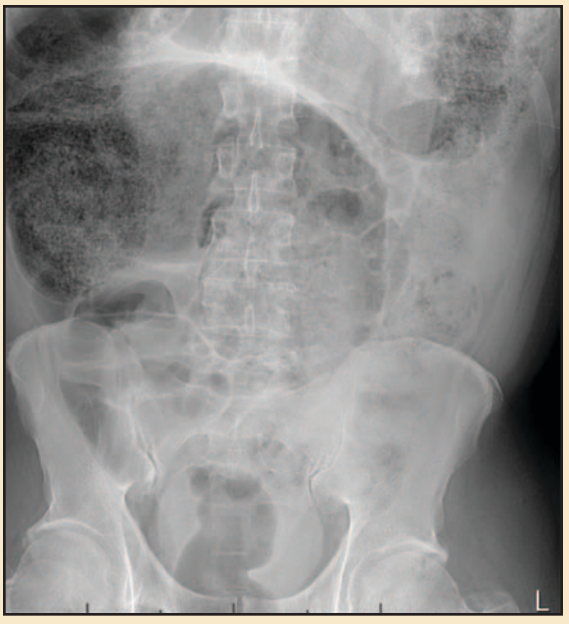


FIGURE 1. Abdominal plain film in a patient receiving systemic therapy for metastatic sigmoid carcinoma. A large amount of stool is evident.



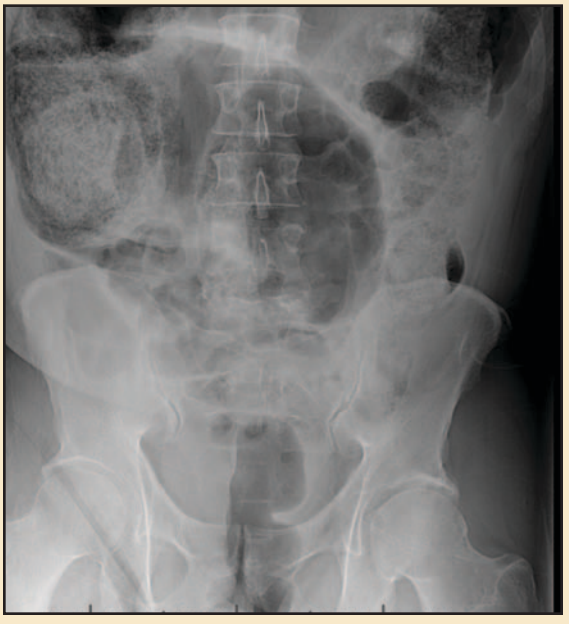


FIGURE 2. Abdominal plain films obtained 6 hours after administration of enema and laxative demonstrate that the amount of stool projecting in the colon has increased from the prior examination (Figure 1). Transverse measurement of the area of the cecum has reached at least 14 cm, increasing colonic distention and creating increased risk of rupture.

individualized, but as a general principle, if a patient defecates fewer than three times per week, constipation may be a problem and the patient should be assessed for it.[2] The Rome III criteria,[2] which are commonly used in constipation research, require two or more of the following signs and symptoms for a positive diagnosis: straining, lumpy or hard stools, feeling of incomplete evacuation, feeling of obstruction or blockage, manual facilitation required during at least one-fourth of defecations, and fewer than three bowel movements per week. A patient may have associated symptoms such as the inability to defecate at will, discomfort when defecating, unproductive urges (tenesmus), flatulence, bloating, nausea, vomiting, abdominal pain, loss of appetite, headache, and distention. Cancer can cause constipation with unusual presentations, such as spurious diarrhea. Liquid stool may leak around the hard stool of fecal impaction and appear as diarrhea. A careful history may reveal that constipation immediately preceded the onset of loose stools.[4,6]

A focused constipation history should note the onset of change and both baseline and current bowel patterns—including duration, frequency, aggravating and alleviating factors, stool volume, and stool appearance (consistency, color, odor, blood, and mucus). After a careful history is taken, the patient should be physically examined for signs of hypothyroidism, hypercalcemia, and neurologic impairment. Abdominal examination should include assessment of bowel sounds and evaluation for the presence of distention, ascites,

Table. Common Causes of Constipation in Cancer Patients

Endocrine or metabolic disorders	Diabetes, hyperthyroidism, dehydration, hypercalcemia, uremia, hypokalemia
Psychological disorders	Depression
Neurologic dysfunction	Parkinson disease, spinal cord compression, sacral nerve infiltration, paraneoplastic syndromes, stroke, multiple sclerosis
Mechanical obstruction or compression	From tumor masses, adhesions, radiation fibrosis
Medications or supplements	CCBs, anticholinergics (antispasmodics, TCAs, phenothiazines, antihistamines), antiserotonergics, opioids, cytotoxic agents (eg, vincristine, oxaliplatin), thalidomide,[5] anticonvulsants, calcium- or aluminum-containing antacids, iron, NSAIDs[4]
Pelvic muscle impairment	Due to cancer invasion, hysterectomy or other procedure

CCB = calcium channel blocker; TCA = tricyclic antidepressant; NSAID = nonsteroidal anti-inflammatory drug.
Data from Thomas and von Gunten[4]; Gay and Palumbo.[5]

and masses. A rectal examination is useful in assessing sphincter tone, strictures, masses, and pelvic floor motion when the patient bears down. If stool is present, its consistency should be assessed. If a low impaction is detected, it should be disimpacted manually. A rectal exam should be avoided in immunocompromised (eg, neutropenic) patients due to their higher risk of complications.[2] Hypothyroidism, diabetes, dehydration, hypercalcemia, and other electrolyte abnormalities can be assessed with laboratory tests. Levels of electrolytes (eg, magnesium, phosphate, and sodium) and renal function should be checked to determine whether a patient can tolerate salt laxatives. A CT image or, as demonstrated in the case patient, a flat plate radiograph of the abdomen and pelvis, may be useful in assessing obstruction or colonic stool load.[3]

MANAGEMENT OF CONSTIPATION

Pharmacologic Agents

When constipation is confirmed in a cancer patient, the appropriate intervention depends on the patient's status, prognosis, and preference. Despite the paucity of clinical trials on the treatment of constipation in cancer patients, especially in the ED setting, there are several treatment options. These include laxatives, colchicine, misoprostol, amidotrizoate, methylnaltrexone, and alvimopan.

Laxatives—There are four common laxative options: surfactant, osmotic, salt, and stimulant.

Surfactant laxatives (ie, stool softeners), such as docusate sodium, increase the water content of stools by breaking down stool fat and allowing water to enter. They may also increase luminal fluid secretion to further increase stool water content. Surfactant laxatives have few side effects but appear to be less efficacious than other types of laxatives. For example, docusate was shown to be inferior to psyllium, an osmotic laxative, in the treatment of constipation in a head-to-head trial.[7] A recent systematic review of randomized controlled trials suggested that docusate calcium is more efficacious than docusate sodium.[8]

Osmotic laxatives, such as lactulose, sorbitol, and polyethylene glycol (PEG), pull water into the colon through osmotic pressure, thus softening stools. Both lactulose and sorbitol can cause gas production and bloating, and while they appear equally efficacious, sorbitol is less expensive.[4] PEG is not metabolized by colonic flora and therefore may result in less gas bloating. In a Cochrane review of 10 randomized controlled trials conducted between 1997 and 2007, PEG was determined to be more effective and better tolerated than lactulose.[9]

Salt laxatives, such as magnesium salts, increase intestinal motility and tend to cause urgent liquid stools, making them less convenient for outpatient use but valuable in the ED. A large volume of magnesium citrate in particular has a faster onset of action than other oral laxatives do. Phosphate laxatives are commonly used as an enema in the ED. Extensive use of magnesium-containing osmotic agents can lead to magnesium toxicity, especially among patients with renal insufficiency. Renal function and serum levels of

magnesium and phosphate should be monitored when salt laxatives are being used.

Stimulant laxatives, such as senna and bisacodyl, work by increasing intestinal propulsive activity and are effective and well tolerated.[10,11] These laxatives are prodrugs that are activated by intestinal bacteria. Bisacodyl is metabolized in the small intestine, while senna is activated in the colon.[4] Bisacodyl may cause more cramping, due to its earlier activation in the gut. It may also be given per rectum in suppository form.[4]

Concurrent treatment with more than one type of laxative may be beneficial. For example, in a recent randomized controlled trial, when the surfactant laxative docusate was combined with a stimulant laxative (ie, senna), it appeared to be quite efficacious, with a number needed to treat of less than 3.[12] The combination of a stimulant laxative and a surfactant laxative[12] or a bulking agent has demonstrated efficacy; for example, senna combined with a bulking agent is far more efficacious than lactulose alone.[13]

Additional Options—Randomized controlled trials have shown that *colchicine*[14,15] and *misoprostol*[8,16] can be effective oral treatments for constipation. However, colchicine also has antimitotic effects,[17] which may interfere with or augment the cancer treatment.

A hyperosmolar water-soluble contrast medium, *amidotrizoate* is an anionic, bitter-flavored mixture of sodium diatrizoate, meglumine diatrizoate, and the wetting agent polysorbate 80. In a randomized controlled trial, oral amidotrizoate was found to be an easy and inexpensive means for inducing a bowel movement in about 45% of patients with advanced cancer who suffered from severe constipation despite laxative treatment, with limited and acceptable adverse effects.[18]

The peripheral μ-opioid receptor antagonist *methylnaltrexone* has been approved by the FDA to treat opioid-induced constipation if laxative therapy has failed in patients with advanced illness who are receiving palliative care. The usual schedule is one dose every other day as needed, but no more than one dose in a 24-hour period. Given subcutaneously as a breakthrough medication, methylnaltrexone can reverse opioid-induced constipation by enhancing laxation within 4 hours in about half of patients.[19,20] Due to the risk of intestinal perforation, this drug should be avoided in patients with potential mechanical obstruction.[11,21]

Methylnaltrexone has shown promise not only in reducing opioid-induced constipation in humans but also in reducing tumor growth and metastasis in mice. Human lung cancer cells are reported to show a fivefold to tenfold increase in μ-opioid receptor (MOR) expression.[22] In mouse experiments, Lewis lung carcinoma (LLC) cells with silenced MOR expression reduced lung metastasis by 65%. In MOR-knockout mice that had been injected with LLC cells, significant tumors failed to develop, whereas such tumors did develop after injection of these cells into wild-type mice.[22] Methylnaltrexone decreased primary LLC tumor growth as well as lung metastasis in mice.[22]

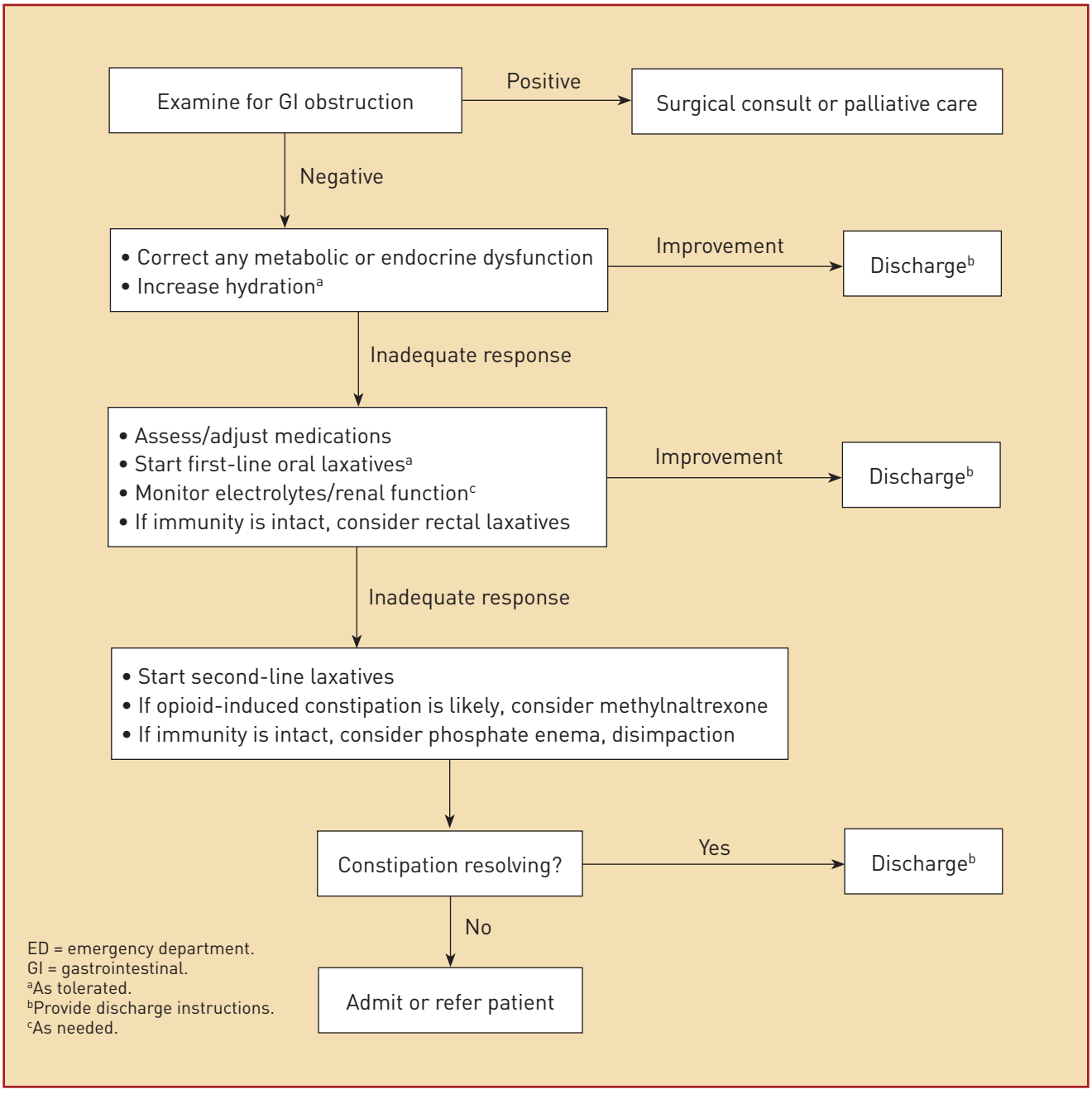
Alvimopan, which is administered orally, is another peripherally acting μ-opioid receptor antagonist. It does not cross the blood-brain barrier and does not reverse analgesia or cause withdrawal symptoms. Although alvimopan is not approved for the treatment of opioid-induced constipation, there is evidence to support its use. In a 3-week study, 168 patients with opioid-induced bowel dysfunction were assigned to receive alvimopan at dosages of 0.5 or 1 mg daily or placebo. Alvimopan increased the proportion of subjects having bowel movements within 8 hours in a dose-dependent fashion, was well tolerated, and did not compromise analgesia.[23] In a second study that included 522 subjects with opioid-induced bowel dysfunction, 0.5 mg of alvimopan administered twice daily was superior to placebo in increasing the number of spontaneous bowel movements, with sustained treatment effects during a 6-week period. The side-effect profile for this dosing regimen was similar to that of placebo.[24]

Lubiprostone is an oral agent derived from prostaglandin E_1. It is a bicyclic fatty acid used to treat chronic constipation and irritable bowel syndrome. It activates CIC-2 chloride channels on the apical aspect of epithelial cells in the gastrointestinal system. The activated epithelial cells produce a secretion of chloride-rich fluid, which softens stool, increases bowel motility, and promotes bowel movements.[25,26]

Approach to Treatment

On the basis of results from recent randomized controlled trials, systematic reviews, guidelines, and con-

FIGURE 3. Algorithm for Treating Constipation in Cancer Patients in the ED



sensus in related fields, the following steps of constipation management may be considered for cancer patients in the ED setting (Figure 3):

First, patients with signs of obstruction should be referred for surgical consultation or for palliative care. If signs of obstruction are not present, metabolic or endocrine dysfunctions should be corrected and hydration should be increased as tolerated.

If the patient's constipation persists, the medication list should be systematically assessed for a potential causal agent of constipation, such as morphine, and adjustments should be made to reduce recurrence.[27] In a randomized crossover trial of transdermal fentanyl and sustained-release oral morphine for the treatment of chronic noncancer pain in 212 patients, significantly more patients experienced constipation with

morphine than with fentanyl (48% vs 29%).[28] Adjuvant analgesic treatment can also reduce the need for opioids. A randomized controlled trial showed that 2.5 to 7.5 mg of olanzapine daily for patients with uncontrolled cancer pain reduced opioid requirements.[29] Switching and rotating opioids may also reduce the constipation associated with opioids,[30] although this approach would require additional follow-up after the ED visit and communication with the outpatient providers.

While the patient's medications are being adjusted, first-line laxative treatment can be initiated. Because of the different latencies of the various laxatives,[2] the combination of an oral magnesium salt (eg, magnesium citrate, provided that the patient's magnesium level and renal function are in a safe range), a stimulant (eg, senna), or a rectal laxative (eg, glycerin or bisacodyl suppositories) can lead to quick relief of constipation. Oral PEG, which is the most effective osmotic laxative available, has a much longer latency but can be combined with one of the aforementioned, faster-acting laxatives to achieve more immediate results. Use of rectal laxatives should be avoided in immunocompromised (eg, neutropenic) patients.

If outpatient laxative use fails and opioid-induced constipation is likely, second-line treatment with methylnaltrexone should be considered.[31] The recommended dose is 8 mg SC every other day for patients weighing 38 to 62 kg or 12 mg SC every other day for patients weighing 62 to 114 kg; for patients whose weight is not within these ranges, the dose is 0.15 mg/kg SC every other day.[32] Due to the risk of renal complications, phosphate enema should be considered as a second-line laxative. Lubiprostone,[13,20] amidotrizoate,[18] colchicine, and misoprostol can also be used. If impaction is present, manual rectal excavation will likely be needed. An enema (eg, phosphate enema) and a stimulant suppository (eg, bisacodyl) can be used to soften and mobilize the stool, respectively. An oral osmotic laxative (eg, PEG) can be used in larger doses to aid in this mobilization.

Once the constipation begins to resolve, the patient should be given discharge instructions. Hydration and high dietary fiber intake are often useful in reducing the risk of constipation. A randomized controlled trial has shown that increasing fluid intake to 2 L per day plus a high-fiber diet can increase stool frequency in adults with chronic functional constipation.[33] The effective and safe use of dietary fiber supplements requires that the patient drink at least 1.5 L of water per day. For patients whose hydration is suboptimal, adding dietary bulk fiber may actually worsen constipation and thus should be avoided. A combination of senna and docusate or magnesium salt given daily or as needed may serve as maintenance treatment. If other agents fail, long-term PEG and stimulant laxatives can be safe and effective. Finally, complementary therapy should be considered.

Complementary Therapies—A variety of complementary therapy options may be recommended at the time of discharge. (Depending on the resources of the ED, some of the complementary modalities, especially the low-cost, low-risk options such as transcutaneous electrical stimulation, may also be part of the ED treatment regimen.) Transcutaneous electrical stimulation has been shown to provide benefit in the treatment of constipation.[34] In a small trial with advanced cancer patients with constipation, aroma massage was effective compared with plain massage or no massage.[35] Another small controlled trial showed that compared with laxative use alone, abdominal massage plus laxatives reduced abdominal pain, increased the number of bowel movements, and improved quality of life; however, massage did not reduce laxative use.[36] Herbal remedies may be helpful. For example, tincture of jalapa showed promise in recent randomized controlled trials for treating constipation.[37] Finally, randomized controlled trials have shown that biofeedback is more effective than PEG in treating constipation due to pelvic floor dyssynergia that is refractory to laxatives.[38-42]

CONCLUSION

Constipation is associated with various complications in cancer patients and commonly contributes to ED visits. Gastrointestinal obstruction secondary to constipation is often seen in emergency settings and requires immediate intervention. Identifying the underlying causes of constipation will lead to more effective treatments and better outcomes. Laxatives are the mainstay of emergent treatments and alternative treatments are also available. Rectal exams, enemas, and suppositories should be avoided in immunocompromised patients. **EM**

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