Guest CME:
McMaster University

Gastrointestinal Symptoms in Terminal Illness

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Case One

Kate, 81, has breast cancer and metastasies to the spine and left femur; she complains of nausea and vomiting that comes and goes, lasting approximately five days at a time. Kate's pain has steadily increased and her opiate dose has been titrated up regularly, with good pain relief. Kate is currently taking domperidone (10 mg orally, four times daily); her bowel function is good, but her appetite is poor.

Question: How would you approach this patient?
Discussion on pages 176-7

Case Two

Sixty-year-old Sam has a two-month history of adenocarcinoma of the lung, metastatic to bone. Sam receives hydromorphone (8 mg orally every four hours) to control the pain; he complains of nausea after eating, which eventually results in vomiting. Sam's bowels are moving every five to six days. Dimenhydrinate has been tried and is not effective for his nausea.

Question: How would you treat this patient?
Discussion on page 177

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Quick Facts

FOUR COMMON GASTROINTESTINAL SYMPTOMS IN THE TERMINALLY ILL

- Nausea and vomiting
- Bowel obstruction
- Bowel care
- Anorexia

Gastrointestinal (GI) symptoms are common problems for many terminally ill patients. If symptoms escalate or are unrelenting, they can cause a great deal of suffering. This article reviews four common GI symptoms: nausea and vomiting, bowel obstruction, bowel care and anorexia. Possible etiologies and common management strategies are outlined, with emphasis on assessment and reassessment. Clinicians are encouraged to adopt an etiology-based approach to management.

While terminally ill patients list pain as the most dreaded symptom, GI problems are often more prevalent and challenging for caregivers to control. Recent advances in treatment approaches to GI symptoms behoove us to integrate these approaches into everyday practice.

Nausea and Vomiting

Nausea and vomiting remain among the most frequent and debilitating symptoms experienced by terminally ill patients; 50% to 65% of advanced cancer patients experience significant nausea or vomiting.[1,2] Nausea alone can be a relentless, 24-hour symptom, affecting every aspect of a patient's sense of well-being. Persistent vomiting can be as devastating to quality of life as uncontrolled pain. A rational and organized approach to both etiology and treatment is essential for effective symptom relief.

Mechanism of Action

The sensation of nausea and the act of vomiting are complex physiologic processes. Since current treatments are designed to have an effect somewhere along the postulated physiologic pathways, understanding these processes is essential for effective management. Causes of nausea and vomiting in terminal illness are numerous and often multifactorial.[3] A detailed history and clinical examination are vital in determining an effective treatment plan. (Figure 1 highlights the relevant physiology and also many common etiologies of nausea and vomiting.)

While terminally ill patients list pain as the most dreaded symptom, gastrointestinal (GI) problems are often more prevalent and challenging for caregivers to control.

The final common pathway is the emetic or vomiting center, located in the lateral reticular formation of the medulla oblongata. Neurotransmitter activation of the chemoreceptor trigger zone is thought to be the most frequent mechanism by which vomiting is triggered in terminally ill patients.[4] Activation of other pathways is also common, however, and requires different treatment approaches. Implementing treatments that have little or no effect on the particular pathway causing a patient's nausea and vomiting may be a common cause of treatment failure. Figure 2 outlines the common pathways, abundant neurotransmitter receptors in these sites and antiemetics known to affect these receptors. Although no single antiemetic affects all neurotransmitter recep-

Figure 1

Nausea and Vomiting in Terminal Illness: Etiology and Physiology

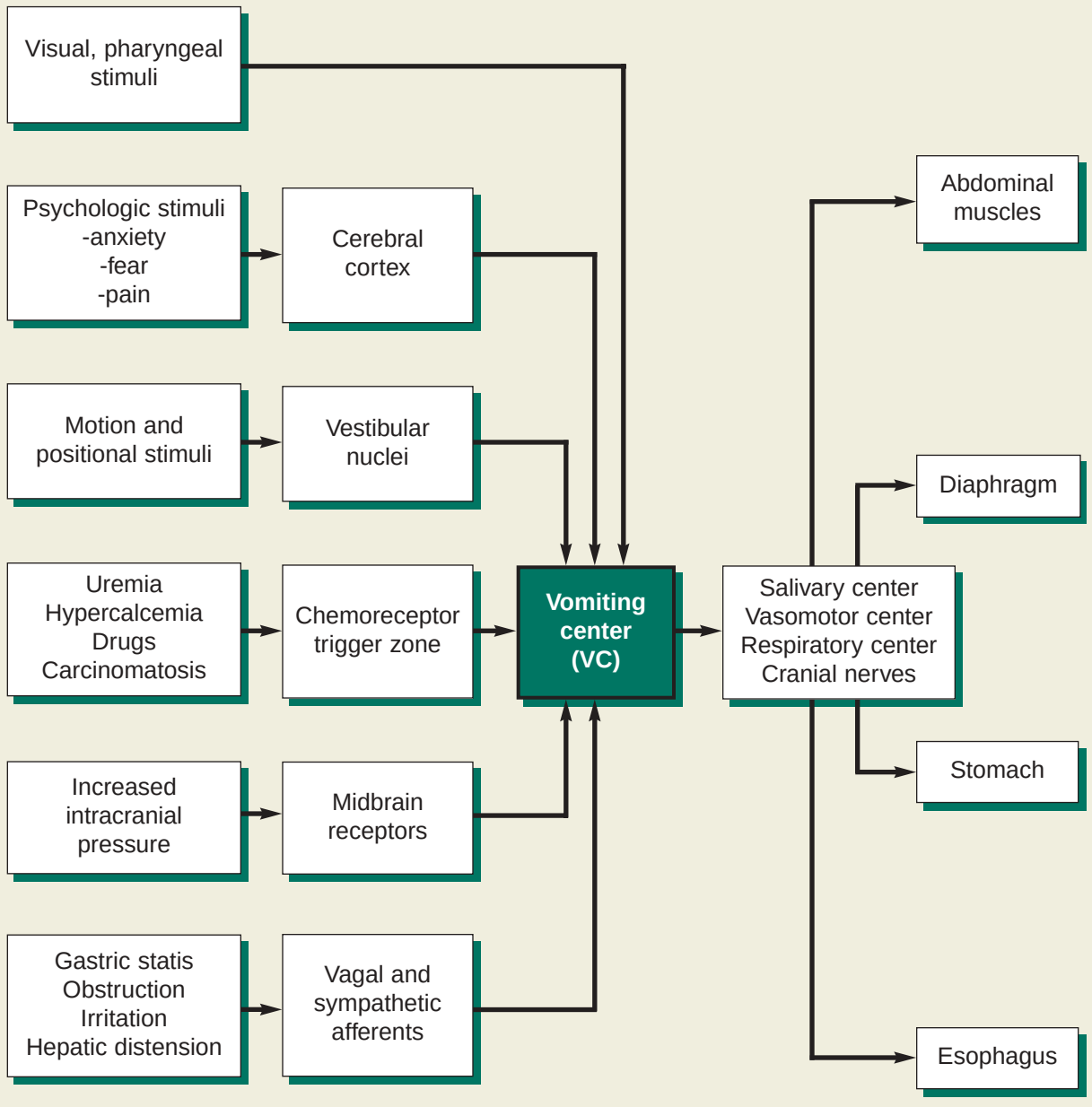
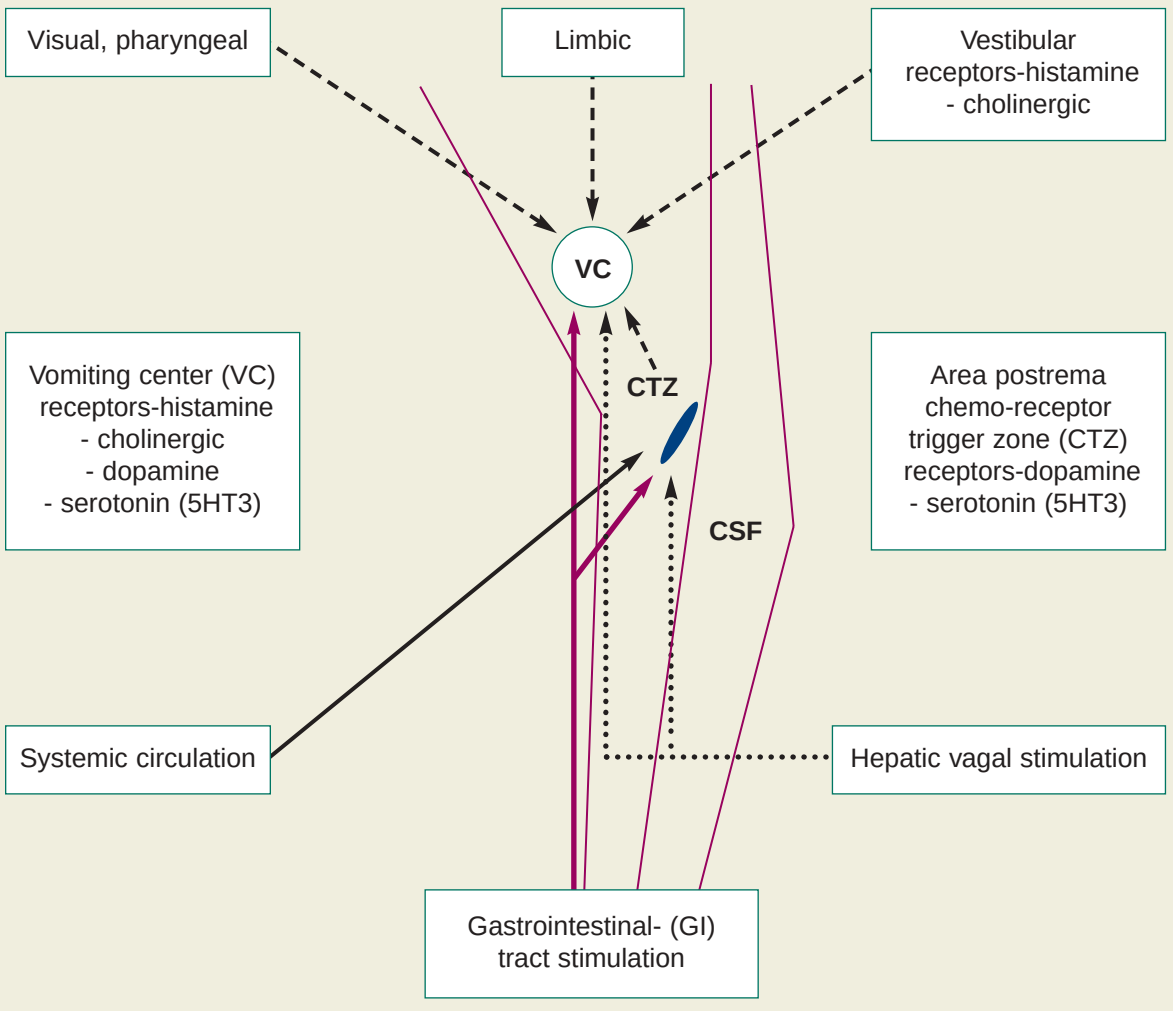


Figure 2

Common Vomiting Pathways and Receptor Sites



tors with equal potency, each is potent to at least one receptor.

Management Options

Good management of nausea and vomiting should include investigation and treatment of underlying causes (if this is in keeping with the patient's goals of care).[5] This may be as straightforward as basic blood tests or discontinuing nonvital emetogenic drugs, or it may involve more invasive procedures (*e.g.*, endoscopy). Discussion with the patient and his or her family is imperative before initiating an investigation and possible treatment.

Table 1 is a useful guide for establishing a pharmacologic management plan. For example, dimenhydramine may not be the best choice of antiemetic for the patient suffering from opiate-induced nausea and vomiting; dimenhydramine affects only a portion of the receptor sites in the vomiting center and may have little effect on blocking the pathway at the chemo-receptor trigger zone. Effective choices may be dopamine-receptor blockers, such as perchlorperazine, metoclopramide and haloperidol.[6] Patients whose clinical history of nausea and vomiting suggests a pattern much like motion sickness (sometimes related to opiates or metabolic abnormalities) may benefit from dimenhydramine or transdermal scopolamine.[7,8]

Dysmotility of the upper-GI tract is a frequent cause of nausea and vomiting. While dysmotility may respond to central-acting antiemetics, better treatment may involve local-acting agents and have fewer central side-effects (Table 1).[13-15] Ondansetron is highly effective at blocking specific serotonin receptors (5HT3) at the gut level. As our understanding of serotonin blockade increases, ondansetron's current use for cytotoxic drug-induced nausea and vomiting may expand to include other etiologies in terminally ill patients.[9-12] The anti-inflammatory effects of steroids make them effective drugs to combat nausea and vomiting due to increased intracranial pressure and liver distention. Although other antiemetic modes of action of steroids are poorly understood, steroids are effective alone or in combination with other antiemetics as treatment for many causes of nausea and vomiting in the terminally ill.[3,5]

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Opiate-Induced Nausea and Vomiting

Opiate-induced nausea and vomiting is a common problem that occurs in approximately 30% of patients receiving opiates; it is frequently experienced when an opiate is first started or when the dose is increased. Ordering antiemetics in anticipation of this problem is good management.[16,17] Most people develop tolerance to this opiate side-effect within three to ten days, and antiemetics can then be weaned or withdrawn.

Opiates can cause nausea and vomiting through three known mechanisms. The most frequent opiate-induced mechanism is through direct gastric stasis and irritation. Patients may describe sluggish bowels, a "full" feeling, early satiety, frequent burping or rather sudden vomiting with seemingly little or no antecedent nausea. Good bowel care and local-acting prokinetics (domperidone) may

Table 1

Useful Antiemetics For Terminal Care

Drug	Mode of Action-Location	Common Dosing
• Phenothiazines-perchlorperazine	antidopaminergic-CTZ, VC	5-10 mg IV, orally/by rectum every four to six hours
• Butryophenones-haloperidol	antidopaminergic-CTZ, VC	0.5-2 mg s/c, orally/by rectum twice daily to every four hours
• Metoclopramide	antidopaminergic-CTZ enhances gastric emptying	5-10 mg IV, s/c, orally/by rectum every four to six hours
• Scopolamine	anticholinergic vestibular, VC	transdermal patch every three days
• Dimenhydramine	antihistamine-vestibular, VC	25-75 mg IV, orally/by rectum every four to six hours
• Corticosteroids-dexamethasone	decrease ICP, hepatic distention, and gut edema; cannibinoid effect ? other effects	2-6 mg, twice daily to four times daily IV, s/c, orally
• Domperidone	enhances gastric emptying	10 mg orally, four times daily
• Benzodiazepines	central dampening effect-cerebral cortex; limbic	drug-specific
• Ondansetron	antiseritonin (5HT3)	8 mg, IV orally, three times daily

(think of regular dosing, not as required; reassess this within 48 to 72 hours)*

CTZ- chemo-receptor trigger zone
VC- vomiting center
s/c- subcutaneously
IV- intravenously
ICP- Intra Cranial Pressure

In cases of nausea and vomiting in terminal illness, a nutrition consult can lend valuable advice about dietary changes or nutrition delivery.

provide relief. In difficult cases, the opiate may be switched from an oral to a parenteral route to bypass the gut effects. Opiates can also cause direct stimulation of the chemo-receptor trigger zone, and the pattern of nauseous periods may be temporally related to drug ingestion. A central-acting antiemetic provides the best results. Less frequently, opiates cause enhanced labyrinth sensitivity in the inner ear, resulting in movement-related nausea. Antihistamines and anticholinergics may be effective drugs for this problem.

Causes of Treatment Failure

A frequent cause of seemingly intractable nausea or vomiting is the failure to initially prescribe an effective antiemetic on a regular basis rather than

Table 2

Classification and Dosing of Useful Laxative in Terminal Bowel Care

Laxative category	Laxative name	Common dosing
1. Bulk agents	bran, psyllium, methyl cellulose	not often recommended (see text)
2. Surfactants (softeners)	docusate sodium	100-300 mg orally, twice daily to three times daily
3. Osmotics* and salines	lactulose	15-60 cc orally every day to three times daily
	magnesium citrate	4-8 oz. orally every day
	glycerine	Once by rectum every day or as required
4. Stimulants	sennosides	1-3 tabs orally/by rectum twice daily
	bisacodyl	1-3 tabs orally or 1 supplement by rectum

(* Note: rectal laxatives differ in terms of their osmotic gradient and thus, harshness and efficacy; for example, tap water is mild; soap suds are moderate; oil retention is harsh)

as required; another cause is the failure to prescribe drugs in doses sufficient to treat symptoms completely. Physicians may hesitate to add a second or third antiemetic to a patient's regimen. A stepwise approach to management requires initial assessment and frequent reassessment, which may include adding a second antiemetic that compliments the action of the first. In some cases, intractable nausea and vomiting represent a chronic, intolerable, opiate side effect, and switching to an alternate opiate is worthwhile. Insidious renal failure from dehydration or other causes may result in poor clearance of opiates, thus contributing to a chronic nausea or vomiting problem. Switching opiates or rehydrating (if appropriate), may relieve the patient's symptoms.

For some terminally ill patients, vomiting continues despite careful history taking, examination, laboratory and other investigations and stepwise application of antiemetics. Ongoing discussion with the patient and his or her family will reassure them that symptoms are not being ignored. Consideration should be given to any treatments that have not been tried. It is rare for

symptoms to remain so severe that the patient prefers sedation.

In all cases of nausea and vomiting in terminal illness, opinions from other consultants and allied health-care providers should be sought and considered. In particular, a nutrition consult can lend valuable advice about dietary changes or nutrition delivery. GI consultation may reveal a hidden pathology. Alternate therapies, such as music and relaxation therapy, may help alleviate the severity of symptoms.

Bowel Obstruction

Intermittent, partial or complete bowel obstruction may cause nausea and vomiting in about 3% of all terminally ill patients.[3] Diagnosis is often readily obtained through knowledge of a patient's GI-tract disease and/or treatment (surgery, radiotherapy). A physical examination and history of symptom onset can contribute greatly, and abdominal X-rays can confirm the clinical picture.[17] Depending on the patient's medical status and disease process, surgical intervention is seldom possible. Conservative management—the highly successful mainstay of palliative management of bowel obstruction—should be tried first in all cases. Bowel rest (nothing orally to clear fluids), parenteral administration of analgesics and antiemetics and hydration (if appropriate) are the cornerstones of treatment. Many seemingly terminal obstructions abate with this conservative treatment, and partial obstructions may wax and wane for months, causing only intermittent symptoms. For bowel obstructions felt to be caused by seeding of the bowel wall with a tumor (often at many levels), intermittent obstruction may be present. Evidence suggests that parenteral steroids (*e.g.*, intravenous [IV] dexamethasone) may reduce edema and inflammation on the bowel wall's luminal side in such cases, allowing enough bowel patency for symptom relief.[3] Octreotide has been used with some success to abate the symptoms of terminal obstruction.[18,19]

Although the use of a nasogastric (NG) tube is an option, symptom control or relief of obstruction is not necessarily improved with its use.[20] Patient opinion regarding NG-tube use is essential; the sense of burdens versus benefits may be very clear and should be respected. Subcutaneous scopolamine (0.4 mg to 0.8 mg every four to six hours) helps slow production of gut secretions; it may allow avoidance of an NG tube, even in the face of a persistent obstruction. Caution should be exercised, however, as scopolamine may precipitate a confused state in some patients.

If appropriate, percutaneous gastrostomy should also be tried. The widespread use of subcutaneous medications, fluids and home IV, make management of a terminal bowel possible in all treatment settings. Near the end of life, the symptoms of nausea and vomiting may naturally abate as gut activity decreases and drowsiness increases. The use of hydration and antiemetics should be reassessed carefully at every step.

Bowel Care

Excellence in bowel care is an important part of palliative care. Constipation is among the most common and undertreated problems that terminally ill patients face.[21] The first step is understanding the causes of constipation, including delayed gut activity from opiates, decreased fluid intake and poor diet, cachexia-anorexia and lack of exercise. There is no convincing evidence that any particular opiate is more or less constipating than another. Constipation is usually multi-factorial in its etiology and requires attempts at improving diet and fluids, optimizing activity and a laxative regimen.[5]

Success in prescribing laxatives lies in understanding their method of action and using sensible combinations. Table 2 outlines the common categories for laxatives, as well as common preparations from each category. Bulk-forming agents are the least desirable for dying patients; fluid intake must be great and there is often insufficient peristaltic activity to move bulk agents through. Combinations of fecal softeners with stimulants or osmotic/saline preparations are common. Success depends on matching not only the specific agents to a patient's needs, but also the form of the agent (liquid, pill, suppository). Consideration needs to be given to a patient's overall pill load, concomittent nausea, location of disease or debility involving the GI tract. Once again, undertreatment is a common cause of failure. As Table 2 outlines, regular and multiple doses of many common laxatives are needed to achieve bowel regularity. Thorough explanations of how each preparation works may also promote compliance.

Refractory constipation may be treated in a stepwise fashion with suppositories, enemas or more potent oral saline preparations. Commercially available saline products—used commonly as preparations before bowel examinations—can be prescribed in moderate doses (4-8 ounces daily), on a "chill and sip, keep at the bedside" routine. Many patients tolerate this well.

Persistent diarrhea is uncommon in terminal patients unless there is predisposing gut pathology (viral or bacterial pathogens), malabsorption syndromes or short-gut syndromes. The relative frequency among terminal acquired immune deficiency syndrome (AIDS) patients, however, has resulted in newer treatment approaches and protocols, ranging from loperamide hydrochloride to somatostatin analogues.[17]

Anorexia

Anorexia is a common problem for many patients long before the terminal phases of illnesses like cancer and AIDS. There is now extensive literature on mechanisms of action and management that help guide treatment approaches.[22]

In the terminal phases of illness, anorexia may be the most frequent GI complaint and, for many patients, one of the most distressing. Many patients feel that the inability to eat represents the end of life. Often an intractable symptom, anorexia may require more attention than other symptoms from caregivers. Patients may silently despair at mealtime. Well-intending families may insist their loved one try to ingest more, resulting in guilt, anger and hopelessness. Discussion is vital; physicians are responsible to anticipate this distress and broach the topic (if appropriate) in ways that are sensitive to the patient's personal, familial and cultural needs. Management may then include revising diets, seeking a nutritionist's advice or, in selected cases, prescribing appetite stimulants. Megestrol acetate (*i.e.*, 160 mg once or twice daily) and steroids (dexamethasone, 2 mg to 8 mg daily) can be tried.[22]

Management in other cases may consist of giving patients and families "permission" to let go of eating well as a goal, and ongoing support for the daily distress that anorexia may bring. Anorexia should not be minimized or disregarded unless that is the approach agreed upon during discussion.

Case One: Discussion

Further questioning reveals that Kate's nausea and vomiting occur with each increase in opiate dose, and that opiate-induced symptoms may be resulting. Opiates have been switched many times in the last several months. haloperidol (1 mg orally three times daily) resulted in a successful decrease of

her nausea and vomiting. The Haloperidol dose was eventually decreased to 0.5 mg twice daily, however, it was transiently increased with each increase in opiate dose. Later in Kate's course with a recurrence of the nausea, brains metastasies were considered, but not definitely explored. The addition of dexamethasone (2 mg to 4 mg twice daily or every day [short course]) was successful in controlling the nausea. Kate's calcium levels were normal.

Case Two: Discussion

Dysmotility of the gastrointestinal tract may be Sam's problem, and local-acting prokinetic agents, combined with regular laxatives, may be the solution. Domperidone before meals, with regular dosing of docusate sodium and sennosides, is reasonable. Once again, other etiologies were explored and ruled out (*e.g.*, hypercalcemia).

Conclusion

GI symptoms in terminally ill patients are common and can be the source of great suffering. As caregivers, physicians can help relieve this suffering by being organized in treatment approaches, vigilant in reassessment and generous in the caring, compassionate time committed to alleviating these distresses in each patient. CME

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