



Management of Gastrointestinal and Respiratory Symptoms in Palliative Care

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Pain is distressing, but is not the only symptom that causes misery for patients with life-threatening illness. Constipation, nausea, vomiting, lack of appetite, dysphagia, shortness of breath, cough, fatigue, delirium, depression and anxiety are other symptoms that need palliation. This article will overview symptom assessment in palliative care, and then, in more detail, it will address specific gastrointestinal as well as respiratory symptoms. Psychological symptoms are discussed in another article in this issue.

Symptom Assessment in Palliative Care

To identify and treat symptoms effectively, assessment is important. History and physical examination are first steps. The history should include the nature and time course of the symptom, along with its severity and consequent effect on the patient's function and quality of life. Caregiver input

is also helpful, particularly if the patient is suffering from dementia or delirium. Careful inquiry about medication use (prescription, over-the-counter and alternative/complementary medications) and comorbidities may affect the diagnostic process and choice of treatment. Physical examination should be directed at identifying the cause of the symptom. Further investigation, including laboratory tests and radiological studies, may be performed if the results will cause a significant change in management.

It is important to discuss goals of care with the patient and family. The question should be asked: "Is our main goal at this time to keep this person alive as long as possible and as functional as possible while maintaining comfort, or is the main goal to preserve comfort and to allow a natural death?" In the early stages of a life-threatening illness,

emergency room visits, invasive diagnostic testing and hospitalization may be very appropriate. In end-stage disease, these interventions may provide discomfort and expense without favorably influencing the outcome of the illness.

In the hospice setting, empiric symptom management may be accepted without knowing the exact cause if diagnostic testing is overly burdensome to the patient. Empiric therapy should be followed by continued assessment to determine if the treatment is effective.

When judging effectiveness of prescribed medications, check to confirm how often they are actually administered. Medications ordered on a “PRN basis” may not have been given. PRN stands for *pro re nata*, which literally means “at the birth,” but is used to mean “as needed.” Unfortunately, too often it ends up being “Patient Receives None.” The patient may not report the symptom to caregivers and, therefore, not receive the medication. It may be useful to regularly schedule administration of the medication, at least for a trial period, to see if it is effective.

Palliative care is most effective when performed by a team. The physician may not always be available to assess the patient in a timely fashion. Nurses (in home health, hospice or long-term care facilities) may see the patient and report symptoms to the physician. Communication may be done via phone or fax and, if necessary, a home or office visit. Further questioning may be needed to obtain important history and results of physical examination.

Gastrointestinal Symptoms

Nausea and vomiting

Nausea has many potential causes and is mediated by neurotransmitters in the GI tract as well as in several areas of the central nervous system: the chemoreceptor trigger zone (CTZ), the vestibular apparatus and the cerebral cortex. These neurotransmitters are serotonin, acetylcholine, dopamine and histamine. Serotonin is an important neurotransmitter in the lining of the gut; acetylcholine and histamine in the vestibular system; and all four neurotransmitters are found in the CTZ. Knowledge of the etiology of symptoms should direct the choice of antiemetic measures, although empiric therapy may be necessary at times.

The history should focus on characterizing the nausea and vomiting in addition to any associated symptoms. Anorexia may represent a constant low-grade nausea. Constipation may also contribute to nausea, but may be underreported by patients who think it is normal to have infrequent bowel

movements when oral intake is limited. Esophageal burning may be from gastroesophageal reflux or infectious esophagitis (candida, herpes). Discomfort associated with eating can be caused by esophagitis, gastritis, bowel obstruction, ileus or impaired mesenteric circulation.

A thorough medication history is essential and should include new and recently discontinued medications, counting prescription and over-the-counter drugs and supplements. Opioids, nonsteroidal anti-inflammatory drugs, antibiotics, antidepressants and chemotherapy drugs can all cause nausea. Diuretics and other medications can cause electrolyte disturbances, which can lead to nausea. Abrupt discontinuation of steroids can cause nausea due to adrenal insufficiency.

Past medical history can give insight into the cause of nausea and may include peptic ulcer disease or gastroesophageal reflux. Disorders causing autonomic neuropathy, including diabetes mellitus, advanced cancer, Parkinson’s disease and others, can impair gastric emptying. Anxiety and depression can be associated with nausea. Anticipatory nausea and vomiting associated with chemotherapy are mediated by the cerebral cortex.

For cancer patients, the type of cancer and site of origin and location of metastatic disease are important to determine the cause of nausea. Bowel obstruction, liver metastases and peritoneal carcinomatosis can all cause nausea and vomiting. Malignant bowel obstruction can occur with almost any malignancy, but it is most common with advanced ovarian and colorectal cancer. Primary tumors or metastases in the brain can also cause nausea.

Physical examination, including rectal examination, may provide evidence of abdominal masses, bowel obstruction or fecal impaction. Papilledema or neurological signs may be evidence of central nervous system tumor. Orthostatic decreases in blood pressure without a corresponding increase in heart rate may be evidence of autonomic insufficiency.

Laboratory studies may be helpful to rule out renal or hepatic failure, electrolyte disturbance, pancreatitis or toxic medication levels. A supine abdominal film may help to identify constipation, particularly in cognitively impaired patients who are unable to give an accurate history. An upright abdominal film may identify bowel obstruction.

Therapy for nausea and vomiting is directed at removing the specific, underlying stimulus when feasible. Antiemetics

should be directed against the involved neurotransmitters for best response. Wood et al. recommend a mechanism-based management scheme, though they acknowledge that nausea may be multifactorial, requiring empiric treatment that addresses several mechanisms at once.¹ Medications that target the dopamine type 2 (D2) receptor, such as metoclopramide or haloperidol, are useful for first-line therapy of nausea and vomiting. However, sedation, stiffness and dysphagia are potential side effects. 5-hydroxytryptamine type 3 (5HT3) antagonists (e.g., ondansetron, granisetron) also target nausea mediated by the CTZ. Evidence supports the use of 5HT3 agents for nausea and vomiting induced by chemotherapy, radiation therapy and post-operative. The 5HT3 antagonists also may be helpful for opioid-induced nausea and vomiting, but they are expensive and may not be more effective than the less expensive D2 antagonists.

Gastroesophageal reflux and peptic ulcer disease can cause nausea and anorexia. Histamine type 2 (H2) receptor blockers (e.g., ranitidine, famotidine) are available over the counter and are inexpensive, but they might not be as effective as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole) for these disorders.

Opioid-induced nausea occurs through several mechanisms, including stimulation of the CTZ, gastroparesis, constipation and vestibular sensitization. The effect on the CTZ is mostly through central D2 receptors, whereas the nausea caused by gastroparesis is mediated through peripheral D2 receptors.

Chemotherapy can cause nausea and vomiting through several mechanisms. Direct stimulation of the CTZ is thought to be mediated by 5HT3 receptors and neurokinin type 1 receptors. Chemotherapeutic agents also can damage the GI mucosa, causing release of neurotransmitters including 5HT3. Chemotherapy-induced nausea and vomiting may be mediated by anxiety as well. Anxiolytics prior to each dose may help to prevent anticipatory nausea and vomiting. Advanced cancer itself can cause autonomic dysfunction, leading to constipation and gastroparesis. Poor gut motility can lead to distension of the bowel wall, stimulating the splanchnic and vagus nerves.

Dexamethasone may reduce tumor-associated edema in the brain or gut, thereby reducing nausea. Malignant bowel obstruction-associated symptoms may also improve with octreotide to reduce secretions within the gut. Gastric suction may be necessary if medical interventions are unsuccessful.

Motion-associated nausea and vomiting may respond to agents that block stimulation via the vestibulocochlear nerve, such as scopolamine or diphenhydramine. However, these medications have anticholinergic properties which may cause delirium and sedation, particularly in elderly patients.

If first-line agents are not sufficient, adding a second agent directed at another neurotransmitter may be useful, because nausea and vomiting at the end of life are often multifactorial.

Constipation and Diarrhea

“Constipation” and “diarrhea” mean different things to different people, so it is important to find out what the patient means by these terms. The normal frequency of bowel movements ranges from three times a day to once every three days, so an individual’s previous bowel pattern is important. The complaint of constipation may be more related to hard stools than to infrequent stools. Diarrhea may refer to increased stool frequency or decreased consistency. Inquiry should be made into the person’s eating habits, including fiber and liquid intake, as well as the presence of associated symptoms such as abdominal pain, nausea and vomiting, bloody stools, or melena. A prolonged time without a full-sized defecation, accompanied by frequent passage of liquid stool, may reflect a fecal impaction with a stool mass having a ball-valve effect so that only liquid stool passes.

Many medications have constipating side effects. Frequent culprits in end-of-life care include opioids, agents with anticholinergic side effects and certain calcium channel blockers such as verapamil and diltiazem. Discontinuing or reducing the dose of these medications may be helpful, but if this is not possible, a bowel regimen should be initiated.

If the problem is infrequent stools, a stool softener will most likely not be helpful. If patients are able to eat an adequate diet, increased fiber and liquid intake may be the first step. Prune juice and bran help some patients. End-stage patients are often unable to maintain adequate fluid intake. A fiber supplement for these patients would only aggravate the constipation, since bulking agents require liquid to pass through the colon.

In end-of-life care a structured bowel program, including scheduled laxatives, is often necessary. Such a program starts with a regularly administered stimulant laxative such as sennosides, which may be combined with a stool softener such as docusate. The dose is increased as needed to the

maximum prescribed amount. If this is not effective, it may be augmented with an osmotic laxative such as milk of magnesia (or in patients with renal insufficiency, sorbitol or lactulose). Suppositories such as bisacodyl or enemas and/or digital rectal stimulation are used as needed.

Opioid-induced constipation should not be treated with fiber, but with stimulant laxatives. A scheduled stimulant laxative should be started along with the first dose of opioid.

Diarrhea may be medication related; antibiotics, selective serotonin reuptake inhibitors (SSRIs) and acetylcholinesterase inhibitors may be culprits. A trial of stopping these medications is warranted. Patients who have recently been treated with antibiotics (especially fluoroquinolones or clindamycin) are at risk for *Clostridium difficile* enterocolitis. This is treated by discontinuation of the contributing antibiotic and initiating treatment with metronidazole or oral vancomycin. Patients suspected of having *Clostridium difficile* enterocolitis should not be treated with antimotility agents until this problem is excluded, because antidiarrheals can increase the risk of toxic megacolon in the setting of enterocolitis. Fecal impaction should also be ruled out. If no reversible underlying cause is found, antimotility agents such as loperamide are of use to reduce symptoms.

Anorexia

Loss of appetite is common at end of life, but reversible causes should be addressed. Anorexia may be the result of nausea, sore mouth, altered taste and smell, dyspepsia, polypharmacy, metabolic disturbances, infection, dysphagia, gastric stasis, anxiety, and depression.

In evaluating anorexia, a medication history is important because of potential effect on appetite. A number of medications are protein bound; as protein stores are depleted by illness or undernutrition, the amount of free drug may rise to toxic levels. Phenytoin, digoxin and other medications may require dose adjustment even if measured levels are in the “therapeutic” range. Medication interactions can also increase drug levels. Drug interactions are inevitable in patients taking eight or more medications; attempts at medication reduction are often helpful. Some medications, such as metronidazole and angiotensin converting enzyme inhibitors, can cause taste perversion.

Physical examination should include assessment of the oral mucosa, teeth, abdominal and rectal. Evaluate for thrush, oral mucosal irritation, dry mouth and dental caries.

Attention should also be paid to the patient’s ability to manipulate utensils and to hold a drinking glass. The one-liter bottles often provided at hospital bedsides may be too heavy for frail patients to lift. Patients should also be observed for evidence of oropharyngeal dysphagia, which will be discussed later in this article.

Anorexia may be more distressing for caregivers than for the patient. If anorexia is not reversible, the patient should be offered food as desired and tolerated. Caregivers should be counseled that it is all right for the patient to eat only a bite or two if he or she is not hungry for more. It may be helpful to present a small amount of food, and then offer more if the patient desires it.

A number of medications have been tried for anorexia. Corticosteroids such as dexamethasone may increase appetite in the short term, but do not increase lean body mass. Systemic side effects such as hyperglycemia, proximal myopathy and fluid retention may limit use. The benefit of corticosteroids may be limited to a few weeks. Megestrol acetate and other progestogens can improve appetite but do not increase lean body mass. Fluid retention may be a problem. Onset of benefit may take up to two weeks. Antidepressants may improve the appetite in depressed patients. The antidepressant mirtazepine has been used successfully for this purpose in elderly persons. Start with a low dose and increase gradually if needed, while monitoring the patient for excessive sedation or other side effects. Antidepressants often require three to four weeks to reach their full effect.

Artificial Feeding and Palliative Care

Families may ask if artificial feeding would be helpful for a patient who cannot eat. In this case, the goals of care should be considered carefully, as well as the burdens and benefits of artificial feeding. Artificial feeding may be appropriate for someone who is recovering from an acute stroke or from surgery for cancer of the throat or GI tract and is otherwise functional and desires artificial nutrition. However, in widely metastatic cancer or advanced dementia, there is little evidence that artificial feeding prolongs or enhances life. Cancer can cause cachexia through the production of cytokines which cause loss of lean body mass as well as anorexia. This cachexia is not reversible by feeding. Tube feedings have not been helpful in healing pressure sores, preventing aspiration pneumonia, or improving quality of life for patients with advanced dementia.^{3,4} Hand feeding with an appropriately modified diet can sustain patients

with advanced dementia for months to years.

If artificial feeding is employed, the enteric route is preferred whenever possible. Intravenous nutrition is very expensive and does not provide as complete an assortment of nutrients as enteral feeding.

Tube feeding requires invasive measures for tube placement. Most demented or delirious patients will not leave a nasogastric tube in place for more than a few hours, even if their arms are restrained. This places them at high risk for aspiration of tube feedings and is highly frustrating for caregivers. Percutaneous feeding tubes are better tolerated, but do not prevent aspiration pneumonia. Insertion sites might become infected, or the tube may become plugged or dislodged (often at an hour when replacement is not readily available without going to the emergency room). Patients and families should be counseled about the risks versus the benefits of artificial feeding prior to placement of a feeding tube.

Dysphagia

Oropharyngeal dysphagia is a common problem at the end of life for patients with neurological disorders.⁵ Patients with advanced dementia, certain strokes or Parkinson disease develop impaired neuromuscular control of swallowing. Delirium can also impair swallowing. Patients with neuromuscular dysphagia may cough and aspirate on thin liquids. Patients who lack the ability to chew due to dental problems or because of oropharyngeal dysphagia may benefit from altered diet textures. Dysphagia diet textures vary from Level I (puree), to Level II (soft and slippery), to Level III (ground or chopped meats and exclusion of crunchy foods such as raw vegetables), to Level IV (regular diet without crunchy foods). Oral dietary supplements may be useful; however, these should only be offered between meals to avoid interfering with meal intake.

Evaluation by a speech pathologist can be helpful to select the appropriate diet for a patient with dysphagia. Thickening the liquids to nectar, honey or pudding consistency may reduce the incidence of aspiration. Unfortunately, thickened liquids may be unpalatable to the patient, making it hard to provide adequate hydration. The diet level that produces the best intake by the patient should be the final choice. Insisting on a restrictive diet that the patient will not eat is counterproductive. If, after evaluation and correction of reversible factors, a patient is not able to consume enough calories and fluids to sustain

life, hospice care may be the most appropriate choice. Recurrent aspiration pneumonias are also an indication for hospice care.

Respiratory Symptoms

Dyspnea is common at the end of life: it is experienced by 70 percent of cancer patients in the last six weeks of life; 50 percent to 70 percent of patients with other illnesses dying in a hospital; and more than 90 percent of those dying of chronic obstructive lung disease (COPD). Dyspnea can cause poor sleep, depression, anxiety, fatigue, social isolation and interfere with activities of daily living.

There are many potential causes of dyspnea. These include primary pulmonary problems such as COPD, asthma, pulmonary fibrosis, pneumonia, pulmonary embolus, cancer, pleural effusions and pneumothorax. Other diseases that can cause dyspnea include heart failure, coronary artery disease, anemia, anxiety, depression, cough, pain and vocal cord dysfunction. Diagnostic testing should be directed toward identifying treatable causes. Disease-specific treatment may be effective to reduce dyspnea.

History taking should be directed not only toward identifying potential reversible causes, but also toward learning the degree of impact on quality of life. Clinicians should inquire about anxiety, which can induce or worsen dyspnea.

Physical examination should include evaluation of intravascular volume status. Though elevation of jugular venous pressure (JVP) can result from severe chronic lung disease, in this case JVP will rise and fall in time with the patient's respirations. A persistent elevation of JVP during respiration suggests volume overload. Chest percussion can indicate the presence of pleural effusion while lung auscultation may demonstrate crackles from pulmonary fibrosis, heart failure or infectious infiltrates. Cardiac examination may disclose murmurs, rubs or gallops. Edema may indicate volume overload, but it is not specific for heart failure. Asymmetric edema may be caused by deep venous thrombosis, which is a risk factor for pulmonary embolus, but the edema may also be a result of previous leg injury or lymphedema.

Non-pharmacologic measures can be helpful for dyspnea.⁶ Patients in the earlier stages of disease may benefit from rehabilitative exercises to improve breathing techniques, anxiety and endurance. Pursed-lip breathing and diaphragmatic breathing are more efficient than rapid breathing using upper airway muscles. Upright posture uses gravity to

assist in lung expansion (though patients who lean forward onto their elbows for extended periods of time should have padding under the elbows to reduce ulnar nerve compression and pressure sores of the elbow area). Energy conservation techniques, such as frequent rest breaks, can be useful. Using a fan or an open window to cause a breeze in the room can relieve feelings of shortness of breath for some patients.

Aerosolized bronchodilator therapy is often helpful for reactive airway disease. It may also be tried in the absence of wheezing to see if it is helpful. If the patient is able to use a metered-dose inhaler with a spacer chamber, this device may be just as effective as a nebulizer machine but is more economical. Long-acting inhaled medications such as salmeterol or tiotropium may reduce the need for shorter-acting beta-agonists or ipratropium. The short-acting preparations should be used for breakthrough symptoms. Levalbuterol may produce less anxiety and tachycardia compared to albuterol, though it is considerably more expensive. Levalbuterol can be considered if albuterol is not helpful or is producing unacceptable side effects.

Oxygen therapy can improve exercise tolerance in patients with chronic lung disease and hypoxia. Pulmonary rehabilitation can be beneficial for reducing dyspnea and improving exercise tolerance in COPD patients, though would not be tolerated by patients who are dying.⁷ The benefit of oxygen therapy in nonhypoxemic cancer patients is less clear. Oxygen therapy may be of symptomatic benefit even with normal oxygen saturations, perhaps via stimulation of trigeminal nerve endings (similar to using a fan). Although oxygen therapy has few side effects, it is expensive and inconvenient for the patient. Patients and families should be counseled to turn the oxygen off if they choose to smoke, since facial burns, smoke inhalation and house fires are a real hazard.

Opioids are the primary non-specific treatment for dyspnea. Opioid therapy reduces the subjective sensation of breathlessness as well as responses to hypoxia and hypercapnea. Nearly all opioids tested have been shown to be effective for dyspnea related to COPD, although the mechanism is not well understood. Opioids may also be helpful for dyspnea related to cancer, although the evidence is not as strong.⁸ Nearly all routes of administration appear to be effective, although the role of nebulized opiates remains controversial. The goal is comfort rather than a target respiratory rate. Opioid-naïve patients should start with 5 to 15 mg of

morphine equivalent. The side effects of opioids are the same as when treating pain (nausea, constipation, drowsiness and confusion).

Benzodiazepines are useful if the patient is experiencing a significant amount of anxiety associated with breathlessness. Trials show mixed results in patients with chronic dyspnea who do not report anxiety. These agents can cause drowsiness, unsteady gait and dysphoria, and should only be used if the benefits outweigh the risks.⁹

Summary

Non-pain symptoms are common at the end of life and careful assessment as well as treatment can alleviate them. Reversible causes should be sought and corrected. Empiric treatment may be appropriate when diagnostic testing is burdensome. Treatments should be assessed to determine whether they are being used appropriately and are effective. Side effects such as constipation should be anticipated and treated as needed. An interdisciplinary team approach can be beneficial to assess outcomes of treatment.

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