



Ian Anderson Continuing Education Program in End-of-Life Care

Module 3

SYMPTOM MANAGEMENT



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Case Scenario

Mrs. Linda Parson is a 40-year-old accountant who presented to hospital with fever, cough productive of purulent sputum and dyspnea. She appeared quite dyspneic and had O₂ Sats of 87% on room air. She was started on 2 L O₂ and Sats improved to 92%. Chest exam revealed bronchial breath sounds in the left base. Her CXR showed an infiltrate in the left lower lung zone, a 4 cm nodule in the right upper lobe and bilateral hilar adenopathy. She was admitted and started on ceftriaxone and azithromycin.

Further questioning revealed that she had noticed a 15-pound weight loss in the last month but she had been under a lot of stress and had been attempting to lose weight. She has a strong family history of breast cancer, however has not been undergoing regular breast exams. When you do a breast exam, you discover a hard fixed 3 cm mass and axillary adenopathy. CT scan shows an inoperable 5 cm mass in right upper lobe and liver mets. A diagnosis of metastatic breast cancer is made. Radiation and Medical oncology have been consulted but have not yet given their opinions.

Mrs. Parson's sputum clears and by O₂ sats, she no longer needs O₂. However she still complains of dyspnea and says she gets short of breath walking down the hospital hallway. You thought she had shared her diagnosis with her husband; however, you overhear her telling him "the doctors don't know why I am short of breath. It's probably from the pneumonia."

You meet with her after he leaves and ask her why she has not yet told her husband and she says she "just can't do it." She refuses your offer to help. You ask her about her shortness of breath and why she hasn't mentioned it. She says, "I did not want to be a bother and I figure there is nothing you can do about it, is there? Besides I don't want to be a drug addict!"

Introduction

Recent literature and media reports have emphasized the fact that too many people still die in pain. However, little mention is made of the fact that dying people commonly experience other symptoms that are just as distressing as pain if not more so. The most common symptom of dying patients with advanced illness is fatigue (or asthenia) occurring in 58-90% of dying patients, followed by anorexia and cachexia. Others are troubled by sleepiness (24-57%) confusion (24%), anxiety (20%), dyspnea (12-74%), and nausea (12-70%) depending on their stage of illness. Still others have problems with constipation, diarrhea, peripheral edema, insomnia, and skin ulcers. Most dying people experience a combination of these symptoms and problems making management quite complex.

Any one or combination of these symptoms/problems can cause suffering and prevent the person from enjoying his/her remaining life by making even simple activities of daily living a challenge, isolating him/her from loved ones and, preventing him/her from fulfilling any remaining life goals. Failure to alleviate or even to control these symptoms and problems may cause a dying person's worst fears to be realized and may destroy any hopes for quality of life.

Research has shown that people consider achieving control, not only of pain but also of these other symptoms an important part of quality end-of-life care. Physicians should be able to manage these symptoms in order to improve the dying person's remaining quality of life.

Objectives

- ❑ Describe the management of other symptoms at the end of life: asthenia, anorexia, cachexia, dyspnea, nausea, vomiting, constipation, diarrhea, sleep disturbances, peripheral edema, skin breakdown
- ❑ Develop a preventive approach to managing patient and family expectations and needs
- ❑ Identify clinical problems whose management and diagnosis may merit further exploration

Symptom Management – General Comments

- ❑ Many physicians have developed perceptions of how painful a particular procedure should be, how much pain an illness causes or how distressing a given symptom should be for their patients. Since most physicians have not had these illnesses or undergone these procedures, these perceptions are often based on what their teachers and previous patients have told them. These

expectations of severity may be helpful in that, if pain or distress seems out of proportion to what would be expected, they may help physicians recognize that a new problem has arisen requiring treatment. On the other hand, these impressions of expected severity may not be accurate since we all have different tolerance levels for pain, dyspnea or fatigue etc.

- Objective measures of the severity of different symptoms do not always exist at the end of life. Three general rules exist:
 1. **Any given symptom is as distressing to an individual person as that person claims it to be and should not be simply dismissed as “whining” or “attention-seeking”.**
 2. **All treatments and their risks, benefits, alternatives need to be discussed and weighed in context of the dying person’s values, culture, beliefs, goals, expectations, and fears (see [End-of-Life Decision-Making](#) and [Culture](#) modules)**
 3. **When a person has advanced illness and is very near death, the exact causes of any given condition are not relevant. Investigations to determine these causes are often inappropriate and do not change outcome. In addition they are burdensome to the patient.**

- Anxiety, fatigue, emotional and psychological stress may worsen the person’s perception of the severity of his/her symptoms. Just because psychological factors can be identified as exacerbating pre-existing symptoms and problems, the person’s distress should not be ignored or brushed aside. Rather, sources of emotional or psychological stress should be explored and alleviated if possible. Exploring and alleviating sources of anxiety, fear and stress may not only help control the symptom in question but will also improve the person’s decision-making abilities, his/her quality of care and quality of life.

- Patients, their families and loved ones should be educated regarding the likely course of illness and possible complications and symptoms. Such knowledge helps decrease the natural fear and anxiety of the “unknown” and helps them plan for the future (see [End-of-Life Decision Making Module](#)).

- Such discussions of symptoms and the treatment plan should also help patients, families and physicians decide how symptoms will be alleviated or controlled – through non-pharmacological and pharmacological means. Discussions should take into account the side effects of any particular treatment in context of the patient’s values, culture and beliefs and how these side effects may affect the patient’s abilities to achieve their remaining life goals.

- Knowledge of expected symptoms can help patients, families and loved ones to identify symptoms and signs of potential complications or acute illness and help them know when to seek prompt medical attention.
- Research has shown that patients may be reluctant to discuss worsening of pain or new symptoms with their physicians fearing that it means they are imminently dying, or from the mistaken impression that distressing symptoms are to be expected and must be endured at the end of life. Many physicians and healthcare providers unfortunately are not aware that good palliative care can help relieve suffering as much as possible at the end of life.
- Education of the patient, family and healthcare team as well as discussions of the expected course of illness and expected symptoms may also serve to reduce the patient's fears over the significance of the symptoms and make it easier for them to discuss any worsening with their physicians. Knowledge that these symptoms do not have to be endured and can be alleviated may encourage them to seek attention and improve their remaining quality of life.
- Teamwork is crucial to alleviating distress and suffering due to physical symptoms. Both pharmacological and non-pharmacological means should be used. Other members of the multidisciplinary team can be very helpful in suggesting and optimizing pharmacological and non-pharmacological therapies therefore minimizing the risk of adverse events and drug interactions.
- If a symptom is present continuously, medication should be prescribed on a continuous or "around-the-clock" basis. Breakthrough doses are usually also required.
- A diary of symptoms, when they occur, what makes them better, what makes them worse, what side effects occur and when can be very helpful. Validated symptoms assessment scales (e.g. Edmonton Symptom Assessment Scale) are a useful way to systematically document and monitor a patient's symptom burden. If symptoms are not responding to treatment as expected or if uncertainty exists on how to proceed, consultation with a palliative care expert is recommended.
- Frequent reassessment is crucial since new symptoms may arise or existing ones may worsen. Changes in the patient's condition can occur rapidly, especially in the last hours of life, and patients, their families and loved ones should develop a plan with the multidisciplinary team to ensure these changes are responded to as quickly as possible and that distress and suffering are alleviated without delay.

Asthenia

- ❑ Fatigue or asthenia is the most distressing symptom in dying patients.
- ❑ Prevents them from achieving their remaining life goals, enjoying even simple activities, and interacting and strengthening relationships with loved ones.
- ❑ Asthenia may be experienced as easy tiring, generalized weakness or mental tiredness.
- ❑ Causes of asthenia are not completely clear but are likely multifactorial including: direct tumor effects on energy consumption and supply, humoral and hormonal influences, paraneoplastic syndromes, anemia, chronic infections, sleep disturbances, fluid and electrolyte disturbances, drugs and over-exertion.
- ❑ As with anorexia and cachexia may be seen as a sign of “failure” or “giving up” by dying person him/herself and by loved ones.
- ❑ Difficult to assess: some tools exist such as 1) Edmonton Functional Assessment Tool (EFAT) which also addresses broader issues of communication, pain, dyspnea, mobility, tiredness motivation, activities of daily living 2) fatigue self-report scale, 3) fatigue symptom checklist (See Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Text of Palliative Medicine*, 2nd ed., 1998, p. 577).
- ❑ Education of the dying person and his/her loved ones that asthenia is a frequent occurrence at the end of life may decrease unrealistic attempts at exertion and attempts to motivate the patient to achieve unrealistic goals.

Management of asthenia

Non Pharmacological Interventions

- ❑ Adapt activities of daily living to coincide with times of maximal energy
- ❑ Arrange for help from loved ones, home care, CCAC, hospice, nursing home
- ❑ Use energy conservation strategies in all activities
- ❑ Work with the dying person and family to decide what is important to them, what he/she enjoys doing and develop a plan to allow them to perform and enjoy as many of these activities as possible
- ❑ Rest during day and try to ensure effective sleep
- ❑ Consider changing medications or time of administration to decrease drowsiness side effects during the day
- ❑ Increasing nutrition may or may not be helpful (see section on anorexia and cachexia)
- ❑ Physiotherapists and occupational therapists may provide invaluable help with assessment, teaching, and assistive devices.

Pharmacological

- Asthenia is among the most difficult symptoms to treat

Steroids:

- Mechanism of action not clear – likely due to increases in euphoria, perhaps through inhibition of tumor mediated substances
- Benefit may decrease after 4-6 weeks
- Example dose: dexamethasone 2-4 mg po q am and q noon

Metamphetamines: Methylphenidate

- Act as psychostimulants and may be of benefit if asthenia is from side effect of opioid use
- Most experience is with methylphenidate – short acting, begin at 2.5 to 5 mg po q am and q noon and increase as needed. Typical dose is 10–30 mg po q am and q noon, but sometimes need more
- Extended-release formulations exist and once stable can switch to once-daily dosing.
- Methylphenidate is safe even in people with advanced illness
- Side effects: tremulousness, anorexia, tachycardia, myocardial ischemia and insomnia

Anorexia/ Cachexia

- Anorexia (loss of appetite) and cachexia (loss of weight) are frequently accompanied by generalized fatigue (asthenia).
- Very common in advanced illness. Anorexia in some studies is the second most common symptom after asthenia, more common even than pain.
- Wasting syndromes are often seen with malignancies, cardiorespiratory illnesses, renal and hepatic failure, and chronic infections, including Acquired Immune Deficiency Syndrome (AIDS).
- Causes are not well understood; however, many different mechanisms likely occur including the effects of hormonal and humoral mediators (e.g. Il-1, Il-6, TNF, leukemia inhibitory factor, D factor), host-tumor interactions, alterations in metabolism and greater energy expenditure from illness than supply.
- Loss of weight and appetite may be seen as a sign of “failure”, as “giving up” by the dying patient, his/her family and loved ones. Unfortunately, even if it is possible to increase appetite and nutrition, cachexia often does not improve. Nutrition will not stop the progression of disease.

- ❑ Dying people and their loved ones need to be educated that anorexia and cachexia is a common part of the dying process. We all know what it feels like to miss a meal, and have experienced the discomfort that accompanies hunger. Natural endorphins prevent the dying patient from experiencing hunger and education regarding this phenomenon may ease their loved ones' anxiety and concern. Anorexia and cachexia are signs of disease progression and are not generally reversible.
- ❑ If cachexia is caused by specific problems (i.e. secondary cachexia) such as nausea, vomiting, anxiety, pain, constipation or diarrhea, these should be treated as discussed in following sections.
- ❑ It is worth attempting to treat anorexia and cachexia in instances where treatment may increase the dying person's ability to eat for enjoyment of food, increase his or her sense of normalcy in activities of daily living, or increase his or her sense of well being.

Non-Pharmacological Interventions

- ❑ Encourage dying patient to try favorite foods
- ❑ Avoid gastric irritants like very spicy foods, milk, etc.
- ❑ Encourage small frequent meals rather than traditional three meals/day
- ❑ Avoid disagreeable or nauseating smells
- ❑ Nutritional supplements with high caloric beverages, etc.

Pharmacological interventions

Steroids

- ❑ Research has shown that steroids will improve sense of appetite and sense of well being
- ❑ Mechanism of action is not completely clear: may be related to euphoria effects and/or to their ability to inhibit prostaglandin metabolism
- ❑ Side effects: mood swings, sleep disturbance, hyperglycemia, edema, delirium, weakness, osteoporosis and cataracts (long term) and immunosuppression
- ❑ Dexamethasone is standardly used because once daily dosing can be used due to its long half-life and because it lacks mineralocorticoid effects. However, any steroid will have the same effects on appetite
- ❑ Consider:
 - dexamethasone in doses of 2–4 mg po q am and q noon

Progesterone Drugs (megestrol acetate)

- ❑ Mechanism of action is again not completely clear. It has been postulated that megestrol acetate works by inhibiting macrophage production of cachexin and TNF and by acting as an appetite stimulant

9

- ❑ Side effects include: nausea and edema, cushingoid appearance, hypercalcemia, and perhaps decreased survival
- ❑ Expensive
- ❑ The optimal dose is not clear and range that has been shown to be effective in studies of cancer patients and those with AIDS is 480-1600 mg/day
- ❑ A good starting dose is 200 mg po q 6–8 h and titrate up or down to maintain effect

Androgens

- ❑ Currently in the process of being studied e.g., oxandrolone, nandrolone
- ❑ Effectiveness not clear

Dyspnea

- ❑ Breathlessness, which can range from shortness of breath on exertion to frank air hunger when severe, can be one of the most frightening and distressing symptoms for patients, families, and health care providers.
- ❑ Respiratory symptoms are one of the most poorly understood areas of palliative medicine. The patient's experience may not correlate with any measurable value of function such as O₂ Sat or pO₂, respiratory rate, or, for that matter, professional and family members' perceptions.
- ❑ Prevalence is variable (12%–74%), depending on the diagnosis and the stage of the illness. In order to assess its importance to the dying person's quality of life, physicians should ask about exercise tolerance and whether the patient has ceased or limited activities they would have previously done or enjoyed.
- ❑ Dyspnea has a multidimensional nature. It can provoke significant anxiety that will exacerbate its severity. Furthermore, the perceptions and anxiety of family members and loved ones frequently may increase tension around the dying person resulting in increasing dyspnea. Therefore, to control and alleviate dyspnea, physicians must not only address the dying person's anxiety but also the families.
- ❑ Since the dying person's respiratory pattern may noticeably change as their illness progresses and especially in the last hours of living, his/her loved ones should be informed that these changes do not necessarily mean the patient is experiencing dyspnea. Open discussion with the dying person about his/her experiences should be encouraged since they may not only alleviate anxiety but will also strengthen his/her relationships with loved ones.

- ❑ Physicians can contribute to these discussions by explaining that drugs such as morphine and benzodiazepines may not change the altered respiratory pattern but will be used to remove any perception of dyspnea by the patient.
- ❑ If anemia is felt to be contributing to dyspnea, transfusions or erythropoietin (EPO) may be considered however, should not be used if they will simply prolong the dying process.

Causes of Dyspnea*

Pulmonary:

Pleural Effusions

Pneumonia

Pulmonary Embolism

Pneumothorax

Radiation pneumonitis

Phrenic nerve paralysis

Bronchospasm

Lymphangitic carcinomatosis

Bronchial obstruction

Tumor invasion of chest wall/diaphragm

Airway obstruction

Cardiac

Ischemia

CHF

Pericardial disease

SVC obstruction

Anemia

Muscle weakness (e.g. Myasthenia, ALS, Eaton Lambert, Malnutrition, Cachexia)

Intra abdominal process: ascites, subpulmonic process

Psychological: Anxiety, fear, fatigue

Non-pharmacological interventions

- ❑ Education about the causes of dyspnea, discussion of and planning to avoid exacerbating activities as well as normalizing effects of emotions on symptom severity may help the person achieve a sense of control over his/her breathlessness.
- ❑ Family, loved ones and other members of the multidisciplinary team can help minimize the sense of isolation that may occur when previously enjoyed activities become limited by symptoms. Exploring spiritual and religious issues may also decrease the sense of loneliness.

- Other practical aspects are to:
 1. Limit the number of people in the patient's room.
 2. Reduce the room temperature, and maintain humidity.
 3. Open a window and allow the dying person to see outside
 4. Use a fan to blow cool air across the dying person's face (may work)
 5. Eliminate environmental irritants such as smoke.
 6. Reposition the patient by elevating the head of the bed, or changing him from one side to another.

- Chest physiotherapy: may be helpful if helps increase sputum clearance however may be physically draining and painful for dying patients. Use is limited and depends on individual situation.

- Suctioning: never pleasant to undergo and may be very distressing to the dying person especially in the last hours of life. Anticholinergic drugs such as scopolamine and glycopyrrolate to decrease sputum production are kinder and gentler. Use of suctioning should be individualized.

- Relaxation, distraction, or hypnotic therapy may allow the dying person to control or decrease his/her dyspnea. Other alternative medical therapies may also help some patients.

- A combination of non-pharmacological and pharmacological therapies is usually needed.

Pharmacological Interventions

Oxygen

- If a patient is breathless, a therapeutic trial of supplemental oxygen may help even if pO₂ or O₂Sats do not indicate a need for oxygen therapy

- Home O₂ is expensive; however, it may be covered under existing provincial payment programs even if the patient does not meet the usual criteria of pO₂, O₂ Sat or exercise induced hypoxemia if the oxygen therapy is deemed palliative. There is usually a time limit for using home O₂ as a palliative intervention (3-6 months), so if the dying person qualifies for home O₂ using the standard criteria, these should be used in the application for financial coverage since the need to apply for renewals is eliminated.

Opioids

- The mechanisms by which opioids alleviate dyspnea are not entirely clear. It is thought that they work by

1. Decreasing ventilation by decreasing the sensitivity of CO₂ receptors in medulla
 2. Depressing the ventilatory response of rib cage muscles
 3. Acting as a venodilator
 4. Acting as a sedative
- ❑ Opioids do not decrease respiratory rate unless they are used inappropriately, e.g. very large doses of morphine are used or repeated large doses are given in a very short amount of time.
 - ❑ If titrated to alleviate dyspnea, opioids will not hasten death. If administering opioids may foreseeably hasten death but the sole intent of the person administering the drug is to palliate the patient, the principle of double effect can be used to justify their use.
 - ❑ If dyspnea is intermittent, opioids may be used intermittently. Treating dyspnea is different than treating pain since dyspnea will not necessarily be worse or more difficult to control if not prevented. Intermittent therapy may also have added benefit of decreasing side effects such as drowsiness.
 - ❑ In the opioid-naive patient, low doses of opioids may be all that is needed (e.g. morphine 5 mg po q 4h). When a person is controlled on a stable amount of opioid, convert into an extended release preparation and dose bid. Pharmacological tolerance usually does not occur if dyspnea progresses.
 - ❑ If a person is receiving regular opioid but is still experiencing intermittent dyspnea, breakthrough doses of short-acting opioid equivalent to 30%–50% of the amount of the opioid taken over 4 hours can be tried q 1 h, and increased as needed. If many breakthrough doses are required, consideration should be given to increasing the regularly administered doses.
 - ❑ Opioids can be administered q5-10 minutes IV or q 30 min SC for severe distress, to gain control of dyspnea and for acute, urgent situations.
 - ❑ When used appropriately opioids do not cause addiction and fears of addiction should not be used to justify failure to palliate a dying person.
 - ❑ As when using any drug, physicians need to be prepared to deal with side effects of opioids, especially constipation (see [Pain Management](#) module).
 - ❑ Nebulized morphine initially showed promise but recent studies have not supported its use. In fact it may increase or provoke bronchospasm due to its ability to cause histamine release.

Benzodiazepines/Anxiolytics

- Benzodiazepines decrease dyspnea by:
 1. Decreasing anxiety
 2. Depressing ventilation by decreasing thoracoabdominal muscle response peripherally and by decreasing central sensitivity to increasing pCO₂
- Since dyspnea is accompanied by anxiety and even in some cases by panic, benzodiazepines are used as first line therapy, often in combination with opioids
- Remember that tolerance to opioid-induced anxiolysis occurs so if anxiety is a problem, should add benzodiazepine.
- As with opioids, use low doses of benzodiazepines and increase as needed. Once stable, change to longer acting drugs to ensure ease of administration.
- Some sample doses include:
 - lorazepam, 0.5–2.0 mg po, SL, against the buccal mucosa, or IV q 1 h prn until settled, then dose routinely q 4–6 h to keep settled
 - diazepam, 5–10 mg po, IV q 1 h until settled, then dose routinely q 6–8 prn
 - clonazepam, 0.25–2.0 mg po q 12 h
 - midazolam, 0.5 mg IV q 15 min until settled, then by continuous SC or IV infusion (from EPEC Module 10)

Steroids

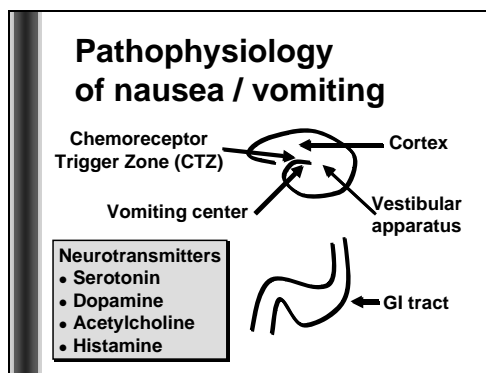
- Are not helpful in all causes of dyspnea
- Greatest benefit is in cases of bronchospasm, SVC obstruction, lymphangitic carcinomatosis and tracheal obstruction
- Adverse effects may be distressing: hyperglycemia, sleep disturbances, mood swings, fluid retention, candidiasis and myopathy

Hemoptysis

- Even more frightening to patients, families and loved ones than dyspnea is hemoptysis which can range from streaking of sputum to massive bleeding (>200cc/24hrs)
- Causes: tumor, bronchitis, pneumonia, pulmonary embolism, low platelets, coagulopathy
- Thankfully, hemoptysis is a rare cause of death
- If due to tumor palliation/treatment is usually:
 - radiation (external beam or endobronchial) or laser therapy
 - OR
 - may consider using tranexamic acid which has been effective in some cases
- If due to PE: discuss with patient and family whether anticoagulation with heparin/warfarin should be undertaken – in dying patients, burdens often exceed any benefits
- If massive hemoptysis: physician should be at the bedside and use frequent, rapid IV boluses of opioids and benzodiazepines to alleviate dyspnea and fear. Hide the blood from patient and family with dark towels.

Nausea/vomiting

- Nausea is a subjective sensation caused by stimulating either the gastrointestinal lining, the chemoreceptor trigger zone in the base of the fourth ventricle, the vestibular apparatus, or the cerebral cortex.
- Vomiting is a neuromuscular reflex centred in the medulla oblongata and is the final common pathway after stimulation of one or more of the areas listed above.
- Natural endorphins exert antiemetic effects. Chemotherapy and other drugs may cause nausea and vomiting not only through effects on serotonin, histamine receptors etc. but also by inhibiting these endorphins



From EPEC, Trainer's Guide, Common Physical Symptoms – Module 10, AMA/Robert Wood Johnson Foundation 1999. Used with permission

- Stimulation of nausea and vomiting is mediated through the neurotransmitters serotonin, dopamine, acetylcholine, and histamine. All four neurotransmitters can be demonstrated in the chemoreceptor trigger zone. Although all are present in the lining of the GI tract, serotonin is particularly important. Acetylcholine and histamine are important in the vestibular apparatus (from EPEC Mmodule 10).
- Nausea and vomiting can also originate in the cerebral cortex. No specific neurotransmitters have been identified and it is thought that a learned response may be more important here: e.g. explains why get nauseated at thought of any unpleasant activity.
- The following table from *EPEC Common Physical Symptoms – Module 10, AMA Robert Wood Johnson Foundation 1999* will discuss causes of nausea and vomiting (11 Ms of emesis) commonly encountered at the end of life and recommended treatment.

Management of Nausea/Vomiting		
Etiology	Pathophysiology	Therapy
Metastases Cerebral (increased ICP) Liver	increased ICP, direct CTZ effect toxin buildup	steroids, mannitol, anti-DA/Hist anti-DA/Hist
Meningeal irritation	increased ICP	Steroids
Movement	vestibular stimulation (may be worse with morphine)	anti-Ach
Mentation , e.g., anxiety	Cortical	anxiolytics, e.g., benzodiazepines, THC
Medications Opioids Chemotherapy Others (NSAIDs, see Mucosal Irritation)	CTZ, vestibular effect, GUT CTZ, GUT CTZ	anti-DA/Hist, anti-Ach, prokinetic agents, stimulant cathartics anti-5HT/DA, steroids anti-DA/Hist
Mucosal irritation NSAIDs Hyperacidity, gastroesophageal reflux	GUT, gastritis GUT, gastritis, duodenitis	cytoprotective agents antacids
Mechanical obstruction Intraluminal Extraluminal	Constipation, obstipation Tumor, fibrotic stricture	manage constipation reversible —surgery irreversible —manage fluids, ster- oids, inhibit secretions with octreotide, scopolamine
Motility Opioids, ileus, cancer cachexia, other medications	GUT, CNS	prokinetic agents, stimulant laxatives
Metabolic Hypercalcemia, hyponatremia, hepatic/renal failure	CTZ	anti-DA/Hist, rehydration, steroids
Microbes Local irritation, e.g., esophagitis, gastritis from <i>Candida</i> , <i>H pylori</i> , herpes, CMV Systemic sepsis	GUT CTZ	antibacterials, antivirals, antifungals, antacids anti-DA/Hist, antibacterials, antivi- rals, antifungals
Myocardial Ischemia, congestive heart failure	Vagal stimulation, cortical, CTZ	Oxygen, opioids, anti-DA/Hist, anxiolytics
Legend: anti-Ach = Acetylcholine antagonists anti-DA = Dopamine antagonists	anti-Hist = Histamine antagonists anti-5HT = Serotonin antagonists CTZ = Chemoreceptor trigger zone	GUT = Gastrointestinal tract ICP = Intracranial pressure THC = Tetrahydrocannabinol

- ❑ Opioids cause nausea in 28% of people when the dose is increased. The cause is thought to be due to gastroparesis. Trial of therapy with anti-dopaminergic agent followed by the addition of a prokinetic agent is indicated since tolerance to this side effect is minimal.

Non- Pharmacological Interventions

- ❑ Relaxation and cognitive therapy such as mental imagery can be used to control the cortical causes of nausea and vomiting and studies have shown that it can also be effective for patients receiving chemotherapy.
- ❑ TENS and acupuncture have also been used to control nausea and vomiting and can add to the effects of antiemetic drugs.

Pharmacological Interventions

Dopamine antagonists

- ❑ Dopamine-mediated nausea is the most common form of nausea and, therefore, antidopaminergic drugs should be used first when cause of nausea is not clear. The dose should be optimized in this situation before changing to or adding another drug.
- ❑ Different drugs in this class work at different areas: haldol works at the CTZ, metoclopramide and domperidone work at the gut by stimulating anticholinergic activity, increasing peristalsis and decreasing gastroparesis
- ❑ Side effects include: hypotension, drowsiness and extrapyramidal effects (incidence is low if use domperidone)
- ❑ Dose of metoclopramide must be reduced in renal failure (max. 5 mg IV/po q6h).
- ❑ Sample doses include:
 - haloperidol, 0.5–2.0 mg po, IV, SC q 6 h, then titrate
 - prochlorperazine, 10–20 mg po q 6 h or 25 mg pr q 12 h or 5–10 mg IV q 6 h
 - metoclopramide, 10–20 mg po q 6 h
 - domperidone 2.5–5 mg IV q 6 h
 - promethazine, 12.5–25 mg IV, 25 mg po/pr q 4–6 h
 - perphenazine, 2–8 mg po, IV q 6 h

Histamine antagonists (antihistamines)

- ❑ Histamine antagonists act on H1 receptors in the vomiting centre and on vestibular afferents. They also have anticholinergic effects.
- ❑ Side effects include: sedation and hypotension, dry mouth, blurred vision.
- ❑ Sample doses:
 - diphenhydramine, 25–50 mg po q 6 h (also have dopaminergic, phenothiazine, anticholinergic effects – watch sedation and dry mouth)
 - meclizine, 25–50 mg po q 6 h

- hydroxyzine, 25–50 mg po q 6 h

Acetylcholine antagonists (anticholinergics)

- Anticholinergics can be particularly useful if nausea and vomiting is triggered by acetylcholine receptors in the vestibular apparatus being activated.
- Use if nausea and vomiting is caused by partial or complete bowel obstruction since they decrease peristalsis, thereby reducing colic and GI secretions.
- Side effects: drowsiness, dry mouth, dry secretions, blurred vision, ileus, urinary retention.
- Sample doses:
 - Scopolamine, 0.1–0.4 mg SC, IV q 4 h
 - Hyoscine bromide 1–3 transdermal patches q 72 h or 10–80 ug/h by continuous IV or SC infusion
 - Glycopyrrolate 0.2 mg sc IV q4-6 hrs prn

Serotonin antagonists

- Serotonin has been particularly implicated in chemotherapy-associated nausea. 5HT₃ receptors are located in VC, CTZ and in the vagal nerves and enterochromaffin cells of gut wall.
- Very expensive so typically used in chemotherapy and radiation associated nausea or if other medications have failed. They can be useful for refractory nausea of diverse types but are typically tried only when other medications have failed.
- They are typically not effective in relieving chemotherapy-induced nausea beyond the first 48 hours after chemotherapy.
- Sample doses:
 - ondansetron, 8 mg po tid
 - granisetron, 1 mg po q d or bid (most specific serotonin receptor blocker, has the highest potency and longest duration of action – no statistically significant difference in effectiveness in clinical trials)
 - dolansetron 100 mg po/IV q 24 h (1.8 mg/kg)

Prokinetic agents

- Altered peristalsis can be an important cause of nausea and vomiting in advanced disease or may be seen as side effects or drugs used to palliate other symptoms such as opioids.
- Sample doses:
 - metoclopramide, 10–20 mg po q 6 h (adjust if in renal failure)
 - erythromycin 250-500 mg IV/po q6h

Antacids/ Cytoprotective agents

- ❑ Hyperacidity, gastroesophageal reflux and/or gastric or duodenal erosions, may also cause nausea and vomiting.
- ❑ Consider using an antacid, or H₂ receptor blockers or proton pump inhibitors such as ranitidine, famotidine, omeprazole.

Other medications

- ❑ Other medications do not have a mechanism of action that can be clearly defined. These include:
 - Steroids: Dexamethasone, 2–8 mg daily. Thought to have intrinsic antiemetic properties and may increase the effects of others drugs.
 - Cannabinoids: Tetrahydrocannabinol, 2.5–5 mg po tid. Marijuana may be more effective than synthetic analogues, use is often limited by psychomimetic effects, especially dysphoria, in elderly and low doses of phenothiazines can help.
 - Benzodiazepines: Lorazepam, 0.5–2 mg po q 4–6 h. These drugs do not have any antiemetic properties but may reduce anticipatory nausea.

Bowel Obstruction

- ❑ Nausea and vomiting caused by a partial or complete bowel obstruction is due to the accumulation of intraluminal fluid and ineffective/altered peristalsis causing colicky abdominal pain and bloating.
- ❑ Anticholinergic drugs such as scopolamine and glycopyrrolate can decrease secretion of fluid into the gut lumen and decrease peristalsis.
- ❑ Octreotide, a synthetic analog of somatostatin, will selectively inhibit secretion of fluids into the gut lumen and will improve symptoms in up to 85% of patients. Octreotide can be given by continuous IV at 10 ug/hr or intermittent subcutaneous injection.
- ❑ Sample doses: octreotide 100 ug q 8-12 h, titrate q 24 to 48 h to effect.

Constipation

- ❑ Constipation is discomfort associated with a reduced frequency of bowel movements and an increase in stool consistency (hard) that leads to difficulty in defecating.

Causes

Drugs: opioids*, phenothiazines, anticholinergic, antacids
(aluminum, calcium), Tricyclic antidepressants, diuretics

Metabolic, hypothyroid, hypokalemia, hypercalcemia

Diet: low fiber intake

Motility: decreased motility

Ileus: acute illness (Ogilvies), electrolyte abnormality, drugs

Mechanical obstruction: tumor, rectocele, hernia, adhesions,

Dehydration

Autonomic dysfunction: diabetes, renal failure, advanced cancer, drugs

Spinal cord compression

* See module on [Pain Management](#) for discussion of opioid related constipation

- ❑ Constipation will lead to pain, bloating, nausea and vomiting, overflow incontinence, tenesmus, fecal impaction, and bowel obstruction.
- ❑ Rectal exam is important to detect stool mass, fecal impaction (98% occurs in rectum), hypotonia from spinal cord invasion, tumor mass etc.
- ❑ In advanced illness, treatment of causes such as tumor mass or spinal cord invasion is not appropriate – need to tailor investigations and treatment to stage of illness

Management of constipation

Non-Pharmacological Interventions

- ❑ Scheduled toileting: same time each day, after meals.
- ❑ Position: try to get onto commode or at least sitting up.
- ❑ Encourage fluid intake if not in advanced stages of illness, last hours of life.
- ❑ Avoid bulk agents like bran since 1) normalize stool but not a good laxative, 2) need to use with a lot of water, 3) tastes bad, 4) in debilitated patients may precipitate obstruction by forming a viscous mass.

Pharmacological Interventions

- ❑ In order of usual preference for patients with advanced illness, poor mobility, and decreased oral intake:

Stimulant laxatives

- Stimulant laxatives irritate the bowel and increase peristaltic activity by stimulating myenteric plexus.
- Consider:
 - prune juice, 120–240 mL q d or bid
 - senna, 2 po q hs, titrate to effect (up to 9 or more per day)
 - bisacodyl, 5 mg po, pr q hs, titrate to effect

Osmotic laxatives

- Osmotic laxatives draw water into the bowel lumen. They undergo bacterial degradation in the colon that decreases intestinal pH, stimulates peristalsis and increases bulk by stimulating bacterial growth.
- Stool moisture is increased, as is the overall stool volume.
- Consider:
 - lactulose, 30 mL po q 4–6 h (sorbitol is cheaper alternative), then titrate
 - milk of magnesia (or other Mg salts), 1–2 tablespoons 1–3 times per day
 - magnesium citrate, 1-2 bottles prn

Detergent laxatives (stool softeners)

- Detergent laxatives facilitate the dissolution of fat in water and increase the water content of stool.
- Docusate also increases the secretion of water and sodium chloride in stool and may increase peristalsis
- Consider:
 - sodium docusate, 1–2 po q d–bid, titrate to effect
 - calcium docusate, 1–2 po q d–bid, titrate to effect
 - phosphosoda enema (Fleet) prn

Prokinetic agents

- Prokinetic agents stimulate the bowel's myenteric plexus and increase peristaltic activity and stool movement.
- Consider:
 - metoclopramide, 10–20 mg po/IV q 6 h (adjust for renal failure)
 - erythromycin 250-500 mg po/IV q6h

Lubricant stimulants

- Lubricant stimulants lubricate the stool and irritate the bowel, thus increasing peristaltic activity and stool movement.
- Use if impacted with hard feces to soften fecal mass. May need manual disimpaction or large volume enemas.
- Consider:
 - glycerin suppositories 1-2 pr OD
 - oils: mineral, peanut

Large-volume enemas

- Large-volume enemas soften stool by increasing its water content. They also distend the colon and induce peristalsis.
- Consider:
 - warm water
 - soap suds (irritates colon to induce peristalsis – may damage wall mucosa if use too often)

Diarrhea

- Diarrhea is the passage of frequent, loose stool, usually more than 3 unformed stool /24 hour period.
- Less common a problem than constipation.
- If persistent, diarrhea can lead to dehydration, malabsorption, fatigue, hemorrhoids, and perianal skin breakdown.
- If duration of diarrhea is greater than 3 weeks, it is defined as chronic.
- Most common cause at the end of life is overuse of laxatives followed by infection including overgrowth by Candida.
- Colonic sources produce watery diarrhea, small bowel sources cause pale, fatty steatorrhea.

Causes

Drugs: laxatives, antibiotics, antacids, Nsaids, iron, sorbitol, enteral

Infection

Enteral feeds

Partial bowel obstruction

Overflow Incontinence due to fecal impaction with overflow incontinence

Malabsorption: CA head of pancreas or after ileal resection > 100 cm ileal resection, colectomy, enterocolic fistula gastrectomy

Emotional, psychological stress

GI bleeding

Radiotherapy (abdomen or pelvis peak incidence 2nd-3rd week of therapy, resolves after therapy completed)

Tumor: rectal increase mucous production or WDHA (watery diarrhea hypokalemia achlorhedria), pancreatic islet tumor VIP, ZE syndrome, carcinoid

- Again investigations will depend on stage of illness. In advanced illness investigations are inappropriate
- Measure stool osmolality and electrolyte content and calculate anion gap: $I [osm - 2(Na + K)]$.
If gap > 50 mmol/l , diarrhea is osmotic

If < 50 mmol/l diarrhea is secretory diarrhea

- If diarrhea is due to ileal resection, a mixed secretory/osmotic picture will be seen and diarrhea will become secretory if fasted.
- If laxatives are to blame may be due to irregular or too high dosing. Usually resolves in 24-48 hours once stopped and should then restart at a lower dose.

Management of diarrhea

Non-Pharmacological Interventions

- Rehydration, electrolyte correction: encourage oral intake of clear fluids
- Avoid milk, gas-forming foods
- Hold laxatives
- Consider bulk agents such as bran but see comments above in section on constipation

Pharmacological Interventions

Adsorbent – kaolin, attapulgite

- Non-specifically adsorb dissolved or suspended substances like bacteria, toxins, water onto surface
- Consider:
 - attapulgite, 30 mL or 2 tabs prn

Mucosal prostaglandin inhibitors – ASA, mesalazine, bismuth

- Blocks prostaglandin mediated increases intestinal water and electrolyte secretions
- Bismuth salts have added benefit as antimicrobial against E coli
- Consider:
 - bismuth salts, 15–30 mL bid–qid

Opioids – codeine, morphine, diphenoxylate, loperamide

- Act by decreasing peristalsis in the colon; however, they preserve fasting peristalsis and increase anal sphincter tone
- Most important class of drugs used for diarrhea in palliative care
- If signs of infection, fever, blood avoid, C. Diff or Shigella do not use opioids; increase risk of toxic megacolon
- Consider:
 - loperamide, 2–4 mg po q 6 h, max. 16 mg/24 hrs
 - diphenoxylate 2.5-5 mg po q6h, max. 20 mg/day

Octreotide

- Inhibits secretion and peristalsis
- Works in cryptosporidial diarrhea, carcinoid, ZE, Verner Morrison, ileostomy or enterocolic fistulas
- Intermittent injections or continuous infusions sc:
 - 50 µg SC q 8–12 h, then titrate up to 500 µg q 8 h SC, or higher, or
 - 10–80 µg q 1 h by continuous SC, IV infusion

Specific Causes

Fat malabsorption: pancreatin (amylase, protease, lipase)

Small bowel resection: cholestyramine 4-12 g tid p 523

Radiation: cholestyramine 4-12 g tid or ASA

Carcinoid: cryoheptadine 12 mg/day to start or methysergide 400 mg tid

Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Text of Palliative Medicine*, 2nd ed., 1998, p. 523

Fluid balance/edema

- All dying people become hypoalbuminemic as their illness progresses and therefore become edematous. In malignancies, venous or lymphatic congestion may also play a role.
- When artificial hydration is used, edema will become worse.

Non-Pharmacological Interventions

- Limit fluid intake
- Increase intake of salty foods
- Elevate feet when sitting
- TEDS stockings to improve venous return
- Watch for skin breakdown since edema will cause stretch and ultimately increase skin fragility

Pharmacological Interventions

- Diuretics: start with furosemide 20 mg po/IV OD and increase as needed according to response. May need to start with a higher dose in presence of renal failure.
- Metolazone may be a useful adjunct to furosemide if difficult to diurese.

- Can also add spironolactone start at 25-50mg po OD or BID and increase according to response. Need to watch for potassium retention and should avoid in renal failure.

Skin

- Physicians are poorly taught in skin and wound care and often relegate this concern to their nursing colleagues.
- Skin breakdown is potentially a significant problem for dying people and may not only cause them significant pain but also can increase their isolation from family and loved ones since the odors that accompany ulceration and infection can cause loved ones or dying people to avoid interactions with each other.
- The management of skin care is preventive.
- Physicians, nurses, occupational therapists, family members and loved ones should all work as a team to prevent skin problems.

Other practical aspects:

- Keep skin clean and dry – consider using foley catheters
- Avoid iodine containing cleaning solutions since damages epithelium, use normal saline to clean
- Protect pressure points with hydrocolloid dressings
- Avoid shearing the skin by using draw sheets to move/turn the dying person
- While foam donuts should be avoided, foam pads (at least 2-3 cm between patient and bed) can be used to decrease pressure
- Consider special mattresses – air or air flotation beds
- Use absorbing dressings if exudative wounds

Dressings

- Three general types exist:
 1. Alginates: for exudative, bleeding wounds,
 2. Hydrogels: for low exudate wounds, leg ulcers, and necrotic wounds
 3. Hydrocolloid: for pressure areas, exudates, leg ulcers

Pressure Ulcers

- Severity graded according to stage:
 - Stage I: precursor phase – redness, blanches with pressure: microcirculation is intact
 - Stage II: redness fails to blanch, excoriation, vesiculation or epidermal breakdown
 - Stage III: full thickness skin loss but not extending into subcutaneous tissue with serosanguinous drainage

Stage IV: ulcer extends into subcutaneous fat and deep fascia with destruction of muscle +/- osteomyelitis

- Risk factors include: CHF, atrial fibrillation, peripheral vascular disease, anemia, myocardial ischemia, malnutrition, altered level of consciousness and hypoalbuminemia
- Mechanism: pressure and shearing forces secondary to gravity, irritation by sweat, urine, feces, perspiration, wound or fistula drainage
- Local Treatment:
 - Grades I and II: use polyurethane film
 - Grade III: hydrocolloid or calcium alginate
 - Grade IV: hydrocolloid, hydrogel (to rehydrate and remove eschar) and enzymatic (to loosen necrotic tissue, pus and exudates) or polysaccharide dantromers (to absorb exudate and treat infection)

Odors

- Usually result of infection and poor hygiene
- Treat superficial infections with topical metronidazole (cream, sprinkle capsules, or spray solution) or silver sulfadiazine bid or tid
- If infection has spread to soft tissues consider systemic metronidazole
- Non-pharmacological control of odors can be achieved with:
 - Opening the windows, doors to the room
 - Opening kitty litter or activated charcoal in a pan under the bed
 - Burning candles
 - Opening a cup of vinegar in the room

Sleep Disturbances

- Anxiety, grief due to impending loss of relationships with loved ones, pain and uncontrolled symptoms and fears of the future can lead to inability to sleep.
- Emotional and psychological support from physicians and healthcare team may help but may not be sufficient.
- May exacerbate asthenia and may prevent achievement of symptom control.
- Take a sleep history: Do they have problems falling asleep? Do they wake up in the middle of the night? etc. to help guide therapy.

Non-Pharmacological

- Regular schedule – regular bedtime, avoid sleeping all day. Naps are OK
- Control symptoms
- Avoid mental stimulation and distress at night
- Increase physical activity during the day
- Relaxation therapy, soothing music, mental imagery
- Avoid caffeine, alcohol, steroids, metamphetamines at night

- Have extra covers available in case of cold

Pharmacological

- Antihistamines: tolerance is rapid, anticholinergic side effects common e.g. diphenhydramine 25 mg po/IV qhs PRN as a starting dose
- Benzodiazepines may worsen delirium in elderly e.g. lorazepam 0.5-1mg po/sl/IV/sc qhs PRN as a starting dose
- Tricyclic antidepressants or sedating ones e.g. trazadone 50 mg po qhs PRN as a starting dose
- Neuroleptics: good if “sundowning” a problem e.g. Haloperidol 0.5-1 mg po/IV qhs PRN or methotrimeprazine maleate (Nozinan) 5-10 mg po qhs PRN as a starting dose

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Detailed Case Scenario

Mrs. Linda Parsons is a 40-year-old accountant, married without children. She has just moved to the area and has been so busy that she has not had time to find a family physician. She has been previously healthy and is not on any medication. She presents to the emergency room with fever, cough productive of prurulent sputum and dyspnea. Her O₂ sats of 87% indicate that she needs O₂ and she admits to feeling better after being started on 2 L. Initial chest exam reveals bronchial breath sounds in the left base. She reluctantly agrees to be admitted to the hospital and is started on ceftriaxone and azithromycin. A CXR is done on her way to the ward.

The CXR shows an infiltrate in the left base and a 5 cm mass in the right upper lobe with bilateral hilar adenopathy. Further questioning reveals that she is a life long non-smoker and has never been exposed to TB. She has had a 15-pound weight loss but attributed it to moving, lifting boxes and stress, in addition to the fact that she had been trying to lose weight. She has a strong family history of breast cancer, her mother and aunt having developed it in their 30's and 40's. While she did receive mammography and yearly breast exams, she decided that mammography was too painful to undergo in view of the fact that recent studies show that mammograms do not detect tumors any sooner. She was quite diligent in having breast exams done but had received a major promotion at work two years ago and has been too busy to go.

On breast exam you detect a 3 cm hard mass in the right breast and there is axillary adenopathy. A CT scan shows an inoperable right upper lobe mass encasing the pulmonary artery and invading pericardium and a nodule in right breast along with some liver metastasis. A breast biopsy confirms poorly differentiated adenocarcinoma. You tell her that she has inoperable metastatic breast cancer and that you need to get radiation and medical oncologists involved. She is upset but says she guessed this is what she would turn out to have as soon as she heard about the CXR.

You offer to tell her husband but she says she will do this alone. Just before going to see her two days from this meeting, you overhear her telling her husband that the doctors don't know why she is still so short of breath and that it was likely just residual effects from the pneumonia. After the husband leaves you ask her why she has not told him and she says she just can't. She again refuses your offer to help. You ask her why she did not tell you that she was still short of breath to which she replies she did not want to be a bother. She says, "I figure you can't do anything about it anyway, can you? Besides I don't want to be a drug addict."

A few days later, when her dose of morphine is increased she becomes nauseated and starts vomiting. She looks and feels miserable. She manages to smile when she sees you and says: "It's not a good day today doctor, I have been sick ... please help me."

Eventually she is discharged home. She had told her husband the diagnosis and both of them worked with you to develop a treatment plan. She is doing quite well and her dyspnea is controlled. In a follow up visit four weeks later, you ask her how she feels and she says: “Surprisingly well ... except I am so tired all the time and I can’t seem to stop losing weight no matter how well my husband cooks.”

Teaching Tips

1. Distribute the case scenario. Allow participants a couple of minutes to read the information or ask one of the participants to read the scenario.
2. Ask what learning issues there are for participants. Have them written on the flipchart.
3. A number of issues should be identified including
 - ❑ Communication of bad news
 - ❑ Management of emotional response/expression of empathy
 - ❑ Influence of emotional response to bad news on treatment
 - ❑ Confidentiality
 - ❑ Etiology and management of dyspnea
 - ❑ Etiology and management of nausea and vomiting
 - ❑ Etiology and management of asthenia
 - ❑ Etiology and management of anorexia/cachexia
 - ❑ The husbands perception of illness, anorexia, support needs
 - ❑ Support needed in home
 - ❑ Role of chemo and radiation therapy
 - ❑ End-of-life decision-making

TIP: An effective teaching intervention is to ask participants to write out a management plan and record these on a flipchart. Ask them to explain reasoning behind their decisions

4. Review the learning issues that have not been dealt with and assign tasks.