

EPEEC-O

Education in Palliative and End-of-life Care - Oncology

Participant's Handbook

Module 3p:

Symptoms –

Nausea/

Vomiting

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EPEC-O: Education in Palliative and End-of-life Care for Oncology.
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ISBN: 0-9714180-9-8

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The EPEC Project™ was created with the support of the American Medical Association and the Robert Wood Johnson Foundation. The EPEC-O curriculum is produced by The EPEC Project™ with major funding provided by the National Cancer Institute, with supplemental funding provided by the Lance Armstrong Foundation. The American Society of Clinical Oncology partners with the EPEC-O Project in dissemination of the EPEC-O Curriculum. Acknowledgment and appreciation are extended to Northwestern University's Feinberg School of Medicine, which houses The EPEC Project.

Special thanks to the EPEC-O Team, the EPEC-O Expert Panel, and all other contributors.

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Case*

P.T. is a 92-year-old farmer with colon cancer metastatic to the liver. Right upper quadrant pain is well controlled with extended-release morphine, 60 mg PO bid, and dexamethasone, 4 mg PO q AM. However, he complains of constant nausea that limits his ability to eat.

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

Introduction

Nausea is *an unpleasant subjective sensation of being about to vomit*.^{1,2} Vomiting is the *reflex expulsion of gastric contents through the mouth*. Nausea may be present without vomiting or vice versa. The awareness of nausea, the inability to keep food or fluids down, the associated acid and bitter tastes, and the unpleasant smells associated with vomitus can be very distressing for patients, families, and caregivers.

There are many potential causes for both nausea/vomiting (see Table 2) in a patient with cancer. Chemotherapy-associated nausea is only one of them. In this section, the management of all nausea is discussed. For a more extensive discussion of chemotherapy-associated nausea and vomiting, refer to the ASCO symptom Control Curriculum.³

Incidence/prevalence

The incidence of chemotherapy-induced acute nausea is related to the drug. Most writers have divided chemotherapeutic agents into 5 emetogenic categories based on the incidence of acute nausea (see Table 1).

Table 1: Emetogenic classes

Emetogenic class	Medications	Incidence of acute nausea
I	Capecitabine, Rituximab	Minimal (< 10 %)
II	Gemcitabine, Paclitaxel	Low (10-30%)
III	Doxorubicin, Carboplatin	Mild (30-60%)
IV		Moderate (80-90%)
V	Cisplatin, high dose cyclophosphamide	High (> 90%)

The incidence of radiation-associated nausea is related to the radiated region. While there is minimal nausea associated with peripheral sites, if a substantial portion of the GI tract is in the radiation field, nausea may occur in nearly all patients.

The prevalence of nausea in patients with advanced cancer not associated with chemotherapy or radiotherapy ranges from 40-70%.¹

Opioids have been associated with acute nausea in up to 30% of patients, particularly young women.

Prognosis

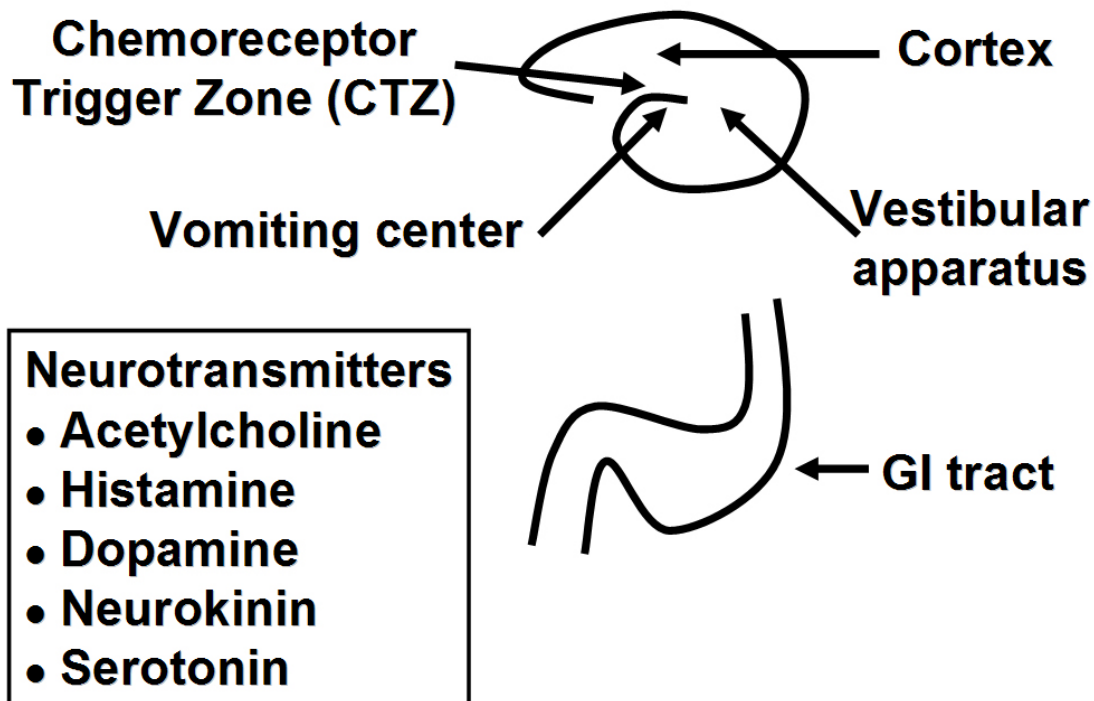
If acute treatment-related nausea/vomiting is not prevented and controlled, treatment is delayed or stopped prematurely. If chronic nausea is not controlled, nutritional status, emotional coping, and ability to function are impaired.

Overall, uncontrolled symptoms are associated with a worse prognosis. When symptom severity is combined with measures of functional status, the resulting measure is more accurate than functional status alone.

Pathophysiology

Two organ systems are particularly important in nausea/vomiting: the brain and the GI tract. These are shown schematically in Figure 1.

Figure 1: Pathophysiology of nausea/vomiting



The motor function of the gut is controlled at three levels: the parasympathetic and sympathetic nervous systems, enteric brain neurons, and smooth muscle cells. The gastric lining, the chemoreceptor trigger zone in the floor of the fourth ventricle, the vestibular apparatus, and the cortex are all involved in the intricate physiology of nausea. The neuromuscular reflex that constitutes the final common pathway after stimulation from one or more of these areas emanates from the vomiting center.⁴

Stimulation is mediated through the neurotransmitters serotonin, dopamine, acetylcholine, and histamine. All 4 neurotransmitters can be demonstrated in the chemoreceptor trigger zone. Although all are present in the lining of the gastrointestinal tract, serotonin is particularly important. Acetylcholine and histamine are important in the vestibular apparatus.

Nausea/vomiting that is mediated by the cortex is more complex and is not associated with specific neurotransmitters. Cortical responses seem to be learned responses, eg, the anticipatory nausea associated with chemotherapy, nausea related to anxiety, etc.

Table 2 relates pathophysiology to the underlying etiology.

Assessment

A thorough assessment of nausea and vomiting is crucial to understanding which of the potential etiologies is present, what the likely pathophysiology is, and what would be most appropriate to prescribe. Different causes will require very different interventions if the symptoms are to be controlled effectively.

Ask the patient to describe the nausea:

- When does it occur?
- Is it acute or chronic?
- Intermittent or constant?
- Associated with sights or smells or events?
- What happens after eating?
- Does the patient vomit right after the food is swallowed (a cortical learned response or anxiety-related) or after about 45 minutes (associated with delayed gastric emptying or a 'squashed stomach' syndrome from an enlarged liver) or hours after eating (suggesting intestinal or bowel involvement)?
- Does vomiting make it better?
- Does the patient only get nauseated for a moment immediately before vomiting? This suggests hyperperistalsis trying to overcome a mechanical obstruction in the intestine.
- What are the patient's bowel patterns? Constipation is a frequently missed cause of chronic nausea.

- What medications have been tried? With what frequency?

The physical examination and selected studies help confirm impressions from the history. For example, changing posture or head position may reproduce or worsen nausea, implicating the vestibular apparatus. Funduscopic examination may confirm increased intracranial pressure. Abdominal examination that shows the absence of bowel sounds suggests obstruction. An enlarged liver crossing the midline or presence of ascites or stool in the rectal vault increase the likelihood that diminished peristalsis plays a role.

There are a range of diagnostic studies that can be judiciously deployed. A plain radiograph of the abdomen looking for presence and quantity of stool, and evidence of ileus is frequently useful. Abdominal ultrasound (for enlarged liver or ascites assessment), computed tomography scans of the head or abdomen, and motility studies may be useful in selected cases.

Management

This module focuses on the general symptomatic management of nausea/vomiting. It does not provide detail of all the possible causes or specific treatments to reverse each of these etiologies.

In the management of nausea/vomiting, it is frequently not possible to identify or specifically correct the underlying etiology. Time-limited therapeutic trials may provide both relief and clues to underlying causes. When causes are known, the burden of the disease-modifying intervention may also outweigh its potential benefit.

Table 2 relates major causes of nausea/vomiting to their principal site of action and lists the “11 M’s” of emesis. This clarification is intended to set the stage for the rational use of the antiemetics, which can be classified by their principal site of action.

Correction of dehydration, hypokalemia, and metabolic alkalosis will sometimes resolve the symptom.

Few high-quality therapeutic trials have compared the efficacy of different drugs in specified types of nausea/vomiting outside of chemotherapy. There are five classes of antiemetic drugs: antidopaminergic drugs, antiserotonergic drugs, antihistamines, anticholinergics, and neurokinins. In addition, there are a group of adjunctive drugs that, while not directly antiemetics, treat specific causes of nausea such as hyperacidity or gut dysmotility or whose mechanism of action is poorly understood.

Empiric therapy with antiemetics usually begins with a single medication targeting the presumed mechanism of nausea/vomiting. The dose should be optimized before a second medication with a different mechanism of action is added. If the first medication is rationally chosen, addition rather than substitution of a second may be wise. Sequential combination therapy may be required in some patients.

**Table 2: Management of nausea/vomiting based on etiology
(the 11 M's of emesis)**

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, steroids, inhibit secretions with octreotide, scopolamine
Motility Opioids, ileus, 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, antivirals, 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

Chemotherapy-associated nausea/vomiting

Three distinct types of chemotherapy-associated nausea/vomiting have been defined: acute, delayed, and anticipatory.⁴

Acute nausea/vomiting occurs within the first 24 hours after chemotherapy. It usually starts within 1-2 hours and peaks at 4-6 hours. Several groups have classified the emetogenic potential of chemotherapy programs in 5 categories and have identified effective oral antiemetic therapy to read (see Table 3).^{4,5}

Delayed nausea/vomiting occurs more than 24 hours after chemotherapy. With cisplatin, this peaks 48-72 hours after therapy, then gradually subsides for 2-3 days. It is also seen with carboplatin, cyclophosphamide, and the anthracyclines. The antiserotonergic and antidopaminergic medications have minimal effect on delayed nausea. The antineurokinin class is the first to show definitive, albeit small, effect on this syndrome.

Anticipatory nausea/vomiting is a conditioned response to previous experiences. If acute and delayed nausea are prevented, anticipatory nausea does not occur. Once it occurs, it is a learned response—it is not mediated by the usual emetic neurotransmitters.

Management is challenging. It is better prevented. Once established, benzodiazepines for their anxiolytic and amnesic properties are most useful. Psychotherapy with a focus on cognitive/behavioral interventions may be adjunctive.

Table 3: Antiemetic regimens based on emetogenic potential of chemotherapy

Emetogenic class	Medications	Incidence of acute nausea	Regimen to prevent acute chemotherapy-associated nausea
I	Capecitabine, Rituximab	Minimal (<10%)	PRN antidopaminergic
II	Gemcitabine, Paclitaxel	Low (10-30%)	Dexamethasone 20 mg orally once
III	Doxorubicin, Carboplatin	Mild (30-60%)	5 FT-3 inhibitor + Dexamethasone 20 mg orally once
IV		Moderate (80-90%)	5 HT-3 inhibitor + Dexamethasone 20 mg orally once
V	Cisplatin, high dose cyclophosphamide	High (> 90%)	5 HT-3 inhibitor + Dexamethasone 20 mg orally once + Aprepitant (NK1 inhibitor)

Opioid-induced nausea/vomiting

Opioids have been associated with acute nausea in up to 30% of patients, particularly young women. This is thought to be due to direct effects in the chemoreceptor trigger zone and the vestibular apparatus. Antidopaminergics, eg, prochlorperazine, can be given as a premedication in patients at high risk. Antihistamines, anticholinergic and antiserotonergic drugs have all been observed to be effective.⁶ Fortunately, patients generally develop pharmacological tolerance to this side effect within 5-7 days of initiating therapy, and the antiemetics can be discontinued. For some patients, changing to a different opioid is also effective.

Nausea that emerges after chronic use is most likely mediated through diminished gut motility and/or constipation causing pseudoobstruction. Management is best directed at increasing gut motility and relieving constipation.

Dopamine antagonists

Dopamine-mediated nausea is probably the most common form of nausea, and the most frequently targeted for initial symptom management outside of the chemotherapy setting, even when the precise mechanism of nausea is not known. These medications are phenothiazines or butyrophenone neuroleptics and have the potential to cause drowsiness and extrapyramidal symptoms, particularly in young women. Haloperidol is less sedating. Medication dosing options include:

- Droperidol, 2.5–5 mg IV q 6 h
- Haloperidol, 0.5–2.0 mg PO, IV, SC q 6 h, then titrate
- Metoclopramide, 10–20 mg PO q 6 h
- Olanzapine, 5 – 10 mg PO daily
- Perphenazine, 2–8 mg PO, IV q 6 h
- Prochlorperazine, 10–20 mg PO q 6 h or 25 mg pr q 12 h or 5–10 mg IV q 6 h
- Promethazine, 12.5–25 mg IV, 25 mg PO/pr q 4–6 h
- Thiethylperazine, 10–20 mg PO q 6 h
- Trimethobenzamide, 250 mg PO q 6–8 h, 200 mg pr q 6–8 h

Histamine antagonists (antihistamines)

All antihistamines typically used to control nausea may also cause sedation.⁷ In some patients, this adverse effect may be an added benefit. Because the antihistamines also have anticholinergic properties, they may do ‘double duty’ as a single agent and cover both mechanisms. Consider using:

- Diphenhydramine, 25–50 mg PO q 6 h

- Hydroxyzine, 25–50 mg PO q 6 h
- Meclizine, 25–50 mg PO q 6 h

Acetylcholine antagonists (anticholinergics)

If a motion-related component is elicited, the vestibular apparatus is implicated. In addition, opioids and anesthetics can trigger acetylcholine-mediated nausea in the vestibular apparatus.⁶ A medication from this class may be added to other antiemetics in empiric therapy. Consider:⁸

- Scopolamine, 0.1–0.4 mg SC, IV q 4 h or
1–3 transdermal patches q 72 h or
10–80 µg/h by continuous IV or SC infusion

Serotonin antagonists

Serotonin (hydroxytryptophan) subtype 3 (commonly abbreviate HT-3) has been particularly implicated in chemotherapy-associated nausea. This class of medications can be exceedingly effective if serotonin is a mediator, but they are very expensive. For each drug, there is a plateau in therapeutic efficacy; titration beyond gives no improvement in outcome. Outside the setting of prophylaxis before chemotherapy and before radiotherapy to the abdomen (which stimulates serotonin release from the gut lining) and postoperative nausea, they can be useful for refractory nausea of diverse types, but are typically tried only when other medications have failed.⁹ They should be promptly stopped if they are not effective after a short trial. Medication and dosing options include:

- Dolasetron, 200 mg PO or 50 mg IV
- Granisetron, 1 mg PO daily or bid
- Ondansetron, 8 mg PO tid
- Palonosetron, 0.25 mg IV

Neurokinin antagonists

The newest class of antiemetics, neurokinin-1 receptor antagonists, is used in combination with a serotonin inhibitor and dexamethasone for highly emetogenic chemotherapy with significant potential for delayed nausea and vomiting. A dosing option is:

- Aprepitant, 125 mg PO day 1 followed by 80 mg days 2 and 3

Prokinetic agents

A ‘sluggish’ or dyskinetic gut, due to carcinomatosis, opioid therapy, other medications, etc, may be a profound source of nausea/vomiting in patients with advanced disease.^{10,11} A large liver may be causing a ‘squashed stomach.’ Ascites or peritoneal disease may be

causing pseudo-obstruction. Constipation can be an exacerbating factor. Medication and dosing options include:

- Domperidone, 10-20 mg PO q 6 h (AC & HS)
- Erythromycin, 250 mg PO q 6 h (AC & HS)
- Metoclopramide, 10–20 mg PO or IV q 6 h (AC & HS)

Antacids

Hyperacidity, with or without gastroesophageal reflux and/or gastric or duodenal erosions, may produce considerable nausea, heartburn, acidity, or bitter taste. It may also be associated with vomiting. Possible therapies include:

- Antacids, 1–2 tablespoons PO q 2 h PRN
- H₂ receptor antagonists, eg, cimetidine 800 mg PO q HS, famotidine 40 mg PO q HS, ranitidine 150 mg PO q HS
- Proton pump inhibitors, eg, omeprazole 20 mg PO daily, lansoprazole 30 mg PO daily, pantoprazole 40 mg PO daily

Other medications

This heterogeneous class of medications has unclear mechanisms of action, but uncontested benefits in some patients.^{12,13,14} Consider:

- Dexamethasone, 6–20 mg PO daily
- Lorazepam, 0.5–2 mg PO, Buccal, SC q 4–6 h
- Tetrahydrocannabinol, 2.5–5 mg PO tid

Bowel obstruction

The nausea associated with bowel obstruction is associated with reverse peristalsis in response to accumulated fluid behind the obstruction. This is discussed in detail in EPEC-O Module 3e: Symptoms - Bowel Obstruction.

Summary

Acute and chronic nausea are associated with misery and poor quality of life, and can impair comprehensive cancer care. Management requires: a solid knowledge of the pathophysiology, including neurotransmitters, a careful evaluation to target likely etiologies, and skillful administration of medications, frequently in combination and titrated to effect.

Key take-home points

1. Nausea is better prevented than treated once it emerges.
2. Untreated nausea may become ‘learned’ and refractory to neurotransmitter-based antiemetics therapy.
3. Control of chemotherapy and radiotherapy associated nausea is as important to cancer therapy as the antineoplastic strategies.
4. Control of chronic nausea that is not associated with antineoplastic strategies is associated both with improved quality of life as well as longevity.

Pearls

1. Use antiemetic agents for their neurotransmitter blocking functions; combine them strategically.
2. Titrate drugs to effect or side effects before adding additional agents.
3. It is better to prevent than treat nausea; err on the side of aggressive overtreatment, initially, then reduce intensity of therapy to maintain control rather than slowly increase therapy while patient remains nauseated.
4. When treating nausea empirically without a firm sense of underlying pathophysiology, cover all of the possible mechanisms.

Pitfalls

1. Changing drugs within a single class. This is a mistake. Add drugs with different mechanisms of action.
2. Using small doses of many drugs because you are unsure. Check your reference source and rationalize your treatment.
3. Serial treatment with single agents. Use a rational, additive approach resulting in patient-tailored regimen.

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Several pharmacologic agents provide antihistamine effects by acting at the H1 histamine receptor site. The classic agents are relatively nonselective, resulting in a wide range of effects, both therapeutic and undesirable. The newer agents preferentially block peripheral H1 receptor sites and, consequently, have fewer side effects, including sedation.

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Controlled trials have indicated that a single transdermal hyoscine (scopolamine) patch is significantly superior to placebo and oral meclizine in preventing motion sickness. Most commonly cited adverse effects have been dry mouth, drowsiness and impairment of ocular accommodation, including blurred vision and mydriasis. Adverse central nervous system (CNS) effects, difficulty in urinating, rashes and erythema have been reported only occasionally.

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