# **Evaluation of Nausea and Vomiting**

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A comprehensive history and physical examination can often reveal the cause of nausea and vomiting, making further evaluation unnecessary. Acute symptoms generally are the result of infectious, inflammatory, or iatrogenic causes. Most infections are self-limiting and require minimal intervention; iatrogenic causes can be resolved by removing the offending agent. Chronic symptoms are usually a pathologic response to any of a variety of conditions. Gastrointes-tinal etiologies include obstruction, functional disorders, and organic diseases. Central nervous system etiologies are

primarily related to conditions that increase intracranial pressure, and typically cause other neurologic signs. Pregnancy is the most common endocrinologic cause of nausea and must be considered in any woman of childbearing age. Numerous metabolic abnormalities and psychiatric diagnoses also may cause nausea and vomiting. Evaluation should first focus on detecting any emergencies or complications that require hospitalization. Attention should then turn to identifying the underlying cause and providing specific therapies. When the cause cannot be determined, empiric therapy with an antiemetic is appropriate. Initial diagnostic testing should generally be limited to basic laboratory tests and plain radiography. Further testing, such as upper endoscopy or computed tomography of the abdomen, should be determined by clinical suspicion based on a complete history and physical examination. (Am Fam Physician 2007;76:76-84. Copyright © 2007 American Academy of Family Physicians.)

> ausea is the unpleasant, painless sensation that one may potentially vomit. Vomiting is an organized, autonomic response that ultimately results in the forceful expulsion of gastric contents through the mouth. Vomiting is intended to protect a person from harmful ingested substances. However, chronic nausea and vomiting are typically a pathologic response to any of a variety of conditions.<sup>1</sup>

> Nausea and vomiting significantly affect quality of life. In a study of 17 gastrointestinal conditions in the United States, it was estimated that the cost of acute gastrointestinal infections exceeds \$3.4 billion annually.<sup>2,3</sup> When other causes of nausea and vomiting are taken into account, the associated medical costs and loss of worker productivity are considerable.

> This article reviews common and significant causes of nausea and vomiting, offers an approach to evaluation, and provides a brief overview of treatment options.

# Causes

The etiologies of nausea and vomiting include iatrogenic, toxic, or infectious causes; gastrointestinal disorders; and central nervous system or psychiatric conditions. A differential diagnosis for nausea and vomiting is provided in *Table 1*,<sup>2,4-10</sup> and each category is discussed in the following.

## IATROGENIC, TOXIC, AND INFECTIOUS

Almost any medication can cause nausea and vomiting. Chemotherapeutic agents are the most well-known; however, many commonly prescribed medications can cause these symptoms. Medications typically cause nausea and vomiting early in their course, although the onset of symptoms may be insidious. Overdoses of alcohol, illicit substances, and other toxins may also cause acute symptoms.<sup>6,7,9</sup>

Infectious etiologies typically result in an acute onset of symptoms. Viral gastroenteritis is particularly common; however, bacteria or their toxins may also be the cause. Infectious and toxic causes of nausea and

Clinical Recommendation	Evidence Rating	References
Most causes of acute nausea and vomiting can be determined from the history and physical examination.	С	2
Initial evaluation should focus on signs or symptoms that indicate urgent treatment, surgical intervention, or hospitalization.	С	2
Diagnostic testing for nausea and vomiting should be targeted at finding the etiology suggested by a thorough history and physical examination.	С	15, 17-19
Fluid imbalances, electrolyte abnormalities, and nutritional deficiencies should be corrected.	С	2
Treatment should be directed at the underlying etiology of the nausea and vomiting. If no etiology is found, the patient should be treated symptomatically with antiemetic and prokinetic therapy, and other etiologies of chronic unexplained nausea and vomiting (e.g., psychogenic, bulimic, rumination, functional) should be considered.		20-23

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vomiting are usually self-limiting. Nausea and vomiting caused by ingestion of a toxin such as the enterotoxin in staphylococcal food poisoning or the toxin produced by *Bacillus cereus* typically occur one to six hours after ingestion and last only 24 to 48 hours.

# GASTROINTESTINAL DISORDERS

Many gastrointestinal disorders cause nausea and vomiting. Acute symptoms are typically the result of an inflammatory process (e.g., appendicitis, cholecystitis, pancreatitis). Obstructions may result in acute or chronic symptoms. Gastric outlet obstructions tend to cause intermittent symptoms, whereas intestinal obstructions typically cause acute symptoms and severe pain.

Motility disorders such as gastroparesis typically produce an insidious onset of symptoms resulting from an inability to move food through the gastrointestinal tract. Patients with disorders such as dyspepsia, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), or irritable bowel syndrome (IBS) may have nausea and vomiting, but these are rarely the primary symptoms.

# CENTRAL NERVOUS SYSTEM AND PSYCHIATRIC CONDITIONS

Any condition that increases intracranial pressure (e.g., mass, infarct, infection) can result in vomiting with or without nausea. Patients with central nervous system pathology usually present with additional neurologic signs such as cranial nerve dysfunction or long-tract signs. Conditions that affect the labyrinthus (e.g., infections, Ménière's disease, tumors) may cause nausea and vomiting and are often associated with vertigo. Migraine headaches classically cause nausea and vomiting.

Patients may also experience symptoms in response to emotional or physical stressors. Psychiatric diagnoses such as anorexia nervosa, bulimia nervosa, depression, and anxiety should be considered.

## OTHER CONDITIONS

Pregnancy is the most common endocrinologic cause of nausea and vomiting and must be considered in any woman of childbearing age. Metabolic etiologies such as acidosis, uremia, hyperthyroidism, adrenal disorders, and parathyroid disorders also can be the cause.

Rare conditions may be considered if the history and physical examination do not support a common diagnosis. Cyclic vomiting syndrome is a poorly understood phenomenon that causes periods of nausea and vomiting alternating with asymptomatic periods. Symptoms are often associated with migraine headaches, motion sickness, or atopy. Cyclic vomiting predominantly affects children; however, it has been described in adults. Cyclic vomiting syndrome is a diagnosis of exclusion.

## Evaluation

The American Gastroenterological Association suggests a three-step approach to the initial evaluation of nausea and vomiting.<sup>2</sup> First, attempt to recognize and correct any consequences of the symptoms, such as dehydration or electrolyte abnormalities. Second, try to identify the underlying cause and provide specific therapies. Third,

# Table 1. Differential Diagnosis of Nausea and Vomiting

Central nervous system	Organic disorders	Hormonal preparations
Closed head injury <sup>4</sup>	Appendicitis	Illicit substances
Increased intracranial pressure	Cholecystitis/cholangitis	Nonsteroidal anti-inflammatory drugs
Cerebrovascular accident	Hepatitis	Opiates
(infarction/hemorrhage)	Inflammatory bowel disease	Overdoses/withdrawal <sup>6</sup>
Hydrocephalus	Mesenteric ischemia	Radiation therapy
Mass lesion	Pancreatitis	Toxins
Meningitis/encephalitis/abscess	Peptic ulcer disease	Arsenic <sup>7</sup>
Pseudotumor cerebri	Peritonitis	Organophosphates/pesticides <sup>8</sup>
Migraine	Infectious	Ricin <sup>9</sup>
Seizure disorders <sup>2</sup>	Acute otitis media	Metabolic
Vestibular	Bacteria	Adrenal disorders
Labyrinthitis	Bacterial toxins	Diabetic ketoacidosis
Ménière's disease	Food-borne toxins	Paraneoplastic syndromes
Motion sickness	Pneumonia⁵	Parathyroid disorders
Gastrointestinal	Spontaneous bacterial peritonitis	Pregnancy
Functional disorders	Urinary tract infection/pyelonephritis	Thyroid disorders
Chronic intestinal pseudo-obstruction	Viruses	Uremia
Gastroparesis	Adenovirus	Miscellaneous
Irritable bowel syndrome	Norwalk	Acute glaucoma <sup>5</sup>
Nonulcer dyspepsia	Rotavirus	Acute myocardial infarction
Obstruction	Medications/Toxins	Nephrolithiasis <sup>10</sup>
Adhesions	Medications	Pain
Esophageal disorders/achalasia	Antiarrhythmics	Psychiatric disorders
Intussusception	Antibiotics	Anorexia nervosa
Malignancy	Anticonvulsants	Anxiety
Pyloric stenosis	Chemotherapeutics	Bulimia nervosa
Strangulated hernia	Digoxin	Conversion disorder
Volvulus	Ethanol overdose	Depression
		Psychogenic/emotional

Information from references 2 and 4 through 10.

if no etiology can be determined, use empiric therapy to treat symptoms. An algorithm for the evaluation of nausea and vomiting is provided in *Figure 1*.<sup>1,11</sup>

Because of the broad range of possible etiologies, an ordered approach to evaluation is essential. The etiology of most acute nausea and vomiting can be determined from the history and physical examination; diagnostic tests should be ordered only when based on clinical suspicion. During initial consultation, the physician must rule out emergencies or any need for hospitalization. Warning signs such as chest pain, severe abdominal pain, central nervous system symptoms, fever, a history of immunosuppression, hypotension, severe dehydration, or older age should prompt immediate evaluation.

#### HISTORY

A clear definition of the patient's symptoms must be determined, with vomiting distinguished from regurgitation and rumination. Vomiting involves the forceful expulsion of stomach contents through involuntary muscular contractions. In regurgitation, food is returned to the mouth without forceful contractions, and in rumination food is returned to the mouth through voluntary contractions.

A detailed history of symptoms can provide clues to a diagnosis (*Table 2*<sup>1,2,11-13</sup>). Symptom duration should be determined because the differential diagnoses differ significantly for acute symptoms (i.e., persisting one month or less) and chronic symptoms (i.e., persisting for longer than one month).<sup>2</sup> Abrupt onset of nausea

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and vomiting is suggestive of cholecystitis, food poisoning, gastroenteritis, pancreatitis, or drug-related etiologies. If a patient has pain, obstructive etiologies must be considered. The insidious onset of acute or chronic symptoms is suggestive of diagnoses such as GERD, gastroparesis, medication, metabolic disorders, or pregnancy. Symptom timing also is important (e.g., occurrence before, during, or after eating; continuous, irregular, or predictable), and the quality and quantity of vomited matter may also suggest specific etiologies (*Table 2*<sup>1,2,11-13</sup>).<sup>12</sup>

The presence of abdominal pain usually suggests an organic cause<sup>2</sup>; the location, severity, and timing of pain may indicate a specific etiology. Other associated symptoms also provide significant information. Acute nausea and vomiting without any warning signs suggests

**Figure 1.** Algorithm for the evaluation of nausea and vomiting. (N&V = nausea and vomiting; CT = computed tomography; MRI = magnetic resonance imaging;  $T_4$  = thyroxine; EGD = esophagogastroduodenoscopy; GERD = gastroesophageal reflux disease.)

# Table 2. Possible Diagnoses Based on the History in Patients with Nausea and Vomiting

History	Possible diagnoses
Onset of symptoms	
Abrupt	Cholecystitis, food poisoning, gastroenteritis, illicit drugs, medications, pancreatitis
Insidious	Gastroesophageal reflux disease, gastroparesis, medications, metabolic disorders, pregnancy
Timing of symptoms	
Before breakfast	Ethyl alcohol, increased intracranial pressure, pregnancy, uremia
During or directly after eating	Psychiatric causes
	Less likely: peptic ulcer disease or pyloric stenosis
One to four hours after a meal	Gastric outlet obstructions (e.g., from peptic ulcer disease, neoplasms), gastropares
Continuous	Conversion disorder, depression
Irregular	Major depression
Nature of vomited matter	
Undigested food	Achalasia, esophageal disorders (e.g., diverticulum, strictures)
Partially digested food	Gastric outlet obstruction, gastroparesis
Bile	Proximal small bowel obstruction
Feculent or odorous	Fistula, obstruction with bacterial degradation of contents
Large volume (> 1,500 mL per 24 hours)	Suggests organic rather than psychiatric causes
Abdominal pain	
Right upper quadrant	Biliary tract disease, cholecystitis
Epigastric	Pancreatic disease, peptic ulcer disease
Severe pain	Biliary disease, pancreatic disease, peritoneal irritation, small bowel obstruction
Severe pain that precedes vomiting	Small bowel obstruction
Associated symptoms/findings	
Weight loss	Malignancy (significant weight loss may also occur secondary to sitophobia in gastric outlet obstructions and peptic ulcer disease)
Diarrhea, myalgias, malaise, headache, contact with ill persons	Viral etiologies
Headache, stiff neck, vertigo, focal neurologic deficits	Central neurologic causes (e.g., encephalitis/meningitis, head injury, mass lesion or other cause of increased intracranial pressure, migraine)
Early satiety, postprandial bloating, abdominal discomfort	Gastroparesis
Repetitive migraine headaches or symptoms of irritable bowel syndrome	Cyclic vomiting syndrome

infectious or iatrogenic etiologies. A detailed medication history is essential. Food ingestions, contact with ill persons, and the presence of coexisting viral symptoms suggest an infectious etiology. A history of weight loss should raise concern for malignancy; however, significant weight loss can occur with sitophobia (fear of eating) secondary to functional disorders. Neurologic symptoms should be investigated because central nervous system etiologies of nausea and vomiting are unlikely in a patient without other neurologic symptoms.<sup>2</sup>

## PHYSICAL EXAMINATION

The physical examination should focus initially on signs of dehydration, evaluating skin turgor and mucous

membranes, and observing for hypotension or orthostatic changes.<sup>1,2,12</sup> The general examination should look for jaundice, lymphadenopathy, and signs of thyrotoxicosis. Fingers should be observed for calluses on the dorsal surfaces suggesting self-induced vomiting. Other suggestive findings may include parotid gland enlargement, lanugo hair, and loss of tooth enamel; however, loss of enamel may also be a consequence of long-standing gastroesophageal reflux. The physician should evaluate for signs of depression or anxiety, which may suggest psychiatric etiologies.

The abdominal examination is extremely important. Abdominal distention with tenderness is suggestive of a bowel obstruction, although bloating may occur with

# Table 3. Diagnostic Tests and Clinical Suspicion for Patients with Nausea and Vomiting

Test	Clinical suspicion
Laboratory tests	
Complete blood count	Leukocytosis in an inflammatory process, microcytic anemia from a mucosal process
Electrolytes	Consequences of nausea and vomiting (e.g., acidosis, alkalosis, azotemia, hypokalemia)
Erythrocyte sedimentation rate	Inflammatory process
Pancreatic/liver enzymes	For patients with upper abdominal pain or jaundice
Pregnancy test	For any female of childbearing age
Protein/albumin	Chronic organic illness or malnutrition
Specific toxins	Ingestion or use of potentially toxic medications
Thyroid-stimulating hormone	For patients with signs of thyroid toxicity or unexplained nausea and vomiting
Radiographic testing	
Supine and upright abdominal radiography	Mechanical obstruction
Further testing	
Esophagogastroduodenoscopy	Mucosal lesions (ulcers), proximal mechanical obstruction
Upper gastrointestinal radiography with barium contrast media	Mucosal lesions and higher-grade obstructions; evaluates for proximal lesions
Small bowel follow-through	Mucosal lesions and higher-grade obstructions; evaluates the small bowel to the terminal ileum
Enteroclysis	Small mucosal lesions, small bowel obstructions, small bowel cancer
Computed tomography with oral and intravenous contrast media	Obstruction, optimal technique to localize other abdominal pathology
Gastric emptying scintigraphy	Gastroparesis (suggestive)
Cutaneous electrogastrography	Gastric dysrhythmias
Antroduodenal manometry	Primary or diffuse motor disorders
Abdominal ultrasonography	Right upper quadrant pain associated with gallbladder, hepatic, or pancreatic dysfunction
Magnetic resonance imaging of the brain	Intracranial mass or lesion

Information from references 1, 2, and 14 through 19.

gastroparesis. The physician should observe for visible peristalsis and pay close attention for abdominal or inguinal hernias and surgical scars. Auscultation may demonstrate increased bowel sounds in obstruction or decreased bowel sounds with an ileus. A succussion splash (heard at the epigastrium while rapidly palpating the epigastrium or shaking the abdomen and pelvis) suggests gastric outlet obstruction or gastroparesis. Epigastric tenderness may suggest an ulcer or pancreatitis. Pain in the right upper quadrant is more consistent with cholecystitis or biliary tract disease.

A neurologic examination is essential. Simple maneuvers can direct the physician toward or away from a central diagnosis. Orthostatic changes may be the result of persistent vomiting; however, a decrease in blood pressure without a change in heart rate may suggest an

autonomic neuropathy with coexisting motility disorders. Any deficit on examination of cranial nerves or a patient's gait suggests brainstem lesions, which may result in gastroparesis. Ophthalmoscopy should be performed to evaluate for elevations in intracranial pressure, because any cause of increased intracranial pressure can stimulate brainstem emesis centers. Abnormal findings should prompt immediate neuroimaging. Finally, observation for nystagmus may suggest a disorder of the labyrinthine system.

# **Diagnostic Approach**

There are no controlled trials to guide the diagnostic evaluation of nausea and vomiting; therefore, most recommendations are based on expert opinion.<sup>1</sup> In most patients with a worrisome history, it is reasonable to begin

# Table 4. Select Antiemetic Agents, Common Uses, and Side Effects

Class of medication	Common uses	Common side effects
Anticholinergic* (scopolamine [Maldemar]	Possible adjunct for cytotoxic chemotherapy, prophylaxis and treatment of motion sickness	Drowsiness, dry mouth, vision disturbances
Antihistamines (cyclizine [Marezine], diphenhydramine [Benadryl], dimenhydrinate [Dramamine], meclizine [Antivert])	Migraine, motion sickness, vertigo	Drowsiness
3enzodiazepines (alprazolam [Xanax], diazepam [Valium], lorazepam [Ativan])	Adjunct for chemotherapy-related symptoms	Sedation
Butyrophenones (droperidol [Inapsine†], haloperidol [Haldol])	Anticipatory and acute chemotherapeutic nausea and vomiting, postoperative nausea and vomiting	Agitation, restlessness, sedation
Cannabinoids (dronabinol [Marinol])	Refractory chemotherapy-related nausea and vomiting	Ataxia, dizziness, euphoria, hypotension, sedation
Corticosteroids (dexamethasone)	Adjunct for chemotherapy-related symptoms	Increased energy, insomnia, mood changes
Phenothiazines (chlorpromazine [Thorazine†], prochlorperazine, promethazine [Phenergan])	Migraine, motion sickness, postchemotherapy nausea and vomiting, postoperative nausea and vomiting, severe episodes of nausea and vomiting, vertigo	Extrapyramidal symptoms (e.g., dystonia, tardive dyskinesia), orthostatic hypotension, sedation
Serotonin 5-hydroxytryptamine antagonists‡ (dolasetron [Anzemet], odansetron [Zofran], granisetron [Kytril], palonosetron [Aloxi])	Postchemotherapy nausea and vomiting, severe nausea and vomiting	Asthenia, constipation, dizziness, mild headache
Substituted benzamides* (metoclopramide [Reglan], trimethobenzamide [Tigan])	Diabetic gastroenteropathy, gastroparesis	Extrapyramidal side effects (e.g., akathisia, dyskinesia, dystonia, oculogyric crises, opisthotonos), fatigue, hyperprolactinemia

Information from references 1, 2, and 6.

with basic laboratory tests and radiographic studies to rule out serious consequences. An overview of diagnostic tests for nausea and vomiting is provided in *Table 3*.<sup>1,2,14-19</sup>

# LABORATORY TESTING

There are no laboratory tests specific to determining etiologies of nausea and vomiting. Tests should be directed by the history and physical examination to determine the underlying cause or to evaluate for the consequences of nausea and vomiting. In patients with unexplained symptoms, it is reasonable to perform a complete blood count and erythrocyte sedimentation rate measurement in conjunction with a complete metabolic profile. A pregnancy test should be performed in any woman of childbearing age. This may reveal the cause of symptoms and is also needed before radiography. If a patient has abdominal pain, pancreatic enzyme measurements should be performed. Additional laboratory tests and their indications are listed in *Table 3*.<sup>1,2,14-19</sup>

#### RADIOGRAPHIC TESTING

Supine and upright abdominal radiography should be performed if there is any concern about a small bowel obstruction,<sup>14</sup> although false-negative results occur in as many as 22 percent of patients with a partial obstruction.<sup>1</sup> If results are negative but an obstruction is still suspected, further testing should be performed.

## FURTHER TESTING

Proximal mucosal lesions and obstructions may be detected by esophagogastroduodenoscopy (EGD) or upper gastrointestinal radiography. EGD is the best study for detecting such lesions<sup>15</sup>; however, the use of double contrast media in radiographic studies reduces error rates and allows a less-expensive, less-invasive approach. The addition of a small bowel follow-through enables visualization of the small bowel to the terminal ilium, but it may not detect smaller mucosal lesions. This has led many to advocate the use of enteroclysis.<sup>16</sup>

Clinical situation	Common treatment
Chemotherapy- and radiation-associated	Acute: ondansetron (Zofran) 32 mg IV or 24 mg orally 30 minutes before chemotherapy and dexamethasone 4 mg
nausea and vomiting Cyclic vomiting syndrome	Delayed: metoclopramide (Reglan) 1 to 2 mg IV or orally every 2 to 4 hours and dexamethasone 4 mg Supportive, and possible tricyclic antidepressants for adults <sup>25,26</sup>
Gastroparesis	Supportive, and possible gastric pacing <sup>24</sup>
Postoperative nausea and vomiting	Droperidol (Inapsine*) 1.25 mg IV and dexamethasone 4 mg IV within 20 minutes of anesthesia; or ondansetron 4 mg IV during the last 20 minutes of surgery <sup>20</sup>
Pregnancy: hyperemesis gravidarum	Prochlorperazine 5 to 10 mg IM, chlorpromazine (Thorazine*) 10 to 25 mg orally, metoclopramide <sup>2</sup> 1 to 2 mg IV, and methylprednisolone (Depo-Medrol) <sup>23</sup>
Pregnancy: morning sickness	Meclizine (Antivert) 25 to 50 mg orally and promethazine (Phenergan) 12.5 to 50 mg orally or IV, electrolyte replacement, thiamine supplementation <sup>21,22</sup>

# Table 5. Specific Therapies for Known Etiologies of Nausea and Vomiting

Information from references 2 and 20 through 26.

Enteroclysis is extremely sensitive but requires placement of an oral/nasal tube directly into the small bowel. Computed tomography may soon become the study of choice for detecting intestinal obstructions and also allows evaluation of the surrounding abdominal structures.<sup>17,18</sup> In patients with unexplained symptoms or with abnormal neurologic findings, magnetic resonance imaging of the brain should be considered.<sup>19</sup>

If no diagnosis is determined after initial evaluation, gastric motility studies (e.g., gastric emptying scintigraphy, cutaneous electrogastrography, antroduodenal manometry) may be considered. However, the utility of such tests is controversial, and many experts suggest a trial of antiemetic or prokinetic medications instead.<sup>1</sup>

Finally, if all organic, gastrointestinal, and central causes of nausea and vomiting have been explored, psychogenic vomiting should be considered.<sup>2</sup>

# Table 6. Alternative Treatments for Nauseaand Vomiting

Treatment	Conditions
Acupuncture (point P6)	Chemotherapy, <sup>27</sup> postoperative nausea and vomiting, <sup>28</sup> early pregnancy nausea and vomiting <sup>2</sup>
Ginger 250 mg (powdered root) before meals and at bedtime	Nausea and vomiting in pregnancy <sup>29</sup>
Pyridoxine (vitamin B <sub>6</sub> )	Early pregnancy nausea and vomiting <sup>22</sup>

Information from references 22 and 27 through 29.

# Treatment

After identification of any warning signs and appropriate emergency interventions, the primary goal of initial treatment is a careful assessment of fluid and electrolyte status with appropriate replacement. A low-fat or liquid diet may be prescribed, because lipids delay gastric emptying and liquids are more readily absorbed.

If an etiology is identified, a targeted therapy can be provided; however, delays in evaluation may require empiric treatment for patient comfort.<sup>1</sup> It is reasonable to begin with a trial of a phenothiazine, such as prochlorperazine, because these medications are effective in a range of clinical situations. A trial of a prokinetic agent (e.g., metoclopramide [Reglan]) may then be beneficial. Serotonin antagonists (e.g., ondansetron [Zofran]) are effective and are better tolerated than phenothiazines and prokinetics, but their high cost (approximately \$20 per dose, even for the recently approved generic ondansetron) makes long-term use impractical. Trials determining the specific effectiveness of medications for nausea and vomiting are limited; therefore, a trial of any medication may be reasonable on an individual basis.<sup>1</sup> Antiemetic agents commonly used for nausea and vomiting are listed in Table  $4^{1,2,6}$ ; therapies for known etiologies of nausea and vomiting are listed in Table 5<sup>2,20-26</sup>; and alternative therapies are listed in Table 6.22,27-29

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