

# Chapter 48: Nausea, Vomiting, and Indigestion

Cardinal Manifestations and Presentation of Diseases | Part 2 – Cardinal Manifestations & Presentation | DETAILED EDITION

## KEY CLINICAL POINTS

1. Nausea requires cognitive input and autonomic responses; vomiting is coordinated by the brainstem.
2. Functional dyspepsia is defined as bothersome postprandial fullness, early satiety, or epigastric pain/burning with onset  $\geq 6$  months in the absence of organic cause.
3. Alarm features (weight loss, dysphagia, bleeding, nocturnal symptoms) mandate upper endoscopy regardless of age.
4. Metoclopramide causes irreversible movement disorders like tardive dyskinesia; use with caution in elderly.
5. Cannabinoid Hyperemesis Syndrome (CHS) resolves with discontinuation of cannabis for  $\geq 6$  months.
6. Cyclic Vomiting Syndrome (CVS) is associated with migraines, autonomic dysfunction, and menstrual cycling.
7. Gastroparesis is diagnosed by gastric scintigraphy or  $^{13}\text{C}$ -labeled breath test showing delayed emptying.
8. PPI therapy is first-line for GERD; confirm *H. pylori* eradication 4–6 weeks after therapy.
9. QTc prolongation is a risk with 5-HT antagonists, NK antagonists, and domperidone; ECG surveillance is advocated.
10. In pregnancy, antihistamines (meclizine) and antidopaminergics (prochlorperazine) have limited efficacy; ginger and pyridoxine are alternatives.

## FIGURES IN THIS CHAPTER

No figures extracted.

## 1. DEFINITION & OVERVIEW

Nausea and vomiting are cardinal manifestations of diseases affecting the gastrointestinal tract, central nervous system, and other organ systems. Indigestion encompasses complaints including nausea, vomiting, heartburn, regurgitation, and dyspepsia.

### 1.1 Definitions

- Nausea: The feeling of a need to vomit.

- Vomiting (Emesis): The oral expulsion of gastrointestinal contents resulting from gut and thoracoabdominal wall contractions.
- Regurgitation: The effortless passage of gastric contents into the mouth (contrasted with emesis).
- Rumination: The repeated regurgitation of food residue (exhibits volitional control).
- Indigestion: Broadly encompasses complaints including nausea, vomiting, heartburn, regurgitation, and dyspepsia (defined as symptoms that are thought to originate in the gastroduodenal region).
- Dyspepsia: Symptoms that are thought to originate in the gastroduodenal region.
- Gastroparesis-like symptoms (GPLS): A syndrome indistinguishable from gastroparesis but with normal gastric emptying.
- Cyclic Vomiting Syndrome (CVS): Presents with discrete episodes of relentless vomiting, has a prevalence of 1.4%, and is associated with migraines, autonomic dysfunction, and menstrual cycling.
- Cannabinoid Hyperemesis Syndrome (CHS): Presents with cyclical vomiting in individuals with long-standing (>1 year) use of large quantities of cannabis at least 4 days weekly and resolves with its discontinuation for  $\geq 6$  months.
- Rumination Syndrome: Often misdiagnosed as refractory vomiting; vomiting occurring minutes after eating characterizes this condition.
- Chronic Nausea Vomiting Syndrome (CNVS): Defined as bothersome nausea and/or one or more vomiting episodes at least weekly.

## 1.2 Dysphagia Overview

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- Dysphagia is a cardinal symptom of several malignancies, making it an important symptom to evaluate.
- Cancer may result in dysphagia, most commonly as the result of intraluminal obstruction (esophageal or proximal gastric cancer, metastatic deposits) and less commonly due to extrinsic compression (lymphoma, lung cancer) or paraneoplastic syndromes.
- Even when not attributable to malignancy, dysphagia is usually a manifestation of an identifiable and treatable disease entity.
- Oropharyngeal dysphagia most commonly results from functional deficits caused by neurologic disorders.
- Esophageal dysphagia: The most relevant pathology is restricted to the esophagus, with the notable exception of skin disease (scleroderma, pemphigoid, lichen planus, epidermolysis bullosa).
- Eosinophilic esophagitis is an important and increasingly recognized cause of dysphagia that is amenable to treatment by elimination of dietary allergens, proton pump inhibition, swallowed topically acting glucocorticoids, and biologic therapies targeting cytokines involved in type 2 inflammation.

## 2. EPIDEMIOLOGY

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Epidemiologic data from the source text regarding prevalence and incidence.

### 2.1 Population Prevalence

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- Nausea alone at least weekly: Reported by 1.9% of the population.
- Nausea plus vomiting: Reported by 1.1% of the population.
- Cyclic Vomiting Syndrome (CVS): Prevalence of 1.4%.
- Gastroesophageal Reflux Disease (GERD): Symptoms of heartburn and regurgitation confer 70% sensitivity and specificity for a diagnosis of GERD; prevalence is 18–28% of the population.
- Functional Dyspepsia: Cause of symptoms in 70–80% of dyspeptic patients; population prevalence of 7.2%.
- Postoperative Emesis: Occurs after 25% of surgeries.

- Nausea in Pregnancy: Affects 70% of women in the first trimester.

## 2.2 Risk Factors

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- Modifiable: Medications (opioids, NSAIDs, chemotherapy), toxins (ethanol), diet (FODMAPs, gluten), lifestyle (smoking, caffeine).
- Non-modifiable: Age (>60 years), gender (pregnancy), genetic factors (predisposition to reflux and dyspepsia), comorbidities (diabetes, Parkinson's disease, scleroderma).

## 3. ETIOLOGY & PATHOPHYSIOLOGY

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Mechanisms underlying nausea and vomiting involve complex interactions between the gut, brain, and autonomic nervous system.

### 3.1 Mechanisms of Vomiting

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- Coordination: Vomiting is coordinated by the brainstem and is effected by responses in the gut, pharynx, and somatic musculature.
- Nausea Mechanisms: Likely involve the cerebral cortex, as nausea requires cognitive and emotional input and is associated with autonomic responses (diaphoresis, pallor, altered heart rate). Functional brain imaging studies support this idea showing activation of cerebral regions including the insula, anterior cingulate cortex, and amygdala during nausea.
- Brainstem Nuclei: Nucleus tractus solitarius; dorsal vagal and phrenic nuclei; medullary nuclei regulating respiration; and nuclei that control pharyngeal, facial, and tongue movements.
- Neurotransmitters: Neurokinin (NK), serotonin 5-HT, endocannabinoid, and vasopressin pathways.
- Muscle Response: Somatic and visceral muscles respond stereotypically during emesis. Inspiratory thoracic and abdominal wall muscles contract, increasing intrathoracic and intraabdominal pressures to help gastric evacuation. During vomiting, propulsive gastroduodenal motor activity is replaced by orally propagating retrograde contractions that facilitate expulsion.
- Emesis Activators: Emetic stimuli act at several sites. Emesis evoked by unpleasant thoughts or smells originates in the brain. Motion sickness and inner ear disorders act on labyrinthine pathways. Gastric irritants and cytotoxic agents like cisplatin stimulate vagal afferent nerves. Nongastric afferents are activated by bowel obstruction and mesenteric ischemia. The area postrema, in the medulla, responds to bloodborne stimuli (emetogenic drugs, bacterial toxins, uremia, ketoacidosis) and is termed the chemoreceptor trigger zone.
- Receptor Specificity: Labyrinthine disorders stimulate vestibular muscarinic M and histaminergic H receptors. Vagal afferent stimuli activate 5-HT receptors. The area postrema is served by 5-HT, M, H, and dopamine D pathways. Central nervous system (CNS) N3K1 receptors mediate both nausea and vomiting. Cannabinoid CB pathways participate in the cerebral cortex and brainstem.

### 3.2 Pathophysiology of Indigestion

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- Gastroesophageal Reflux: Results from many defects. Reduced lower esophageal sphincter (LES) tone causes reflux in scleroderma and pregnancy and may also be a factor in some patients without systemic illness. Other cases exhibit frequent transient LES relaxations (TLESRs). Reductions in esophageal body motility or saliva production prolong esophageal acid clearance. Increased intra-gastric pressure promotes gastroesophageal reflux with obesity. Large hiatal hernias can increase symptomatic acid reflux.
- Gastric Motor Dysfunction: Disturbed gastric motility may contribute to gastroesophageal reflux in up to one-third of cases. Delayed gastric emptying is also found in ~30% of functional dyspeptics, while rapid gastric emptying affects 5%. Impairment of gastric fundus relaxation after eating (i.e., accommodation) may underlie selected dyspeptic symptoms like bloating, nausea, and early satiety in ~40% of patients and may predispose to TLESRs and acid reflux.

- **Visceral Afferent Hypersensitivity:** Disturbed gastric sensation is another pathogenic factor in functional dyspepsia. Approximately 30% of dyspeptic patients note discomfort with gastric or duodenal distention to lower pressures than in healthy controls. Other individuals with dyspepsia exhibit hypersensitivity to chemical stimulation of the stomach and duodenum with capsaicin or with duodenal acid or lipid perfusion. Some patients with heartburn without increased reflux of acidic or nonacidic fluid exhibit heightened perception of normal esophageal acidity and are conferred a diagnosis of esophageal hypersensitivity.
- **Immune Activation:** Increases in duodenal epithelial permeability in functional dyspepsia may relate to increases in eosinophils and mast cells adjacent to submucosal neurons, most prominently in the 20% of patients who report symptom onset after a viral illness. Increased activation of these cells may contribute to gastric emptying delays and altered sensory function in functional dyspepsia and may elicit early satiety and epigastric pain.
- **Microbiome:** Populations of selected duodenal bacteria are altered in functional dyspepsia and correlate with symptom severity, suggesting a role for microbiome alterations. Food antigens, gluten, and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) increase duodenal inflammation.
- **Other Factors:** *Helicobacter pylori* has a proven etiologic role in peptic ulcer disease but is a minor factor in functional dyspepsia pathogenesis. Anxiety, depression, and stress play contributing roles in some functional dyspepsia cases. Other studies observe that 20% of patients with functional dyspepsia note predominance of pain rather than nausea and vomiting.

### 3.3 Pathophysiology of Dysphagia

- **Oropharyngeal Dysphagia:** Most commonly results from functional deficits caused by neurologic disorders (e.g., cerebrovascular accident, myasthenia gravis, polymyositis, Parkinson's disease, amyotrophic lateral sclerosis).
- **Esophageal Dysphagia:** Most relevant pathology is restricted to the esophagus. Structural causes include Schatzki's ring, gastroesophageal reflux disease, eosinophilic esophagitis, and malignancy.
- **Motility Disorders:** Suspected esophageal motility disorders may manifest with severe oropharyngeal dysphagia. Feeding by a nasogastric tube or an endoscopically placed gastrostomy tube may be considered for nutritional support; however, these maneuvers do not provide protection against aspiration of salivary secretions or refluxed gastric contents.

## 4. CLINICAL FEATURES

Detailed symptoms and signs associated with nausea, vomiting, indigestion, and dysphagia.

### 4.1 Nausea and Vomiting Symptoms

- Vomiting with pancreatitis, cholecystitis, and appendicitis or one or more vomiting episodes at least weekly results from visceral irritation and ileus.
- Biliary vomiting excludes gastric obstruction.
- Emesis of undigested food is consistent with a Zenker's diverticulum or achalasia.
- Vomiting can relieve abdominal pain from a bowel obstruction but has no effect in pancreatitis or cholecystitis.
- Weight loss raises concern about malignancy or ischemia.
- Taking prolonged hot baths or showers is associated with CHS and CVS but is less common with CNVS or gastroparesis.
- Intracranial sources are considered if there are headaches or visual changes.
- Vertigo or tinnitus indicates labyrinthine disease.

- Hematemesis raises suspicion of ulcer, malignancy, or Mallory-Weiss tear.
- Feculent emesis is noted with distal intestinal or colonic obstruction.
- Intense episodic emesis with intervening intervals with much less severe symptoms suggests CVS or CHS.

## 4.2 Indigestion Symptoms

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- GERD: Heartburn or regurgitation is reported weekly by 18–28% of the population. Symptoms of heartburn and regurgitation confer 70% sensitivity and specificity for a diagnosis of GERD.
- Functional Dyspepsia: Defined as bothersome postprandial fullness, early satiety, or epigastric pain or burning with symptom onset  $\geq 6$  months before diagnosis in the absence of organic cause.
- Postprandial Distress Syndrome (PDS): Characterized by meal-induced fullness and early satiety (prevalence 6.1%).
- Epigastric Pain Syndrome (EPS): With epigastric pain or burning that may or may not be meal-related (prevalence 2.4%).
- Overlap of PDS and EPS: Has a prevalence of 1.3%.
- Dyspeptic patients report symptoms referable to the upper abdomen that may be meal-related or independent of food ingestion.
- Atypical GERD symptoms: Pharyngitis, asthma, cough, bronchitis, hoarseness, and chest pain.
- Dyspeptics may exhibit epigastric tenderness or distention.
- Biliary colic: Can cause unexplained chronic upper abdominal pain, but most patients report discrete acute episodes of right upper quadrant or epigastric pain rather than chronic burning or fullness.
- Gastroparesis: 20% of patients note predominance of pain rather than nausea and vomiting.

## 4.3 Dysphagia Symptoms

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- Oropharyngeal dysphagia: Manifests with severe oropharyngeal dysphagia in chronic neurologic disorders.
- Esophageal dysphagia: Manifests as difficulty swallowing due to obstruction or motility issues.
- Skin disease: Changes in the skin and oral mucosa may suggest a diagnosis of scleroderma or mucocutaneous diseases such as pemphigoid, lichen planus, and epidermolysis bullosa, all of which can involve the esophagus.

## 4.4 Alarm Features

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- Unexplained weight loss.
- Recurrent vomiting.
- Dysphagia.
- Occult or gross bleeding.
- Nocturnal symptoms.
- Jaundice.
- Palpable mass or adenopathy.
- Fever.
- Family history of gastrointestinal neoplasm.
- Odynophagia suggests esophageal infection.
- Dysphagia is concerning for esophageal blockage.

# 5. DIFFERENTIAL DIAGNOSIS

Systematic list of causes for nausea, vomiting, and indigestion.

## 5.1 Causes of Nausea and Vomiting

- **Intraperitoneal Disorders:** Obstruction and inflammation of hollow and solid viscera may elicit vomiting. Ulcers and malignancy cause gastric obstruction, while adhesions, masses, volvulus, intussusception, or inflammatory diseases like Crohn's disease cause small intestinal and colonic obstruction.
- **Extraperitoneal Disorders:** Myocardial infarction and congestive heart failure may cause nausea and vomiting. Increased intracranial pressure from tumors, bleeding, abscess, or blockage of cerebrospinal fluid outflow produces vomiting with or without nausea.
- **Medications and Metabolic Disorders:** Many medications cause nausea and vomiting including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), glucagon-like peptide-1 receptor agonists, oral hypoglycemics, antiparkinsonian drugs, agents for restless legs, antidepressants (especially selective serotonin norepinephrine reuptake inhibitors), smoking cessation drugs, antibiotics, cardiac antiarrhythmics, antihypertensives, and contraceptives.
- **Metabolic Disorders:** Uremia, ketoacidosis, adrenal insufficiency, and parathyroid and thyroid disease are other etiologies.
- **Circulating Toxins:** Endogenous toxins are generated in fulminant liver failure, whereas exogenous enterotoxins may be produced by enteric bacterial infection. Ethanol intoxication is a common toxic etiology of nausea and vomiting.
- **Specific Syndromes:** Gastroparesis, Intestinal pseudoobstruction, Gastroesophageal reflux, Chronic nausea vomiting syndrome (CNVS), Gastroparesis-like symptoms (GPLS), Cyclic vomiting syndrome (CVS), Cannabinoid hyperemesis syndrome (CHS), Rumination syndrome, Mesenteric insufficiency, Celiac artery stenosis, Median arcuate ligament syndrome, Biliary colic, Abdominal irradiation.

**Table 1 Table 48-1 Causes of Nausea and Vomiting**

Category	Intraperitoneal	Extraperitoneal	Medications/Metabolic Disorders
Obstructing disorders	Pyloric obstruction	Cardiopulmonary disease	Cancer chemotherapy
Small-bowel obstruction	Small-bowel obstruction	Opioids	
Colonic obstruction	Colonic obstruction	Analgesics	
Superior mesenteric artery syndrome	Superior mesenteric artery syndrome	Glucagon-like peptide-1 (GLP-1) receptor agonists	
Enteric infections	Viral	Intracerebral disorders	Parkinson's disease/restless legs therapies
Bacterial	Bacterial	Antidepressants	
Inflammatory diseases	Cholecystitis	Abscess	Smoking cessation agents
Pancreatitis	Pancreatitis	Antibiotics	
Appendicitis	Appendicitis	Cardiac antiarrhythmics/antihypertensives	
Hepatitis	Hepatitis	Oral contraceptives	

Category	Intraperitoneal	Extraperitoneal	Medications/Metabolic Disorders
Altered sensorimotor function	Gastroparesis	Endocrine/metabolic disease	
Intestinal pseudoobstruction	Intestinal pseudoobstruction	Pregnancy	
Gastroesophageal reflux	Gastroesophageal reflux	Uremia	
Chronic nausea vomiting syndrome (CNVS)	Chronic nausea vomiting syndrome (CNVS)	Ketoacidosis	
Gastroparesis-like symptoms (GPLS)	Gastroparesis-like symptoms (GPLS)	Thyroid and parathyroid disease	
Cyclic vomiting syndrome (CVS)	Cyclic vomiting syndrome (CVS)	Adrenal insufficiency	
Cannabinoid hyperemesis syndrome (CHS)	Cannabinoid hyperemesis syndrome (CHS)	Toxins	
Rumination syndrome	Rumination syndrome	Liver failure	
Mesenteric insufficiency	Mesenteric insufficiency	Ethanol	
Celiac artery stenosis	Celiac artery stenosis		
Median arcuate ligament syndrome	Median arcuate ligament syndrome		
Biliary colic	Biliary colic		
Abdominal irradiation	Abdominal irradiation		

## 5.2 Causes of Indigestion

- Gastroesophageal Reflux Disease (GERD): Heartburn or regurgitation is reported weekly by 18–28% of the population.
- Functional Dyspepsia: Cause of symptoms in 70–80% of dyspeptic patients.
- Ulcer Disease: Most common causes are *H. pylori* infection and NSAID use.
- Malignancy: Esophageal adenocarcinoma usually complicates prolonged acid reflux. Esophageal squamous cell carcinoma occurs most often with long-standing tobacco or ethanol intake.
- Other Causes: Opportunistic fungal or viral esophageal infections, eosinophilic esophagitis, pill esophagitis, biliary colic, intestinal lactase deficiency, intolerance of other carbohydrates, small-intestinal bacterial overgrowth, celiac disease, nonceliac gluten sensitivity, pancreatic disease, hepatocellular carcinoma, Ménétrier's disease, infiltrative diseases (sarcoidosis, mastocytosis, eosinophilic gastroenteritis), mesenteric ischemia, thyroid and parathyroid disease, abdominal wall strain, congestive heart failure, tuberculosis.

## 5.3 Causes of Dysphagia

- Malignancies: Intraluminal obstruction (esophageal or proximal gastric cancer, metastatic deposits) and extrinsic compression (lymphoma, lung cancer).
- Structural: Schatzki's ring, gastroesophageal reflux disease, eosinophilic esophagitis.

- Motility: Achalasia, esophageal spasm.
- Neurologic: Myasthenia gravis, polymyositis, Parkinson's disease, amyotrophic lateral sclerosis.
- Skin Disease: Scleroderma, pemphigoid, lichen planus, epidermolysis bullosa.

## 6. INVESTIGATIONS & DIAGNOSIS

Complete workup for nausea, vomiting, indigestion, and dysphagia.

### 6.1 Diagnostic Procedures for Dysphagia

- Fluoroscopic Swallow Study: Usually done by a swallow therapist; procedure of choice for oral or pharyngeal dysphagia.
- Otolaryngoscopic and Neurologic Evaluation: Important depending on circumstances.
- Upper Endoscopy: Single most useful test for suspected esophageal dysphagia. Allows better visualization of mucosal lesions than barium radiography and allows for procurement of mucosal biopsies.
- Esophageal Manometry: Done if dysphagia is not adequately explained by endoscopy or to confirm the diagnosis of a suspected esophageal motor disorder.
- Barium Radiography: Can provide useful adjunctive information in cases of subtle or complex esophageal strictures, prior esophageal surgery, esophageal diverticula, or paraesophageal herniation.
- Barium Tablet: Use of a barium tablet in conjunction with fluoroscopy can identify strictures and esophageal motility disorders that may be overlooked with liquid barium.
- Computed Tomography (CT): Examination may be useful in specific cases.
- Endoscopic Ultrasonography: May be useful in specific cases.
- Impedance Planimetry: Using the functional lumen imaging probe (FLIP) device is increasingly used in the evaluation of dysphagia, particularly for disorders of the esophagogastric junction (esophagogastric junction outflow obstruction and achalasia).
- Advantages of FLIP: Patient tolerance, procedure done at the time of upper endoscopy with sedation, and information regarding the dynamic opening characteristics of the esophagogastric junction in response to distension that complements esophageal manometry.

### 6.2 Diagnostic Testing for Nausea and Vomiting

- Electrolyte Replacement: Indicated for hypokalemia or metabolic alkalosis.
- Iron-deficiency Anemia: Mandates exclusion of mucosal causes.
- Abnormal Pancreatic or Liver Biochemistries: Found with pancreaticobiliary disease.
- Endocrinologic, Rheumatologic, or Paraneoplastic Etiologies: Suggested by hormone or serologic abnormalities.
- Small-bowel Obstruction: Indicated by intestinal air-fluid levels and reduced colonic air on abdominal radiography.
- Ileus: Characterized by diffusely dilated air-filled bowel loops.
- Upper Endoscopy: Detects ulcers, malignancy, and food retention in gastroparesis.
- Computed Tomography (CT): Can diagnose partial bowel obstruction. CT and magnetic resonance imaging (MRI) enterography provide detailed definition of bowel wall thickening and inflammation as seen with Crohn's disease.
- Ultrasound: Helpful for biliary etiologies.
- Mesenteric Angiography, CT, or MRI: Useful for suspected ischemia.
- Brain CT or MRI: Delineates intracranial disease.
- Gastrointestinal Motility Testing: Can detect underlying motor disorders.

- Gastric Scintigraphy: Measures emptying of a radiolabeled meal; commonly used to diagnose gastroparesis.
- <sup>13</sup>C-labeled Gastric Emptying Breath Test: Nonradioactive alternative to scintigraphy.
- Intestinal Scintigraphy or Contrast Radiography: Suggests intestinal pseudoobstruction.
- Small-intestinal Manometry: Confirms a diagnosis of pseudoobstruction and discriminates between neuropathic or myopathic disease.
- Esophageal pH Monitoring: Can diagnose GERD.
- Combined Esophageal pH/Impedance Testing with High-resolution Manometry: Facilitates diagnosis of rumination syndrome.
- Impedance Planimetry: Detects reduced pyloric distensibility and diameter in some cases of gastroparesis.

### 6.3 Diagnostic Testing for Indigestion

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- H. pylori Status: Assessment by fecal antigen or urea breath testing should be performed as initial diagnostic testing for uninvestigated dyspepsia.
- Confirmation of H. pylori Eradication: Should be conducted 4–6 weeks after completing therapy.
- Upper Endoscopy: Advocated to exclude malignancy for patients with unexplained dyspepsia who are >60 years old, who report alarm symptoms, or who fail to respond to these therapies.
- Blood Count: Can exclude anemia in cases of associated bleeding.
- Thyroid Chemistries or Calcium Levels: Screen for metabolic etiologies.
- Serologies: May suggest celiac disease.
- Pancreatic and Liver Chemistries: Obtained for suspected pancreaticobiliary causes, which are further investigated with ultrasound, CT, or MRI.
- Gastric Emptying Testing: Considered to exclude gastroparesis in patients who report symptoms resembling PDS when therapy fails.
- Breath Testing after Carbohydrate Ingestion: Detects lactase deficiency, intolerance to other carbohydrates, or small-intestinal bacterial overgrowth.

### 6.4 Diagnostic Algorithm for Dysphagia

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- Step 1: Suspected Oral or Pharyngeal Dysphagia -> Fluoroscopic Swallow Study (usually done by a swallow therapist).
- Step 2: Suspected Esophageal Dysphagia -> Upper Endoscopy (single most useful test).
- Step 3: Suspected Esophageal Motility Disorder -> Esophageal Manometry (if dysphagia is not adequately explained by endoscopy).
- Step 4: Suspected Structural/Complex Issues -> Barium Radiography (adjunctive information for subtle/complex strictures, prior surgery, diverticula, paraesophageal herniation).
- Step 5: Suspected Ischemia -> Mesenteric Angiography, CT, or MRI.
- Step 6: Suspected Intracranial Disease -> Brain CT or MRI.
- Step 7: Suspected GERD -> Esophageal pH Monitoring.
- Step 8: Suspected Rumination Syndrome -> Combined Esophageal pH/Impedance Testing with High-resolution Manometry.

## 7. MANAGEMENT & TREATMENT

Therapy of vomiting is tailored to correct remediable abnormalities if possible. Patients with severe dehydration should be hospitalized if oral replenishment is unsustainable.

## 7.1 General Principles

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- Once oral intake is tolerated, low-fat liquid nutrients are initially restarted.
- Low-residue, small-particle diets have shown durable efficacy in gastroparesis.
- Glycemic control should be optimized in diabetic gastroparesis patients.
- If feasible, medications deemed to contribute to a patient's nausea should be discontinued or their doses reduced.
- Enteral feedings through a jejunostomy reduce hospitalizations and improve overall health in some patients with refractory gastroparesis.
- The utilities of surgical gastric bypass and sleeve gastrectomy for gastroparesis are unproven.
- Implanted gastric electrical stimulators may reduce symptoms and health care expenditures in medication-refractory gastroparesis.
- A controlled trial confirmed greater improvements in vomiting during gastric electrical stimulation versus sham treatment.
- Combining a 5-HT antagonist, an NK antagonist, and a glucocorticoid can control acute and delayed vomiting after highly emetogenic cancer chemotherapy.
- Anticipatory nausea and vomiting is managed with benzodiazepines like lorazepam or behavioral therapy.
- Other therapies that benefit chemotherapy-induced emesis include cannabinoids, olanzapine, metoclopramide, gabapentin, and alternative therapies like ginger.

## 7.2 Antiemetic Medications

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- Antihistaminergic: Dimenhydrinate, meclizine (Motion sickness, inner ear disease).
- Anticholinergic: Scopolamine (Motion sickness, inner ear disease).
- Antidopaminergic: Prochlorperazine, thiethylperazine, haloperidol (Medication-, toxin-, or metabolic-induced emesis, chemotherapy-induced emesis, cannabinoid hyperemesis syndrome).
- 5-HT Antagonist: Ondansetron, granisetron (Chemotherapy- and radiation-induced emesis, postoperative emesis, opioid-induced nausea and vomiting).
- Cannabinoids: Tetrahydrocannabinol, cannabidiol (Chemotherapy-induced emesis, gastroparesis).
- Tricyclic Antidepressant: Amitriptyline, nortriptyline (Chronic nausea vomiting syndrome, cyclic vomiting syndrome, gastroparesis).
- Other Antidepressant/Atypical Antipsychotic: Mirtazapine, olanzapine (Functional dyspepsia, chemotherapy-induced emesis, gastroparesis).
- Neuropathic Modulator: Gabapentin (Chemotherapy-induced emesis).
- Neurokinin (NK) Receptor Antagonists: Aprepitant, fosaprepitant, netupitant, rolapitant (Chemotherapy-induced emesis).
- 5-HT Agonist and Antidopaminergic: Metoclopramide (Gastroparesis).
- Motilin Agonist: Erythromycin (Gastroparesis, intestinal pseudoobstruction).
- Peripheral Antidopaminergic: Domperidone (Gastroparesis).
- Pure 5-HT Agonist: Prucalopride (Idiopathic gastroparesis).
- Somatostatin Analogue: Octreotide (Intestinal pseudoobstruction).
- Acetylcholinesterase Inhibitor: Pyridostigmine (Small-intestinal dysmotility/pseudoobstruction).
- Special Settings - Benzodiazepines: Lorazepam (Anticipatory nausea and vomiting with chemotherapy, cyclic vomiting syndrome).
- Special Settings - 5-HT Agonist: Buspirone, tandospirone (Functional dyspepsia).

- Special Settings - Glucocorticoids: Methylprednisolone, dexamethasone (Chemotherapy-induced emesis).
- Special Settings - Anticonvulsants: Topiramate, zonisamide, levetiracetam (Cyclic vomiting syndrome).
- Special Settings - Antimigraine Agents: Sumatriptan (Cyclic vomiting syndrome).
- Special Settings - Topical Analgesic: Capsaicin cream (Cannabinoid hyperemesis syndrome).
- Note: Indication is uncertain for some uses (marked with ?).
- Safety: Dopamine antagonists that cross the blood-brain barrier cause anxiety, mood disturbances, movement disorders, and hyperprolactinemic effects (galactorrhea, sexual dysfunction). Metoclopramide causes irreversible movement disorders like tardive dyskinesia, particularly in older patients. Domperidone rarely causes dystonias but can induce hyperprolactinemic side effects. 5-HT antagonists, NK antagonists, and domperidone increase risks of cardiac arrhythmias and sudden cardiac death in those with QTc interval prolongation on ECG. Surveillance ECG testing is advocated for some agents.

**Table 2 Table 48-2 Treatment of Nausea and Vomiting**

Treatment	Mechanism	Examples	Clinical Indications
Antiemetic agents	Antihistaminergic	Dimenhydrinate, meclizine	Motion sickness, inner ear disease
Antiemetic agents	Anticholinergic	Scopolamine	Motion sickness, inner ear disease
Antiemetic agents	Antidopaminergic	Prochlorperazine, thiethylperazine, haloperidol	Medication-, toxin-, or metabolic-induced emesis, chemotherapy-induced emesis, cannabinoid hyperemesis syndrome
Antiemetic agents	5-HT antagonist	Ondansetron, granisetron	Chemotherapy- and radiation-induced emesis, postoperative emesis, opioid-induced nausea and vomiting
Antiemetic agents	Cannabinoids	Tetrahydrocannabinol, cannabidiol	Chemotherapy-induced emesis, gastroparesis
Antiemetic agents	Tricyclic antidepressant	Amitriptyline, nortriptyline	Chronic nausea vomiting syndrome, cyclic vomiting syndrome, gastroparesis
Antiemetic agents	Other antidepressant/atypical antipsychotic	Mirtazapine, olanzapine	Functional dyspepsia, chemotherapy-induced emesis, gastroparesis
Antiemetic agents	Neuropathic modulator	Gabapentin	Chemotherapy-induced emesis
Antiemetic agents	Neurokinin (NK) receptor antagonists	Aprepitant, fosaprepitant, netupitant, rolapitant	Chemotherapy-induced emesis
Prokinetic agents	5-HT agonist and antidopaminergic	Metoclopramide	Gastroparesis

Treatment	Mechanism	Examples	Clinical Indications
Prokinetic agents	Motilin agonist	Erythromycin	Gastroparesis, intestinal pseudoobstruction
Prokinetic agents	Peripheral antidopaminergic	Domperidone	Gastroparesis
Prokinetic agents	Pure 5-HT agonist	Prucalopride	Idiopathic gastroparesis
Prokinetic agents	Somatostatin analogue	Octreotide	Intestinal pseudoobstruction
Prokinetic agents	Acetylcholinesterase inhibitor	Pyridostigmine	Small-intestinal dysmotility/pseudoobstruction
Special settings	Benzodiazepines	Lorazepam	Anticipatory nausea and vomiting with chemotherapy, cyclic vomiting syndrome
Special settings	5-HT agonist	Buspirone, tandospirone	Functional dyspepsia
Special settings	Glucocorticoids	Methylprednisolone, dexamethasone	Chemotherapy-induced emesis
Special settings	Anticonvulsants	Topiramate, zonisamide, levetiracetam	Cyclic vomiting syndrome
Special settings	Antimigraine agents	Sumatriptan	Cyclic vomiting syndrome
Special settings	Topical analgesic	Capsaicin cream	Cannabinoid hyperemesis syndrome

### 7.3 Gastrointestinal Motor Stimulants

- Metoclopramide: A 5-HT agonist and D2 antagonist, is effective in gastroparesis.
- Erythromycin: Increases gastroduodenal motility by action on receptors for motilin, a transmitter that regulates fasting motility. May be useful for short-term use, but its long-term benefits are limited by development of tolerance.
- Domperidone: A D2 antagonist not available in the United States, exhibits prokinetic and antiemetic effects but does not penetrate most brain regions.
- Prucalopride: A 5-HT<sub>4</sub> agonist, accelerates gastric emptying and improves symptoms in idiopathic gastroparesis.
- Octreotide: Induces propagative small-intestinal contractions. May respond to the somatostatin analogue octreotide, which induces propagative small-intestinal contractions.
- Pyridostigmine: Benefits some patients with small-bowel dysmotility.
- Pyloric Botulinum Toxin Injections: Reduced gastroparesis symptoms in uncontrolled studies, but small controlled trials observed benefits no greater than sham treatments.
- Surgical Pyloroplasty and Gastric Peroral Endoscopic Myotomy (G-POEM): Of the pylorus improved symptoms in uncontrolled studies.

### 7.4 Indigestion Management

- Lifestyle, Diet, and Nonmedication Recommendations: Patients with mild indigestion are reassured that careful evaluation revealed no serious disease and are offered no other intervention.

- GERD Patients: Should limit ethanol, caffeine, chocolate, and tobacco use and can ingest smaller low-fat meals with no snacks before bedtime, avoid tight clothing, and elevate the head of the bed.
- Functional Dyspepsia Patients: Are advised to reduce intake of fat, spicy foods, caffeine, and alcohol.
- Dietary Lactose Restriction: Appropriate for lactase deficiency.
- Gluten Exclusion: Indicated for celiac disease.
- Small Studies Suggest Benefits: Of low FODMAP, six-food elimination, and gluten-free diets. These findings warrant confirmation in larger functional dyspepsia cohorts.
- H. pylori Therapy: Those who are H. pylori positive are given therapy to eradicate the infection.
- PPI Therapy: Empiric PPI therapy is reserved for those who are negative for infection or who fail to respond to H. pylori treatment.
- Upper Endoscopy: Indicated for cases with persistent symptoms, atypical presentations, or alarm factors.
- For Heartburn >5 Years in Duration: Especially in patients >50 years old, endoscopy is advocated to screen for Barrett's metaplasia.

## 7.5 Dysphagia Management

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- Treatment of esophageal dysphagia depends on both the locus and the specific etiology.
- Oropharyngeal Dysphagia: Treatment focuses on utilizing postures or maneuvers devised to reduce pharyngeal residue and enhance airway protection learned under the direction of a swallow therapist.
- Aspiration Risk: May be reduced by altering the consistency of ingested food and liquid.
- Cerebrovascular Accident: Dysphagia usually, but not always, spontaneously improves within the first few weeks after the event. More severe and persistent cases may require consideration of gastrostomy and enteral feeding.
- Myasthenia Gravis and Polymyositis: May respond to medical treatment of the primary neuromuscular disease.
- Surgical Intervention: Cricopharyngeal myotomy is usually not helpful, with the exception of specific disorders such as symptomatic cricopharyngeal bar, Zenker's diverticulum, and oculopharyngeal muscular dystrophy.
- Chronic Neurologic Disorders: Parkinson's disease and amyotrophic lateral sclerosis may manifest with severe oropharyngeal dysphagia.
- Feeding Support: Feeding by a nasogastric tube or an endoscopically placed gastrostomy tube may be considered for nutritional support; however, these maneuvers do not provide protection against aspiration of salivary secretions or refluxed gastric contents.
- Esophageal Dysphagia Treatment: The majority of causes of structural, esophageal dysphagia are effectively managed by means of esophageal dilation using bougie or balloon dilators.
- Cancer and Achalasia: Often managed surgically, although endoscopic techniques are available for both palliation and primary therapy, respectively.
- Infectious Etiologies: Respond to antimicrobial medications or treatment of the underlying immunosuppressive state.
- Eosinophilic Esophagitis: Amenable to treatment by elimination of dietary allergens, proton pump inhibition, swallowed topically acting glucocorticoids, and biologic therapies targeting cytokines involved in type 2 inflammation.
- Esophageal Dilation: Used adjunctively for persistent strictures.

## 7.6 CVS and CHS Management

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- CVS: Prophylaxis with tricyclic agents or anticonvulsants (topiramate, zonisamide, levetiracetam) reduces the severity and frequency of CVS attacks in uncontrolled reports.

- Acute CVS Episodes: Combining intravenous 5-HT or NK antagonists with the sedating effects of lorazepam is a mainstay for aborting acute flares in the emergency department.
- CVS: Studies report benefits with aprepitant and injectable or intranasal forms of the 5-HT agonist sumatriptan to manage acute CVS episodes.
- CHS: These treatments are less effective for CHS, but intravenous or intramuscular haloperidol, topical capsaicin cream, or benzodiazepines may reduce acute CHS attacks.
- Taking Prolonged Hot Baths or Showers: Associated with CHS and CVS but is less common with CNVS or gastroparesis.

## 8. PROGNOSIS & COMPLICATIONS

Prognostic considerations for nausea, vomiting, and indigestion.

### 8.1 Gastroparesis

- Idiopathic gastroparesis occurring in the absence of systemic illness is the most prevalent etiology and follows a viral illness in ~15–20% of cases.
- Gastroparesis also occurs after vagotomy or with neoplasm, mesenteric vascular insufficiency, or organic diseases like diabetes, connective tissue diseases including scleroderma, Parkinson's disease, and amyloidosis.
- Rapid gastric emptying is associated with nausea and vomiting in some conditions.
- Intestinal pseudoobstruction is characterized by disrupted intestinal motility with retention of food residue and secretions; bacterial overgrowth; nutrient malabsorption; and symptoms of nausea, vomiting, bloating, pain, and altered defecation.
- Intestinal pseudoobstruction may be idiopathic, inherited, related to a mitochondrial disorder, result from systemic disease like scleroderma or an infiltrative process like amyloidosis, or occur as a paraneoplastic consequence of malignancy.

### 8.2 Malignancy Risk

- Weight loss raises concern about malignancy or ischemia.
- Esophageal adenocarcinoma usually complicates prolonged acid reflux.
- Eight to 20% of GERD patients exhibit esophageal intestinal metaplasia, termed Barrett's metaplasia, which predisposes to esophageal adenocarcinoma.
- Esophageal squamous cell carcinoma occurs most often with long-standing tobacco or ethanol intake.
- Other risks include prior caustic ingestion, achalasia, and the hereditary disorder tylosis.
- Gastric malignancies include adenocarcinoma, which is prevalent in certain Asian societies, and lymphoma.

### 8.3 Safety Considerations

- Dopamine antagonists that cross the blood-brain barrier cause anxiety, mood disturbances, movement disorders, and hyperprolactinemic effects (galactorrhea, sexual dysfunction).
- Metoclopramide causes irreversible movement disorders like tardive dyskinesia, particularly in older patients. This risk should be explained and documented in the medical record.
- Domperidone rarely causes dystonias but can induce hyperprolactinemic side effects by penetrating pituitary regions with a porous blood-brain barrier.
- Domperidone, erythromycin, tricyclic antidepressants, and 5-HT antagonists increase risks of cardiac arrhythmias and sudden cardiac death in those with QTc interval prolongation on ECG.
- Surveillance ECG testing is advocated for some agents.

- Studies of teratogenic effects of antiemetic agents provide conflicting results.
- Antihistamines like meclizine and doxylamine, antidopaminergics like prochlorperazine, and antiserotonergics like ondansetron demonstrate limited efficacy in pregnancy.

## 9. SPECIAL CONSIDERATIONS

Specific considerations for subgroups mentioned in the source text.

### 9.1 Pregnancy

- Nausea affects 70% of women in the first trimester of pregnancy.
- Hyperemesis gravidarum is a severe form of nausea of pregnancy that produces dehydration and electrolyte disturbances and may result from excessive amounts of blood protein—growth differentiation factor 15.
- Clinicians should exercise caution in managing nausea of pregnancy.
- Some obstetricians recommend alternative therapies including pyridoxine, acupuncture, or ginger.

### 9.2 Elderly

- Metoclopramide causes irreversible movement disorders like tardive dyskinesia, particularly in older patients.
- This risk should be explained and documented in the medical record.

### 9.3 Immunocompromised

- Opportunistic organisms like cytomegalovirus or herpes simplex in immunocompromised individuals cause enteric infectious causes of vomiting.

### 9.4 Renal/Hepatic Impairment

- Endogenous toxins are generated in fulminant liver failure.
- Uremia is a metabolic disorder that elicits nausea and vomiting.

## 10. KEY PEARLS & CLINICAL TRAPS

Board-exam favorites, common diagnostic pitfalls, must-not-miss diagnoses, useful mnemonics.

### 10.1 Diagnostic Clues

- Bilious vomiting excludes gastric obstruction.
- Emesis of undigested food is consistent with a Zenker's diverticulum or achalasia.
- Taking prolonged hot baths or showers is associated with CHS and CVS but is less common with CNVS or gastroparesis.
- Vertigo or tinnitus indicates labyrinthine disease.
- Hematemesis raises suspicion of ulcer, malignancy, or Mallory-Weiss tear.
- Feculent emesis is noted with distal intestinal or colonic obstruction.
- Odynophagia suggests esophageal infection.
- Dysphagia is concerning for esophageal blockage.
- Weight loss raises concern about malignancy or ischemia.
- Intracranial sources are considered if there are headaches or visual changes.

### 10.2 Exclusion Criteria

- Upper endoscopy is indicated for cases with persistent symptoms, atypical presentations, or alarm factors (unexplained weight loss, recurrent vomiting, dysphagia, occult or gross bleeding, nocturnal symptoms, jaundice, palpable mass or adenopathy, fever, and a family history of gastrointestinal neoplasm).
- For heartburn >5 years in duration, especially in patients >50 years old, endoscopy is advocated to screen for Barrett's metaplasia.
- Empiric PPI therapy is reserved for those who are negative for infection or who fail to respond to H. pylori treatment.
- Upper endoscopy is advocated to exclude malignancy for patients with unexplained dyspepsia who are >60 years old, who report alarm symptoms, or who fail to respond to these therapies.

### 10.3 Safety Traps

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- Metoclopramide causes irreversible movement disorders like tardive dyskinesia, particularly in older patients.
- Domperidone, erythromycin, tricyclic antidepressants, and 5-HT antagonists increase risks of cardiac arrhythmias and sudden cardiac death in those with QTc interval prolongation on ECG.
- Surveillance ECG testing is advocated for some agents.
- Dopamine antagonists that cross the blood-brain barrier cause anxiety, mood disturbances, movement disorders, and hyperprolactinemic effects (galactorrhea, sexual dysfunction).