Chapter 45: Nausea, Vomiting, and Indigestion

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INTRODUCTION

Nausea is the feeling of a need to vomit. *Vomiting* (emesis) is the oral expulsion of gastrointestinal contents resulting from gut and thoracoabdominal wall contractions. Vomiting is contrasted with *regurgitation,* the effortless passage of gastric contents into the mouth. *Rumination* is the repeated regurgitation of food residue, which may be rechewed and reswallowed. In contrast to emesis, these phenomena exhibit volitional control. *Indigestion* encompasses a range of complaints including nausea, vomiting, heartburn, regurgitation, and dyspepsia (symptoms thought to originate in the gastroduodenal region). Some individuals with dyspepsia experience postprandial fullness, early satiety (inability to complete a meal due to premature fullness), bloating, eructation (belching), and anorexia. Others report predominantly epigastric burning or pain. Nausea, vomiting, and dyspepsia have been correlated with a condition now called avoidant/restrictive food intake disorder.

NAUSEA AND VOMITING

MECHANISMS

Vomiting is coordinated by the brainstem and is effected by responses in the gut, pharynx, and somatic musculature. Mechanisms underlying nausea are poorly understood but likely involve the cerebral cortex, as nausea requires cognitive and emotional input and is associated with autonomic responses including diaphoresis, pallor, and 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.

Coordination of Emesis

Brainstem nuclei—including the nucleus tractus solitarius; dorsal vagal and phrenic nuclei; medullary nuclei regulating respiration; and nuclei that control pharyngeal, facial, and tongue movements—coordinate initiation of emesis involving neurokinin NK_1, serotonin 5-HT_3, endocannabinoid, and vasopressin pathways.

Somatic and visceral muscles respond stereotypically during emesis. Inspiratory thoracic and abdominal wall muscles contract, increasing intrathoracic and intraabdominal pressures to evacuate the stomach. Under normal conditions, distally migrating gut contractions are coordinated by an electrical phenomenon, the slow wave, which cycles at 3 cycles/min in the stomach and 11 cycles/min in the duodenum. During emesis, slow waves are abolished and replaced by orally propagating spikes that evoke retrograde contractions to facilitate expulsion of gut contents.

Activators of Emesis

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 gastroduodenal 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, hypoxia, ketoacidosis) and is termed the *chemoreceptor trigger zone.*

Neurotransmitters mediating vomiting are selective for different sites. Labyrinthine disorders stimulate vestibular muscarinic M_1 and histaminergic H_1 receptors. Vagal afferent stimuli activate 5-HT_3 receptors. The area postrema is served by nerves acting on 5-HT_3, M_1, H_1, and dopamine D_2 subtypes. NK_1 receptors in the central nervous system (CNS) mediate both nausea and vomiting. Cannabinoid CB_1 pathways may participate in the cerebral cortex and brainstem. Therapies for vomiting act on these receptor-mediated pathways.

DIFFERENTIAL DIAGNOSIS

Nausea and vomiting are caused by conditions within and outside the gut, drugs, and circulating toxins **(Table 45-1)**. Unexplained chronic nausea and vomiting is reported by 2–3% of the population.

TABLE 45-1

Causes of Nausea and Vomiting

INTRAPERITONEAL	EXTRAPERITONEAL	MEDICATIONS/METABOLIC DISORDERS
Obstructing disorders	Cardiopulmonary disease	Drugs
Pyloric obstruction	Cardiomyopathy	Cancer chemotherapy
Small-bowel obstruction	Myocardial infarction	Analgesics
Colonic obstruction	Labyrinthine disease	Opioids
Superior mesenteric artery syndrome	Motion sickness	Antibiotics
Enteric infections	Labyrinthitis	Cardiac antiarrhythmics
Viral	Malignancy	Digoxin
Bacterial	Intracerebral disorders	Oral hypoglycemics
Inflammatory diseases	Malignancy	Oral contraceptives
Cholecystitis	Hemorrhage	Antidepressants
Pancreatitis	Abscess	Restless legs/Parkinson's therapies
Appendicitis	Hydrocephalus	Smoking cessation agents
Hepatitis	Psychiatric illness	Endocrine/metabolic disease
Altered sensorimotor function	Anorexia and bulimia nervosa	Pregnancy
Gastroparesis	Depression	Uremia
Intestinal pseudoobstruction	Postoperative vomiting	Ketoacidosis
Gastroesophageal reflux		Thyroid and parathyroid disease
Chronic nausea vomiting syndrome		Adrenal insufficiency
Cyclic vomiting syndrome		Toxins
Cannabinoid hyperemesis syndrome		Liver failure
Rumination syndrome		Ethanol
Mesenteric insufficiency		
Celiac artery stenosis		
Median arcuate ligament syndrome		
Biliary colic		
Abdominal irradiation		

Intraperitoneal Disorders

Obstruction and inflammation of hollow and solid viscera may elicit vomiting. Ulcers and malignancy cause gastric obstruction, while adhesions, benign or malignant tumors, volvulus, intussusception, or inflammatory diseases like Crohn's disease cause small intestinal and colonic obstruction. The superior mesenteric artery syndrome, occurring after weight loss or prolonged bed rest, results when the duodenum is compressed by the overlying superior mesenteric artery. Median arcuate ligament syndrome, with compression of the celiac artery, is a rare cause of vomiting. Abdominal irradiation impairs intestinal motility and induces strictures. Biliary colic causes nausea by acting on afferent nerves. Vomiting with pancreatitis, cholecystitis, and appendicitis results from visceral irritation and induction of ileus. Enteric infectious causes of vomiting include viruses (norovirus, rotavirus), bacteria (*Staphylococcus aureus, Bacillus cereus*), and opportunistic organisms like cytomegalovirus or herpes simplex in immunocompromised individuals.

Gut sensorimotor dysfunction often causes nausea and vomiting. *Gastroparesis* presents with these symptoms with evidence of delayed gastric emptying and occurs after vagotomy or with pancreatic carcinoma, mesenteric vascular insufficiency, or organic diseases like diabetes, scleroderma, and amyloidosis. Idiopathic gastroparesis is the most prevalent etiology; it occurs in the absence of systemic illness and follow a viral illness in ~15–20% of cases. 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, result from systemic disease like scleroderma or an infiltrative process like amyloidosis, or occur as a paraneoplastic consequence of malignancy (e.g., small-cell lung carcinoma). Patients with gastroesophageal reflux, irritable bowel syndrome (IBS), or chronic constipation often report nausea and vomiting.

Other functional gastroduodenal disorders without organic abnormalities have been characterized. *Chronic nausea vomiting syndrome* is defined as bothersome nausea at least 1 day and/or one or more vomiting episodes weekly in the absence of an eating disorder or psychiatric disease. *Cyclic vomiting syndrome (CVS)* causes 3–14% of cases of unexplained nausea and vomiting and presents with discrete episodes of relentless vomiting and is associated with migraines. Some adult cases have been associated with rapid gastric emptying. A related condition, *cannabinoid hyperemesis syndrome (CHS)*, presents with cyclical vomiting in individuals (mostly men) with long-standing use of large quantities of cannabis and resolves with its discontinuation. *Rumination syndrome* is often misdiagnosed as refractory vomiting.

Extraperitoneal Disorders

Myocardial infarction and congestive heart failure may cause nausea and vomiting. Postoperative emesis occurs after 25% of surgeries, especially abdominal and orthopedic surgery. Increased intracranial pressure from tumors, bleeding, abscess, or blockage of cerebrospinal fluid outflow produces vomiting with or without nausea. Patients with anorexia nervosa, bulimia nervosa, anxiety, and depression often report significant nausea associated with delayed gastric emptying.

Medications and Metabolic Disorders

Drugs evoke vomiting by action on the stomach (analgesics, erythromycin) or area postrema (opioids, anti-parkinsonian drugs). Other emetogenic agents include antibiotics, cardiac antiarrhythmics, antihypertensives, oral hypoglycemics, antidepressants (selective serotonin and serotonin norepinephrine reuptake inhibitors), smoking cessation drugs (varenicline, nicotine), and contraceptives. Cancer chemotherapy causes acute (within hours of administration), delayed (after 1 or more days), or anticipatory vomiting. Acute emesis from highly emetogenic agents (e.g., cisplatin) is mediated by 5-HT_3 pathways. Delayed emesis is more dependent on NK_1 mechanisms. Anticipatory nausea may respond to anxiolytic therapy rather than antiemetics.

Metabolic disorders elicit nausea and vomiting. 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 has been proposed to result from excessive amounts of a blood protein—growth differentiation factor 15. Uremia, ketoacidosis, adrenal insufficiency, and parathyroid and thyroid disease are other metabolic etiologies.

Circulating toxins evoke emesis via effects on the area postrema. 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.

APPROACH TO THE PATIENT WITH NAUSEA AND VOMITING

History and Physical Examination

The history helps define the etiology of nausea and vomiting. Drugs, toxins, and infections often cause acute symptoms, whereas established illnesses evoke chronic complaints. Gastroparesis and pyloric obstruction elicit vomiting within an hour of eating. Emesis from intestinal blockage occurs later. Vomiting occurring minutes after meal consumption prompts consideration of rumination syndrome. With severe gastric emptying delays, vomitus may contain food residue ingested days before. Hematemesis raises suspicion of ulcer, malignancy, or Mallory-Weiss tear. Feculent emesis is noted with distal intestinal or colonic obstruction. Bilious vomiting excludes gastric obstruction, whereas 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. Taking prolonged hot baths or showers is associated with CHS and CVS. Intracranial sources are

considered if there are headaches or visual changes. Vertigo or tinnitus indicates labyrinthine disease.

The physical examination complements the history. Orthostatic hypotension and reduced skin turgor indicate intravascular fluid loss. Pulmonary abnormalities raise concern for aspiration of vomitus. Bowel sounds are absent with ileus. High-pitched rushes suggest bowel obstruction, whereas a succussion splash is found with gastroparesis or pyloric obstruction. Involuntary guarding raises suspicion of inflammation. Fecal blood suggests ulcer, ischemia, or tumor. Neurologic disease presents with papilledema, visual loss, or focal neural abnormalities. Neoplasm is suggested by palpable masses or adenopathy.

Diagnostic Testing

For intractable symptoms or an elusive diagnosis, screening testing can direct care. Electrolyte replacement is indicated for hypokalemia or metabolic alkalosis. Iron-deficiency anemia mandates exclusion of mucosal causes. Abnormal pancreatic or liver biochemistries are found with pancreaticobiliary disease. Endocrinologic, rheumatologic, or paraneoplastic etiologies are suggested by hormone or serologic abnormalities. Supine and upright abdominal radiographs may show intestinal air-fluid levels and reduced colonic air with small-bowel obstruction. Ileus is characterized by diffusely dilated air-filled bowel loops.

Anatomic studies are indicated if initial testing is nondiagnostic. Upper endoscopy detects ulcers, malignancy, and retained food in gastroparesis. Small-bowel barium radiography or computed tomography (CT) diagnoses partial bowel obstruction. Colonoscopy or contrast enema radiography detects colonic obstruction. Ultrasound or CT defines intraperitoneal inflammation; CT and magnetic resonance imaging (MRI) enterography define inflammation in Crohn's disease. Brain CT or MRI delineates intracranial disease. Mesenteric angiography, CT, or MRI is useful for suspected ischemia.

Gastrointestinal motility testing can detect an underlying motor disorder. Gastroparesis commonly is diagnosed by gastric scintigraphy, which measures emptying of a radiolabeled meal. A nonradioactive ^{13}C-labeled gastric emptying breath test is an alternative to scintigraphy. Intestinal pseudoobstruction is suggested by luminal dilation on imaging or abnormal transit on contrast radiography or intestinal scintigraphy. Wireless motility capsules diagnose gastroparesis or small-bowel dysmotility by detecting local or generalized transit delays in the stomach or small bowel from characteristic pH changes between regions. Small-intestinal manometry confirms a diagnosis of pseudoobstruction and discriminates between neuropathic or myopathic disease based on contractile patterns. Manometry can obviate the need for surgical intestinal biopsy to detect smooth muscle or neuronal degeneration. Combined ambulatory esophageal pH/impedance testing and high-resolution manometry facilitates diagnosis of rumination syndrome. Impedance planimetry detects reduced pyloric distensibility in some cases of gastroparesis.

TREATMENT OF NAUSEA AND VOMITING

General Principles

Therapy of vomiting is tailored to correct remediable abnormalities if possible. Patients with severe dehydration should be hospitalized if oral fluid replenishment is unsustainable. Once oral intake is tolerated, low-fat liquid nutrients are restarted because lipids delay gastric emptying. Low-residue, small-particle diets have shown efficacy in gastroparesis. Glycemic control should be optimized to reduce diabetic gastroparesis symptoms.

Antiemetic Medications

Most antiemetic agents act on CNS sites **(Table 45-2)**. Antihistamines like dimenhydrinate and meclizine and anticholinergics like scopolamine act on vestibular pathways to treat motion sickness and labyrinthine disorders. D_2 antagonists treat emesis evoked by area postrema stimuli including medications, toxins, and metabolic disturbances. Dopamine antagonists cross the blood-brain barrier and cause anxiety, movement disorders, and hyperprolactinemic effects (galactorrhea, sexual dysfunction).

TABLE 45-2

Treatment of Nausea and Vomiting

TREATMENT	MECHANISM	EXAMPLES	CLINICAL INDICATIONS
Antiemetic	Antihistaminergic	Dimenhydrinate, meclizine	Motion sickness, inner ear disease

agents			
	Anticholinergic	Scopolamine	Motion sickness, inner ear disease
	Antidopaminergic	Prochlorperazine, thiethylperazine, haloperidol	Medication-, toxin-, or metabolic-induced emesis, chemotherapy-induced nausea and vomiting, ?cannabinoid hyperemesis syndrome
	5-HT_3 antagonist	Ondansetron, granisetron	Chemotherapy- and radiation-induced emesis, postoperative emesis, opioid-induced nausea and vomiting
	Cannabinoids	Tetrahydrocannabinol	Chemotherapy-induced emesis
	Tricyclic antidepressant	Amitriptyline, nortriptyline	Functional vomiting, chronic idiopathic nausea, cyclic vomiting syndrome, ? gastroparesis
	Other antidepressant	Mirtazapine, olanzapine	Functional dyspepsia, ?gastroparesis
	Neuropathic modulator	Gabapentin	Chemotherapy-induced nausea and vomiting
	Neurokinin (NK1) receptor antagonists	Aprepitant, fosaprepitant, netupitant, rolapitant	Chemotherapy-induced emesis
Prokinetic agents	5-HT_4 agonist and antidopaminergic	Metoclopramide	Gastroparesis
	Motilin agonist	Erythromycin	Gastroparesis, ?intestinal pseudoobstruction
	Peripheral antidopaminergic	Domperidone	Gastroparesis
	Pure 5-HT_4 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
	5-HT_{1A} agonist	Buspirone	Functional dyspepsia
	Glucocorticoids	Methylprednisolone, dexamethasone	Chemotherapy-induced emesis
	Anticonvulsants	Topiramate, zonisamide, levetiracetam	Cyclic vomiting syndrome

	Antimigraine agents	Sumatriptan	Cyclic vomiting syndrome
	Topical analgesic	Capsaicin cream	?Cannabinoid hyperemesis syndrome
	Atypical antipsychotic agent	Olanzapine	Chemotherapy-induced and breakthrough emesis

Note: ?, indication is uncertain.

Other classes exhibit antiemetic properties. 5-HT_3 antagonists like ondansetron and granisetron prevent postoperative vomiting, radiation therapy–induced symptoms, and cancer chemotherapy–induced emesis, but also are used for other conditions. NK_1 antagonists like aprepitant are approved for chemotherapy-induced vomiting. Aprepitant reduces gastroparesis symptoms. Tricyclic antidepressants reduce symptoms in some patients with functional causes of vomiting, but did not show benefits in a controlled trial in gastroparesis. Other antidepressants such as mirtazapine and olanzapine and the pain-modulating agent gabapentin also exhibit antiemetic effects in some clinical settings.

Gastrointestinal Motor Stimulants

Drugs that stimulate gastric emptying are used for gastroparesis (Table 45-2). Metoclopramide, a combined 5-HT_4 agonist and D_2 antagonist, is effective in gastroparesis, but antidopaminergic side effects, including dystonias and mood disturbances, limit use in ~25% of cases. Erythromycin increases gastroduodenal motility by action on receptors for motilin, an endogenous transmitter that regulates fasting motility. Intravenous erythromycin is useful for inpatients with refractory gastroparesis. Benefits of long-term oral erythromycin are limited by development of tolerance. Domperidone, a D_2 antagonist not available in the United States, exhibits prokinetic and antiemetic effects but does not cross into most brain regions. The drug rarely causes dystonic reactions but can induce hyperprolactinemic side effects via penetration of pituitary regions served by a porous blood-brain barrier. Prucalopride, a 5-HT_4 agonist, has shown efficacy in accelerating gastric emptying and improving symptoms in idiopathic gastroparesis.

Refractory motility disorders pose challenges. Intestinal pseudoobstruction may respond to the somatostatin analogue octreotide, which induces propagative small-intestinal motor complexes. Acetylcholinesterase inhibitors like pyridostigmine benefit 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 case series. Enteral feedings through a jejunostomy reduce hospitalizations and improve overall health in some patients with refractory gastroparesis. Subtotal gastric resection may improve some cases of postvagotomy gastroparesis, but its utility for other gastroparesis etiologies is unproven. Implanted gastric electrical stimulators may reduce symptoms, enhance nutrition, improve quality of life, and decrease health care expenditures in medication-refractory gastroparesis; a controlled trial has confirmed modest improvement in vomiting.

Safety Considerations

Safety concerns have been raised about selected antiemetics. Metoclopramide can cause irreversible movement disorders like tardive dyskinesia, particularly in older patients. This complication should be explained and documented in the medical record. Domperidone, erythromycin, tricyclic antidepressants, and 5-HT_3 antagonists increase risk of cardiac arrhythmias and sudden cardiac death in those with QTc interval prolongation on electrocardiography (ECG). Surveillance ECG testing is advocated for some of these agents.

Other Clinical Settings

Some cancer chemotherapies are intensely emetogenic **(Chap. 73)**. Combining a 5-HT_3 antagonist, an NK_1 antagonist, and a glucocorticoid can control both acute and delayed vomiting after highly emetogenic chemotherapy. Benzodiazepines like lorazepam reduce anticipatory nausea and vomiting. Other therapies with benefit in chemotherapy-induced emesis include cannabinoids, olanzapine, gabapentin, and alternative therapies like ginger. Most antiemetic regimens produce greater reductions in chemotherapy-induced vomiting than nausea.

Clinicians should exercise caution in managing nausea of pregnancy. Studies of the teratogenic effects of antiemetic agents provide conflicting results.

Antihistamines like meclizine and doxylamine, antidopaminergics like prochlorperazine, and antiserotonergics like ondansetron demonstrate limited efficacy. Some obstetricians recommend alternative therapies including pyridoxine, acupressure, or ginger.

Managing CVS and CHS is challenging. Prophylaxis with tricyclic antidepressants or anticonvulsants (topiramate, zonisamide, levetiracetam) reduces the severity and frequency of CVS attacks in uncontrolled reports. Combining intravenous 5-HT_3 antagonists with the sedating effects of a benzodiazepine like lorazepam are mainstays for aborting acute flares. Small studies report benefits with aprepitant and injectable or intranasal forms of the 5-HT_1 agonist sumatriptan to manage acute CVS episodes. These treatments are reportedly less effective for CHS, but haloperidol and topical capsaicin cream may reduce acute CHS attacks.

INDIGESTION

MECHANISMS

Several mechanisms may contribute to indigestion, including acid reflux, altered gut motility or sensation, inflammation, and microbial processes.

Gastroesophageal Reflux

Gastroesophageal reflux results from many defects. Reduced lower esophageal sphincter (LES) tone causes reflux in scleroderma and pregnancy and may 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 fluid clearance. Increased intragastric pressure promotes gastroesophageal reflux with obesity. Many reflux patients have hiatal hernias, and large hernias can increase symptomatic reflux.

Gastric Motor Dysfunction

Disturbed gastric motility may contribute to gastroesophageal reflux in up to one-third of cases. Delayed gastric emptying is found in ~30% of functional dyspeptics, while rapid gastric emptying affects 5%. Impaired 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 35% of dyspeptic patients note discomfort with fundic distention to lower pressures than in healthy controls. Other individuals with dyspepsia exhibit hypersensitivity to chemical stimulation of the stomach with capsaicin or with duodenal acid or lipid perfusion. Some cases of functional heartburn without increased acid or nonacid reflux exhibit heightened perception of normal esophageal acidity.

Immune Activation

Increases in duodenal epithelial permeability in functional dyspepsia may relate to increases in eosinophils and mast cells adjacent to submucosal neurons. Increased activation of these cells is proposed to contribute to gastric emptying delays and altered sensory function in functional dyspepsia and may selectively elicit early satiety and epigastric pain. Proliferations in duodenal bacteria were shown to correlate with meal-induced symptoms in functional dyspepsia, suggesting a role for microbiome alterations. Intestinal bile salt release also is proposed to worsen dyspeptic symptoms after eating. Both dysbiosis and bile may contribute to mucosal permeability defects.

Other Factors

Helicobacter pylori has a proven etiologic role in peptic ulcer disease but is a minor factor in the genesis of functional dyspepsia. Anxiety and depression may play contributing roles in some functional dyspepsia cases. Functional MRI studies show increased activation of several brain regions, emphasizing CNS contributions. Up to 20% of functional dyspepsia patients report symptom onset after a viral illness, suggesting an infectious trigger. Analgesics cause dyspepsia, whereas nitrates, calcium channel blockers, theophylline, and progesterone promote gastroesophageal reflux. Ethanol, tobacco, and caffeine induce LES relaxation and reflux. Genetic factors predispose to development of reflux and dyspepsia in some cases.

DIFFERENTIAL DIAGNOSIS

Gastroesophageal Reflux Disease

Heartburn or regurgitation is reported weekly by 18–28% of the population, highlighting the prevalence of gastroesophageal reflux disease (GERD). Most cases of heartburn result from excess acid reflux, but reflux of weakly acidic or nonacidic fluid can produce similar symptoms. Alkaline reflux esophagitis elicits GERD symptoms in patients who have had surgery for peptic ulcer disease. Ten percent of patients with heartburn exhibit no acidic or nonacidic esophageal reflux and are considered to have functional heartburn.

Functional Dyspepsia

Approximately 20% of the populace has dyspepsia at least six times yearly, but only 10–20% present to clinicians. Functional dyspepsia, the cause of symptoms in 70–80% of dyspeptic patients, is defined as bothersome postprandial fullness, early satiety, or epigastric pain or burning with symptom onset ≥6 months before diagnosis in the absence of organic cause. Functional dyspepsia is subdivided into postprandial distress syndrome (61% of cases), characterized by meal-induced fullness and early satiety, and epigastric pain syndrome (18% of cases), with epigastric pain or burning that may or may not be meal related. Twenty-one percent of individuals present with overlapping postprandial distress and epigastric pain syndromes. Functional dyspepsia is associated with other functional gut disorders including irritable bowel syndrome and nongastrointestinal disorders like fibromyalgia, chronic fatigue, and anxiety. Most cases follow a benign course, but some with *H. pylori* infection or on nonsteroidal anti-inflammatory drugs (NSAIDs) develop ulcers.

Ulcer Disease

Most GERD patients do not exhibit esophageal injury, but 5% develop esophageal ulcers. Symptoms cannot distinguish nonerosive from erosive or ulcerative esophagitis. A minority of cases of dyspepsia stem from gastric or duodenal ulcers. The most common causes of ulcers are *H. pylori* infection and NSAID use. Other rare causes of gastroduodenal ulcers include Crohn's disease **(Chap. 326)** and Zollinger-Ellison syndrome **(Chap. 324)**, resulting from gastrin overproduction by an endocrine tumor.

Malignancy

Dyspeptic patients may seek care because of fear of cancer, but few cases result from malignancy. 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. 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 **(Chap. 80)**. Gastric malignancies include adenocarcinoma, which is prevalent in certain Asian societies, and lymphoma.

Other Causes

Opportunistic fungal or viral esophageal infections may produce heartburn but more often cause odynophagia. Other causes of esophageal inflammation include eosinophilic esophagitis and pill esophagitis. Biliary colic is a potential cause unexplained upper abdominal pain, but most patients report discrete acute episodes of right upper quadrant or epigastric pain rather than chronic burning or fullness. Twenty percent of gastroparesis patients note a predominance of pain rather than nausea and vomiting. Intestinal lactase deficiency may cause gas, bloating, and discomfort and occurs more commonly in blacks and Asians. Intolerance of other carbohydrates (e.g., fructose, sorbitol) produces similar symptoms. Small-intestinal bacterial overgrowth may cause dyspepsia, as well as bowel dysfunction, distention, and malabsorption. Celiac disease, nonceliac gluten sensitivity, pancreatic disease (chronic pancreatitis, malignancy), hepatocellular carcinoma, Ménétrier's disease, infiltrative diseases (sarcoidosis, mastocytosis, eosinophilic gastroenteritis), mesenteric ischemia, thyroid and parathyroid disease, and abdominal wall strain cause dyspepsia. Extraperitoneal etiologies of indigestion include congestive heart failure and tuberculosis.

APPROACH TO THE PATIENT WITH INDIGESTION

History and Physical Examination

Managing indigestion requires a thorough interview. GERD classically produces heartburn, a substernal warmth that moves toward the neck.

Heartburn often is exacerbated by meals and may awaken the patient. Associated symptoms include regurgitation of acid or nonacidic fluid and water brash, the reflex release of salty saliva into the mouth. Atypical symptoms include pharyngitis, asthma, cough, bronchitis, hoarseness, and chest pain that mimics angina. Some patients with acid reflux on esophageal pH testing note abdominal pain instead of heartburn.

Dyspeptic patients report symptoms referable to the upper abdomen that may be meal-related (postprandial distress syndrome) or independent of food ingestion (epigastric pain syndrome). The history in functional dyspepsia may also report symptoms of GERD, IBS, or idiopathic gastroparesis.

The physical exam with GERD and functional dyspepsia usually is normal. In atypical GERD, pharyngeal erythema and wheezing may be noted. Recurrent regurgitation may cause poor dentition. Dyspeptics may exhibit epigastric tenderness or distention.

Discriminating functional from organic causes of indigestion mandates excluding certain historic and exam features. Odynophagia suggests esophageal infection. Dysphagia is concerning for a benign or malignant esophageal blockage. Other alarm features include unexplained weight loss, recurrent vomiting, dysphagia, occult or gross bleeding, nocturnal symptoms, jaundice, palpable mass or adenopathy, and a family history of gastrointestinal neoplasm. Patients with an abdominal wall source of upper abdominal pain may exhibit a positive Carnett's sign of increased tenderness with tensing of abdominal muscles upon lifting the head from the exam table.

Diagnostic Testing

Because indigestion is prevalent and most cases result from GERD or functional dyspepsia, it is generally recommended to perform no more than limited and directed diagnostic testing in most individuals.

After excluding alarm factors **(Table 45-3)**, patients with typical GERD do not need further evaluation and are treated empirically. Upper endoscopy is indicated only in cases with atypical symptoms or these alarm factors. For heartburn >5 years in duration, especially in patients >50 years old, endoscopy is advocated to screen for Barrett's metaplasia. Endoscopy is not needed in low-risk patients who respond to acid suppressants. Ambulatory esophageal pH testing using a catheter method or a wireless capsule endoscopically attached to the esophageal wall is considered for drug-refractory symptoms and atypical symptoms like unexplained chest pain. High-resolution esophageal manometry is ordered when surgical treatment of GERD is considered. A low LES pressure predicts failure of drug therapy and provides a rationale to proceed to surgery. Poor esophageal body peristalsis raises concern about postoperative dysphagia and directs the choice of surgical technique. Nonacidic reflux may be detected by combined esophageal impedance-pH testing in medication-unresponsive patients.

TABLE 45-3

Alarm Symptoms in Gastroesophageal Reflux Disease

Odynophagia or dysphagia
Unexplained weight loss
Recurrent vomiting
Occult or gross gastrointestinal bleeding
Jaundice
Palpable mass or adenopathy
Family history of gastroesophageal malignancy

Upper endoscopy is recommended as the initial test in patients with unexplained dyspepsia who are >60 years old to exclude malignancy—a finding in only 0.3% of endoscopies performed for uninvestigated dyspepsia. Management of patients <60 years old depends on the local *H. pylori* prevalence. In regions with low prevalence (<10%), a 4-week trial of an acid-suppressing medication such as a proton pump inhibitor (PPI) is recommended. If empiric

acid suppression fails, a "test and treat" approach for *H. pylori* status is initiated with urea breath testing or stool antigen measurement. Those who are *H. pylori* positive are given therapy to eradicate infection. For patients in areas with high *H. pylori* prevalence (>10%), an initial "test and treat" approach is advocated, and empiric PPI therapy is reserved for those who are negative for infection or who fail to respond to *H. pylori* treatment. Patients who are treated for *H. pylori* should undergo confirmation of eradication with repeat urea breath testing or fecal antigen testing 4–6 weeks after completing therapy. Those under age 60 only warrant upper endoscopy if their symptoms fail to respond to these therapies. Some advocate initial endoscopy for patients <60 years old who report alarm symptoms, but some guidelines have not endorsed this practice unless symptoms persist despite treatment.

Further testing is indicated in some settings. For suspected bleeding, a blood count can exclude anemia. Thyroid chemistries or calcium levels screen for metabolic disease. Specific serologies may suggest celiac disease. Pancreatic and liver chemistries are obtained for suspected pancreaticobiliary causes, which are further investigated with ultrasound, CT, or MRI. Gastric emptying testing is considered to exclude gastroparesis for dyspeptic symptoms resembling postprandial distress when therapy fails. Breath testing after carbohydrate ingestion detects lactase deficiency, intolerance to other carbohydrates, or small-intestinal bacterial overgrowth.

TREATMENT OF INDIGESTION

Lifestyle, Diet, and Nonmedication Recommendations

Patients with mild indigestion can be reassured that a careful evaluation revealed no serious disease and are offered no other intervention. If possible, drugs that cause gastroesophageal reflux or dyspepsia should be stopped. GERD patients should limit ethanol, caffeine, chocolate, and tobacco use and can ingest a low-fat diet, avoid snacks before bedtime, and elevate the head of the bed. Functional dyspepsia patients can be advised to reduce intake of fat, spicy foods, caffeine, and alcohol. Dietary lactose restriction is appropriate for lactase deficiency, while gluten exclusion is indicated for celiac disease. Low FODMAP (fermentable oligosaccharide, disaccharide, monosaccharide, and polyol) diets are effective for gaseous symptoms in IBS. In a systematic review, FODMAP intake correlated with functional dyspepsia symptoms, suggesting potential utility in this disorder as well.

Acid-Suppressing or -Neutralizing Medications

Drugs that reduce or neutralize gastric acid are often prescribed for GERD. Histamine H_2 antagonists like cimetidine, ranitidine, famotidine, and nizatidine are useful in mild to moderate GERD. For severe symptoms or for many cases of erosive or ulcerative esophagitis, PPIs like omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, or dexlansoprazole are needed. These drugs inhibit gastric H^+, K^+-ATPase and are more potent than H_2 antagonists. Up to one-third of GERD patients do not respond to standard PPI doses; one-third of these patients have nonacidic reflux, whereas 10% have persistent acid-related disease. Heartburn responds better to PPI therapy than regurgitation or atypical GERD symptoms. Some individuals respond to doubling of the PPI dose or adding an H_2 antagonist. Complications of long-term PPI therapy include diarrhea (*Clostridium difficile* infection, microscopic colitis), small-intestinal bacterial overgrowth, nutrient deficiency (vitamin B_{12}, iron, calcium), hypomagnesemia, bone demineralization, interstitial nephritis, and impaired medication absorption (clopidogrel). Many patients started on a PPI can be stepped down to an H_2 antagonist or switched to on-demand use.

Acid suppressants also are effective for both the postprandial distress and epigastric pain subtypes of functional dyspepsia. A meta-analysis of 18 controlled trials calculated a risk ratio of 0.88, with a 95% confidence interval of 0.82–0.94, favoring PPI therapy over placebo in functional dyspepsia. H_2 antagonists also improve symptoms in functional dyspepsia, but a guideline has advocated PPIs over H_2 antagonists as first-line therapies for functional dyspepsia. In addition to acid suppression, PPIs may have the additional action of reducing duodenal eosinophil counts in dyspepsia.

Antacids are useful for short-term control of mild GERD but have less benefit in severe cases unless given at high doses that cause side effects (diarrhea and constipation with magnesium- and aluminum-containing agents, respectively). Alginic acid combined with antacids forms a floating barrier to reflux in patients with upright symptoms. Sucralfate, a salt of aluminum hydroxide and sucrose octasulfate that buffers acid and binds pepsin and bile salts, shows efficacy in GERD similar to H_2 antagonists.

Helicobacter Pylori Eradication

H. pylori eradication is indicated for peptic ulcer and mucosa-associated lymphoid tissue gastric lymphoma. The benefits of eradication therapy in

functional dyspepsia are limited but are statistically significant. A systematic review of 25 controlled trials calculated a pooled risk ratio of 1.24, with a 95% confidence interval of 1.12–1.37, favoring *H. pylori* eradication over placebo. Most drug combinations **(Chaps. 163 and 324)** include 7–14 days of a PPI with two or three antibiotics with or without bismuth products. *H. pylori* infection is associated with reduced prevalence of GERD. However, eradication of infection does not worsen GERD symptoms. No consensus recommendations regarding *H. pylori* eradication in GERD patients have been offered.

Agents that Modify Gastrointestinal Motor Activity

The γ-aminobutyric acid B (GABA-B) agonist baclofen reduces esophageal exposure to acid and nonacidic fluids by reducing TLESRs by 40%. This drug can be used in patients with refractory acid or nonacid reflux. Several studies have promoted the efficacy of agents that stimulate gastric emptying in functional dyspepsia with 33% relative risk reductions, but publication bias and small sample sizes raise questions about reported benefits of these agents. Some clinicians suggest that patients with the postprandial distress subtype may respond preferentially to such prokinetic drugs. The newer 5-HT_4 agonist prucalopride was reported to reduce symptoms in patients with idiopathic gastroparesis, but no similar studies have been conducted in functional dyspepsia. The 5-HT_{1A} agonists buspirone and tandospirone may improve some functional dyspepsia symptoms by enhancing meal-induced gastric accommodation. Acotiamide stimulates gastric emptying and augments accommodation by enhancing acetylcholine release via muscarinic receptor antagonism and acetylcholinesterase inhibition. This agent is approved for functional dyspepsia in Japan and India.

Antidepressants

Some patients with refractory functional heartburn may respond to antidepressants in the tricyclic and selective serotonin reuptake inhibitor (SSRI) classes, although studies are limited. Their mechanism of action may involve blunting of visceral pain processing in the brain. In a controlled trial in functional dyspepsia, the tricyclic drug amitriptyline produced symptom reductions, whereas the SSRI escitalopram had no benefit in a three-way comparison with placebo. In another controlled trial in functional dyspepsia, the antidepressant mirtazapine produced superior symptom reductions versus placebo. However, in a meta-analysis of 13 trials, SSRIs and serotonin-norepinephrine reuptake inhibitors showed no benefits in functional dyspepsia.

Other Options

Antireflux surgery (fundoplication) to enhance the barrier function of the LES may be offered to GERD patients who are young and require lifelong therapy, have typical heartburn, are responsive to PPIs, and show acid reflux on pH monitoring. Surgery also is effective for some cases of nonacidic reflux. Individuals who respond less well to fundoplication include those with atypical symptoms, those who have functional heartburn without reflux on testing, or those who have esophageal body motor disturbances. Dysphagia, gas-bloat syndrome, and gastroparesis are long-term complications of fundoplication; ~60% develop recurrent GERD symptoms over time. Magnetic sphincter augmentation may be appropriate for GERD treatment, while endoscopic radiofrequency therapies can be considered for some patients. Other endoscopic options including transoral incisionless fundoplication, endoscopic stapling, and antireflux mucosectomy are not yet advocated.

Gas and bloating are bothersome in some patients with indigestion and are difficult to treat. Simethicone, activated charcoal, and alpha-galactosidase provide benefits in some cases. One trial suggested possible benefits of the nonabsorbable antibiotic rifaximin in functional dyspepsia, while another reported improvement with the probiotic *Lactobacillus gasseri*. Herbal remedies like STW 5 (Iberogast, a mixture of nine herbal agents) and formulations of caraway oil and menthol are useful in some dyspeptic patients. Psychological treatments (e.g., behavioral therapy, psychotherapy, hypnotherapy) may be offered for refractory functional dyspepsia; a meta-analysis of four trials reported benefits in patients with persistent dyspepsia.

FURTHER READING

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