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tongue atrophy, in addition to evidence of generalized neuromuscular disease, should be elicited. The neck should be examined for thyro megaly or lymphadenopathy. A careful inspection of the mouth and pharynx should disclose inflammatory or infectious lesions. Missing dentition can interfere with mastication and exacerbate an exist ing cause of dysphagia. Physical examination is less helpful in the evaluation of esophageal dysphagia as the most relevant pathology is restricted to the esophagus. The notable exception is skin disease. Changes in the skin and oral mucosa may suggest a diagnosis of sclero derma or mucocutaneous diseases such as pemphigoid, lichen planus, and epidermolysis bullosa, all of which can involve the esophagus. PART 2 Cardinal Manifestations and Presentation of Diseases DIAGNOSTIC PROCEDURES Although most instances of dysphagia are attributable to benign disease processes, dysphagia is also a cardinal symptom of several malignancies, making it an important symptom to evaluate. Cancer may result in dysphagia, most commonly as the result of intralumi nal obstruction (esophageal or proximal gastric cancer, metastatic deposits) and less commonly due to extrinsic compression (lym phoma, lung cancer) or paraneoplastic syndromes. Even when not attributable to malignancy, dysphagia is usually a manifestation of an identifiable and treatable disease entity, making its evaluation beneficial to the patient and gratifying to the practitioner. The spe cific diagnostic algorithm to pursue is guided by the details of the history (Fig. 47-2). If oral or pharyngeal dysphagia is suspected, a fluoroscopic swallow study, usually done by a swallow therapist, is the procedure of choice. Otolaryngoscopic and neurologic evalu ation also can be important, depending on the circumstances. For suspected esophageal dysphagia, upper endoscopy is the single most useful test. Endoscopy allows better visualization of mucosal lesions than does barium radiography and also allows for procure ment of mucosal biopsies. Endoscopic or histologic abnormalities are evident in the leading causes of esophageal dysphagia: Schatzki’s ring, gastroesophageal reflux disease, and eosinophilic esophagi tis. Furthermore, therapeutic intervention with esophageal dilation can be done as part of the procedure if it is deemed necessary. The emergence of eosinophilic esophagitis as a leading cause of dyspha gia in both children and adults has led to the recommendation that esophageal mucosal biopsies be obtained routinely in the evalua tion of unexplained dysphagia even if characteristic, endoscopically identified esophageal mucosal features are absent. For cases of sus pected esophageal motility disorders, endoscopy is still the appro priate initial evaluation as neoplastic and inflammatory conditions can secondarily produce patterns of either achalasia or esophageal spasm. Esophageal manometry is 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 para esophageal herniation. Use of a barium tablet in conjunction with fluoroscopy can identify strictures and esophageal motility disor ders that may be overlooked with liquid barium. In specific cases, computed tomography (CT) examination, esophageal manometry with solid meal challenge, and endoscopic ultrasonography may be useful. Impedance planimetry using the functional lumen imaging probe (FLIP) device is increasingly used in the evaluation of dys phagia, particularly for disorders of the esophagogastric junction (esophagogastric junction outflow obstruction and achalasia) (see Chap. 334). Advantages of this technology include patient tolerance, as the procedure is done at the time of upper endoscopy with seda tion, and, more importantly, the information regarding the dynamic opening characteristics of the esophagogastric junction in response to distension that complements esophageal manometry. TREATMENT Treatment of dysphagia depends on both the locus and the specific etiology. Oropharyngeal dysphagia most commonly results from functional deficits caused by neurologic disorders. In such circum stances, the treatment focuses on utilizing postures or maneuvers

devised to reduce pharyngeal residue and enhance airway protec tion learned under the direction of a swallow therapist. Aspiration risk may be reduced by altering the consistency of ingested food and liquid. Dysphagia resulting from a cerebrovascular accident 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. Patients with myasthenia gravis (Chap. 459) and polymyositis (Chap. 377) may respond to medical treatment of the primary neuromuscular disease. Surgical intervention with 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 disor ders such as Parkinson’s disease and amyotrophic lateral sclerosis 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. Treatment of esophageal dysphagia is covered in detail in Chap. 334. The majority of causes of structural, esophageal dysphagia are effectively managed by means of esophageal dila tion using bougie or balloon dilators. Cancer and achalasia are 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. Finally, eosinophilic esophagitis is an important and increasingly recog nized cause of dysphagia that is amenable to treatment by elimi nation of dietary allergens, proton pump inhibition, swallowed, topically acting glucocorticoids, and biologic therapies targeting cytokines involved in type 2 inflammation. While diet and medi cal therapies are effective at reducing dysphagia, esophageal dila tion is used adjunctively for persistent strictures. ■ ■FURTHER READING Hirano I: Esophagus: Anatomy and structural anomalies, in Yamada Atlas of Gastroenterology, 7th ed. New York, Wiley-Blackwell Publishing Co., 2022, pp 42–59. Kim JP, Kahrilas PJ: How I approach dysphagia. Curr Gastroenterol Rep 21:49, 2019. Pandolfino JE, Kahrilas PJ: Esophageal neuromuscular function and motility disorders, in Sleisenger and Fordtran’s Gastrointestinal and Liver Disease, 11th ed, Feldman M, Friedman LS, Brandt LJ (eds). Philadelphia, Elsevier, 2020, pp 638–660. Shaker R et al (eds): Principles of Deglutition: A Multidisciplinary Text for Swallowing and Its Disorders. New York, Springer, 2016. Yadlapati R et al: The Chicago Classification of esophageal motility disorders, v4.0.

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Nausea, Vomiting, and Indigestion 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. In contrast to

emesis, these phenomena exhibit volitional control. Indigestion broadly encompasses complaints including nausea, vomiting, heartburn, regur gitation, and dyspepsia (defined as symptoms that are thought to origi nate in the gastroduodenal region). Some individuals with dyspepsia experience postprandial fullness, early satiety (inability to complete a meal due to premature fullness), bloating, belching, and anorexia. Oth ers report predominant epigastric pain or burning. 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 likely involve the cerebral cortex, as nausea requires cognitive and emotional input and is associated with autonomic responses (dia phoresis, 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. Coordination of Vomiting 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 vomiting involving neurokinin NK1, serotonin 5-HT3, 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 help gastric evacuation. During vomiting, propulsive gastroduodenal motor activity is replaced by orally propagating retrograde contractions that 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 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. Neurotransmitters mediating vomiting are selective for different sites. Labyrinthine disorders stimulate vestibular muscarinic M1 and histaminergic H1 receptors. Vagal afferent stimuli activate 5-HT3 recep tors. The area postrema is served by 5-HT3, M1, H1, and dopamine D2 pathways. Central nervous system (CNS) NK1 receptors mediate both nausea and vomiting. Cannabinoid CB1 pathways participate in the cerebral cortex and brainstem. These receptor-mediated pathways are targets for many agents that treat nausea and vomiting. ■ ■DIFFERENTIAL DIAGNOSIS Nausea and vomiting are caused by conditions within and outside the gut, medications, and circulating toxins (Table 48-1). In an epidemio logic study, nausea alone at least weekly was reported by 1.9% while nausea plus vomiting was noted by 1.1% of the population. Intraperitoneal Disorders Obstruction and inflammation of hollow and solid viscera may elicit vomiting. Ulcers and malignancy cause gastric obstruction, while adhesions, masses, volvulus, intus susception, or inflammatory diseases like Crohn’s disease cause small intestinal and colonic obstruction. The superior mesenteric artery syndrome, occurring after weight loss or prolonged immobilization, results when the duodenum is compressed by the overlying superior mesenteric artery. Median arcuate ligament syndrome, with celiac artery compression, is a rare cause of vomiting. 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. 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 ileus.

TABLE 48-1 Causes of Nausea and Vomiting MEDICATIONS/ METABOLIC DISORDERS INTRAPERITONEAL EXTRAPERITONEAL Obstructing disorders Pyloric obstruction Small-bowel Cardiopulmonary disease Cardiomyopathy Myocardial infarction Labyrinthine disease Motion sickness Labyrinthitis Malignancy Intracerebral disorders Malignancy Hemorrhage Abscess Hydrocephalus Psychiatric illness Anorexia and bulimia Drugs Cancer chemotherapy Opioids Analgesics Glucagon-like obstruction Colonic obstruction Superior mesenteric peptide-1 (GLP-1) receptor agonists Oral hypoglycemics Parkinson’s disease/ artery syndrome Enteric infections Viral Bacterial Inflammatory diseases Cholecystitis Pancreatitis Appendicitis Hepatitis Altered sensorimotor function Gastroparesis Intestinal Nausea, Vomiting, and Indigestion CHAPTER 48 restless legs therapies Antidepressants Smoking cessation agents Antibiotics Cardiac antiarrhythmics/ antihypertensives Oral contraceptives Endocrine/metabolic disease Pregnancy Uremia Ketoacidosis Thyroid and nervosa Depression Postoperative vomiting pseudoobstruction Gastroesophageal reflux Chronic nausea vomiting syndrome (CNVS) Gastroparesis-like parathyroid disease Adrenal insufficiency Toxins Liver failure Ethanol 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 Gut motor and sensory dysfunction often causes nausea and vomit ing. Gastroparesis presents most often with nausea and is documented by demonstrating delayed gastric emptying. Idiopathic gastroparesis occurring in the absence of systemic illness is the most prevalent etiol ogy and follows a viral illness in ~15−20% of cases. Gastroparesis also occurs after vagotomy or with neoplasm, mesenteric vascular insuf ficiency, 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; bac terial overgrowth; nutrient malabsorption; and symptoms of nausea, vomiting, bloating, pain, and altered defecation. Intestinal pseudoob struction may be idiopathic, inherited, related to a mitochondrial dis order, result from systemic disease like scleroderma or an infiltrative process like amyloidosis, or occur as a paraneoplastic consequence of malignancy. Patients with gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), or chronic constipation often report nausea and vomiting. Other gastroduodenal disorders of gut-brain interaction (DGBIs) without organic abnormalities have been characterized. Chronic nausea vomiting syndrome is defined as bothersome nausea and/ or one or more vomiting episodes at least weekly. A syndrome termed gastroparesis-like symptoms (GPLS) presents with symptoms

indistinguishable from gastroparesis but with normal gastric empty ing. 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. Some cases exhibit rapid gastric emptying. A related condition, cannabinoid hyper emesis 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 ≥6 months. 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. 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 nausea associated with delayed gastric emptying. PART 2 Cardinal Manifestations and Presentation of Diseases Medications and Metabolic Disorders Many medications cause nausea and vomiting including opioids, nonsteroidal anti-

inflammatory drugs (NSAIDs), glucagon-like peptide-1 receptor ago nists, oral hypoglycemics, antiparkinsonian drugs, agents for restless legs, antidepressants (especially selective serotonin norepinephrine reuptake inhibitors), smoking cessation drugs, antibiotics, cardiac antiarrhythmics, antihypertensives, and contraceptives. Cancer che motherapy causes acute (within hours of administration), delayed (after ≥1 day), or anticipatory vomiting. Acute emesis from highly emetogenic agents is mediated by 5-HT3 pathways while delayed emesis is dependent on NK1 mechanisms. Anticipatory nausea responds better to anxiolytic therapy 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 may result from excessive amounts of a blood protein—growth differentiation factor 15. Uremia, ketoacidosis, adrenal insufficiency, and parathyroid and thyroid disease are other 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 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 eating characterizes rumination syndrome. With severe gastric emptying delays, vomitus may contain food residue ingested days before. Intense episodic emesis with intervening intervals with much less severe symptoms suggests CVS or CHS. Hematemesis raises suspicion of ulcer, malignancy, or Mallory-Weiss tear. Fecu lent emesis is noted with distal intestinal or colonic obstruction. Bilious vomiting excludes gastric obstruction. Emesis of undigested food is consistent with a Zenker’s diverticulum or achalasia. Vomit ing 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 laby rinthine disease. The physical examination complements the history. Orthostatic hypotension and reduced skin turgor indicate fluid loss. Pulmonary

abnormalities raise concern for aspiration of vomitus. Bowel sounds are absent with ileus. High-pitched rushes suggest bowel obstruc tion. A succussion splash is found with gastroparesis or pyloric obstruction. Involuntary guarding raises suspicion of inflamma tion. Fecal blood suggests ulcer, ischemia, or tumor. Neurologic disease presents with papilledema or focal neural abnormalities. Neoplasm is suggested by palpable masses or adenopathy. DIAGNOSTIC TESTING

For intractable symptoms or an elusive diagnosis, screening testing directs 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, rheu matologic, or paraneoplastic etiologies are suggested by hormone or serologic abnormalities. Small-bowel obstruction is indicated by intestinal air-fluid levels and reduced colonic air on abdominal radiography, while ileus is characterized by diffusely dilated airfilled bowel loops. Anatomic studies are performed if initial testing is nondiagnos tic. 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 or inflammation as seen with Crohn's disease. Ultrasound is helpful for biliary etiologies. Mesenteric angiography, CT, or MRI is useful for suspected ischemia. Brain CT or MRI delineates intracranial disease. Gastrointestinal motility testing can detect underlying motor disorders. Gastroparesis commonly is diagnosed by gastric scintig raphy, which measures emptying of a radiolabeled meal. A nonra dioactive 13C-labeled gastric emptying breath test is an alternative to scintigraphy. Intestinal pseudoobstruction is suggested by luminal dilation on imaging or abnormal transit on intestinal scintigraphy or contrast radiography. Small-intestinal manometry confirms a diagnosis of pseudoobstruction and discriminates between neuro pathic or myopathic disease. Nausea as a manifestation of atypical GERD can be diagnosed by esophageal pH monitoring. Combined esophageal pH/impedance testing with high-resolution manometry facilitates diagnosis of rumination syndrome. Impedance planim etry detects reduced pyloric distensibility and diameter in some cases of gastroparesis. TREATMENT 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 replenishment is unsustainable. Once oral intake is tolerated, low-fat liquid nutrients are initially restarted. Low-residue, smallparticle diets have shown durable efficacy in gastroparesis. Glyce mic 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. ANTIEMETIC MEDICATIONS Most antiemetic agents act on CNS sites and have been evaluated for specific indications (Table 48-2). Antihistamines like dimenhy drinate and meclizine and anticholinergics like scopolamine act on vestibular pathways to treat motion sickness and labyrinthine dis orders. D2 antagonists treat emesis evoked by area postrema stimuli including medications, toxins, and metabolic disturbances. 5-HT3 antagonists like ondansetron prevent postoperative vomiting, radiation–induced symptoms, and cancer chemotherapy–induced emesis. NK1 antagonists such as aprepitant and cannabinoids like dronabinol are approved for chemotherapy-induced vomiting.

TABLE 48-2 Treatment of Nausea and Vomiting TREATMENT MECHANISM EXAMPLES CLINICAL INDICATIONS Antiemetic agents Antihistaminergic Dimenhydrinate, meclizine Motion sickness, inner ear disease Anticholinergic Scopolamine Motion sickness, inner ear disease Antidopaminergic Prochlorperazine, thiethylperazine, haloperidol 5-HT3 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 (NK1) receptor

antagonists Aprepitant, fosaprepitant, netupitant, rolapitant Prokinetic agents 5-HT4 agonist and antidopaminergic Metoclopramide Gastroparesis Motilin agonist Erythromycin Gastroparesis,? intestinal pseudoobstruction Peripheral antidopaminergic Domperidone Gastroparesis Pure 5-HT4 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-HT1A agonist Buspirone, tandospirone 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 Note:? , indication is uncertain. Although these drug classes have divergent mechanisms of action, they are broadly employed in a range of settings for their antinausea and antiemetic actions. Aprepitant can reduce symptoms in CVS and gastroparesis. The cannabinoid agent cannabidiol was benefi cial in a controlled trial in gastroparesis. Tricyclic antidepressants can reduce symptoms in CVS and func tional causes of vomiting but did not show benefits in a controlled trial in gastroparesis. Other neuromodulators with antiemetic action in some settings include the antidepressant mirtazapine, the atypical antipsychotic olanzapine, and the pain-modulating agent gabapentin. GASTROINTESTINAL MOTOR STIMULANTS Drugs that stimulate gastric emptying are used for gastroparesis (Table 48-2). Metoclopramide, a 5-HT4 agonist and D2 antagonist, is effective in gastroparesis. Erythromycin increases gastroduode nal motility by action on receptors for motilin, a transmitter that regulates fasting motility. Erythromycin may be useful for shortterm 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-HT4 agonist, accelerates gastric emptying and improves symptoms in idiopathic gastroparesis. Refractory motility disorders pose challenges. Intestinal pseu doobstruction may respond to the somatostatin analogue octreo tide, which induces propagative small-intestinal contractions. Acetylcholinesterase inhibitors like pyridostigmine benefit some patients with small-bowel dysmotility. Pyloric botulinum toxin injections reduced gastroparesis symptoms in uncontrolled stud ies, but small controlled trials observed benefits no greater than sham treatments. Surgical pyloroplasty and gastric peroral endo scopic myotomy (G-POEM) of the pylorus improved symptoms

Medication-, toxin-, or metabolic-induced emesis, chemotherapy-induced emesis,? cannabinoid hyperemesis syndrome Nausea, Vomiting, and Indigestion CHAPTER 48 Chemotherapy-induced emesis in case series and one sham-controlled trial. Enteral feedings through a jejunostomy reduce hospitalizations and improve over all health in some patients with refractory gastroparesis. The utilities of surgical gastric bypass and sleeve gastrectomy for gas troparesis are unproven. Implanted gastric electrical stimulators may reduce symptoms and health care expenditures in medicationrefractory gastroparesis. A controlled trial confirmed greater improvements in vomiting during gastric electrical stimulation versus sham treatment. SAFETY CONSIDERATIONS Safety concerns have been raised about selected antiemetics and prokinetics. Dopamine antagonists that cross the blood-brain bar rier cause anxiety, mood disturbances, movement disorders, and hyperprolactinemic effects (galactorrhea, sexual dysfunction). Metoclopramide causes irreversible movement disorders like tar dive 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-HT3 antagonists increase risks of cardiac arrhythmias and sudden cardiac death in those with QTc interval prolongation on electro cardiography (ECG). Surveillance ECG testing is advocated for some agents. OTHER CLINICAL SETTINGS Combining a 5-HT3 antagonist, an NK1 antagonist, and a glu cocorticoid can control acute and delayed vomiting after highly emetogenic cancer chemotherapy (Chaps. 74 and 78). Antici patory 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 thera pies like ginger.

Clinicians should exercise caution in managing nausea of preg nancy. 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. Some obstetricians rec ommend alternative therapies including pyridoxine, acupressure, or ginger. Managing CVS and CHS is challenging. Prophylaxis with tri cyclic agents or anticonvulsants (topiramate, zonisamide, leve tiracetam) reduces the severity and frequency of CVS attacks in uncontrolled reports. Combining intravenous 5-HT3 or NK1 antagonists with the sedating effects of lorazepam is a mainstay for aborting acute flares in the emergency department. Studies report benefits with aprepitant and injectable or intranasal forms of the 5-HT1 agonist sumatriptan to manage acute CVS episodes. These treatments are less effective for CHS, but intravenous or intramus cular haloperidol, topical capsaicin cream, or benzodiazepines may reduce acute CHS attacks. PART 2 Cardinal Manifestations and Presentation of Diseases INDIGESTION ■ ■MECHANISMS Several mechanisms contribute to indigestion, including acid reflux, altered gut motility or sensation, inflammation, microbial processes, and other factors. Gastroesophageal Reflux 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 con tribute 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 dys pepsia 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 non acidic 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. Populations of selected duodenal bacteria are altered in functional dyspepsia and correlate with symptom sever ity, 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 dyspep sia pathogenesis. Anxiety, depression, and stress play contributing roles in some functional dyspepsia cases. Other studies observe

hypothalamic-pituitary-adrenal axis dysregulation. Parasympathetic and sympathetic autonomic nervous system abnormalities also have been found. Functional MRI and positron emission tomography stud ies show increased activation of several brain regions, emphasizing CNS contributions. Bile salt composition is abnormal in functional dyspepsia and relates to dyspeptic symptoms and gastric emptying. Analgesics cause dyspepsia, whereas nitrates, calcium channel block ers, theophylline, and progesterone promote gastroesophageal reflux. Ethanol, tobacco, and caffeine induce LES relaxation and reflux. Genetic factors can predispose to development of reflux and dyspepsia. ■ ■DIFFERENTIAL DIAGNOSIS Gastroesophageal Reflux Disease Heartburn or regurgitation is reported weekly by 18–28% of the population, highlighting GERD prevalence. Symptoms of heartburn and regurgitation confer 70% sen sitivity and specificity for a diagnosis of GERD. Other causes of these symptoms include esophageal hypersensitivity, hypervigilance, and regurgitation of nonacidic fluid. Functional Dyspepsia Functional dyspepsia is the cause of symp toms in 70–80% of dyspeptic patients and has a population prevalence of 7.2%. The disorder 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 (PDS) (prevalence 6.1%), characterized by meal-induced fullness and early satiety, and epigastric pain syndrome (EPS) (prevalence 2.4%), with epigastric pain or burning that may or may not be meal-related. The overlap of PDS and EPS has a prevalence of 1.3%. Functional dyspepsia is associated with other DGBIs including IBS and nongastrointestinal disorders like fibromyalgia, chronic fatigue, and anxiety. 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. 337) and Zollinger-Ellison syndrome (Chap. 335), 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 adenocar cinoma usually complicates prolonged acid reflux. Eight to 20% of GERD patients exhibit esophageal intestinal metaplasia, termed Bar rett’s metaplasia, which predisposes to esophageal adenocarcinoma (Chap. 85). 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. 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 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. Twenty percent of gastroparesis patients

note predominance of pain rather than nausea and vomiting. Intestinal lactase deficiency may cause gas, bloating, and discomfort, 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 malab sorption. 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 Indigestion HISTORY AND PHYSICAL EXAMINATION Managing indigestion requires a thorough interview. GERD classi cally 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. 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 or independent of food ingestion. The history in functional dyspepsia may also report symptoms of GERD or IBS. 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 structural causes of indigestion mandates excluding certain historic and exam features. Odyno phagia suggests esophageal infection. Dysphagia is concerning for esophageal blockage. Other alarm features include 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. Patients with an abdominal wall source of upper abdominal pain may exhibit a posi tive Carnett's sign of increased tenderness with tensing of abdomi nal 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 48-3), patients with typical GERD do not need further evaluation and are treated empirically for 4–8 weeks with single or double dosing of a proton pump inhibi tor (PPI) acid suppressant. Upper endoscopy is 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. Endoscopy is not needed in low-risk patients who respond to acid suppressants. Up to one-third of patients with presumed GERD do not respond to PPI therapy. Ambulatory esophageal pH measure ment for 48–96 hours off acid-suppressing medications using a wireless capsule endoscopically attached to the esophageal wall is considered for drug-refractory symptoms. Combined esophageal pH and impedance testing using a transnasal catheter while on PPI therapy can define if a patient with persistent or atypical symp toms has esophageal hypersensitivity or regurgitation of nonacidic or incompletely controlled acid fluid. High-resolution esophageal manometry is ordered when fundoplication is considered for treat ment of GERD. Poor esophageal body peristalsis raises concern about postoperative dysphagia and directs the choice of surgical technique. TABLE 48-3 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

In the absence of alarm features and for patients <60 years old, assessment of H. pylori status by fecal antigen or urea breath testing should be performed as initial diagnostic testing for uninvestigated dyspepsia. Those who are H. pylori positive are given therapy to eradicate the infection. Confirmation of H. pylori eradication should be conducted 4–6 weeks after completing therapy. 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. Nausea, Vomiting, and Indigestion CHAPTER 48 Further testing is indicated in some settings. For associated bleeding, a blood count can exclude anemia. Thyroid chemistries or calcium levels screen for metabolic etiologies. Serologies may sug gest 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 in patients who report symptoms resem bling PDS when therapy fails. Breath testing after carbohydrate ingestion detects lactase deficiency, intolerance to other carbohy drates, or small-intestinal bacterial overgrowth. TREATMENT Indigestion LIFESTYLE, DIET, AND NONMEDICATION RECOMMENDATIONS Patients with mild indigestion are reassured that careful evaluation revealed no serious disease and are offered no other interven tion. If possible, drugs that cause GERD or dyspepsia should be stopped. 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 restric tion is appropriate for lactase deficiency, while gluten exclusion is indicated for celiac disease. Small studies suggest benefits of low FODMAP, six-food elimination, and gluten-free diets. These find ings warrant confirmation in larger functional dyspepsia cohorts. ACID-SUPPRESSING OR -NEUTRALIZING MEDICATIONS Drugs that reduce or neutralize gastric acid are commonly pre scribed for GERD. Histamine H2 antagonists like cimetidine and famotidine are useful in mild to moderate GERD. For severe symp toms or for erosive or ulcerative esophagitis, PPIs like omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, or dexlan soprazole are needed. These drugs inhibit gastric H+, K+-ATPase and are more potent than H2 antagonists. Heartburn responds better to PPI therapy than regurgitation or atypical GERD symp toms. Some individuals respond to doubling of the PPI dose or adding an H2 antagonist. Complications of long-term PPI ther apy include diarrhea (Clostridioides difficile infection, microscopic colitis), small-intestinal bacterial overgrowth, nutrient deficiency (vitamin B12, iron, calcium), hypomagnesemia, bone demineral ization, interstitial nephritis, and impaired medication absorp tion (clopidogrel). Many patients started on a PPI can be stepped down to an H2 antagonist or switched to on-demand use. Nor mal acid exposure on 96-hour esophageal pH testing predicts successful PPI withdrawal. Vonoprazan is a new potassium-

competitive acid blocker, more potent than PPI medications, that was recently approved for erosive esophagitis. Acid suppressants are also effective for both the PDS and EPS subtypes of functional dyspepsia as initial therapy in H. pylori–negative patients or for persisting symptoms after H. pylori eradication. 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. A 4- to 8-week PPI trial is

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