Vomiting in Children

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Education Gaps

1. There are at least 4 known physiologic pathways that can trigger vomiting, 3 of which are extraintestinal.

2. Understanding which pathway is causing a patient's vomiting will help determine best treatment options, including which antiemetic is most likely to be helpful to mitigate symptoms.

3. Bilious emesis in a newborn should indicate bowel obstruction.

4. Cyclic episodes of vomiting may be indicative of a migraine variant.

Objectives   After completing this article, readers should be able to:

1. Understand the main pathways that trigger vomiting via the emetic reflex.

2. Differentiate among acute, chronic, and cyclic causes of vomiting.

3. Create a broad differential diagnosis for vomiting based on a patient's history, physical examination findings, and age.

4. Recognize red flag signs and symptoms of vomiting that require emergent evaluation.

5. Recognize when to begin an antiemetic medication.

6. Select antiemetic medications according to the presumed underlying mechanism of vomiting.

ABBREVIATIONS

5-HT	5-hydroxytryptamine
CHS	cannabinoid hyperemesis syndrome
CTZ	chemoreceptor trigger zone
CVS	cyclic vomiting syndrome
EGD	esophagogastroduodenoscopy
FPIES	food protein–induced enterocolitis syndrome
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
IEM	inborn error of metabolism
PS	pyloric stenosis
SMA	superior mesenteric artery

Vomiting is a common symptom of numerous underlying conditions for which children frequently present for healthcare. Although vomiting can originate from the gastrointestinal (GI) tract itself, it can also signal more generalized, systemic disorders. Vomiting in children is often benign and can be managed with supportive measures only. Still, clinicians must be able to recognize life-threatening causes of vomiting and to avoid serious associated complications, including electrolyte abnormalities, dehydration, or even bowel necrosis.

DEFINITIONS

Vomiting is defined as the *forceful* expulsion of gastric contents through the mouth and/or nose. Vomiting differs from gastroesophageal reflux (GER) and regurgitation in

that the latter 2 conditions are characterized by *effortless* retrograde flow of duodenal or gastric fluids into the esophagus and oral cavity. Vomiting is also different from rumination syndrome, in which patients self-promote to electively regurgitate, and often chew and swallow their regurgitated food again.

PATHOPHYSIOLOGY

Vomiting is the end point of the emetic reflex, a neuropathic process by which the body protects itself against toxins, intestinal distention, and a myriad of other triggers. The emetic reflex is mediated by the central processing unit in the brain, which consists of the chemoreceptor trigger zone (CTZ), the dorsal motor vagal nucleus, and the nucleus of the tractus solitarius. The central processing unit is often also referred to as the "vomiting center" of the brain. However, this may be a misnomer as the central processing unit is not an anatomically differentiated region, and instead is best conceptualized as physiologically connected neurologic components that work together to stimulate the emetic reflex (Fig 1).

Once a stimulus to vomit has been received by the central processing unit, retrograde contractions of the intestine are initiated and coordinated by the vagus nerve. Before retching, a retrograde giant intestinal contraction forces duodenal fluid into the stomach.

Retching begins when the upper esophageal sphincter and glottis close, and the diaphragm, external intercostal muscles, and abdominal muscles contract strongly together. Subsequently, elevated positive pressure in the abdominal cavity is generated and the esophagus contracts and then dilates. This allows a relaxed stomach to be drawn up into the thoracic cavity, effectively removing the antireflux ability of the lower esophageal sphincter. With each cycle of retching, intra-abdominal pressure is increased, and intestinal contents are pushed closer to the oral cavity, until they are eventually expelled.

The Pathways that Cause Vomiting

There are 4 main stimulating pathways that can induce the emetic reflex: mechanical, blood-borne toxins, motion, and
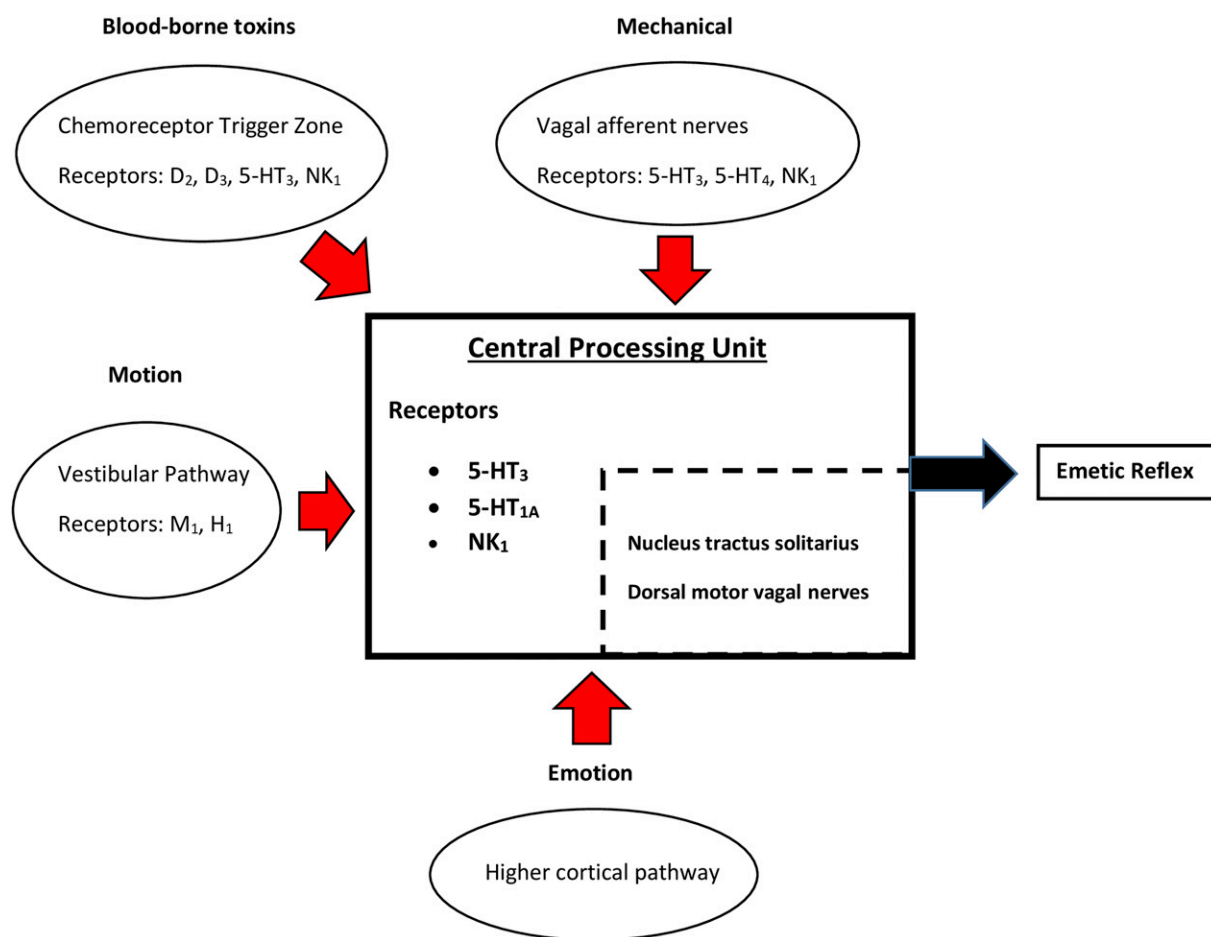

Figure 1. The various physiologic pathways and cellular receptors that can trigger vomiting. 5-HT=5-hydroxytryptamine, NK1=neurokinin 1.

emotional response. (1) Each pathway includes 1 or multiple receptors activated by various specific neurotransmitters and can occur either in isolation or in combination. For most children with vomiting, regardless of pathway induced, no treatment is necessary. However, a variety of neurotransmitter receptors have become the targets of antiemetic medications. Understanding which of the 4 pathways may be involved is the key to selecting an antiemetic medication that will most likely alleviate vomiting. Even if symptoms improve, it is still critical to look for the underlying cause.

Mechanical. The mechanical pathway is activated when either mechanoreceptors or chemoreceptors in the gut wall are stimulated. Mechanoreceptors in the intestine are responsible for monitoring the amount that the bowel distends. If a child eats too much or if the bowel becomes obstructed, mechanoreceptors will sense stretched mucosa and stimulate vagal afferents through the activation of 5-hydroxytryptamine (5-HT_3, 5-HT_4) and neurokinin 1 receptors. In turn, the central processing unit stimulates the efferent (motor) limb of the emetic reflex. The mechanical pathway is also activated when chemoreceptors in the wall of the intestine sense the presence of an irritant. Irritants may include cellular byproducts or toxins, such as those involved in food poisoning.

Blood-borne Toxins. Blood-borne toxins target receptors in the CTZ of the area postrema. These chemoreceptors can also be triggered by substance P, a neuropeptide produced by the body in response to neurotoxic agents and other stressors. Binding of substance P to neurokinin 1 receptors can induce the emetic reflex.

The CTZ is found in the floor of the fourth ventricle, which itself lies in the medulla oblongata. It is not protected by the blood-brain barrier and can easily recognize toxins. The CTZ includes various neuroreceptors, including dopamine receptors D_2 and D_3, 5-HT_3, and neurokinin 1. An example of a blood-borne toxin is the chemotherapeutic drug cisplatin, which is known to significantly increase serotonin levels that activate 5-HT_3 receptors peripherally and centrally in the CTZ. (1)

Motion. Aberrant motion of the human body can stimulate vomiting via the vestibular system, which is critical for maintaining our perception of our body position with relationship to the environment. If this perception becomes altered, such as when riding in a car, muscarinic and histamine receptors can be activated, triggering the emetic reflex.

Emotional Response. Some patients will vomit in response to strong emotions such as anxiety, fear, or even strong smells. Emesis in emotional responses is thought to be mediated by release of corticotrophin-releasing factor.

Causes of vomiting may stimulate more than 1 pathway, but there is usually 1 pathway that predominates. Table 1 lists the differential diagnosis of vomiting broken down by primary pathway.

DIFFERENTIATING BETWEEN CAUSES OF VOMITING BY AGE AND DEFINING CHARACTERISTICS

The list of causes of vomiting is extensive and includes common, benign disorders, such as viral gastroenteritis, as well as rare, life-threatening conditions, such as intussusception. In some circumstances, the actual cause of vomiting might not represent an emergency, but the consequences of excessive fluid loss can include severe dehydration or electrolyte abnormalities, including hypochloremia and/or hypokalemia. Identifying the cause of vomiting, even when benign, may, therefore, be critical, because ideally this will allow therapeutic efforts to be targeted to prevent ongoing symptoms, as well as complications.

One approach to organizing the differential diagnosis of vomiting in pediatrics can be by age and symptom pattern. The latter can generally be categorized according to whether it represents acute, chronic or cyclic vomiting (Table 2).

Acute Vomiting

Acute vomiting presents rapidly over 24 to 48 hours and can be associated with severe symptoms and dehydration. Causes of acute vomiting include viral gastroenteritis, food poisoning, or bowel obstruction. Acute vomiting can be self-limited or can recur episodically. Examples of conditions with a symptom pattern of acute, episodic vomiting include intestinal malrotation with intermittent volvulus, inborn errors of metabolism (IEMs), and food protein–induced enterocolitis syndrome (FPIES). Cannabinoid hyperemesis syndrome (CHS) is another newly recognized diagnosis associated with severe, episodic vomiting that may be more common than previously appreciated in adolescent populations.

Chronic Vomiting

Chronic vomiting is seen in children who have had symptoms for several days to weeks. Chronic vomiting tends to be of low volume and infrequent, and it is rarely associated with dehydration. Causes of chronic vomiting include peptic ulcer disease, gall bladder disease, eosinophilic esophagitis, gastritis, and adverse reactions to ingested foods.

TABLE 1. Causes of Vomiting by Pathway

MECHANICAL	BLOOD-BORNE TOXINS
Annular pancreas	Acute intermittent porphyria
Appendicitis	Adrenal insufficiency
Bezoar	Alcohol
Celiac disease	Carcinoid syndrome
Choledocholithiasis	Chemotherapeutic agent
Choledochal cyst	Diabetic ketoacidosis
Cholelithiasis	Fatty acid oxidation defect
Constipation	Food poisoning
Duodenal hematoma	FPIES
Eosinophilic esophagitis	Galactosemia
Esophageal achalasia	Hereditary fructose intolerance
Foreign body	Hypercalcemia
Gastritis	Hyperthyroidism
Gastroparesis	Liver failure
GERD	Marijuana/CHS
Hirschsprung disease	MCAD deficiency
Hydronephrosis	Medications
Ileus	Cisplatin
Infections	Digoxin
Acute otitis media	Opioids
Gastroenteritis	Theophylline
Hepatitis/hepatic abscess	OTC deficiency
Meningitis	Pharyngitis
Pharyngitis	Phenylketonuria
Pyelonephritis	Pregnancy
Pneumonia	Pyruvate carboxylate deficiency
Sinusitis	Renal tubular acidoses
Intestinal atresia	Tyrosinemia type 1
Intestinal stricture/obstruction	Urea cycle defects
Intracranial tumor	Uremia
Intussusception	
Malrotation with volvulus	
Nephrolithiasis	
Pancreatitis	
Peritonitis	

TABLE 1. (Continued)

MECHANICAL

Pseudo-obstruction

Pseudotumor

Pyloric stenosis

SMA syndrome

UPJ obstruction

MOTION/VESTIBULAR RESPONSE	EMOTIONAL RESPONSE
Abdominal migraine	Anger
Cyclic vomiting syndrome	Anxiety
Meniere disease	Eating disorder
Migraine headache	Fear
Motion sickness	Psychogenic vomiting
	Strong smell/taste

CHS=cannabinoid hyperemesis syndrome, FPIES=food protein–induced enterocolitis syndrome, GERD=gastroesophageal reflux disease, MCAD=medium-chain acyl-CoA dehydrogenase, OTC=ornithine transcarbamylase, SMA=superior mesenteric artery, UPJ=ureteropelvic junction.

Cyclic Vomiting

Cyclic vomiting is characterized by both symptomatic periods with a sudden onset, as well as by asymptomatic periods between episodes. It is important to differentiate between cyclic vomiting and episodic vomiting. Although intervals between symptoms may vary, cyclic vomiting is characterized by its stereotypical episodes and repetitive nature. The most common etiology of cyclic vomiting is cyclic vomiting syndrome (CVS), a migraine variant that typically involves severe episodes of recurrent retching and emesis, leading children to become lethargic and struggle to tolerate oral fluids.

OBTAINING A MEDICAL HISTORY IN PATIENTS PRESENTING WITH VOMITING

When taking a medical history about pediatric vomiting, one should begin by asking about characteristics of the emesis. When did it begin? How often does it occur? Has it happened before? Is it forceful or effortless? Does it contain bile or blood?

It can be helpful to have the patient or patient's family identify the color of vomitus by using a color card. Bilious emesis in an infant always warrants emergent evaluation to exclude a bowel obstruction.

It is important to realize that color alone is not a specific sign and is not pathognomonic of any particular diagnosis. Although emesis that is characterized from first presentation by being bilious or forceful may be suggestive of bowel obstruction, repeated bouts of vomiting, such as that seen in CVS, can result in the bile-colored reflux of duodenal fluid contents into the stomach. Gastric fluid is often yellow-tinged.

If there are reports of or witnessed blood in the emesis, it can be useful to determine whether the blood is bright red or coffee-ground. Bright red blood that is noticeable immediately with the first bout of emesis may be more consistent with active bleeding that is seen due to ruptured esophageal varices or an ingestion. In contrast, coffee-ground emesis is generally suggestive of a slow bleed or oozing, such as that seen with gastritis or peptic ulcer disease. Blood itself acts as an emetic, likely by triggering chemoreceptors. The presence of blood in vomitus in relationship to other symptoms is also important. Blood that develops after initial episodes of retching or emesis may be suggestive of a Mallory-Weiss tear.

The temporal relationship between food ingestion and vomiting may also provide clues to a diagnosis. Vomiting that begins immediately after eating may be suggestive of an esophageal etiology. This may be particularly the case if the vomitus contains undigested food, which can be caused by eosinophilic esophagitis or achalasia. In contrast, vomitus that includes food and that begins several minutes or hours after eating may be consistent with a gastric source or even gastroparesis. Vomiting from gastroparesis rarely presents without accompanying complaints

TABLE 2. Causes of Vomiting by Age and Temporal Pattern

PATTERN	0-1 MO	1–12 MO	1–4 Y	5–11 Y	12–18 Y
Acute	- FPIES - Hirschsprung disease - Intestinal atresia - Meningitis - Pyloric stenosis - Sepsis	- Foreign body - FPIES - Gastroenteritis - Intussusception - UTI	- Foreign body - Gastroenteritis - Pharyngitis - Toxic ingestion - UTI - Constipation	- Appendicitis - Diabetic ketoacidosis - Pancreatitis	- Choledocholithiasis - Diabetic ketoacidosis - Drug overdose
Chronic	- Adrenal insufficiency - GERD - Hirschsprung disease - Intestinal atresia	- GERD	- Celiac disease - Eosinophilic esophagitis	- Celiac disease - Eosinophilic esophagitis - Gastritis +/- *Helicobacter pylori* - Gastroparesis - PUD	- Bezoar - CHS/marijuana use - Pregnancy
Cyclic	- Adrenal insufficiency - IEMs - Malrotation with volvulus	- Adrenal insufficiency - IEMs - Intussusception - Malrotation with volvulus	- Adrenal insufficiency - Constipation	- Abdominal migraine - Cyclic vomiting syndrome - UPJ obstruction	- Abdominal migraine - CHS/marijuana use - Cyclic vomiting syndrome - Eating disorder - SMA syndrome - UPJ obstruction

CHS=cannabinoid hyperemesis syndrome, FPIES=food protein–induced enterocolitis syndrome, GERD=gastroesophageal reflux disease, IEM=inborn error of metabolism, PUD=peptic ulcer disease, SMA=superior mesenteric artery, UPJ=ureteropelvic junction, UTI=urinary tract infection.

of chronic nausea and early satiety. Vomiting after repeated bouts of fasting or with a large protein meal may be suggestive of IEMs. Vomiting after ingestion of fatty foods may suggest a biliary origin, including gallstones.

If abdominal pain is present, questions that can help to clarify its localization become critical. Lower abdominal pain may be consistent with constipation, inflammatory bowel disease, or kidney disease. Epigastric abdominal pain may suggest gastritis, peptic ulcer disease, or pancreatitis. Right upper quadrant pain is more consistent with hepatobiliary disease, including gallstones or hepatitis. Understanding the relationships between food consumption and the onset of pain may also provide clues. Pain associated with vomiting that resolves after eating may be consistent with a gastric ulcer. Pain that worsens with food may be suggestive of eosinophilic GI disease or a functional GI condition, such as functional dyspepsia. Patients with lactose intolerance generally present with diffuse abdominal pain, bloating, and nausea within 1 to 2 hours after exposure to lactose. Shortly thereafter, they usually describe urgency to "run to the bathroom" and may pass loose stools or diarrhea. They usually do not present with vomiting.

Increased intracranial pressure may be accompanied by headaches or focal neurologic deficits, which may help to differentiate intracranial mass effect due to ominous diagnoses from more benign conditions, such as abdominal migraine. Patients with increased intracranial pressure that occurs due to hydrocephalus, intracranial mass, or pseudotumor cerebri may exhibit a change in mental status, cranial nerve palsies, and visual disturbances. Inborn errors of metabolism will also often present with a change in mental status and should be considered in patients with developmental or growth delay. Intussusception can also present with lethargy and a history of sporadic vomiting.

A review of medications in the home, recent travel, and family history of migraines may be helpful in establishing a diagnosis. Vomiting that wakes a child from sleep is always concerning and should be investigated for underlying etiologies that may be life-threatening. On the other hand, a classic sign of abdominal migraine may be early morning vomiting. Chronic sinusitis can also result in morning vomiting. These patients often awake from sleep and then, within a few minutes of wakening, will vomit mucus, often in association with coughing.

Posttussive emesis is common in children and occurs due to increased abdominal pressure. It is important to consider GI causes of vomiting, but the provider must also expand the differential diagnosis to consider

extraintestinal etiologies of vomiting, such as sinusitis or pneumonia.

Last, it is important to query adolescent patients about use of alcohol and illicit drugs. Many adolescents may engage in binge drinking, which can lead to acute vomiting. Opioid use has been increasing and may induce vomiting via central effects and by delaying intestinal motility throughout the entire GI tract. As discussed earlier, excessive marijuana use has been clearly shown to induce vomiting. Obtaining a medical history for use of recreational marijuana is becoming increasingly pertinent to pediatric evaluation of vomiting, especially in an era of increasing state legalization and access to marijuana.

PHYSICAL EXAMINATION

The evaluation of vomiting should be targeted to the patient's medical history and physical examination findings. In terms of the latter, the abdominal examination may be the most useful. Bowel obstruction should be considered if the abdomen appears distended or if there are high-pitched bowel sounds (borborygmi) along with a taut abdominal wall. This would require emergent evaluation. Absence of bowel sounds may suggest an ileus. An enlarged liver may suggest a metabolic process.

Growth parameters are an essential part of the physical examination. Weight loss can indicate a more concerning etiology of vomiting, such as an intestinal stricture or pancreatitis. Most causes of vomiting do not result in weight loss.

A thorough neurologic examination should always be performed when examining a child who presents with vomiting. This should include evaluation for papilledema, ataxia, abnormal reflexes, and weakness. Changes in mental status, including lethargy, may be suggestive of increased intracranial pressure, metabolic shock, or an overdose of a toxic substance. Mental status changes can also be seen in IEMs but do not usually occur acutely.

Red Flag Signs and Symptoms

Red flag symptoms that should prompt referral for urgent evaluation include hematemesis (especially with the first episode of vomiting), hematochezia, recurrent bilious emesis, clinical dehydration, evidence of shock, focal neurologic changes, abdominal distention, and absent or tympanic bowel sounds. In addition, it is critical to carefully evaluate vomiting that wakes a child from sleep.

GI CAUSES OF VOMITING

GER and GERD

It is important to distinguish vomiting from "spitting up" in a child with benign gastroesophageal reflux (GER) or pathological gastroesophageal reflux disease (GERD). The former is a common physiologic occurrence in infants who exhibit painless spitting up after feeds but are otherwise growing and developing appropriately. Infants with GER are commonly referred to as "happy spitters" and do not require any acid suppressant therapy. Instead, reassurance should be provided to the family that physiologic reflux will peak at 4 months of age, and almost always resolves by a year of age. Avoiding unnecessary treatments of physiologic GER in infants is part of the *Choosing Wisely* campaign, an initiative of the American Board of Internal Medicine Foundation endorsed by the American Academy of Pediatrics (http://www.choosingwisely.org).

GERD is diagnosed in infants with GER who also have additional troublesome symptoms, such as irritability, poor feeding, or weight loss. These patients may benefit from dietary changes, including exclusion of milk and eggs from the diet of breastfeeding mothers or use of hypoallergenic infant formulas. Infants with GERD may also be treated with gastric acid–suppressing agents, but it is important to recognize that these are helpful for treating irritation or injury related to acid exposure, not for reducing the spitting up.

Constipation

Constipation is one of the most common causes of vomiting through the mechanism of delayed gastric emptying. Symptoms may initially present as nausea and early satiety but can progress to vomiting in more severe cases of fecal impaction. Children can attempt oral medications, but if they are not tolerated, rectal therapy, including suppositories or enemas, may need to be given.

Pyloric Stenosis

One relatively common example of a GI cause of vomiting in newborn infants is pyloric stenosis (PS), which involves a narrowing of the pyloric channel due to a thickening of the pyloric muscle. The incidence of PS is 2 to 3.5 per 1,000 live births and is associated with male sex, age 2 to 7 weeks, being first-born, maternal smoking, preterm delivery, small for gestational age, cesarean delivery, and congenital malformations. (2)

Patients with PS often present with forceful, nonbilious emesis around 1 month of age. Parents often state that their child is "always hungry." A palpable "olive" in the right upper quadrant is considered pathognomic for PS, but an abdominal fluid wave is more frequently seen on physical

examination. Failure to thrive, or signs and symptoms consistent with dehydration, should prompt further laboratory and radiologic evaluation.

Initial laboratory evaluation in PS classically reveals a hypokalemic, hypochloremic, metabolic alkalosis. Radiologic evaluation usually begins with ultrasonography. Diagnosis of PS is supported when the thickness of the pyloric muscle is greater than 3 mm and the length of the pyloric channel is greater than 15 mm. (3) An upper GI series can also be obtained to make the diagnosis and is characterized by the finding of a small "trickle" of contrast passing through the pyloric channel.

The initial steps in managing PS include correction of dehydration and correction of any electrolyte imbalances. This should be done before any surgical intervention. Once the child is fully resuscitated, a surgeon typically proceeds with pyloromyotomy.

Gastric Outlet Obstruction

Gastric outlet obstruction is an anatomical abnormality that often presents in infancy. An example of a gastric outlet obstruction is an antral web. In this congenital condition, an upper GI series will suggest an inability of contrast to exit the stomach. More definitive evaluation to diagnose an antral web requires direct visualization via upper endoscopy.

Malrotation with Volvulus

Malrotation with volvulus should always be considered in patients with acute or episodic vomiting, particularly if bilious vomiting is present. During episodes of malrotation with volvulus, older children may cry excessively or complain of severe abdominal pain, and infants may appear limp and lethargic, and meet the clinical criteria for shock. Malrotation can also occur without volvulus and lead to chronic vomiting that is often painless.

The diagnosis of malrotation requires either a barium study to delineate the ligament of Treitz, abdominal ultrasonography, or a computed tomographic scan of the abdomen. An abdominal radiograph obtained during an episode of volvulus usually shows an air-filled, dilated bowel proximal to the level of the obstruction and a paucity of air distal to the obstruction. An upper GI series often reveals an incomplete C sweep of the duodenum, with the small intestine remaining on the right side of the abdomen with failure to cross the midline. Decompression of the intestine with a nasogastric tube followed by emergent surgical consultation is required (Fig 2).

Intestinal Atresia

Intestinal atresia classically presents with bilious emesis in infants within the first few hours of life. Location of atresias
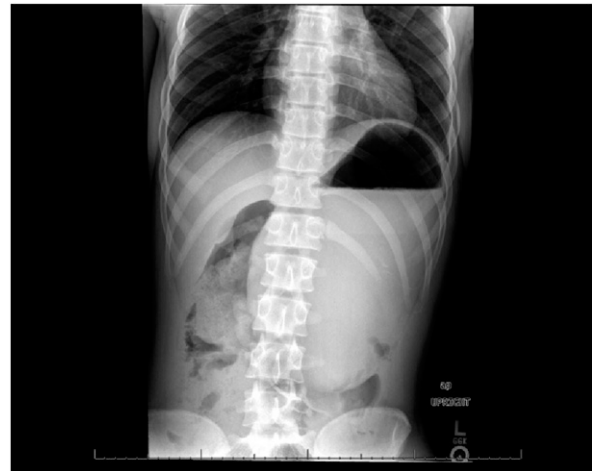

Figure 2. Severely dilated stomach in a patient with intestinal malrotation with volvulus.

along the GI tract may be variable, with abdominal distention often seen with more distal lesions. Intestinal atresia may be associated with a variety of genetic disorders. In particular, duodenal atresia should be investigated in a neonate with trisomy 21 who presents with bilious vomiting and can be diagnosed by a "double bubble" sign on plain film imaging.

Intussusception

Intussusception, or telescoping of the bowel, can occur physiologically. However, if intussusception fails to reduce, it can result in life-threatening obstruction with dilation and necrosis of the bowel. Patients presenting with intussusception are predominantly male, between 3 months and 3 years of age, and have symptoms of abdominal pain and vomiting that begin suddenly and then resolve just as quickly. As with volvulus, these patients can develop bowel ischemia and may appear limp and lethargic, with evidence of shock. Over time, the vomiting can become bilious, and the patient may develop bloody stools. There can also be an appearance of a "red currant jelly" stool, which occurs when blood mixes with mucus.

The mortality rate of discovered intussusception is less than 1%. However, if not identified and treated in a timely manner, intussusception can be fatal. Abdominal ultrasonography is the best method of radiologic evaluation for intussusception, and an air contrast enema can be both diagnostic and therapeutic. Persistent intussusception may require surgical intervention.

Eosinophilic Esophagitis

Eosinophilic esophagitis is a lifelong clinicopathologic inflammatory condition associated with other atopic diseases,

with an increasing worldwide prevalence. The emesis in patients with eosinophilic esophagitis is often chronic and is characterized by expulsion of undigested food within a few minutes of eating. Over a lifetime, chronic inflammation due to eosinophilic esophagitis may be associated with fibrostenosis of the mucosa, and esophageal strictures can form. The natural history of eosinophilic esophagitis may explain why older patients will often note dysphagia, particularly with solid foods, whereas younger patients and infants can present with vomiting, food refusal, or failure to thrive.

Eosinophilic esophagitis should be considered in patients with episodic or chronic vomiting and a history of asthma, allergic rhinitis, or eczema. Fluoroscopic examination of the esophagus may reveal a small-caliber or ringed esophagus, as well as stricturing disease (Fig 3). Eosinophilic esophagitis is characterized by various mucosal signs of inflammation that can be noted on upper endoscopy. According to current guidelines, eosinophilic esophagitis must be confirmed by biopsies revealing at least 15 eosinophils per high-power field. (4)

Pancreatitis

Acute and chronic pancreatitis, characterized by inflammation and swelling of the pancreas, can occur for many
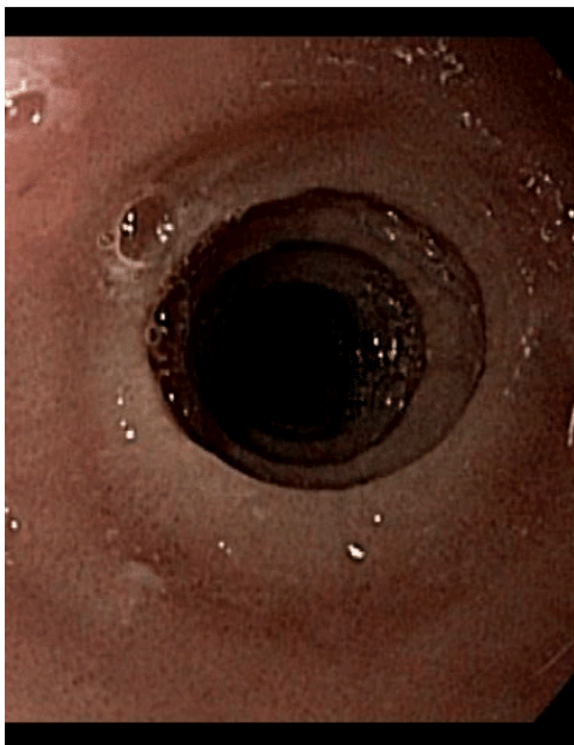

Figure 3. Esophageal stricture in a patient with eosinophilic esophagitis.

underlying reasons. Both types can be highly associated with a systemic inflammatory response syndrome, leading to shock and other life-threatening conditions. Necrotizing pancreatitis occurs when the pancreas becomes infected and may present as persistent fever, worsening abdominal pain, and even sepsis. Pancreatitis causes vomiting primarily through inflammatory cytokines, which trigger chemoreceptors. It is important to recognize that an enlarged pancreas can also have a mass effect in the abdomen, leading to obstruction of the duodenum.

Physical examination of patients with pancreatitis often reveals epigastric abdominal pain with radiation to the back. Laboratory evaluation will often demonstrate elevated amylase and lipase levels. Abdominal ultrasonography may be sufficient for diagnosis. However, a computed tomographic scan of the abdomen may be warranted if there is concern for necrotizing pancreatitis.

Gastroparesis

Gastroparesis—a functional delay in stomach emptying—can present with nausea and early satiety. Vomiting secondary to gastroparesis is usually nonbilious and occurs generally at least several minutes after eating. Gastroparesis in children most often follows from viral infections, but the condition is also often idiopathic. (5) Several months may pass before motility of the intestines returns to baseline when gastroparesis follows an infection. There are a variety of other causes of gastroparesis, including type 1 diabetes mellitus, acidosis, and cerebral palsy. Diagnosis is often made by a scintigraphic gastric emptying scan that demonstrates delayed gastric emptying. More formal GI motility testing, including antroduodenal manometry, can also be considered.

Superior Mesenteric Artery Syndrome

Superior mesenteric artery (SMA) syndrome should be considered in a patient with a history of recent weight loss and severe postprandial vomiting. Athletes involved in weight-dependent sports (ie, gymnastics, wrestling, and crew), patients with eating disorders, and those in critical care settings are at particular risk. In SMA syndrome, adipose tissue that normally suspends the SMA over the third portion of the duodenum is reduced. This results in a "nutcracker effect" where the SMA compresses the duodenum, resulting in bowel obstruction.

The best method of evaluation for SMA syndrome is an upper GI series, which may reveal a sharp cutoff sign of contrast that is unable to pass through the duodenum. It may also show a to-and-fro motion of the contrast column. Once identified, resolution of SMA syndrome involves

weight gain, which may require bypassing the level of obstruction with a nasal jejunal tube or the use of total parenteral nutrition. Patients may also find it more comfortable to eat while leaning forward.

Intestinal Stricture

Intestinal strictures are rare causes of vomiting and can occur as a complication of various conditions in children. In particular, small-bowel Crohn disease can result in stricturing of the intestine from chronic inflammation; this condition most commonly occurs at the level of the ileum. Patients with intestinal strictures may present with the sudden onset of right lower quadrant abdominal pain and vomiting that improves after a few hours of bowel rest and intravenous fluid resuscitation. An intestinal stricture should also be considered in a patient with a history of intestinal resection with anastomosis or in a patient with a history of necrotizing enterocolitis. In both circumstances, chronic inflammation can lead to the development of fibrotic tissue (Fig 4).

NON-GI CAUSES OF VOMITING

Cyclic Vomiting Syndrome

Considered a migraine variant, CVS is characterized by episodic vomiting spells that present suddenly, occasionally waking a patient in early morning hours, and persist for variable durations, from 1 hour to several days. Many patients with this condition will have a family history of atypical and typical migraine headaches. During episodes, patients are at risk for severe dehydration and may require intravenous fluid resuscitation.

International consensus as outlined in the Rome III criteria for CVS includes stereotypical episodes of vomiting that are acute and last less than 1 week, 3 or more separate episodes in the past year, and absence of any symptoms between episodes.

It is thought that mitochondrial defects or other IEMs may predispose to cyclic vomiting episodes. For these reasons, it is important to inquire about developmental delay and symptoms triggered by certain meal types, such as high-protein meals or prolonged fasting in infants and young children.
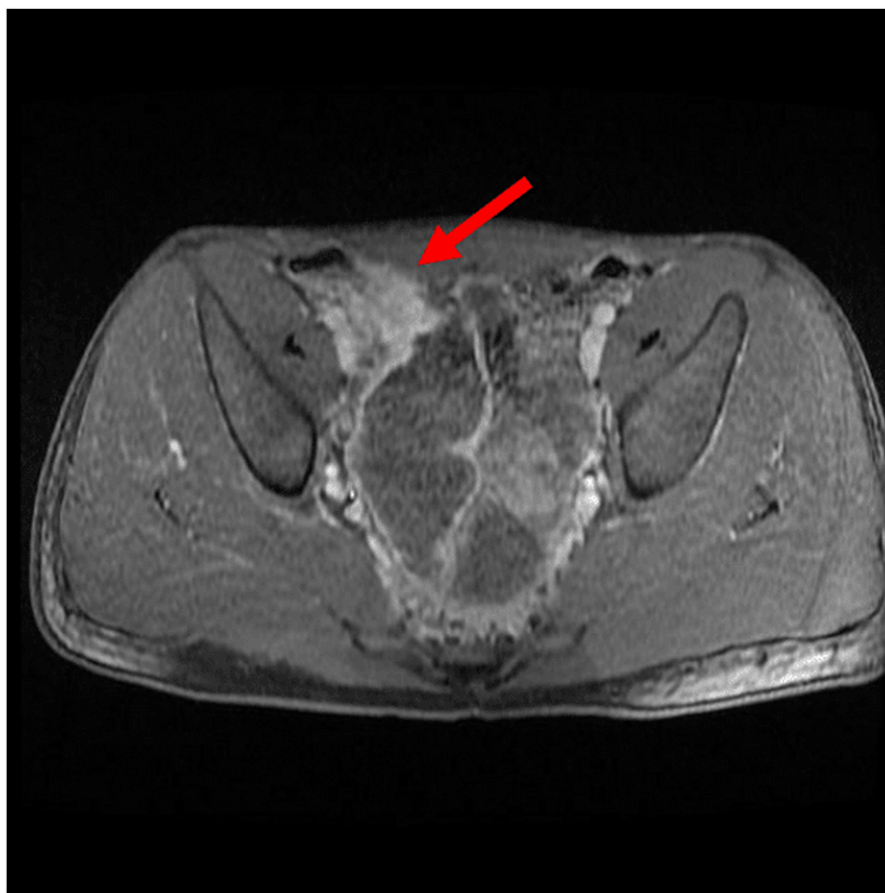

Figure 4. Ileal stricture (arrow) with bowel dilation in a teenager with Crohn disease.

Cannabinoid Hyperemesis Syndrome

This syndrome is an emerging condition associated with chronic marijuana exposure that was first described in 2005 as a mimic of CVS. Although marijuana is generally considered an antiemetic, it is becoming clear that it can also induce a chronic and profound pattern of hyperemesis. Patients with stereotypical CHS have an intriguing hydrophilia, and eliciting a history of seeking hot showers to alleviate vomiting can help differentiate CHS from CVS in teenagers with the condition. Treatment of CHS involves abstinence from marijuana for at least 2 weeks.

Food Protein–Induced Enterocolitis Syndrome

This rare but severe cause of vomiting presents most often during infancy and generally resolves by age 3 years. Although the exact pathophysiology is unknown, FPIES is triggered by non–immunoglobulin E–mediated reactions to the protein component of foods. Unlike immunoglobulin E–mediated food allergy, FPIES often presents 2 to 6 hours after exposure to the offending foods with vomiting and diarrhea, in the absence of respiratory symptoms, swelling, or hives. Foods that are most often implicated as triggers for FPIES include cow milk and soy proteins, as well as glutenin proteins in rice cereal and oatmeal. (6)

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction can cause episodic vomiting due to either intrinsic or extrinsic obstruction of the kidney at the renal pelvis, resulting in hydronephrosis. The resultant dilation of the urinary collecting system and stretching of the renal capsule stimulates vagal afferents through the mechanical pathway to trigger the emetic reflex. Patients with ureteropelvic junction obstruction often present with episodic bouts of vomiting and unilateral flank pain. Their symptoms typically resolve as the obstruction improves. Hydronephrosis noted on ultrasonography during acute episodes that resolves when the child is asymptomatic is highly suggestive of this condition and warrants referral to a pediatric urologist. (7)

Adrenal Insufficiency

The most common cause of adrenal insufficiency is congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Patients with congenital adrenal hyperplasia often present with chronic vomiting and are found to be hyponatremic, hyperkalemic, and hypotensive. Current state-mandated newborn screening generally analyzes for 21-hydroxylase deficiency, which has helped improve detection of this condition before complications occur.

Inborn Errors of Metabolism

Vomiting is a common feature of most IEMs. These conditions include organic acidemias, urea cycle defects, and defects with carbohydrate metabolism such as galactosemia. It is important to have a high index of suspicion for an IEM in patients with vomiting and growth or developmental delay owing to the high morbidity and mortality associated with IEMs.

Increased Intracranial Pressure

One particularly ominous cause of chronic vomiting is increased intracranial pressure, which can occur from either mass effects or pseudotumor cerebri. Vomiting that occurs with positional changes or that causes a patient to wake from sleep should be recognized as red flags for this condition. Increased intracranial pressure may also be associated with other neurologic features, including recurrent and focal headache, difficulties with ambulation, changes in vision or changes in mental status. Findings of the Cushing triad, which includes bradycardia, hypertension, and irregular breathing, should increase suspicion for increased intracranial pressure and prompt urgent evaluation.

EVALUATION OF CHILDREN WITH VOMITING

Laboratory and radiographic evaluation should be based on the characteristic type of vomiting (Table 3). In a pediatric patient with acute vomiting, most laboratory studies will not be helpful in identifying a specific cause of the vomiting but will be important for assessing hydration status. In particular, specific gravity from a urinalysis can be helpful to assess the hydration status of the child, as well as serum electrolyte, blood urea nitrogen, and creatinine levels.

Patients with chronic vomiting are not usually at risk for dehydration. However, evaluation for *Helicobacter pylori* gastritis (urease breath test, *H pylori* stool antigen) should be considered. Non–*H pylori* gastritis or peptic ulcer disease may also be considered with initial screening in appropriate settings by testing stool for occult blood. Occult or visible blood in the stool may also be present with bacterial gastroenteritis and adverse reactions to foods, such as with milk protein allergy.

Inborn errors of metabolism can result in vomiting, but laboratory abnormalities may not be detected unless a patient is acutely ill. For example, a patient with ornithine transcarbamylase deficiency may develop vomiting only after eating a meal high in protein. For that reason, it is important for primary care providers and emergency medicine providers to evaluate for an IEM at the time that vomiting occurs. These laboratory values often include serum amino acids,

TABLE 3. **Laboratory and Radiologic Evaluation for Patients with Vomiting by Temporal Pattern**

ACUTE	CHRONIC	CYCLIC
Electrolytes (Na+, K+, Cl-)	Electrolytes (Na+, K+, Cl–)	Electrolytes (Na+, K+, Cl–)
BUN	BUN	BUN
Creatinine	Creatinine	Creatinine
Abdominal radiograph	Celiac screen	Glucose
	Amylase	Upper GI series
	Lipase	Serum amino acids
	Urine β-HCG	Urine organic acids
	Hepatic function panel	Urine ketones
	Stool *Helicobacter pylori* antigen	Carnitine profile
	Upper endoscopy	Ammonia
	MRI brain/CT head	Lactate
		Pyruvate
		US abdomen

BUN=blood urea nitrogen, CT=computed tomographic, GI=gastrointestinal, HCG=human chorionic gonadotropin, MRI=magnetic resonance imaging, US=ultrasonography.

urine organic acids, urine ketones, carnitine profile, ammonia, lactate, pyruvate, and a basic metabolic panel.

An upper esophagogastroduodenoscopy (EGD) is an excellent means to evaluate the mucosa of the intestine but almost always requires deep sedation or anesthesia and involves the slight risk of bowel perforation. Endoscopy is most useful to exclude eosinophilic esophagitis, gastritis, peptic ulcer disease, or gastric outlet obstruction as the cause of a child's vomiting. An upper endoscopy may also be necessary to remove a foreign body in the esophagus or stomach that can be the cause of a child's vomiting. Biopsies of the stomach from an EGD can reveal an *H pylori* gastritis not picked up by stool antigen testing. An EGD can also reveal a nodular appearance of the gastric mucosa caused by an *H pylori* infection (Fig 5).

Endoscopy cannot be used to identify malrotation of the intestine or other possible anatomical conditions that can lead to chronic vomiting. The role of upper endoscopy is controversial in suspected CVS. If a child with presumed CVS responds well to medications, and both intracranial pathology and intestinal malrotation are excluded, then it is reasonable to wait to perform an upper endoscopy and to monitor the patient clinically.

Most importantly, endoscopy should never be performed on an unstable child. Fluid resuscitation and electrolyte abnormalities should always be corrected before performing the procedure.

Intestinal manometry represents an emerging modality for evaluating the motility of the intestinal tract in children with vomiting of unclear etiologies. Unfortunately, availability of this technology is limited to larger, tertiary care institutions, and it is often not performed until many other causes of vomiting have been excluded. For example, esophageal manometry may be helpful in evaluating patients with dysphagia when there is concern for achalasia and eosinophilic esophagitis has been excluded.

Limitations of using manometry in children include its invasiveness and poor patient compliance. By definition, a manometry probe must be placed and left in the esophagus for a clinically useful duration of time (generally, 30–90 minutes). The child cannot be put to sleep for the procedure because he or she must be able to swallow on command.

TREATMENT

For most children with vomiting, no treatment is needed. Overtreatment can lead to harm and misdiagnosis. However, in children at risk for dehydration and electrolyte abnormalities, the first steps in managing vomiting should be clinical stabilization with emphasis on the correction of
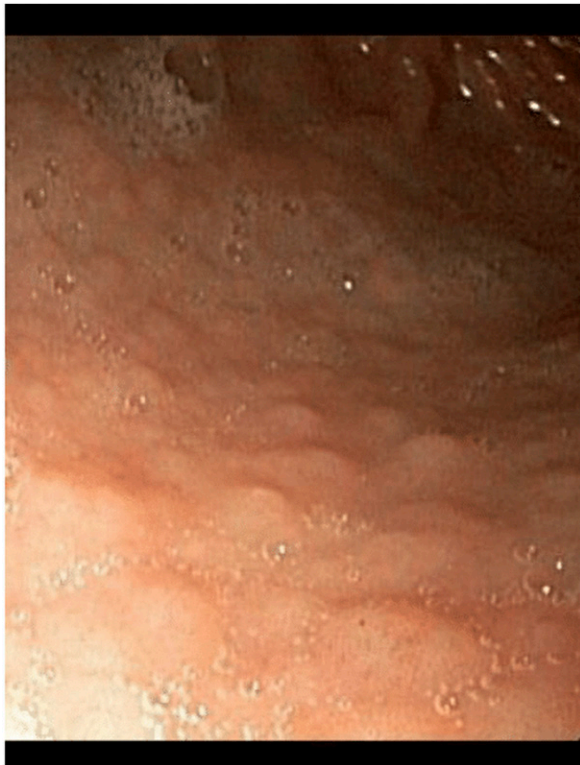
Figure 5. Gastric nodularity due to chronic *Helicobacter pylori* infection.

fluid deficit and electrolyte abnormalities. (1) Often, supportive care with oral or intravenous fluid resuscitation will help relieve vomiting. Identification and correction of the primary problem is obviously the next most important step.

There are several antiemetic medications and a few prokinetic medications that can be considered to minimize vomiting while the etiology is being investigated. Most have poor efficacy and are associated with significant adverse effects. Identifying the underlying pathway that causes a child to vomit is challenging but may be key in selecting a medication that is most likely to be successful. It is important to stress to families that while these medications may decrease episodes of vomiting, the sensation of nausea will often persist.

Table 4 outlines antiemetic medications in accordance with their target receptors and recommended doses. In extreme cases of chronic nausea and vomiting—particularly from chronic gastroparesis—gastric pacing may be considered to relieve symptoms. Gastric pacing is a surgical intervention that involves implanting a pacemaker attached to the external portion of the stomach, with leads that are placed into the intestinal mucosa to stimulate GI motility.

Mechanical

If the cause of vomiting is thought to have a mechanical etiology, such as overdistention of the stomach or a chemotoxin

(ie, food poisoning), then antagonists of 5-HT receptors, which are found in the afferent vagal nerves and the CTZ, will be most helpful. Serotonin receptor antagonists include ondansetron, granisetron, dolasetron, and palonosetron. Evidence suggests that the use of ondansetron limits the need for intravenous fluids and hospital admission in pediatric patients with gastroenteritis. (8) Ondansetron has also been shown to be one of the most effective medications in patients receiving chemotherapy and in postoperative induced nausea and vomiting. (9) One of the main adverse effects of ondansetron is diarrhea. It should be used with caution because it can be associated with cardiac arrhythmia (ie, prolongation of the QT interval).

Ginger is also used frequently for chronic nausea and vomiting. Although its mechanism of action is not entirely understood, one of its proposed mechanisms of actions is as a 5-HT$_3$ antagonist.

Dopamine D$_2$ receptor antagonists are likely to be most helpful in patients with gastroparesis. Examples of these antagonists include metoclopramide, domperidone, prochlorperazine, and chlorpromazine. The D$_2$ receptors are found in the CTZ. Unfortunately, the adverse effect profile of D$_2$ receptor antagonists is significant and can include extrapyramidal reactions. In particular, metoclopramide can easily cross the blood-brain barrier and induce tardive dyskinesia. This has led to a black box warning by the Food and Drug Administration (FDA). Domperidone does not cross the blood brain barrier and does not cause the central nervous system effects seen with metoclopramide.

Blood-borne Toxins

Chemotoxic agents can cause severe vomiting in either an immediate or a delayed fashion. Neurokinin receptor antagonists such as aprepitant and fosaprepitant work by blocking receptors activated by substance P.

To treat vomiting due to chemotoxic agents, it may be most helpful to use serotonin receptor antagonists. These can be used in conjunction with a neurokinin receptor antagonist and dexamethasone for optimal effects. (10)

Motion

Those with motion sickness that affects the vestibular system are most likely to respond to an antihistamine, such as diphenhydramine, cyproheptadine, promethazine, or hydroxyzine. Abdominal migraine syndrome and CVS may also respond to antihistamines, which supports the concept that both conditions are mediated by a common neurologic pathway. Muscarinic receptor blockade, such as

TABLE 4. Antiemetic Medications and Their Dosages and Target Receptors

MEDICATION	DOSE	RECEPTOR	NOTES
Ondansetron	0.3–0.4 mg/kg per dose q 4–6 h	5-HT$_3$	Diarrhea is an adverse effect
Granisetron	40 μg/kg/dose q 12 h	5-HT$_3$	
Ginger	250 mg TID	5-HT$_3$ (?)	The mechanism of action of ginger is not completely understood
Cyproheptadine	0.25–0.5 mg/kg per day	5-HT$_{2A}$, 5-HT$_{2B}$, H$_1$	Stimulates appetite
Amitriptyline	0.25 mg/kg per day (max 1 mg/kg per day)	Serotonin	Increased risk of cardiac arrhythmia
Erythromycin	5 mg/kg per dose q 6 h	Motilin	Can increase risk of pyloric stenosis in infants
Diphenhydramine	5 mg/kg per day divided TID or QID	H$_1$, D$_2$	
Promethazine	0.25–1 mg/kg per dose q 4–6 h	H$_1$	Contraindicated in children <2 y old due to respiratory depression
Meclizine	25–50 mg 1 h before travel	H$_1$	For patients 12 y and older
Prochlorperazine	5–10 mg q 6–8 h (≥40 kg)	D$_1$, D$_2$	
Metoclopramide	0.1–0.2 mg/kg per dose q 6–8 h	D$_2$	Black box warning: increased risk of tardive dyskinesia
Scopalamine	1 mg transdermal disc applied behind ear q 3 d	M$_1$	
Aprepitant	Children 6–30 kg: 3 mg/kg on day 1, then 2 mg/kg on days 2 and 3 Children >30 kg: 125 mg on day 1, then 80 mg on days 2 and 3	NK$_1$	Indicated for chemotherapy-induced nausea Causes fatigue, dizziness Not for long-term use

5-HT=5-hydroxytryptamine, q=every, QID=4 times per day, TID=3 times per day.
From Li BUK. Nausea, vomiting, and pyloric stenosis In: Kleinman RE, Goulet O, Meili-Virgani G, et al, eds. Walker's Pediatric Gastrointestinal Disease; adapted from both the 5th (2008) and 6th (2018) editions; used with permission from PMPH USA Ltd, Raleigh, NC.

scopolamine, is also effective prophylactically in treating patients with motion sickness. Scopolamine is administered as a transdermal patch.

Emotional Response
Patients with emotional triggers of vomiting are most likely to benefit from cognitive behavioral therapy and biofeedback.

SPECIAL CIRCUMSTANCES

Bilious Emesis in Infants
Bilious emesis is *never* acceptable in a neonate and should always be concerning for intestinal obstruction. The level of the obstruction cannot be differentiated based on bilious emesis itself. It can represent a proximal obstruction such as duodenal atresia or a distal obstruction such as Hirschsprung disease. Abdominal distention usually represents a more distal bowel obstruction.

The first step in managing a neonate with presumed bowel obstruction is decompression with a nasogastric tube. This should be followed by correction of dehydration and any electrolyte abnormalities.

An abdominal radiograph can help localize the obstruction. Follow-up with an upper GI series with or without a small-bowel follow-through is often warranted. However, if Hirschsprung disease is suspected, a contrast enema is the preferred study. Ideally, an unprepped contrast enema is most helpful so as not to obscure the transition line. A CT scan of the abdomen can evaluate the entire intestine quickly but carries a higher radiation exposure than contrast imaging.

Projectile Vomiting
As with bilious emesis, projectile or forceful vomiting should always be evaluated carefully. Projectile vomiting can be seen in cases of PS, gastric outlet obstruction, or even increased intracranial pressure. Concerns about conditions associated with projectile vomiting have been widely spread in parenting literature, and families will often use the term indiscriminately. As the clinician, it may be helpful to ask a parent to identify where in the room the vomitus would land

with the patient sitting in the parent's lap to determine whether the description matches the symptom.

WHEN SHOULD YOU REFER?

Referral for vomiting—acute, chronic, or cyclic—may be appropriate when symptoms are persistent and the cause of vomiting cannot be established. Specialists who may be useful for diagnosing and managing persistent or chronic vomiting in children include gastroenterologists, neurologists, endocrinologists, metabolic specialists, and surgeons, depending on the presumed pathway. Regardless of the underlying cause, it is also critical for primary care physicians to recognize signs and symptoms of dehydration and shock and to refer them to emergency departments for urgent rehydration and stabilization.

Summary

- Vomiting is a common symptom of a myriad of conditions that can cause tremendous stress for the child and caregivers. Finding an etiology can be challenging because vomiting can involve a variety of different organ systems in the body.

- There are 4 main physiologic pathways that can trigger the emetic reflex: mechanical, blood-borne toxins, motion, and emotional triggers. (1) Each pathway is triggered by different organ systems and involves different neurotransmitters.

- Establishing a differential diagnosis for vomiting should take into account both a child's age and temporal characteristics of their vomiting.

- Based on strong research evidence, (1) the first step in management should be correction of dehydration or any electrolyte abnormalities, as well as decompression if there is concern for a bowel obstruction.

- It is critically important to recognize red flag signs and symptoms that may suggest more life-threatening causes of vomiting, including nocturnal vomiting that awakens the patient from sleep, weight loss, hematemesis, severe abdominal distention, mental status changes, and bilious emesis, particularly in a neonate.

References for this article are at http://pedsinreview.aappubli- cations.org/content/39/7/342.

PIR Quiz

1. A 17-year-old developmentally appropriate boy comes to the clinic for evaluation of vomiting. He reports that he has had episodes of nausea with nonbloody, nonbilious emesis on awakening. These episodes occurred 2 to 3 times each week, mostly over weekends for the past 2 months. He denies any abdominal pain, diarrhea, weight loss, fever, or difficulty swallowing. His vomiting never causes him to awaken from sleep. There is no family history of migraine headaches. Results of physical examination, including abdominal and neurologic examinations, are normal. Which of the following is the most likely possible explanation of this patient's symptoms that needs further investigation?

   A. Adrenal insufficiency.
   B. Inborn error of metabolism.
   C. Intestinal malrotation with volvulus.
   D. Intussusception.
   E. Marijuana use.

2. A 4-month-old boy is seen for a health maintenance visit. Since his 2-month health maintenance visit he has been doing well and has not had any major problems except for episodes of spitting up after feedings. These episodes have worsened in the past few weeks and occur after every feed. There is no history of fever, runny nose, cough, rashes, or diarrhea. The baby was exclusively breastfed until a month ago when mom returned to work. He is currently on human milk supplemented with cow milk–based formula. He is a good eater and takes 6 oz of formula every 3 to 4 hours with breastfeeding in between 3 to 4 times a day. On physical examination, his height and weight are on the 90th percentile for age. The results of his physical examination are normal. Which of the following is the next best step in the management in this patient?

   A. Esophageal manometry.
   B. Ph probe.
   C. Reassurance.
   D. Switch to a soy-based formula.
   E. Upper endoscopy.

3. A 6-week-old baby boy is brought to the emergency department (ED) by his parents because of recurrent episodes of emesis. The vomiting started 2 weeks ago but worsened during the past 10 days. The parents describe the emesis as "forceful" and "shooting" and lately occurring after every feed. The baby has had no fever or diarrhea, no decrease in activity, and seems hungry all the time. He was noted today to be more sleepy than usual and has had a decrease in wet diapers in the past 24 hours, which prompted the ED visit. On physical examination, the baby is sleepy but arousable. His weight is unchanged from his last visit at 4 weeks of age. Physical examination is significant for tachycardia, dry mucous membranes, and a sunken anterior fontanelle. Abdominal examination shows a nondistended, nontender abdomen with sluggish bowel sounds. Which of the following is the best immediate next step in the management of this patient?

   A. Abdominal ultrasonography.
   B. Correction of dehydration and electrolyte imbalances.
   C. Start oral ondansetron therapy.
   D. Upper endoscopy and biopsies.
   E. Upper gastrointestinal and small-bowel follow-through.

4. A 10-year-old boy is brought to the clinic by his parents. He frequently becomes nauseous when going on car rides longer than 1 hour. From the following list of medications that are used for vomiting, which is not likely to improve his symptoms?

    A. Cyproheptadine.
    B. Diphenydramine.
    C. Ondansetron.
    D. Promethazine.
    E. Scopalamine.

5. You are called by the newborn nursery nurse because a 1-day-old girl had an acute episode of bilious emesis. The baby is being breastfed. There is no history of fever. The baby passed meconium but has no diarrhea. On physical examination, the abdomen is soft and mildly distended. Which of the following is the most appropriate next step in the management of this patient?

    A. Perform abdominal ultrasonography.
    B. Perform an upper endoscopy.
    C. Place a nasogastric tube.
    D. Reassurance and continued observation.
    E. Switch the baby to an elemental formula.