Vomiting

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Practice Gap

Clinicians must be cognizant of the common, more benign but often treatable causes of vomiting as well as the less common but life-threatening surgical, metabolic and infectious disorders of which vomiting is a symptom. Practitioners should stay abreast of evolving recommendations on newer, effective anti-emetic therapies for treating chemotherapy patients and others with non-cancerous disorders.

Objectives

After completing this article, readers should be able to:

1. **Know the causes of vomiting in children of different age groups.**
2. **Distinguish between nonorganic and organic causes of vomiting.**
3. **Diagnose and treat eosinophilic esophagitis (EE).**
4. **Develop an initial management plan for a child with intestinal obstruction.**
5. **Evaluate and manage rumination syndrome and cyclic vomiting syndrome (CVS) in children.**
6. **Understand the role of various antiemetic medications in the treatment of vomiting in children.**

Definitions

We will use the following terms as defined by the American Gastroenterological Association (AGA). (1)

- Vomiting: Forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature.
- Nausea: The unpleasant sensation of the imminent need to vomit, usually referred to the throat or epigastrium; a sensation that may or may not ultimately lead to the act of vomiting.
- Regurgitation: The act by which food is brought back into the mouth without the abdominal and diaphragmatic muscular activity that characterizes vomiting.
- Retching: Spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents, referred to as "dry heaves."
- Rumination: Chewing and swallowing of regurgitated food that has come back into the mouth through a voluntary increase in abdominal pressure within minutes of eating or during eating.

Abbreviations

AGA:	American Gastroenterological Association
CVS:	cyclic vomiting syndrome
EE:	eosinophilic esophagitis
GER:	gastroesophageal reflux
GERD:	gastroesophageal reflux disease
GI:	gastrointestinal
PPI:	proton pump inhibitor

Pathophysiology

Vomiting is a complex process that involves various systems that influence the vomiting center (Fig 1). The vomiting center is located in the lateral medullary reticular formation of the brainstem and is the final pathway for the physiologic

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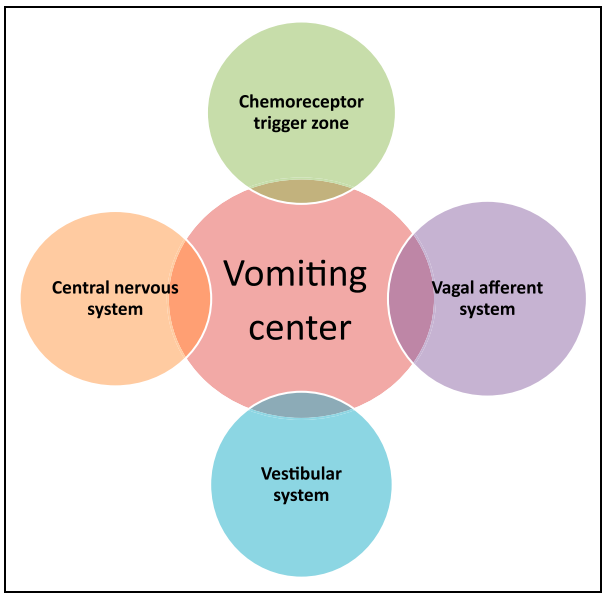

Figure 1. Pathophysiology of vomiting. The figure demonstrates various systems that influence the vomiting center.

processes that result in vomiting. The center has predominantly muscarinic M_1 (M_1), histamine 1 (H_1), neurokinin 1, and serotonin receptors. The vomiting center receives input from 4 distinct centers: chemoreceptor trigger zone, vagal afferent system, vestibular system, and high cortical centers.

The chemoreceptor trigger zone, also known as area postrema, is located at the caudal portion of the fourth ventricle. The zone is located outside the blood brain barrier and serves as the emetic chemoreceptor for the vomiting center; thus, it is influenced by triggers of vomiting in the blood or cerebrospinal fluid. The center mainly has dopamine 2 (D_2) receptors. Other involved receptors are M_1- and H_1-receptors.

Vagal Afferent System

The vagal afferent system primarily receives input from the GI tract and is activated by distention or irritation of the GI tract from various causes. It is mediated by serotonin receptors.

Vestibular System

The vestibular system is involved in the vomiting associated with motion sickness and labyrinthine disorders. It is mediated via M_1- and H_1-receptors.

Higher Cortical Centers

This pathway is not well understood. This system may be involved in other nonanatomical causes of vomiting, such as stress-induced vomiting and vomiting that results from behavioral or psychiatric disorders. Conduction pathways between the higher and the lower centers of the brain enable constant communication and interaction between the 2 regions.

The act of vomiting has multiple phases: a preejection phase, a retching phase, and an ejection phase. In the preejection phase, gastric relaxation and retroperistalsis occur. In the retching phase, rhythmic contractions of respiratory, abdominal wall, intercostal, and diaphragm muscles occur against a closed glottis. In the final phase, intense contraction of the abdominal muscles combined with relaxation of the pharyngoesophageal sphincter results in ejection. Vomiting can also occur abruptly without the preejection and retching phases; such vomiting is often forceful and is referred to as projectile vomiting, which is seen in cases of gastric outlet obstruction.

Differential Diagnosis of Vomiting

Vomiting is a symptom with a wide differential diagnosis, ranging from lesions of the GI tract to systemic illnesses. A detailed history, including dietary history, review of systems, family history, medication history, medical history, and surgical history, is important in the initial evaluation to identify a cause.

Acute onset of vomiting with severe abdominal pain may suggest a surgical origin; common associated symptoms include localized or generalized abdominal tenderness, signs of peritonitis, and absent or hyperactive bowel sounds. When vomiting is chronic, identifying the pattern of vomiting often provides clues to the diagnosis.

Vomiting is often characterized as nonbilious, bilious, or bloody based on the content. Vomitus from the esophagus, stomach, and first part of the duodenum usually consists of ingested food and is clear or yellow. Bilious vomiting denotes the presence of bile and appears light green to dark green. Bilious vomiting suggests obstruction of the intestine beyond the ampulla of Vater until proven otherwise. Hematemesis is the presence of blood in the vomitus. The presence of bright red blood in emesis or gastric lavage indicates active upper GI tract bleeding that may require immediate attention. The presence of coffee-ground material in the vomitus indicates that blood has been acted on by gastric acid. Vomiting is often described as projectile or nonprojectile. Projectile vomiting is commonly seen in gastric outlet obstruction, such as pyloric stenosis, and in conditions that result in raised intracranial pressure. However, this expression is commonly misused by parents. Table 1 lists several red flags

Table 1. Distinguishing Features of Organic Causes of Vomiting "Red Flags" That Suggest Serious Underlying Conditions

Poor weight gain or weight loss: may suggest chronic disease, such as inflammatory bowel disease, celiac disease, or metabolic disease	Localized abdominal pain: less likely to be functional (eg, localized right upper quadrant pain may suggest gallbladder disease, whereas localized epigastric pain may suggest esophagitis)
Bilious emesis: may be indicative of postampullary obstruction	Severe dehydration: suggests severe vomiting and warrants exclusion of serious underlying conditions, such as obstruction
Hematemesis: may suggest esophagitis, gastritis, or peptic ulcer disease	Nocturnal vomiting: may suggest conditions such as gastroesophageal reflux disease or postnasal drainage
Early morning headache: may suggest increased intracranial pressure	Short stature: may suggest conditions such as inflammatory bowel disease, hypothyroidism, or celiac disease
Hematochezia/melena: may suggest mucosal disease of the gastrointestinal tract, such as inflammatory bowel disease	Fever: if persistent (>72 hours), if child appears ill, or if in an infant younger than 6 months may be due to serious bacterial infection

that should alert one to look for an organic cause in a patient who presents with vomiting, Table 2 provides a list of differential diagnoses based on individual organ systems, and Table 3 lists potential causes of vomiting based on age at presentation.

Common Causes of Emesis in Infancy

GER and GERD

Gastroesophageal reflux (GER) is the passage of stomach contents into the esophagus and can be a normal physiologic process. It is common in healthy term infants, children, and adults. Regurgitation is often used interchangeably with GER. It is the effortless and nonprojectile passage of stomach contents into the oropharynx. If a large volume of stomach contents exit the mouth with force, it may be erroneously labeled as *projectile vomiting* by the family. Infantile regurgitation peaks at 3 to 4 months (67% of infants), gradually decreases to 14% at 7 months, and decreases to less than 5% by 12 to 14 months. (2) Common symptoms associated with this are feeding refusal, irritability, fussiness, cough, apnea, and wheezing. Given that regurgitation is commonly transient, esophageal injury is rarely seen on endoscopy in infants. The presence of an appropriate weight for age is a good marker suggestive of a "happy spitter" who does not warrant additional investigation. Parental education about the natural course of infantile gastroesophageal reflux is the key to successful management. Symptoms resolve in most infants by 12 months of age. If symptoms persist past 18 months of age the child warrants an evaluation. (3)

Gastroesophageal reflux disease (GERD) is when the passage of stomach contents into the esophagus causes adverse symptoms or complications.

Investigation

BARIUM STUDY OF THE UPPER GI TRACT. A barium study of the upper GI tract is not useful for diagnosing GERD but is primarily used to rule out anatomical abnormalities of the upper GI tract, which may cause emesis.

SCINTIGRAPHY. A gastroesophageal scintiscan, like a barium study of the upper GI tract, is not useful to diagnose GERD but may diagnose delayed gastric emptying, which could be contributing to vomiting.

ESOPHAGEAL PH MONITORING. Esophageal pH monitoring is not indicated to establish the diagnosis of uncomplicated GER, but in cases of complicated gastroesophageal reflux, it may help to establish the diagnosis and severity of GER and correlate symptoms with reflux. It allows an extended monitoring of esophageal pH for 18 to 48 hours. A reflux index (the percentage of the study period when esophageal pH was less than 4) and a symptom index (the percentage of a reported symptom, such as apnea, bradycardia, and wheezing) that correlated with GER can be calculated. In addition, information on the duration of prolonged episodes of acid reflux is useful. However, there is no correlation between acid reflux severity and infant symptom severity.

Esophageal pH monitoring with impedance monitoring is used to detect acid and nonacid reflux. It is

Table 2. **Differential Diagnosis of Emesis by System**

Gastrointestinal disorders	Metabolic disorders
• Esophagus: gastroesophageal reflux, eosinophilic esophagitis, achalasia, esophageal atresia, stricture, web, ring, foreign body	• Carbohydrate: galactosemia, hereditary fructose intolerance, pyruvate carboxylase deficiency
• Stomach: gastroenteritis, gastritis, peptic ulcer disease, pyloric stenosis, gastroparesis, bezoar	• Organic acid: phenylketonuria, urea cycle defect, maple syrup urine, tyrosinemia type 1
• Small intestine: malrotation, atresia, duplication, intussusception, volvulus, ileus, pseudoobstruction, necrotizing enterocolitis, celiac disease, Crohn's disease, duodenal hematoma, superior mesenteric artery syndrome, milk protein enteropathy	• Fatty acid oxidation defect: carnitine deficiency, MCAD, LCAD
• Colon: Hirschsprung disease, ulcerative colitis, appendicitis, constipation, hernia	• Lysosomal storage: mucopolysaccharidoses, Niemann-Pick disease, Wolman disease
• Liver: hepatitis, acute liver failure, hepatic abscess • Gallbladder: cholecystitis, cholelithiasis, choledocholithiasis, gallbladder dyskinesia, choledochal cyst • Pancreas: pancreatitis, annular pancreas, pancreatic divisum	• Peroxisomal disorders: Zellweger disease, infantile Refsum disease, acyl-CoA oxidase deficiency, adrenal leukodystrophy
• Peritoneum: peritonitis, peritoneal adhesion	Endocrine disorders • Diabetic ketoacidosis, adrenal insufficiency/adrenal crisis, hyperparathyroidism, pregnancy
Renal disorders • Renal tubular acidosis, ureteropelvic junction obstruction, nephrolithiasis, renal insufficiency, uremia, hydronephrosis	Neurologic disorders • Hydrocephalus, tumor, intracranial bleeding (subdural hematoma), meningoencephalitis, abscess, seizure, migraine, pseudotumor cerebri, motion sickness, ventriculoperitoneal shunt failure or infection
Infectious disorders • Urinary tract infection, meningitis, pharyngitis, sinusitis, otitis media, pneumonia, sepsis	Toxins and medications: • Aspirin, iron, lead, digoxin, alcohol, marijuana, chemotherapeutic agent Other • Eating disorders (anorexia, bulimia), cyclic vomiting syndrome, rumination, overfeeding, psychogenic

LCAD=long chain acyl-CoA dehydrogenase; MCAD=medium chain acyl-CoA dehydrogenase.

commonly used to determine whether there is a correlation between acid and nonacid reflux and extraesophageal symptoms, such as apnea, bradycardia, hypoxia, and asthma. Normal values for nonacid reflux are not well established in children.

ENDOSCOPY. Endoscopy is considered if a patient's symptoms persist or fail to respond to conservative medical management. An endoscopic biopsy is helpful in diagnosing esophagitis, gastritis, or duodenitis, as well as specifically ruling out EE.

Treatment

Parental education and support are important in the management of GER and GERD. The anticipatory guidance should emphasize the benign nature and discuss the natural history of infantile GER, with a peak incidence at 4 months and resolution in most infants by 12 to 18 months. Educational materials should stress that most infants do well with conservative management, including feeding modification (avoidance of overfeeding) and positioning, in the absence of red flags. In uncomplicated GER no testing is required, and the goal is to improve symptoms. Milk protein intolerance can mimic GER; therefore, in an infant with poor weight gain or feeding refusal, GER, and/or extreme fussiness, a 2- to 4-week trial of a hypoallergenic formula is appropriate as initial treatment. In breastfed infants, the efficacy of elimination of cow milk protein in the mother's diet is controversial but may be considered. Thickening feeds decreases observed regurgitation but not the reflux index or reflux height. (4) It appears to reduce irritability and is beneficial in an infant with poor weight gain because it provides extra calories. Elevation of the head of the crib, although commonly recommended, has not been found to improve reflux symptoms. Prone position decreases reflux because the esophagus enters the stomach posteriorly; however, the risk of sudden infant death

Table 3. **Age-Related Differential Diagnosis of Emesis**

Neonate (<1 month)	Infant (>1–12 months)	Toddler (>1–4 years)	Child (4–12 years)	Teenager (13–19 years)
• GER or GERD	• GER or GERD	• Gastroenteritis	• Gastroenteritis	• Gastroenteritis
• Feeding intolerance	• Acute otitis media	• Urinary tract infection	• Pharyngitis	• Peptic ulcer disease
• Pyloric stenosis	• Protein intolerance	• Pharyngitis	• Post infectious gastroparesis	• Cyclic vomiting
• Meconium ileus	• Gastroenteritis	• GERD	• Eosinophilic esophagitis	• Eosinophilic esophagitis
• Congenital atresia or webs	• Pyloric stenosis	• Eosinophilic esophagitis	• Appendicitis	• Pregnancy
• Malrotation with midgut volvulus	• Intussusception	• Celiac disease	• Celiac disease	• Poisoning/toxic ingestion
• Necrotizing enterocolitis	• UTI	• Intracranial lesion	• Pancreatitis	• Migraine
• Metabolic disorders	• Malrotation with midgut volvulus	• Malrotation	• IBD	• Diabetic ketoacidosis
• Hirschsprung disease	• Intracranial lesion	• Poisoning/toxic ingestion	• Trauma (duodenal hematoma)	• Rumination syndrome
• Protein intolerance	• Metabolic disorders	• Adrenal insufficiency	• Poisoning/toxic ingestion	• Drug abuse
• Infection (UTI or meningitis)	• Child abuse • Munchausen syndrome by proxy			• Appendicitis • Gallstone • Pancreatitis • Bulimia • IBD

IBD=inflammatory bowel disease; GER=gastroesophageal reflux; GERD=gastroesophageal reflux disease; UTI=urinary tract infection.

syndrome outweighs the benefit. Thus, infants need to continue to be in a supine position during sleep. A semisupine position increases reflux; left side positioning may improve reflux symptoms but may also be associated with an increased risk for SIDS. Infants can be prone while awake and under direct observation.

In uncomplicated GER, acid blockers are not beneficial and not recommended; parental education, reassurance, and anticipatory guidance are recommended but not always easily accepted. If an infant has complicated GER, such as feeding refusal, poor weight gain, and no improvement on dietary modification, a trial of once daily proton pump inhibitors (PPIs) is preferred. An H_2-blocker also may be used, although tachyphylaxis may develop with long-term H_2-blocker use. Infants with biopsy-proven reflux esophagitis require PPI treatment. All PPIs are equally effective. (Esomeprazole is approved by the US Food and Drug Administration for erosive esophagitis in infants). Prokinetic agents, such as erythromycin and metoclopramide, have a limited role in the management of GER but may be beneficial if delayed gastric emptying is documented. Baclofen to decrease spontaneous relaxation of the lower esophageal sphincter is the newest treatment, but this is an off-label use of this medication, and use should be restricted.

Pyloric Stenosis

Pyloric stenosis occurs in 2 to 3 infants per 1000 live births. It occurs much more commonly in males, with a male-female ratio of 4:1 to 6:1. Up to one-third of cases of pyloric stenosis are seen in first-born infants. Genetic factors play a role in pyloric stenosis; studies show that a maternal history of pyloric stenosis is a risk factor for development of pyloric stenosis in offspring (20% of males and 10% of females). Also among twins, the risk for pyloric stenosis is higher in monozygotic twins compared with dizygotic twins. A defect in the *NOS1* gene loci, resulting in decreased neuronal nitric oxide, has been implicated in the development of pyloric stenosis. Use of erythromycin in infants, especially within the first weeks of life, is a well-established risk factor for

development of pyloric stenosis. (5) Ten cases associating the use of azithromycin with pyloric stenosis have been reported. (6) Maternal use of macrolide antibiotics during late pregnancy and during breastfeeding have also been linked to the development of pyloric stenosis. The typical presentation is a 3- to 6-week-old infant with progressive or intermittent vomiting after feeding. The vomiting is often projectile in nature, and 1.4% of patients present with bilious emesis. The infant is hungry after vomiting. Infants with continued vomiting develop hypochloremic, hypokalemic contraction alkalosis and aciduria. On physical examination an olivelike mass is appreciated in the right midepigastrium, mostly after emesis. Visible gastric peristalsis is seen with feeding. Icteropyloric syndrome is a combination of hyperbilirubinemia and pyloric stenosis seen in up to 8% of infants. The hyperbilirubinemia is usually indirect and thought to be secondary to increased enterohepatic circulation and decreased glucuronyl transferase activity. The diagnosis of pyloric stenosis is usually made by abdominal ultrasonography. Ultrasonographic diagnostic criteria consist of pyloric thickness of 3 to 4 mm, pyloric length of 15 to 19 mm, and pyloric diameter of 10to 14 mm (Fig 2). (7) A barium study of the upper GI tract can also be used to make the diagnosis and has the added advantage of excluding other obstructive lesions, such as antral web or malrotation with volvulus, although it carries considerable radiation exposure and expense. The typical features of pyloric stenosis on a barium study of the upper GI tract are elongated pyloric canal (string sign), a bulge of the pyloric muscle into the antrum (shoulder sign), narrowed ending of pyloric canal (beak sign), and parallel streaks of barium seen in the narrowed channel (double tract sign).

Once the diagnosis is made, the goal is to correct the fluid, electrolyte, and acid-base imbalance before proceeding to surgery. There is a risk of postoperative apnea if alkalosis is not corrected before the surgery. The surgery performed is pyloromyotomy in which the pylorus is split longitudinally down to the submucosa to relieve the stenosis. Several randomized controlled studies have reported that there is no significant difference between open vs laparoscopic pyloromyotomy, except for cosmetic reasons and center availability of laparoscopy. (8)

Intestinal Atresia

The small intestine is the most common site of intestinal atresia, with an occurrence of 2.8 per 10, 000 live births. Duodenal atresia contributes 49%, followed by jejunal atresia at 36% and ileal atresia at 14%. Intestinal atresia is thought to result from a lack of revacuolization of the intestinal solid cord stage and a late intrauterine mesenteric vascular incident along with genetic factors. Jejunoileal atresia may be seen in normal full-term infants; however, it is usually associated with congenital anomalies, such as gastroschisis, internal hernia, and volvulus. Fifty percent of duodenal atresia cases are seen in premature infants. Duodenal atresia is seen in 25% to 50% of infants with Down syndrome. Other associated congenital anomalies include congenital heart disease, annular pancreas, malrotation, renal anomalies, skeletal malformations, and esophageal atresia. (9) Infants present with bilious vomiting, abdominal distension, and failure to pass meconium. There is a history of maternal polyhydramnios, and one-third of patients have jaundice. Abdominal radiographs show the pathognomonic "double

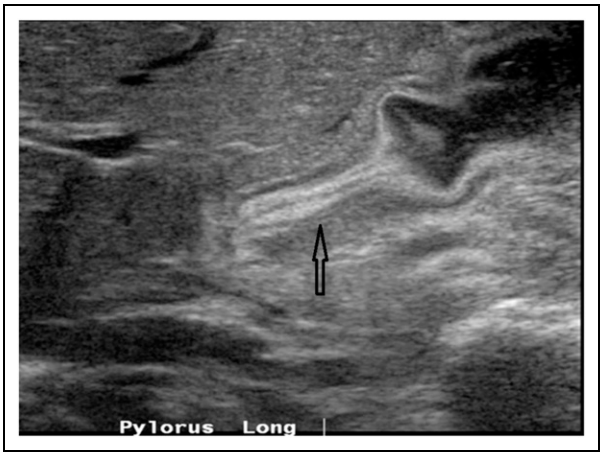

Figure 2. Abdominal ultrasonogram showing elongated pyloric muscle suggestive of pyloric stenosis.

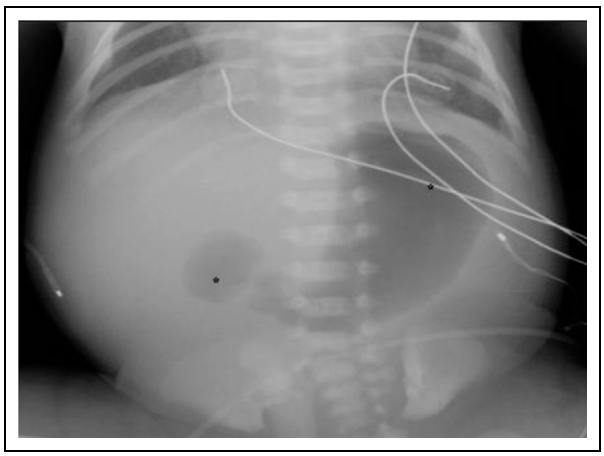

Figure 3. Plain abdomen radiograph showing double bubble sign suggestive of duodenal atresia.

bubble sign" (Fig 3). Additional imaging studies (eg, echo, renal ultrasonography, and vertebral radiograph) should be performed to exclude associated malformations. Initial management includes bowel rest along with nasogastric or orogastric decompression. Correction of dehydration and electrolyte abnormalities should be promptly undertaken. Once the patient is hemodynamically stable, surgical intervention is essential.

Congenital anomalies that cause bowel obstruction (eg, duodenal web, malrotation, and annular pancreas) usually present during infancy; however, they may present later in life if the obstruction is partial.

Causes of Vomiting Beyond Infancy

Acute Gastroenteritis

Although it may occur in infants, acute gastroenteritis is the most common reason for vomiting beyond infancy. Viruses are the most common cause of gastroenteritis followed by bacteria and parasites. The typical presentation is acute onset of vomiting followed by diarrhea. Vomiting is a self-protective process that may reduce the load of the infectious organisms and associated toxins or irritants that cause the vomiting. The use of antiemetics in acute gastroenteritis has been controversial. Recent meta-analyses of reported studies, however, suggest that ondansetron reduces vomiting and the need for hospitalization or intravenous fluids in children with acute gastroenteritis. However, ondansetron also may increase diarrhea in such patients. Rehydration (oral, enteral, or intravenous) is key to successful management of acute gastroenteritis.

Eosinophilic Esophagitis

Severe EE previously was thought to be due to severe GERD, but patients with this condition failed to respond to medical management of GERD. Now this condition is considered a different disease entity. The etiopathogenesis of EE remains unknown, although it is postulated that in some patients infiltration with eosinophils may be related to food allergen hypersensitivity. In many patients, however, no specific food allergen is identified. Other etiologic possibilities mentioned in the literature include reaction to aeroallergens, particularly because in some patients EE is seasonal, and to T-cell–mediated immune dysregulation. The incidence of EE is 1.2 per 10,000 children. (10) The prevalence of EE in population-based studies is 4.2 per 10,000 children, but the literature shows that the prevalence is increasing. The male-female ratio is 3:1. The mean age of diagnosis is 8.6 years. The presenting symptoms vary based on the age at presentation; feeding dysfunction is seen in the toddler age group (1-4 years old), vomiting in the child age group (4-12 years old), abdominal pain in the 10- to 15-year-old age group, dysphagia in the 10- to 17-year-old age group, and food impaction in the 14- to 20-year-old age group. Other symptoms include failure to thrive and chest pain. Often EE is seen in patients with other allergic diseases, such as asthma, eczema, food allergy, allergic rhinitis, and urticaria.

Endoscopy of the upper GI tract with biopsy is required to make the diagnosis of EE. The endoscopic features suggestive of EE include linear furrowing or vertical lines, white exudates, circular rings or trachealization, and strictures of the esophagus (Fig 4). The histologic features of EE include increased number of eosinophils (≥15 intraepithelial eosinophils per high-power field of the microscope) at multiple levels of the

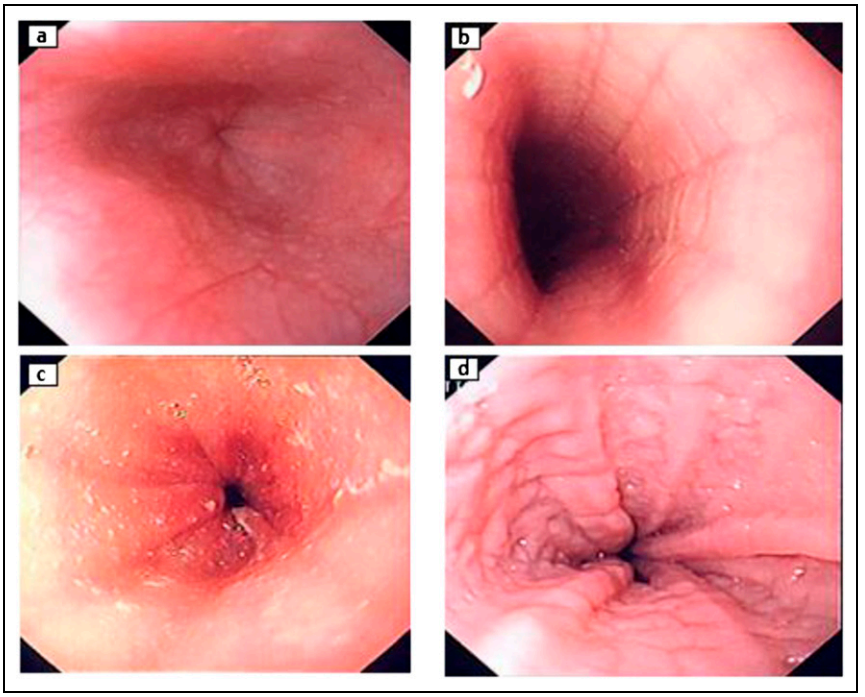

Figure 4. Endoscopic images of esophagus showing normal mucosa (a), vertical line (b), white specks (c), and) rings (trachealization) (d).

esophagus, eosinophilic microabscesses, and basal cell hyperplasia. (11)

Treatment options for EE include acid suppression, corticosteroids (topical and systemic), and dietary modifications. Esophageal eosinophilia that responds to PPIs is called PPI-responsive EE and is considered a separate entity from EE. It is hypothesized that the mechanisms by which a PPI may improve the symptoms of EE include treatment of coexisting GERD and/or a direct anti-inflammatory effect of the PPI. Swallowed fluticasone given usually as 2 puffs swallowed 2 times a day has been effective in treating EE. The dose varies, based on patient age, from 44 to 220 μg per swallowed puff. Response is appreciated by patients within a week; however, symptom relapse once the treatment is discontinued is common. Indications for maintenance therapy are not well established. Dietary modification treatment options include an elimination diet based on allergy testing, an empiric elimination diet (milk, soy, egg, peanut, wheat, and fish), or a complete elemental diet (amino acid formula). (11) Cautious esophageal dilation is helpful in patients with esophageal stricture causing dysphagia and recurrent food impaction. The prognosis of EE is unknown.

Rumination Syndrome

Rumination is defined as effortless regurgitation of recently ingested food into the mouth with subsequent mastication and reswallowing or expulsion. Rumination is seen in 3 distinct populations: infants, persons with a psychiatric disorder, and healthy adolescents or adults.

The incidence and prevalence of rumination syndrome are unknown, but recent literature suggests that it is occurring more frequently. It is more common in adolescent and older females than males. Weight loss (42%) is commonly seen in adolescents at the onset of rumination syndrome. Other associated symptoms include abdominal pain (38%), constipation (21%), nausea (17%), and diarrhea (8%). (12) Rumination syndrome also affects the quality of life of the patient, including absenteeism from school or work (72%) and frequent hospitalizations. The exact cause is unknown, but in some patients the onset of symptoms coincides with the occurrence of a stressful event. In the literature, an association with eating disorders (20%) has been reported.

The hypothesized pathophysiologic finding in rumination syndrome is repeated voluntary abdominal muscle wall contraction, causing increased gastric pressure and resulting in movement of gastric content to the esophagus and out.

The diagnosis of rumination is usually made by history as described in the Rome III criteria for diagnosis of functional GI disorders and must include *all* of the following:

1. Repeated painless regurgitation and rechewing or expulsion of food that:
   a. Begins soon after ingestion of a meal
   b. Does not occur during sleep
   c. Does not respond to standard treatment for GER
2. Absence of retching
3. Absence of evidence of an inflammatory, anatomical, metabolic, or neoplastic process that explains the patient's symptoms.

These criteria should have been present for the last 3 months, and the onset of symptoms should have been at least 6 months before diagnosis.

Physicians' lack of familiarity can result in missed diagnosis of rumination syndrome. These patients are often misdiagnosed as having GERD, dyspepsia, or gastroparesis.

Additional diagnostic testing can be considered if there is diagnostic ambiguity or if the patient or family fails to accept the diagnosis. This may include an esophageal pH study that reveals rapid fluctuation in luminal pH secondary to repeated regurgitation and reswallowing within the first 1 to 2 hours after eating but not during sleep and/or antroduodenal manometry that reveals the pathognomonic synchronous increase in pressure (R wave) across multiple recording sites (Fig 5). The R wave represents increased intra-abdominal pressure from voluntary abdominal wall muscle contraction. Fasting manometry results are otherwise normal. Endoscopy has no role in diagnosis but rules out other causes, such as GER and EE. The differential diagnosis for rumination syndrome includes GERD, gastroparesis, and achalasia.

MANAGEMENT OF RUMINATION SYNDROME.

The most effective treatment option is behavioral therapy (85% success rate). Diaphragmatic breathing acts as a habit reversal technique by teaching the patient relaxation of the diaphragm instead of contraction, which then prevents regurgitation. (12)

Initiation of a multidisciplinary approach by involving the patient, parents, primary care physicians, and behavioral therapist at the earliest is key to successful management.

If the patient has had a significant amount of weight loss transpyloric enteral nutritional support may be considered. If there is evidence of esophagitis, a PPI should be prescribed. Other treatment options, such as chewing gum, use of a prokinetic agent, baclofen, antidepressants, and antireflux surgery, have been offered, but there is no evidence that these treatment options are effective.

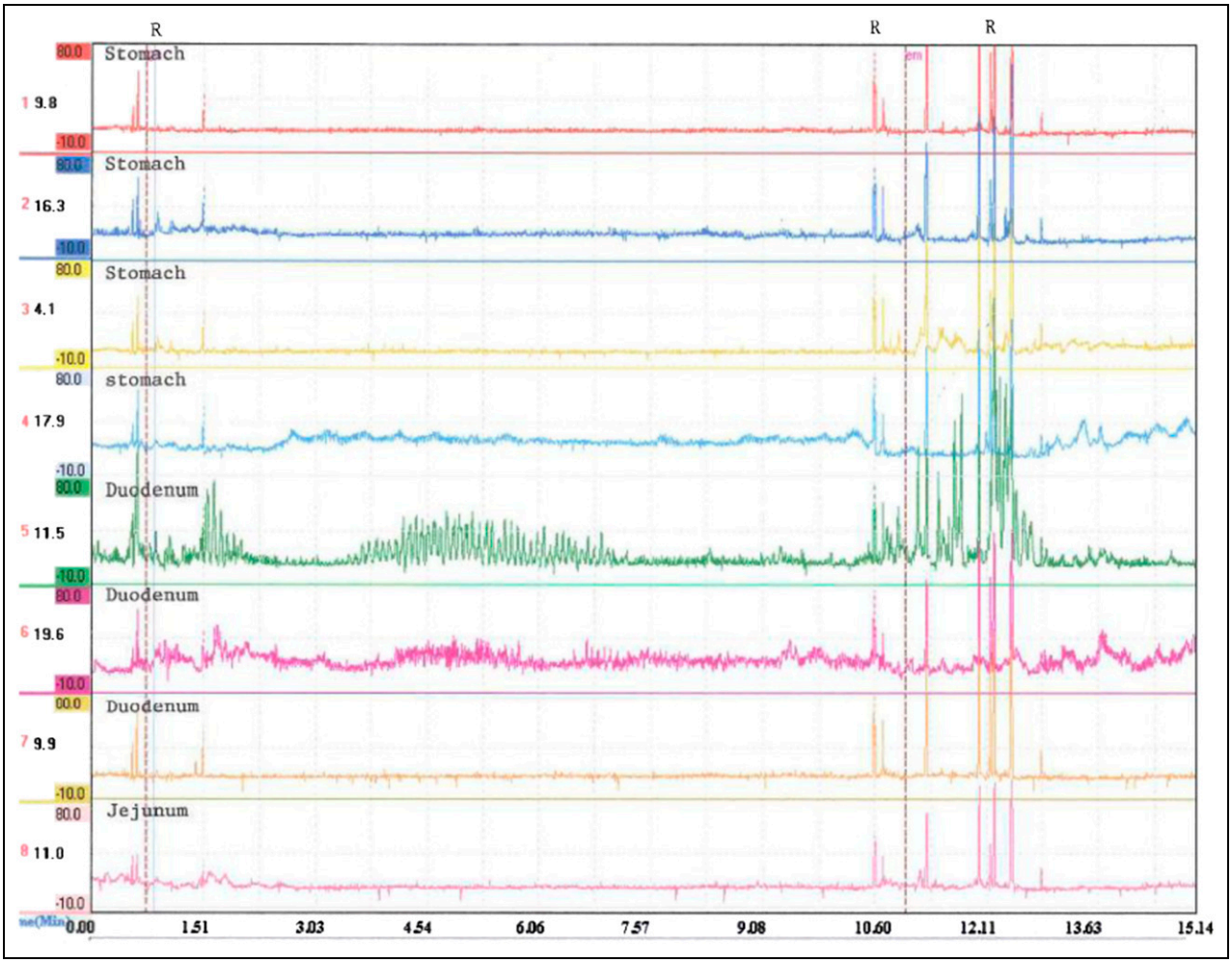

Figure 5. Antroduodenal manometry showing an R wave suggestive of rumination syndrome.

Cyclic Vomiting Syndrome

CVS is a functional disorder characterized by stereotypical episodes of nausea and vomiting lasting for hours to days, with the patient being asymptomatic and healthy between the episodes of vomiting. The exact incidence and prevalence are unknown. The estimated prevalence is between 1.9% and 2.3%. (13) CVS starts during the preschool years in most patients, but it is usually diagnosed around 9 years of age. The male-female ratio is 4:6.

CVS is strongly associated with migraine headaches; 80% of patients with CVS have a family history of migraine headaches, and 80% of patients with CVS respond to antimigraine treatment. Most patients with CVS will outgrow it by the teenage years; however, approximately 75% will develop migraine headaches by adulthood. Some patients with CVS develop abdominal migraines before developing migraine headaches. The origin of CVS is idiopathic in 90% of patients. Various mitochondrial disorders have been strongly linked to CVS. Mitochondrial DNA polymorphisms, specifically 1651T and 3010A, have been reported to be associated with CVS. Other associated conditions include hereditary sensory autonomic neuropathy, cannabis hyperemesis syndrome, metabolic and endocrine disorders. Patients with CVS typically have acute onset of nausea and vomiting beginning in the early morning hours. Other associated symptoms include pallor, photophobia, lethargy, anorexia, headache, diarrhea, visual changes, and abdominal pain. Each episode lasts for a few hours to a few days followed by symptom-free intervals, which, like associated symptoms such as the time of onset of vomiting, the pattern of vomiting, and duration of vomiting, is stereotypical for the individual but is at least 1 week long. Common triggers are infection and emotional changes. The emotional stress may be positive

(eg, birthday event) or negative (eg, school examination). Two additional distinct CVS syndromes have been described in the literature:

CVS plus indicates the presence of neurologic features (eg, seizure, developmental delay, hypotonia) in addition to CVS symptoms. Patients with CVS plus present at an earlier age and have increased occurrence of migraine headaches and pain syndrome. Catamenial CVS is the presence of CVS symptoms at the onset of the menstrual cycle.

The Rome III diagnostic criteria for CVS include all of the following:

1. Stereotypical episodes of vomiting regarding onset (acute) and duration (<1 week)
2. Three or more discrete episodes in the prior year
3. Absence of nausea and vomiting between episodes

These criteria should have been fulfilled within the last 3 months, and the symptom onset should have been at least 6 months before diagnosis.

A supportive criterion is the presence of a history or family history of migraine headaches.

Initial evaluation should include an upper GI tract series to exclude malrotation and a basic metabolic profile to exclude electrolyte abnormalities and hypoglycemia. Additional evaluation depends on the presence of other risk factors or alarm symptoms. If the patient has localized abdominal pain, abdominal ultrasonography and serum amylase and lipase measurement may be warranted. Patients with hematemesis require endoscopy.

If the symptoms are triggered by fasting, a high protein diet, or an intercurrent illness, the patient requires a metabolic workup, including blood glucose, ammonia, lactate, pyruvate, urine ketone, serum AA, acylcarnitine profile, and urine organic acid, to rule out metabolic disorders.

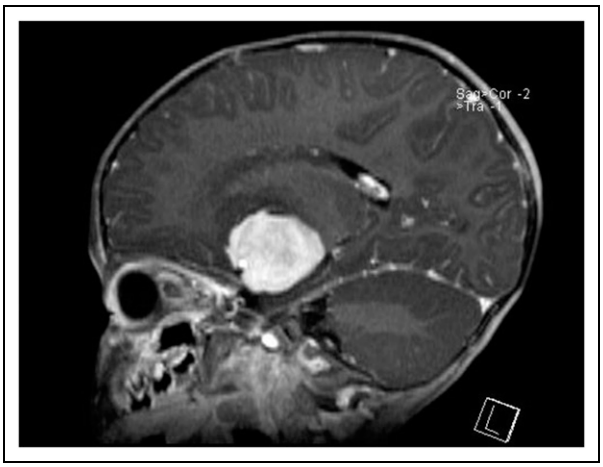

Figure 6. Magnetic resonance image of the head showing a well-circumscribed, enhancing suprasellar mass.

Patients in the CVS plus subcategory warrant serum amino acid and urine organic acid testing.

Patients with neurologic signs and symptoms and progressive vomiting should undergo brain magnetic resonance imaging to evaluate for an intracranial process. (Fig 6)

Cannabis overuse can result in cannabis hyperemesis syndrome, which is similar to CVS. These patients need to abstain from using cannabis for 2 weeks before any additional workup is initiated.

Treatment

Lifestyle modification is important in preventing episodes of CVS and includes sleep hygiene and avoidance of triggers, such as fasting, caffeine, and chocolate. Educating the patient and family about CVS is helpful. Any underlying disease should be treated. (13)

The treatment of CVS includes treatment of an acute episode followed by prophylactic therapy. Prophylactic therapy is used if symptoms are frequent (>1 every other month), if the patient requires hospitalization, or if the vomiting is affecting the patient's quality of life. Tricyclic antidepressants are effective in 68% of pediatric patients with CVS. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines recommend cyproheptadine for children younger than 5 years and amitriptyline for children older than 5 years. A combination of amitriptyline and L-carnitine was effective in 73% of patients with CVS. Amitriptyline takes a few months to be effective, which should be made clear to the patient and family. Electrocardiography before the initiation of amitriptyline treatment is warranted to evaluate for cardiac arrhythmias, specifically, prolonged QTc interval. Recent evidence also supports the use of propranolol as first-line prophylactic therapy; 87% of patients treated with propranolol had improvement in CVS symptoms. Other drugs used include phenobarbital, topiramate, and sumatriptan, which are used in migraine therapy. Birth control pills are used in females with catamenial CVS symptoms.

During acute episodes, hydration with, with appropriate electrolytes should be used to prevent dehydration. Hydration is also effective in decreasing the duration of the acute illness. Ondansetron provides symptomatic relief. Sedation is usually beneficial for the patient and controls the vomiting. Diphenhydramine, lorazepam, and chlorpromazine have been used successfully to sedate

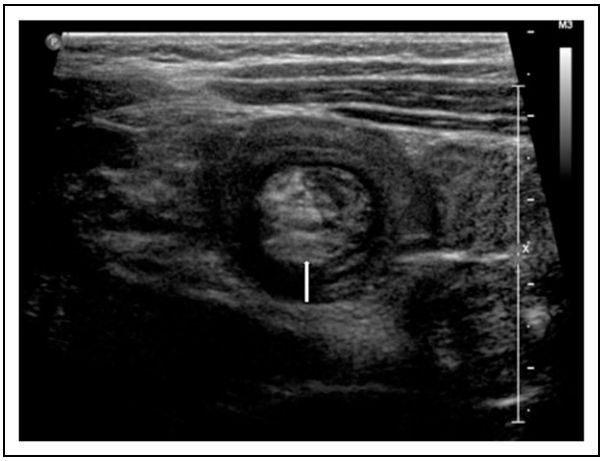

Figure 7. Abdominal ultrasonogram showing small bowel to small bowel intussusception in a patient with Peutz-Jeghers syndrome. Target sign is the layers of the small intestine within the small intestine.

patients during an acute episode of cyclic vomiting. If associated abdominal pain is bothersome, ketorolac may be used to relieve the pain.

Acute Intestinal Obstruction After infancy

Toddlers and older children can present with acute-onset intestinal obstruction. The typical patient presents with abdominal pain, nausea, vomiting (often bilious), abdominal distension, and signs of peritonitis if the obstruction has been present for a prolonged period. Bilious vomiting is characteristic of intestinal obstruction distal to the ampulla of Vater. The differential diagnosis is extensive and includes the following:

1. Intussusception (Fig 7)
2. Malrotation with or without midgut volvulus (Fig 8)
3. Incarcerated hernias
4. Strictures (eg, Crohn disease [Fig 9], nonsteroidal anti-inflammatory drugs, and irradiation)
5. Adhesions
6. Bezoars (Fig 10)
7. Superior mesenteric artery syndrome (Fig 11)
8. Small intestinal tumors (eg, carcinoid and lymphoma)

Initial Evaluation

Once intestinal obstruction is strongly suspected, gastric decompression via a nasogastric tube should be initiated to prevent further episodes of emesis and minimize the risk of aspiration. On the basis of the degree of obstruction, the nasogastric tube can be placed to gravity or low

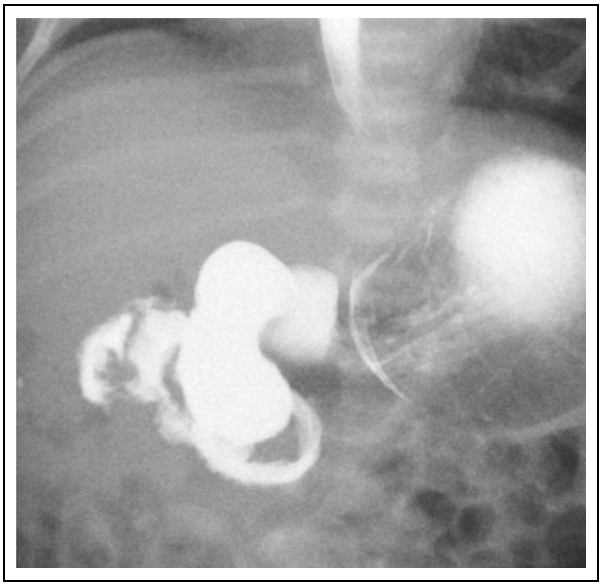

Figure 8. Barium study of the upper gastrointestinal tract showing failure of duodenal C loop to cross the vertebral column and corkscrewing of third part of duodenum suggestive of small bowel malrotation with volvulus.

intermittent suction; bowel rest is key in the management of intestinal obstruction. The degree of dehydration should be determined based on vital signs, physical examination findings, and urinalysis results. Electrolyte

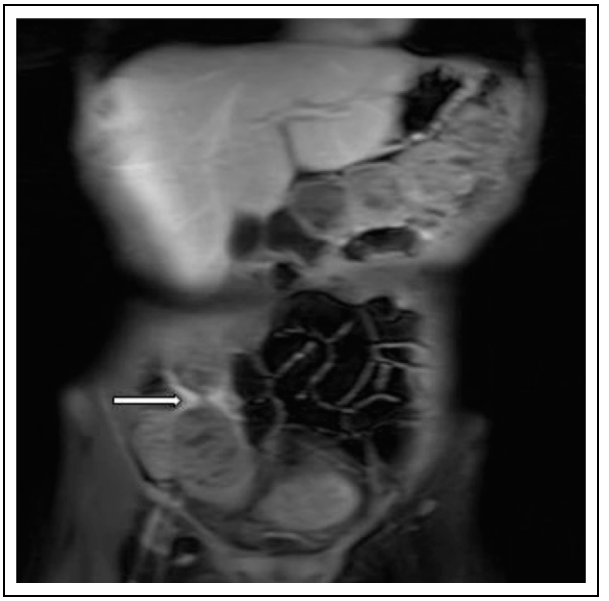

Figure 9. Magnetic resonance image of the abdomen showing stricture of the bowel with prestricture and poststricture bowel dilation in a patient with Crohn disease.

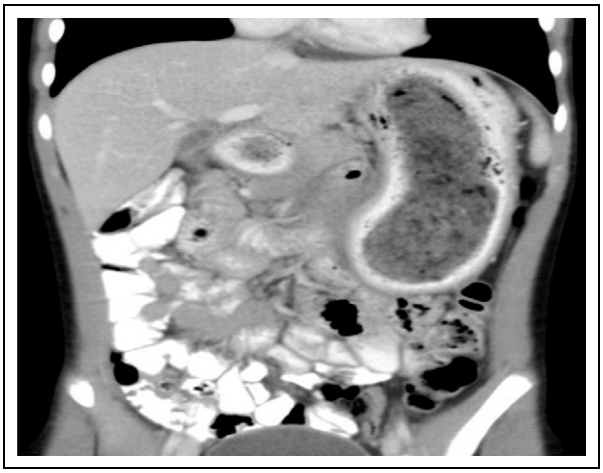

Figure 10. Computed tomograph of the abdomen showing heterogeneous mass in the stomach with mottled air pattern and oral contrast material surrounding the mass in a patient with gastric bezoar.

abnormalities are commonly encountered and should be managed appropriately. Symptomatic control of nausea, vomiting, and pain should be undertaken.

Once the patient is hemodynamically stabilized, appropriate radiologic studies should be performed to confirm and determine the site of obstruction. A plain radiograph of the abdomen may show air fluid levels suggestive of an ileus; it may also help to exclude a perforation as a complication of prolonged obstruction. A barium study of the upper GI tract is most helpful in the evaluation for small bowel obstruction. A barium enema may be necessary if the obstruction is in the lower GI tract. Pediatric surgery consultation is mandated when intestinal obstruction is suspected.

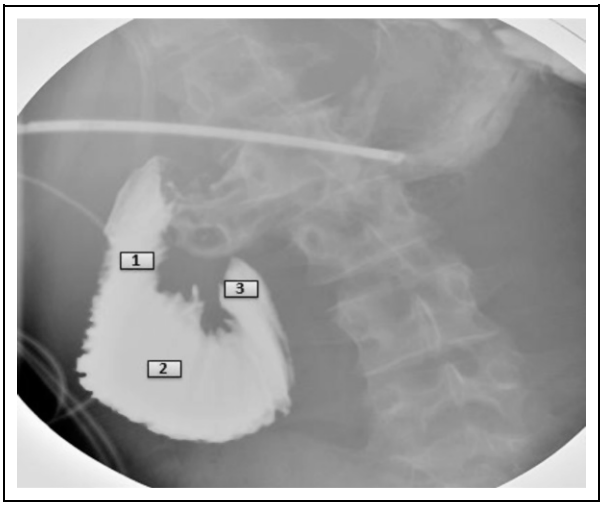

Figure 11. Barium study of the upper gastrointestinal tract showing dilation of the first and second portions of the duodenum with abrupt narrowing of the third position of the duodenum suggestive of superior mesenteric artery syndrome.

Antiemetic Medications

Antiemetics are categorized into 6 groups based on the receptor of action. Serotonin receptor antagonists are the most commonly used antiemetics in clinical practice. Drugs in this category include ondansetron, granisetron, dolasetron, and palonosetron. These drugs act on serotonin receptors located at the solitary tract nucleus, vagal afferents, and the chemoreceptor trigger zone to suppress nausea and vomiting. Common indications for this group of medications are chemotherapy-induced nausea and vomiting and postoperative and postirradiation nausea and vomiting. These drugs are well tolerated. Common adverse effects include headache, asthenia, constipation and dizziness.

Dopamine receptor antagonists include phenothiazines (prochlorperazine and chlorpromazine), butyrophenones (droperidol and haloperidol), and benzamides (metoclopramide and domperidone). Phenothiazines are commonly used as antiemetics. They act on D_2-receptors at the chemoreceptor trigger zone. They also have antihistaminic (H_1) and anticholinergic (M_1) effects. Common adverse effects are extrapyramidal reactions, which can be treated with diphenhydramine, and drowsiness

Metoclopramide has peripheral antidopamine (D_2) effects in addition to central antidopamine effects. It also stimulates cholinergic receptors, resulting in gastric peristalsis. It has a black box warning from the US Food and Drug Administration because of tardive dyskinesia with long-term use. It is commonly used to treat gastroparesis.

Domperidone has a selective peripheral antidopamine (D_2) effect in the upper GI tract. It does not cross the blood brain barrier and so does not have the central nervous system adverse effects seen with metoclopramide. This drug, however, is not available in the United States.

H_1-receptor antagonists include cyclizine, hydroxyzine, promethazine, and diphenhydramine. These drugs are commonly used as antiemetic agents. A common adverse effect is sedation.

The muscarinic receptor antagonist scopolamine acts on M_1 receptors. It is used as a prophylactic medication to prevent motion sickness. It is supplied as a transdermal patch.

Neurokinin receptor antagonists are a new class of antiemetic drugs that block the substance P–mediated

nausea and vomiting via neurokinin receptors. Drugs in this category include aprepitant (oral formulation) and fosaprepitant (parenteral formulation). These medications are primarily used for prevention and treatment of chemotherapy-induced nausea and vomiting. Compared with serotonin receptor antagonists, these drugs prevent delayed emesis associated with strongly emetogenic chemotherapy agents, such as cisplatin. An optimal result is achieved if used in conjunction with a serotonin receptor antagonist and dexamethasone.

The cannabinoid receptor agonist dronabinol is used to treat chemotherapy-induced nausea and vomiting when other antiemetics are not effective.

Summary

- Vomiting can be the presenting symptom of a variety of disorders, ranging from self-limited diseases to life-threatening diseases.
- The causes of vomiting vary with age of presentation, and pediatricians should develop the skill to identify serious conditions at the earliest stage based on the age of presentation.
- Bilious emesis at any age is a sign of intestinal obstruction until proven otherwise and needs immediate attention.
- Vomiting is not always due to a GI disorder, and pediatricians should look for causes outside the GI tract if no GI disease is identified.

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Parent Resources from the AAP at HealthyChildren.org

The reader is likely to find material relevant to this article to share with parents by visiting these links:

- http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Treating-Vomiting.aspx
- http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Infant-Vomiting.aspx
- http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Drinks-to-Prevent-Dehydration-in-a-Vomiting-Child.aspx

PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Learners can take Pediatrics in Review quizzes and claim credit online only. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for AMA PRA Category 1 CreditTM. In order to successfully complete 2013 Pediatrics in Review articles for AMA PRA Category 1 CreditTM, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

In Pediatrics in Review, AMA PRA Category 1 CreditTM may be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. A 3-month-old boy is seen by his pediatrician because of frequent vomiting. His parents report that since birth he spit up small amounts of formula after each feed but, over time, the amount regurgitated during each episode increased. Currently, regurgitation follows every feeding; it is non-projectile and non-bilious. The infant is otherwise healthy and developing normally; length and weight are each in the 75% for age. What is the most appropriate first step in management?

   A. Initiate a trial of once daily proton pump inhibitor therapy.
   B. Institute a 2-4 week trial of a hypoallergenic formula.
   C. Reassure parents that regurgitation is likely to gradually resolve.
   D. Schedule an esophageal endoscopy study with biopsy.
   E. Schedule an esophageal pH monitoring study.

2. A 34-week premature male developed bilious vomiting and abdominal distention within hours after birth. Prenatal course was complicated by maternal polyhydramnios and a sinus infection. A small amount of meconium was passed in the delivery room but since that time no further meconium stools were passed. Abdominal radiographs reveal a "double bubble sign." Physical examination and additional imaging studies reveal no other abnormalities or malformations. Stabilization of fluid and electrolytes are conducted as the patient is prepared for surgery. Which of the following is the most likely diagnosis?

   A. Duodenal atresia.
   B. Duodenal web.
   C. Ileal atresia.
   D. Jejunal atresia.
   E. Malrotation.

3. A previously healthy 4-year-old girl presents with a history of intermittent vomiting occurring 10-12 times in the previous eight months. During each bout the child vomits 8-10 times during a 24-48 hour period. Each episode begins early in the day with nausea followed by repeated vomiting and is accompanied by dizziness, anorexia and mild abdominal pain. Several of the episodes have been accompanied by an upper respiratory infection or acute otitis media. Between episodes, the child has felt well, with no complaints. She is doing well in pre-kindergarten. Her mother and maternal grandmother have migraine headaches. History is otherwise unrevealing and physical examination, including growth parameters and vital signs and neurologic exam, is normal. A basic metabolic profile and upper GI series were normal. In addition to lifestyle modification, such as sleep hygiene, which of the following is the most appropriate next step in management for this child?

   A. Amitriptyline.
   B. Cyproheptadine.
   C. Diphenhydramine.
   D. Ketorolac.
   E. Phenobarbital.

4. A previously healthy 2-year-old girl developed nonbilious vomiting and fever to 103.5 F (39.72C). She was fussy and somewhat difficult to console. She had one loose stool but continued to vomit and remained febrile for 72 hours. On physical examination, she appears mildly dehydrated, with a soft, nontender abdomen. Except for a 5% weight loss, the rest of her physical examination is normal. Which of the following etiologies should be pursued as the most likely cause of this child's symptoms?
   A. Acute gastroenteritis.
   B. Esophagitis.
   C. Intestinal malrotation.
   D. Pharyngitis.
   E. Urinary tract infection.

5. A 12-year-old male has migraines and motion sickness. Which of the following medications is most appropriate to prescribe for the prevention of motion sickness?
   A. Aprepitant.
   B. Chlorpromazine.
   C. Hydroxyzine.
   D. Ondansetron.
   E. Scopalamine.

Poetic License

Vomiting causes surprises!
No choices when the gorge rises.
Before writing prescriptions,
Get careful descriptions –
Symptoms are often disguises.
–MCM

Vomiting

Kalyan Ray Parashette and Joseph Croffie

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