Nausea, Vomiting, and Cannabinoid Hyperemesis Syndrome

By Christina L. Cox, Pharm.D., BCPS, BCPPS

Reviewed by: Lauren M. Oliveri, Pharm.D., BCPPS; and Meghan Baldo, Pharm.D., BCPPS

LEARNING OBJECTIVES

1. Evaluate nausea, vomiting, and other supporting symptoms to differentiate between acute, chronic, and cyclic causes of vomiting.
2. Design appropriate treatment for nausea/vomiting on the basis of the underlying cause.
3. Develop a treatment plan for cyclic vomiting syndrome to include abortive and prophylactic therapy, when indicated.
4. Evaluate treatment options for cannabinoid hyperemesis syndrome in the pediatric population.

ABBREVIATIONS IN THIS CHAPTER

CHS	Cannabinoid hyperemesis syndrome
CINV	Chemotherapy-induced nausea and vomiting
CTZ	Chemoreceptor trigger zone
CVS	Cyclic vomiting syndrome
H_1	Histamine-1
M_1	Muscarinic-1
PONV	Postoperative nausea and vomiting
TCA	Tricyclic antidepressant

Table of other common abbreviations.

INTRODUCTION

Nausea and vomiting in children can be the result of a GI tract disorder, like viral gastroenteritis, or a systemic illness. An understanding of the definitions outlined by the American Gastroenterological Association helps identify specific disorders and select treatment according to the underlying cause, especially for vomiting. Prompt recognition of nausea, the unpleasant sensation of the imminent need to vomit that may or may not ultimately lead to the act of vomiting, can lead to prevention of vomiting, if appropriate, and its complications.

Vomiting is the forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature. Regurgitation differs from vomiting because regurgitation does not involve the abdominal and diaphragmatic muscular activity that characterizes vomiting. Retching or "dry heaving" can accompany vomiting and is characterized by spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents. Rumination occurs within minutes of eating or during eating as a result of voluntary increased abdominal pressure, causing food regurgitation and subsequent chewing and swallowing of the contents (Quigley 2001).

This chapter will focus on vomiting and the accompanying nausea, as well as specific functional disorders associated with nausea and vomiting, including cyclic vomiting syndrome (CVS) and cannabinoid hyperemesis syndrome (CHS).

VOMITING IN CHILDREN

The true incidence of nausea and vomiting is difficult to estimate because of their many associations and causes, and their impact is far-reaching. Recently, a multinational cross-sectional study showed that 2.2% of the population fit the Rome IV criteria for functional nausea and vomiting disorders, which include chronic nausea and vomiting syndrome, CVS, and CHS. Of interest, the United States had

a higher prevalence than Canada or the United Kingdom, at 3% versus 1.9% and 1.8%, respectively (Aziz 2019).

Pathophysiology

As a response to a trigger, including toxins, the vomiting reflex is mediated by the vomiting center in the brain stem, which incorporates the response and activity to the muscarinic-1 (M_1), histamine-1 (H_1), neurokinin-1, and serotonin receptors. The listed receptors are housed in one or more of the four centers of the vomiting center. The chemoreceptor trigger zone (CTZ), located outside the blood-brain barrier, is influenced by triggers in the blood or CSF and involves dopaminergic (D_2 and D_3), serotonin, M_1, H_1, and neurokinin-1 receptors. Because these receptors are outside the blood-brain barrier, they can recognize toxins easily. The vagal afferent system, which is activated by distention or irritation of the GI tract, involves serotonin receptors, whereas the vestibular system, associated with motion sickness, triggers M_1 and H_1 receptors. The fourth center, the high cortical center, may be associated with nonanatomic sources of vomiting, like behavioral or psychiatric disorders, including stress-induced vomiting. Understanding the cause and resulting receptor involvement helps in selecting an optimal pharmacotherapy regimen (Shields 2018).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of nausea and vomiting
- Distinguishing characteristics of vomiting and potential causes
- Drug knowledge of the pharmacologic agents used to treat nausea and vomiting

Table of common pediatric laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Drossman D. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. Gastroenterology 2016;150:1262-79.
- North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 2008;47:379-93.
- Shields TM, Lightdale JR. Vomiting in children. Pediatr Rev 2018;39:342-58.
- Richards JR, Gordon BK, Danielson AR, et al. Pharmacologic treatment of cannabinoid hyperemesis syndrome: a systematic review. Pharmacotherapy 2017;37:725-34.

Cause

Vomiting can be the result of variety of disorders, ranging from acute causes, like viral gastroenteritis or bowel obstruction, to chronic conditions, like inflammatory bowel or peptic ulcer disease. Medications may also contribute to acute or chronic nausea and vomiting.

Acute vomiting, often lasting 24–48 hours, can be self-limiting or episodic, depending on the underlying cause. Inborn errors of metabolism and CHS are examples of acute, episodic vomiting. Acute vomiting is associated with more severe symptoms and dehydration. Chronic vomiting typically involves low-volume, infrequent episodes over several days to weeks and is less associated with dehydration.

Recognizing the mechanism of action and the related receptor and center being triggered helps determine treatment, either through avoidance of causative factors or initiation of receptor-targeted therapy. Four general pathways can trigger nausea and vomiting through activating the pathway-related receptors mentioned previously: bloodborne toxins (acting on the CTZ through the various receptors listed earlier), mechanical (through vagal afferent nerve stimulation), motion (vestibular pathway), and emotion (higher cortical pathway).

Medications cause nausea and vomiting through the bloodborne toxin pathway. Neurotoxic agents or stressors can trigger the release of substance P, a neuropeptide that binds to neurokinin-1 receptors within the CTZ, and cause an emetic response. In addition to neurokinin-1, the D_2, D_3, and serotonin-3 receptors within the CTZ are targets for these toxins/medications. The chemotherapy agent cisplatin is highly emetogenic by increasing serotonin concentrations that activate serotonin-3 receptors in the CTZ. Other medications implicated in this pathway include other highly emetogenic chemotherapy agents (cyclophosphamide, ifosfamide, and aldesleukin), theophylline, digoxin, opioids, volatile anesthetics (sevoflurane, isoflurane, halothane, enflurane, and desflurane), anticonvulsants, and antibiotics (Gravatt 2017; Grunberg 2011). In a study of GI adverse effects with anticonvulsant medications, around 30% of patients taking gabapentin, carbamazepine, valproate, lamotrigine, and phenytoin had nausea, and about 20% of patients taking carbamazepine, phenytoin, valproate, oxcarbazepine, and gabapentin reported vomiting (Jahromi 2011). Although most antibiotics are associated with GI adverse effects, including nausea and vomiting, penicillins, cephalosporins, fluoroquinolones, and macrolides are commonly implicated. Medication withdrawal syndrome can also cause nausea and vomiting, as in opioid and benzodiazepine withdrawal.

Stimulation of mechano- or chemoreceptors in the intestinal wall activates the mechanical pathway. Mechanoreceptor activation through obstruction or stretched mucosa (e.g., ileus or eating too much) leads to stimulation of vagal afferents

by serotonergic and neurokinin-1 receptors. Chemoreceptors may be triggered through cellular byproducts or toxins (e.g., food poisoning). Other examples of mechanical causes are included in Table 1.

Motion triggers the emetic pathway through the vestibular system, which is responsible for the body's ability to perceive its position in relation to the surrounding environment. Riding in a car, for example, may alter this perception, causing an

Table 1. Common Causes of Vomiting by Primary Pathways, Age Group, and Temporal Pattern

Age Group		Bloodborne Toxins	Mechanical
0–1 mo	Acute	• Food protein–induced enterocolitis syndrome	• Pyloric stenosis • Hirschsprung disease • Intestinal atresia • Meningitis • Sepsis
	Chronic	• Adrenal insufficiency	• Hirschsprung disease • Intestinal atresia • GI reflux disease
	Cyclic	• Adrenal insufficiency • Inborn errors of metabolism	• Malrotation with volvulus
1–12 mo	Acute	• Gastroenteritis • Food protein–induced enterocolitis syndrome	• Foreign body • Gastroenteritis • Intussusception • UTI
	Chronic		• GI reflux disease
	Cyclic	• Adrenal insufficiency • Inborn errors of metabolism	• Intussusception • Malrotation with volvulus
1–4 yr	Acute	• Toxic ingestion	• Foreign body • Gastroenteritis • Pharyngitis • UTI • Constipation
	Chronic		• Celiac disease • Eosinophilic esophagitis
	Cyclic	• Adrenal insufficiency	• Constipation
5–11 yr	Acute	• Diabetic ketoacidosis	• Appendicitis • Pancreatitis
	Chronic		• Celiac disease • Eosinophilic esophagitis • Gastritis (± *Helicobacter pylori*) • Gastroparesis • Peptic ulcer disease
	Cyclic		• Ureteropelvic junction obstruction
12–18 yr	Acute	• Diabetic ketoacidosis • Drug overdose	• Choledocholithiasis
	Chronic	• CHS • Marijuana use • Pregnancy	• Bezoar
	Cyclic	• Marijuana use, CHS	• Superior mesenteric artery syndrome • Ureteropelvic junction obstruction

CHS = cannabinoid hyperemesis syndrome.

Information from: Shields TM, Lightdale JR. Vomiting in children. Pediatr Rev 2018;39:342-58.

activation of muscarinic and histamine receptors that lead to an emetic response. Patients with motion sickness are more likely to develop abdominal migraines or CVS, which will be discussed later.

Fear, anxiety, and even strong smells can elicit an emetic response. The emotional pathway is not as well understood but is thought to involve the release of corticotropin-releasing factor. In adolescent patients, emotional pathways may lead to eating disorders and self-induced vomiting.

Although several pathways may be activated, identification of the predominant pathway may help clinicians select the most appropriate treatment.

Evaluation of Patients with Vomiting

In addition to a thorough medication and surgical history, details of the type of emesis, pattern, timing, and age of the patient help identify the underlying cause and best treatment. Emesis is generally classified as either bilious/nonbilious or bloody/nonbloody. Age can play an important role in differentiating the cause. For example, during infancy, emesis with regurgitation or reflux is common. In addition, projectile, nonbilious emesis accompanied by hypochloremic metabolic acidosis in infancy is classic pyloric stenosis. In children and adolescents, the most common cause of vomiting is acute gastroenteritis. See Table 1 for more information on age- and pathway-related causes of nausea and vomiting.

Treatment

After complete evaluation, treatment should target the potential cause. This section evaluates treatment options for mechanical, toxin (chemotherapy), and motion-induced causes of vomiting. Treatment pathways are outlined in Figure 1. Table 2 provides receptor, agent, and dosing information.

Serotonin Receptor Antagonists

Serotonin receptor antagonists treat nausea and vomiting caused by various factors. Although the treatment mainstay for vomiting includes hydration (discussed in the CVS section), serotonin-3 receptor antagonists may help decrease the need for intravenous fluids and hospital admission in severe cases, particularly gastroenteritis (DeCamp 2008). The American Academy of Pediatrics supports a CDC recommendation to use the serotonin-3 receptor antagonist ondansetron for pediatric gastroenteritis (CDC 2004). Serotonin-3 receptor antagonists are also effective for patients receiving chemotherapy. A 2016 Cochrane review on the use of antiemetics for preventing and treating chemotherapy-induced nausea and vomiting (CINV) in children confirmed increased efficacy with serotonin antagonists over other agents. Adding steroids to the other agents did not alter these results. However, when treating acute vomiting in these patients, adding steroids to any regimen may improve control, but the risk-benefit profile should be considered. In this review, when comparing serotonin-3 agents for acute vomiting, granisetron or palonosetron may be more effective than ondansetron (Phillips 2016). However, in a 2016 meta-analysis, ondansetron had efficacy similar to granisetron and tropisetron (not approved in the United States) and greater efficacy than dolasetron for acute vomiting. For delayed nausea and vomiting, palonosetron had greater efficacy than ondansetron. Granisetron compared with ondansetron did not differ for any outcome (Simino 2016). These reviews suggest that granisetron and ondansetron have similar efficacy and should be selected on the basis of patient-important differences, age, cost profile, and potential adverse effects/drug interactions. Serotonin-3 receptor antagonists also prevent and treat postoperative nausea and vomiting (PONV). Ondansetron is the most widely used serotonin-3 receptor antagonist; however, one dose of granisetron at the end of surgery is also effective in pediatric patients. The ideal timing to administer serotonin-3 receptor antagonists to prevent PONV is still unknown, but most studies recommend giving these agents with the first incision or immediately postoperatively (Gan 2014; Cieslak 1996).

Although widely used, serotonin-3 receptor antagonists should be used cautiously because of their association with QT interval prolongation. Data analyses are conflicting surrounding this warning. A 2011 FDA report warns of QTc prolongation and fatal dysrhythmia. Most reports included adult patients, and the limited data analyses in pediatric patients suggest no clinically relevant QTc prolongation after a single dose of ondansetron in children 6 months to 18 years of age (Krammes 2018). In 2018, a prospective study evaluated the impact of one intravenous dose of ondansetron (0.15 mg/kg) on the QTc interval in children younger than 14 years with gastroenteritis. No QTc prolongation was found except in one patient who had it before ondansetron administration, and the relationship was not believed to be causal. Nevertheless, the authors of this 2018 prospective study do recommend monitoring in patients with known prolonged QTc, those using concomitant medications that prolong QTc, and those with electrolyte abnormalities (hypokalemia, hypomagnesemia) associated with prolonged QTc. In patients with preexisting QTc prolongation, the oral route of ondansetron or an alternative antiemetic agent is recommended (Hoffman 2018). Other adverse effects of serotonin-3 receptor antagonists include headache, asthenia, constipation, and dizziness. Ondansetron uniquely has been associated with diarrhea.

Neurokinin-1 Receptor Antagonists

Neurokinin-1 receptor antagonists are the newest class of medications to be used for nausea and vomiting in the pediatric population. Neurokinin-1 receptor antagonists are available in both intravenous (fosaprepitant) and oral (aprepitant) formulations. Most data analyses show benefit with these agents in controlling CINV and preventing delayed emesis with highly emetogenic chemotherapy (e.g., cisplatin) (Radhakrishnan 2019). The 2017 American Society of

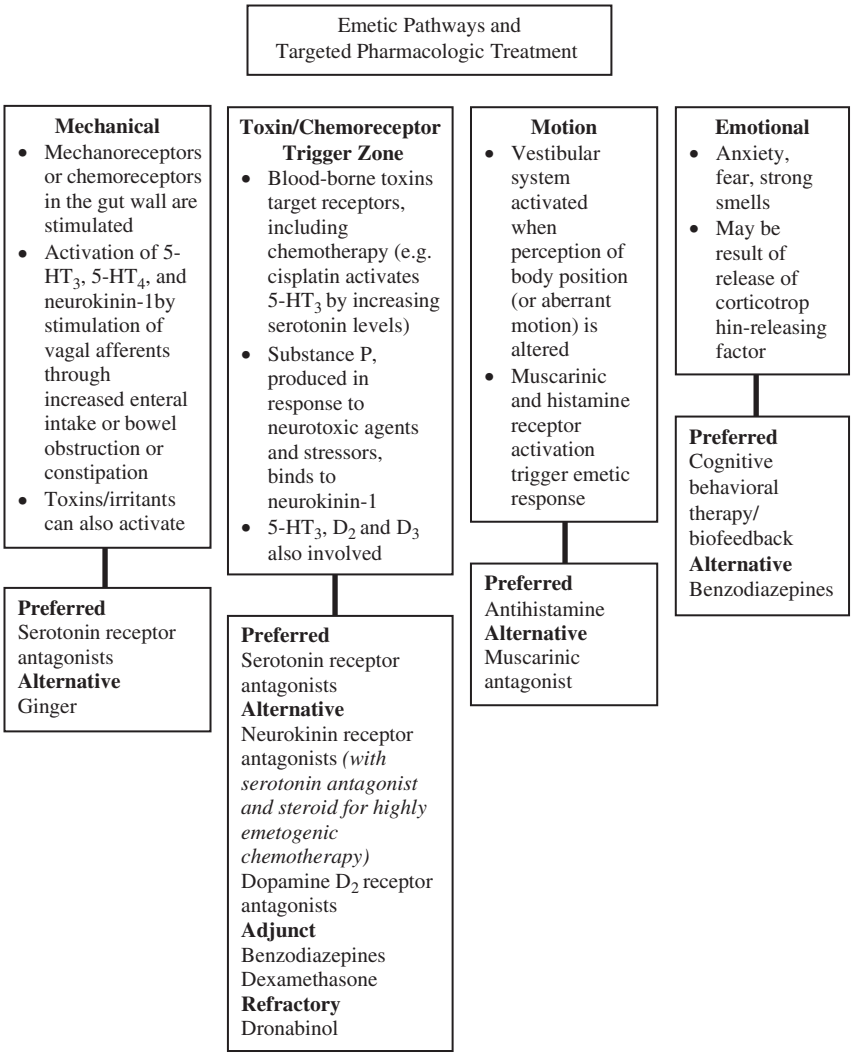

Figure 1. Pharmacologic treatment recommendations by emetic pathway.

D = dopamine.

Information from: Shields TM, Lightdale JR. Vomiting in children. Pediatr Rev 2018;39:342-58; Bashashati M, McCallum RW. Neurochemical mechanisms and pharmacologic strategies in managing nausea and vomiting related to cyclic vomiting syndrome and other gastrointestinal disorders. Eur J Pharmacol 2014;722:79-94.

Clinical Oncology clinical practice guideline update includes recommendations for children to receive these agents while receiving highly emetogenic chemotherapy (Hesketh 2017).

Fosaprepitant was recently approved for preventing CINV in patients as young as 6 months. Many reports suggest using fosaprepitant in combination with a serotonin-3 receptor antagonist and dexamethasone. Dexamethasone doses should be reduced by 50% when initiating fosaprepitant and serotonin-3 receptor antagonists because these agents increase the AUC of dexamethasone and other steroids. A recent 2019 pharmacokinetic/pharmacodynamic safety and tolerability study evaluated fosaprepitant versus placebo concomitantly with ondansetron with or without dexamethasone in children 2–17 years of age against a historical adult data set. Because antiemetic regimens in younger children are generally less effective than in adults, this study also examined the dose response up to 5 mg/kg (up to 150 mg) in children younger than 12 years. As predicted, younger children required higher doses to have results similar to those of the adolescents (12–17 years of age) and the historical adult cohort. Adverse events were reported in 6.8% of patients, the most common being hiccups (2.1%) (Mora 2019). Additional studies reinforce the decreased dose response in younger children with both fosaprepitant and aprepitant, whereas overall efficacy is similar between the two agents (Saito 2019; Timaeus 2018).

Table 2. Antiemetic Agents and Clinical Considerations

Receptor	Medication	Notes
Serotonin-3	Ondansetron	Diarrhea (more common with oral dosage form) *(constipation may also occur)* Higher dosing indicated for CVS
	Granisetron	Constipation (higher incidence with oral tablets and extended-release subcutaneous injection)
	Ginger	Mechanism is not fully understood, but is thought to act on serotonin-3
Serotonin	Amitriptyline	Risk of cardiac arrhythmias
Serotonin-2A, serotonin-2B, H_1	Cyproheptadine	Stimulates appetite
H_1	Promethazine	Contraindicated in children < 2 yr (respiratory depression) Not recommended for PONV – use replaced by newer agents
	Meclizine	For patients at least 12 yr of age
H_1, D_2	Diphenhydramine	Drowsiness
D_1, D_2	Prochlorperazine	Oral dosing Intravenous route reserved for refractory treatment, usually chemotherapy induced
D_2	Metoclopramide	Boxed warning for tardive dyskinesia Intravenous use discouraged
M_1	Scopolamine	Dosing for adolescents only with transdermal dosage form
NK_1	Aprepitant	Oral dosage forms only approved in children For chemotherapy-induced nausea Not for long-term use
Motilin	Erythromycin	Risk of pyloric stenosis in infants
Benzodiazepine receptors on postsynaptic $GABA_A$	Lorazepam	For anticipatory nausea and vomiting with chemotherapy: Administer a dose the night before chemotherapy and again the next day before chemotherapy administration
Cannabinoid	Dronabinol	Most data analyses for CINV Minimum reported age in pediatric patients is 9 yr (use caution in patients 6–12 yr of age)

CINV = chemotherapy-induced nausea and vomiting; CVS = cyclic vomiting syndrome; D = dopamine; H_1 = histamine-1; M_1 = muscarinic-1; NK_1 = neurokinin-1; PONV = postoperative nausea and vomiting.

Information from: Lexicomp Online.

Long-term use and safety studies are lacking in the pediatric population. A recent follow-up case series in pediatric patients with bone cancer over 8 years compared the adverse events with aprepitant use in this group with the adverse events in published drug information resources. The frequency of anorexia, febrile neutropenia, and headache (over 40% for each adverse event) was increased with aprepitant compared with previously reported estimates. The report calls for increased investigation of aprepitant use in this population (Okumura 2019). These safety concerns would likely be equitable for all agents in this class.

In addition to the steroid interaction listed earlier, drug interactions must be considered with neurokinin-1 receptor antagonists. Aprepitant and fosaprepitant are substrates of CYP3A4, CYP1A2, and CYP2C19 and have weak CYP2C9 induction and CYP3A4 inhibition. Birth control (decreased estrogen concentrations), warfarin (decreased warfarin concentrations), and the chemotherapy agents imatinib (increased neurokinin- 1 concentrations), irinotecan (increased chemotherapy effect), and vincristine (increased chemotherapy effect) are examples in the extensive list.

Dopamine Receptor Antagonists

Dopamine receptor antagonists include phenothiazines (prochlorperazine and chlorpromazine), butyrophenones (droperidol and haloperidol), and benzamide derivatives (domperidone and metoclopramide). These agents are widely used as antiemetics and act on the D_2 receptors within the CTZ. Phenothiazines also have H_1 and M_1 activity, which may help with motion-related causes of nausea and vomiting. As a group, adverse effects include extrapyramidal reactions and drowsiness. Extrapyramidal effects can be treated with diphenhydramine, which may also increase drowsiness.

Butyrophenones, particularly droperidol, alone and in combination with other agents, have gained some attention for use in preventing PONV in addition to treating intractable emesis from gastritis. However, a 2017 study documented no advantage of adding droperidol to ondansetron and dexamethasone in patients at high risk of PONV after general anesthesia, but patients had more drowsiness and headache with triple therapy (p=0.01) (Bourdaud 2017). Another study comparing droperidol with placebo or ondansetron for PONV after tonsillectomy in children also receiving dexamethasone showed that 49% of patients using droperidol had nausea or vomiting within 24 hours after surgery compared with 21% with ondansetron. The incidence of adverse effects did not differ between groups. In this study, ondansetron was more effective than droperidol for PONV after tonsillectomy (Flubacher 2017). Butyrophenones can cause QTc prolongation, and a baseline ECG is recommended. If the patient has QTc prolongation and use of these agents is unavoidable, continuous ECG monitoring during and 2–3 hours after intravenous or intramuscular administration should be completed. If a patient is to receive more than one dose, follow-up ECG monitoring is also recommended.

The benzamide derivative metoclopramide has both peripheral and central D_2 receptor antagonism and cholinergic receptor stimulation, leading to increased gastric motility. This mechanism offers preferential use in the treatment of gastroparesis. However, metoclopramide has a black box warning for tardive dyskinesia with long-term use. Domperidone, in contrast to metoclopramide, is selective to the D_2 receptors in the GI tract and does not cross the blood-brain barrier; thus, domperidone has no CNS adverse effects. However, domperidone is no longer routinely available in the United States because of significant warnings of cardiac arrhythmias, cardiac arrest, and sudden death. This risk was originally associated with intravenous domperidone use, but similar reports have occurred with oral dosage formulations. Today, use of domperidone is limited to patients in the Expanded Access Program. This program allows patients 12 years and older with the following conditions to be eligible for domperidone use: gastroparesis, chronic constipation, or gastroesophageal reflux disease with upper GI symptoms. Special coordination with the FDA must occur before obtaining the domperidone. Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, clarithromycin, most protease inhibitors) increase domperidone's plasma concentration, further increasing the risk of cardiac toxicity.

Antihistamines or Agents with Antihistaminic Activity

Agents with antihistaminic activity – diphenhydramine, hydroxyzine, promethazine, meclizine, and cyproheptadine – are mainly used for motion-triggered emetic responses. Patients with abdominal migraines and cyclic vomiting may also respond to antihistamines. Age considerations exist for meclizine (for patients 12 years and older) and promethazine (not for children younger than 2 years secondary to respiratory depression). Cyproheptadine may be more useful in patients with decreased appetite and nausea/vomiting and will be discussed more for cyclic vomiting. Adverse effects include typical anticholinergic effects and sedation.

Scopolamine is the most widely used antimuscarinic agent, especially in treating motion sickness. Scopolamine has the added advantage of being available as a transdermal patch lasting 72 hours. Currently, the patch is approved for adolescents and adults. However, the patch should not be cut or applied with heat because this may increase absorption of the medication. Occlusion of the backing is possible, but not recommended. Some case reports outline the risk of scopolamine withdrawal syndrome, particularly with long-term use (greater than 4 years in one report) (Chowdhury 2017). Withdrawal syndrome includes symptoms of rebound cholinergic activity, including paresthesias of the distal extremities, dysphoria, nausea, vomiting, dizziness, and vomiting. Symptoms appear within 18–72 hours after patch removal and can last weeks, with most recovery occurring after 9 days. Successful treatment of this withdrawal syndrome has been reported with meclizine use in adults. The reported adult regimen using oral meclizine is 50 mg three or four times daily, followed by a week-long taper. Use of meclizine in children younger than 12 years is less well described but is common in clinical practice. Use of scopolamine in PONV remains more robust in the adult population. A 2018 review reinforced avoiding its use in pediatric and older adult populations (Kassel 2018).

Intravenous promethazine has a black box warning for extravasation risk and severe tissue injury. The Institute for Safe Medication Practices recommends removal of intravenous promethazine use in hospitals.

Ginger

Ginger has been used for chronic nausea and vomiting and studied in patients receiving highly emetogenic chemotherapy. Although ginger's mechanism of action is not thoroughly understood, it is thought to act as a serotonin-3 antagonist. In one report of children and adult patients receiving a cisplatin and doxorubicin combination for bone sarcoma, ginger powder or placebo was added to ondansetron and dexamethasone during the first 3 days of the chemotherapy cycle. Ginger

was dosed at 1000 mg/day for patients weighing 20–39 kg or 2000 mg/day for patients weighing 40–59 kg. Acute moderate to severe nausea and vomiting were significantly reduced in the ginger group compared with the control group (55.6% vs. 93.3% [p=0.003], 33.33% vs. 76.7% [p=0.002]). Delayed nausea and vomiting were also reduced in the patients receiving ginger (25.9% vs. 73.3% [p<0.001], 14.81% vs. 46.67% (p=0.022]). No observed adverse effects, including rash or bleeding, were observed in the study because ginger extract has been known to inhibit platelet aggregation (Pillai 2011). Other evidence is conflicting, and the exact role of ginger still needs to be elucidated. Ginger is a natural product, and no FDA-approved products exist. Adverse reactions are uncommon but include heartburn, diarrhea, and mouth irritation. Additional information on ginger is available in the U.S. *Pharmacopeia*'s *Dietary Supplements Compendium*.

Cannabinoid Receptor Agonists

Dronabinol and nabilone, cannabinoid receptor agonists, have also been used last line for CINV after failure of other agents in adults. Cannabinoid receptor agonists have not been approved for pediatric patients; however, they have been used off-label for pediatric patients with cancer patients to prevent and treat refractory CINV. The 2013 clinical practice guidelines for acute chemotherapy-induced vomiting have a weak recommendation for the use of nabilone with a serotonin-3 antagonist for patients taking moderate to high emetogenic risk chemotherapy who could not receive dexamethasone therapy. However, because of the lack of efficacy data, the 2017 guidelines removed that recommendation (Patel 2017). In 2018, a study evaluating the use of nabilone in pediatric patients with cancer receiving any chemotherapy to control chemotherapy-induced vomiting found no benefit and an adverse effect incidence of 34%. The most common adverse effects with nabilone were sedation (20%) and dizziness (10%), with fewer patients having euphoria (3.6%). The authors recommended consistent prophylactic regimens versus widespread use of nabilone (Polito 2018).

CYCLIC VOMITING SYNDROME

Cyclic vomiting syndrome is a type of functional nausea and vomiting disorder characterized by recurring, intense episodes of nausea and vomiting that may last a few hours to days (Foreman 2018). The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) diagnostic criteria for CVS follow.

"All of the following criteria must be met:

- At least 5 attacks in any interval, or a minimum of 3 attacks during a 6-month period
- Episodic attacks of intense nausea and vomiting lasting 1 hour to 10 days occurring at least 1 week apart
- Stereotypical patterns and symptoms in individual patients
- Vomiting during attacks occurring at least 4 times per hour for at least 1 hour
- A return to baseline health between episodes
- Vomiting cannot be attributable to any other disorder."

Other diagnostic criteria also exist. The updated Rome IV criteria recommend at least two episodes within 6 months (Zeevenhooven 2017; Hyams 2016). The criteria outlined by the International Headache Society mimic the NASPGHAN criteria with at least five attacks, but do not list a time or interval for these attacks (IHS 2013). Other reasons for vomiting must be ruled out, and an appropriate laboratory workup should be obtained, including an upper GI series with a small-bowel follow-through and a pregnancy test, if applicable (Li 2008). Cyclic vomiting in children younger than 4 years may also indicate adrenal insufficiency, an inborn error of metabolism, or structural malrotation or volvulus.

Characteristics of CVS include morning episodes (reported in 16%–75% of patients) and a family history or presence of migraines (Hikita 2016). A diagnosis of CVS is often delayed from onset of symptoms anywhere from 1–4 years and is most common in white school-aged children, though this delay can affect all age groups and several ethnicities of patients. A younger patient age at symptom onset has been associated with a longer duration, but reports show that up to 75% of cases will resolve. The overall prevalence of CVS has been stated to be 1%–2%, with a more recent population-based study suggesting a prevalence of 6% in children younger than 2 years (Chogle 2016). Cyclic vomiting syndrome significantly affects missed school days and health care costs (Foreman 2018).

Episodic Phases

Symptoms of CVS are divided into prodromal, vomiting, recovery, and asymptomatic phases, which dictate the recommended therapy (Romano 2018). The vomiting phase includes both supportive and abortive therapy. The prodromal phase begins with a feeling that the episode is coming, followed by pallor and nausea and sweating with or without abdominal pain. This feeling may last a few minutes to several hours. The vomiting phase includes nausea, vomiting, and retching, which can last up to 30 minutes each episode. Vomiting is most intense the first hour, with a median of six episodes per hour, and decreases in frequency over the next 8 hours. The patient may be immobile, unresponsive, or writhing with intense abdominal pain. This phase may last days and is considered the longest phase. The recovery phase begins when vomiting and retching cease and includes a period of improving appetite and energy return. Patients may sleep for longer periods during this phase. The asymptomatic phase is the symptom-free period of wellness between episodes.

In patients with CVS, anxiety is a common comorbidity, occurring in 25% of the population. Anxiety and CVS are

correlated with decreased quality of life and may encourage appropriate prophylactic therapy to treat both (Redon 2017; Tarbell 2015).

Treatment According to CVS Phase

Treatment of CVS is difficult and involves both nonpharmacologic and pharmacologic strategies. Early identification of symptoms and CVS phase is ideal to determine optimal treatment (Box 1). Over the past 10 years, recommendations have encouraged prompt and aggressive treatment during even the prodromal stage. Similar to migraine treatment, NSAIDs should be used during the prodromal period, or before vomiting begins.

Throughout the prodromal phase and into the vomiting phase, supportive care measures are encouraged. These measures include keeping the patient in a quiet, dark environment free of significant stimulation; replacing fluids, electrolytes, and carbohydrates; using antiemetics (with or without sedatives); and providing pain management. In severe cases, patients are at risk of dehydration and hematemesis from Mallory-Weiss tears of the esophageal mucosa. Intravenous fluids containing a higher dextrose concentration (usually dextrose 10%) at 1.5 times the maintenance rate are recommended in children unable to maintain adequate enteral hydration or if the symptoms persist beyond 24 hours. Increased dextrose or carbohydrate intake provides additional energy during periods of high energy demands (Li 2000). Failure to replace energy needs in a timely manner may prolong the illness and lead to the need for parenteral nutrition to provide adequate intake. Pain management also plays an important role in supportive care. Abdominal pain can be severe with CVS and should be treated. Ketorolac, in combination with an histamine-2 receptor antagonist, is recommended as first line. Proton pump inhibitors also prevent gastritis with NSAIDs. Opioids are widely discouraged for pain management in both adult and pediatric CVS treatment recommendations. Morphine and hydromorphone have been used in refractory cases but should be reserved for those with severe pain in a hospital setting because of the risks of tolerance, addiction, and dependence.

Antiemetics can be initiated during the prodromal phase and once vomiting begins to decrease nausea and vomiting. Serotonin-3 receptor antagonists are well tolerated and more effective at higher doses within the dosing range. Of the serotonin-3 agents, ondansetron has the most data analyses and is the most widely used. Other antiemetics used alone (i.e., promethazine and prochlorperazine) are ineffective compared with ondansetron (Li 2000). Benzodiazepines, lorazepam and midazolam, have also been used in case studies and are more effective when used in combination with ondansetron. Benzodiazepines serve as a sedative and provide symptomatic relief, and they may shorten the nausea and vomiting episode (Li 2000). Benzodiazepines can be added to therapy once antiemetics fail to control nausea and vomiting. As with migraine management, sleep may be a mode of symptomatic relief and may shorten the episode. A regimen combining two sedatives, an antihistamine and benzodiazepine, has been reported (i.e., alternating rectal promethazine [10–25 mg] and rectal diazepam gel [2.5–10 mg] every 4–6 hours) (Kaul 2015).

Abortive therapy should begin at the onset of the vomiting phase. Sumatriptan, a serotonin-1B/1D agonist, used early in therapy aborts attack in about 30%–50% of patients, depending on route (increased efficacy with subcutaneous vs. intranasal therapy) (Hikita 2011). Another serotonin-1B/1D agonist, zolmitriptan, is also available in a nasal form. The nasal formulation may be more effective than the oral route because, during emesis, the medications may not reach the duodenum. Serotonin-1B/1D agonists should be used even before the onset of a headache. They are not approved for patients younger than 18 years but have been recommended in children 12 years and older on the basis of the Child Neurology Society Practice Parameters and the NASPGHAN Task Force on cyclic vomiting. Other agents have also been used for abortive therapy. In some patients, ondansetron alone or in combination with a benzodiazepine, has aborted episodes. The neurokinin-1 receptor antagonist aprepitant was efficacious for both prophylaxis and abortive therapy in one study evaluating children 4–16½ years of age with CVS refractory to conventional treatment. Success, defined as a decreased duration and intensity of symptoms, was increased if aprepitant was administered at least 30 minutes before the emetic phase (Cristofori 2014). In older studies, clonidine, both enteral and transdermal, has also been used, particularly in combination with a benzodiazepine in severe cases (Palmer 2005). More recent data analyses and therapy reviews do not include clonidine because of lack of efficacy. In patients with refractory symptoms not responding to the earlier treatments, combinations of agents or other

Box 1. Cyclic Vomiting Syndrome Treatment by Phase

Prodromal
- NSAIDs
- Combination of ondansetron and lorazepam
  OR
  chlorpromazine and diphenhydramine

Vomiting – Supportive
- Low-stimulation environment
- Intravenous dextrose-containing fluids
- Serotonin-3 agents (ondansetron)
- Analgesics (ketorolac) as needed
- Antihistamines (diphenhydramine)
- Benzodiazepines (lorazepam)

Vomiting – Abortive
- Sumatriptan (intranasal or subcutaneous)
- Alternatives – ondansetron with/without lorazepam

investigational options can be recommended. Continuous infusion dexmedetomidine also aborted refractory cases in a small case series of pediatric patients. Dexmedetomidine's shorter half-life and ability to be titrated make it better than clonidine (Tobias 2005; Khasawinah 2003). Intravenous ketamine is being studied in adult patients, but to date, no published clinical trials exist (Ahuja 2018; Kovacic 2018). Use of dexmedetomidine and ketamine would likely require admission to the pediatric ICU and close monitoring.

Prophylactic therapy is indicated if symptoms occur more often than once a month, if the patient requires hospitalization, or if quality of life is affected. Nonpharmacologic therapy includes avoiding triggers (e.g., stress, fatigue, fasting, excessive excitement). Specific diet recommendations include avoiding foods with additives or those known to be a trigger. Eating small snacks containing carbohydrates between meals, before exercise, and at bedtime is recommended. Pharmacologic prophylaxis is based on age and presence of refractory symptoms and should begin during symptom-free periods. The Pediatric Migraine Disability Assessment (PedMIDAS) has been used for CVS to monitor response to therapy (Hershey 2001). General principles for prophylaxis include considering appropriate dosage formulations for patients of different ages, starting with low initial doses and titrating doses to achieve clinical benefit, and keeping a "vomiting diary" to have the patient evaluate the effectiveness of therapy (Li 2008). For an adequate clinical trial, medications should be titrated to achieve an average therapeutic dose for at least two CVS cycles. If a medication cannot be tolerated or is not effective, another agent may be initiated.

Antihistamines and tricyclic antidepressants (TCAs) are the preferred first-line agents for children older than 5 years (Li 2008; Haghighat 2007). In children 5 years and younger, cyproheptadine is recommended. In a more recent head-to-head study randomizing antihistamines and TCAs regardless of age (age range of study 3–15 years old), neither agent was superior. This suggests that either agent can be used at any age (Badihian 2017). Cyproheptadine at doses of 0.25–0.5 mg/kg/day divided two or three times daily have had a moderate response rate in retrospective reviews and noncontrolled studies. Adverse effects are included in the earlier section on antiemetic therapy. Cyproheptadine may be preferred for underweight patients. Amitriptyline, though having moderate to high efficacy, may take a few months to be effective (at least 4 weeks). For amitriptyline, it is recommended to start at doses of 0.25–0.5 mg/kg/day taken at night and to increase weekly by 0.25 mg/kg/day to a maximum of 1–1.5 mg/kg/day. Higher dosing has been associated with a higher response rate. An ECG to monitor for QTc prolongation should be obtained before starting therapy and 10 days after the peak dose. Adverse effects include constipation, sedation, behavioral changes (especially in young children), and arrhythmias. In patients who cannot swallow tablets, amitriptyline has been compounded into a liquid formulation. Nortriptyline has also been used as an alternative and is available in a liquid dosage form; however, supporting data analyses in children are limited. Doxepin and imipramine also have limited data analyses for this indication and in the pediatric population but may offer a better adverse effect profile than other TCAs. More data analyses are needed to recommend these agents over other TCAs.

Second-line therapy includes propranolol, which may be preferred in patients having adverse effects with first-line therapy. Propranolol is considered to have moderate efficacy, and in one study, 87% of patients treated with propranolol had improved symptoms (Lee 2012). Propranolol dosing should begin at 0.25–1 mg/kg/day (usually 10 mg/dose) divided two or three times daily. Monitoring includes maintaining a resting heart rate above 60 beats/minute. Adverse effects include lethargy and reduced exercise tolerance. Propranolol is contraindicated in patients with asthma, diabetes, heart disease, or depression. Propranolol should be discontinued as a taper over 1–2 weeks. Atenolol and nadolol have been used as alternative to propranolol with fewer adverse effects; however, atenolol and nadolol may be less effective because of their inability to cross the blood-brain barrier.

As mentioned previously, aprepitant has also gained attention for promising data as a prophylactic agent. When aprepitant was used prophylactically twice weekly in one study, about 80% of patients had either a partial or a complete response at 12 months (Cristofori 2014).

Other agents, including anticonvulsants, used to treat migraines are also effective for prophylaxis. Phenobarbital at a dose of 2 mg/kg nightly was effective in an older study (Gokhale 1997). Adverse effects of phenobarbital include sedation and cognitive impairment, which limit its usefulness as a first-line prophylactic therapy. Because of the link to migraines, other seizure medications have shown efficacy in CVS. If these seizure medications are initiated, neurology should be consulted to monitor dosage titration and adverse effects. In a recent retrospective study of 38 patients, topiramate had better efficacy, defined as "freedom from attacks," than propranolol (81% vs. 59%). Patients were treated for at least 12 months. However, a 50% decrease or more in episodes per year occurred in more patients in the propranolol group than in those receiving topiramate (23% vs. 13%). The total responder rates for topiramate and propranolol were 94% and 82%, respectively (p=0.001). Two patients in the topiramate group had adverse effects (drowsiness, dizziness), and three patients in the propranolol had treatment-related adverse effects (drowsiness, nervousness, and dizziness). Patients in the topiramate group had weight loss versus weight gain in the propranolol group (Sezer 2016). Potential adverse effects of topiramate include renal stones and cognitive dysfunction. Valproate's efficacy as a migraine prophylactic agent led to an investigation into its ability to prevent CVS in children whose other prophylactic therapy failed (propranolol, amitriptyline, cyproheptadine, phenobarbital, phenytoin, and carbamazepine). Thirteen children were initiated on valproate at a dose of 10 mg/kg/day divided twice daily

and slowly increased to 40 mg/kg/day. This study did monitor serum concentrations and doses were titrated to maintain therapeutic, anticonvulsant-range, drug levels. Three patients also required the addition of phenobarbital to see improvement. Only two of the patients had no change in frequency of episodes. Most patients had a marked response, defined as less than two episodes in a year (9 of 13 patients). Treatment duration ranged from 2 weeks to 98 months. No adverse effects were observed in this study (Hikita 2009). Despite many options for prophylactic therapy, long-term efficacy remains limited. In a 5-year follow-up study of pediatric patients with CVS, only amitriptyline, phenobarbital, and valproic acid were effective (Hikita 2016). In adult patients, zonisamide and levetiracetam are also effective.

Other agents, including the supplements levocarnitine, coenzyme Q10, and riboflavin and oral contraceptives, have been used in combination with other prophylactic agents. The 2019 adult CVS guidelines "conditionally recommend [Coenzyme Q10, L-carnitine, and riboflavin] as alternate prophylactic medications, either alone or concurrently with other prophylactic medications" (Venkatesan 2019). Carnitine is a transport cofactor for long-chain fatty acids into mitochondria, which may target the proposed mechanism of CVS being a mitochondrial or metabolic dysfunction. In studies, levocarnitine is dosed 50–100 mg/kg/day divided twice daily (up to 4 g) (Van Calcar 2002). Patients and caregivers should be counseled to monitor patients for diarrhea or the presence of a fishy body odor. Coenzyme Q10 in doses of 10 mg/kg/day (maximum 200 mg) divided twice daily has also been evaluated for prophylactic use (Boles 2011). These supplements are generally used in combination with another prophylactic agent, the most studied being amitriptyline. Data analyses are limited on the use of riboflavin 400 mg daily or divided twice daily (Martinez-Esteve Melnikova 2016). Oral contraceptive use is beneficial in treating girls with menstrual-related CVS.

Resolution of CVS occurs, on average, 2.5–5 years after diagnosis and by late childhood or adolescence (mean age at resolution is 10 years). In one study, 60% of children had symptom resolution within a 4-year follow-up (Fitzpatrick 2008). About 50% of patients with a diagnosis of CVS will progress to a chronic migraine syndrome (Hikita 2016). Younger age at first onset is associated with an increased likelihood of developing these migraines. It is important to note the significant burden on quality of life and impact on school attendance such that appropriate treatment and avoidance of triggers are strongly recommended.

CANNABINOID HYPEREMESIS SYNDROME

Epidemiology

Before the increased legalization of cannabis products within the United States, they were the most widely used illicit substances. A 2014 report states that among Americans 12 years and older, over 22 million have used cannabis in some form (SAMHSA 2014). In youth age 12–17 years in the United States, 1.6% used marijuana as a single drug, with an alarming 128.6% increase in use from 2002 to 2014 (Han 2017). It is postulated that the increase in use among youth reflects their perception that cannabis use is low risk (HHS 2018). With more states allowing recreational marijuana, the incidence of ED visits in those states has increased, specifically a doubling of cyclic vomiting visits, which includes CHS (Kim 2016, 2015). Data regarding increased prevalence of cannabis use by parents with children in the home during 2002–2015 (4.9%–6.8%) are also of concern (Goodwin 2018). In addition to increased use of cannabis by adults and children, there is significant use of ED resources, including expensive, nondiagnostic abdominal imaging studies (Sorenson 2017; Patterson 2010; Chang 2009). In one observational study of 20 patients with suspected CHS, there were a mean of 17.3 (±13.6) ED visits and 6.8 (±9.4) hospital admissions over 2 years (Perrotta 2012). Cannabinoid hyperemesis syndrome has mainly been associated with marijuana inhalation (traditional smoking or e-cigarettes) but can also be associated with oils, waxes, and synthetic cannabinoids. In a 2018 article, no reported cases of edible marijuana were associated with CHS (Lapoint 2018).

Cause and Pathophysiology

The exact mechanism of CHS with marijuana is unknown, and it is uncertain why only some patients with chronic marijuana use develop CHS (Sorenson 2017). Cannabis, as stated earlier in the chapter, has antiemetic effects. The cannabinoid receptors CB_1 and CB_2 are in two main areas: the CNS and the peripheral tissues, respectively. However, CB_1 receptors have also been identified in the GI tract (Richards 2017; Sorenson 2017). CB_1 receptor activity causes alterations in cognition, memory, and nausea/vomiting (Lapoint 2015). The proposed hypothesis for CHS with cannabinoid use is a down-regulation or desensitization of the receptors with chronic use (Lundberg 2005; Darmani 2001). Another potential mechanism is the disruption of peripheral receptors in enteric nerves leads to decreased gastric motility and hyperemesis (Krowicki 1999; McCallum 1999). Down-regulation or desensitization of receptors is likely associated with prolonged and frequent use of cannabis. At least weekly use of cannabis for more than 1 year is highly correlated with CHS (Lapoint 2018).

Tetrahydrocannabinol (THC) serum concentrations peak within minutes of smoking marijuana and rapidly decline, but its cognitive effects last. Tetrahydrocannabinol is highly lipophilic and will rapidly distribute into the brain. Tetrahydrocannabinol is also rapidly metabolized to an active metabolite, 11-hydroxy-THC, making serum detection difficult. An additional inactive metabolite, THC-COOH, is highly concentrated in the urine and is used for urine detection up to 3–5 days after single drug exposure. Patients who are frequent marijuana users, or those with a higher body fat

percentage, can have longer periods of urine detection, up to 1 month after last use (Blohm 2019).

Clinical Characteristics and Diagnosis

Cannabinoid hyperemesis syndrome is characterized by cyclic nausea and vomiting with regular cannabis use and elimination of symptoms after cessation of cannabis use. Characteristics of patients with CHS are outlined in Table 3 (Sorenson 2017). Distinguishing CHS from CVS can be difficult, but the history of cannabis use is required for a CHS diagnosis. In addition, patients often have compulsive hot shower or bath-seeking behavior and report spending hours in the shower. When presenting to the ED, patients usually report nonspecific symptoms of vomiting and abdominal pain and may have had previous visits with negative workups. Abdominal pain is usually diffuse and generalized. Cannabinoid hyperemesis syndrome should be suspected in healthy young patients without diabetes with a history of gastroparesis-type symptoms during those previous visits.

Laboratory testing is usually inconclusive and nonspecific. Depending on the symptom duration, patients may have electrolyte abnormalities and other signs of dehydration, including ketonuria. Patients may also have mild leukocytosis. Even in patients who deny cannabis use, a high suspicion for CHS warrants a urine drug screen; however, synthetic cannabinoids (i.e., K2, Spice) are not detected on a urine drug screen. Abdominal imaging should be avoided, especially with a benign physical examination (Lapoint 2018).

Table 3. Characteristic Diagnostic Symptoms in Patients with CHS

Characteristic	% of Patients Presenting with Symptom
History of regular cannabis use for > 1 yr	74.8
At least weekly cannabis use	97.4
Severe nausea and vomiting	100
Abdominal pain	85.1
Vomiting that recurs in a cyclic pattern over months	100
Resolution of symptoms after stopping cannabis	96.8
Compulsive hot baths or showers leading to symptom relief	92.3

Information from: Sorenson CH, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology and treatment – a systematic review. J Med Toxicol 2017;13:71-87.

Treatment and Resolution

In 2018, an expert consensus guideline outlined a novel approach to CHS treatment. Treatment should focus on symptom relief, cannabis cessation, and related education (Lapoint 2018).

Patients should be evaluated for duration of emesis and presence of dehydration. Fluid replacement is considered first line for severe cases. Hot water (greater than 41°C) relieves CHS symptoms in most patients (Richards 2017). Patients should be counseled to avoid extremely hot and long (reports of over 4 hours) showers to prevent burns. The proposed mechanism of this is that hot water activates TRPV1, a G-protein–coupled receptor in peripheral tissues that interacts with the endocannabinoid system. This receptor is also the only known capsaicin receptor, leading to the use of topical capsaicin cream for CHS treatment (Lapoint 2014). Capsaicin is available for topical use and can be used as first-line treatment. Although data analyses supporting capsaicin are limited, the guideline uses its low cost and low adverse effect profile as rationale for its early use. A 2017 case series found that capsaicin use can lead to CHS resolution (Dezieck 2017).

Treatment with antiemetics was ineffective in 10 of 13 patients included in the 2017 study, and all patients had symptom relief after capsaicin use (Dezieck 2017). Instructions for use include applying capsaicin 0.075% to the abdomen or the backs of the arms using gloves and washing hands thoroughly after application. In addition, if a patient identifies an area of the body on which hot water has worked, capsaicin should be applied to those areas first. Application to the face, eyes, genitourinary region, or areas of sensitive or broken skin should be avoided. Occlusive dressings are not recommended. Patients can expect initial discomfort after application, but this should subside, with relief similar to hot showers/baths ensuing. Capsaicin should be used three or four times daily, as needed, but should be discontinued if significant skin irritation or burns develop.

Antihistamines, antiemetics, and benzodiazepines can provide symptomatic relief, though abortive effectiveness data analyses are limited. Antihistamines, antiemetics, and benzodiazepines are considered supportive and adjunctive therapy to hydration. Benzodiazepines, namely lorazepam, have been mentioned more often as an effective therapy for the acute management of CHS in the ED, but confirmative efficacy data analyses are lacking. In a 2017 review of pharmacologic agents used for acute CHS treatment, benzodiazepines and ondansetron were listed as effective monotherapy in some case series or reports. Most studies included in the review listed a combination of these agents, so elucidating the effectiveness of one over the other is difficult.

Haloperidol and olanzapine have also been used in some case reports at doses of 5 mg intravenously/intramuscularly or intravenously/intramuscularly/orally disintegrating tablet, respectively. In the same 2017 review, haloperidol was the second most common treatment for acute symptoms. Many studies or reports included metoclopramide, phenothiazines,

Patient Care Scenario

A 16-year-old male adolescent with a medical history of asthma presents to the ED with a 4-day history of abdominal pain and intractable nonbilious, nonbloody emesis. He presented with similar episodes three times previously at an outside hospital, with no definitive diagnosis. He denies diarrhea and is afebrile. He states that hot showers improve his abdominal pain and emesis and most recently has been taking eight hot showers per day. He was prescribed esomeprazole for presumed gastritis 1 month ago but takes no other medications. He states he does use marijuana often. His vital signs are within normal range except a heart rate of 115 beats/minute. His laboratory values are remarkable for a slight leukocytosis, hypernatremia, and hypochloremia. What is the likely diagnosis for this patient and what is the most appropriate management?

ANSWER

The patient likely has CHS. Frequent and long-term use of cannabinoids with symptoms of cyclic vomiting are associated with CHS. Other causes are less likely with a negative workup and a history of no definite diagnosis. Imaging is likely unnecessary, given that data analyses support decreased resource use with a likely CHS diagnosis in the absence of any other worrisome symptoms. The history of taking hot baths/showers to relieve symptoms is also very characteristic of patients with CHS. This patient's treatment should begin with intravenous rehydration. According to a recommended treatment guideline, capsaicin is also used for early treatment. Capsaicin cream 0.075% is applied to the abdomen or the backs of the arms using gloves, washing hands thoroughly after application. In addition, if a patient identifies areas of the body for which hot water has worked, capsaicin should be applied to these areas first. Application to the face, eyes, genitourinary region, and areas of sensitive or broken skin should be avoided. Occlusive dressings are not recommended. Patients can expect initial discomfort after application, but this should subside, and relief similar to that obtained in hot showers/baths will ensue. Application of capsaicin cream is recommended three or four times daily, as needed, but should be discontinued if significant skin irritation or burns develop. Capsaicin cream is also easily accessible. Antiemetics, mainly ondansetron, can be used for supportive care in acute settings. This patient would likely benefit from combination therapy with capsaicin. The patient may also continue hot showers/baths, if beneficial, but should be cautioned to avoid extremely hot water. If symptoms do not subside, data analyses are limited on other adjunctive therapy. Benzodiazepines have been reported as the most effective adjunctive therapy, with some data on monotherapy effectiveness. Other therapies have fewer overwhelming data.

1. Richards JR, Gordon BK, Danielson AR, et al. Pharmacologic treatment of cannabinoid hyperemesis syndrome: a systematic review. Pharmacotherapy 2017;37:725-34.
2. Dezieck L, Hafez Z, Conicella A, et al. Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: a case series. Clin Toxicol (Phila) 2017;55:908-13.
3. Sorenson CH, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology and treatment – a systematic review. J Med Toxicol 2017;13:71-87.
4. Lapoint J, Meyer S, Yu C, et al. Cannabinoid hyperemesis syndrome: public health implications and a novel model treatment guideline. West J Emerg Med 2018;19:380-6.

and antiepileptics, often in combination with antiemetics and antihistamines. No case report using metoclopramide alone found it effective. Data analyses with phenothiazines were always in combination with other agents without temporal resolution of symptoms (Richards 2017). The antiepileptics zonisamide and levetiracetam were effective in 3 of 20 patients with chronic cannabis use and cyclic vomiting who had no response to TCAs (Clouse 2007).

Tricyclic antidepressants have been studied for CHS in chronic cannabis users because of their effectiveness in CVS treatment. Seventy-four percent of patients in one study responded to amitriptyline, nortriptyline, or doxepin, but many patients also stopped cannabis use. It was unclear whether the acute CVS symptoms resolved because of TCA effectiveness or because TCAs helped patients stop using cannabis (Hejazi 2010). Duration of TCA use may also play a role in their effectiveness, given that a study evaluating long-term therapy showed a high rate of symptom cessation. In this investigation of 31 patients with cyclic vomiting, which included 13 chronic cannabis users, 93% of patients had decreased symptoms at 3 months (26% with complete resolution) and 78% at 12 months. In the cannabis subgroup analysis, two had cessation and seven had improved symptoms (Namin 2007). Tricyclic antidepressants may significantly benefit those with recurrent cyclic vomiting who also use cannabis regularly.

Opioids should be avoided if a CHS diagnosis is confirmed. No data analyses show any benefit of opioids for CHS. In fact, the national opioid epidemic and increasing public health concerns with opioid use have led to guidelines advocating avoidance of opioids.

Education on the link between cannabis use and CHS should be explicit and state that immediate cessation of cannabis use is the only way to eliminate symptoms and prevent further episodes. Episodes of CHS usually last 24–48 hours; however, episodes can last up to 7–10 days, even after cessation of cannabis use. Symptoms may return with continued exposure to cannabis, and many patients will have repeat episodes without cessation.

Practice Points

The clinical pharmacist faces many challenges in optimizing pharmacotherapy for nausea and vomiting in pediatric patients.

- **Understanding which emetic pathway is causing a patient's vomiting will help target pharmacotherapy recommendations.**
- **Mechanical causes of emesis are most often the result of obstruction or increased enteral intake and activate serotonin receptors and some neurokinin-1 activation.**
- **Bloodborne toxins, including medications, activate serotonin receptors, neurokinin-1 receptors, and some dopaminergic response.**
- **Motion sickness or activation of the vestibular system activates both muscarinic and histaminergic receptors.**
- **Emotional triggers like anxiety and fear may release corticotrophin-releasing factor and are targets for behavioral therapy. Benzodiazepines may also be helpful.**
- **CVS is linked to migraines, so treatment options are often similar.**
- **Initiating prompt therapy in CVS is linked with shorter duration of episodes. Therapy can be classified by phase: supportive, abortive, and prophylactic. Pharmacotherapy should be targeted by phase.**
- **Prophylactic therapy should be considered for patients with recurrent symptoms, if patients are hospitalized, or if their quality of life is being significantly affected. An antihistamine or a TCA is usually preferred, depending on age.**
- **Alternative prophylactic therapies depend on comorbidities and avoidance of adverse effects.**
- **CHS is becoming more common, particularly in states where marijuana has been legalized. In patients presenting with symptoms like cyclic vomiting and with cannabinoid use, CHS should be considered.**
- **Complete resolution of CHS occurs only with cessation of cannabinoid use; however, promising agents, including capsaicin, can help mitigate symptoms in addition to hot water hydrotherapy.**

REFERENCES

Ahuja A, Kingsley M, Diable C, et al. Ketamine as a novel abortive therapy for cyclic vomiting syndrome attacks. Gastroenterology 2018;154:S558-9.

Aziz I, Palsson O, Whitehead W, et al. Epidemiology, clinical characteristics, and associations for Rome IV functional nausea and vomiting disorders in adults. Clin Gastroenterol Hepatol 2019;17:878-86.

Badihian N, Saneian H, Badihian S, et al. Prophylactic therapy of cyclic vomiting syndrome in children: comparison of amitriptyline and cyproheptadine: a randomized clinical trial. Am J Gastroenterol 2018;113:135-40.

Blohm E, Sell P, Neavyn M. Cannabinoid toxicity in pediatrics. Curr Opin Pediatr 2019;31:256-61.

Boles RG. High degree of efficacy in the treatment of cyclic vomiting syndrome with combined co-enzyme Q10, L-carnitine and amitriptyline, a case series. BMC Neurol 2011;11:102.

Bourdaud N, Francois C, Jacqmarcq O, et al. Addition of droperidol to prophylactic ondansetron and dexamethasone in children at high risk for postoperative vomiting. A randomized, controlled double-blind study. Br J Anesth 2017;118:918-23.

Centers for Disease Control and Prevention (CDC). Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. Pediatrics 2004;114:507.

Chang YH, Windish DM. Cannabinoid hyperemesis relieved by compulsive bathing. Mayo Clin Proc 2009;84:76-8.

Chogle A, Velasco-Benitez CA, Koppen IJ. A population-based study on the epidemiology of functional gastrointestinal disorders in young children. J Pediatr 2016;179:139-43.

Chowdhury NA, Sewatsky ML, Kim H. Transdermal scopolamine withdrawal syndrome case report in the pediatric cerebral palsy population. Am J Phys Med Rehabil 2017;96:e151-4.

Cieslak GD, Watcha MF, Phillips MB, et al. The dose-response relation and cost-effectiveness of granisetron for the prophylaxis of pediatric postoperative emesis. Anesthesiology 1996;85:1076-85.

Clouse RE, Sayuk GS, Lustman PJ, et al. Zonisamide or levetiracetam for adults with cyclic vomiting syndrome: a case series. Clin Gastroenterol Hepatol 2007;5:44-8.

Cristofori F, Thapar N, Saliakellis E, et al. Efficacy of the neurokinin-1 receptor antagonist aprepitant in children with cyclical vomiting syndrome. Aliment Pharmacol Ther 2014;40:309-17.

Darmani NA. The cannabinoid CB1 receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55, 212-2. Eur J Pharmacol 2001;430:49-58.

DeCamp LR, Byerley JS, Doshi N, et al. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. Arch Pediatr Adolesc Med 2008;162:858-65.

Dezieck L, Hafez Z, Conicella A, et al. Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: a case series. Clin Toxicol (Phila) 2017;55:908-13.

Fitzpatrick E, Bourke B, Drumm B, et al. The incidence of cyclic vomiting syndrome in children: population-based study. Am J Gastroenterol 2008;103:991-5.

Flubacher P, Fournier N, Cherpillod J, et al. A randomised controlled trial of placebo, droperidol or ondansetron to prevent nausea and vomiting after tonsillectomy in children receiving dexamethasone. Anaesthesia 2017;72:859-63.

Foreman MS, Camp T. Cyclic vomiting syndrome. Pediatr Rev 2018;39:100.

Gokhale R, Huttenlocher PR, Brady L, et al. Use of barbiturates in the treatment of cyclic vomiting during childhood. J Pediatr Gastroenterol Nutr 1997;25:64-7.

Goodwin RD, Cheslack-Postava K, Santoscoy S, et al. Trends in cannabis and cigarette use among parents with children at home: 2002 to 2015. Pediatrics 2018;141:e20173506.

Gravatt L, Donohoe KL, DiPiro CV. Nausea and vomiting. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill, 2017.

Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity – an update. Support Care Cancer 2011;19(suppl 10):S43-7.

Haghighat M, Rafie SM, Dehghani SM, et al. Cyclic vomiting syndrome in children: experience with 181 cases from southern Iran. World J Gastroenterol 2007;13:1833-6.

Han B, Compton WM, Blanco C, et al. National trends in substance use and use disorders among youth. J Am Acad Child Adolesc Psychiatry 2017;56:747-54.

Hejazi RA, Reddymasu SC, Namin F, et al. Efficacy of tricyclic antidepressant therapy in adults with cyclic vomiting syndrome: a two-year follow-up study J Clin Gastroenterol 2010;44:18-21.

Hershey AD, Powers SW, Vockell AL, et al. PedMIDAS: development of a questionnaire to assess disability of migraines in children. Neurology 2001;57:2034-9.

Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2017;35:3240-61.

HHS. Substance Abuse and Mental Health Services Administration (SAMHSA). Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS publication SMA 18-5068, NSDUH Series H-53). 2018.

Hikita T, Kodama H, Kaneko S. Sumatriptan as a treatment for cyclic vomiting syndrome: a clinical trial. Cephalalgia 2011;31:504-7.

Hikita T, Kodama H, Nakamoto N, et al. Effective prophylactic therapy for cyclic vomiting syndrome in children using valproate. Brain Dev 2009;31:411-3.

Hikita T, Kodama H, Ogita K, et al. Cyclic vomiting syndrome in infants and children: a clinical follow-up study. Pediatr Neurol 2016;57:29-33.

Hoffman RJ, Alansari K. Effect of intravenous ondansetron on QTc interval in children with gastroenteritis. Am J Emerg Med 2018;36:754-7.

Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and adolescents. Gastroenterology 2016;150:1456-68.

International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.

Jahromi SR, Togha M, Fesharaki SH, et al. Gastrointestinal adverse effects of antiepileptic drugs in intractable epileptic patients. Seizure 2011;20:343-6.

Kassel L, Nelson M, Shine J, et al. Scopolamine use in the perioperative patient: a systematic review. AORN J 2018;108:287-95.

Kaul A, Kaul K. Cyclic vomiting syndrome: a functional disorder. Pediatr Gastroenterol Hepatol Nutr 2015;18:224-9.

Khasawinah TA, Ramirez A, Berkenbosch JW, et al. Preliminary experience with dexmedetomidine in the treatment of cyclic vomiting syndrome. Am J Ther 2003;10:303-7.

Kim HS, Anderson JD, Saghafi O, et al. Cyclic vomiting presentations following marijuana liberalization in Colorado. Acad Emerg Med 2015;22:694-9.

Kim HS, Monte AA. Colorado cannabis legalization and its effect on emergency care. Ann Emerg Med 2016;68:71-5.

Kovacic K, Sood M, Venkatesan T. Cyclic vomiting syndrome in children and adults: what is new in 2018? Curr Gastroenterol Rep 2018;20:46.

Krammes SK, Jacobs TJ, Clark JM, et al. Effect of intravenous ondansetron on the QT interval of patients' electrocardiograms. Pediatr Emerg Care 2018;34:38-41.

Krowicki ZK, Moerschbaecher JM, Winsauer PJ, et al. Delta(9)-Tetrahydrocannabinol inhibits gastric motility in the rat through cannabinoid CB1 receptors. Eur J Pharmacol 1999;37:187-96.

Lapoint J. Capsaicin cream for treatment of cannabinoid hyperemesis syndrome. In: American College of Medical Toxicology Annual Scientific Meeting abstracts. Abstract 51. 2014.

Lapoint J, Meyer S, Yu C, et al. Cannabinoid hyperemesis syndrome: public health implications and a novel model treatment guideline. West J Emerg Med 2018;19:380-6.

Lapoint JM. Cannabinoids. In: Hoffman RS, Howland M, Lewin NA, et al., eds. Goldfrank's Toxicologic Emergencies, 10th ed. New York: McGraw-Hill, 2015.

Lee LY, Abbott L, Mahlangu B, et al. The management of cyclic vomiting syndrome: a systematic review. Eur J Gastroenterol Hepatol 2012;24:1001-6.

Li B, Lefevre F, Chelimsky G, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 2008;47:379-93.

Li BU. Cyclic vomiting syndrome. Curr Treat Options Gastroenterol 2000;3:395-402.

Lundberg DJ, Daniel AR, Thayer SA. Delta(9)-Tetrahydrocannabinol-induced desensitization of cannabinoid-mediated inhibition of synaptic transmission between hippocampal neurons in culture. Neuropharmacology 2005;49:1170-7.

Martinez-Esteve Melnikova A, Schappi MG, Korff C. Riboflavin in cyclic vomiting syndrome: efficacy in three children. Eur J Pediatr 2016;175:131-5.

McCallum RW, Soykan I, Sridhar KR, et al. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. Aliment Pharmacol Ther 1999;13:77-80.

Mora J, Valero M, DiCristina C, et al. Pharmacokinetics/pharmacodynamics, safety, and tolerability of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients. Pediatr Blood Cancer 2019;66:e27690.

Namin F, Patel J, Lin Z, et al. Clinical, psychiatric and manometric profile of cyclic vomiting syndrome in adults and response to tricyclic therapy. Neurogastroenterol Motil 2007;19:192-202.

Okumura LM, da Silva Ries SA, Meneses CF, et al. Adverse events associated with aprepitant pediatric bone cancer patients. J Oncol Pharm Pract 2019;25:735-8.

Palmer GM, Cameron DJ. Use of intravenous midazolam and clonidine in cyclical vomiting syndrome: a case report. Paediatr Anaesth 2005;15:68-72.

Patel P, Robinson PD, Thackray J, et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: a focused update. Pediatr Blood Cancer 2017;64.

Patterson DA, Smith E, Monahan M, et al. Cannabinoid hyperemesis and compulsive bathing: a case series and paradoxical pathophysiological explanation. Am J Board Fam Med 2010;23:790-3.

Perrotta G, Miller J, Stevens T, et al. Cannabinoid hyperemesis: relevance to emergency medicine. Acad Emerg Med 2012;19:S286-S7.

Phillips RS, Friend AJ, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. Cochrane Database Syst Rev 2016;2:CD007786.

Pillai AK, Sharma KK, Gupta YK, et al. Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy. Pediatr Blood Cancer 2011;56:234-8.

Polito S, MacDonald T, Romanick M, et al. Safety and efficacy of nabilone for acute chemotherapy-induced vomiting prophylaxis in pediatric patients: a multicenter, retrospective review. Pediatr Blood Cancer 2018;65:e27374.

Radhakrishnan V, Joshi A, Ramamoorthy J, et al. Intravenous fosaprepitant for the prevention of chemotherapy-induced vomiting in children: a double-blind, placebo-controlled, phase III randomized trial. Pediatr Blood Cancer 2019;66:e27551.

Redon S, Mareau C, Guedj E, et al. Cyclic vomiting syndrome in adults and children: a hypothesis. Headache 2017;57:943-51.

Richards JR, Gordon BK, Danielson AR, et al. Pharmacologic treatment of cannabinoid hyperemesis syndrome: a systematic review. Pharmacotherapy 2017;37:725-34.

Romano C, Dipasquale V, Rybak A, et al. An overview of the clinical management of cyclic vomiting syndrome in childhood. Curr Med Res Opin 2018;34:1785-91.

Saito Y, Kumamoto T, Arima T, et al. Evaluation of aprepitant and fosaprepitant in pediatric patients. Pediatr Int 2019;61:235-9.

Sezer OB, Sezer T. A new approach to the prophylaxis of cyclic vomiting: topiramate. J Neurogastroenterol Motil 2016;22:656-60.

Shields TM, Lightdale JR. Vomiting in children. Pediatr Rev 2018;39:342-58.

Simino GP, Marra LP, Andrade EI, et al. Efficacy safety and effectiveness of ondansetron compared to other serotonin-3 receptor antagonists (5-HT3RAs) used to control chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. Expert Rev Clin Pharmacol 2016;9:1183-94.

Sorenson CH, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology and treatment – a systematic review. J Med Toxicol 2017;13:71-87.

Substance Abuse and Mental Health Services Administration (SAMHSA). Results from the 2014 National Survey on Drug Use and Health: Summary of National Findings. 2014.

Tarbell SE, Li BU. Anxiety measures predict health-related quality of life in children and adolescents with cyclic vomiting syndrome. J Pediatr 2015;167:633-8.

Timaeus S, Elder J, Franco K. Evaluation of the use of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting in pediatric patients. J Pediatr Hematol Oncol 2018;40:527-31.

Tobias JD. Dexmedetomidine in the treatment of cyclic vomiting syndrome. Pediatr Anesth 2005;15:709-10.

Van Calcar SC, Harding CO, Wolff JA. L-carnitine administration reduces number of episodes in cyclic vomiting syndrome. Clin Pediatr (Phila) 2002;41:171-4.

Venkatesan T, Levinthal D, Tarbell S, et al. Guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association. Neurogastroenterol Motil 2019;31(suppl 2):e13604.

Zeevenhooven J, Koppen IJ, Benninga MA. The new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers. Pediatr Gastroenterol Hepatol Nutr 2017;20:1-13.

Self-Assessment Questions

1. A 9-year-old boy with osteosarcoma is admitted to the hospital for surgery, after which he has complications that result in a 14-day ICU stay and the need for continuous pain and sedation medications. His current drugs include hydromorphone 2 mg intravenously every 4 hours as needed for pain and lorazepam 2 mg intravenously every 6 hours for withdrawal prevention. The patient did receive isoflurane in the operating room. The patient has also begun the next cycle of chemotherapy, which includes cisplatin 60 mg/m^2/day for 2 days. He has significant nausea and vomiting requiring treatment. Which one of the following is most likely responsible for this patient's nausea and vomiting?

   A. Cisplatin
   B. Hydromorphone
   C. Isoflurane
   D. Lorazepam

2. A 2-month-old girl presents to the clinic for a routine follow-up and vaccines. The infant's mother mentions that the patient has had several episodes of emesis, sometimes up to 15 minutes after eating. The patient is not in any acute distress and is afebrile; at the time of the examination, her abdomen is soft and non-tender. The mother reports that the patient has no diarrhea or other symptoms and that she is not fussy; also, the emesis does not have an unusual color during these episodes. Which one of the following is the best evaluation of this patient's presentation?

   A. Pyloric stenosis
   B. Regurgitation
   C. Rumination
   D. Viral gastroenteritis

3. An 8-year-old girl is brought to her primary care provider by her mother. They will be traveling to a water park about 6 hours away, but the mother reports that her daughter often becomes nauseated when traveling in the car for long periods. Which one of the following is best to recommend to prevent this patient's nausea symptoms?

   A. Cyproheptadine
   B. Diphenhydramine
   C. Promethazine
   D. Scopolamine

4. A 10-year-old patient in the pediatric ICU has been intubated for 14 days after a motor vehicle crash. The patient is being weaned from continuous infusion sedation and analgesia medications with methadone and lorazepam and has evidence of ICU delirium being treated with haloperidol. The last wean was 2 days ago. Within the past 12 hours, the patient has begun having significant nausea and some vomiting. Abdominal radiography and examination reveal a large amount of stool and a slightly distended but soft abdomen. Vital signs are stable, and the patient has had some increased feeding residuals. Which one of the following is best to recommend for this patient?

   A. Administer scheduled intravenous ondansetron.
   B. Administer intravenous granisetron as needed and increase weaning agents.
   C. Initiate a bowel regimen and administer scheduled intravenous granisetron.
   D. Initiate a bowel regimen and obtain an ECG before initiating ondansetron.

5. A 13-year-old male adolescent (weight 40 kg) has a medical history that includes cerebral palsy and significant spasticity and sialorrhea. The patient is admitted to the hospital for botulinum toxin A to treat sialorrhea refractory to scopolamine treatment, which the patient has used for the previous 4 years. The procedure is planned to be completed using local anesthetics. His home drugs include baclofen pump (intrathecal), enteral clonazepam three times daily (8 a.m., 2 p.m., and 8 p.m.), as-needed diazepam for spasticity, a scopolamine patch, and polyethylene glycol as needed for constipation (patient usually takes once or twice weekly). All enteral medications were held after midnight for the procedure to be restarted afterward. The patient's last scopolamine patch was placed 4 days before admission and will not be replaced after the procedure. On the morning of the procedure, the patient develops emesis, nausea, lethargy, and crying spells. Which one of the following is best to recommend for this patient's nausea and vomiting?

   A. Administer ondansetron 4 mg intravenously every 8 hours as needed for postoperative nausea and vomiting (PONV).
   B. Administer meclizine 25 mg three times daily followed by a week-long taper.
   C. Cut 1 scopolamine patch and administer half for 3 days, then one-fourth patch for 3 days, then discontinue.
   D. Administer lorazepam 4 mg intravenously every 4 hours as needed.

6. A 4-year-old girl (height 39.8 inches [101 cm], weight 18 kg) is receiving cisplatin and etoposide for high-risk neuroblastoma. She is having significant and continued nausea and vomiting. She currently receives scheduled intravenous ondansetron and intravenous

dexamethasone at standard doses. The team orders a low dose of fosaprepitant. Which one of the following is best to recommend for this patient?

A. Complete order for fosaprepitant as directed.
B. Decrease dexamethasone by 50% and complete fosaprepitant order as directed.
C. Discontinue dexamethasone and increase ondansetron dose by 50%.
D. Increase fosaprepitant dose and reduce dexamethasone dose to 2 mg.

7. A 4-year-old girl admitted to the hospital with a diagnosis of cyclic vomiting is having acute symptoms and is being treated with ondansetron 0.15 mg/kg/dose orally scheduled every 8 hours. The family asks about prophylaxis for cyclic vomiting. Which one of the following is best to recommend for this patient?

A. No prophylaxis is indicated at this time.
B. Administer ondansetron 0.15 mg/kg/dose orally every 8 hours as needed.
C. Administer cyproheptadine 0.25 mg/kg/day orally divided in two or three doses.
D. Administer amitriptyline 0.25 mg/kg/dose orally at bedtime.

8. A 9-year-old previously healthy boy presents with periods of intense nausea and paroxysmal vomiting that have lasted about 2 days. He has no sick contacts, and his laboratory values are all within normal limits, with a normal abdominal examination, radiograph, and CT scan. The patient had a similar episode 2 months ago, for which he was hospitalized for dehydration. After hospitalization and rehydration, the patient returned to baseline health. His medical history includes asthma. Which one of the following best assesses this patient regarding cyclic vomiting syndrome (CVS)?

A. He does not meet the criteria for CVS.
B. He meets the ICHD-3 (International Classification of Headache Disorders, third edition) beta criteria outlined by the International Headache Society.
C. He meets the NASPGHAN criteria.
D. He meets the Rome IV criteria.

Questions 9–12 pertain to the following case.

L.T., an 11-year-old girl (weight 40 kg), is admitted to the hospital for dehydration secondary to emetic episodes over the past 5 days with moderate abdominal pain. She was given a diagnosis of CVS 4 years ago and was hospitalized once previously. L.T. reports significant missed days from school and now has anxiety about her attacks. In addition, her medical history includes a diagnosis of depression currently managed with counseling. A basic metabolic panel shows the following: Na 140 mEq/L, K 3.5 mEq/L, Cl 111 mEq/L, HCO_3 22 mmol/L, BUN 30 mg/dL, SCr 0.9 mg/dL, and glucose 75 mg/dL. The patient's urinary output has been 0.9 mL/kg/hour since today's admission.

9. Which one of the following fluid regimens is best to recommend for L.T.?

A. Dextrose 5% in water and one-half normal saline plus 20 mEq/L of potassium chloride at 80 mL/hour
B. Dextrose 5% in water and one-half normal saline plus 20 mEq/L of potassium chloride at 120 mL/hour
C. Dextrose 10% in water and one-half normal saline plus 20 mEq/L of potassium chloride at 80 mL/hour
D. Dextrose 10% in water and one-half normal saline plus 20 mEq/L of potassium chloride at 120 mL/hour

10. Which one of the following is best to recommend regarding L.T.'s CVS?

A. Treat acutely with promethazine 10 mg rectally every 6 hours.
B. Treat acutely with ondansetron 4 mg intravenously every 8 hours.
C. Treat with ondansetron 4 mg intravenously every 8 hours and lorazepam 2 mg intravenously every 6 hours as needed.
D. Treat with ondansetron 4 mg intravenously every 8 hours and sumatriptan 50 mg orally as a single dose.

11. Which one of the following is best to recommend for L.T.'s abdominal pain?

A. Enteral ibuprofen
B. Intravenous ketorolac and ranitidine.
C. Intravenous hydromorphone
D. Intravenous morphine

12. Which one of the following is best to recommend regarding prophylactic therapy for L.T.?

A. The patient does not qualify for prophylactic therapy.
B. Initiate amitriptyline.
C. Initiate propranolol.
D. Initiate topiramate.

13. A 17-year-old female adolescent presents to the ED with a 2½-week history of bilious emesis and left upper quadrant pain. She had a similar episode 4 months ago that lasted 2 weeks and another episode that lasted 1 week 1 month ago. The patient was treated with intravenous fluids and antiemetics in the ED for the previous episodes but was never hospitalized. Workup for those episodes was negative. The patient denies diarrhea, hematemesis, or fever. She cannot identify a particular food or smell that triggers these episodes and has no history of migraines. The patient reports that the only helpful treatment is taking hot baths. She uses ethanol and cannabis recreationally. She last smoked marijuana over 3½ weeks ago but denies any recent use with this current episode. Her weight is at the 80th percentile and

BMI is at the 85th percentile. The patient's vital signs are normal except for blood pressure 140/90 mm Hg, and her heart rate will decrease to 50 beats/minute during a pain episode. Abdominal examination reveals mild periumbilical and left upper quadrant tenderness. The rest of the physical examination is normal. After fluids, which one of the following is best to recommend for this patient?

A. Intravenous haloperidol
B. Intravenous morphine
C. Intravenous ondansetron
D. Topical capsaicin 0.075%

14. A patient with cannabinoid hyperemesis syndrome (CHS) is being admitted from the ED for severe dehydration and refractory emesis with significant abdominal pain. The patient has been cooperative and helpful when questioned. The patient's vital signs are stable. The patient is receiving intravenous fluids and has received two doses of ondansetron in the ED. The pharmacy cannot obtain capsaicin cream but has ordered it to arrive tomorrow. Which one of the following is best to recommend for this patient?

A. Enteral amitriptyline
B. Enteral metoclopramide
C. Intravenous haloperidol
D. Intravenous lorazepam

15. Which one of the following patients is most likely to be given a diagnosis of CHS?

A. Patient smoking marijuana every 2–3 months with vomiting once after smoking recently
B. Patient with episodic vomiting who has smoked marijuana daily for about 3 years
C. Patient presenting with abdominal pain and vomiting who smoked a large amount of marijuana for the first time 2 days ago while consuming alcohol
D. Patient with a 4-day history of abdominal pain and paroxysmal vomiting after consuming six edible "cookies" from a trip to Colorado