Cyclic vomiting syndrome

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INTRODUCTION — Cyclic vomiting syndrome (CVS) is an idiopathic disorder characterized by recurrent, stereotypical bouts of vomiting with intervening periods of normal health [1]. Although it appears to primarily affect children, it is being recognized increasingly in adults.

CVS was first described in France in 1861 [2]. The first English-language publication, in 1882, described three essential clinical features of the disorder, which still hold true today [3]:

- Three or more recurrent discrete episodes of vomiting
- Varying intervals of completely normal health between episodes
- Episodes are stereotypical with regard to timing of onset, symptoms, and duration

A critical fourth criterion that has been added subsequently includes the absence of an organic cause of vomiting [4].

This topic review will provide an overview of cyclic vomiting syndrome in adults and children. A guideline on this topic has also been published [4].

EPIDEMIOLOGY — Cyclic vomiting syndrome (CVS) is no longer considered to be rare in children. A cross-sectional study of school-age children in Aberdeen, Scotland, estimated that 34 of 2165 children (1.6 percent) fulfilled the diagnostic criteria for CVS [5]. Their average age was 9.6 years at the time of diagnosis, while the average age at the onset of symptoms was 5.3 years. The overall gender ratio was equal, although, among younger children, it was more common in boys. A similar age distribution has been described in other reports of children, although many have suggested that it may be more common in girls [4,6-10]. A family in which CVS appears to be inherited has been described [11].

The disorder appears to be less common in adults, although there are no population-based studies from which estimates of its prevalence can be devised. One of the largest studies, which included 17 adult patients seen during a 10-year period at an academic medical center, found that the CVS began at an average age of 35 (range 14 to 73 years) but was not diagnosed until patients were on average 41 years old [12]. The gender distribution was equal. The average length of episodes was six days (range 1 to 21 days), with symptom-free intervals averaging three months (range 0.5 to 6 months). Similar findings have been described in other reports in adults [13,14].

Although there appear to be similarities in CVS across age groups [7], a few differences between adults and children have been observed [12]:

- Adults have on average approximately four cycles per year in contrast with 12 cycles per year in children [15].
- The age of onset covers a broad span in adults, while in children the age of onset is often in the toddler or preschool years.

- Adults have usually been symptomatic for longer prior to diagnosis, possibly reflecting the increased recognition of CVS by pediatricians.
- Triggering events are less common in adults.
- Nausea between episodes is more common in adults.
- CVS in children, but not in adults, is highly associated with two common mitochondrial DNA polymorphisms, 16519T and 3010A [16].

PATHOGENESIS — The pathogenesis of cyclic vomiting syndrome (CVS) remains unknown, although it may represent a heterogeneous group of disorders. An association between CVS and migraine headaches has been most consistently described, suggesting that there may be a common pathophysiologic process. However, CVS has also been linked to food allergy, mitochondrial, metabolic, and endocrine disorders.

CVS and migraines — CVS has been linked to migraine headaches and abdominal migraine (table 1) [17,18]. This connection is based upon the discreteness of episodes, the progression from cyclic vomiting to migraine headaches in many patients, the presence of a strong family history of migraine headaches in affected children (approximately 80 percent), and the response to antimigraine therapy in up to 80 percent of children [4,19]. Sympathetic autonomic dysfunction may predispose children to both CVS and migraine headaches [20,21]. (See "Pathophysiology, clinical features, and diagnosis of migraine in children".)

One hypothesis is that CVS may lead to abdominal migraines, which in turn lead to migraine headaches. However, more children progress directly from CVS to migraines than from CVS to abdominal migraines to migraines. Abdominal migraines can be distinguished from CVS in that the core symptom of abdominal migraines is abdominal pain, not vomiting. Both syndromes may have headache as a feature and respond to antimigraine therapy [22].

Metabolic disorders — Mitochondrial disorders of fatty acid oxidation (eg, medium-chain acyl coenzyme A dehydrogenase deficiency), respiratory chain defects (eg, MELAS: Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Syndrome), and mitochondrial DNA deletions can be associated with episodes of metabolic crisis and vomiting, usually with infection or prolonged fasting [23]. (See "Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features" and "Overview of the hereditary ataxias".)

One group suggested that about one-half of patients with cyclic vomiting syndrome have evidence for maternal inheritance of a mitochondrial DNA sequence variation [24]. Compared with controls, mothers of patients with cyclic vomiting syndrome were more likely to have a history of migraine, depression, irritable bowel syndrome, and hypothyroidism, disorders that the researchers hypothesized may segregate with cyclic vomiting syndrome in families due to predisposing mitochondrial DNA sequence variants. The authors speculated that cyclic vomiting syndrome represents a rare clinical presentation in individuals who carry the predisposing mitochondrial variants that are more commonly associated with migraine, depression, irritable bowel syndrome, hypothyroidism, and other functional/dysautonomic conditions [25,26]. The efficacy of mitochondrial-targeted therapies, co-enzyme Q10 [27,28] and L-carnitine [27,29], in CVS strengthens the hypothesis of a metabolic/mitochondrial component in disease pathogenesis. This hypothesis is further strengthened by an association of both CVS and migraine headache with the same two mitochondrial DNA polymorphisms [30].

Dysautonomia — Patients who have a hereditary sensory autonomic neuropathy (such as Riley Day Syndrome) can also have clinical features resembling CVS. (See "Hereditary sensory and autonomic neuropathies".)

Hypothalamic-pituitary-adrenal axis defects — Elevated corticotropin, cortisol, vasopressin, prostaglandin E2, and catecholamines have been described in a group of children with cyclic vomiting, profound lethargy, and hypertension [31]. Animal studies suggest that CVS may be a brain-gut disorder in which corticotropin-releasing factor induces gastric stasis and vomiting by vagal stimulation [32].

Food allergy — Sensitivity to cow's milk, soy, and egg white protein may be related to CVS in children [6]. Other food triggers include chocolate, cheese, and monosodium glutamate. The relationship between food allergy and CVS is uncertain.

Catamenial CVS — Similar to menstrual migraine headaches, some girls develop catamenial CVS at the onset of their menstrual period. Some respond to treatment with a low-dose estrogen or progesterone-only birth control pill, although oral contraceptives and other steroids can also precipitate vomiting episodes and other symptomatology in some. An association between symptoms and menses has also been described in adults [12].

Chronic cannabis use — Cessation of chronic cannabis use has been associated with resolution of persistent vomiting in case reports suggesting a causal association [33-36]. In one series, the association was characterized by repetitive washing behavior during vomiting cycles, which is not a feature of CVS [33]. Also, patients with "cannabis hyperemesis syndrome" vomit daily, without the periods of completely normal health required as one of the essential features of CVS described above (see 'Introduction' above). However, many adults with CVS self-medicate with cannabis to alleviate their nausea, and this can be a source of diagnostic confusion. In general, patients who use cannabis most days, and who exhibit frequent bathing/showering behavior, are most likely to have “cannabis hyperemesis syndrome” and not CVS. CVS cannot be diagnosed until patients abstain from cannabis for at least one to two weeks; if the emesis continues, then further work-up for CVS can be undertaken.

CLINICAL MANIFESTATIONS — Each of the proposed diagnostic criteria suggests two essential features of cyclic vomiting syndrome (CVS). (See 'Diagnosis' below.)

- Stereotypical episodes of vomiting regarding onset (acute) and duration (hours to days)
- The absence of nausea and vomiting between episodes

Supportive criteria for the diagnosis of CVS include a history or family history of migraine headaches, the self-limited nature of the attacks, associated symptoms of nausea, abdominal pain, headache, motion sickness, photophobia, and lethargy, and associated signs of fever, pallor, diarrhea, dehydration, excess salivation, and social withdrawal. In children, nausea and possibly lethargy are considered to be key diagnostic features.

The specific pattern of vomiting episodes is variable among patients but, importantly, is stereotypical for an individual patient [37]. In general, CVS episodes tend to begin in the early morning hours (2:00 to 7:00 AM) and may involve a prodromal period of pallor, anorexia, nausea, abdominal pain, and/or lethargy (table 2). In children, the attacks last an average of 24 to 48 hours. Approximately one-half of children have attacks at regular intervals, commonly occurring every two to four weeks, while the others have an unpredictable temporal pattern of vomiting. Approximately two-thirds of parents can identify a trigger, which is usually infectious (upper respiratory) or psychological (negative or positive) [38].

As noted above, episodes tend to be longer in adults (approximately three to six days) with longer intervening intervals of normal health (approximately three months) [12-14]. Intervening episodes of normal health are important for distinguishing CVS from functional nausea and vomiting in which symptoms are present continuously or nearly continuously (figure 1).

The characteristics on presentation (and difficulty establishing the diagnosis) were illustrated in a group of 17 adults [12]:

- Each patient had been evaluated by at least two physicians (typically with repeated imaging and endoscopic studies) and had been hospitalized at least once. Three patients (18 percent) required nutritional support.

- Three patients had undergone surgical exploration and partial gastrectomy, pyloroplasty, or fundoplication without improvement.

- Abdominal pain was present during episodes in approximately two-thirds of patients.
- Only 20 percent of patients had a psychiatric diagnosis (either anxiety or another affective disorder).
- Erosive esophagitis was observed in 50 percent of patients during or shortly after a vomiting episode (including one patient who had a Mallory-Weiss tear). However, in no patients did vomiting episodes improve with antireflux measures.
- Only one-third of patients described a prodrome of nausea, epigastric pain, or both, while the others reported the onset of symptoms without warning.
- Four of seven reproductive age women described a link to their menstrual cycle; two had severe episodes precipitated by pregnancy.
- Sleep was beneficial in relieving symptoms in four patients (23 percent).
- A history of migraine headaches was described in only four patients (23 percent).

NATURAL HISTORY — Many children outgrow cyclic vomiting syndrome (CVS) by their preteen or early teenage years [39]. However, some authors have observed that up to 75 percent of children with CVS will go on to develop migraine headaches by age 18 [19]. A minority of children who progress from CVS to migraine headaches will first pass through a phase of abdominal migraines [40]. One retrospective study of 51 children followed for up to 13 years found that vomiting resolved in 60 percent [41]. However, 42 percent continued to have regular headaches and 37 percent had abdominal pain; these features were present even in patients whose vomiting had resolved.

The natural history in adults has not been well studied. In the series of 17 adults described above [12], 13 had at least a partial response to antidepressant therapy while an additional 3 responded to other types of treatment. One patient had persistent symptoms during two years of follow-up.

DIAGNOSIS — Cyclic vomiting syndrome (CVS) remains a diagnosis based upon the history and exclusion of alternative diagnoses (table 3). At least two sets of criteria have been proposed based upon a consensus of experts.

Rome IV criteria — Rome IV criteria include the presence of all of the following [42]:

- Stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week)
- Three or more discrete episodes in the prior year, and two episodes in the past six months, occurring at least one week apart
- Absence of vomiting between episodes, but other milder symptoms can be present between cycles

The criteria should be fulfilled for the last three months with symptom onset at least six months before diagnosis.

Supportive criteria include:

- History or family history of migraine headaches.

North American Society for Pediatric Gastroenterology Hepatology and Nutrition — A consensus statement issued by the North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) suggests the following diagnostic criteria (all of which must be met) [4]. These recommendations apply to children and adolescents:

- At least five attacks in any interval, or a minimum of three attacks during a six-month period
- Episodic attacks of intense nausea and vomiting lasting 1 hour to 10 days and occurring at least one week apart
- Stereotypical pattern and symptoms in the individual patient

- Vomiting during attacks occurs at least four times per hour for at least one hour
- Return to baseline health between episodes
- Not attributed to another disorder

The recommendations for diagnosis and treatment from NASPGHAN (which apply to children and adolescents) are summarized in the algorithms (algorithm 1 and table 4A-D).

Warning signs — Warning signs alerting to an alternative diagnosis include the presence of severe headaches, altered mental status, gait disturbances or other new "neurological signs", gastrointestinal bleeding, unilateral abdominal pain, weight loss, failure to respond to treatment, progressive worsening, prolonged episodes requiring hospitalization, and a change in pattern or symptoms [4]. An upper gastrointestinal series should be performed in children to exclude intestinal malrotation (see "Intestinal malrotation in children"). Ureteropelvic junction obstruction has been reported to be an overlooked mimic of CVS in a case series of four children [43]. CVS should be considered among other diagnoses in patients presenting with nausea and vomiting. (See "Approach to the adult with nausea and vomiting" and "Approach to the infant or child with nausea and vomiting".)

One approach to excluding other disorders of recurrent vomiting includes a complete, extensive evaluation of standard blood work (electrolytes, glucose, ALT, GGTP, amylase, lipase), urinalysis, and (in children) evaluation for metabolic disorders (eg, lactate, ammonia, amino acids, urine organic acids) during an acute episode (see "Approach to the infant or child with nausea and vomiting"). Patients should also be asked about frequent bathing behavior. If present, this can be used as a springboard to probe deeper into the possibility of chronic cannabis use and "cannabis hyperemesis syndrome." An upper gastrointestinal series with small bowel follow-through X-ray (UGI/SBFT), CT/MRI of the head, and endoscopy can be performed between episodes. As noted above, the presence of esophagitis on endoscopy (performed during or near an episode) does not necessarily imply that reflux is an underlying cause, since as many as one-half of patients will have esophagitis but will not respond to antireflux measures.

Only one in eight children with cyclical episodes of vomiting who were evaluated with this approach has been found to have another underlying disorder that required intervention [4]. However, the cost of initial diagnostic testing and annual ambulatory and hospital treatment of CVS using the above approach was estimated to be $17,035 per child in one report [22]. A decision-analysis concluded that a more cost-effective diagnostic strategy in children was to obtain a UGI/SBFT to rule out malrotation with volvulus, followed by a two-month trial of antimigraine therapy, with further studies reserved for those with continued symptoms [44]. In adults, a CT scan of the abdomen and pelvis has been suggested to exclude malignancy and other structural disorders.

TREATMENT — Patients may require supportive care during severe bouts of cyclic vomiting, which may include admission to a hospital, intravenous fluids, antiemetics, and occasionally analgesics. Children should be referred to a pediatric gastroenterologist, neurologist, or metabolic specialist. Recognized precipitating factors (more commonly observed in children) should be avoided whenever feasible. Examples include physical exhaustion, motion (car rides, amusement park rides), fasting, and certain foods (eg, chocolate, cheese).

No specific therapy has been proven to be effective for cyclic vomiting syndrome (CVS) in controlled trials. However, several empiric treatments have been effective in case series. Treatment with medications should be guided by three considerations [23]:

- Whether there is a family history of migraines
- Frequency of episodes
- Severity of episodes

Treatment can also be considered as abortive, prophylactic, and supportive.

A trial of antimigraine medications is reasonable in patients with a family history of migraine headaches. Some authors recommend antimigraine therapy even in the absence of a personal or family history of migraines if, after careful evaluation, the diagnosis of CVS seems certain.

The decision to administer abortive and/or prophylactic antimigraine medications depends upon the frequency and severity of the attacks, similar to the principles that guide treatment of patients with migraine headaches. Prophylactic daily therapy with antimigraine medications is warranted if attacks occur more than once every one to two months or are severe enough to require hospitalization or substantial disability. In contrast, abortive therapy can be used if episodes occur less than once every one to two months or are mild. The choice of specific agents is discussed separately. (See "Acute treatment of migraine in children" and "Acute treatment of migraine in adults" and "Preventive treatment of migraine in adults".)

Agents that have been used empirically (with variable success) in children include sumatriptan, erythromycin, carnitine, coenzyme Q10, propranolol, cyproheptadine, and tricyclic antidepressants [27-29,45,46]. Some authorities advocate use of amitriptyline for prophylaxis in children older than five even if there is no history of headache or a family history of migraine [26]. A common starting dose is 0.5 mg/kg per day at bedtime, although many patients require a higher dose, often 1 mg/kg per day at bedtime. It typically takes one to three months for the effects of amitriptyline to become evident.

Some CVS patients who do not respond to 1 mg/kg per day have very low or undetectable blood levels of amitriptyline, and respond when the amitriptyline dosage is further increased. Many patients do not respond until the blood amitriptyline plus nortriptyline level exceeds 150 micrograms/L [28]. As a general rule, a blood amitriptyline level should be obtained before attempting to exceed 1 mg/kg/ per day to avoid a toxic level.

Retrospective studies have demonstrated substantial efficacy of the dietary supplements coenzyme Q10 and L-carnitine [27-29]. These supplements can be purchased over-the-counter and/or by prescription, which varies by location. The efficacy of coenzyme Q10 may be as great as that for amitriptyline [27]. One article presented a protocol that was 90 percent effective in substantially reducing vomiting episodes by combining these supplements with amitriptyline [28]. A common starting dose for coenzyme Q10 is 10 to 20 mg/kg per day, or 200 mg twice daily. A common starting dose for L-carnitine is 50 or 100 mg/kg per day, or one gram twice daily. Many patients require higher dosages, and suggested blood levels were >3.0 to 4.0 mg/L for coenzyme Q10, and a free carnitine level >40 micromol/L [28]. Note that many commercially available preparations of coenzyme Q10 have poor bioavailability as judged by blood levels, and monitoring of blood levels is an important aspect of disease management.

Use of amitriptyline may be limited in infants and toddlers under 5 years of age due to side effects (such as personality changes, anticholinergic effects, and tachyarrhythmias). The EKG (particularly the QTc interval) and electrolytes (K+, Mag+) should be monitored. Cyproheptadine and propranolol are often used as alternatives. Cyproheptadine is recommended as first-line treatment in children under age five years. Therapies of unproven efficacy that have been used include topiramate and riboflavin.

Sumatriptan, ketorolac, prochlorperazine, and tricyclic antidepressants have been used in case reports in adults [13,46-48]. Low-dose estrogen or progesterone-only birth control pills can be used as directed in females with catamenial CVS in whom vomiting attacks occur at the time of menses; however, birth control pills can also exacerbate symptoms in CVS patients [4,49]. (See "Estrogen-associated migraine".) A variety of antiemetic medications have been used unsuccessfully, including high dose dexamethasone, metoclopramide, ondansetron, and naloxone [48].

A clinical response to tricyclic antidepressants was observed in 13 of 17 adults in the report described above (although only three patients had a complete response) [12]. Antidepressants used included amitriptyline, doxepin, and nortriptyline (median dose for each is 50 mg daily). Two other patients responded to fluoxetine or cyproheptadine. Another report described improvement with zonisamide or levetiracetam (antiepileptic drugs) in adults who had symptoms refractory to tricyclic antidepressants [50]. However, side-effects (such as fatigue, confusion, headache, and poor concentration) were common.

During vomiting episodes, the goal is to abort or shorten the episode. Anecdotal experience in children suggests that intravenous administration of a 10 percent dextrose solution can decrease the frequency and duration of vomiting episodes [26] in about one-half of patients. Between episodes, frequent low fat feedings have been advocated to decrease the frequency of episodes. These observations may have a pathophysiologic basis in the impaired carbohydrate and fat metabolism that has been described in children with mitochondrial variants that may predispose to cyclic vomiting syndrome. (See 'Metabolic disorders' above.)

In addition to 10 percent intravenous dextrose, anecdotal experience suggests that high dose ondansetron (0.3 to 0.4 mg/kg/dose, maximum about 20 mg/dose), sedation (eg, with diphenhydramine or lorazepam), and a quiet, dark room are often helpful. However, it has been recommended that intravenous doses of ondansetron not exceed 16 mg (8 mg for patients ≥75 years old) because of the risk of QT prolongation [51]. Drinking water to induce vomiting (and thus lessening nausea) is common, and does not indicate a factitious or psychiatric etiology [52].

INFORMATION FOR PATIENTS — Support and counseling may be helpful for selected patients. The Cyclic Vomiting Syndrome Association (CVSA), an international organization, was established in 1993 to provide support to patients with CVS.

For more information on the CVSA, contact:

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Additional resources that might be useful are listed in the table (table 5).

SUMMARY AND RECOMMENDATIONS

- Cyclic vomiting syndrome (CVS) is an idiopathic disorder characterized by recurrent, stereotypical bouts of vomiting with intervening periods of normal health. Although it appears to affect primarily children, it is being recognized increasingly in adults. (See 'Introduction' above.)

- The pathogenesis of CVS remains unknown, although it may represent a heterogeneous group of disorders. An association between CVS and migraine headaches has been most consistently described, suggesting that there may be a common pathophysiologic process. However, CVS has also been linked to food allergy, mitochondrial, metabolic, and endocrine disorders. (See 'Pathogenesis' above.)

- Diagnostic criteria have been proposed based upon consensus of experts. The specific pattern of vomiting is variable among patients but, importantly, is stereotypical for an individual patient. Cyclic vomiting syndrome remains a diagnosis based upon the history and exclusion of alternative diagnoses. (See 'Diagnosis' above.)

- Treatment can be considered as abortive, prophylactic, and supportive. Most treatments have been based upon observational data or clinical experience, forming the basis for the following suggested approach (**Grade 2C**).

If episodes occur more often than monthly, or if they are prolonged or debilitating, daily prophylactic therapy is recommended. If episodes are less frequent or are mild, abortive therapy at the onset of episodes is often preferred. If abortive therapy fails after two or three attempts, then switch to prophylactic therapy. (See "Acute treatment of migraine in children" and "Acute treatment of migraine in adults" and "Preventive treatment of migraine in adults".)

Some authorities advocate use of amitriptyline (0.5 mg/kg per day increased as needed to 1 mg/kg or higher per day at bedtime, aim for a blood level of 150 to 200 micrograms/L) for prophylaxis even if there is no history of headache or a family history of migraine. However, its use may be limited due to side effects in infants and toddlers under age five years. The EKG (particularly the QTc interval) should be monitored. In children under age five years, cyproheptadine is the first choice (or pizotifen outside of the United States).

Coenzyme Q10 (10 to 20 mg/kg per day, or 200 mg twice daily) and L-carnitine (50 or 100 mg/kg per day, or one gram twice daily) have been advocated in prophylaxis, as data suggest that these dietary supplements may be highly effective, and side effects are infrequent and mild.

Topiramate is an unproven therapy that is gaining in popularity due to anecdotal experiences of efficacy, although side effects are frequent and often significant. Abortive therapy with intravenous dextrose (10 percent) and high-dose ondansetron (0.3 to 0.4 mg/kg per dose, or 12 to 16 mg/dose) have been found to be helpful in anecdotal reports in children. It has been recommended that intravenous doses of ondansetron not exceed 16 mg (8 mg for patients ≥75 years old) because of the risk of QT prolongation. Comfort measures during episodes include a dark quiet room, and sedation as appropriate. In addition, patients should be instructed to avoid fasting.

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REFERENCES

1. Li BU. Cyclic vomiting syndrome: light emerging from the black box. J Pediatr 1999; 135:276.
2. Lombard HC. Evrose de la digestion, caracteriseo par des crises periodiques de vomissements et une profonde modification de l'assimilation. Gazette Medicale de Paris 1861:312.
3. Gee S. On fitful or recurrent vomiting. St Bartholomew Hospital Reports 1882; 18:1.
4. Li BU, Lefevre F, Chelimsky GG, 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.
5. Abu-Arafeh I, Russell G. Cyclical vomiting syndrome in children: a population-based study. J Pediatr Gastroenterol Nutr 1995; 21:454.
6. Lucarelli S, Corrado G, Pelliccia A, et al. Cyclic vomiting syndrome and food allergy/intolerance in seven children: a possible association. Eur J Pediatr 2000; 159:360.
7. Prakash C, Staiano A, Rothbaum RJ, Clouse RE. Similarities in cyclic vomiting syndrome across age groups. Am J Gastroenterol 2001; 96:684.
8. Withers GD, Silburn SR, Forbes DA. Precipitants and aetiology of cyclic vomiting syndrome. Acta Paediatr 1998; 87:272.
9. HOYT CS, STICKLER GB. A study of 44 children with the syndrome of recurrent (cyclic) vomiting. Pediatrics 1960; 25:775.

10. Lee WS, Kaur P, Boey CC, Chan KC. Cyclic vomiting syndrome in South-East Asian children. J Paediatr Child Health 1998; 34:568.
11. Haan J, Kors EE, Ferrari MD. Familial cyclic vomiting syndrome. Cephalalgia 2002; 22:552.
12. Prakash C, Clouse RE. Cyclic vomiting syndrome in adults: clinical features and response to tricyclic antidepressants. Am J Gastroenterol 1999; 94:2855.
13. Scobie BA. Recurrent vomiting in adults. A syndrome? Med J Aust 1983; 1:329.
14. Abell TL, Kim CH, Malagelada JR. Idiopathic cyclic nausea and vomiting--a disorder of gastrointestinal motility? Mayo Clin Proc 1988; 63:1169.
15. Fleisher DR, Matar M. The cyclic vomiting syndrome: a report of 71 cases and literature review. J Pediatr Gastroenterol Nutr 1993; 17:361.
16. Boles RG, Zaki EA, Lavenbarg T, et al. Are pediatric and adult-onset cyclic vomiting syndrome (CVS) biologically different conditions? Relationship of adult-onset CVS with the migraine and pediatric CVS-associated common mtDNA polymorphisms 16519T and 3010A. Neurogastroenterol Motil 2009; 21:936.
17. Welch KM. Scientific basis of migraine: speculation on the relationship to cyclic vomiting. Dig Dis Sci 1999; 44:26S.
18. Jernigan SA, Ware LM. Reversible quantitative EEG changes in a case of cyclic vomiting: evidence for migraine equivalent. Dev Med Child Neurol 1991; 33:80.
19. Li BU, Murray RD, Heitlinger LA, et al. Is cyclic vomiting syndrome related to migraine? J Pediatr 1999; 134:567.
20. To J, Issenman RM, Kamath MV. Evaluation of neurocardiac signals in pediatric patients with cyclic vomiting syndrome through power spectral analysis of heart rate variability. J Pediatr 1999; 135:363.
21. Chelimsky TC, Chelimsky GG. Autonomic abnormalities in cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 2007; 44:326.
22. Li BU, Balint JP. Cyclic vomiting syndrome: evolution in our understanding of a brain-gut disorder. Adv Pediatr 2000; 47:117.
23. Boles RG, Chun N, Senadheera D, Wong LJ. Cyclic vomiting syndrome and mitochondrial DNA mutations. Lancet 1997; 350:1299.
24. Boles RG, Adams K, Li BU. Maternal inheritance in cyclic vomiting syndrome. Am J Med Genet A 2005; 133A:71.
25. Wang Q, Ito M, Adams K, et al. Mitochondrial DNA control region sequence variation in migraine headache and cyclic vomiting syndrome. Am J Med Genet A 2004; 131:50.
26. Boles RG, Adams K, Ito M, Li BU. Maternal inheritance in cyclic vomiting syndrome with neuromuscular disease. Am J Med Genet A 2003; 120A:474.
27. Boles RG, Lovett-Barr MR, Preston A, et al. Treatment of cyclic vomiting syndrome with co-enzyme Q10 and amitriptyline, a retrospective study. BMC Neurol 2010; 10:10.
28. 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.
29. Van Calcar SC, Harding CO, Wolff JA. L-carnitine administration reduces number of episodes in cyclic vomiting syndrome. Clin Pediatr (Phila) 2002; 41:171.
30. Zaki EA, Freilinger T, Klopstock T, et al. Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. Cephalalgia 2009; 29:719.
31. Sato T, Igarashi N, Minami S, et al. Recurrent attacks of vomiting, hypertension and psychotic depression: a syndrome of periodic catecholamine and prostaglandin discharge. Acta Endocrinol (Copenh) 1988; 117:189.

32. Taché Y. Cyclic vomiting syndrome: the corticotropin-releasing-factor hypothesis. Dig Dis Sci 1999; 44:79S.
33. Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut 2004; 53:1566.
34. Roche E, Foster PN. Cannabinoid hyperemesis: not just a problem in Adelaide Hills. Gut 2005; 54:731.
35. Sontineni SP, Chaudhary S, Sontineni V, Lanspa SJ. Cannabinoid hyperemesis syndrome: clinical diagnosis of an underrecognised manifestation of chronic cannabis abuse. World J Gastroenterol 2009; 15:1264.
36. Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc 2012; 87:114.
37. Fleisher DR, Gornowicz B, Adams K, et al. Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management. BMC Med 2005; 3:20.
38. Li BU, Issenman RM, Sarna SK. Consensus statement--2nd International Scientific Symposium on CVS. The Faculty of The 2nd International Scientific Symposium on Cyclic Vomiting Syndrome. Dig Dis Sci 1999; 44:9S.
39. 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.
40. Symon DN, Russell G. Abdominal migraine: a childhood syndrome defined. Cephalalgia 1986; 6:223.
41. Fitzpatrick E, Bourke B, Drumm B, Rowland M. Outcome for children with cyclical vomiting syndrome. Arch Dis Child 2007; 92:1001.
42. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal Disorders. Gastroenterology 2016; 150:1380.
43. Schulte-Bockholt A, Kugathasan S, Mesrobian HG, Werlin SL. Ureteropelvic junction obstruction: an overlooked cause of cyclic vomiting. Am J Gastroenterol 2002; 97:1043.
44. Olson AD, Li BU. The diagnostic evaluation of children with cyclic vomiting: a cost-effectiveness assessment. J Pediatr 2002; 141:724.
45. Vanderhoof JA, Young R, Kaufman SS, Ernst L. Treatment of cyclic vomiting in childhood with erythromycin. J Pediatr Gastroenterol Nutr 1993; 17:387.
46. Andersen JM, Sugerman KS, Lockhart JR, Weinberg WA. Effective prophylactic therapy for cyclic vomiting syndrome in children using amitriptyline or cyproheptadine. Pediatrics 1997; 100:977.
47. Benson JM, Zorn SL, Book LS. Sumatriptan in the treatment of cyclic vomiting. Ann Pharmacother 1995; 29:997.
48. Pasricha PJ, Schuster MM, Saudek CD, et al. Cyclic vomiting: association with multiple homeostatic abnormalities and response to ketorolac. Am J Gastroenterol 1996; 91:2228.
49. Boyle CA. Management of menstrual migraine. Neurology 1999; 53:S14.
50. Clouse RE, Sayuk GS, Lustman PJ, Prakash C. Zonisamide or levetiracetam for adults with cyclic vomiting syndrome: a case series. Clin Gastroenterol Hepatol 2007; 5:44.
51. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/39943a-eng.php (Accessed on June 16, 2014).
52. Pareek N, Fleisher DR, Abell T. Cyclic vomiting syndrome: what a gastroenterologist needs to know. Am J Gastroenterol 2007; 102:2832.

Topic 2588 Version 18.0

GRAPHICS

Profile of symptoms in cyclic vomiting syndrome, abdominal migraine, and migraine headaches

	Percentage of patients with symptom		
	CVS	**Abdominal migraine**	**Migraine headache**
Core symptoms			
Vomiting	100	39 to 72	40 to 69
Abdominal pain	3 to 81	100	10 to 55
Headache	38 to 59	31 to 50	100
Associated symptoms			
Lethargy	91		
Pallor	87	90 to 100	23 to 88
Anorexia	74	91 to 98	13 to 93
Nausea	72	73 to 91	46 to 100
Photophobia	32	1 to 42	27 to 81

Adapted from: Li BU, Balint JP. Cyclic vomiting syndrome: Evolution in understanding of a brain-gut disorder. Adv Pediatr 2000; 47:117.

Graphic 80667 Version 3.0

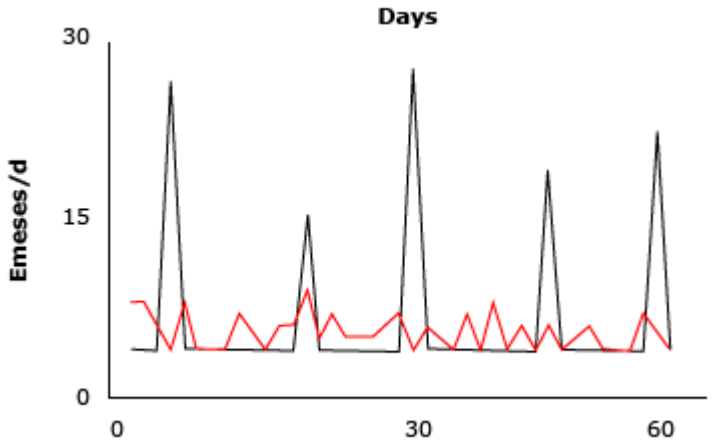
Clinical/epidemiological features of cyclic vomiting syndrome

Feature	Characterization
Female:male ratio	55:45
Age of onset	5.3 years
Morbidity	20 days of missed school per year, 50 percent of patients require intravenous hydration
Symptoms:	
Vomiting	6 times/hr at peak, with bile (76 percent) and blood (32 percent)
Autonomic	Lethargy (91 percent), pallor (87 percent), fever (29 percent), salivation (13 percent)
Gastrointestinal	Abdominal pain (80 percent), retching (78 percent), anorexia (74 percent), nausea (72 percent), diarrhea (36 percent)
Neurologic	Headache (40 percent), photophobia (32 percent), phonophobia (28 percent), vertigo (22 percent)
Temporal pattern	24 to 48 hours duration; 47 percent of patients have episodes at regular intervals, usually two to four weeks; episodes occur at night or early morning in 34 to 60 percent of patients; 98 percent of patients show a stereotypical pattern
Precipitating events	Infection (41 percent), psychological stress (34 percent), dietary (26 percent), menstrual (13 percent), some trigger identified in 68 percent of patients
Natural history	3.4 year duration; 28 percent of patients progress to migraine headaches; predicted 75 percent progress to migraines by age 18 years
Family history of migraine	Present in 82 percent of patients

Adapted from: Li BU, Balint JP. Cyclic vomiting syndrome: Evolution in understanding of a brain-gut disorder. Adv Pediatr 2000; 47:117 and Li BU. Cyclic vomiting: New understanding of an old disorder. Contemp Pediatr 1996; 17:48.

Graphic 62483 Version 3.0

Differences between cyclic and chronic temporal patterns of vomiting



Differences between cyclic and chronic temporal patterns of vomiting can be compared when the number of emeses is plotted over a two-month period. The chronic pattern (red line) is characterized by low-grade, nearly daily episodes whereas the cyclic pattern (black line) is marked by high-intensity episodes every several weeks.

Adapted from: Li BU. New hope for children with cyclic vomiting syndrome. Contemp Pediatr 2002; 19:121.

Graphic 54863 Version 3.0

Differential diagnosis of cyclic vomiting syndrome

Medications and toxic etiologies

- Cancer chemotherapy
  - Severe-cisplatinum, dacarbazine, nitrogen mustard
  - Moderate-etoposide, methotrexate, cytarabine
  - Mild-fluorouracil, vinblastine, tamoxifen
- Analgesics
  - Aspirin
  - Nonsteroidal antiinflammatory drugs
  - Auranofin
  - Antigout drugs
- Cardiovascular medications
  - Digoxin
  - Antiarrhythmics
  - Antihypertensives
  - β-blockers
  - Calcium channel antagonists
- Diuretics
- Hormonal preparations/therapies
  - Oral antidiabetics
  - Oral contraceptives
- Antibiotics/antivirals
  - Erythromycin
  - Tetracycline
  - Sulfonamides
  - Antituberculous drugs
  - Acyclovir
- Gastrointestinal medications
  - Sulfasalazine
  - Azathioprine
- Nicotine
  - CNS active
  - Narcotics
  - Antiparkinsonian drugs
  - Anticonvulsants
- Antiasthmatics
  - Theophylline
- Radiation therapy
- Ethanol abuse
- Jamaican vomiting

Disorders of the gut and peritoneum

- Mechanical obstruction
  - Gastric outlet obstruction
  - Small bowel obstruction
- Functional gastrointestinal disorders
- Gastroparesis
- Chronic intestinal pseudo-obstruction
- Nonulcer dyspepsia
- Irritable bowel syndrome
- Gastrointestinal malignancies
  - Pancreatic adenocarcinoma
  - Inflammatory intraperitoneal disease
  - Peptic ulcer disease
  - Cholecystitis/cholelithiasis/biliary dyskinesia
  - Pancreatitis
  - Hepatitis
  - Crohn disease
  - Mesenteric ischemia
  - Retroperitoneal fibrosis
  - Mucosal metastases
  - Recurrent subacute appendicitis
  - Duodenal atresia/web/diverticulum
  - Choledochal cysts
  - Gastrointestinal infections (pinworms, *Blastocystis hominis*, *Entamoeba histolytica*, *Giardia*, *Gastrospirillum*)

Neurological causes

- Increased intracranial pressure
  - Malignancy
  - Hemorrhage
  - Infarction
  - Abscess
  - Meningitis
  - Congenital malformation
  - Hydrocephalus
  - Pseudotumor cerebri
- Seizure disorders
- Demyelinating disorders
- Emotional responses
- Psychiatric disease
  - Psychogenic vomiting
  - Anxiety disorders
  - Depression
  - Pain
  - Anorexia nervosa
  - Bulimia nervosa
- Labyrinthine disorders
  - Benign positional vertigo
  - Motion sickness
  - Labyrinthitis
  - Tumors
  - Meniere disease
  - Iatrogenic
  - Fluorescein angiography
  - Chronic sinusitis

Endocrinologic and metabolic causes

- Other endocrine and metabolic
  - Uremia
  - Diabetic ketoacidosis
  - Hyperparathyroidism
  - Hypoparathyroidism
  - Hyperthyroidism
  - Addison's disease
  - Acute intermittent porphyria
- Postoperative nausea and vomiting

Miscellaneous causes

- Cardiac disease
  - Myocardial infarction
  - Heart failure
  - Radiofrequency ablation
- Starvation

Urologic/gynecologic disorders

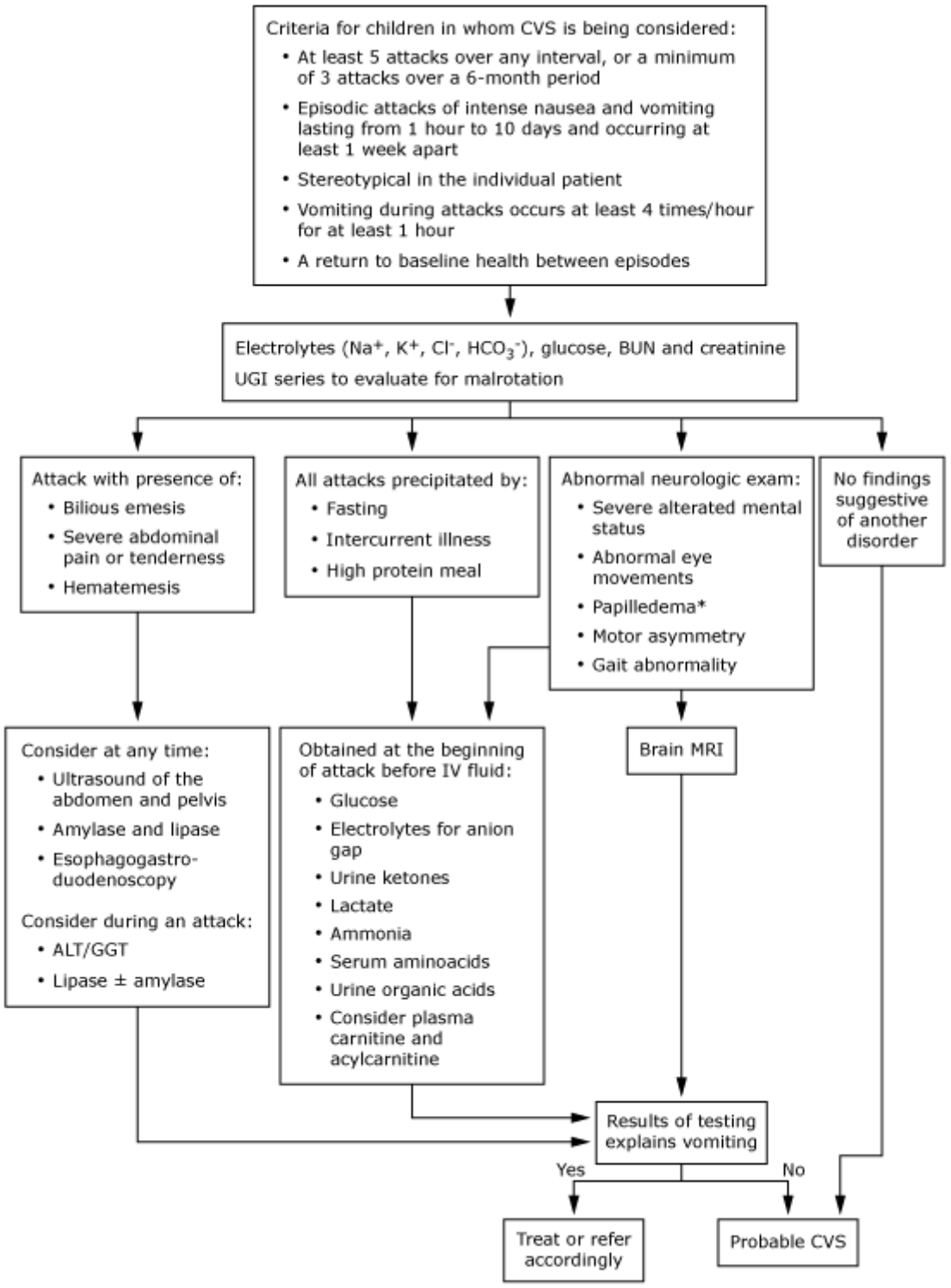
- Urolithiasis
- Ureteropelvic junction obstruction
- Ovarian cyst
- Pregnancy
- Premenstrual syndrome

sickness
Hypervitaminosis
Cannabis hyperemesis syndrome

Original table modified for this publication. Reproduced with permission from: the American Gastroenterological Association. Gastroenterology 2001; 120:263.

Graphic 57659 Version 4.0

Evaluation of cyclic vomiting pattern in children older than 2 years



* May not need metabolic evaluation.

Graphic 53337 Version 8.0

Lifestyle changes in CVS

Lifestyle changes (for one to two months or one to two cycles)
Reassurance (eg, episodes are not self-induced) and anticipatory guidance (eg, natural history)
Avoidance of triggers
Keep a "vomiting diary" of potential precipitating factors
Avoid fasting
Recognize the potential role of excitement as a trigger (eg, downplay big events)
Maintain good sleep hygiene (eg, avoid sleep deprivation)
Avoid triggering foods: chocolate, cheese, monosodium glutamate, antigenic foods
Avoid excessive energy output
Supplemental carbohydrate: for fasting-induced episodes
Provide fruit juices, other sugar-containing drinks
Provide extra snacks between meals, before exertion, or at bedtime
Migraine headache lifestyle interventions
Regular aerobic exercise (avoid overexercising)
Regular meal schedules (ie, avoid skipping meals)
Moderation in consuming or avoidance of caffeine

Graphic 77478 Version 10.0

Prophylactic or preventive medications* in CVS

Children 2 to 5 years old
Antihistamines: cyproheptadine (first choice) and pizotifen (available in UK, Canada)
Cyproheptadine 0.25-0.5 mg/kg/day orally divided twice daily or three times daily (maximum 12 mg per 24 hours). (Available in 2 mg/5 mL liquid).
Side effects: increased appetite, weight gain, sedation
Alternatives: pizotifen (available in UK, Canada)
Beta-blockers: propranolol (second choice)
Propranolol 0.25-1 mg/kg/day orally divided twice daily or three times daily, most often 10 mg twice daily or three times daily. Initiate at 0.25 mg/kg/day and increase every 1-4 weeks in increments of 0.25 mg/kg/day as needed and tolerated. (<35 kg maximum 60 mg per 24 hours. ≥35 kg maximum 120 mg per 24 hours). (Available in liquid).
Monitor: resting heart rate maintain ≥60 bpm
Side effects: lethargy, reduced exercise intolerance
Contraindications: asthma, diabetes, heart disease, depression
Discontinuation: tapered for 1-2 weeks
Children older than 5 years
Tricyclic antidepressants: amitriptyline (first choice)
Amitriptyline begin at 0.25-0.5 mg/kg/day orally at bedtime, increase every 1-4 weeks as needed and tolerated by 5-10 mg, until 1-1.5 mg/kg/day (maximum 75 mg per 24 hours). (For dose >1 mg/kg/day, divide twice daily).
Monitor: √EKG QT_C interval before starting and 10 days after peak dose
Side effects: constipation, sedation, arrhythmia, behavioral changes (especially in young children)
Alternatives: nortriptyline¶ (available in 10 mg/5 mL liquid)
Beta-blockers: propranolol (second choice) - see above
Other agents
Anticonvulsants: phenobarbital¶
Phenobarbital 2 mg/kg/day orally administered at bedtime (maximum 40 mg per 24 hours)
Side effects: sedation, cognitive impairment
Alternatives: topiramate, valproic acid, gabapentin, levetiracetam - consult Pediatric neurologist
Supplements¶
L-carnitine 50-100 mg/kg/day orally divided twice daily or three times daily (maximum 1 g three times daily)
Coenzyme Q_{10} 10 mg/kg/day orally divided twice daily or three times daily (maximum 100 mg three times daily)
Side effects: diarrhea, fishy body odor (for L-carnitine)

* All medication recommendations are made for off-label use.

¶ Limited or no published experience regarding efficacy.

Adapted from: Li BU, Lefevre F, Chelimsky GG, 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. Copyright © 2008 Lippincott Williams & Wilkins.

Graphic 68579 Version 11.0

Supportive and abortive treatment approaches in CVS

Supportive care
Fluid, electrolyte and nutritional management
Infuse 10% dextrose, 0.45% (half normal) saline solution and potassium chloride as appropriate at 1.5 times maintenance fluid rates OR through a Y-connector 10% dextrose infusion at one times maintenance and normal saline at 0.5 times maintenance
If no enteral intake for 3-5 days, initiate peripheral parenteral nutrition with 1.5 g of amino acids/kg/day and energy units above the catabolic threshold of 55-70 kcal/kg/day
Antiemetic ($5HT_3$ antagonist) agents
Ondansetron 0.3-0.4 mg/kg/dose intravenously every 4-6 hours (maximum 16 mg per dose if younger than 75 years old, 8 mg per dose if 75 years old or older)
Side effects: constipation
Alternatives: granisetron
Sedatives
Diphenhydramine 1-1.25 mg/kg/dose intravenously every 6 hours (maximum 50 mg per dose)
Lorazepam 0.05-0.1 mg/kg/dose intravenously every 6 hours (maximum 2 mg per dose)
Side effects: respiratory depression, hallucinations
Chlorpromazine 0.5-1 mg/kg/dose intravenously every 6 hours + diphenhydramine (see above) intravenously:
<5 years or <23 kg maximum 10 mg per dose, 40 mg per 24 hours chlorpromazine
>5 years or ≥23 kg maximum 18 mg per dose, 75 mg per 24 hours chlorpromazine
Side effects: dystonic reactions with chlorpromazine alone
Analgesics (nonsteroidal and narcotic) agents
Ketorolac 0.4-1 mg/kg intravenously every 6 hours x 48 hours (maximum 30 mg per dose, maximum 120 mg per 24 hours); avoid in renal insufficiency or dehydration
Side effects: gastrointestinal hemorrhage
Alternatives: narcotics, intravenous morphine or fentanyl by bolus or by patient-control infusion
Treatment of specific signs and symptoms: epigastric pain, diarrhea, and hypertension
Epigastric pain: acid suppression by H_2RAs or PPIs, (eg, intravenous ranitidine, pantoprazole)
Diarrhea: antidiarrheals (eg, loperamide)
Hypertension: short-acting ACE inhibitors (eg, captopril)
Treatment of specific complications
Dehydration and electrolyte deficit: replace calculated deficits
Metabolic acidosis: determine cause and treat accordingly
SIADH: restrict free water intake
Hematemesis: intravenous H_2RAs or PPIs
Weight loss: nasogastric or parenteral nutrition
Abortive care
Antimigraine (triptan) agents
Sumatriptan: 20 mg once intranasally as early as possible at episode onset for children 12 years and older (maximum 40 mg/24 hours)
Side effects: neck pain/burning, coronary vasospasm
Contraindications: basilar artery migraine
Recovery and refeeding
Feed ad libitum when child declares episode is over

H_2RAs: histamine-2 receptor antagonists; PPIs: proton pump inhibitors; ACE: angiotensive converting enzyme; SIADH: syndrome of inappropriate antidiuretic hormone.

Adapted from: Li BU, Lefevre F, Chelimsky GG, 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. Copyright © 2008 Lippincott Williams & Wilkins.

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Sample treatment protocol order sheet for a child having an acute attack of CVS

In Emergency Department and in-hospital settings, an example of a regimen would include:
Darkened, quiet room, take vital signs every 4-6 hours
If child is dehydrated, rehydrate with initial intravenous fluid bolus of 10 mL/kg normal 0.9% saline and repeat as clinically necessary
Infuse 10% dextrose 0.45% (half normal) saline solution with potassium chloride as appropriate at 1.5 times maintenance rates
Intravenous ondansetron 0.3 mg/kg/dose every 6 hours x 24 hours (maximum 20 mg per dose)
Intravenous lorazepam 0.05 mg/kg/dose every 6 hours x 24 hours (maximum 2 mg per dose)
If child has moderate to severe abdominal pain, intravenous ketorolac 0.5 to 1 mg/kg/dose (maximum 30 mg per dose) every 6 hours x 24 hours (avoid in renal insufficiency or prior to hydration if dehydrated)
Admit child if >5 percent dehydrated, no urine output >12 hours, Na^+ <130 mEq/L, anion gap >18 mEq/L, or inability to stop emesis
Allow oral fluid intake

%: percent.

Adapted from: Li BU, Lefevre F, Chelimsky GG, 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.

Graphic 59920 Version 10.0

Family support and informational resources

Cyclic Vomiting Syndrome Association (CVSA)
2819 W Highland Blvd, Milwaukee, WI 53208 Phone: 414-342-7880 Fax: 414-342-8980 cvsa@cvsaonline.org, www.cvsaonline.org
International Foundation for Functional Gastrointestinal Disorders (IFFGD)
PO Box 170864, Milwaukee, WI 53217 Phone: 414-964-1799 Children: http://www.aboutkidsgi.org Adults: http://www.iffgd.org
Migraine Awareness Group (MAGNUM)
113 S Saint Asaph, Suite 300, Alexandria, VA 22314 Phone: 703-739-9384 www.migraines.org
National Organization for Rare Disorders
55 Kenosia Ave, PO Box 1968, Danbury, CT 06813-1968 Phone: 203-744-0100, 800-999-6673 TDD number: 203-797-9590 Fax: 203-798-2291 www.nord-rdb.com
United Mitochondrial Disease Foundation
PO Box 1151, Monroeville, PA 15146-1151 Phone: 412-793-8077 www.umdf.org

Graphic 74868 Version 9.0

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Conflict of interest policy