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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⁺, Mg⁺) 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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