

## Clinical Report

# North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Consensus Statement on the Diagnosis and Management of Cyclic Vomiting Syndrome

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### ABSTRACT

Cyclic vomiting syndrome (CVS) is a disorder noted for its unique intensity of vomiting, repeated emergency department visits and hospitalizations, and reduced quality of life. It is often misdiagnosed due to the unappreciated pattern of recurrence and lack of confirmatory testing. Because no accepted approach to management has been established, the task force was charged to develop a report on diagnosis and treatment of CVS based upon a review of the medical literature and expert opinion. The key issues addressed were the diagnostic criteria, the appropriate evaluation, the prophylactic therapy, and the therapy of acute attacks. The recommended diagnostic approach is to avoid "shotgun" testing and instead to use a strategy of targeted testing that varies with the presence of 4 red flags: abdominal signs (eg, bilious vomiting, tenderness), triggering events (eg, fasting, high protein meal), abnormal neurological examination (eg, altered mental status, papilledema), and progressive

worsening or a changing pattern of vomiting episodes. Therapeutic recommendations include lifestyle changes, prophylactic therapy (eg, cyproheptadine in children 5 years or younger and amitriptyline for those older than 5), and acute therapy (eg, 5-hydroxytryptamine receptor agonists, termed triptans herein, as abortive therapy, and 10% dextrose and ondansetron for those requiring intravenous hydration). This document represents the official recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition for the diagnosis and treatment of CVS in children and adolescents. *JPGN* 47:379–393, 2008. **Key Words:** CVS—Cyclic vomiting syndrome—Diagnosis—Treatment. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Cyclic vomiting syndrome (CVS) is a disorder characterized by recurrent, discrete, self-limited episodes of vomiting and is defined by symptom-based criteria and the absence of positive laboratory, radiographic, and endoscopic testing (1–3). Affected children are more often girls than boys (60:40), of elementary school age (ranging from infants to young adults), and more often white. Despite this being an episodic disorder, a large case series found that although it affects only 5% to 15% of a child's lifetime, it results in 24 days of missed school and an annualized cost of care of \$17,035 (4). Affected children usually experience a stereotypical pattern of vomiting typified by a consistent time of onset, duration,

and symptoms. The vomiting is intense (median 6 times/hour at peak), often bilious (83% in some series), and accompanied by disabling nausea (4). The resulting dehydration necessitates a high rate of intravenous replenishment. The accompanying symptoms including pallor, listlessness, anorexia, nausea, retching, abdominal pain, headache, and photophobia may make it difficult to distinguish episodes of CVS from other causes of acute abdomen and altered consciousness. Episodes often commence in the early morning (eg, 3–4 AM or upon awakening) and are frequently triggered by psychological (eg, birthdays, holidays, school-related) and physical stress (eg, infections, lack of sleep, menstrual periods). CVS starts commonly in early childhood, and the vomiting symptoms may abate with the onset of classical migraine headaches during adolescence. Less commonly

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the condition persists into adulthood or starts in adulthood (5–7).

The etiology and pathogenesis remain unknown but there appears to be a strong link between CVS and migraine, based upon similarities in symptoms, common coexistence of both conditions in the same individual, a high family prevalence of migraine in patients with CVS, and the effectiveness of antimigraine therapy (8–11). Postulated mechanisms include episodic dysautonomia, mitochondrial DNA mutations that cause deficits in cellular energy production and/or heightened hypothalamic stress response that activates the emetic response (12–14). CVS presents with vomiting and a variety of associated symptoms that could represent either differing levels of severity or even distinct pathophysiological mechanisms. These presentations include subgroups such as migraine-associated, menses-associated, and Sato subtype (15,16) with episode-associated hypertension and elevated adrenocorticotropin hormone.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) appointed a task force to develop a consensus report for CVS to improve the recognition and treatment of a disorder that lacks standard medical approaches. An absence of controlled trials and high-quality scientific evidence in this disorder necessitated that these recommendations be based primarily upon small clinical trials and expert opinion. Despite these limitations, the committee used a rigorous review process, akin to that used for development of clinical practice guidelines, to provide useful recommendations for patient management based upon the available literature and clinical experience. These recommendations are intended for use by pediatricians, family physicians, pediatric gastroenterologists, pediatric neurologists, and emergency department physicians. Although there appear to be an increasing number of adults diagnosed with this disorder, it was beyond the purview of this task force to develop management principles for adult patients.

## METHODOLOGY

The expert task force reviewed the evidence and proposed recommendations for the evaluation and treatment of CVS. The task force consisted of 9 experts drawn from the fields of pediatric gastroenterology, pediatric neurology, pediatric genetics, and epidemiology. This report was developed by consensus of the CVS task force, using a modified Delphi technique for algorithm development.

A systematic review of the literature was performed to identify all of the published articles through 2007 that contained primary data on the epidemiology, clinical features, natural history, and/or treatment of CVS. Particular attention was directed toward articles

that addressed the efficacy of treatment modalities for CVS. The task force addressed four primary questions:

- *How is CVS defined?* The task force considered the most appropriate clinical and laboratory data to be used in diagnosing CVS. Recognizing the lack of definitive laboratory markers, the heterogeneous nature of the disorder, and the variability of diagnostic criteria in the literature, the task force developed an operational definition of CVS by nominal group technique.
- *What is the appropriate laboratory, radiographic, and endoscopic evaluation in children with a pattern of cyclic vomiting?* After discussion that addressed the known differences among international pediatric gastroenterologists as to the extent of laboratory evaluation that is performed in patients with suspected CVS, the task force focused on the following: the initial screening evaluation in an undifferentiated patient with episodic pattern of vomiting meeting the cyclic vomiting criteria; the sensitivity of the various tests for serious surgical and metabolic disorders; and alarm symptoms that should instigate a more thorough laboratory evaluation. The task force considered but did not focus on the issues of subdividing patients by age, sex, race, ethnicity and clinical subgroups (eg, neurologically impaired).
- *In patients with CVS, does prophylactic treatment improve long-term outcomes, as compared to no treatment or alternative treatment options?* The task force evaluated the efficacy of prophylactic treatment including lifestyle changes such as avoidance of triggers, reassurance, education, and family support, and antimigraine and anticonvulsant medications. The outcomes of prophylactic treatment included frequency of subsequent episodes, duration and severity of episodes including number of emeses, nausea, and other constitutional symptoms. The task force did divide treatment groups by age above and below 5 years, but did not focus on other subgroups.
- *During an acute attack of CVS, does treatment improve outcomes, as compared to no treatment or alternate treatment options?* The task force evaluated the efficacy of abortive and supportive treatment including intravenous fluid(s) containing dextrose, as well as medication including antiemetics, antimigraine triptans, sedatives, and nonsteroidal anti-inflammatory drugs. The outcomes of the acute attack included length of episode, number of emeses, severity of nausea, and other constitutional symptoms. The task force did consider but did not focus on issues of treatment of various subgroups and criteria for successful treatment.

### Literature Search Strategy

MEDLINE was searched via PubMed using the following terms: (“cyclic vomiting” OR “cyclic vomiting syndrome” OR “cyclical vomiting” OR “CVS” OR “abdominal migraine” OR “periodic syndrome” OR “biliary attacks” OR “recurrent vomiting”) AND (pediatrics OR children OR infants) NOT Review [Publication Type] during the years 1980 to the present. The electronic search was supplemented with the related articles function in PubMed; with a hand-search of recent bibliographies; and by consultation with experts. Using this strategy, 236 citations were identified. The abstracts of all of the citations were reviewed, and potentially relevant articles were identified that included patients with CVS and reported primary data, other than in case report format. Using these criteria, a total of 67 full-length articles were retrieved for full review.

Studies were selected for final inclusion in the evidence base, if they met the following criteria: full-length article published in the peer-reviewed literature between the years 1980 and 2007; included patients with CVS, using parameters of periodicity of attacks, including healthy intervals between attacks, characteristic pattern of symptoms during attack, and lack of other explanation(s) for nausea/vomiting; and evaluated 1 or more of the specified treatments for either abortive therapy or prophylactic therapy and reports on 1 or more relevant outcomes. Following application of these selection criteria, a total of 12 articles met the criteria for inclusion in review of evidence.

The study qualities were assessed as follows. Levels of evidence (ranging from I—randomized controlled trial to III—expert opinion) were assigned according to the system originally developed by the Canadian Task Force on the Periodic Health Examination (17) and refined by the US Preventative Services Task Force (18). For single-arm studies, 4 quality indicators (relevant, representative patient population; uniform, unbiased treatment delivery; most important outcomes measures represented; appropriate statistical analysis) were used to assign an overall quality of “good” (meets all criteria), “fair” (does not meet all criteria but no fatal flaws), or “poor” (study has fatal flaws for 1 or more indicators). From these levels, grades of recommendations were derived (A—level I evidence to D—expert opinion only). In all of the studies, the grades of recommendation were D.

### CONSENSUS DIAGNOSTIC CRITERIA

Recognizing the lack of definitive criteria, the heterogeneous nature of the disorder, and the variability of diagnostic criteria in the literature, the task force developed an operational definition of CVS. Using a combination of expert opinion, definitions used in the literature, and the clinical and research experience of the task force,

**TABLE 1.** *Criteria for cyclic vomiting syndrome\**

At least 5 attacks in any interval, or a minimum of 3 attacks during a 6-mo period
Episodic attacks of intense nausea and vomiting lasting 1 h–10 days and occurring at least 1 wk apart
Stereotypical pattern and symptoms in the individual patient
Vomiting during attacks occurs at least 4 times/h for at least 1 h <sup>†</sup>
Return to baseline health between episodes
Not attributed to another disorder

\* All of the criteria must be met to meet this consensus definition of CVS.

<sup>†</sup> This quantitative threshold was observed in a series of 35 patients with CVS when compared to patients with chronic vomiting (22). Some task force members recognized that atypical CVS may exist with less frequent vomiting. However, the task force opted for this definition to ensure appropriate specificity.

nominal group technique was used to achieve the consensus diagnostic criteria shown in Table 1. The committee considered adoption of the Rome III criteria for CVS (2 periods of intense nausea and vomiting and return to normal health). However, the lack of specificity raised concerns about the utility of that definition in this report (19–21).

### DIAGNOSTIC APPROACH TO RECURRENT, EPISODIC VOMITING

A pattern of recurrent, episodic vomiting in children that fulfills the revised historical criteria listed in Table 1 is likely (about 90%) to be ultimately diagnosed as idiopathic CVS (22). The challenge to the practitioner is to differentiate individuals with specific and serious underlying causes of vomiting (about 10%) for which prompt treatment may alter outcomes (23). Testing to exclude all of the possible diagnoses would subject many children to unnecessary and costly radiographic and endoscopic procedures (24). Therefore, the diagnostic principles outlined below are intended to help identify those children with a cyclic vomiting pattern between ages 2 and 18 years at the greatest risk for having an organic cause. Although children younger than 2 years may have CVS, serious underlying metabolic and surgical disorders are more frequent and more difficult to diagnose in that age range.

There are no specific laboratory markers to diagnose CVS. The diagnostic criteria were modified by nominal group technique from previously published consensus criteria (21) and those established by the Headache Classification Subcommittee of the International Headache Society (25) (Table 1). The diagnosis of CVS is thus based upon the fulfillment of these criteria in the absence of another explanation for the symptoms. Clinicians experienced in evaluating CVS may treat without performing an extensive evaluation, but expert opinion

supported performing screening tests in all children with a cyclic vomiting pattern just before administration of intravenous fluids to include electrolytes ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ), glucose, and upper gastrointestinal radiographs to exclude malrotation (26–28). An abdominal ultrasound to rule out transient hydronephrosis, preferably during a crisis, could also be considered in refractory cases (29,30). If a patient has hyponatremia or hypoglycemia, then further evaluation should be performed to exclude Addison disease (31,32) and disorders of fatty acid oxidation (33). A thorough history and physical examination at presentation helps identify those children in whom further diagnostic testing is prudent. Suspicious symptoms and physical findings include the following:

1. Bilious vomiting, abdominal tenderness and/or severe abdominal pain
2. Attacks precipitated by intercurrent illness, fasting, and/or high protein meal
3. Abnormalities on neurological examination including severe alteration of mental status, abnormal eye movements, papilledema, motor asymmetry, and/or gait abnormality (ataxia)
4. Progressively worsening episodes or conversion to a continuous or chronic pattern

Depending upon the presenting symptoms and signs other than vomiting, different diagnostic approaches are recommended as illustrated in Fig. 1.

### Evaluation of Children With Cyclic Vomiting Pattern and Alarm Symptoms or Signs

#### *Bilious Emesis, Severe Abdominal Pain, and/or Hematemesis*

Although children with CVS frequently have bilious emesis (83%) and/or severe abdominal pain (80%) (4), serious surgical and nonsurgical disorders can present similarly. These disorders include intermittent bowel obstruction from malrotation with volvulus (26,27,34) and postoperative adhesions/strictures, gallbladder disease (35), choledochal cyst (36), hepatitis, pancreatitis, or uretero-pelvic junction obstruction (30). When bile-stained vomitus or severe discomfort are present, the task force recommends, in addition to an upper gastrointestinal radiograph, obtaining amylase (37) and lipase (38) to detect pancreatitis, alanine aminotransferase and  $\gamma$ -glutamyltransferase to screen for hepatitis and gallbladder disease, and an abdominal ultrasound and/or abdominal CT scan to evaluate the biliary (39) and urinary tracts (40). Abnormal results warrant further testing. If test results do not suggest an alternate diagnosis, then empirical treatment of CVS is recommended.

Recurrent episodes of vomiting accompanied frequently by small amounts of hematemesis raise the question about the role of esophagogastroduodenoscopy

in the evaluation of these children. Because the endoscopic biopsies usually do not reveal an etiologic cause of the vomiting and typically demonstrate mild esophagitis or prolapse gastropathy as a cause of the acute bleeding, the task force did not recommend a routine endoscopy unless patients present with chronic symptoms between episodes that are suggestive of a specific disorder (peptic/bacterial, allergic, inflammatory, or celiac disease), or large amounts of hematemesis warrant endoscopic intervention (41). If histological evidence of mild to moderate esophagitis is found, then a standard 4- to 6-week course of acid suppression (eg, proton pump inhibitor) is warranted.

Acute intermittent porphyria occurs infrequently and generally does not present before puberty (42). It can present with recurrent vomiting and abdominal pain, mimicking CVS, but usually has 1 or more symptoms of anxiety, depression, hallucination, seizures, cranial nerve weakness, and paresis of the extremities. The diagnosis can be confirmed by finding an increased urinary  $\delta$ -aminolevulinic acid and porphobilinogen in a spot urine during the episode (43).

#### *Attacks Precipitated by Intercurrent Illness, Fasting, and/or a High Protein Meal*

Vomiting induced by metabolic disorders, including disorders of fatty acid oxidation, the urea cycle, organic and amino acid metabolism, and mitochondrial energy metabolism often follow a catabolic state induced by acute illness, fasting, or a high protein meal. Fasting can result from the anorexia and vomiting that accompanies mild viral upper respiratory or gastrointestinal infections, dieting, or presurgical preparation. Although severe enzymatic deficiencies generally present immediately after birth, partial enzymatic defects tend to affect toddlers.

A symptomatic metabolic disorder constitutes a medical emergency with substantial risks for morbidity and mortality if appropriate treatment is not instituted promptly. If a metabolic disorder is suspected, then blood and urine for testing should be obtained immediately (Fig. 1), followed by delivery of 10% dextrose-containing intravenous fluid at a rate of 1.5 times maintenance (simultaneously with fluid boluses as necessary). Consultation with a metabolic specialist should be considered.

In partial urea cycle enzyme deficiencies, ammonia accumulation may present following the ingestion of a high protein meal or with fasting. Although both sexes can be affected, most are heterozygote girls with partial ornithine transcarbamylase deficiency because the gene is located on the X chromosome. A urea cycle disorder is suggested by a plasma ammonia level of  $\geq 150 \mu\text{m/L}$  when symptomatic. Amino and organic acidemias often present in the first days of life, but a subset with

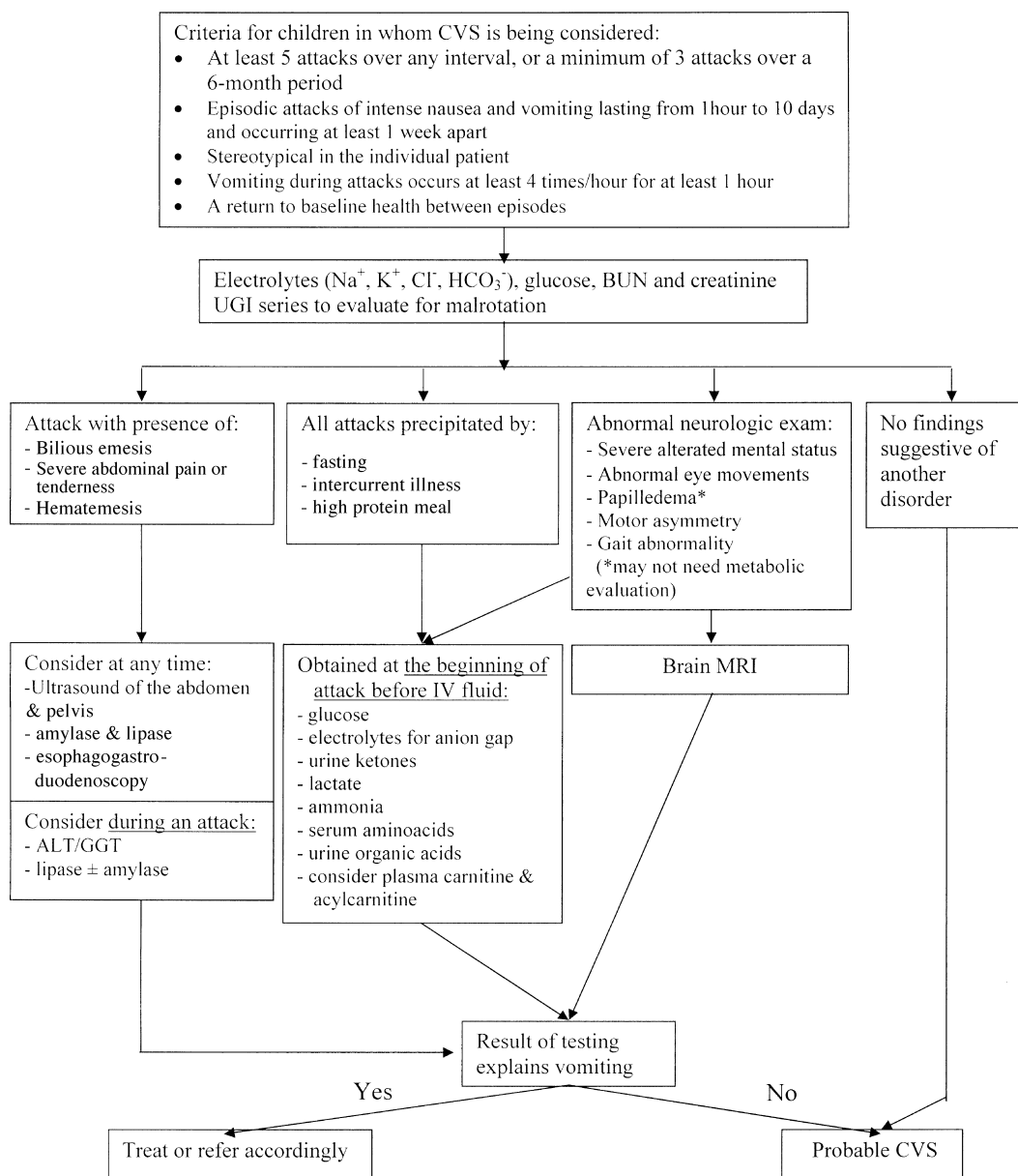


FIG. 1. Evaluation of cyclic vomiting pattern in children older than 2 y.

partial enzymatic deficiencies remain silent until an illness-related fast precipitates symptoms that can include episodes of vomiting. Altered mental status (see “Abnormalities on Neurological Examination”), severe anion gap metabolic acidosis, substantial ketosis, and/or an unusual odor are possible clues to the presence of the underlying condition. Developmental and growth delay are present in many but not all cases and can be subtle. Fatty acid oxidation disorders, including medium-chain acyl-coenzyme A dehydrogenase deficiency, can present with a cyclic vomiting pattern.

The diagnosis of these disorders is established with plasma amino acid and urine organic acid analyses. The sensitivity of metabolic testing, both screening and sophisticated analyses, is improved when performed early in an acute episode before dextrose-containing intravenous fluid is given (33). Analyses of plasma acylcarnitines and urine acylglycines are more sensitive than urine organic acids in fatty acid oxidation disorders (44), and may be diagnostic even when asymptomatic (33). If any of the screening tests are abnormal, then the patient should be referred to a metabolic specialist for further evaluation.

Biochemical, enzymatic, and pedigree (maternal inheritance) data suggests that some degree of mitochondrial dysfunction is present in many cases of CVS, and although not the sole cause, may contribute via insufficient cellular energy production (12,45,46). It is typical to find mild-to-moderate degrees of an anion gap metabolic acidosis (calculated serum  $\text{Na}^+$  minus  $\text{Cl}^-$  minus  $\text{HCO}_3^-$  is often 15–20 mg/dL), lactic acidosis, urinary ketosis (early in an episode and thus not a direct result of fasting), and/or hypoglycemia during vomiting episodes. These findings are consistent with CVS and by themselves do not necessitate a comprehensive metabolic workup. However, when encountered, quantitative urine organic acids and plasma amino acid analyses obtained early in an episode can confirm mild mitochondrial dysfunction by finding elevated urine ketones, Krebs cycle intermediates, and/or dicarboxylic acids, and exclude other metabolic disorders. When obtained either while asymptomatic or after several hours of intravenous dextrose, urine organic acids are typically normal.

In some cases, episodic vomiting may be 1 manifestation of mitochondrial disease; vomiting episodes can then be associated with a severe anion gap metabolic acidosis ( $>20$  mg/dL), insulin resistance, and/or multi-system failure (eg, cardiomyopathy, seizures).

#### *Abnormalities on Neurological Examination*

Progressive or focal neurological findings as well as new-onset ataxia, abnormal eye movements, papilledema, motor asymmetry, gait abnormality, developmental regression or stagnation, or recent personality changes are not typical of CVS and should alert the clinician to evaluate for increased intracranial pressure or a metabolic disorder. Intracranial pressure can be due to a posterior fossa or hypothalamic tumor, Chiari malformation, hydrocephalus, or subdural hematoma. Although one fourth of children with brain tumors initially present with vomiting, the majority will have other symptoms such as headache (often occipital), seizures or behavioral changes, and demonstrable neurological signs of papilledema, abnormal eye movements, motor asymmetry, gait ataxia, or abnormal deep tendon reflexes (47). In cerebellar medulloblastoma, the most common brain tumor in childhood, about three fourths of patients present with chronic vomiting, rarely cyclical, usually along with other signs such as papilledema, abnormal eye movements, or ataxia (48).

If the vomiting is associated with progressive focal or diffuse neurological symptoms or signs, then neuroimaging with magnetic resonance imaging (MRI) is warranted. MRI is superior to CT scanning for visualization of the posterior fossa. Skull x-rays have no value in this clinical setting.

Rarely, certain forms of complex partial seizures (eg, temporal lobe, benign occipital epilepsy) may be

associated with episodic vomiting. Some degree of transient alteration of mental status, postictal confusion, and abnormal involuntary movements will likely be present. If seizures are suspected, then electroencephalography during awake, drowsy, and sleep states is indicated (49,50).

The most difficult sign to clarify is alteration of mental status. Children with CVS often have altered consciousness during episodes that parents describe as a “conscious coma,” in which the child is lethargic, listless, withdrawn, disoriented, and/or difficult to arouse. Because acute or episodic neurological or metabolic diseases commonly produce distortions of mental status, it is important to distinguish true encephalopathy from the listlessness typical of CVS. In CVS, the child is usually oriented and able to respond appropriately to commands, but prefers not to because of incapacitating nausea. In metabolic encephalopathy, the patient is frequently disoriented, confused, excessively irritable, and/or difficult to arouse. With hyperammonemic states, a rapidly shifting mental status and/or psychosis also can be observed.

Static nonfocal neurological findings, including global developmental delay, generalized seizures, and/or hypotonia are found in up to 25% of CVS cases. When these findings are present, the term “CVS+” has been applied (12,45,51), which predicts an earlier age of onset for vomiting episodes, and a 3- to 8-fold increased prevalence for certain dysautonomic-related (migraine, chronic fatigue, regional pain syndromes) and constitutional (growth retardation and birth defects) disorders. Because these static nonfocal neurological findings are also present in many metabolic disorders associated with episodic vomiting, the expert task force recommends that a screening metabolic evaluation be performed to include quantitative plasma amino acids and quantitative urine organic acids obtained early in an episode (Fig. 1).

#### *Suggested Evaluation in Patients at Higher Risk for Neurometabolic Disease*

The task force recommends that children with cyclic vomiting be evaluated for a possible metabolic or neurological disorder if any of the following conditions are met (Fig. 1):

- Presentation under age 2 years (with cyclic vomiting or comorbidities below)
- Vomiting episodes associated with intercurrent illnesses, prior fasting, increased protein intake
- Any neurological finding: ataxia, dystonia, or another gait disturbance; mental retardation; seizure disorder; or acute encephalopathy (including true lethargy, severe irritability, confusion, psychosis or rapidly changing/unstable mental status)

- Laboratory metabolic findings: hypoglycemia, substantial anion gap metabolic acidosis, respiratory alkalosis, or hyperammonemia

A referral to a specialist in metabolic disorders and/or a neurologist is suggested for patients with any of the above findings.

*No Finding Suggestive of Another Disorder*

An initial trial of empiric therapy can be considered in children with a cyclic pattern of vomiting and no alarm findings in their history and physical examination. If the patient responds to therapy with at least a 50% reduction in episode frequency and/or severity of vomiting during attacks, then further evaluation is not required. If the patient does not improve with initial therapy during a 2-month period, further evaluation is recommended.

Although uncommon as a cause of episodic vomiting, Munchausen by proxy syndrome may mimic CVS. The perpetrator may describe vomiting episodes in a dehydrated child who has had feedings withheld or may give the victim syrup of ipecac to induce vomiting (52). However, patients have been inappropriately diagnosed with Munchausen by proxy when in fact CVS was causing recurrent vomiting.

**TREATMENT APPROACH TO RECURRENT, EPISODIC VOMITING**

**Overall Approach**

The clinical course of CVS can be divided simply into the episode phase and the well phase, during which the child returns to his or her normal or baseline state of health (4). The episode phase is further divided into the prodrome as the child becomes ill up to the point at which vomiting begins, the vomiting phase, and the recovery phase during which the vomiting ceases and the child returns to baseline health. Each phase has therapeutic implications (53). During the well phase, the avoidance of identified triggers can lead to fewer episodes. Treatment with abortive therapy as early as possible in the prodrome or vomiting phase may terminate the attack. If the vomiting phase becomes full blown, then supportive therapy at home or in the hospital is focused on providing relief from nausea, vomiting, and abdominal pain. If abortive therapy fails consistently or if episodes are frequent and/or severe, then daily prophylactic therapy to prevent subsequent episodes is recommended.

The management of CVS requires an individually tailored regimen that takes into consideration the clinical course, frequency and severity of attacks, and resultant disability balanced against the potential side effects of treatment. The 2 key treatment arms are prophylactic (or preventive) measures and medications administered

**TABLE 2.** Family support and informational resources

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<b>Cyclic Vomiting Syndrome Association (CVSA)</b> , 2819 W Highland Blvd, Milwaukee, WI 53208, P 414-342-7880, F 414-342-8980, <a href="mailto:cvsa@cvsaonline.org">cvsa@cvsaonline.org</a> , <a href="http://www.cvsaonline.org">www.cvsaonline.org</a>
<b>Gastroparesis and Dysmotilities Association (GDPA)</b> , 5520 Dalhart Hill NW, Calgary, AB, Canada T3A 1S9, P 403-247-3215, <a href="http://www.gpda.net">www.gpda.net</a>
<b>International Foundation for Functional, Gastrointestinal Disorders (IFFGD)</b> , PO Box 170864, Milwaukee, WI 53217, P 414-964-1799, Children: <a href="http://www.aboutkidsgi.org">http://www.aboutkidsgi.org</a> , Adults: <a href="http://www.iffgd.org">http://www.iffgd.org</a>
<b>Migraine Awareness Group (MAGNUM)</b> , 113 S Saint Asaph, Suite 300, Alexandria, VA 22314, P 703-739-9384, <a href="http://www.migraines.org">www.migraines.org</a>
<b>National Organization for Rare Disorders</b> , 55 Kenosia Ave, PO Box 1968, Danbury, CT 06813-1968 P 203-744-0100, 800-999-6673, TDD Number 203-797-9590, F 203-798-2291, <a href="http://www.nord-rdb.com">www.nord-rdb.com</a>
<b>United Mitochondrial Disease Foundation</b> , PO Box 1151, Monroeville, PA 15146-1151, P 412-793-8077, <a href="http://www.umdf.org">www.umdf.org</a>

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between attacks, and acute and supportive interventions given during attacks. Despite the absence of US Food and Drug Administration–approved medications for use in children with CVS, the task force recommendations below include off-label uses. In the larger context of pediatric medication use, more than 70% of prescribed medications lack pediatric approval (54).

The experience of a recurring, unpredictable, and disruptive disorder that results in frequent encounters with emergency departments and hospitals and repeated misdiagnosis (mean time to diagnosis 2.6 years) often causes families frustration. Even after diagnosis, uncertainty about effective therapy and inadequate data on clinical course and prognosis affect a family’s ability to cope with this challenging disorder. To provide information and support that may not be available locally, families should be strongly encouraged to obtain information from one of several available online and print sources (Table 2), to seek consultation from a pediatric specialist familiar with management of CVS, and to contact the Cyclic Vomiting Syndrome Association for ongoing support.

**Prophylactic Measures**

There is a paucity of controlled data on the prophylactic treatment of CVS (mostly case series—level II evidence) (Table 3). The existing evidence consists of small, retrospective clinical series that evaluate symptomatic responses to medications. The treatment recommendations are based on limited evidence (level II) and consensus opinion (level III, grade D) of an expert task force of clinicians with broad experience with CVS.

During the well phase, lifestyle changes such as avoidance of excessive excitement, energy-depleted states (eg, fasting, illness), sleep deprivation, triggering foods (eg, chocolate, cheese), menses, and motion sickness may reduce episode frequency. If episodes occur frequently

**TABLE 3.** Summary of evidence for efficacy of prophylactic treatment of CVS

Treatment	No. of studies	No. of patients	Level of evidence	Study quality	Response rates			Comments
					100%*	50%–100%	<50%	
Propranolol (11,12,62,63)	4	101	II-3	Fair (2/4) Poor (2/4)	75% (18/24)	65% (66/101)	35% (35/101)	
Cyproheptadine (11,12,63,64)	4	69	II-3	Fair (3/4) Poor (1/4)	40% (8/20)	61% (42/69)	39% (27/69)	
Amitriptyline (5,11,12,64)	4	64	II-3	Fair (3/4) Poor (1/4)	73% (16/22)	81% (52/64)	19% (12/64)	
Pizotifen (67)	1	16	II-1	Poor	↓ 66% in number of days of abdominal pain			RCT of poor quality; $P < 0.01$ for all comparisons
Pizotifen (83)	1	20	II-3	Poor	70% (14/20)	100% (20/20)	0% (0/20)	20% response rate in no-treatment comparison group
Erythromycin (84)	1	20	II-3	Poor	65% (13/20)	75% (15/20)	25% (5/20)	
Other tricyclic antidepressants (5)	1	15	II-3	Fair	NR	67% (10/15)	33% (5/15)	
L-carnitine (71)	1	6	II-3		↑ 87% in average time between episodes			Pre- and post-comparison, statistical testing not reported

NR, none reported.

\*The % reduction in numbers of episodes following treatment.

(eg, more than every 1–2 months), are severe enough to cause repeated hospitalization and school absences, and/or fail to respond to abortive therapy, preventive prophylactic pharmacotherapy is recommended.

Because fear and anticipation of future episodes can trigger episodes of CVS, the use of reassurance and anticipatory guidance may help reduce the frequency of attacks. This guidance includes confirming that the attacks are not self-induced and the child will typically improve with age, and providing an individualized management protocol.

### Lifestyle Changes

Although there are no published trials that evaluate the impact of lifestyle alterations on CVS attacks, the task force's consensus experience is that lifestyle changes reduce episode frequency in children with CVS (Table 4). Fleisher reported that 70% of patients initially respond to consultation alone without drug therapy by reduced episode frequency (55). This response may result from alleviation of known precipitating factors and/or from reductions in stress (commonly a trigger of episodes) due to a positive diagnosis, knowledge that effective therapies are available, and interaction with a caring physician. Because of common parental concerns about the potential side effects of preventive medications, lifestyle changes may be recommended first and may delay or occasionally circumvent the use of daily medications. A time-limited trial to assess the impact of lifestyle changes for 1 or 2 months or through 1 or 2 typical cycles may be insti-

tuted concurrent with the testing to exclude organic causes of vomiting (see "Diagnostic Approach to Recurrent, Episodic Vomiting").

### Avoidance of Triggers

A careful history and/or detailed "vomiting diary" that records intervals between episodes, time of onset and ending, contents of preceding meals, and aggravating life events can help identify potentially avoidable triggers in three fourths of children (4,56). It is important that families recognize that episodes can be precipitated by

**TABLE 4.** Lifestyle changes in CVS

Lifestyle changes (for 1–2 mo or 1–2 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



common infections, exciting occasions such as birthdays and holidays, and lack of sleep and/or overexertion.

Avoidance of triggering foods (eg, chocolate, cheese) or food allergens can reduce episode frequency in CVS. In 1 small study, 7 of 8 children with documented food sensitivities to cow, soy, or egg white proteins, improved following specific dietary elimination (57). Some examples of foods that are thought to precipitate migraines include cheese, chocolate, hot dogs, aspartame, monosodium glutamate, caffeine withdrawal, and alcohol (red wine and beer) (56). Although extensive dietary restriction of potential triggering and/or allergenic foods is not recommended by the task force, it may be prudent to test eliminating particular foods or chemical substances that appear to be consistent aggravating factors. Marijuana has been used for treatment of chronic nausea and vomiting of chemotherapy and also by some adolescents to self-treat CVS. However, in 1 series of adult patients with CVS, marijuana use was found to worsen the cyclic hyperemesis and its cessation decreased episodes of vomiting (58).

*Supplemental Carbohydrate*

The use of supplemental carbohydrate can provide additional energy during times of high energy demands. Published observations have noted that fasting induces some episodes and, conversely, frequent feedings prevent others, even in the absence of documented hypoglycemia (12). Furthermore, a rapid response to intravenous dextrose infusion can be seen during acute attacks (4). When a patient's history suggests fasting-induced attacks, high-carbohydrate snacks may be given between meals, before physical exertion, and at bedtime.

*Interventions for Migraine*

Given that CVS is considered to be within the migraine spectrum as a so-called childhood precursor to migraine, it is appropriate to mention lifestyle changes commonly incorporated into pediatric migraine management strategies. These include good sleep hygiene (eg, regular sleep schedules, avoidance of sleepovers), regular aerobic exercise, regular meal schedules (ie, avoid skipping meals), maintenance of good hydration, and moderation (30 mg/day) or avoidance of caffeine (59–61).

**Prophylactic/Preventive Medications: General Approach**

Published clinical trials consist of uncontrolled or retrospective reports (ie, level II evidence) (Table 3). The literature does not permit the task force to provide evidence-based recommendations. The recommendations that follow are based on expert opinion (ie, level II and III evidence, grade D recommendations) (Table 5).

**TABLE 5. Prophylactic or preventive medications\* in CVS**

Children 5 y or younger
Antihistamines: cyproheptadine (first choice) and pizotifen (available in UK, Canada)
Cyproheptadine 0.25–0.5 mg · kg <sup>-1</sup> · day <sup>-1</sup> divided bid or tid
Side effects: increased appetite, weight gain, sedation
Alternatives: pizotifen (available in UK, Canada)
β-Blockers: propranolol (second choice)
Propranolol 0.25–1.0 mg · kg <sup>-1</sup> · day <sup>-1</sup> , most often 10 mg bid or tid
Monitor: resting heart rate maintain ≥60 bpm
Side effects: lethargy, reduced exercise intolerance
Contraindications: asthma, diabetes, heart disease, depression
Discontinuation: tapered for 1–2 wk
Children older than 5 y
Tricyclic antidepressants: amitriptyline (first choice)
Amitriptyline begin at 0.25–0.5 mg/kg qhs, increase weekly by 5–10 mg, until 1.0–1.5 mg/kg
Monitor: √ EKG QT <sub>c</sub> interval before starting and 10 days after peak dose
Side effects: constipation, sedation, arrhythmia, behavioral changes (especially in young children)
Alternatives: nortriptyline (available in liquid)
β-Blockers: propranolol (second choice)—see above
Other agents
Anticonvulsants: phenobarbital
Phenobarbital 2 mg/kg qhs
Side effects: sedation, cognitive impairment
Alternatives: topiramate, valproic acid, gabapentin, levetiracetam—consult Neurology Dept
Supplements
L-carnitine 50–100 mg · kg <sup>-1</sup> · day <sup>-1</sup> divided bid or tid (max 1 g tid)
Coenzyme Q <sub>10</sub> 10 mg · kg <sup>-1</sup> · day <sup>-1</sup> divided bid or tid (max 100 mg tid)
Side effects: diarrhea, fishy body odor (for L-carnitine)

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

Before initiating daily prophylactic pharmacotherapy, clinicians must consider the age of the child, medical and psychological comorbidities, dosage format, and side effect profiles of the medications. We recommend beginning a low initial dose, and then increasing it incrementally, titrating to effect. The rationale is that the lower doses may be therapeutic in some cases and may limit side effects that emerge at higher doses.

**Medications**

Cyproheptadine, propranolol (62,63), amitriptyline (5,11,12,64), phenobarbital (65) and pizotifen (66,67) are 5 medications for which high response rates were observed in at least 10 patients (level II evidence). However, these studies were prone to bias because they did not account for nonspecific treatment effects (eg, placebo response, recall [ie, retrospective reporting] effects). The differing inclusion criteria and qualitative outcomes used in these studies do not allow for comparison of relative efficacies.

The antihistamine and serotonin receptor antagonist cyproheptadine has a moderate response rate in young children and is the first choice of the expert task force for children 5 years old or younger (Table 5) (5,11,12,64). Increased weight due to enhanced appetite may be an unacceptable side effect in school-age girls, although cyproheptadine may be the appropriate first choice in an underweight patient. Although typically administered on a bid or tid dosing schedule, some clinicians have used it effectively as a single nighttime dose to reduce the sedation experienced during the school day from taking a dose in the morning. Pizotifen was shown to be highly efficacious in a case series of 6 subjects with CVS (68) and 1 randomized placebo-controlled trial in 16 abdominal migraine patients (67). However, pizotifen is available only in Canada and the United Kingdom.

The tricyclic antidepressant amitriptyline has a moderate to high response rate and is the preferred first choice in the older child (older than 5 years) (Table 5) (5,11,12,64). Clinical experience indicates a higher response rate if given at an adequate dosage ( $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , occasionally  $1.5\text{--}2.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) for at least 4 weeks. To minimize side effects, dosing is commonly initiated at a single nighttime dose of  $0.25\text{--}0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  (likely subtherapeutic) and increased incrementally by 5 to 10 mg. The risk of ventricular arrhythmia is reduced by monitoring the QTc interval (to maintain  $\leq 460$  msec) before and after reaching the targeted dose (69). If a tricyclic medication is effective but the child cannot tolerate tablets, then amitriptyline can be solubilized by a compounding pharmacist or at home. As an alternative to amitriptyline, nortriptyline in liquid or tablet form can be considered, but there are no supporting studies and limited experience in children. Although anecdotal experience has shown potential efficacy in younger ages, the task force has not recommended use in younger children because of frequent side effects and a risk for overdose.

The  $\beta$ -blocker propranolol has moderate efficacy and is recommended as the second choice in children of all ages (Table 5) (11,12,62,63). The resting heart rate should be monitored for potential bradycardia ( $<60$  bpm) and, if propranolol is discontinued, it should be tapered for 1 to 2 weeks. Alternatives to propranolol, atenolol and nadolol, have fewer side effects, but may be less effective because of inability to cross the blood-brain barrier.

The anticonvulsant phenobarbital demonstrated efficacy in 1 study at a low single nighttime dose of  $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  (65). Potential cognitive impairment limits the task force's enthusiasm for recommending this drug as a first-line therapy. In migraine there is an evolving literature supporting the efficacy of other anticonvulsants (eg, topiramate), but the side effects and necessary titration of each of these medications require that an individual experienced in the use of these agents in children (eg, a pediatric neurologist) should guide the use of these agents in patients with CVS (61,70).

## RECOMMENDATIONS FOR PROPHYLAXIS

The task force recommends cyproheptadine or propranolol prophylaxis for children 5 years old and younger. In the older child (older than 5 years), amitriptyline or propranolol are recommended, as shown in Table 4. The dose can be titrated to effect by increasing it every 1 to 4 weeks to achieve at least an average therapeutic dose for 2 CVS cycles (eg, if monthly, then for 2 months). If the medication causes intolerable side effects and/or proves to be ineffective, then it is appropriate to switch to another medication. The common side effects tend to be dose related and may be addressed by reducing the dosage.

In the task force's experience, most CVS patients will respond to amitriptyline, cyproheptadine and/or propranolol. If a patient does not respond, consider the following:

- Diagnoses other than CVS and need for additional diagnostic testing
- Whether an adequate trial was administered (eg, a high-end dose given for at least a 2-cycle trial period), or there was lack of adherence
- Combination therapy of 2 medications (especially amitriptyline with 1 of the other main drugs)
- Complementary therapy such as carnitine, coenzyme Q, low estrogen oral contraceptives, acupuncture, or psychotherapy (see following section)

### Alternate Prophylactic Approaches

Carnitine (commonly prescribed dose of  $50\text{--}100 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , adults = 1.0 g tid), a nutrient that serves as a transport cofactor for long-chain fatty acids into mitochondria, may help patients with suspected mitochondrial or metabolic dysfunction, and has a benign side effect profile (71). Another mitochondrial cofactor, coenzyme Q (commonly prescribed dose of  $5\text{--}10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , adults = 100 mg tid) is receiving interest, but there are no data regarding efficacy. Although there are no published data, low estrogen oral contraceptives have been used to treat girls with catamenial (menstrual related) CVS (72). Anecdotal experience suggests that acupuncture at the P6 (pericardial) point may attenuate the severity of CVS attacks (73). Psychotherapy, especially stress reduction, may help as an adjunctive therapy (74).

### ACUTE INTERVENTION

There are no controlled or open trials of supportive measures (eg, nonstimulating environment), pharmacological (eg, antimigraine, antiemetic) agents, or complementary approaches (eg, acupuncture) in managing acute CVS (Table 6). Based on small case series (level II evidence), anecdotal experience and expert opinion (level III), the task force recommends supportive

**TABLE 6.** Summary of evidence for treatment of acute attacks of CVS

Treatment	No. of studies	No. of patients	Level of evidence	Study quality	Response rates			Comments
					100%	50%–100%	<50%	
Sumatriptan (11)	1	38	II-3		NR	66% (25/38)	34% (13/38)	
Ondansetron (11,12,62)	3	83	II-3	Fair (1/3) Poor (2/3)	NR	64% (53/83)	36% (30/83)	
Phenothiazines (11)	1	63	II-3	Fair	NR	21% (13/63)	79% (50/63)	
Carbohydrate (12)	1	60	II-3	Poor	NR	58% (35/60)	42% (25/60)	
Prokinetic agents (11)	2	41	II-3	Fair (1/2) Poor (1/2)	NR	20% (8/41)	80% (33/41)	Includes erythromycin (1 patient)
Isometheptene (11)	1	13	II-3	Fair	NR	31% (4/13)	69% (9/13)	

NR, none reported.

and symptomatic care during acute episodes (grade D recommendation) (Table 7).

Expert opinion supports the efficacy of early intervention within the first several hours of onset of CVS. Some experts advocate an approach similar to that used for migraine headache in which nonsteroidal analgesics (eg, ibuprofen) are administered orally during the early prodrome before vomiting begins. Once the vomiting starts, evaluation in an emergency department or direct admission to the hospital ward before dehydration ensues is appropriate in some patients for treatment protocols specifying intravenous fluids, medications, and admission criteria. Providing the patient with a letter that explains CVS and specifies an individualized management protocol can facilitate prompt institution of therapy. A template of such a letter is provided at (<http://www.cvsaonline.org>), and a sample protocol is shown in Table 8.

Some behaviors during episodes may appear to be odd but are in fact common in CVS episodes. Many children become noncommunicative and curl into a fetal position because, in their hypersensitive state, any further stimulation heightens their nausea and can trigger more vomiting (75). At best, the child should not be unnecessarily disturbed. There are other children who drink obsessively to induce vomiting. Reductions in these behavioral responses generally are observed when patients receive adequate symptom relief with antiemetics and sedation.

Most patients with CVS will respond partially to one of the regimens discussed below. If a child does not respond, or the episode differs substantially from previous ones by greater severity, longer duration, or new or different symptoms, then the clinician should reconsider the possibility of an underlying surgical lesion and the need for new or to repeat diagnostic testing (eg, abdominal ultrasound, brain MRI).

### Supportive Care

Supportive care during acute episodes includes providing a less stimulating (eg, dark, quiet) environment; replacement of fluids, electrolytes, and energy; use of

antiemetics with or without sedation to lessen the nausea and vomiting; and provision of analgesia for pain (53).

Some experts recommend higher amounts of intravenous dextrose-containing fluids (D<sub>10</sub> 0.45 normal saline) (Table 7). The intent of 10% dextrose concentration is to attenuate the incipient metabolic crisis that can be worsened by catabolism. If the child is evaluated in the later phases and substantial fluid and/or electrolyte deficits are found, then the task force recommends infusing 0.9% NaCl replacement fluid through a “Y” connector parallel to the D<sub>10</sub>. An increased anion gap (>18–20 mEq/L) may reflect either severe dehydration or signal metabolic decompensation and the need for hospital admission. The ensuing catabolism following 2 to 3 days of minimal energy and/or protein intake can prolong the illness and can be reversed with parental nutrition to provide an adequate energy intake and 1.5 g of protein per kilogram per day.

Episodic vomiting can occasionally result from metabolic decompensation in frank mitochondrial disease and can be associated with metabolic acidosis with an anion gap (ie, lactic acidosis), hyperglycemia (insulin resistance) and/or multisystem failure. In such seriously ill patients, administering higher amounts of glucose (eg, 8–12 mg glucose/kg/min) with or without concomitant insulin, closely monitoring the acidosis, and obtaining a metabolic consultation are critical to management.

### Abortive and Supportive Therapies

There are no controlled and no open trials of pharmacological (eg, antimigraine, antiemetic) agents in >10 patients. Task force recommendations for their off-label use are made in the following paragraphs (see also Table 7):

*Triptans*, 5HT<sub>1B/1D</sub> agonists, are not approved for use in children younger than 18 years old. However, following the Child Neurology Practice Parameters, the task force recommends a trial of abortive agents in children 12 years and older who have infrequent and/or mild episodes (eg, <1/month) (76). One open-label report and expert experience indicate that triptans can terminate an episode

**TABLE 7.** Supportive and abortive treatment approaches in CVS

Supportive care
Fluid, electrolyte and nutritional management
D <sub>10</sub> 0.45 normal saline + KCl as appropriate at 1.5 times maintenance fluid rates OR through a Y-connector
D <sub>10</sub> W at 1.0 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 <sup>-1</sup> · day <sup>-1</sup> and energy units above the catabolic threshold of 55–70 kcal · kg <sup>-1</sup> · day <sup>-1</sup>
Antiemetic (5HT <sub>3</sub> antagonist) agents
Ondansetron 0.3–0.4 mg · kg <sup>-1</sup> · dose <sup>-1</sup> intravenously every 4–6 h (up to 20 mg)
Side effects: constipation
Alternatives: granisetron
Sedatives
Diphenhydramine 1.0–1.25 mg · kg <sup>-1</sup> · dose <sup>-1</sup> intravenously every 6 h
Lorazepam 0.05–0.1 mg · kg <sup>-1</sup> · dose <sup>-1</sup> intravenously every 6 h
Side effects: respiratory depression, hallucinations
Chlorpromazine 0.5–1.0 mg · kg <sup>-1</sup> · dose <sup>-1</sup> every 6 h + diphenhydramine intravenously
Side effects: dystonic reactions with chlorpromazine alone
Analgesics (nonsteroidal and narcotic) agents
Ketorolac 0.4–1.0 mg/kg intravenously every 6 h (max dose 30 mg, max daily 120 mg)
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 <sub>2</sub> RAs or PPIs (eg, intravenous ranitidine, pantoprazole)
Diarrhea: antidiarrheals (eg, Imodium)
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 <sub>2</sub> RAs or PPIs
Weight loss: nasogastric or parenteral nutrition
Abortive care
Antimigraine (triptan) agents
Sumatriptan: 20 mg intranasally at episode onset
Side effects: neck pain/burning, coronary vasospasm
Contraindications: basilar artery migraine
Recovery and refeeding
Feed ad libitum when child declares episode is over

PPIs, proton pump inhibitors; ACE, angiotensin converting enzyme; SIADH, syndrome of inappropriate antidiuretic hormone.

when administered early (77). The transient burning sensation in the neck and upper chest appears to be uncommon with the nasal form of triptans. Zolmitriptan also comes in a nasal form.

5HT<sub>3</sub> receptor antagonists are supportive rather than abortive antiemetic agents available in oral (liquid, tablet, or dissolving tablet), rectal (reconstituted by pharmacy), and intravenous forms (12,22,62). Because they are well tolerated and more effective at higher doses, expert experience recommends ondansetron doses of 0.3 to

**TABLE 8.** 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 h
If child is dehydrated, rehydrate with initial fluid bolus of 10 mL/kg normal saline and repeat as clinically necessary
D <sub>10</sub> 0.45 NS + KCl as appropriate at 1.5 times maintenance rates
Intravenous ondansetron 0.3 mg · kg <sup>-1</sup> · dose <sup>-1</sup> every 6 h × 24 h
Intravenous lorazepam 0.05 mg · kg <sup>-1</sup> · dose <sup>-1</sup> every 6 h × 24 h
If child has moderate to severe abdominal pain, intravenous ketorolac 1.0 mg · kg <sup>-1</sup> · dose <sup>-1</sup> (≤30 mg total dose) every 6 h
Admit child if >5% dehydrated, no urine output >12 h, Na <sup>+</sup> <130 mEq/L, anion gap >18 mEq/L, or inability to stop emesis
Allow oral fluid intake

0.4 mg/kg with a usual upper limit of 20 mg/dose. Safe use of doses up to 32 mg has been reported in children (78). Granisetron is also available in intravenous form, but there is little experience in CVS. Widely used promethazine (H<sub>1</sub> antagonist) and prochlorperazine (D<sub>2</sub> antagonists) antiemetics are ineffective when compared to ondansetron (22% vs 58%, *P* < 0.05) (4).

When antiemetics fail to control unrelenting nausea and vomiting, expert opinion recommends adding sedatives. Paralleling the experience in severe migraine, sleep may be the only mode that provides symptomatic relief, and may occasionally shorten the nausea and vomiting episode. The most effective combination therapy is ondansetron and lorazepam. Alternatively, chlorpromazine and diphenhydramine can be used together, but this provides less antiemetic and more sedative effect (4,53).

### Treatment of Pain, Hypertension, and Complications

Midline abdominal pain can be severe and treated empirically with analgesics. On physical examination, even when the child is writhing in pain, the abdominal wall is typically soft to palpation. To manage pain, the expert task force recommends the use of intravenous H<sub>2</sub>RAs (eg, ranitidine) and ketorolac, then morphine or hydromorphone (79,80). If the pain has an epigastric location and dyspeptic quality, then intravenous administration of a H<sub>2</sub> receptor antagonist or proton pump inhibitor may be necessary to lessen the distress (53). The transient hypertension found in the Sato subset of CVS should be treated, if needed, with short-acting ACE inhibitors during the episode only, because it resolves promptly when the episode ends.

The main complications of an acute episode include dehydration, electrolyte derangement including inappropriate secretion of antidiuretic hormone, metabolic acidosis, hematemesis from prolapse gastropathy or Mallory-Weiss tear, chronic esophagitis, and weight loss (53). If secretion of antidiuretic hormone with hyponatremia, low serum osmolality, and high urine specific gravity (despite adequate hydration) occurs, water intake

should be restricted until values normalize. Because metabolic acidosis can have several potential causes including hypovolemia, sepsis, lactic acidosis and ketosis from mitochondrial dysfunction, and hyperventilation (respiratory alkalosis with renal compensation), obtaining serum electrolytes, urine pH and ketones, and taking an arterial blood gas may clarify the situation. Hematemesis most commonly results from prolapse gastropathy in which vomiting bruises the stomach fundus by forcing it retrograde through the gastroesophageal junction; it usually resolves without therapy (81). If the bleeding persists and/or vital signs are affected, then fluid replacement and endoscopic management may be necessary. Moderate esophagitis may require ongoing acid suppression. Growth failure can result from frequent and/or prolonged episodes without oral intake or other causes and may require dietary counseling as well as nasogastric or parenteral nutrition between episodes to provide restorative energy units.

### Alternative Abortive Approaches

For patients who have panic anxiety-triggered episodes or anticipatory attacks (eg, akin to anticipatory vomiting before undergoing chemotherapy), the use of either anxiolytic medications or relaxation techniques (eg, deep breathing, guided imagery) has been reported anecdotally to abort episodes (53,82).

### Recovery and Refeeding

The recovery phase from the last emesis to the point of being able to retain foods typically lasts a few hours. Once children state that they are hungry and want to eat food, they can generally resume a normal diet without gradual progression. However, this should be individualized because some children require stepwise reintroduction of foods to prevent the recurrence of nausea.

### RECOMMENDATIONS FOR SUPPORTIVE AND ABORTIVE INTERVENTIONS

During the acute episode of vomiting, the task force recommends supportive measures including placing children in less stimulating environments; replenishing fluids, electrolytes, and energy; and treating symptomatic nausea, vomiting, and severe abdominal pain. Early intervention within the first 2 to 4 hours of onset either at home or at a hospital may be more effective than later intervention. At all ages, use of intravenous D<sub>10</sub> and high-dose 5HT<sub>3</sub> antagonist antiemetics (eg, ondansetron 0.3–0.4 mg · kg<sup>-1</sup> · dose<sup>-1</sup>) off-label rather than H<sub>1</sub> or D<sub>2</sub> antiemetics is recommended to treat energy deficits and vomiting, respectively. If these are ineffective, then concomitant sedation is recommended. Severe abdominal pains are treated with parenteral acid suppression and/or nonsteroidal anti-inflammatory drugs or narcotics. As

an abortive approach, intranasal triptans may be used off-label in children age 12 and older with infrequent (<1/month) or milder episodes (≤24 hours).

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