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PRACTICE GUIDELINE

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition 2025 guidelines on the diagnosis of cyclic vomiting syndrome in children

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Abstract

Objectives: Cyclic vomiting syndrome (CVS) is characterized by distinct clinical features and symptom overlap with migraine disorders. Cannabinoid hyperemesis syndrome (CHS) is a related condition with similar symptom expression. Due to a lack of diagnostic biomarkers, there is a need for optimal symptom-based diagnostic criteria. These evidence-based guidelines from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) were formulated to assist clinicians in the diagnosis of pediatric CVS.

Methods: The NASPGHAN council approved a multidisciplinary content expert panel. The panel prioritized a set of clinical questions and outcomes. The recommendations were developed based on a systematic review that applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. To formulate the recommendations and suggested diagnostic algorithm, the panel linked decisions to current evidence and utilized the Delphi Method for expert consensus when available literature was insufficient. A systematic review of available research evidence informed the summary on pediatric CHS. A separate document provides GRADE-based treatment guidelines for pediatric CVS.

Results: The panel voted and agreed on one prioritized recommendation on the utility of diagnostic screening tests for pediatric CVS and updated the past consensus-based diagnostic algorithm. A consensus-based clinical approach to the diagnosis of pediatric CHS as a related but separate entity is also provided.

Conclusions: The panel recommends screening serum and urine laboratory testing and an upper gastrointestinal radiographic series for all patients with

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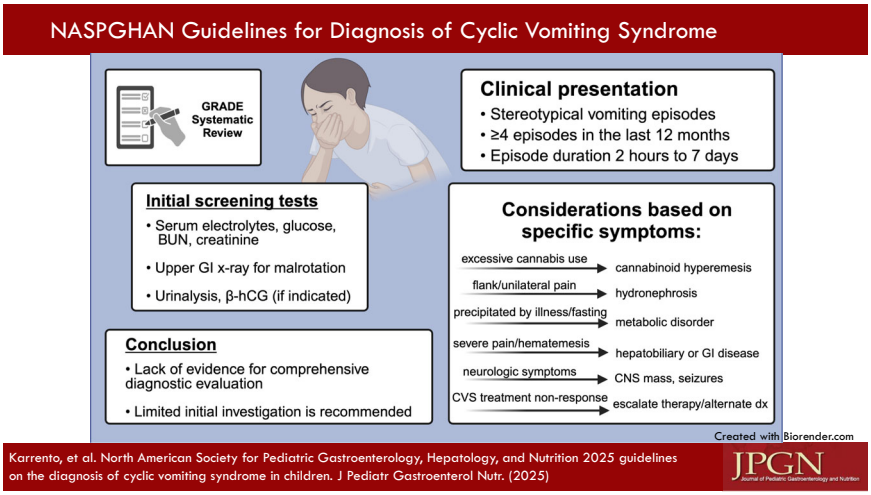
symptoms suggestive of CVS. The panel concluded that there is low yield and cost-effectiveness of other diagnostic screening tests. A set of recommended diagnostic criteria for CVS was formulated based on the characteristics of vomiting attack frequency, duration, and associated symptoms.



KEYWORDS

cyclic vomiting characteristics, diagnostic criteria, pediatric cannabinoid hyperemesis syndrome, pediatric cyclic vomiting syndrome, pediatric disorders of gut-brain interaction

1 | INTRODUCTION

Cyclic vomiting syndrome (CVS) is characterized by recurrent, disabling attacks of severe nausea and vomiting separated by symptom-free periods.[1] The prevalence of pediatric CVS is as high as 1.9%–3.2% according to several population-based studies.[2–5] The disorder is associated with substantial healthcare costs and reduced quality of life, often relating to delay in care due to extensive diagnostic evaluation and prolonged time to diagnosis.[6–9] The absence of diagnostic biomarkers and the lack of evidence-based diagnostic criteria hamper a timely and accurate diagnosis. CVS also shares close clinical resemblance with migraine and cannabinoid hyperemesis syndrome (CHS), adding to the diagnostic challenge.[10,11]

To date, medical evaluation and diagnostic criteria for CVS and CHS have been entirely driven by expert consensus recommendations.[12] In the absence of specific alarm signs, there is a lack of direct evidence for extensive diagnostic testing in children who present with episodic vomiting and fit symptom-based CVS criteria.[13,14] In the past, several different organizations, including the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN; 2008), the Rome IV (2016), and the International Classification of Headache Disorders-3 (ICHD-3; 2018), used expert consensus to define symptom-based diagnostic criteria. A nationwide survey among Italian gastroenterologists and neurologists found very poor agreement in the diagnostic approach to CVS.[15] Another study highlighted the growth of CVS publications over the past two decades, but a general lack of reference to ICHD-3 criteria among gastroenterologists.[16] A unified, evidence-supported set of criteria is thus

What is Known

- There is insufficient evidence to support a broad-based exclusionary screening approach to the diagnosis of pediatric cyclic vomiting syndrome (CVS) and cannabinoid hyperemesis syndrome (CHS).
- Current diagnostic criteria are based solely on expert opinion.

What is New

- There is no evidence for comprehensive diagnostic testing in children with typical CVS features.
- CVS attacks are defined by specific parameters for timing (≥4 episodes/12 months) and duration (2 h to 7 days), occurring at least 1 week apart.
- Associated features may include listlessness, diaphoresis, photophobia, unrelenting nausea, abdominal pain, and incessant retching.
- CHS is similar to CVS but presents after prolonged and frequent cannabis exposure, supported by high urinary Δ-9-tetrahydrocannabinol levels.

necessary to aid timely diagnosis and facilitate research. A recent study provided the first prospective investigation specifically aimed at distinguishing the unique quantitative and qualitative clinical characteristics of CVS compared to non-CVS vomiting conditions.[17] This study documented a distinct pattern of vomiting frequency, duration, and specific symptoms associated with pediatric CVS.

The purpose of these guidelines is to provide the most up-to-date, evidence-based recommendations on the diagnosis of pediatric CVS. A clinical approach to the diagnosis of CHS as a subtype or related entity was also considered. The overall goal is to facilitate a timely and accurate diagnosis to reduce the high healthcare burden associated with CVS and related conditions.

2 | METHODS

2.1 | Panel composition and process

These NASPGHAN recommendations are based on systematic reviews of scientific evidence by a panel of multidisciplinary experts and supplemented by expert consensus in areas with limited evidence. The guidelines adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach and best practices for guideline development to prioritize questions and outcomes and to formulate consensus recommendations.[18–23] Of note, a separate document provides GRADE-based guidelines for the management of pediatric CVS.[24]

The NASPGHAN Clinical Care and Quality Committee and NASPGHAN Council provided project oversight and approval of the guideline panel composition and the final guideline recommendations. The panel included pediatric specialists in the fields of gastroenterology (GI), emergency medicine, metabolic genetics, psychology, and neurology with both clinical and research content expertise, along with a patient representative (KA). A guideline methodologist (WW) coordinated the guideline-development process, applying criteria from the GRADE approach to inform panel discussion and consensus recommendations. The work was completed using internet-based tools (www.gradepro.org and www.covidence.org) and online meetings. Supporing Information presents additional details on the methodology, including literature search strategy for systematic reviews, selection of questions and outcomes of interest, and description of the GRADE criteria applied.

The consensus statements were subjected to journal peer review, followed by approval by the NASPGHAN Clinical Care and Quality Committee and Council for publication under the imprimatur of NASPGHAN.

2.2 | Target population and audience

The target population includes children of all ages with symptoms consistent with CVS. Specific CVS subgroups include migraine-related, catamenial, calendar-timed and Sato-variant as further described below[25] Autonomic nervous system dysfunction is documented in several studies although it is unclear if this represents a specific CVS subset or a common underlying mechanism.[26,27] As pediatric CHS is currently considered a probable subtype of CVS that presents after prolonged cannabis use,[11] the target population also included children with CHS. A separate systematic review was conducted for CHS.

The target audience includes patients, primary care providers, pediatric subspecialists, as well as other clinicians and policy decision-makers.

2.3 | Values and outcomes

The panel used a PICO (population, intervention, comparator, and outcomes) framework and formulated a question on the utility of screening diagnostic testing in children with symptoms of CVS. The guideline panel rated the frequency of alternate diagnoses as the most critical outcome. The panel took into consideration resource use and cost-effectiveness, acceptability, patients' values and preferences, and feasibility of diagnostic testing when formulating recommendations.

2.4 | Development of recommendations

It was expected that there would be limited available data on the direct and comparative effects of specific diagnostic strategies to establish evidence-based clinical practice protocols. Case reports and case series were therefore included in the evidence review. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or by voting when required (≥80% majority was required for a strong recommendation). The final guidelines, including all recommendations, were reviewed and approved by all panel members.

When developing the diagnostic criteria, the panel used available evidence combined with consensus recommendations developed via the Delphi Method. Delphi is a consensus method that utilizes expert opinion to make knowledge-based decisions and recommendations on key clinical questions where there is insufficient scientific evidence.[27] Expert panelists reviewed available evidence and answered anonymous REDCap surveys with numerical scores as follows: Strongly Disagree (score = 1), Disagree (=2), Neutral (=3), Agree (=4), or Strongly Agree (=5). Mean scores for each item were computed. Consensus was reached for a mean score of >4 (Agree/Strongly Agree) or <2 (Disagree/Strongly Disagree). If consensus

was not reached, items were returned to the panelists with the results from the first round available. A face-to-face online meeting was held to discuss areas of persistent disagreement. The procedure was repeated until consensus was reached for all items.

2.5 | Interpretation of recommendations

The guideline summary and Supporting Information S1 provide GRADE's interpretation of strong and conditional recommendations by patients, clinicians, healthcare policymakers, and researchers.

2.6 | How to use these guidelines

The NASPGHAN clinical practice guidelines and position papers are evidence-based decision-making tools for managing health conditions. This document is not a disease management requirement or rule and should not be construed as establishing a legal standard of care, or as encouraging, advocating for, mandating, or discouraging any particular diagnostic methodology or treatment. Our clinical practice guidelines and position papers should also not be used in support of medical complaints, legal proceedings, and/or litigation, as they were not designed for this purpose. The NASPGHAN clinical practice guidelines and position papers should also not be utilized by insurance companies or pharmacy benefit managers to deny treatment that is deemed medically necessary by a patient's physician. The healthcare team, patient, and family should make all decisions regarding the care of a patient after consideration of individual-specific medical circumstances. While NASPGHAN makes every effort to present accurate and reliable evidence-based information, these clinical practice guidelines and position papers are provided "as is" without any warranty of accuracy, reliability, or otherwise, either express or implied. NASPGHAN does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither NASPGHAN nor its officers, directors, members, employees, or agents will be liable for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with the clinical practice guidelines and/or position papers or reliance on the information presented.

3 | RESULTS

A total of 167 studies were screened, and 140 full-text studies were reviewed. Of these, 52 were used in the decision-making process (Figure 1). Four of these were used to answer the PICO question and formulate the GRADE recommendation.

3.1 | CVS subtypes

Multiple CVS subtypes have emerged from studies of large CVS cohorts.[10,17,25] These include migraine, calendar-timed, catamenial, Sato variant (hypothalamic surge), and CHS. Notably, individual patients may fall into more than one subgroup. It is unclear whether the combined effect is synergistic or forms another subtype.

3.1.1 | Migrainous

This largest CVS subgroup closely resembles migraine headaches (pallor, lethargy, photo- and/or phonophobia, etc.), supported by shared mitochondrial DNA polymorphisms.[10,29–31] A personal and/or family history of migraine (found in over 80% of children with CVS) and response to migraine-targeted therapies further supports this subtype.[10] One long-term study demonstrated progression to migraine in 26% of patients with pediatric CVS.[32] While there is significant symptom overlap between migraine, abdominal migraine, and CVS, CVS is the preferred diagnosis when the predominant symptom is vomiting.[10] Yet, abdominal pain and vomiting can occur in each disorder, respectively, and therefore be difficult to separate. Patients with migraine headache generally do not seem to experience the severe abdominal pain that is characteristic of abdominal migraine or the intense autonomic response (diaphoresis, salivation, etc.) that is common in CVS.[32]

3.1.2 | Calendar-timed

A predictable, calendar-type pattern is described in a subset (25%) who can predict the start of an emetic cycle regularly within 1–2 days.[17,25,34] Within those with very regular intervals, a subset has unusually long intervals of more than 1 month, for example, 60–80 days. While this long-cycled, calendar-timed CVS may be more refractory to typical therapies, recognition can facilitate abortive interventions before symptom onset.

3.1.3 | Catamenial

A smaller subgroup (9%) of females with CVS experience vomiting attacks in conjunction with menstrual periods.[25] The attacks are thought to be precipitated by decline in estrogen similar to that in menstrual-related migraine.[35] Reports with small sample sizes suggest that low-dose estrogen or long-acting medroxyprogesterone acetate birth control agents may be effective in preventing catamenial CVS.[36,37]

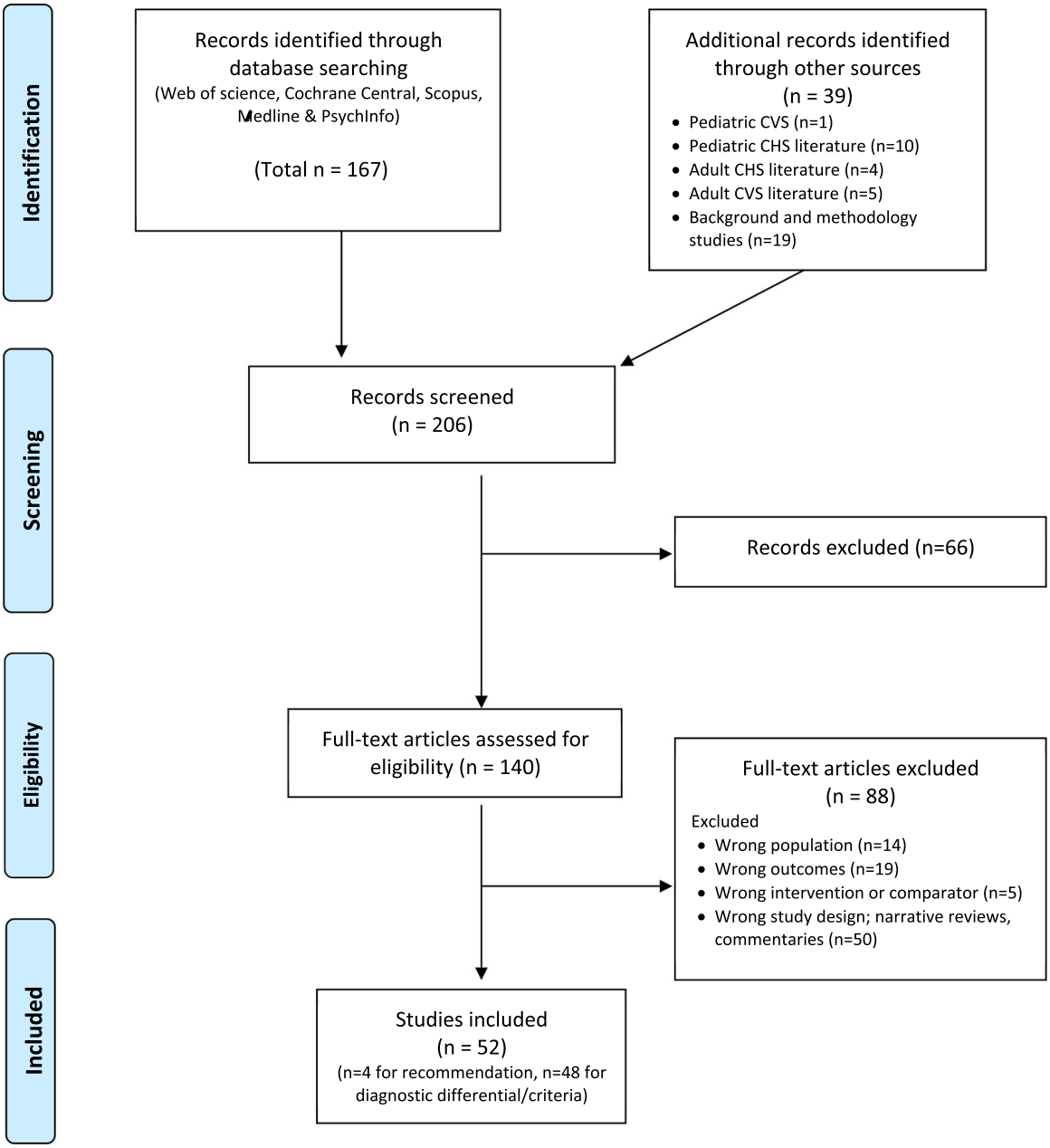


FIGURE 1 PRISMA flow diagram of systematic review process. CHS, cannabinoid hyperemesis syndrome; CVS, cyclic vomiting syndrome; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

3.1.4 | Sato-variant

A smaller subset (6%) of patients with CVS display a clinical and biochemical profile of an overreactive hypothalamic-pituitary-adrenal axis, first described by Wolff and fully characterized by Sato et al.[38,39] Clinically, this group has more severe episodes with more emeses per episode and longer episode duration along with characteristic intra-episodic hypertension and profound lethargy.[1] The elevated levels of adrenocorticotropin hormone (ACTH), cortisol, antidiuretic hormone (ADH), catecholamines and prostaglandin E_2, contribute to hypertension and syndrome of inappropriate ADH.[25] If suspected, this subtype can be confirmed by laboratory profiling of elevated cortisol, ACTH, and/or ADH early in the episode before providing intravenous glucose. While there are no published data for management, electrolyte monitoring and treatment with short-acting antihypertensives may be warranted.

3.1.5 | Autonomic dysfunction

Emerging data demonstrate vagal dysfunction and resultant sympathetic overdrive during the inter-episodic wellness phase in children with CVS.[26,27]

An underlying autonomic dysregulation is also supported by clinical features during attacks (diaphoresis, listlessness, palpitations, and peripheral vasoconstriction) and a study demonstrating that 40% of children with CVS develop chronic dysautonomia during adolescence.[40] Recent data suggest that some of these patients experience inter-episodic symptoms of orthostatic intolerance and migraine.[17]

3.1.6 | Cannabinoid hyperemesis syndrome

CHS is likely a subset of CVS[11] that presents with phenotypical CVS but *triggered* by prolonged and excessive recreational cannabis use.[11] Low, intermittent doses of cannabinoids may produce therapeutic effects such as pain relief, reduced anxiety, and decreased nausea.[11,41] Higher, sustained doses of cannabinoids (>4 days/week for several years) may instead induce symptoms similar to CVS.[42] Although not completely understood, this response may occur due to receptor downregulation in genetically susceptible individuals who carry polymorphisms in the cannabinoid 1 (CB1) receptor.[11,43,44]

Legalization of cannabis across the United States and Canada has resulted in a significant rise in CHS cases and hospitalizations, including amongst adolescents.[45,46] While adult CHS occurs more commonly among young males, pediatric CHS mostly affects adolescent girls after daily usage for 1–4 years.[42,47] A proper diagnosis requires symptom resolution or improvement after sustained cessation (minimum 6 months or the equivalent of three emetic cycles) of cannabis.[11,48] The nearly identical symptoms can otherwise result in misdiagnosis of CVS as CHS and vice versa. It is important to avoid presumptions of drug abuse by misclassifying CVS as CHS, or to misclassify a child who is suffering from CHS and needs drug abuse counseling as having CVS. For example, symptom improvement with hot water bathing behavior once thought to be pathognomonic of CHS occurs in 48% of adults as well as in younger children with CVS with no cannabis exposure.[11,41] When unclear, the CHS diagnosis is strengthened by a positive urine Δ-9-tetrahydrocannabinol (THC) test.[49,50] However, providers need to be vigilant to the possibility of false positive and prolonged duration of positive urine THC tests after last exposure.[51,52] Quantitative urine carboxy THC (THC-COOH) may provide clarity as infrequent THC exposure is likely to yield a maximum THC-COOH level of 56.3 ng/mL, while chronic exposure should result in higher levels.[49,53] Complete cannabis cessation is currently the only known effective long-term treatment. While there are no pediatric data, adult CHS guidelines recommend consideration of typical CVS treatment modalities.[11] Additional research is needed to delineate whether CHS is a separate clinical entity or a CVS subtype such as catamenial CVS with a unique trigger.

3.1.7 | Disorders mimicking CVS

A variety of GI and extra-intestinal conditions may closely mimic the clinical presentation of CVS (Table 1). While most other conditions present with specific symptoms indicating an alternate diagnosis, symptom overlap necessitates a thorough history, physical exam, and discerning clinical judgment. Additional testing is only needed in case of non-response to treatment, atypical presentation (e.g., very prolonged episodes), or the presence of specific warning symptoms (Figure 2).

Underlying GI conditions that may result in periodic flare-ups of vomiting include motility disorders (e.g., gastroparesis and constipation), eosinophilic disorders, and gastroesophageal reflux disease.[17,54–59] While some studies have considered a role for rapid gastric emptying in adult CVS, these are inconsistent findings without evidence of diagnostic utility.[60,61] Importantly, such studies are difficult to interpret and confounded by the lack of pediatric normative cutoff values for gastric emptying in children.[62] Chronic sinusitis coupled with gastroesophageal reflux has been found to serve as trigger for CVS.[54] *H. pylori* gastritis and superior mesenteric artery syndrome are also described to present similarly to CVS.[63–65]

Several different classes of metabolic conditions may have presentations that mimic CVS, especially in infants and toddlers.[66–68] Broad categories include fatty acid oxidation disorders (e.g., medium-chain acyl-CoA dehydrogenase deficiency),[58,69,70] organic acidurias (e.g., propionic acidemia),[57] urea cycle defects (partial ornithine transcarbamylase deficiency triggered by a high protein meal),[68] mitochondrial disorders (e.g., complex I deficiency),[14,30,71–75] disorders of ketone body metabolism (β-ketothiolase deficiency), and diabetic ketoacidosis.[76–79]

Symptoms due to various neurological causes may also be similar to CVS. These rarely include structural lesions (e.g., Chiari 1 malformation and brainstem neoplasms) and epilepsy.[80–82] While vomiting is unusual as the only symptom of epilepsy, it can be a prominent symptom in specific syndromes (e.g., Panayiotopoulos syndrome).[68,83–87] Migraine-related conditions, including vestibular migraine and other periodic syndromes such as benign paroxysmal vertigo and benign paroxysmal torticollis, have overlapping features and possibly shared pathophysiology with CVS.[88–92] Prominent vertigo should prompt considerations for these neurological etiologies. Autonomic dysfunction may present with chronic or episodic vomiting.[93–95] It is considered to be a contributor to

TABLE 1 Differential diagnoses to consider in the evaluation of children with episodic emesis.

	Example(s)
Gastrointestinal	
Anatomic	Intestinal malrotation with/without volvulus
	Intussusception
	Intestinal stricture/atresia
	Superior mesenteric artery syndrome
Peptic	GERD
	Peptic gastritis/ulcer
Allergic	Eosinophilic disorders
Infectious	*H. pylori* gastritis
	Acute gastroenteritis
Hepatobiliary	Cholelithiasis
	Pancreatitis
DGBI	Constipation
	Rumination syndrome
	Abdominal migraine
Dysmotility	Gastroparesis
Non-gastrointestinal	
Allergic	Mast cell activation syndrome
	Alpha-gal syndrome
Endocrine	Diabetic ketoacidosis
	Addison's disease
Metabolic	Fatty acid oxidation disorders
	Organic acid disorders
	Urea cycle defects
	Mitochondrial dysfunction
	Fructose intolerance
	Disorders of ketone body metabolism
	Acute intermittent porphyria
Neurological	Epilepsy (i.e., Panayiotopoulos syndrome)
	Brainstem tumor
	Chiari malformation
	Neuromyelitis optica
	Migraine
	Benign paroxysmal vertigo
	Autonomic dysfunction
Renal	Hydronephrosis (ureteropelvic junction obstruction)
Pharmacologic	Cannabinoid hyperemesis syndrome
Psychological	Bulimia nervosa
	Trauma/anxiety-triggered vomiting
	Factitious disorder (Munchausen by proxy)
Other	Chronic sinusitis
	Food poisoning
	Post-concussion syndrome

Abbreviations: DGBI, disorders of gut-brain interaction; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*.

CVS pathophysiology in some patients and possibly represents a CVS subtype.[17,40]

Acute hydronephrosis (e.g., Dietl's crisis) may closely mimic the presentation of CVS.[96,97] Ureteropelvic junction obstruction, the most common cause of hydronephrosis in younger males, should be considered in patients presenting with episodic vomiting. Studies suggest that this condition is found in 1% of children presenting as CVS.[13,58,96] The yield is improved when imaging is performed during or soon after the illness attack, as the dilated calyces may resolve within 9 days of symptom resolution.[14,98]

Episodic vomiting can also be a manifestation of other etiologies such as concussion[99] and psychological disorders including generalized anxiety and eating disorders.[100,101] In many cases, delineating whether anxiety serves as a CVS trigger, a symptom accelerator, or as the underlying cause of vomiting can be challenging.

3.2 | Genetic factors

A subset of children with CVS experience neuromuscular manifestations with additional medical complexity. These children may comprise as many as 1/3 of pediatric CVS and manifest various medical comorbidities (neuromuscular, cognitive, autonomic, and constitutional) and an earlier onset.[102,103] Predisposing genetic factors may be relevant based on the common maternal inheritance and familial patterns described.[75,104] Jansen-de Vries Syndrome (JdVS) was recently linked to CVS and results from de novo truncating mutations in the PPM1D gene (protein phosphatase Mg^{2+}/Mn^{2+} dependent 1D).[105] JdVS is associated with neurodevelopmental delay in the vast majority, hypotonia, short stature, small hands and feet, feeding difficulties, constipation and cyclic vomiting.[106] Behavioral features include anxiety, hypersocial affect, autism, and ADHD.[106] In a child with CVS

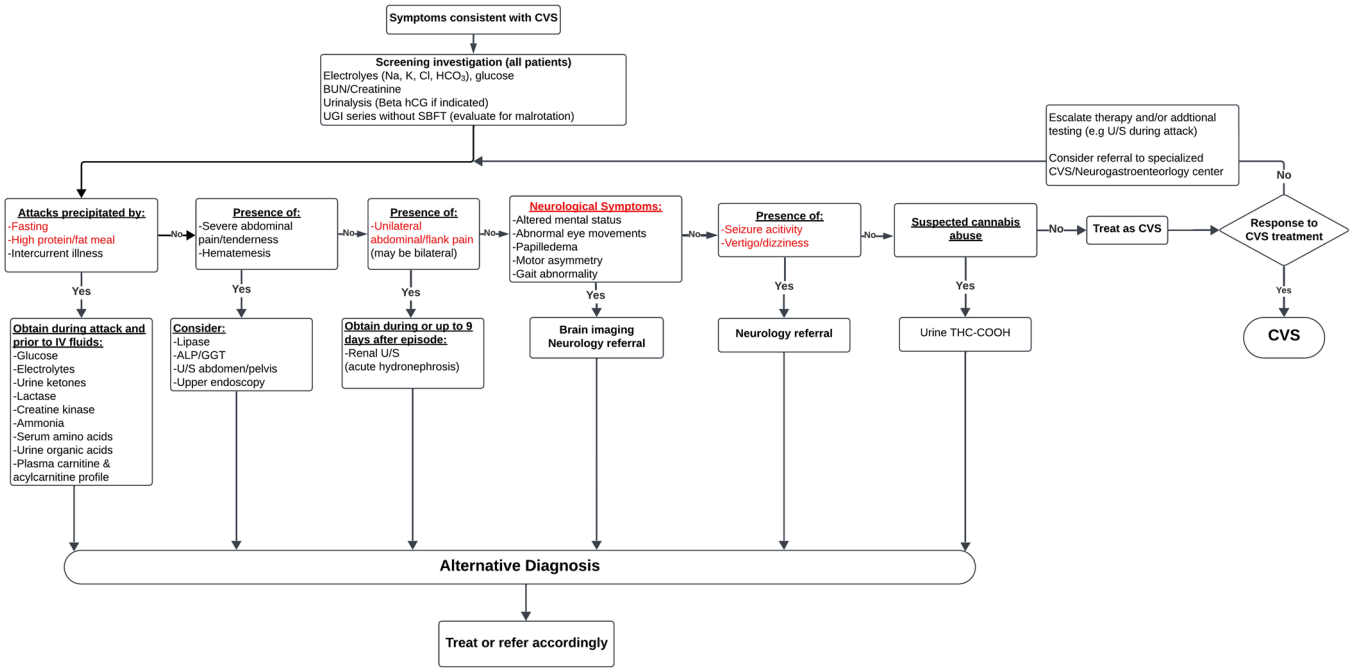


FIGURE 2 Suggested diagnostic algorithm for children presenting with symptoms consistent with CVS. The presence of symptoms/signs marked in red warrants urgent medical attention. This algorithm should serve as guidance and is not intended to replace clinical judgment. Due to symptom similarity between CVS and CHS, the recommended diagnostic evaluations also apply to CHS before a confirmed CHS diagnosis. ALT, alanine transaminase; CVS, cyclic vomiting syndrome; GGT, gamma-glutamyl transferase; IV, intravenous; SBFT, small bowel follow through; THC-COOH, 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol; UGI, upper gastrointestinal; U/S, ultrasound.

and unexplained neurodevelopmental delay, genetic screening for JdVS should be considered.

Mitochondrial dysfunction due to mitochondrial polymorphisms is a suggested pathophysiologic factor based on several lines of circumstantial evidence. There is (1) a matrilineal inheritance pattern (maternal migraine), (2) two identified mitochondrial DNA polymorphisms in a small cohort of children with CVS and migraine, and (3) some evidence of the efficacy of mitochondrial supplements in CVS.[30,75,107] However, there are only a small number of patients with documented mitochondrial dysfunction (e.g., complex I deficiency). A recent study using whole exome/genome sequencing in CVS suggests that *nuclear* susceptibility plays a role with mitochondrial dysfunction.[108] Gene variants in SCN4A, CACNA1A, RYR2, TRAP1, MEFV, and others were documented in CVS in significantly higher frequency than other susceptibility genes. These candidate genes may involve either cation transport or energy metabolism, and resulting dysfunction could lead to vagal hyperexcitability and CVS episodes. However, these findings and their therapeutic implications need further validation.

3.3 | Recommendations for diagnostic testing

The panel framed a recommendation based on available evidence that answered the question: "Does diagnostic testing (i.e. screening for specific anatomical, mucosal, genetic, metabolic, mitochondrial, motility or autonomic disorders), improve the accuracy of pediatric CVS diagnosis?"

Recommendation: The guideline panel suggests screening with limited serum and urine tests during a vomiting episode and an upper GI contrast series at any time in all children and adolescents with symptoms suggestive of CVS (conditional recommendation, very low certainty in the evidence of effects).

3.3.1 | Remarks

An upper GI contrast series (without small bowel follow through) as a one-time screen for intestinal malformation coupled with time-limited, empiric therapy was considered the most cost-effective strategy. As it screens for an anatomical anomaly, the upper GI contrast series can be performed at any time. One-time urinalysis along with serum glucose, electrolytes, and blood urea nitrogen/creatinine during a vomiting episode to screen for metabolic, endocrine, and renal disorders is also suggested. Selective, additional diagnostic testing should be performed in the presence of any alarm signs or atypical symptoms, such as progressively worsening (e.g., increasing episode frequency or hospital admissions), and based on lack of response to initial treatment trial over 2–3 months. To

limit healthcare spending and to avoid family and child stress related to extensive testing, the use of blanket screening tests for patients with typical symptoms of CVS should be avoided.

3.3.2 | Background and summary of the evidence

There were four studies that addressed this question in pediatric CVS. These included two retrospective studies on the yield and cost-effectiveness of diagnostic workup[13,109] and two retrospective studies assessing rate of other diagnoses in children with symptoms suggestive of CVS.[14,58] Included studies assessed the utility and cost-effectiveness of screening diagnostic tests such as screening laboratory studies, urine and plasma metabolic testing, upper endoscopy, and imaging studies of the abdomen (GI tract), kidneys, and brain.

3.3.3 | Benefits, harms, and resource use

The panel judged the desirable effects as moderate, relating to the benefit of diagnosing an alternate and potentially treatable condition. The cost effectiveness studies documented low yield of extensive diagnostic testing but cost efficacy of screening all patients with an upper GI contrast series, coupled with empiric prophylactic therapy for those with moderate disease severity.[13,24,109] Comprehensive testing resulted in a change in medical management in only 4% of patients.[13] The panel judged that the balance of effects probably favors performing limited blood and urine laboratory testing and an upper GI contrast series in all patients. The costs of performing comprehensive screening tests in every patient were noted as high, coupled with a low yield of revealing another diagnosis in the absence of specific red flags (Figure 2). Lack of insurance coverage and high costs for families may also prohibit the feasibility of extensive evaluation.

One retrospective study, published before consensus diagnostic criteria, noted a 12% incidence of surgical conditions (intestinal malrotation, hydronephrosis, and brain neoplasms) and a 2% incidence of endocrine or metabolic conditions in children with symptoms suggestive of CVS.[58] However, subsequent large series note an overall low rate of discovering alternate, treatable conditions.[14,58] While nonspecific findings of mitochondrial dysfunction were documented in a proportion of CVS patients, a monogenic mitochondrial disorder was not identified and it remains unclear how mitochondrial dysfunction fits into the pathophysiology of CVS.[14] Potential harms due to excessive investigations, exposure to ionizing radiation, and missed serious conditions that require surgical interventions were judged as moderate but relevant in the final recommendation to perform limited testing.

3.3.4 | Decision criteria and additional considerations

The panel rated the overall certainty of the evidence as very low based on the lack of comparison cohorts for the diagnostic strategies and the limited number of studies and participants in the studies. The panel judged that there is probably no impact on health equity due to equal access to basic testing. The interventions were judged to be probably acceptable and feasible. The Evidence to Decision framework is available here.

3.3.5 | Conclusions and implementation considerations

The guideline panel determined that there is very low certainty evidence for specific diagnostic testing in children with symptoms suggestive of CVS. The evidence included data from four studies in pediatric CVS. While data support the cost-effectiveness of limited diagnostic evaluation such as a one-time upper GI contrast series coupled with a time-limited (2–3 months) empiric treatment trial, there were limitations in the study designs evaluating diagnostic strategies, with most studies having retrospective designs and imprecision in the diagnostic accuracy estimates, as well as in the cost analyses. There was an overall low yield of extensive diagnostic evaluations, with a low percentage (4%) of testing that alters medical management. The panel therefore suggested basic urine and serum testing during a vomiting episode, along with an upper GI contrast series (without small bowel follow-through) at any time point to evaluate for intestinal malrotation in all children with symptoms consistent with CVS.

3.3.6 | Subgroup considerations

Diagnostic testing should be guided by the presence of alarm signs, age, and nonresponse to initial therapy. Increased vigilance is warranted in younger children (<3 years) to exclude metabolic disorders, anatomical conditions, and brain pathology. Some examples are fasting-triggered episodes (i.e., medium-chain acyl-CoA dehydrogenase deficiency) and unilateral abdominal or flank pain (hydronephrosis). Brain imaging should be performed in case of neurological symptoms (i.e., persistently altered mental status, motor asymmetry, ataxia, gait or speech abnormality) or progressively worsening (e.g., increasing episode frequency or hospital admissions) of vomiting attacks that do not respond to a time-limited treatment trial.

Progressive weight loss may also warrant additional medical workup. While mitochondrial dysfunction is identified in CVS, it remains uncertain how this relates to the pathophysiology.[30,110] A monogenic metabolic or mitochondrial disorder is unlikely in otherwise healthy children with CVS without neurodevelopmental delay. In children with cognitive delay, hypotonia, short stature, anxiety, and periodic vomiting, gene testing for JdVS should be considered.

3.3.7 | Monitoring and evaluation

A time-limited (2–3 months) treatment trial coupled with screening serum, urine, and upper GI contrast testing is warranted in all patients without alarm signs before performance of any additional testing. Consider evaluating for acute hydronephrosis with an abdominal ultrasound either *during an acute attack or within 9 days of symptom resolution*[98] in children who do not respond to initial therapy or who present with severe, unilateral/flank pain. Careful assessment for neurological symptoms is warranted in all patients. Progressively worsening pattern of emesis should prompt consideration of brain imaging, particularly in children <3 years of age. Upper endoscopy is warranted in patients who present with more frequent, chronic emesis (>weekly) or symptoms suggestive of a mucosal etiology.

3.3.8 | Research priorities

The panel recommends prospective studies with long-term follow-up to assess the sensitivity and specificity of specific diagnostic screening tests as well as downstream patient outcomes.

3.4 | Diagnostic algorithm

Figure 2 displays a suggested diagnostic algorithm based on GRADE review evidence and expert consensus.

3.5 | Diagnostic criteria

The timing of CVS attacks is of particular importance to an accurate diagnosis.[111] Retrospective studies and one small, prospective study documented a lower frequency of emesis but a higher peak rate of emesis per hour in children with CVS compared to other conditions.[32,112–114] A recent large, prospective study examined the diagnostic characteristics of children with CVS diagnosed in a specialized CVS center compared to children with episodic vomiting due to other etiologies.[17] An episode frequency of 4–10 episodes/12 months ($p = 0.002$) and a duration of >2 h ($p < 0.001$) yielded 74% (95% cofidence iterval [CI] = [51.6–89.9]) and 93% (95% CI = [79.6–98.4]) sensitivity respectively for distinguishing CVS from non-CVS conditions. Nearly all patients with CVS reported an average episode duration of ≤7 days and ≥1 week of symptom freedom between episodes. While prior studies have reported a highly variable range of episode duration (1 h to 10 days),[2–4,115] most of the literature supports a maximum duration of 5–7 days with more prolonged episodes representing atypical patients.[14,112,113] During episodes, patients with CVS more commonly experience multiple bouts of vomiting per hour for several hours, ($p < 0.001$), stereotypical symptoms ($p = 0.008$) and continued retching despite emptying stomach contents ($p = 0.008$).[17] As noted, many studies document a high prevalence of personal and/or family history of migraine in children with CVS.[10,32] Taken together, these data inform updated, evidence-based diagnostic criteria for pediatric CVS (Table 2a).

TABLE 2 (a) Recommended diagnostic criteria for pediatric CVS and (b) pediatric CHS. All listed criteria are required for a diagnosis of CVS or CHS. Supportive remarks include additional findings that may support the diagnosis.

(a)

1. Stereotypical episodes of acute onset, repetitive vomiting multiple times per hour
2. ≥4 discrete episodes in the prior 12 months, lasting 2 h to 7 days
3. Episodes at least 1 week apart
4. Return to baseline health between episodes

Supportive remarks:

History or family history of migraine

Episodes associated with listlessness, diaphoresis, photophobia, unrelenting nausea, abdominal pain, and/or incessant retching after emptying stomach

Less acute or intermittent symptoms, such as abdominal pain and nausea, can be present between episodes

(b)

1. Stereotypical episodes of vomiting resembling CVS in terms of onset, duration, and frequency
2. Presentation after prolonged (e.g., 1–2 years), excessive (e.g., near daily) cannabis use
3. Resolution of vomiting episodes by sustained (at least 6 months) cessation of cannabis use

Supportive remarks:

May be associated with pathological bathing behavior (prolonged hot baths or showers)

Diagnosis strengthened by positive urine THC test

Abbreviations: CHS, cannabinoid hyperemesis syndrome; CVS, cyclic vomiting syndrome; THC = Δ, Δ9-tetrahydrocannabinol.

There is a lack of data on the diagnostic characteristics of pediatric CHS. Therefore, symptom-based diagnostic criteria are largely based on expert consensus and evidence derived from adult populations (see Table 2b for recommended diagnostic criteria).

4 | DISCUSSION

CVS is a highly prevalent, yet underdiagnosed disorder associated with a substantial healthcare burden.[2,4,116] While a variety of conditions may mimic its clinical presentation, evidence supports a clinical approach that utilizes history-based criteria coupled with judicious use of diagnostic testing and a time-limited treatment trial as the most cost-effective strategy. One-time, basic urine and serum laboratory testing, along with an upper GI contrast series to rule out intestinal malrotation, is recommended for all patients. Additional diagnostic testing should be guided by specific warning signs, worsening of symptoms, and inadequate response to standard therapy.

CHS is a condition related to CVS. Evidence suggests a rising prevalence of CHS in the United States, presumably due to the legalization of recreational cannabis in the United States.[45,46] There is ongoing scientific interest in understanding whether CHS is best categorized as a CVS subtype or an independent CVS-related entity that presents after prolonged and excessive cannabis use. Children and adolescents with CVS and CHS display nearly identical symptom patterns in terms of timing and characteristics of vomiting attacks, and it is critical to avoid misclassification of these entities. Eventual definitive differentiation of these two overlapping entities will require robust characterization of CHS with regard to the frequency, duration, and dosages of use to define minimum thresholds combined with correlation with urinary THC-COOH levels.

The strength of these guidelines includes the use of the evidence-based GRADE approach and a systematic literature review as a basis for the recommendations. These guidelines are limited by indirectness and lack of large-scale studies evaluating the utility of diagnostic tests in children with symptoms suggestive of CVS. Future studies should include prospective investigations of the sensitivity and specificity, along with the cost-effectiveness of diagnostic screening tests.

5 | CONCLUSION

In summary, these guidelines formulate diagnostic testing recommendations and provide updated, evidence- and symptom-based diagnostic criteria for pediatric CVS. They also highlight the emerging need to evaluate for CHS when diagnosing CVS. As the first diagnostic practice guideline for pediatric CVS utilizing the GRADE approach, this document should replace prior NASPGHAN (2008) expert consensus recommendations.

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CONFLICT OF INTEREST STATEMENT

Katja Karrento served as a consultant for Takeda Pharmaceuticals, Neurogastrx, AbbVie, and Eli Lilly. John M. Rosen received honoraria from Focus Medical Communications and Elsevier. Sally E. Tarbell served as a consultant for Takeda Pharmaceuticals. Amy A. Gelfand received royalties from UpToDate and honoraria from Elsevier, the American Academy of Neurology, the Taiwan Headache Society, and the Weill Cornell Neurology Department. She received a stipend from the American Headache Society. B.U.K. Li serves as a consultant for Takeda Pharmaceuticals, UpToDate, and GLG Consulting. Robert M. Issenman has served on a drug monitoring committee for Takeda Pharmaceuticals. The remaining authors declare no conflicts of interest.

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REFERENCES

1. Li BUK, Balint JP. Cyclic vomiting syndrome: evolution in our understanding of a brain-gut disorder. *Adv Pediatr*. 2000; 47(1):117-160.
2. Fitzpatrick E, Bourke B, Drumm B, Rowland M. The incidence of cyclic vomiting syndrome in children: population-based study. *Am J Gastroenterol*. 2008;103(4):991-995. doi:10.1111/j.1572-0241.2007.01668.x.
3. Abu-Arafeh I, Russell G. Cyclical vomiting syndrome in children: a population-based study. *J Pediatr Gastroenterol Nutr*. 1995; 21(4):454-458. doi:10.1097/00005176-199511000-00014
4. Ertekin V, Selimoğlu MA, Altnkaynak S. Prevalence of cyclic vomiting syndrome in a sample of Turkish school children in an urban area. *J Clin Gastroenterol*. 2006;40(10):896-898. doi:10.1097/01.mcg.0000212627.83746.0b
5. Chang C-H, Hikita T, Takabayashi N, Sakaguchi M. Prevalence and incidence of cyclic vomiting syndrome in Japan: a study using Japanese claims data. *PLoS One*. 2022; 17(12):e0279502.
6. Tarbell SE, Li BUK. Health-related quality of life in children and adolescents with cyclic vomiting syndrome: a comparison with published data on youth with irritable bowel syndrome and organic gastrointestinal disorders. *J Pediatr*. 2013;163(2): 493-497. doi:10.1016/j.jpeds.2013.01.025
7. Tarbell SE, Li BUK. Anxiety measures predict health-related quality of life in children and adolescents with cyclic vomiting

syndrome. *J Pediatr*. 2015;167(3):633-638.e1. doi:10.1016/j.jpeds.2015.05.032.

8. Wang-Hall J, Li BUK, Tarbell SE. Family health-related quality of life in pediatric cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr*. 2018;66(5):738-743.
9. Thavamani A, Umapathi KK, Khatana J, Bhandari S, Kovacic K, Venkatesan T. Cyclic vomiting syndrome-related hospitalizations trends, comorbidities & health care costs in children: a population based study. *Children*. 2022;9(1):55. doi:10.3390/children9010055
10. Li BUK, Murray RD, Heitlinger LA, Robbins JL, Hayes JR. Is cyclic vomiting syndrome related to migraine? *J Pediatr*. 1999;134(5):567-572. doi:10.1016/s0022-3476(99)70242-8.
11. Venkatesan T, Levinthal DJ, Li BUK, et al. Role of chronic cannabis use: cyclic vomiting syndrome vs cannabinoid hyperemesis syndrome. *Neurogastroenterol Motil*. 2019;31(Suppl 2):e13606. doi:10.1111/nmo.13606.
12. 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(3):379-393. doi:10.1097/MPG.0b013e318173ed39.
13. Lucia-Casadonte CJ, Whaley KG, Chogle AS. Yield and costs of evaluating children with cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr*. 2018;67(1):13-17. doi:10.1097/MPG.0000000000001901.
14. Moses J, Keilman A, Worley S, Radhakrishnan K, Rothner AD, Parikh S. Approach to the diagnosis and treatment of cyclic vomiting syndrome: a large single-center experience with 106 patients. *Pediatr Neurol*. 2014;50(6):569-573.
15. Isoldi S, Di Nardo G, Mallardo S, et al. Cyclic vomiting syndrome in children: a nationwide survey of current practice on behalf of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) and Italian Society of Pediatric Neurology (SINP). *Ital J Pediatr*. 2022;48(1):156.
16. Redon S, Donnet A. Cyclic vomiting syndrome, a common language? A 20-year bibliometric study. *Acta Neurol Belg*. 2023;123(4):1241-1245.
17. Bujarska M, Bora G, Li BU, et al. Diagnostic characteristics of pediatric cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr*. 2025;80(3):417-425.
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
19. Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P. Guidelines international network: toward international standards for clinical practice guidelines. *Ann Intern Med*. 2012;156(7):525-531.
20. Schünemann HJ, Al-Ansary LA, Forland F, et al. Guidelines international network: principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med*. 2015;163(7):548-553.
21. Langer G, Meerpohl JJ, Perleth M, Gartlehner G, Kaminski-Hartenthaler A, Schünemann H. GRADE-Leitlinien: 1. Einführung—GRADE-Evidenzprofile und Summary-of-Findings-Tabellen. *Z Evid Fortbild Qual Gesundhwes*. 2012;106(5):357-368.
22. Graham R, Mancher M, Wolman D, Greenfield S, Steinberg E. *Clinical Practice Guidelines We Can Trust*. National Academies Press; 2011.
23. Schünemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *Can Med Assoc J*. 2014;186(3):E123-E142.
24. Karrento K, Rosen JM, Tarbell SE, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition 2025 guidelines for management of cyclic vomiting syndrome in children. *J Pediatr Gastroenterol Nutr*. 2025;80:1028-1061. doi:10.1002/jpn3.70020
25. Li BUK. Managing cyclic vomiting syndrome in children: beyond the guidelines. *Eur J Pediatr*. 2018;177(10):1435-1442. doi:10.1007/s00431-018-3218-7
26. 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(3):363-366. doi:10.1016/s0022-3476(99)70135-6
27. Kolacz J, Kovacic K, Dang L, Li BUK, Lewis GF, Porges SW. Cardiac vagal regulation is impeded in children with cyclic vomiting syndrome. *Am J Gastroenterol*. 2023;118:1268-1275. doi:10.14309/ajg.0000000000002207
28. Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. *Inf Manag*. 2004;42(1):15-29.
29. Lee LY, Abbott L, Mahlangu B, Moodie SJ, Anderson S. The management of cyclic vomiting syndrome: a systematic review. *Eur J Gastroenterol Hepatol*. 2012;24(9):1001-1006.
30. Zaki E, Freilinger T, Klopstock T, et al. Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. *Cephalalgia*. 2009;29(7):719-728. doi:10.1111/j.1468-2982.2008.01793.x
31. 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(1):50-58.
32. Dipasquale V, Falsaperla R, Bongiovanni A, Ruggieri M, Romano C. Clinical features and long-term outcomes in pediatric cyclic vomiting syndrome: a 9-year experience at three tertiary academic centers. *Neurogastroenterol Motil*. 2022;34(3):e14224.
33. Yu ES, Priyadharsini SSY, Venkatesan T. Migraine, cyclic vomiting syndrome, and other gastrointestinal disorders. *Curr Treat Options Gastroenterol*. 2018;16:511-527.
34. Karrento K, Venkatesan T, Zhang L, Pawela L, Simpson P, Li BUK. Percutaneous electrical nerve field stimulation for drug-refractory pediatric cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr*. 2023;77(3):347-353. doi:10.1097/MPG.0000000000003876
35. Barone JC, Butler MP, Ross A, Patterson A, Wagner-Schuman M, Eisenlohr-Moul TA. A scoping review of hormonal clinical trials in menstrual cycle-related brain disorders: studies in premenstrual mood disorder, menstrual migraine, and catamenial epilepsy. *Front Neuroendocrinol*. 2023;71:101098.
36. El Hassani MEM, Saad B, Mounir M, Kouach J, Rahali DM. Catamenial cyclic vomiting syndrome responding to oestrogen therapy: an adolescent case report. *Pan Afr Med J*. 2019;33(1).
37. Patino SH, Kaur N, Azhar M, Gutman DS. S2051 catamenial cyclic vomiting syndrome in a young adult. *Am J Gastroenterol*. 2020;115:S1076.
38. Sato T, Uchigata Y, Uwadana N, Kita K, Suzuki Y, Hayashi S. A syndrome of periodic adrenocorticotropin and vasopressin discharge. *J Clin Endocrinol Metab*. 1982;54(3):517-522. doi:10.1210/jcem-54-3-517.
39. Wolff SM, Adler RC, Buskirk ER, Thompson RH. A syndrome of periodic hypothalamic discharge. *Am J Med*. 1964;36(6):956-967.
40. Gosalvez-Tejada A, Li BUK, Simpson P, Zhang L, Kovacic K. Natural history of pediatric cyclic vomiting syndrome: progression to dysautonomia. *J Pediatr Gastroenterol Nutr*. 2023;76(6):737-742. doi:10.1097/MPG.0000000000003738
41. Venkatesan T, Sengupta J, Lodhi A, et al. An Internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome (CVS). *Exp Brain Res*. 2014;232:2563-2570.
42. Lonsdale H, Kimsey KM, Brown JM, et al. Pediatric cannabinoid hyperemesis: a single institution 10-year case series. *J Adolesc Health*. 2021;68(2):255-261. doi:10.1016/j.jadohealth.2020.09.024

43. DeVuono MV, Parker LA. Cannabinoid hyperemesis syndrome: a review of potential mechanisms. *Cannabis Cannabinoid Res*. 2020;5(2):132-144. doi:10.1089/can.2019.0059
44. Darmani NA, Belkacemi L, Zhong W. Δ9-THC and related cannabinoids suppress substance P-induced neurokinin NK1-receptor-mediated vomiting via activation of cannabinoid CB1 receptor. *Eur J Pharmacol*. 2019;865:172806.
45. Bhandari S, Jha P, Lisdahl KM, Hillard CJ, Venkatesan T. Recent trends in cyclic vomiting syndrome-associated hospitalisations with liberalisation of cannabis use in the state of Colorado. *Intern Med J*. 2019;49(5):649-655. doi:10.1111/imj.14164
46. Dosani K, Koletic C, Alhosh R. Cannabinoid hyperemesis syndrome in pediatrics: an emerging problem. *Pediatr Rev*. 2021;42(9):500-506.
47. Zhu JW, Gonsalves CL, Issenman RM, Kam AJ. Diagnosis and acute management of adolescent cannabinoid hyperemesis syndrome: a systematic review. *J Adolesc Health*. 2021;68(2):246-254.
48. Allen JH. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut*. 2004;53(11):1566-1570. doi:10.1136/gut.2003.036350
49. Cordova J, Biank V, Black E, Leikin J. Urinary cannabis metabolite concentrations in cannabis hyperemesis syndrome. *J Pediatr Gastroenterol Nutr*. 2021;73(4):520-522. doi:10.1097/mpg.0000000000003220
50. Shah M, Jergel A, George RP, Jenkins E, Bashaw H. Distinguishing clinical features of cannabinoid hyperemesis syndrome and cyclic vomiting syndrome: a retrospective cohort study. *J Pediatr*. 2024;271:114054.
51. Moeller KE, Kissack JC, Atayee RS, Lee KC. Clinical interpretation of urine drug tests. *Mayo Clin Proc*. 2017;92(5):774-796. doi:10.1016/j.mayocp.2016.12.007
52. Goodwin RS, Darwin WD, Chiang CN, Shih M, Li S-H, Huestis MA. Urinary elimination of 11-Nor-9-Carboxy-Δ9-tetrahydrocannnabinol in cannabis users during continuously monitored abstinence*. *J Anal Toxicol*. 2008;32(8):562-569. doi:10.1093/jat/32.8.562
53. Spindle TR, Cone EJ, Schlienz NJ, et al. Urinary excretion profile of 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH) following smoked and vaporized cannabis administration in infrequent cannabis users. *J Anal Toxicol*. 2019;44(1):1-14. doi:10.1093/jat/bkz038
54. Selimoglu MA, Ertekin V, Tan H, Selimoglu E. Idiopathic cyclic vomiting syndrome associated with gastroesophageal reflux and chronic sinusitis. *J Pediatr*. 2003;143(4):545.
55. Williams JC, Abell TL. Maternal predominance in cyclic vomiting pattern in gastroparesis.: 311. *J Investig Med*. 2007;55(1):S299.
56. Christensen CJ, Johnson WD, Abell TL. Patients with cyclic vomiting pattern and diabetic gastropathy have more migraines, abnormal electrogastrograms, and gastric emptying. *Scand J Gastroenterol*. 2008;43(9):1076-1081.
57. Weinstein M. Underlying disorders in cyclic vomiting syndrome. *Clin Pediatr*. 2005;44(9):805-808.
58. Li BUK, Murray RD, Heitlinger LA, Robbins JL, Hayes JR. Heterogeneity of diagnoses presenting as cyclic vomiting. *Pediatrics*. 1998;102(3 Pt 1):583-587. doi:10.1542/peds.102.3.583
59. Arifuddin RM, Baichi MM, Philips G, Maliakkal BJ. Eosinophilic gastritis—a rare entity masquerading as cyclical vomiting: 145. *Am J Gastroenterol*. 2005;100:S71.
60. Kamal A, Sarvepalli S, Selvakumar P, Lopez R, Radhakrishnan K, Gabbard S. Assessment of gastric emptying times between pediatrics and adults with cyclic vomiting syndrome. *J Clin Gastroenterol*. 2020;54(9):e89-e92. doi:10.1097/MCG.0000000000001352
61. McCallum RW. Rapid or normal gastric emptying as new supportive criteria for diagnosing cyclic vomiting syndrome in adults. *Med Sci Monit*. 2014;20:1491-1495. doi:10.12659/MSM.890547
62. Kovacic K, Elfar W, Rosen JM, et al. Update on pediatric gastroparesis: a review of the published literature and recommendations for future research. *Neurogastroenterol Motil*. 2020;32(3):e13780. doi:10.1111/nmo.13780
63. Dimopoulou A, Zavras N, Alexopoulou E, Fessatou S, Dimopoulou D, Attilakos A. Superior mesenteric artery syndrome mimicking cyclic vomiting syndrome in a healthy 12-year-old boy. *J Paediatr Child Health*. 2020;56(1):168-170.
64. Egritas Gurkan O, Unlusoy Aksu A, Demirtas Z, Dalgic B. Rare disorders can be an underlying cause of cyclic vomiting: familial Mediterranean fever, *Helicobacter pylori* gastritis, and cavernous transformation of the portal vein. *Turk J Gastroenterol*. 2015;26:461-467.
65. Cotticelli G, Gravina AG, Miranda A, et al. Cyclic vomiting in a young patient with superior mesenteric artery syndrome. *Acta Gastro-Enterol Belg*. 2013;76(3):351-352.
66. Korson M. Metabolic etiologies of cyclic or recurrent vomiting. *J Pediatr Gastroenterol Nutr*. 1995;21:S15-S19.
67. Gelfand AA, Gallagher RC. Cyclic vomiting syndrome versus inborn errors of metabolism: a review with clinical recommendations. *Headache*. 2016;56(1):215-221.
68. McAbee GN, Morse AM, Cook W, Tang V, Brosgol Y. Neurological etiologies and pathophysiology of cyclic vomiting syndrome. *Pediatr Neurol*. 2020;106:4-9.
69. Fitzgerald M, Crushell E, Hickey C. Cyclic vomiting syndrome masking a fatal metabolic disease. *Eur J Pediatr*. 2013;172:707-710.
70. Rinaldo P. Mitochondrial fatty acid oxidation disorders and cyclic vomiting syndrome. *Dig Dis Sci*. 1999;44(8 Suppl):S97.
71. Teneva BH, Popov NT, Ivanov IS, Minkov IN, Vachev TI. Identification of mtDNA 7028C and 16519T polymorphisms in a pediatric-onset cyclic vomiting syndrome (CVS) patient. *Biotechnol Biotechnol Equip*. 2013;27(5):4111-4114.
72. Salpietro CD, Briuglia S, Merlino MV, Di Bella C, Rigoli L. A mitochondrial DNA mutation (A3243G mtDNA) in a family with cyclic vomiting. *Eur J Pediatr*. 2003;162:727-728.
73. Boles RG, Baldwin EE, Prezant TR. Combined cyclic vomiting and Kearns-Sayre syndromes. *Pediatr Neurol*. 2007;36(2):135-136.
74. Boles RG, Adams K, Ito M, Li BUK. Maternal inheritance in cyclic vomiting syndrome with neuromuscular disease. *Am J Med Genet A*. 2003;120(4):474-482.
75. Boles RG, Adams K, Li BUK. Maternal inheritance in cyclic vomiting syndrome. *Am J Med Genet A*. 2005;133(1):71-77.
76. Tripathy NR. Cyclic vomiting syndrome in a case of type II diabetes. *Int J Diabetes Dev Ctries*. 2016;36(3):378-379.
77. Niehaus AD, Cooper H, Lee CU. Mitochondrial HMG-CoA synthase deficiency: a cyclic vomiting mimic without reliable biochemical markers. *J Investig Med High Impact Case Rep*. 2024;12:23247096241267154. doi:10.1177/23247096241267154
78. Bancel L-P, Germain N, Guemann A-S, Joncquel Chevalier Curt M, Dessein A-F. Abnormal ketone bodies in a 22-month-old boy presenting with recurrent vomiting and metabolic acidosis. *Clin Chem*. 2019;65(11):1460-1462. doi:10.1373/clinchem.2019.306712
79. Ogiso K, Koriyama N, Akao A, et al. Type 1 diabetes complicated with uncontrollable adult cyclic vomiting syndrome: a case report. *J Diabetes Metab Disord*. 2015;14:72.
80. White WL, Bagga V, Campbell DI, Hart AR, Ushewokunze S. Cyclical vomiting syndrome secondary to a Chiari I malformation—a case report. *Childs Nerv Syst*. 2017;33:2083-2085.
81. Chopra SS, Kulkarni SD, Hegde AU, Shah KN. Cyclical vomiting syndrome with bilateral epileptiform discharges. *Indian Pediatr*. 2011;48(2):143-145.

82. Jernigan SA, Ware LM. Reversible quantitative EEG changes in a case of cyclic vomiting: evidence for migraine equivalent. *Dev Med Child Neurol*. 1991;33(1):80-85.
83. Michael M, Tsatsou K, Ferrie CD. Panayiotopoulos syndrome: an important childhood autonomic epilepsy to be differentiated from occipital epilepsy and acute non-epileptic disorders. *Brain Dev*. 2010;32(1):4-9.
84. Covanis A. Panayiotopoulos syndrome: a benign childhood autonomic epilepsy frequently imitating encephalitis, syncope, migraine, sleep disorder, or gastroenteritis. *Pediatrics*. 2006; 118(4):e1237-e1243.
85. Ozkara C, Benbir G, Celik AF. Misdiagnosis due to gastrointestinal symptoms in an adolescent with probable autonomic status epilepticus and Panayiotopoulos syndrome. *Epilepsy behav*. 2009;14(4):703-704.
86. Pietrafusa N, de Palma L, De Benedictis A, et al. Ictal vomiting as a sign of temporal lobe epilepsy confirmed by stereo-EEG and surgical outcome. *Epilepsy Behav*. 2015;53:112-116.
87. Lope RJR, Wong SW, Wu LL. Episodic vomiting and headache in children: consider occipital epilepsy. *J Paediatr Child Health*. 2010;46(4):204-206.
88. Stickler GB. Relationship between cyclic vomiting syndrome and migraine. *Clin Pediatr*. 2005;44(6):505-508.
89. Redon S, Elzière M, Lambert I, Donnet A. Cyclic vomiting syndrome associated with benign paroxysmal vertigo: a case report. *Acta Neurol Belg*. 2020;120:1207-1208.
90. Al-Twaijri WA, Shevell MI. Pediatric migraine equivalents. *Pediatr Neurol*. 2002;26(5):365-368.
91. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1): 1-211. doi:10.1177/0333102417738202
92. Good PA. Neurologic investigations of childhood abdominal migraine: a combined electrophysiologic approach to diagnosis. *J Pediatr Gastroenterol Nutr*. 1995;21:S44-S48.
93. Chelimsky G, Madan S, Alshekhlee A, Heller E, McNeeley K, Chelimsky T. A comparison of dysautonomias comorbid with cyclic vomiting syndrome and with migraine. *Gastroenterol Res Pract*. 2009;2009(1):701019.
94. Hong SJ, Choe B-H. A case of visceral autonomic neuropathy complicated by Guillain-Barre syndrome accompanied with cyclic vomiting syndrome-like disorder in a child. *Pediatr Gastroenterol Hepatol Nutr*. 2015;18(2):128-133.
95. Enokizono T, Nemoto K, Fujiwara J, Tanaka R, Ohto T. Cyclic vomiting syndrome after acute autonomic and sensory neuropathy. *Pediatr Int*. 2017;59:503-505.
96. Schulte-Bockholt A, Kugathasan S, Mesrobian HGO, Werlin SL. Ureteropelvic junction obstruction: an overlooked cause of cyclic vomiting. *Am J Gastroenterol*. 2002;97(4): 1043-1045.
97. Rosman PN, Dutt M, Nguyen HT. A curable and probably often-overlooked cause of cyclic vomiting syndrome. *Semin Pediatr Neurol*. 2014;21(2):60-65.
98. Tsai J-D, Huang F-Y, Lin C-C, et al. Intermittent hydronephrosis secondary to ureteropelvic junction obstruction: clinical and imaging features. *Pediatrics*. 2006;117(1):139-146.
99. Jan MMS, Camfield PR, Gordon K, Camfield CS. Vomiting after mild head injury is related to migraine. *J Pediatr*. 1997; 130(1):134-137.
100. Fennig S, Fennig S. Diagnostic delays and dilemmas. *Gen Hosp Psychistry*. 1999;21(2):122-127.
101. Thavamani A, Velayuthan S, Patel D, Al-Hammadi N, Sferra TJ, Sankararaman S. Association of anxiety and gastrointestinal comorbidities in repeat hospital admissions in pediatric cyclic vomiting syndrome. *Am J Gastroenterol*. 2023; 118(8):1439-1445.
102. Boles RG, Powers ALR, Adams K. Cyclic vomiting syndrome plus. *J Child Neurol*. 2006;21(3):182-189.
103. Sandomirsky K, Marchi E, Gavin M, Amble K, Lyon GJ. Phenotypic variability and gastrointestinal manifestations/interventions for growth in NAA10-related neurodevelopmental syndrome. *Am J Med Genet, Part A*. 2023;191(5):1293-1300.
104. Haan J, Kors E, Ferrari M. Familial cyclic vomiting syndrome. *Cephalalgia*. 2002;22(7):552-554.
105. Jansen S, Geuer S, Pfundt R, et al. De novo truncating mutations in the last and penultimate exons of PPM1D cause an intellectual disability syndrome. *Am J Hum Genet*. 2017; 100(4):650-658.
106. Wojcik MH, Srivastava S, Agrawal PB, et al. Jansen-de Vries syndrome: expansion of the PPM1D clinical and phenotypic spectrum in 34 families. *Am J Med Genet, Part A*. 2023; 191(7):1900-1910.
107. Boles RG, Lovett-Barr MR, Preston A, Li BU, Adams K. Treatment of cyclic vomiting syndrome with co-enzyme Q10 and amitriptyline, a retrospective study. *BMC Neurol*. 2010; 10:10. doi:10.1186/1471-2377-10-10
108. Bar O, Ebenau L, Weiner K, Mintz M, Boles RG. Whole exome/genome sequencing in cyclic vomiting syndrome reveals multiple candidate genes, suggesting a model of elevated intracellular cations and mitochondrial dysfunction. *Front Neurol*. 2023;14:1151835.
109. Olson AD, Li BUK. The diagnostic evaluation of children with cyclic vomiting: a cost-effectiveness assessment. *J Pediatr*. 2002;141(5):724-728.
110. Chelimsky G, Simpson P, Zhang L, et al. Impaired mitochondrial bioenergetics function In pediatric chronic overlapping pain conditions with functional gastrointestinal disorders. *Pain Res Manag*. 2021;2021:6627864. doi:10.1155/2021/6627864
111. Li BUK. Cyclic vomiting: the pattern and syndrome paradigm. *J Pediatr Gastroenterol Nutr*. 1995;21:S6-S10.
112. Pfau BT, Li BUK, Murray RD, Heitlinger LA, McClung HJ, Hayes JR. Differentiating cyclic from chronic vomiting patterns in children: quantitative criteria and diagnostic implications. *Pediatrics*. 1996;97(3):364-368.
113. Drumm BR, Bourke B, Drummond J, et al. Cyclical vomiting syndrome in children: a prospective study. *Neurogastroenterol Motil*. 2012;24(10):922-927.
114. Dong M, Li ZH, Li G. Clinical characteristics of 41 children with cyclic vomiting syndrome. *Zhonghua Er Ke Za Zhi*. 2008;46(6): 450-453.
115. Haghighat M. Cyclic vomiting syndrome in children: experience with 181 cases from southern Iran. *World J Gastroenterol*. 2007; 13(12):1833-1836. doi:10.3748/wjg.v13.i12.1833
116. Sagar RC, Sood R, Gracie DJ, et al. Cyclic vomiting syndrome is a prevalent and under-recognized condition in the gastroenterology outpatient clinic. *Neurogastroenterol Motil*. 2018; 30(1):e13174.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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