Acute Management of Pediatric Cyclic Vomiting Syndrome: A Systematic Review

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Objectives To synthesize quantitative and qualitative data on pharmacologic interventions of pediatric cyclic vomiting syndrome and their effectiveness in disease management in the acute care setting.

Study design Using keywords, 799 studies published up from December 1954 to February 2018 were extracted from MEDLINE via Pubmed, Embase via OVID, CINAHL via EBSCO, and Cochrane Controlled Trials Registry. Studies were evaluated for inclusion and exclusion by 2 independent reviewers using predetermined inclusion and exclusion criteria.

Results The search yielded 84 studies for full review, of which 54 were included in the systematic review. Studies were subsequently separated into 1 group of 6 case series studies containing quantitative data on sumatriptan, ondansetron, phenothiazines, prokinetic agents, carbohydrate, isometheptene, and aprepitant; 1 one group consisting only of qualitative studies containing expert recommendations.

Conclusions Ondansetron has the most quantitative and qualitative evidence to support its inclusion in pediatric emergency department protocols as a rescue therapy. Sumatriptan and aprepitant are potential candidates for inclusion as abortive therapies. Qualitative data from retrospective studies and case reports are not applicable to a larger patient population. This report informs a need for controlled, prospective cohort studies and randomized, controlled trials to optimize current management protocols and to develop new medical interventions. *(J Pediatr 2019;214:158-64)*.

Cyclic vomiting syndrome (CVS) was first described in 1882 by Samuel Gee in the St. Bartholomew's Hospital Reports.[1,2] It is characterized by acute attacks of vomiting occurring sporadically or regularly, lasting hours to days, and resulting in repeated emergency department (ED) visits and hospitalizations.[3-5] The onset of vomiting typically occurs at the same time of the day, often in early morning or late night. The recurrent episodes of vomiting are followed by symptom-free interval periods lasting weeks to months.[4] Because CVS symptoms are common to a plethora of other diseases, it is a generally misrecognized and underdiagnosed disease. The diagnosis of CVS in both adults and children in the ED is particularly poor despite the heavy reliance of these patient populations on acute care services.[6] The pathophysiology of CVS is largely unknown, but it is postulated to be multifactorial in origin. It is thought to involve aberrant brain–gut pathways leading to migraine, mitochondrial abnormalities, calcium channel abnormalities, and hyperactivity of the hypothalamic–pituitary–adrenal axis.[5,7]

The peak prevalence of CVS occurs between 2 and 7 years of age, but the disorder can persist into adult life.[4] Although pediatric CVS is not a highly prevalent disease, affecting up to 1.9%-2.3% of the pediatric population, it occupies 15% of the children's time and they miss a mean of 20 days of school each year.[2,8] Additionally, the average cost of ED visits, hospital stays, diagnostic tests, and missed work amounts to $17 035 per year per child with CVS.[3]

To date, there have been no controlled trials on the management of pediatric CVS in the acute care setting, nor do standardized, evidence-based protocols exist. As a result, much of available treatment protocols are based on empirical evidence and expert opinion. This systematic review aims to synthesize all available evidence on acute pharmacologic interventions used in the management of pediatric CVS. Furthermore, it serves to inform the quality of and potential updates to current treatment protocols as well as the need for future controlled clinical trials.

Diagnosis

The first diagnostic criteria for CVS were created in 1994, and the most recent Rome IV criteria for functional gastrointestinal disorders was published 22 years

CVS	Cyclic vomiting syndrome
ED	Emergency department
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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later in 2016.[2] Before the publication of the Rome IV criteria, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) published its own diagnostic criteria[3]: at least 5 attacks in any interval, or a minimum of 3 attacks during a 6-month period; episodic attacks of intense nausea and vomiting lasting 1 hour to 10 days and occurring at least 1 week apart; stereotypical pattern and symptoms in the individual patient; vomiting during attacks occurs at least 4 times per hour for at least 1 hour; and return to baseline health between episodes.

Different to the NASPGHAN criteria, the Rome IV criteria preserved from Rome III the criterion of only "at least 2 attacks in any interval," maintaining that early diagnosis is important. Rome IV also omits "nausea" as a criterion because it is difficult for children to communicate the symptom.[4]

Four Phases of CVS and Treatment

There are 4 phases recognized in the CVS literature that a patient undergoes during an episode of cyclic vomiting (**Figure 1**). Differential management is applied according to the patient's phase at presentation, with the ultimate goal of improving quality of life at each phase.[9,10] This systematic review specifically focuses on the abortive and rescue therapies targeting the prodromal and vomiting phases of CVS, which can be prescribed in an acute care setting such as the pediatric ED.[6]

Interepisodic Phase

During the interepisodic phase, the patient is free of CVS symptoms and is managed with daily prophylactic therapies to prevent attacks or decrease their number. Common prophylactic pharmacologic interventions include propranolol, cyproheptadine and pizotifen with both antihistamine and 5-HT_2 receptor antagonist actions, and the tricyclic antidepressant amitriptyline.

Prodromal Phase

The prodromal phase may last from minutes to hours, and it portends the onset of vomiting through symptoms such as extreme nausea, abdominal pain, lethargy, pallor, and anorexia. This phase is managed with abortive therapies such as antiemetics, antimigraine agents, and sedatives in an effort to prevent an incipient vomiting attack.

Vomiting Phase

The vomiting phase involves vomiting and retching every 5-10 minutes, and these episodes can last from 1 to 3 days. This phase is managed with rescue therapies such as antiemetics and sedatives to stop the vomiting attack and break the cyclic vomiting cycle. Intravenous fluid therapy is a critical adjunct to antiemetics and sedatives at this phase for hydration and correction of metabolic acidosis and electrolyte imbalance.

Recovery Phase

The recovery phase marks the end of 1 cyclic vomiting cycle, during which the patient is often fatigued. Intravenous fluids and rest are recommended to prevent relapse.

Methods

The literature search included all reviews, case studies, case series, case control studies, retrospective cohorts, prospective cohorts, randomized controlled trials in English, French, Spanish, and Chinese on the subject of acute care medications for pediatric CVS (**Figure 2**). Studies were excluded if the study sample included subjects greater than 18 years old or if the study only focused on prophylactic and ongoing care.

There were 529 studies extracted from MEDLINE via Pubmed, Embase via OVID, CINAHL via EBSCO, and Cochrane Controlled Trials Registry (all articles published up to February 2018) using keyword searches consisting of variations on "pediatric" and "cyclic vomiting syndrome." References from the retrieved studies were searched manually to yield additional papers.

Two reviewers independently scrutinized titles and abstracts and judged articles to be excluded or to undergo full-text article review according to predetermined inclusion and exclusion criteria. The full-text article was obtained if it was judged eligible by at least 1 reviewer. The full-text articles were then selected to be included or excluded, by 2 independent reviewers, and consensus for inclusion was reached by discussion.

Quantitative data were extracted with sample sizes and age of onset pooled for each pharmacologic intervention. Patients were stratified into 3 response rate categories (100%, >50%-<100%, <50%) for all studies containing quantitative data. Stratification was based on outcomes reported by each study. The percentage of patients in each category was calculated. Qualitative clinical recommendations were extracted and summarized as expert opinion and anecdotal evidence. Owing to the lack of controlled trials on the management of pediatric CVS in the acute care setting, statistical analysis was unable to be performed.

The level of evidence of quantitative studies was evaluated based on the hierarchy of research design set by the US Preventive Services Task Force. Level I, the highest level of the hierarchy, indicates evidence of randomized controlled trials and level III, the lowest level of the hierarchy, indicates opinions of clinical experts based on experience or case reports.[11] Level II is numerically subdivided into levels 1-3. All evaluated studies in this systematic review received a grading of II-3, indicating evidence obtained from dramatic results in uncontrolled experiments.

The study quality for quantitative studies was evaluated using the Quality Appraisal Checklist for Case Series Studies developed by the Institute of Health Economics as guidance.[12] The Checklist is composed of 20 items appraising

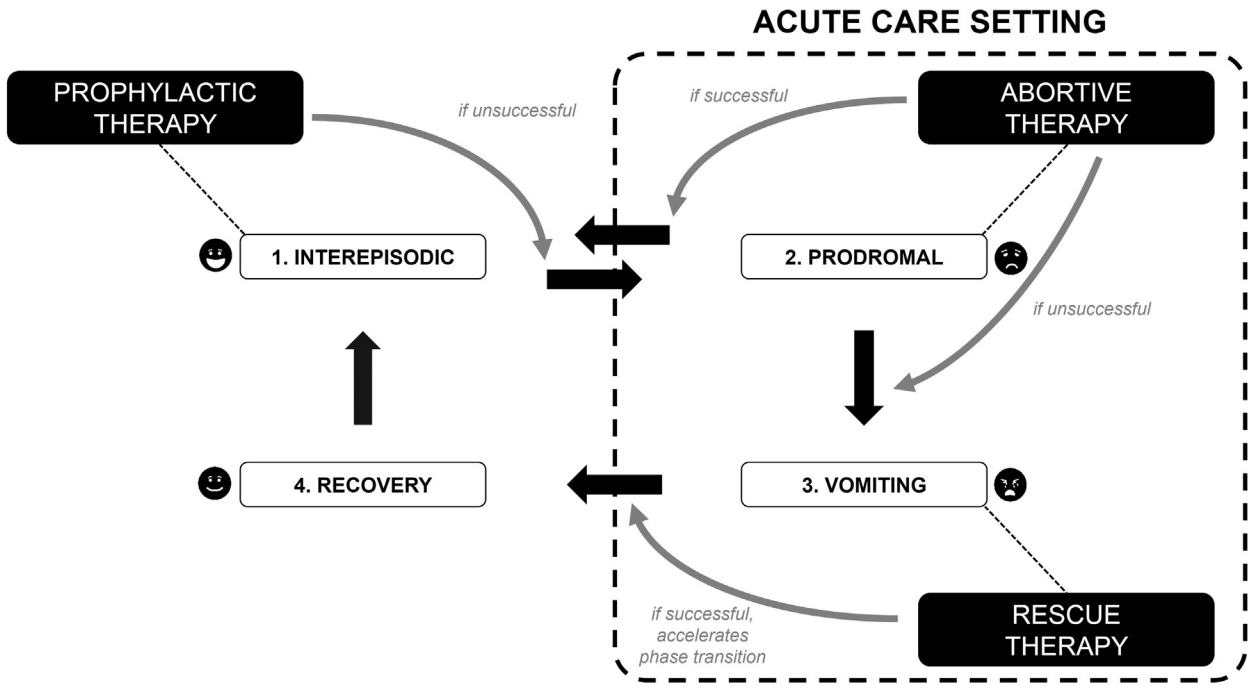

Figure 1. The 4 phases of CVS. A typical CVS attack entails the progression through phases 1 to 4, particularly if prophylactic therapy during the interepisodic phase and abortive therapy during the prodromal phase are unsuccessful. In the acute care setting, successful abortive therapy leads the patient to avoid phases 3 and 4 and regress back to phase 1, while successful rescue therapy accelerates the patient's progression from phase 3 to phase 4 and 1.

study objective, design, population, intervention and co-intervention, outcome measurement, statistical analysis, results and conclusions, and competing interests and sources of support. However, the checklist was not developed with a scoring system.[13] For the purposes of this systematic review, a scoring system was devised a priori based on the recommendations of the Institute of Health Economics methodology paper. Depending on the number of checklist items met, the studies were scored according to criteria determined as poor (<50% yes responses, and/or >50% no responses), fair (>50% yes responses, and/or <50% no responses), and good (>70% yes responses).

Results

There are no controlled trials on pharmacologic interventions for the management of CVS in the acute care setting to date. Six single-arm studies were deemed eligible for quantitative data extraction, including 2 open-label trials,[14,15] 1 prospective case series,[16] and 3 retrospective case series[17-19] (**Table I**; available at www.jpeds.com). In 2 of the included studies, the data of interest on CVS management were only included as additional patient information but not as the primary or secondary outcome.[16,17] Of the 7 pharmacologic interventions for which there exist quantitative data, ondansetron had the highest sample size (n = 97), with 59%-66% of patients experiencing at least a 50% decrease in vomiting duration or frequency during the vomiting phase.

Subcutaneous sumatriptan and aprepitant studies were more limited in sample size but showed promising results. When subcutaneous sumatriptan was administered during the prodromal phase, 69% of patients experienced at least a 50% decrease in vomiting frequency after progressing to the vomiting phase, compared with the last CVS attack before treatment initiation.[14] With administration of aprepitant during the prodromal phase, 76% of patients experienced at least a 50% decrease in vomiting duration and frequency during the vomiting phase, compared with the year before treatment initiation.[15] Phenothiazines (eg, promethazine), prokinetic agents (eg, cisapride), and isometheptene had a higher percentage of patients who experienced less than 50% reduction of vomiting frequency.[18]

Fifty-three studies were deemed eligible for qualitative data extraction. These included case studies, case series, and reviews containing original expert recommendations (**Table II**; available at www.jpeds.com). The acute CVS pharmacologic treatments that most frequently appeared in this literature include ondansetron, sumatriptan, lorazepam, chlorpromazine, diphenhydramine, and promethazine. It is important to note that not every medication listed in the table indicates a positive patient response; individual patients have been unresponsive to select medications on a case-by-case basis.

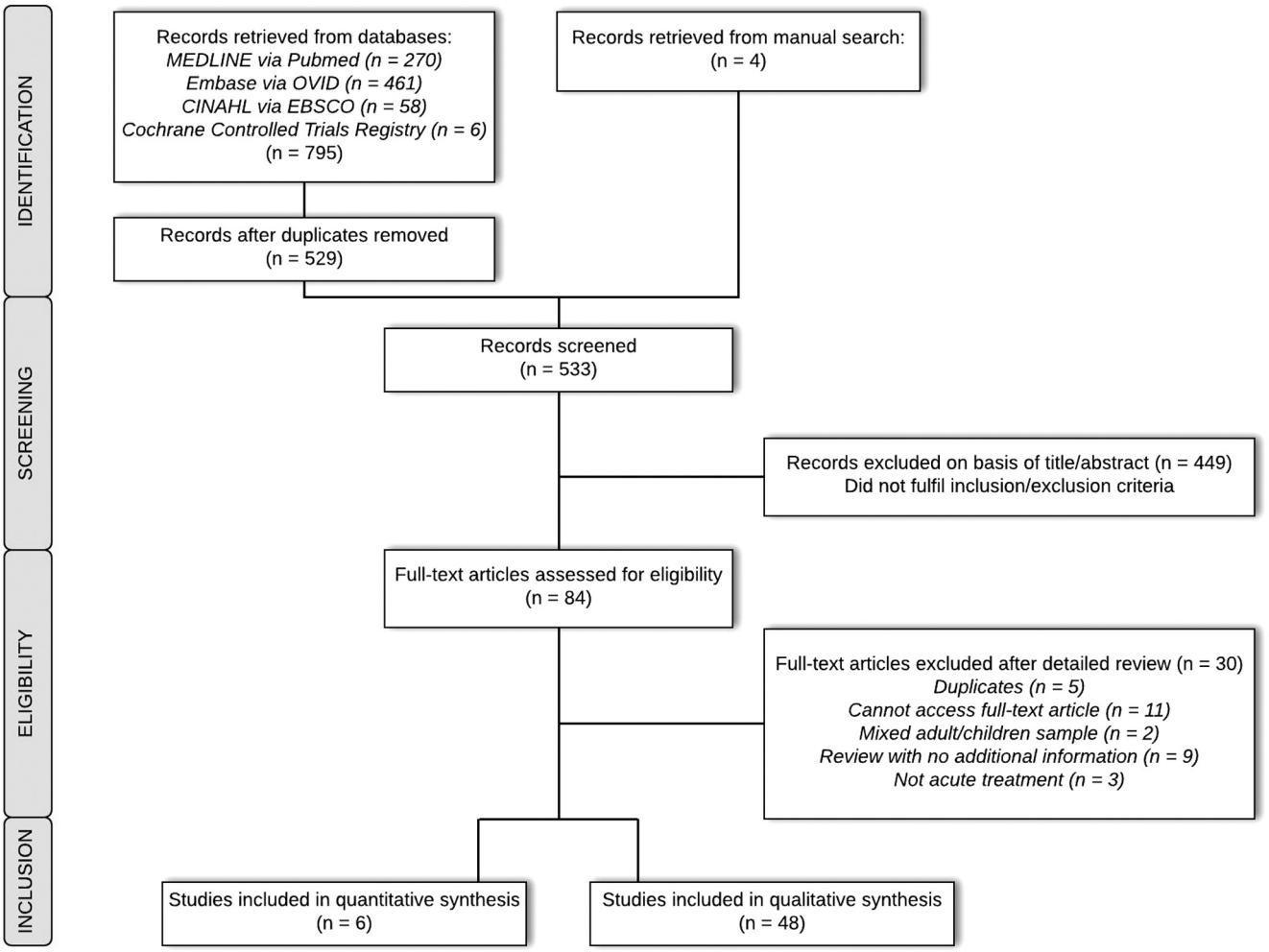

Figure 2. Systematic review search strategy.

Discussion

Although there is no existing standardized, evidence-based CVS protocol across pediatric EDs, 2 sample protocols for the management of CVS in acute care settings are separately proposed by Sunku and Li in 2004 and the NASPGHAN Task Force in 2008.[3,20] According to Sunku and Li, the treatment protocol depends on whether concomitant migraine is present. For migraine-associated and abdominal migraine-associated CVS, the analgesic ketorolac and antimigraine agent sumatriptan or frovatriptan are recommended. Recommended for non–migraine-associated CVS are intravenous fluid therapy, the antiemetic ondansetron with the sedative lorazepam, or chlorpromazine with diphenhydramine, both of which exert antiemetic and sedative effects.[20] Similarly, the NASPGHAN Task Force recommended intravenous fluid therapy, the combination of ondansetron and lorazepam, the combination of chlorpromazine and diphenhydramine for more sedative effects, and ketorolac for abdominal pain. The task force also recommended triptans such as sumatriptan to be used in children 12 years and older.[3]

Comparing these sample protocols with the results of this systematic review, ondansetron is a promising antiemetic that is and has been widely used in the acute management of pediatric CVS, particularly targeting the vomiting phase as a rescue therapy. Relative to all other pharmacologic interventions in this systematic review, ondansetron has the most quantitative and qualitative evidence to support its inclusion in pediatric ED protocols for CVS.[16-19] The data illustrate its role in terminating vomiting episodes, but its effectiveness in aborting incipient vomiting attacks in the prodromal phase is not reported.[17,18] Treatment decisions involving ondansetron should therefore be made with caution, emphasizing accurate identification of the phase at presentation and allowing for optimal, phase-specific therapy. Sedation, achieved by medications such as lorazepam, plays a prominent role in the acute care setting both as a rescue therapy in the vomiting phase as well as an abortive therapy in the prodromal phase. The purpose of sedation is 2 pronged; it

both provides symptomatic relief and termination of the phase. The combination of ondansetron and lorazepam has been recommended in numerous publications, although there is a lack of quantitative data to support this approach.[3,21,22]

Since the publication of these sample protocols, 2 open-label trials on sumatriptan and aprepitant in the last decade have shown promising results.[14,15] At the time of the NASPGHAN publication, triptans were not approved for use in children younger than 18 years of age, but the limit has since been reduced to 12 years and older.[3] In contrast with these recommendations, the more recent trial included children as young as 3.3 years up to 11.6 years of age for treatment with subcutaneous sumatriptan. Additionally, despite being an antimigraine agent, sumatriptan demonstrated a greater than >50% decrease in vomiting in 1 subject among a 3-subject, non–migraine-associated CVS group. Although the result does not reach statistical significance ($P = .217$), the potential therapeutic benefits of sumatriptan in this CVS subtype should be explored.[18] The aprepitant trial included children from 4.0 to 15.8 years of age. Owing to the wide age range for which sumatriptan and aprepitant are suitable, and preliminary results supporting efficacy, they are potential candidates for inclusion in pediatric CVS management protocols in acute care settings.

Owing to the abundance of case studies in CVS literature, it is common to find anecdotal evidence describing the lack of efficacy of any select medication used in CVS management. In particular, the phenothiazines promethazine and prochlorperazine, as well as metoclopramide, seem to be ineffective according to data from numerous quantitative and qualitative studies despite their wide use.[3,21,23] The use of these medications also entails the risk of extrapyramidal reactions. Owing to the nature of the included studies, which are considered the lowest level of evidence, no conclusions can be drawn with regard to the generalizability of these cases to a larger population. However, based on the evidence, it may be prudent to exclude these medications in management protocols until further trials are conducted.

In general, commonly prescribed medications for CVS management in the acute care setting, including ketorolac and chlorpromazine with diphenhydramine, lack sufficient quantitative evidence to support their use. Despite their known analgesic and sedative effects, respectively, future clinical trials should ideally be carried out to confirm their level of efficacy in the context of pediatric CVS. Considering the difficulties of running clinical trials on medications already so extensively used in practice, however, retrospective studies that more closely examine pooled data from pediatric EDs on the use of these medications in CVS should be considered. The use of repurposed medications such as ketamine and subsedative dosages of propofol are unexplored in the pediatric CVS literature, but warrant further investigation.[6,24]

Last, the importance of intravenous fluid therapy in the CVS management protocol cannot be overstated.[3] Generally, fluid prevents or corrects dehydration, which can occur owing to excessive vomiting. A 5%-10% dextrose solution is indicated to attenuate metabolic crises that are exacerbated by catabolism after minimal food intake. A 0.45% or 0.9% NaCl + KCl can be used to replenish electrolytes. Although the optimal intravenous fluid concentration of dextrose and NaCl varies according to the extent of dehydration, metabolic acidosis, and electrolyte depletion, intravenous fluid therapy is considered standard for CVS patients, as is their inclusion in CVS management protocols.

Based on the current best evidence, sumatriptan and aprepitant are potential abortive therapies to be included in acute management protocols for pediatric CVS. For rescue therapies during the vomiting phase, ondansetron has the most quantitative and qualitative evidence to support its inclusion, although its use in adjunct with lorazepam is recommended in the literature despite lack of quantitative data. Intravenous fluid therapy is essential in the acute care setting (**Table II**).

This systematic review was limited in its ability to perform statistical analysis owing to the lack of control groups in CVS studies. Furthermore, 4 of the 6 studies included in quantitative data extraction did not report patient characteristics such as age of onset, family history of migraines, or vomiting pattern on an individual basis. The median age of onset in each pooled sample was therefore unknown and was not presented in **Table I**. A family history of migraines and vomiting pattern, if found in the included studies, were presented as percentages of the entire sample population. The heterogeneity of pharmacologic interventions received within a sample population was another limitation of the data extraction and analysis, because patient characteristics were not specific to each intervention. A family history of migraines and vomiting pattern were therefore not included in **Table I**.

To date, there are no double-blind, multicenter, controlled trials on pharmacologic interventions for CVS in the acute care setting.[25] Evidence is limited, most of which is extracted from retrospective case series. This systematic review informs a need for controlled, prospective studies and randomized controlled trials to assess the efficacy of potential pharmacologic interventions and to optimize current CVS management protocols in the pediatric ED. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

The Diagnostic Value of Gamma Glutamyl Transpeptidase in Children and Adolescents with Liver Disease

Cohen MI, McNamara H. J Pediatr 1969;75:838-42.

Gamma-glutamyl transpeptidase (GGTP) was first reported as a potential marker for liver disease in 1961. Cohen and McNamara, in the first study to do so, sought to understand the usefulness of GGTP in children with liver disease. The authors enrolled 41 participants with known liver disease and 74 control participants with no signs or symptoms of liver disease. They found that serum GGTP levels were higher in the participants with known hepatic disease. Furthermore, when the investigators compared GGTP levels in patients with hepatitis vs those with cirrhosis, they found higher GGTP levels in the patients with cirrhosis. The authors postulated that the difference in relative GGTP elevation could be explained by chronic scarring. That is, in patients with cirrhotic disease, the scarring process causes an elevation of GGTP.

We now know gamma-glutamyltransferase (GGT) is a microsomal enzyme located in the bile canaliculi as well as the heart, lungs, pancreas, and seminal vesicles.[1] In children, GGT is a more sensitive measure of biliary obstruction or biliary disease than alkaline phosphatase because alkaline phosphatase can vary with age. Importantly, GGT reference ranges change with age. The normal range is higher in the neonatal period and declines to adult ranges by about 5-7 months of age.

GGT can be a useful laboratory test in the workup of neonatal cholestasis. An elevated GGT could indicate extrahepatic biliary disease such as biliary atresia[1] and a low GGT could indicate the presence of intrahepatic cholestasis (eg, PFIC 1, PFIC 2). GGT is also useful in children who have undergone liver transplantation and could indicate acute cellular rejection or biliary complications.[1] Elevated GGT levels can be seen with a number of drugs and may not represent liver disease; therefore, caution is advised when interpreting an elevated GGT.

We are grateful to Cohen and McNamara for their contribution in establishing that GGTP is a useful biomarker to differentiate children with and without liver disease. Given how frequently GGT is obtained in a tertiary pediatric liver clinic, it is easy to forget that this laboratory test was first studied in pediatrics only 50 years ago.

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Reference

1. Cabrera-Abreu JC, Green A. Gamma-glutamyltransferase: value of its measurement in paediatrics. Ann Clin Biochem 2002;39:22-5.

Table I. Synthesized evidence of pharmacologic interventions for acute attacks of CVS

Treatments	No. of studies	Referenced study	CVS diagnostic criteria	Level of evidence	Study quality	Age of onset (y)	No. of patients	Response rate		
								100%	>50%-<100%	<50%
Sumatriptan (subcutaneous)	2	14	ICHD-II criteria	II-3	Fair	5.6 ± 5.4	49	4/49 (8%)*	30/49 (61%)*	15/49 (31%)*
		18	Rome I criteria	II-3	Fair					
Sumatriptan (nasal spray)	1	14	ICHD-II criteria	II-3	Fair	6.4 ± 4.6	5	1/5 (20%)*	1/5 (20%)*	3/5 (60%)*
Ondansetron (intravenous)	3	17	Research definition of CVS ([65,66])	II-3	Poor	5.2 ± 5.2	97	NR	57/97 (59%)†	40/97 (41%)†
		18	Rome I criteria	II-3	Fair					
		19	Criteria of authors' devising	II-3	Poor					
Ondansetron (oral)	1	16	NR	II-3	Fair	8.9 ± 5.0	85	NR	56/85 (66%)†	29/85 (34%)†
Carbohydrate	2	17	Research definition of CVS ([65,66])	II-3	Poor	3.9 ± 6.5	60	NR	35/60 (58%)	25/60 (42%)
Phenothiazine (eg, promethazine)	3	18	Rome I criteria	II-3	Fair	5.8 ± 4.2	63	NR	13/63 (21%)†	50/63 (79%)†
Prokinetic agents (cisapride)	1	18	Rome I criteria	II-3	Fair	5.8 ± 4.2	40	NR	8/40 (20%)†	32/40 (80%)†
Isometheptene	1	18	Rome I criteria	II-3	Fair	5.8 ± 4.2	13	NR	4/13 (31%)†	9/13 (69%)†
Aprepitant	1	15	NASPGHAN criteria	II-3	Good	4.3 ± 3.0	25	3/25 (12%)‡	16/25 (64%)‡	6/25 (24%)‡

ICHD-II, International Classification of Headache Disorders, second edition; *NR*, not reported.
*100%: no vomiting or progression to vomiting phase; >50%-<100%, <50%: reduction in vomiting frequency after progressing to the vomiting phase, compared with the last CVS attack before treatment initiation.
†>50%-<100%, <50%: decrease in vomiting duration or frequency during the vomiting phase.
‡100%: no CVS episodes; >50%-<100%, <50%: reduction in frequency (number of episodes/year) and intensity (episode duration in days) of CVS episodes.

Table II. Pharmacologic interventions used in the acute management of pediatric CVS q2h[36]

Medications	Referenced studies	Route of administration	Dose	Frequency	Goal	Action	Side effects	Note
Abortive therapy in prodromal phase based on best evidence								
Sumatriptan (triptan)	1,3,7,9,10,14,17, 20-23,26-38	Oral	25.0 mg[36]	Max 1 dose daily	Antimigraine	5-$HT_{1B/1D}$ agonist	Weakness, chest and neck burning, arrhythmias, coronary vasospasm, headache, flushing, dizziness, bad aftertaste, induration and swelling at the injection site, hyperreflexia, incoordination, and chest, jaw and neck tightness.	
		Subcutaneous	(age × 4 + 20) / (100 × 3.0 mg)[14]	NR				
		Intranasal	5.0-20.0 mg[3,7,10,14]	Max 1 dose daily				
Zolmitriptan* (triptan)	9,10,22,33, 37,39,40	Intranasal	5.0 mg[10]	Max 1 dose daily				Alternatives to sumatriptan
Frovatriptan* (triptan)	9,20,33,37	Oral	2.5 mg[36]	Max 1 dose daily				
Rizatriptan* (triptan)	9,20	Oral	5.0-10.0	q2h[36]				
Aprepitant	3,7,9,15,22, 27,37,41	Oral	30 min before vomiting/day 2/ day 3 < 15 kg: 80/40/40 mg 15–20 kg: 80/80/80 mg > 20 kg: 125/80/80 mg[15]	NR	Antiemetic	Neurokinin-1 receptor antagonist	Alopecia, constipation, dyspepsia, fatigue, hiccups, and weakness.	Used in combination with a corticosteroid and 5-HT_3 receptor antagonist
Rescue therapy in vomiting phase based on best evidence								
Ondansetron	1,3,7,9,10,19-22, 24,26,28,29, 32,34,36, 37,39-52	Intravenous	0.3-0.4 mg/kg (Max: 20.0 mg or 0.45 mg/kg/day)[7,10]	q4-6h[7,10]	Antiemetic	5-HT_3 antagonist	Constipation, headache, drowsiness, dry mouth, bronchospasm, tachycardia, hypokalemia, seizures, pancytopenia, lightheadedness, diarrhea, and transient increases in alanine amino transferase, aspartate aminotransferase, and bilirubin.	
		Oral	4.0-8.0 mg[22]	q12h[22]				
		Rectal	0.15-0.4 mg/kg[40]	q6-8h[40]				
Granisetron*	3,9,20,22,28, 37,39,40,42	Intravenous	10.0 mcg/kg	q4-6h				Alternative to ondansetron
Lorazepam (benzodiazepine)	3,7,9,10,17,20, 21,23,24, 27-29,32,34, 36,39,40,42-45,49,50,52-55	Intravenous	0.05-0.2 mg/kg (Max: 4.0 mg)[3,7,10,29]	q4-6h[7]	Sedatives, antianxiety, anticonvulsant	5-HT_3 antagonist	Disorientation, dizziness, GI symptoms, hypotension, mild ataxia, mood changes, rashes, respiratory depression, hallucinations, and sedation.	Useful in adjunct to ondansetron
		Oral	0.05-0.2 mg/kg (Max: 4.0 mg)[3,7,10,29]	q4-6h[7]				
Diazepam* (benzodiazepine)	26	NR	NR	NR				
5%-10% dextrose, 0.45% NaCl + KCl	3,10,23,28, 37,39,43, 47,53,54	Intravenous	Variable	Variable	Fluid and electrolyte maintenance and terminate ketosis	NA	NA	
Others								
Carbohydrate	3,16	Intravenous/ enteral	NR	NR	NR	NR	NR	

(*continued*)

Table II. Continued

Medications	Referenced studies	Route of administration	Dose	Frequency	Goal	Action	Side effects	Note
Promethazine (phenothiazine)	3,15,18,26,32,34, 36,41,44,46, 48,56,57	Oral Intravenous	0.25-0.5 mg/kg[34] NR	NR NR	Antiemetic	D_2-antagonist, H_1 antagonist	Extrapyramidal reactions, somnolence, tardive dyskinesia, and anti-cholinergic effects.	
Prochlorperazine (phenothiazine)	3,34,36,41,44	Oral	2.5-5.0 mg[34]	bid[34]	Antiemetic	D_2-antagonist	NR	
Chlorpromazine	3,9,10,20,21,24, 26,27,29,37, 40,42-44,49, 51,53,58-60	Intravenous Oral Rectal	0.5-1.0 mg/kg (Max: <5 years: 40 mg/day 5-12 years: 75 mg/day)[10,37] 0.15-0.3 mg/kg[53] 0.5-1.0 mg/kg[40]	q6-12h[10,37,53] q6-8h[40]	Antiemetic, Anxiolytic, Antihypertensive sedative, Antipsychotic	D_2-antagonist	Drowsiness, hypotension, seizure, drowsiness, jaundice, extrapyramidal/anticholinergic symptoms, hypotension (more with intravenous), arrhythmias, agranulocytosis, neuroleptic malignant syndrome, and dystonic reactions with chlorpromazine alone.	Used in adjunct with diphenhydramine intravenously
Diphenhydramine	3,9,10,20,21, 24,34,37,40, 42-44,46,49,56	Intravenous Oral	0.25-1.25 mg/kg (Max: 5.0 mg/kg/day, not to exceed 300 mg)[10,37]	q6h[10,37]	Sedative, antiemetic, antihistamine	H_1-antagonist	Respiratory depression, hallucinations, hypotension, dizziness, sedation, nausea, vomiting, xerostomia, blurred vision, and reactions common to antihistamines. CNS side effects more common than GI disturbances. May cause paradoxical excitement in children.	Used in adjunct with chlorpromazine
Metoclopramide	7,23,34,51,57, 58,61,62	Intravenous	1.0-2.0 mg/kg (Max: 10.0 mg)[34]	bid[34]	Prokinetic agent	5-HT_4 agonist	Extrapyramidal reactions	
Cisapride	18,19,58	Intravenous	NR	NR			NR	
Ketorolac	3,7,9,10,20,28, 33,37,54	Intravenous Oral	0.4-1.0 mg/kg (Max: 10-30 mg, 120 mg/day)[3,7,37] 0.4-1.0 mg/kg (Max: 10-30 mg, 120 mg/day)[3,7,37]	q6h[3,7,37] q6h[3,7,37]	Antimigraine	NSAID	GI hemorrhage and dyspepsia.	
Isometheptene (Midrin)	3,18,28	Oral	NR	q1h ≤ 5/12 hours	Antimigraine	Vasoconstrictor	NR	
Midazolam (benzodiazepine)	58	Intravenous	1.0-2.0 mg[58]	q1h[58]	Anxiolytic, sedative	NR	Bilious taste	
Clonidine	21,22,53,58,63	Intravenous	1.0-2.0 mcg/kg[58,63]	Bid[58] q6-8h[63]	Sedative	α2-Adrenergic agonist	NR	
Dexmedetomidine	21,22,53	Intravenous	0.25-0.5 mcg/kg over 5 minutes followed by an infusion of 0.25 mcg/kg/h over 12-18 hours[21]	NR			Nausea, atrial fibrillation, bradycardia, hypotension and alterations in central ventilator function.	

(*continued*)

Table II. Continued

Medications	Referenced studies	Route of administration	Dose	Frequency	Goal	Action	Side effects	Note
Ranitidine	21,29,43,49	Intravenous	NR	NR	Decreases stomach acid production	H_2-antagonist	NR	
Cimetidine	21,62	Intravenous	NR	NR			NR	
Famotidine	21	Intravenous	NR	NR			NR	
Omeprazole	29,62	Oral	20.0 mg[29]	q24h[29]	Decreases stomach acid production	Proton pump inhibitor	NR	
Rabeprazole	56	Oral	NR	NR			NR	
Lansoprazole	50	Intravenous	NR	NR			NR	
Dexamethasone	17,22,27,64	Oral	NR	NR	Antiemetic	Glucocorticoid receptor agonist	NR	Used in adjunct with aprepitant or 5-HT_3 antagonists
Ibuprofen	10,29,42	Oral	4.0-10.0 mg/kg[10] (Max: Children: 50.0 mg/kg/day or 2400 mg/day Adolescent: 3200 mg/day)	q6-8h[10]	Antiemetic	NSAID	Abdominal or epigastric pain.	
Cyclizine	45,51	NR	NR	NR	Antiemetic	H_1-antagonist	NR	
Erythromycin	3,42	NR	NR	NR	Antiemetic	Antibiotic	NR	Normally used in prophylactic treatment
Domperidone	51,58	NR	NR	NR	Antiemetic	D_2-antagonist	NR	
Droperidol	58	Intravenous	NR	NR	Antidopaminergic, antiemetic, antipsychotic, sedative	D_2-antagonist	NR	
Pentobarbital	24	Intravenous	NR	NR	Sedative	Barbiturate	NR	

CNS, central nervous system; *GI*, gastrointestinal; *NA*, not applicable; *NR*, not reported; *NSAID*, nonsteroidal anti-inflammatory drug.
Therapies are categorized by their usefulness as abortive or rescue therapies based on current best evidence.
*Included as alternatives to best evidence medications.