Predictors of Hospital Admission for Pediatric Cyclic Vomiting Syndrome

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Objectives To identify predictors of hospitalization in pediatric patients presenting to an emergency department (ED) for a cyclic vomiting syndrome (CVS) attack.

Study design We retrospectively reviewed patients with CVS seen at our institution between 2015 and 2018 and included those who met the Rome IV criteria for CVS. We identified all CVS-related ED visits and subsequently performed a case-control analysis, utilizing multivariate logistic regression, to identify clinical and demographic factors that may predict hospitalization.

Results In total, 219 patients with CVS (using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*) were identified, of which 65% met the inclusion criteria (median age 11 years). We identified 152 CVS-related ED visits, of which 62% resulted in hospitalization. Factors found to predict hospitalization using multivariate analyses included male sex ($P = .04$), younger age ($P = .027$), delayed presentation (>24 hours) to the ED ($P < .001$), and longer wait time prior treatment with antiemetics ($P = .029$).

Conclusion One-quarter of all patients with CVS had presented to the ED and nearly two-thirds of these ED visits resulted in hospitalization. A delayed presentation to the ED following the onset of symptoms was the strongest independent predictor of hospital admission, alongside male sex, younger age, and longer ED wait times before treatment with antiemetics. These findings suggest that early intervention may be key to successfully mitigating the risk of hospitalization for a CVS attack. *(J Pediatr 2021;232:154-8)*.

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First described by Samuel Gee in 1882,[1] cyclic vomiting syndrome (CVS) is a functional gastrointestinal disorder characterized by episodic attacks of intense nausea and vomiting lasting hours to days. Approximately 2% of school-age children may suffer from the disorder.[2] Although the exact etiopathologic mechanisms leading to the development of CVS are yet to be fully delineated, several hypotheses have been proposed. These include, among others, autonomic dysfunction, neuroendocrine dysregulation, comorbid psychiatric disorders, and mitochondrial dysfunction secondary to mitochondrial DNA abnormalities.[3-6]

Although most patients with CVS are generally managed in the outpatient setting, those more severely affected can require emergency department (ED) care and hospitalization to manage symptoms and dehydration during an attack, leading to significant resource utilization and associated healthcare costs. Despite significant advances in both the diagnosis and treatment of CVS, an analysis showed that both the number of unique hospitalizations per year and the mean cost per hospitalization have steadily increased between 2008 and 2018.[7] Yet, despite this alarming trend, little is known regarding factors that increase patients' risk of hospitalization for an attack. The primary objective of our study was to compare CVS-related ED visits that led to hospitalization with those that did not, and to subsequently develop a predictive model to evaluate the impact of such factors on patients' risk of hospitalization.

Methods

We used *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) diagnostic codes G43.A0 and G43.A1 (CVS) to identify patients diagnosed with CVS who were evaluated by pediatric gastroenterologists or neurologists at our institution between 2015 and 2018. We performed an initial review of all charts and excluded those of patients who did not meet Rome IV criteria for diagnosing CVS. We subsequently identified all ED visits for patients with confirmed CVS and extracted the relevant

CVS	Cyclic vomiting syndrome
ED	Emergency department
NSB	Normal saline bolus
IV	Intravenous
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*

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data. ED visits that occurred before patients' CVS diagnosis were excluded, whereas patients with charts containing only equivocal documentation pertaining to their diagnosis were reviewed by a second physician prior to determining their eligibility. We used the Research Electronic Data Capture platform to enter and store all extracted data.

Dependent and Independent Variables

The dependent variable was disposition from the ED (hospitalization vs discharge). Independent variables included sex, age, history of prior ED visits, use of prophylactic medications for CVS, use of rescue medications before presenting to the ED, duration of time from the onset of symptoms to presentation to the ED, number of antiemetics and total volume of normal saline boluses (NSB) prescribed by ED providers, and duration of time from arrival to the ED to treatment with an intravenous (IV) antiemetic and an IV NSB.

Statistical Analyses

All statistical analyses were performed with IBM SPPS Statistics Subscription (build 1.0.0.1327; Microsoft Windows 64-bit edition). We compared all ED visits for CVS that led to discharge with those that led to hospitalization. We first performed univariate analyses of categorical variables using the Pearson χ^2) and continuous variables using the Mann-Whitney *U* test. We subsequently performed a multivariate logistic regression analysis, using an Enter method, to identify variables that may predict hospitalization. For our logistic regression model, we only entered variables shown to be significantly associated with hospitalization on univariate analysis, using a cut-off *P* value of <.1. As in our univariate analyses, a *P* value of <.05 in our model was considered statistically significant.

Results

We identified 219 charts of patients diagnosed with CVS using ICD-10 codes G43.A0 and G43.A1, of which 139 met the eligibility criteria and are the subjects of the study (Figure); 53% were female (n = 74), and the mean age was 11.8 years (range 5-22 years). There was a total of 152 ED visits for acute CVS attacks; 77% (n = 107) of study participants had never presented to the ED for CVS, whereas 13.8% (n = 19) had presented between 1 and 2 times (low ED utilizers), 2.9 % (n = 4) presented between 3 and 5 times (medium ED utilizers) and 6.5% (n = 9) presented more than 5 times (high ED utilizers). As shown in Table I, there were no significant differences in the overall rate of hospitalization between the groups (44.4%, 76.9%, and 64.3% in the low, medium, and high utilization groups, respectively; *P* = .089). Overall, 61.8% of ED visits in our sample led to hospitalization (n = 94).

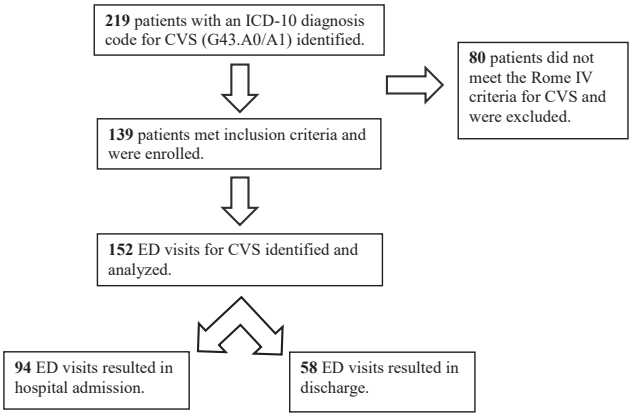

Figure. Flow chart showing the patient identification and enrollment process. Eligibility was determined using the Rome IV diagnostic criteria for CVS.

Univariate Analysis of Predictors of Hospitalization

A smaller percentage of first-time ED visits for CVS (47.2%) resulted in hospitalization compared with repeat ED visits (47.2% vs 66.4%; *P* = .039) (Table II). Patients hospitalized from the ED had a mean age of 9.6 ± 0.45 years compared with a mean age of 12.2 ± 0.63 years in discharged patients (*P* = .0001), whereas a larger percentage of male patients were hospitalized compared with female patients (77.4% vs 51.1%; *P* = .001). Overall, 71% (n = 61) of patients hospitalized were on daily prophylactic medications, compared with 50% of those who were discharged (n = 32) (*P* = .009), whereas the use of a rescue medication prior to presentation did not affect disposition (*P* = .49). Eighty percent (80.3%) of visits where the patient presented to the ED more than 24 hours after the onset of symptoms resulted in hospitalization, compared with 66.7% and 36.5% of visits where the patient presented to the ED between 12 and 24 hours, and less than 12 hours, following the onset of symptoms, respectively (*P* < .001). Patients who were hospitalized experienced longer wait times in the ED before receiving treatment with antiemetics (2.93 hours vs 2.09 hours in discharged patients; *P* = .001), whereas both the total number of IV antiemetics administer by the ED, and the wait time prior to receiving IV NSBs following arrival to the ED, was similar between the 2 groups (*P* = .49 and *P* = .173, respectively). Finally, a higher

Table I. Rate of hospital admission from the ED among low, medium, and high ED utilizers

ED utilization	Hospitalized (%)	Discharged (%)	All	*P* value
Low (1-2 visit)	12 (44.4)	15 (55.6)	27	
Medium (3-5visits)	10 (76.9)	3 (23.1)	13	**.082**
High (>5 visits)	72 (64.3)	40 (35.7)	112	
Total	94 (61.8)	58 (38.2)	152	

Values in bold are statistical significance at *P* values <.05.

Table II. Comparison of clinical and demographic factors by disposition status

Variables	Hospitalized	Discharged	All	*P* value
Sex (%)				**.001**
Male	48 (77)	14 (23)	62 (41)	
Female	46 (51)	44 (49)	90 (59)	
Age, y (SD)	9.57 (4.3)	12.18 (4.8)	10.6 (4.6)	**.001**
Prophylaxis for CVS (%)				**.009**
No	32 (50)	32 (50)	64 (43)	
Yes	61 (71)	25 (30)	86 (57)	
Rescue medication used pre-ED (%)				.491
No	40 (59)	28 (41)	68 (45)	
Yes	54 (64)	30 (36)	84 (55)	
Time to ED presentation (%)				**<.001**
Less than 12 h	19 (37)	33 (64)	52 (35)	
12-24 h	24 (68)	12 (33)	36 (24)	
>24 h	49 (80)	12 (20)	61 (42)	
History of prior ED visit (%)				**.039**
No	17 (47)	19 (53)	36 (24)	
Yes	77 (66)	39 (34)	116 (76)	
No. of IV antiemetics administered (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	.489
Time to treatment (antiemetic), h (SD)	2.93 (1.4)	2.09 (0.97)	2.61 (1.3)	**.001**
Volume of NSB (%)				**.004**
None	4 (25)	12 (75)	16 (11)	
10 mL/kg	1 (33)	2 (67)	3 (2)	
20 mL/kg	63 (71)	26 (29)	89 (61)	
>20 mL/kg	24 (62)	15 (39)	39 (27)	
Time to treatment (NSB), h (SD)	2.67 (1.3)	2.29 (0.87)	2.54 (0.10)	.173

Values in bold are statistical significance at *P* values <.05.

percentage of patients who received either 20 mL/kg, or >20 mL/kg, of IV NSBs were hospitalized than were discharged, whereas discharge was more likely when less than 20 mL/kg, or no IV NSBs, were administered ($P = .004$).

Multivariate Analysis of Predictors of Hospitalization

The logistic regression model explained 52.5% of the variance in ED disposition (Nagelkerke R^2), correctly predicted the outcome in 78.9% of cases, and was overall statistically significant ($\chi^2 = 64.657$; $P < .001$) (Table III).

Factors found to predict hospital admission from the ED for an acute CVS attack included male sex (OR 4.02; $P = .04$), decreasing age (OR 1.15; $P = .027$), wait time in the ED prior to receiving treatment with IV antiemetics (OR 1.7; $P = .029$), and a delayed (>24 hours) presentation to the ED following the onset of symptoms (OR 11.8; $P < .0001$). With regards to the latter, ED visits involving patient presenting between 12 and 24 hours following the onset of symptoms, compared with less than 6 hours, were also more likely to result in hospital admission, however, this was not statistically significant in our sample (OR 2.44; $P = .135$). A history of prior ED visits for CVS ($P = .143$), use of daily prophylactic medications ($P = .141$), and total volume of NSBs administered (0.445) were not found to predict hospital admission in our sample.

Table III. Predictors of hospitalization from the ED

Variables	B	SE	OR (CI 95%)	*P* value
Sex, male	−1.39	0.68	4.02 (1.06-15.2)	**.04**
Decreasing age	−1.38	0.062	1.15 (1.02-1.3)	**.027**
Time to presentation				
12-24 h	0.89	0.56	2.44 (0.75-7.80)	.135
>24 h	2.47	0.62	11.8 (3.53-39.5)	**<.0001**
Daily prophylaxis	0.79	0.54	0.45 (0.16-1.29)	.141
History of prior ED visit	1.09	0.75	3.0 (0.69-13.04)	.143
Time to treatment (antiemetic)	0.53	0.243	1.70 (1.06-2.73)	**.029**
Volume of NSB				
Up To 10 mg/kg	−0.95	1.03	0.19 (0.03-1.42)	.106
Up To 20 mg/kg	−0.71	1.68	0.49 (0.02-13.3)	.67
>20 mg/kg	0.273	0.53	0.76 (0.27-2.15)	.61

B, coefficient for the constant in the null model.
Values in bold are statistical significance at *P* values <.05.

Discussion

We found that a delay in presentation to the ED following the onset of symptoms was the strongest independent predictor of hospital admission, particularly for patients with CVS presenting >24 hours after symptom onset. Moreover, patients were more likely to be hospitalized the longer they waited in the ED before receiving their first antiemetic dose. These findings suggest an association between the timing of interventions following the start of an attack and the subsequent risk of hospitalization, with earlier interventions, even by 1 hour as shown in our study, more likely to produce favorable outcomes. Although further studies are needed to better delineate this association, this finding nevertheless provides valuable insight that may help shape future management guidelines. Furthermore, our findings are consistent with and provide evidential support for the expert opinions set forth by the North American Society for Pediatric Gastroenterology, Nutrition, and Hepatology in their consensus statement regarding the diagnosis and management of CVS that recommends earlier intervention within few hours of symptom onset.[8] Similarly, our findings are parallel to those of a landmark clinical trial investigating early vs delayed almotriptan use for aborting migraine headaches, a disorder closely related to CVS, which found that almotriptan was significantly more effective when taken earlier in the course of an attack when symptoms were mild.[9]

Furthermore, we found that both male sex and younger age independently increased the likelihood of hospitalization. The latter finding is not surprising given that younger patients are more likely to become dehydrated due to the intense vomiting often experienced during an attack. Parents and providers are also likely to have a lower threshold for admission in younger patients. As this is often an important consideration when determining patients' disposition, it likely contributed to the elevated risk for hospitalization for younger patients in our sample.

On the other hand, the increased risk of hospitalization for male patients in our sample conflicts with prior studies investigating sex and gender differences in patients with other functional gastrointestinal disorders or with migraine headaches, conditions that have shown higher perceived symptom severity and higher healthcare utilization rates in female patients compared with male patients.[10-12] Studies investigating such measures in patients with CVS are noticeably absent, although some studies have reported a higher prevalence of CVS in female pateints.[8] One possible explanation is that given their higher perceived symptom severity, female patients may be more likely to seek emergency care earlier in the course of an attack, thereby lowering their risk of hospitalization.

Although CVS is uniquely characterized by stereotypical episodes of intense nausea and vomiting, there nevertheless exists significant heterogeneity and variability in its phenotypic manifestations, particularly about the attack frequency and intensity, attack triggers, and occurrence of comorbid conditions, among others. Thus, the actual impact of any given factor on the patients' risk of hospital admission for a CVS attack is challenging to quantify accurately, and care should be taken not to disregard factors that failed to predict the need for hospitalization in our sample. Some factors, such as use of rescue medications prior to presentation to the ED and wait time in the ED before receiving IV NSBs, were not found to impact patients' risk of hospitalization despite our findings generally supporting earlier intervention. However, these and other similar factors, including the use of a daily prophylactic medication, should be interpreted with caution as they can also serve as proxies for more severe disease with inherently higher hospitalization risks. Regarding the use of rescue medications specifically, it is important to note that patients who successfully aborted their attacks with rescue medications in the outpatient setting would not have presented to the ED and therefore were not included in our analyses. Moreover, for patients in the ED, providers may have failed to accurately document the type or dose of rescue medications, if any, they used prior to arriving. Nevertheless, the role of various pharmacologic and nonpharmacologic interventions in mitigating the need for emergency care and/or hospitalization warrants further investigation, ideally through well-designed longitudinal prospective studies.

The phenotypic heterogeneity of CVS can also partially explain or provide context for the variability in the reported ED utilization rates for patients with CVS in the current literature. In our sample, over one-quarter (28%) of all patients presented to the ED for an attack, and nearly two-thirds (62%) of all ED visits led to hospitalization. In comparison, Li et al found that 62% of all patients referred to a pediatric gastroenterologist with cyclical vomiting endorsed a prior history of receiving intravenous fluids for dehydration brought on by the vomiting.[13] This variability may also be a reflection of the relative lack of exposure to the disorder among ED providers, as demonstrated in a 2010 survey analysis on the pattern of ED use in patients with CVS.[2] The survey results showed that over 85% of patients, including those with an established diagnosis of CVS, reported a history of being misdiagnosed by ED providers who failed to recognize their distinctive constellation of signs and symptoms.[14] Given enough time, frequent misdiagnoses will invariably lead to underreporting of ED utilization rates in studies. These factors, and others like them, further highlight the need for future studies investigating the marked heterogeneity in ED utilization rates seen both within our sample of patients and between studies published in the literature, both to enable risk-stratification of patients in the outpatient setting and to gain valuable insight into the primary drivers of phenotype severity.

When we compare the hospitalization rate from the ED for patients with CVS in our sample with patients without CVS, however, the differences are more profound. In a cross-specialty analysis of all pediatric ED visits nationwide conducted by the Healthcare Cost and Utilization Project, only 3.3% of visits resulted in hospitalization,[15] compared with 62% in our study. In another example, a study evaluating ondansetron use in patients in the ED with acute gastroenteritis demonstrated a substantially lower hospitalization rate than in our sample (7.5% and 14.2% in the treatment and control groups, respectively, vs 62% in our sample).[16] As with the ED utilization rate, our sample's markedly high hospitalization rate from the ED for a CVS attack, even when compared with patients presenting with vomiting not due to CVS, may be attributed to the disorder's unique pathophysiological and clinical features. To abort attacks, patients with CVS often require a combination of abortive, antiemetic, and sedative drugs but may be unable to take them orally due to the intensity of vomiting. Moreover, patients frequently need dextrose-containing fluids (eg, D10%) to counteract the fasting-induced production and release of emetogenic ketone molecules by liver.[17] However, it is important to note that, despite these features, the majority of patients with CVS in our sample were managed exclusively in the outpatient setting. This re-emphasizes the need to further investigate the likely substantial role these factors play in the observed patterns of emergency care and hospitalizations in these patients.

There are several limitations to our study, some of which are inherent to its retrospective design. First, we relied exclusively on the ICD-10 G43.A1 and ICD-10 G43.A0 diagnostic codes to identify patients with CVS seen at our institution between 2015 and 2018. This was necessary given that prior iterations of the ICD (eg, ICD, *Ninth Revision*) captured CVS using the considerably less specific code for "persistent vomiting," alongside disorders that included, among others, Leyden syndrome (periodic vomiting), habitual vomiting, and hyperemesis gravidarum.[18] Further, we relied exclusively on information documented in patients' medical charts to confirm their ICD-10 diagnosis (as per the Rome IV criteria) prior to enrolling them. As such, patients with charts that lacked appropriate documentation may have been ineligible despite truly having CVS. To reduce the likelihood of this occurring, however, patients with charts containing only equivocal documentation pertaining to their diagnosis were

reviewed by a second physician prior to determining their eligibility. Finally, given both our single-institutional design and the inherent interprovider variability regarding any given patient's need for hospitalization, we recognize that our findings may not be generalizable to all patients with CVS presenting to any ED.

Despite its limitations, we believe that our study represents a critical first step in the effort to mitigate the burden of hospitalization for children and adolescents with CVS. In particular, by demonstrating a significant association between the timing of interventions and attack outcomes, our findings identify a potentially key target for future system-wide initiatives intending to lower patients' risk of hospitalization for CVS attacks. Such efforts may include implementation of an expedited ED triage process for prompt administration of IV fluids and antiemetics and providing patients with specific at-home instructions for aborting attacks during the critical early phases. As with any intervention, however, consistent and successful implementation will depend on securing buy-in from various stakeholders across the healthcare system, from patients and providers to hospital-wide leadership. ■

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