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Research Article

Characterizing Nighttime Acid Reflux in Children

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Abstract

Background: In adults, it has been demonstrated that nighttime gastroesophageal reflux (GER) occurs primarily in the first half of sleep. It is unknown if the same reflux pattern occurs in children with GER.

Objective: To characterize the association between age and GER symptoms with the frequency and severity of nighttime GER in children.

Study Design: Esophageal pH monitoring studies performed in 135 symptomatic children were analyzed retrospectively. Children were divided into 3 age groups: Children <1 year of age, children between 1 and 3 years of age, and children greater than 3 years of age. Nighttime was defined as the period from 6 pm to 6 am, and sub-divided into early and late nighttime (6 pm to 12 midnight, 12 midnight to 6 am, respectively). The total number of acid reflux episodes, reflux index (RI), and esophageal acid clearance time (AC) was monitored and compared between different periods throughout the monitoring period. We also examined the association between clinical symptoms of acid reflux and objective measures of GER severity.

Results: Children <3 years of age had a higher frequency of acid reflux during the daytime (63.5 versus 33.0, $p<0.01$), nighttime (46.0 versus 19.0, $p<0.01$), early nighttime (29.0 versus 13.0, $p<0.01$) and late nighttime (14.5 versus 2.0, $p<0.01$) compared to children ≥3 years of age. Children less than 1 year of age had similar acid reflux episodes during the early and late-night, whereas children 1-3 and ≥3 years of age had more frequent early nighttime acid reflux than late nighttime acid reflux. We found no consistent association between clinical symptoms and severity of acid reflux, other than a higher frequency of acid reflux episodes among children with complaints of vomiting.

Conclusions: There are a significantly more episodes of nighttime GER among children <3 years of age compared to children ≥3 years of age, and more frequent acid reflux during the early nighttime compared to the late nighttime only among children ≥3 years of age. This may be a result of more frequent nighttime feeding among younger children and infants. We also found that the RI and AC were not significantly different between the early and late nighttime periods among all patient age groups, which contrast with data from adult studies.

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ABBREVIATIONS

GER: Gastroesophageal Reflux; RI: Reflux Index; ALTE: Apparent Life Threatening Event; AC: Acid Clearance

INTRODUCTION

The high prevalence of gastroesophageal reflux (GER) in early infancy with an expected decrease by age 1 to 2 years, poses some unique challenges in interpreting esophageal pH probe data in the pediatric population. Curiously, in asymptomatic infants (without GER), pH probe values for acid reflux are similar to that in adults, while fluoroscopic studies show decreasing frequency of GER as children age [1]. This difference in results has been attributed to the buffering effect of milk formula which could potentially "mask" reflux events in infants but raises the possibility that GER is still present and is not being seen as clinical regurgitation.

In adults, nocturnal or nighttime GER "breakthrough" has been accepted as a significant characteristic of GER in this population. Study of this area has established that nighttime GER is mostly an "early" event, meaning that most nighttime reflux episodes happen in the first half of a recumbent period [2]. This finding has led to specific recommendations to abstain from eating before sleep and adjunctive medication at night to counteract these episodes. While this nighttime acid GER in adults is a time related event, it is unclear if such a similar pattern exists in children. In a small study of children with GER (acid reflux >4%), pH probe values suggests that acid reflux episodes occur in peaks in the early afternoon (noon to 6:00 PM) and night-time (mid-night to 3:00 AM) [3]. If this or another pattern of nocturnal GER is present, this may have implications in the way GER is behaviorally, pharmacologically and surgically treated in children.

This paper is a retrospective, descriptive study of pH probe data to examine the patterns of reflux in children with respect to age and time of day. Demographic information of children with GER and symptoms of nighttime GER were analyzed. Our primary goal was to determine if the pattern of early nighttime esophageal acid reflux found in adults is a phenomenon similarly observed in children. Our hypothesis was that nighttime esophageal acid reflux in children occurs primarily in the early part of the night, similar to findings in adults. In addition, we also examined the association between clinical symptoms of esophageal acid reflux and objective measures of GER severity.

MATERIALS AND METHODS

Records from patients referred to pediatric gastroenterology for 24 or 48 hours esophageal pH monitoring from January 2004 to December 2007 were retrospectively analyzed. Patients included were those 0-18 years of age and without any specific pathology that would make GER happen, like uncorrected hiatal hernias, surgical (Nissen type) fundoplications or Eosinophilic Esophagitis. All patients were being evaluated for GER based on clinical signs and symptoms as determined by the primary care physician and the pediatric gastroenterologist upon referral regarding their symptoms. Patients eligible for pH monitoring included those with signs and symptoms suggestive of GER disease, including abdominal pain and/or heartburn, chest pain, excessive regurgitation and vomiting, weight loss not associated with an acute illness, upper respiratory symptoms or apparent life threatening events (ALTE). These studies were conducted to determine if GER was the etiology of their signs and symptoms. Studies from patients with gastrostomy tubes were analyzed; results did not appear to be different from the other patients, so they were included in the analysis. Patient diet and eating schedules were not adjusted or regulated for the purposes of this study.

All 24- hour pH recordings conducted at our hospital were considered for analysis. To be included in the study, at least 20 hours of uninterrupted data were required, and the study must have been conducted with the patient off any medication that affects gastric pH or gastric emptying. Patients normally on medication were required to hold their medication before the studies; 72 hours for patients on H2-blockers and 5 days for patients on proton pump inhibitors. Studies that were less than 20 hours long or missing periods of data from the recordings were considered incomplete and a-priori ineligible for this study.

The pH studies were conducted with either standard pH probes (Medtronic Inc., Minneapolis, MN and Sandhill Scientific Inc., Highlands Ranch, CO) or Bravo wireless probes (Bravo pH Monitoring System, Medtronic Inc., Minneapolis, MN). The studies were analyzed using the Polygram Net software (Medtronic Inc., Minneapolis, MN). Patients that completed 48 hours of monitoring were treated as two 24hour studies to standardize the length of each study.

Our population was categorized by age group because of suspected differences in reflux patterns between the infant and child populations. We defined three age groups: Infants (patients younger than 1 year of age), children between 1 and 3 years of age, and children 3 years of age and older.

Since nighttime symptoms were of particular interest, "night" was defined as the period between 6 pm and 6 am. This time period was chosen to cover individual variance in the bedtime of children and the amount of time spent sleeping. Nighttime was subdivided into two periods: early and late nighttime. Early nighttime was defined as 6 PM to midnight and late nighttime was defined as midnight to 6 AM.

For each study, several characteristics were examined. These included the total number of acid reflux episodes (total instances of GER during the study period), the reflux index (RI, percent time pH<4), Euler score (total number of episodes of pH<4 + 4 times number of episodes pH <4 lasting longer than 5 minutes) and esophageal acid clearance time (AC, defined as the number of minutes pH<4 divided by the total number of episodes). The number of episodes and reflux index were divided into time groups and analyzed by 24- hour total, total daytime, total nighttime, early nighttime and late nighttime periods based on the above definitions.

Each patient's pH study was also analyzed for associations between clinical symptoms and measures of acid reflux. Chart reviews were conducted to determine the presence of clinical symptoms that were associated with GER in each patient. The symptoms included were abdominal pain, regurgitation, excessive vomiting, dysphagia, recurrent upper respiratory difficulties, recurrent lower respiratory difficulties, excessive burping and hiccupping, arching or posturing, poor feeding and

occurrence of ALTEs. These symptoms were analyzed to assess their association with the objective measures of severe GER or different patterns of GER throughout the day or night.

Statistical analyses were performed to assess differences in reflux events within each age group and differences in outcomes between different age groups. Acid reflux episodes and RI were compared between day and night and between early nighttime and late nighttime periods among the different age groups. The incidence of symptoms among children of the different age groups and between age groups was also analyzed. The mean number of reflux episodes and RI in different time periods was compared between patients with and without a given symptom. Statistical analyses were performed using Excel (Microsoft, Seattle, WA) and Stata (Version 9, College Station, TX) software. A Chi-square analysis was used to assess statistical significance for categorical variables. For continuous variables, either the Mann-Whitney Rank Sum test for non-normally distributed data or the Student's t-test for normally distributed data was used.

RESULTS AND DISCUSSION

A total of 135 24-hour pH studies were available for analyses. The number of children in each age group was as follows: Children < 1 year of age, n=29; children between 1 and 3 years of age, n=13; and children older than 3 years of age, n=93. The presenting symptoms among the different age groups varied considerably (Table 1). For children less than 3 years of age, the most common presenting symptoms were poor feeding (45%), irritability (36%), regurgitation (31%), and excessive vomiting (31%). Among children greater than 3 years of age, the most common presenting symptoms were epigastric abdominal pain (61%) and regurgitation (49%).

Children younger than 1 year of age had a median of 98 (range 10-437) acid reflux episodes over the 24 hour period and a median RI of 4.2 (range 0.2-29.1) (Table 2). During the daytime, on they experienced a median of 51 (range 3-210) episodes of acid reflux. During the nighttime, the median frequency of acid reflux episodes was 42 (range 1-232), with a median of 22(range 0-116) episodes occurring in the early nighttime and 15 (range 0-116) episodes occurring in the late nighttime. The frequency of acid reflux episodes was not significantly different between day and nighttime (p=0.10) and between early and late nighttime (p=0.27) (Table 3). The RI was not significantly different between the early and late nighttime late nighttime (p=0.32). The median AC for the daytime was 0.48 (range 0.11-1.53) minutes/episode and 0.71 (range 0-2.59) minutes/episode in the nighttime (p=0.05).

Children between 1 and 3 years of age had a median of 151 (range 46-334) acid reflux episodes over the 24- hour period and a median RI of 4.9 (range 1.1-15.7). These children had a median of 94 (range 18-227) daytime episodes and 67 (range 14-139) nighttime episodes. There were significantly more episodes of acid reflux during the early nighttime (median 57, range 11-123) compared to the late nighttime (median nighttime (14, range 0-65, p=0.004). There was also a significantly higher median RI in the early night period (6.2, range 1.5-21.6) compared to the late nighttime period (median 1.8, range 0-10.2) (p=0.02). No differences were found comparing AC times between daytime and nighttime, and early nighttime and late nighttime.

When the younger age groups were combined, children less than 3 years of age had a median of 117(range 10-437) episodes throughout the 24- hour period. This included a median of 63.5 (range 6-227) daytime episodes and a median of 46 (range 1-232) nighttime acid reflux episodes (p= 0.03). Children under 3 also had a median of 29 (range 0-123) early nighttime episodes and 14.5 (0-116) late nighttime episodes (p=0.005). However, the median RI between early (3.95, range 0-37.3) and late nighttime (1.95, range 0-65.5) was not significantly different (p=0.78).

Children 3 year of age and older had a median of 55 (range 0-453) reflux episodes with a median RI of 3 (range 0-51.8). They had more acid reflux episodes during the daytime (median 33, range 0-168) compared to the nighttime (median 19, range 0-285, p=0.003). They also had significantly more acid reflux episodes in the early nighttime (median 13, range 0-127) compared to late nighttime (median 2, range 0-159, p<0.001). There was not a significant difference in mean RI between the early nighttime (median 2.6, range 0-71.3) and the late nighttime (median 0.6, range 0-66.6, p=0.94).

Children under 3 years of age had significantly more frequent acid reflux than children over 3 of age during the daytime, nighttime, early nighttime and late nighttime (p <0.001 for total episodes, daytime episodes, nighttime episodes, and early nighttime episodes; p=0.008 for late nighttime episodes). However, differences in RI between age groups were not statistically significant. Total AC was significantly longer in children ≥3 compared to children <3 (0.80 vs 0.575, p= 0.01) and during the daytime (0.70 vs 0.44, p=0.03) but not during the nighttime.

When comparing clinical symptoms to objective measures of GER disease, vomiting was the only symptom that consistently indicated worse acid reflux in children with the symptom compared to those without (Tables 4 and 5). Children with vomiting had more nighttime acid reflux episodes (44.59 episodes compared to 24.24, p=0.02) and higher nighttime RI (10.05% compared to 4.24%, p=0.01) than children without vomiting. Children that were G-tube fed had significantly more acid reflux episodes during the late nighttime than those without G-tubes.

Children whose parents complained of swallowing problems had significantly less acid reflux episodes and lower RIs than those without swallowing problems. Children with subjective reflux (sensation of retrograde bolus movement in the esophagus reported by the patient) had significantly less acid reflux episodes than children without subjective reflux except during the daytime. For children with subjective reflux, the RI was significantly lower during the nighttime and late nighttime compared to children without subjective reflux. Children with abdominal pain similarly had fewer acid reflux episodes during the day than those without abdominal pain. There were no significant differences in acid reflux frequency or RI between neurologically normal and abnormal children.

Comparisons between the early and late nighttime acid reflux among children with or without a given symptom revealed similar patterns (Table 6). All children had a significantly higher mean number of acid reflux episodes during the early nighttime period compared to late nighttime period, but the RIs were not significantly different between the early and late nighttime.

Table 1: Presenting signs and symptoms by age group.

Age Group	Male-Female, N	Mean Age (daysdays)	Neurologically Abnormal (%)	G-Tube Fed (%)	Number Presenting with Symptom										
					Regurgitation (%)	Vomiting (%)	Irritability (%)	Poor Feeding (%)	Upper Respiratory Symptoms (%)	Lower Respiratory Symptoms (%)	Arching/ Posturing (%)	Burping/ Hiccups (%)	Abdominal Pain (%)	Dysphagia (%)	ALTE (%)
< 1	13/16	171.9	10 (34)	12(41)	8 (28)	10 (34)	11 (31)	14 (48)	0 (0)	8 (28)	2 (7)	0 (0)	3(10)	5 (17)	6 (21)
1-3	5/8	658.2	6 (46)	8 (62)	5 (38)	3 (23)	4 (31)	5 (38)	0 (0)	4 (31)	1 (8)	1 (8)	2 (15)	1 (8)	1 (8)
< 3	18/24	322.4	16 (38)	21 (50)	13 (31)	13 (31)	15 (36)	19 (45)	0 (0)	12 (29)	3 (7)	1 (2)	5 (11)	6 (14)	8 (7)
≥ 3	46/47	4111.1	24 (26)	13 (14)	46 (49)	22 (24)	8 (9)	16 (17)	4 (4)	12 (29)	3 (7)	7 (8)	57 (61)	27 (29)	0 (0)
All	64/71	2932.4	38 (28)	34 (25)	59 (43)	35 (25)	23 (17)	35 (25)	4 (3)	24 (17)	6 (4)	8 (6)	62 (46)	33 (24)	8(6)

Table 2: GER measures compared by age group. Data presented as median (range).

	Children < 1 year N=29	Children 1-3 year N=13	P*	Children < 3 year N=42	Children ≥ 3 year N=93	P**
Total Reflux Episodes	98 (10-437)	151 (46-334)	0.07	117 (10-437)	55 (0-453)	<0.001
Daytime Reflux Episodes	51 (3-205)	94 (18-227)	0.08	63.5 (6-227)	33 (0-168)	<0.001
Nighttime Reflux Episodes	42 (1-232)	67 (14-139)	0.16	46 (1-232)	19 (0-285)	<0.001
Early Nighttime Reflux Episodes	22 (0-116)	57 (11-123)	0.009	29 (0-123)	13 (0-127)	<0.001
Late Nighttime Reflux Episodes	15 (0-116)	14 (0-65)	0.62	14.5 (0-116)	2 (0-159	0.008
Total RI	4.2 (0.2-29.1)	4.9 (1.1-15.7)	0.96	4.3 (0.2-29.1)	3 (0-51.8)	0.75
Nighttime RI	3.9 (0-37.3)	6.2 (0.8-13.1)	0.59	3.95 (0-37.3)	2.1 (0-68.9)	0.65
Early Nighttime RI	3.9 (0-36.4)	6.2 (1.5-21.6)	0.63	3.95 (0-36.4)	2.6 (0-71.3)	0.50
Late Nighttime RI	2.5 (0-65.5)	1.8 (0-10.2)	0.29	1.95 (0-65.5)	0.6 (0- 66.6)	0.81
AC Total	0.62 (0.11-1.6)	0.41 (0.09-0.95)	0.05	0.58 (0.09-1.60)	0.80 (0-8.78)	0.01
AC Day	0.48 (0.11-1.53)	0.40 (0.07-0.96)	0.63	0.44 (0.07-1.53)	0.70 (0-9.43)	0.03
AC Nighttime	0.71 (0-2.59)	0.45 (0.11-1.9)	0.18	0.59 (0.88-2.59)	0.67 (0-4.88)	0.11
AC Early Nighttime	0.43 (0-2.32)	0.39 (0,07-1.9)	0.73	0.42 (0-2.82)	0.55 (0-4.88)	0.19
AC Late Nighttime	0.81 (0-4)	0.46 (0-1.66)	0.38	0.46 (0-4)	0 (0-33)	0.29

*p-value comparing < 1 year to 1-3 years
**p-value comparing < 3 years to ≥ 3 years
RI= reflux index, AC= acid clearance time

Table 3: GER Measures by time period in different age groups. Data presented as mean (range).

	Children < 1 year	Children 1-3 year	Children < 3 year	Children ≥ 3 year
Daytime Reflux Episodes	51 (3-205)	94 (18-227)	63.5 (6-227)	33 (0-168)
Nighttime Reflux Episodes	42 (1-232)	67 (14-139)	46 (1-232)	19 (0-285)
p value Daytime vsNighttime Episodes	p=0.10	p=0.15	p=0.03	p=0.003
Early Nighttime Reflux Episodes	22 (0-116)	57 (11-123)	29 (0-123)	13 (0-127)
Late Nighttime Reflux Episodes	15 (0-116)	14 (0-65)	14.5 (0-116)	2 (0-159
p value Early vs Late Episodes	p=0.27	p=0.004	p=0.005	p<0.001
Early Nighttime RI	3.9 (0-36.4)	6.2 (1.5-21.6)	3.95 (0-36.4)	2.6 (0-71.3)
Late Nighttime RI	2.5 (0-65.5)	1.8 (0-10.2)	1.95 (0-65.5)	0.6 (0- 66.6)
p value Early vs Late RI	p=0.32	p=0.02	p=0.78	p=0.94
AC Day	0.48 (0.11-1.53)	0.40 (0.07-0.96)	0.44 (0.07-1.53)	0.70 (0-9.43)
AC Nighttime	0.71 (0-2.59)	0.45 (0.11-1.9)	0.59 (0.88-2.59)	0.67 (0-4.88)
p value AC Day vs Night	p=0.05	p=0.70	p=0.05	p=0.81
AC Early Nighttime	0.43 (0-2.32)	0.39 (0,07-1.9)	0.42 (0-2.82)	0.55 (0-4.88)
AC Late Nighttime	0.81 (0-4)	0.46 (0-1.66)	0.46 (0-4)	0 (0-33)
p value AC Early Nighttime vs Late Nighttime	p=0.44	p=0.94	p=0.49	p=0.14

Table 4: Comparison of amount of reflux episodes for patients with and without symptoms in children over 3. Data presented as mean.

Symptom	Presence of Symptom	Total Reflux Episodes	Day Episodes	Night Episodes	Early Episodes	Late Episodes
Abdominal Pain	With	58.00	32.54	25.45	17.86	8.25
	Without	82.72	47.97	34.75	20.92	13.94
	p value	0.06	0.02	0.22	0.47	0.18
Swallowing Difficulty	With	40.56	25.30	15.26	10.52	4.78
	Without	78.62	43.92	34.70	22.53	12.77
	p value	0.01	0.01	0.02	0.01	0.08
Reflux	With	54.04	36.02	18.02	13.39	4.50
	Without	80.81	40.96	39.85	24.57	16.28
	p value	0.03	0.46	0.003	0.006	0.004
Vomiting	With	88.86	44.27	44.59	26.23	18.5
	Without	60.97	36.73	24.24	16.82	7.96
	p value	0.06	0.33	0.02	0.05	0.03
Neurologically Normal	Yes	61.12	35.62	25.44	17.81	8.25
	No	86.38	46.96	39.42	22.42	17.13
	p value	0.08	0.13	0.10	0.33	0.06
G-tube Fed	Yes	84.92	42.23	42.69	21.00	21.85
	No	64.75	37.91	26.84	18.73	8.60
	p value	0.27	0.65	0.14	0.70	0.03

Table 5: Comparison of RI in patients with and without a given symptom in children over 3. Data presented as mean.

Symptom	Presence of Symptom	Total RI	RI Night	Early RI	Late RI
Abdominal Pain	With	4.92	4.99	4.82	4.90
	Without	7.23	6.60	6.58	6.64
	p value	0.17	0.44	0.39	0.50
Swallowing Difficulty	With	3.87	2.34	2.83	2.14
	Without	6.61	6.95	6.59	6.98
	p value	0.13	0.04	0.08	0.08
Reflux	With	4.65	3.33	3.92	2.98
	Without	6.96	7.84	7.05	8.10
	p value	0.16	0.03	0.11	0.04
Vomiting	With	9.06	10.05	9.43	10.40
	Without	4.81	4.24	4.28	4.08
	p value	0.02	0.01	0.02	0.03
Neurologically Normal	Yes	5.00	4.69	4.50	4.74
	No	8.15	8.26	8.36	7.96
	p value	0.09	0.13	0.08	0.26
G-tube Fed	Yes	8.57	8.58	8.70	8.60
	No	5.37	5.13	4.98	5.08
	p value	0.17	0.24	0.19	0.33

DISCUSSION

In this study, we retrospectively collected and analyzed pediatric pH probe data to investigate patterns of acid reflux in children of different ages with GER related signs and symptoms. We found that children less than 1 year of age had similar amounts of acid reflux during the daytime and nighttime, while children greater than age 1 year of age had more acid reflux during the daytime compared to the nighttime. Further, we found that children less than 1 year of age had a similar amount of acid reflux throughout the nighttime, whereas older children (3 years and older), similar to adults, had more acid reflux during the early nighttime compared to late nighttime. It is likely that these differences are due to the increased frequency of meals and

Table 6: Comparison of early nighttime and late nighttime reflux episodes and RI in patients with given symptoms in children over 3.

Symptom	Presence of Symptom	Early Episodes	Late Episodes	Early RI	Late RI
Abdominal Pain	With	17.86	8.25	4.82	4.90
	p value		<0.001		0.96
	Without	20.92	13.94	6.58	6.64
	p value		0.02		0.96
Swallowing Difficulty	With	10.52	4.78	2.83	2.14
	p value		0.03		0.61
	Without	22.53	12.77	6.59	6.98
	p value		<0.001		0.76
Reflux	With	13.39	4.50	3.92	2.98
	p value		<0.001		0.48
	Without	24.57	16.28	7.05	8.10
	p value		0.001		0.47
Vomiting	With	26.23	18.5	9.43	10.40
	p value		0.05		0.71
	Without	16.82	7.96	4.28	4.08
	p value		<0.001		0.84
Neurologically Normal	Yes	17.87	8.13	4.50	4.74
	p value		<0.001		0.84
	No	22.42	17.13	8.36	7.96
	p value		0.18		0.83
G-tube Fed	Yes	21.00	21.84	8.70	8.60
	p value		0.86		0.95
	No	18.73	8.6	4.98	5.08
	p value		<0.001		0.93

Table 7: GER Measures by age and reflux index. Data presented in mean (range).

	Children < 3 RI>4 N=22	Children <3 RI<4 N=20		Children >3 RI>4 N=58	Children >3 RI<4 N=35	
Total Reflux Episodes	159 (48-437)	69 (10-233)	p<0.001	106 (41-453)	35 (0-82)	p<0.001
Daytime Reflux Episodes	89 ((28-227)	30.5 (3-137)	p<0.001	52.5 (17-168)	20 (0-64)	p<0.001
Nighttime Reflux Episodes	69 (16-232)	34 (1-139)	p=0.003	43 (1-285)	14 (0-57)	p<0.001
Early Nighttime Reflux Episodes	43.5 (0-116)	11.5 (0-123)	p=0.003	27.5 (1-127)	11 (0-46)	p<0.001
Late Nighttime Reflux Episodes	23.5 (0-116)	4.5 (0-65)	p=0.03	17.5 (0-159)	0 (0-35)	p<0.001
Total RI	7.45 (4.2-29.1)	2.1 (0.2-3.8)	p<0.001	8.1 (4-51.8	1.8 (0-3.8)	p<0.001
Nighttime RI	7.4 (1.1-37.3)	2.0 (0-6.1)	p<0.001	9.6 (0.2-68.9)	0.9 (0-6.3)	p<0.001
Early Nighttime RI	7.9 (0-36.4)	2.2 (0-7.9)	p<0.001	6.4 (0.2-71.3)	1.0 (0-12.4)	p<0.001
Late Nighttime RI	3.3 (0-65.5)	0.5 (0-10.6)	p=0.001	6.15 (0-66.6)	0 (0-5.9)	p<0.001
AC Total	0.75 (0.34-1.45)	0.35 (0.09-1.60)	p=0.001	1.42 (0.43-8.78)	0.6 (0-4.5)	p<0.001
AC Day	0.65 (0.32-1.53)	0.38 (0.07-1.33)	p=0.002	1.00 (0.28-9.43)	0.59 (0-7.0)	p<0.001
AC Nighttime	0.85 (0.27-2.59)	0.4 (0-2.55)	p=0.001	1.63 (0.29-4.88)	0.5 (0-2.89)	p<0.001
AC Early Nighttime	0.65 (0-2.82)	0.33 (0-2.55)	p=0.001	1.00 (0-4.88)	0 (0-8)	p<0.001
AC Late Nighttime	0.52 (0-4)	0.25 (0-1.81)	p=0.02	1.43 (0-7.25)	0.6 (0-4.5)	p<0.001

RI= Reflux index, AC= acid clearance time

nighttime feedings in younger children and prolonged recumbent periods in children <1 year of age. This could also represent a physiological difference between younger children and older children [4].

While children above the age of 1 year had more acid reflux episodes in the early nighttime compared to the late nighttime, the RI was not significantly different between the early and late nighttime. This suggests that while these children are experiencing acid reflux more frequently in the early nighttime the acid reflux episodes last longer in the late nighttime, indicating longer esophageal dwell time for refluxate. There are several possibilities that may explain these findings. First, because of the methodological definition of nighttime, in spite of our recommendations, many children may have eaten during the

early nighttime, which may have contributed to more acid reflux episodes in early nighttime. Also, known physiological changes that occur during sleep could have contributed to increased duration of reflux during the late nighttime, including less swallowing and decreased esophageal motility [5].

Among children greater than 3 years of age, vomiting was the only symptom associated with more frequent acid reflux episodes and higher RI. Patients with other symptoms (swallowing problems, regurgitation, abdominal pain, neurological status, G-tube fed), had no association with more frequent acid reflux or other objective measures of GER severity. In fact, patients with a given symptom often had less reflux than those without the symptom. In addition, even when stratified by symptom specific groups, all patients had more acid reflux episodes in the early nighttime, but not higher RI's, indicating that no specific symptoms correlated with increased reflux in the early versus the late nighttime. A prospective study using impedance monitors, which can detect acidic and non acidic esophageal reflux episodes, may better characterize if these patients' symptoms are caused by non acidic GER.

Castell, *et al,* found that nighttime acid reflux in adults is primarily an early nighttime event, demonstrating that almost all nocturnal acid reflux episodes happen in the first half of a supine period. Our study found similar results, but only among the older children (3 years and older). While children as a whole had more frequent acid reflux episodes in the first half of the nighttime, the RI was not different between the early and late nighttime.

Steiner, *et al*, found two patterns: a positive acid reflux group with peak periods of reflux in the afternoon and evening, and a negative reflux group with a peak in the early morning (0600-0900) [3]. In contrast to Steiner et al, we analyzed all children studied according to age, regardless of the level of the reflux index. In this way, our data highlights the importance of analyzing specific time periods and events in a typical referral population of children with indications for pH probe study. Our findings showed that acid reflux was generally higher during the day than during the night, higher in the early nighttime period, but did not show any difference between early and late nighttime esophageal acid exposure time (RI). Overall, our study suggests that there is a relationship between acid reflux and time of day in some patients. Older children seem to mimic what was reported by Hila and Castell [2] in adults but here, our RI data was conflicting.

Because children of different ages have a wide range of bedtimes and nighttime activities, we used a broad definition for nighttime (6 pm to 6 am). The intent was to control for individual differences in nighttime activities, bedtimes, and variations in sleep patterns. However, this may also have caused some degree of bias due to the differences in bedtimes and activities as children age. This period usually includes a dinnertime meal, which may have artificially increased the apparent amount of reflux during this period because of postprandial reflux. In addition, the nighttime definition would include awake time for many older children, where reflux would be expected to be higher [6]. This could have also increased the frequency of reflux episodes in the early nighttime. In order to control for these differences, a prospective study could be designed that looked at reflux only while children are asleep, with attention to sleep stages.

Lastly, our patient population was drawn from patients that were referred to specialist care for evaluation of GER. Further study will need to be done to specifically address nocturnal extra-intestinal symptoms, such as sleep disturbances, cough, failure to thrive, morning nausea, etc.

CONCLUSION

This study examined the GER patterns among a large cohort of diverse children. Among children less than 1 year of age, acid reflux appears to occur throughout the day and nighttime. Among children greater than 3 year of age, we found more frequent acid reflux during the daytime than the nighttime, and more frequent reflux episodes in the early nighttime compared to the late nighttime. However, RIs were not different between early and late nighttime in these children. Vomiting was the only clinical symptom identified that may indicate more severe GER. This data may suggest that adult models of reflux are not applicable to children, particularly those less than 3 year of age. Nighttime GER frequency in children >3 years of age does mimic what has been reported in adults, by Castell *et al*. [2] A larger, prospective trial is needed to fully understand the factors involved in patterns of reflux in children and look at the impact of lifestyle modification in reducing frequency and severity of nighttime reflux in children. A study conducted with impedance monitors may better characterize the occurrence of acidic acid and non-acidic gastro esophageal reflux in children, with correlation between both types of reflux and symptoms.

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