High Rate of Clinical and Endoscopic Relapse After Healing of Erosive Peptic Esophagitis in Children and Adolescents

Erica Yamamoto, Helena S.H. Brito, Silvio K. Ogata, Rodrigo S. Machado, and Elisabete Kawakami

ABSTRACT

Objectives: The aim of the present study was to estimate the rate of clinical and endoscopic relapse after initial treatment of erosive peptic esophagitis in children and adolescents.

Methods: A total of 24 patients (2.1–16.4 years old, mean ± standard deviation [SD] 9.9 ± 3.1; male:female 3) with healed endoscopic erosive esophagitis and without gastroesophageal reflux disease (GERD)–predisposing conditions were followed up for 4 to 32.9 months (mean 20.8 ± 10.6 years). Structured clinical evaluation was performed every other week during the initial treatment and maintenance, and every 3 months after that. Whenever a clinical relapse happened, a new endoscopic evaluation was performed. Severity and frequency were scored on 10-point and 6-point semiquantitative scales, respectively.

Results: At baseline, epigastric pain was the most reported symptom (70.8%), with intensity scored as >5 in 88.3% of patients, and median frequency of 3 (weekly; daily in 5, 20.8%). Clinical relapse was detected in 20 of 24 (83.3%) patients after a median period of 14.65 months (95% confidence interval [CI] 6.7–25.7 months). Endoscopic relapse was observed in 9 of 20 (45%) patients after a median of 25.7 months. The dose of lansoprazole needed to heal the esophagitis was not significantly associated with the risk for clinical relapse (hazard ratio [HR] 1.74, 0.94, 7.72, $P = 0.06$), whereas the body mass index (BMI) was directly associated with endoscopic relapse (HR 1.3, 1, 1.69, $P = 0.05$).

Conclusions: Children with healed erosive esophagitis have up to 83% clinical relapse and of the 83%, 45% had endoscopic relapse. Correlation of endoscopic relapse with clinical symptom is poor. Higher grades of esophagitis and higher BMI are risk factors for endoscopic relapse.

Key Words: esophagitis, gastroesophageal reflux disease, lansoprazole

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Erosive esophagitis (EE) is an important manifestation of gastroesophageal reflux disease (GERD) (1–3). Studies of the natural history of treated EE are few (3–5). The largest and the longest-term follow-up pediatric studies (4,5) showed high rates of chronicity and relapse of EE, mostly in children with GERD-predisposing conditions, that is, neurologic impairment, repaired esophageal abnormalities, chronic lung disease, and obesity (1,2). They also showed that most children with severe, chronic EE had at least one of these GERD-predisposing conditions; however, these studies were not randomized or placebo controlled. In contrast, Boccia et al (3), in a randomized controlled study of 46 children without GERD-predisposing conditions, reported that relapse of EE occurred in only 2.2% of patients, after a 30-month follow-up. The goal of our study was to evaluate the incidence of clinical relapse of symptoms and endoscopic recurrences of EE after initial treatment and healing in children and adolescents.

METHODS

Patients

A total of 35 patients with erosive peptic esophagitis identified during a 32-month period (July 2006 to March 2009) were prospectively enrolled from 2 pediatric gastrointestinal endoscopy services in São Paulo, Brazil (Hospital Infantil Cândido Fontoura and Hospital São Paulo—university hospital). Exclusion criteria were age >18 years, hiatal hernia, peptic ulcer disease, esophageal stricture, previously treated GERD, GERD-predisposing conditions (chronic neurologic disease, obesity, chronic lung disease, congenital esophageal abnormalities), substance abuse, and chronic diseases requiring continuous therapy other than GERD. Hiatal hernia was endoscopically defined by observing the upper margin of the gastric folds above the diaphragmatic indentation—1 patient was ruled out based on this criterion. The enrollment flowchart is displayed in Figure 1. A total of 11 patients were excluded after initial enrollment. Baseline features of these patients as compared with those who were included in the study are displayed in Table 1. The study was approved by the institutional review board at the Universidade Federal de São Paulo, and parents gave informed consent for the study.

Endoscopy

Esophagitis was graded according to the Los Angeles criteria (grade A: ≥1 mucosal breaks <5 mm; grade B: ≥1 mucosal breaks >5 mm; grade C: mucosal breaks extend between the tops of 2 mucosal folds, but <75% of the circumference; grade D: mucosal breaks extend for >75% of the circumference) (6). All of the patients had esophageal biopsies, at least 3 fragments collected at distal and middle esophagus, from 2 cm above the esophagogastric junction and above that point, with standard biopsy forceps for a 2.8-mm working channel. Biopsies were evaluated with hematoxylin and eosin.

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From the Pediatric Gastroenterology Division, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil.

Address correspondence and reprint requests to Rodrigo S. Machado, MD, PhD, Rua Coronel Lisboa, 826 Vila Mariana, São Paulo, SP 04020-041, Brazil (e-mail: Rodrigo.Strehl@UNIFESP.br).

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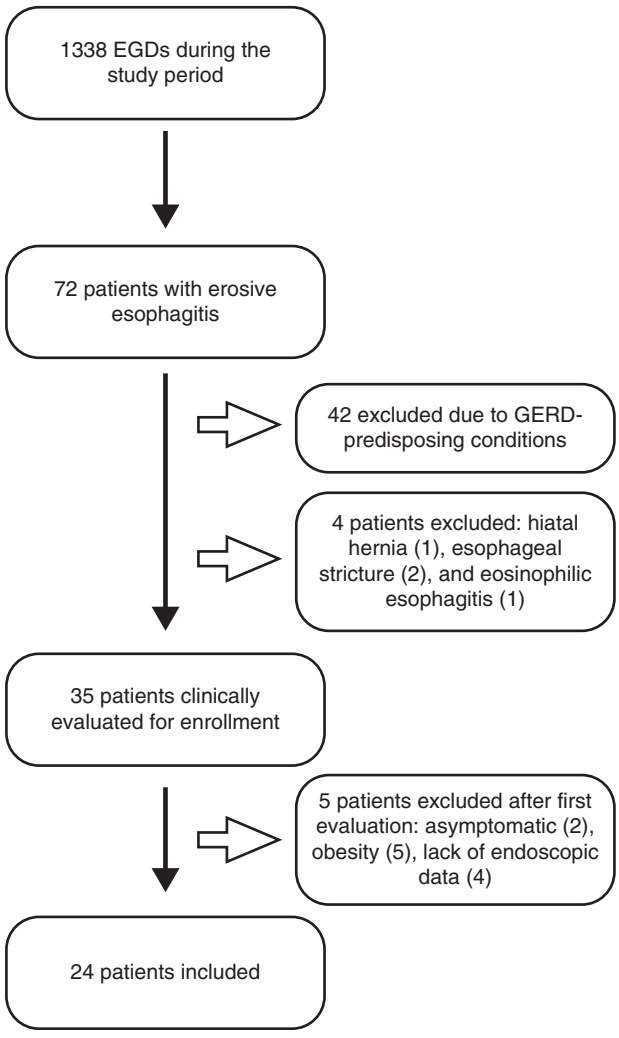

FIGURE 1. Study flowchart. EGD = esophagogastroduodenoscopy; GERD = gastroesophageal reflux disease.

Clinical Evaluation and Treatment

Initial clinical evaluation and the following medical appointments were performed by the same physician (E.Y.). A structured clinical questionnaire was answered at each medical visit by the patient or by the patient's parent if younger than 6 years old. Epigastric pain (intensity, frequency, duration, relation with meals, nocturnal occurrence), vomiting, heartburn, regurgitation, nausea, choking, belching, and familial history of peptic disease were evaluated. Pain intensity was graded according to a 10-point visual scale, whereas symptom frequency was characterized by a 5-point semiquantitative scale (1 = once, 2 = less than weekly, 3 = weekly, 4 = more than weekly, 5 = daily). Nutritional status was defined by the body mass index (BMI, weight [kg]/[height]^2 [m^2]), and obesity was defined by BMI above the 95th percentile (7). Obese patients were ruled out of the study. Finally, patients underwent blood tests including complete blood panel, serum iron, ferritin, serum glucose, electrolytes including calcium, urea, creatinine, albumin, alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, coagulogram, blood lipid profile, and urine sediment analysis at baseline, at the end of the treatment and yearly during the follow-up.

TABLE 1. Clinical baseline data from 24 patients with erosive esophagitis included in the study and 11 patients excluded at enrollment (2 asymptomatic, 5 obese, and 4 with endoscopy performed in other facility)

Variable	Patients, n (%)	Excluded, n (%)	Total (%)
Age, y			
2–6	3 (12.5)	2 (18.2)	5 (14.3)
6–10	8 (33.3)	5 (45.5)	13 (37.1)
>10	13 (54.2)	4 (36.4)	17 (48.6)
Sex			
Boys	18 (75.0)	7 (63.6)	25 (71.4)
Symptoms			
Epigastric pain	17 (70.8)	8 (72.7)	25 (71.4)
Heartburn	10 (41.2)	2 (18.2)	12 (34.3)
Nausea	10 (41.2)	4 (36.4)	14 (40.0)
Vomiting	9 (37.5)	5 (45.5)	14 (40.0)
Hiccups	4 (16.7)	4 (36.4)	8 (22.9)
Nocturnal pain	4 (16.7)	3 (27.3)	7 (20.0)
Choking	3 (12.5)	1 (9.1)	4 (11.4)
Abdominal pain (periumbilical)	3 (12.5)	0 (0.0)	3 (8.6)
Esophagitis grade			
A	11 (45.8)	2 (18.2)*	13 (37.1)
B	12 (50.0)	5 (45.5)	17 (48.6)
C	1 (4.2)	0 (0.0)	1 (2.9)
D	0 (0.0)	0 (0.0)	0 (0.0)
Familial history of dyspepsia	21 (87.5)	7 (63.4)	28 (80.0)
Total	24 (100)	11 (100)	35 (100)

$P > 0.05$ in all of the comparisons.
* Four (36.4%) patients who were scoped in another facility did not have enough data to grade according to the Los Angeles system.

Patients were initially treated with lansoprazole (15 mg if weight <15 kg, 30 mg otherwise) for 8 weeks, and compliance was assessed by counting remaining capsules at each visit (every other week during initial treatment). Also, parents were asked to call the principal investigator (E.Y.) if symptoms reappeared. At the end of the treatment, endoscopic evaluation was repeated to verify healing. If the lesions were healed, maintenance treatment for an additional period of 8 weeks was prescribed at the end of the treatment, with half initial dosage of lansoprazole, but if the lesions were not healed, then the patient would be treated with a second course of lansoprazole (double dosage) for 8 weeks. At clinical relapses, patients would be treated with the effective dose used during primary treatment.

Patients who had their lesions healed were clinically reevaluated on a quarterly basis. This frequency of follow-up visits was maintained during the study period, up to March 2009, and all of the patients adhered to it. When symptomatic relapse was noticed, a new endoscopic evaluation was performed and a new treatment regimen initiated, even if there was no endoscopic lesion. At the end of their participation in the study, all of the patients were offered the option of maintaining their medical follow-up in the pediatric gastroenterology division of the university hospital.

Statistical Analysis

Continuous variables were described by their mean and standard deviation (SD), and qualitative variables were described by their proportions. Discrete variables were described by their median and proportion for each grade. Clinical and endoscopic

variables were related to the occurrence of clinical or endoscopic relapse with the Fisher exact test. In this particular analysis, the group was divided into 2 age groups (group A, younger; and group B, older than 9 years at baseline) because the presentation of GERD in most adolescents and young adults is with typical symptoms, whereas younger children may present with atypical symptoms. Groupwise comparisons for continuous variables were performed with the Student *t* test.

The primary outcome of the study was clinical relapse, which was defined by the reoccurrence of symptoms after successful healing of the erosive lesions. The secondary outcome was endoscopic relapse, as defined by the recurrence of endoscopic lesions in the endoscopy performed because of a clinical relapse.

A Kaplan-Meier survival curve was built to estimate medians and 95% confidence intervals (CIs) for clinical and endoscopic relapses. A Cox proportional hazard ratio (HR) model was used to determine the HRs with 95% CIs for variables associated with the primary (clinical relapse) and the secondary (endoscopic relapse) outcome. All of the statistical tests were performed in R for Macintosh (R Project for Statistical Computing, Vienna, Austria), and a 2-tailed P value <0.05 was regarded as significant.

RESULTS

Clinical Features at Baseline

The age of 24 patients ranged from 2.1 to 16.4 years (mean ± SD 9.9 ± 3.1, males:females 3). Baseline data are displayed in Table 1. The most frequent symptom was epigastric pain (70.8%—as an isolated symptom in 8, 33.3%), whereas heartburn was reported by 10 (41.2%) patients. Epigastric pain intensity was graded from 1 to 10 (median 8, ≥5 in 88.3%), whereas the median frequency score was 3 (weekly, daily in 5, 20.8%). There was no relation between endoscopic findings and clinical presentation (Table 2).

Treatment

Patients were treated with 1.01 mg/kg (SD 0.23) of lansoprazole (group A 1.2 mg/kg [SD 0.22], group B 0.93 mg/kg [SD 0.18], $P = 0.006$, 95% CI for the difference 0.08–0.45 mg/kg). No adverse effects were reported. Complete resolution of symptoms was achieved in the first 2 weeks in 20 (83.3%) patients, in the sixth-week evaluation in 2 (8.3%) patients, and only after 8 weeks in the remaining 2 (8.3%) patients. No clinical relapse was observed during maintenance therapy.

Primary healing was achieved in 20 of 24 (83.3%) patients in the control endoscopy. Age, sex, BMI, and dosage were not different between successfully treated patients and those who had a primary failure (data not shown). Patients who had not healed in the first control endoscopy were treated with a double dosage of lansoprazole (1.32, 1.66, 2, and 3.18 mg/kg). The patient who received 1.32 mg/kg presented with grade A esophagitis even after the second course of treatment, and the dosage was again increased, to 1.98 mg/kg, which resulted in healing. After initial treatment, all of the patients received 8-week maintenance therapy with 0.36 to 1.59 (mean 0.59, SD 0.25) mg/kg of lansoprazole.

Clinical Follow-Up

A total of 24 patients were followed up for 4 to 32.9 months (mean 20.8 ± 10.6 months) after the end of maintenance therapy. Clinical relapses were observed in 20 of 24 patients (83.3%—6/7 [85.7%] of children younger than 9 years old)—2 (8.3%) patients presented with 2 clinical relapses, and no patient presented with >2 clinical relapses. During the clinical relapses, patients from group B received a mean dose of 1.01 mg/kg of lansoprazole (SD 0.33), whereas those from group A received 1.43 mg/kg (SD 0.81, $P = 0.27$).

The most common symptom reported at clinical relapse was epigastric pain (Table 3). Figure 2 displays the Kaplan-Meier survival curve for clinical relapses. The median time for the first clinical relapse after the end of maintenance treatment was 14.65 months (95% CI 6.73–25.72). Table 4 shows clinical features at baseline of patients who presented with clinical relapses as compared with those who did not present with them. In the univariate Cox model, patients who presented with clinical relapse required significant higher lansoprazole dosage for primary healing (Table 5).

All of the patients presenting with clinical relapse underwent upper gastrointestinal endoscopy, and endoscopic relapse was observed in 9 of 20 patients (45%, Table 3). In group A (younger than 9 years), 2 of 6 patients presented with endoscopic relapse, whereas in group B 7 of 14 patients presented with erosive lesions in the endoscopy performed because of a clinical relapse ($P = 0.64$). The median time for the endoscopic relapse was 25.7 months (range 9.2–32.9 months, lower limit of 95% CI 23 months, upper limit undetermined) (Fig. 3). Patients who presented with endoscopic relapse presented significantly more often with grade B or C esophagitis at baseline (88.9% vs 33.33%, $P = 0.01$), and in the univariate Cox model the association provided an HR of 6.21 (95%

TABLE 2. Symptoms at presentation according to the grade of esophagitis (Los Angeles criteria) in groups A (age <9.0 y) and B (age >9.0 y)

	Group A, n = 7 (%)				Group B, n = 17 (%)			
	Esophagitis grade				Esophagitis grade			
Symptom	A	B or C	Total	*P*	A	B or C	Total	*P*
Epigastric pain	2 (40)	3 (60)	5 (100)	1	5 (41.7)	7 (58.3)	12 (100)	0.62
Heartburn	0 (0)	1 (100)	1 (100)	1	3 (33.3)	6 (66.7)	9 (100)	0.34
Nausea	0 (100)	3 (100)	3 (100)	0.14	3 (42.9)	4 (57.1)	7 (100)	1
Vomiting	1 (25)	3 (75)	4 (100)	0.48	1 (20)	4 (80)	5 (100)	0.29
Hiccups	0 (0)	1 (100)	1 (100)	1	2 (66.7)	1 (33.3)	3 (100)	0.58
Nocturnal pain	0 (0)	0 (0)	0	1	1 (25)	3 (75)	4 (100)	0.58
Choking	0 (0)	1 (100)	1 (100)	1	0 (0)	2 (100)	2 (100)	0.47
Abdominal pain	1 (50)	1 (50)	2 (100)	1	0 (0)	1 (100)	1 (100)	1
Total	3 (42.9)	4 (57.1)	7 (100)		8 (47.1)	9 (52.9)	17 (100)	

TABLE 3. Clinical and endoscopic features in 20 patients at the first clinical relapse

	n (%)
Symptoms	
Epigastric pain	10 (50.0)
Heartburn	8 (40.0)
Nausea	8 (40.0)
Hiccups	6 (30.0)
Vomiting	5 (25.0)
Dysphagia	1 (5.0)
Grade of esophagitis	
No esophagitis	11 (55.0)
A	5 (25.0)
B	3 (15.0)
D*	1 (5.0)

* This patient also had esophageal stricture.

CI 0.77–49.84, $P = 0.09$) (Tables 5 and 6). Moreover, a higher BMI was significantly associated with endoscopic relapse ($P = 0.05$).

Only 2 patients presented with 2 clinical relapses. The first patient was a 12-year-old boy who presented with a peptic stricture and circumferential erosions at the patient's first relapse. The patient was given the standard dosage of lansoprazole (1.03 mg/kg) at baseline, and primary healing was achieved. After the patient's first relapse, the patient was prescribed a double dosage (60 mg, ie, 1.71 mg/kg) for 8 weeks because of the severity of the patient's lesions, followed by half-dosage maintenance therapy. The second relapse happened 6 months after the end of the treatment of the first relapse, and the endoscopy showed no macroscopic lesions. The second patient was a 10-year-old boy who presented with normal endoscopy during the patient's first relapse. This patient was successfully treated at baseline with the standard dosage of lansoprazole (1.15 mg/kg), and the same dosage (30 mg, ie, 1.06 mg/kg) was used during the patient's first relapse. The second relapse happened 2 months after the end of maintenance treatment for the first relapse, and a new endoscopy revealed normal esophageal mucosa.

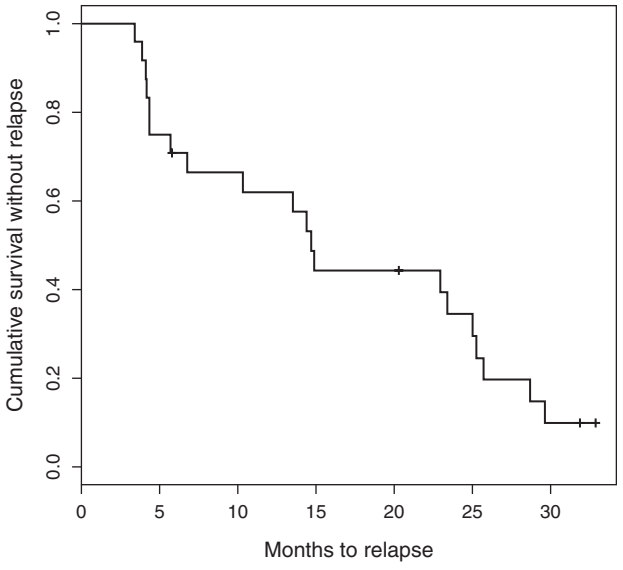

FIGURE 2. Time to clinical relapse according to Kaplan-Meier survival curve in 24 patients.

DISCUSSION

The present study shows that relapses of GERD are frequent in children and adolescents with erosive GERD because clinical relapses happened in 83.3% of patients after a median follow-up of 14.65 months and 45% of those relapses were also endoscopic relapses, with EE detected at the time of the relapse. In a study evaluating maintenance therapy after initial healing of EE, Boccia et al (3) reported only a 6.8% recurrence of symptoms in 44 patients followed up for 30 months after the end of their maintenance therapy—25% of clinical relapse, mostly with mild symptoms, not requiring further endoscopic evaluation. In that study, patients were evaluated every 6 months, whereas in the present study, the clinical evaluation occurred quarterly. Although the more frequent clinical evaluation may justify part of the difference between both studies, we must also consider that other clinical differences between both groups are likely. For instance, patients in this study group were 1 year older, and no patient with hematemesis was included.

Endoscopic relapses were also frequent, and they were observed in 45% of patients with clinical relapse (37.5% of all of the followed patients), after a median follow-up of 25.7 months. In the aforementioned study, Boccia et al (3) reported that only 1 patient (2.2%) presented with endoscopic relapse after 3 months of the end of maintenance therapy. We did not perform endoscopy on asymptomatic patients after primary healing was achieved, and therefore we cannot compare that figure. EE may present mild symptoms, and even can be asymptomatic, and the actual rate of mucosal relapse cannot be determined in our study.

A significant strength of the present study is that we included only patients with erosive peptic esophagitis. The majority of studies in children have included both EE and non-EE, with a predominance of nonerosive disease (9). Another important strength is the strict exclusion criteria, which included hiatal hernia and GERD-predisposing disorders, allowing for a homogeneous study group.

The study presents also some important limitations. First, the maintenance therapy was prescribed for a short period (8 weeks), whereas most researchers use 3 to 9 months (3,10,11). Continuous use of proton pump inhibitors (PPIs) for up to 11 years has been reported, even in children without GERD-predisposing disorders (15/35 with EE), for a median time of 512 days, and only minor adverse effects have been reported, making this class of drugs suitable for longer maintenance periods (4). There is not enough evidence, however, to recommend a standard maintenance therapy in children without chronic and relapsing erosive GERD, such as our patients, previously healthy children without GERD-predisposing conditions. Hassall et al (5) reported that 56% of patients required more than half of the therapeutic dosage as maintenance, whereas the relapses reported in our study occurred after the end of the maintenance therapy, which was shorter than that used by Hassall et al. On-demand therapy has been compared with both no maintenance and continuous maintenance therapy in erosive GERD, and on-demand therapy was equally effective in preventing symptoms (12). Although not ethically justifiable in the present study design, an untreated (placebo) arm in the study would enable a more strict appraisal of clinical and endoscopic relapses.

Another important limitation is that we did not perform endoscopy on asymptomatic patients after documented healing of their primary lesions and, as a result, we were not able to detect asymptomatic relapses of erosive lesions. We believe that asymptomatic relapses of erosive GERD could have happened often, but when the study was designed, we considered it to be unethical to submit asymptomatic patients to research-only endoscopies. Finally, a larger sample size would enable us to power the study

TABLE 4. Baseline features and the occurrence of clinical relapse

	Clinical relapses (n = 20)	No clinical relapses (n = 4)	*P*
Age	10.01 (3.38)	9.49 (0.94)	0.56
Sex, male	16 (80)	2 (50)	0.25
BMI	17.28 (2.8)	18 (4)	0.75
Esophagitis grade B or more	10 (50)	3 (75)	0.59
Effective dosage of lansoprazole*	1.22 (0.56)	0.94 (0.15)	0.06
Primary failure after first course of PPI	4 (25)	0 (0)	1

Quantitative data presented as mean (standard deviation) and qualitative data as number (proportion). BMI = body mass index; PPI = proton pump inhibitor.
* Dosage associated with healing.

to evaluate more thoroughly variables associated with relapses of EE and more detailed age group analysis.

Among the predictors of clinical relapse, interestingly, a higher dosage of lansoprazole was associated with clinical relapse, although it did not reach statistical significance. All of the patients who presented with a primary failure demonstrated clinical relapses, which may constitute an important confounding factor because those patients were treated with a higher dosage of lansoprazole. There are no such data in pediatric studies, but a significant protective effect of primary healing against relapses has been reported in a study with adult patients, with an odds ratio of 0.46 (95% CI 0.22–0.97) (13). In the study protocol, the initial dose was estimated according to weight groups (>15 or <15 kg), which generates lower dosage ''per kilogram'' in older patients. Children ages 1 to 10 years apparently need a higher per-kilogram dose than do adolescents and adults, whereas small infants may require a lower effective dose (2). Age-related differences in drug disposition may be dramatic in children, depending not only on the body mass but also on the relative activity of hepatic enzymes and volume distribution (14).

Although obese patients were excluded, higher BMI was associated with endoscopic relapses. Obesity is a GERD-predisposing condition (1,2), but the present study did not include obese children, which highlights the importance of the BMI in the prognosis of GERD. It was reported in a retrospective study that overweight children do not present more frequently (23.9% vs 24.5%) with reflux esophagitis than normal-weight children (15). In another study, a similar result was reported, and the main reason for that finding is that in both studies the authors defined reflux esophagitis based on histological findings (16). Malaty et al reported that children with GERD symptoms are more likely (odds ratio 1.7, 95% CI 1.2–2.6) to be obese in a population-based study (National Health and Nutrition Examination Survey) (17). We believe that in children with reflux EE, avoiding being overweight is a treatment target.

As expected, there was no relation between clinical presentation and endoscopic severity of the esophagitis. In spite of little being known on the relation between symptom awareness and the severity of lesions in children, the authors have reported that symptoms are poor predictors of the severity of GERD in children (18,19). On the contrary, the threshold for acid infusion in distal esophagus varies from patient to patient and this variation was not affected by the presence of macroscopic esophagitis in healthy volunteers (20). Evidently, some clinical relapses may have been related to other conditions, such as functional abdominal pain and/or functional dyspepsia; however, during those clinical relapses, all of the patients improved on GERD treatment.

We conclude that clinical and endoscopic relapses are frequent in children and adolescents with erosive GERD, and they may happen in the short term or in the long term. Although there is no

TABLE 5. Hazard ratios and 95% confidence intervals of variables associated with clinical and endoscopic relapse in univariate and multivariate Cox model

Variable	Hazard ratio	95% confidence interval	*P*
Clinical relapse, univariate analysis			
Sex, male	1.23	0.41–3.73	0.71
Age	0.89	0.73–1.09	0.26
BMI	1.09	0.92–1.29	0.34
Effective dosage	2.7	0.94–7.72	0.06
Failure of primary therapy	1.74	0.57–5.33	0.33
Grade B or C esophagitis	0.76	0.31–1.83	0.54
Endoscopic relapse, univariate analysis			
Sex, male	1.06	0.22–5.15	0.94
Age	0.96	0.69–1.33	0.79
BMI	1.3	1–1.69	0.05
Effective dosage	2.05	0.5–8.35	0.32
Failure of primary therapy	2.95	0.73–11.87	0.13
Grade B or C esophagitis	6.21	0.77–49.84	0.09

BMI = body mass index.

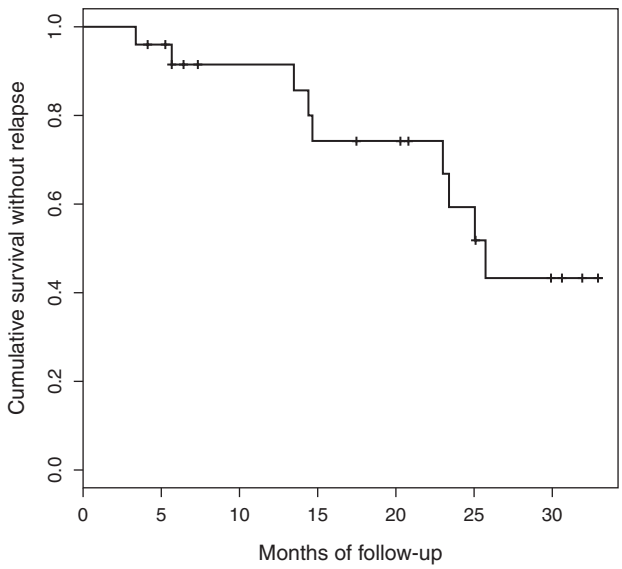

FIGURE 3. Time to endoscopic relapse according to Kaplan-Meier survival curve in 24 patients.

TABLE 6. Baseline features and the occurrence of endoscopic relapse

	Endoscopic relapses (n = 9)	No endoscopic relapses (n = 15)	*P*
Age	10.58 (1.89)	9.53 (3.64)	0.37
Sex, male	7 (77.78)	11 (73.33)	1
BMI	18.5 (2.83)	16.75 (2.9)	0.16
Esophagitis grade B or more	8 (88.89)	5 (33.33)	0.01
Effective dosage of lansoprazole*	1.23 (0.41)	1.15 (0.59)	0.71
Primary failure after first course of PPI	3 (33.33)	1 (6.67)	0.14

Quantitative data presented as mean (standard deviation) and qualitative data as number (proportion). BMI = body mass index; PPI = proton pump inhibitor.
* Dosage associated with healing.

evidence that mild erosive GERD leads to complications, the clinician must be aware that those patients present with clinical relapses. Long-term use of PPIs may be necessary in some patients. The only significant risk factor herein identified was a BMI; however, further studies are warranted to identify groups, including among individuals with GERD-predisposing conditions, with a higher risk for relapses and an appropriate and specific strategy to avoid relapses.

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