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Original article

Impact of antisecretory treatment on respiratory symptoms of gastroesophageal reflux disease in children

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SUMMARY. **The effect of antisecretory treatment on extraesophageal symptoms of gastroesophageal reflux disease was evaluated. Seventy-eight children presenting with typical and extraesophageal symptoms of gastroesophageal reflux disease underwent a multichannel intraluminal impedance and pH monitoring (MII/pH). Children with a positive MII/pH were randomly treated with proton pump inhibitors (PPIs) or histamine H_2-receptor antagonists (H_2RAs) during 3 months. At the end of the treatment period, all patients were recalled. A second treatment period of 3 months was given to those patients who were not symptom-free after 3 months. Thirty-five of the forty-one (85.4%) children with a pathologic MII/pH presented with extraesophageal symptoms and were treated with PPIs (omeprazole; n:19) or H_2RAs (ranitidine; n:16) for 12 weeks. After 3 months, 11/19 (57.9%) PPI-treated patients had a complete resolution of symptoms; 6/8 nonresponders were treated with PPI for another 3 months and became all symptom-free. The other two underwent a Nissen fundoplication. Only 5/16 (31.2 %) patients treated with H_2RAs had a complete resolution of symptoms after 3 months; 1/11 was treated again with H_2RAs during 3 months, and 10/11 were changed to PPIs. In 3/10, a partial resolution of symptoms was achieved, while in 7/10, a complete remission was obtained ($P < 0.05$). Antisecretory reflux treatment improves extraesophageal reflux symptoms. The efficacy of PPIs is superior to that of H_2RAs in these children.**

KEY WORDS: **gastroesophageal reflux (disease), multichannel intraluminal impedance, pH monitoring, proton pump inhibitor, respiratory symptom.**

INTRODUCTION

Extraesophageal manifestations associated with gastroesophageal reflux disease (GERD) include respiratory conditions or symptoms such as asthma, wheezing, bronchitis, pneumonia, bronchiectasis, cough, apnea, apparent life-threatening events, conditions affecting the ear, nose, and throat (ENT), such as sinusitis, otitis media, and laryngotracheitis, and dental erosion.[1]

The diagnostic yield of esophageal pH monitoring in patients with respiratory symptoms is limited to acid reflux, and its sensitivity is higher in erosive than in nonerosive GERD.[2] Sensitivity and specificity is improved by using a combination of multichannel intraluminal impedance and pH monitoring (MII/pH).[3] Combined MII/pH detects acid, weakly acid, and non-acid reflux episodes. MII/pH is superior to pH monitoring alone for the evaluation of a temporal relation between symptoms and reflux episodes.[3,4]

In children, proton pump inhibitors (PPIs) have been shown to be effective and safe for short-term treatment of erosive esophagitis and GERD symptoms that are refractory to other drugs.[4,5] Studies in adults and children have reported that in comparison with H_2-receptor antagonists (H_2RAs), PPIs results in higher and faster rates of healing of erosive esophagitis compared with H_2RAs.[4,5] Adult patients with extraesophageal manifestations, such as laryngopharyngeal reflux, of GERD may require longer (4 months are considered better than 2 months) and high-dose (twice daily) acid-suppressive therapy for symptom control[4,5] than those with esophageal symptoms. However, no evidence has emerged for the optimal treatment of reflux-related extraesophageal symptoms in children. The aim of this study was to evaluate the effect of antisecretory treatment on

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extraesophageal symptoms of GERD diagnosed by MII/pH in children.

METHODS

A prospective study was conducted during 1 year, including 78 consecutive children (mean age ± SD: 40.6 ± 36.4 months; range: 1–181 months) referred to the Gastrointestinal Endoscopy and Motility Unit of the Department of Pediatrics, University of Naples 'Federico II,' Italy, with esophageal and extraesophageal symptoms. The diagnosis of GERD was based on the impact of symptoms on the general well-being of the children[4] and the results of the MII/pH.

Criteria for exclusion were esophageal abnormalities caused by general or systemic disease, previous esophageal and/or gastric surgery, and the presence of esophageal stenosis, renal, cardiac, hepatic, or severe chronic pulmonary diseases such as cystic fibrosis, organ transplantation, central nervous system disease, known food allergy, or celiac disease.

At enrollment, all patients underwent a clinical evaluation. Esophageal and extraesophageal symptoms were recorded with a validated questionnaire by one caregiver (DU) in order to obtain baseline data on symptom severity and frequency.[6] The severity of symptoms was classified as follows: grade 0, no symptoms; grade 1, mild symptoms with spontaneous remission and no interference with normal activity or sleep; grade 2, moderate symptoms with spontaneous but slow remission and mild interference with normal activity or sleep; and grade 3, severe symptoms without spontaneous remission and marked interference with normal activity or sleep.[6]

The frequency of symptoms was classified as follows: grade 0, absent; grade 1, occasional (symptoms present less than 2 days a week); grade 2, frequent (symptoms present 2–4 days a week); and grade 3, very frequent (symptoms present more than 4 days a week).[6] A score for each symptom and a total symptom score were calculated. The score for each symptom was calculated by multiplying the severity grade by the frequency grade, with a possible range for each score of 0–9 (Table 1).

Combined MII/pH was performed in all patients. Acid suppression therapy was discontinued 2 weeks before testing, if applicable. A 2.1-mm diameter MII/pH catheter with six impedance channels and two (esophageal and gastric) antimony pH sensors with external reference were used. Prior to the procedure, the pH sensor was calibrated using buffered solutions of pH 4.0 and 7.0, as specified by the manufacturer (Sandhill Scientific, Inc., Highland Ranch, CO, USA). The probe was then inserted through the nose into the stomach, and the esophageal pH sensor was positioned 5 cm above the LES, based on the Strobel formula (length from nares to LES in cm = 5 + 0.252[height][7,8]). The six impedance channels were located 3, 4.5, 6, 7.5, 9, and 10.5 cm from the distal tip for the infantile MII/PH probe for infants younger than 1 year, and 3, 5, 7, 9, 11, and 13 cm from the distal tip for the pediatric MII/PH probe for children older than 1 year. The catheter was connected to a data logger (Sleuth System, Sandhill Scientific, Inc.) that stores data from all impedance channels with a frequency of 50 Hz. Acid beverages were not allowed during registration. Parents filled in a diary recording times of meals, body position, and any symptom suggesting gastroesophageal reflux (GER) occurrence during the recording period.

MII/pH tracings were evaluated using the BioVIEW analysis software (Sandhill Scientific, Inc.) and each study was manually reviewed. The following parameters were analyzed: number of reflux episodes according to pH-metry and impedance criteria, total duration of acid GER, reflux index (RI), and bolus exposure index (BEI). Gas reflux, liquid reflux, and mixed (combined gas and liquid) were determined by MII and analyzed through manual read out by the same operator. All reflux events were categorized as acid or non-acid, as determined by the pH sensor, with acid <4 and non-acid >4. BEI was calculated as the total percentage of time with retrograde movement of intraluminal esophageal material.

The lack of pediatric normal values for impedance did not allow the determination of a clear-cut impedance threshold. The analysis of the pH-metry was considered abnormal if the RI was >10% in infants and more than or equal to 5% in children.[9] However, because a BEI >1.4% has been proposed as an upper limit (95th percentile) of normal impedance in adults,[10] this cut-off was also used in the analysis of our results.[11] In addition, to increase the accuracy of the techniques, we have evaluated the symptom index (SI) and the symptom association probability (SAP). The SI ([number of reflux-associated symptoms/total number of symptoms during 24 hours]/100) and the SAP index was evaluated automatically by the software, evaluating the relation between reflux episodes and symptoms through the Fisher formula. A SI of >50 % and a SAP >95 % were defined as pathologic.[12,13]

Patients with pathologic MII/pH were randomly treated with a PPI (omeprazole, 1.4 mg/kg/day) or H_2RA (ranitidine, 15 mg/kg/day) during 3 months and referred to their treating general pediatricians. The caregivers of each child were contacted with a telephone call at the end of the 3-month treatment. At follow-up, the questionnaire was replicated for the symptom score to evaluate the response to treatment and clinical outcome. The patients were considered to be healed when there was a complete remission of the symptoms (score 0). If the children were not symptom-free, a second treatment period of 3 months

Table 1 Distribution of the score in the study population

Symptom	Score	PPI, 19 patients				H_2RA, 16 patients			
		BT		AT		BT		AT	
		Patient	%	Patient	%	Patient	%	Patient	%
Vomiting	1	8	42.1	4	21	4	25	1	6.2
	2	2	10.5	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	2	10.5	0	0	1	6.2	0	0
	6	0	0	0	0	0	0	0	0
	9	2	10.5	0	0	4	25	3	18.7
Chest pain	1	4	21	1	5.3	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0
	9	1	5.3	0	0	1	6.2	1	6.2
Irritability	1	3	15.8	1	5.3	0	0	0	0
	2	0	0	0	0	1	6.2	0	0
	3	0	0	0	0	0	0	0	0
	4	1	5.3	0	0	1	6.2	1	6.2
	6	0	0	0	0	1	6.2	0	0
	9	1	5.3	0	0	0	0	0	0
Difficulty swallowing	1	3	15.8	0	0	1	6.2	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	6	0	0	0	0	1	6.2	1	6.2
	9	0	0	0	0	1	6.2	1	6.2
Cough	1	3	15.8	0	0	1	6.2	2	12.5
	2	5	26.3	1	5.3	6	37.5	0	0
	3	6	31.6	1	5.3	4	25	3	18.7
	4	3	15.8	0	0	5	31.2	4	25
	5	0	0	0	0	0	0	0	0
Other respiratory symptoms, such as wheezing	1	2	10.5	0	0	3	18.7	2	12.5
	2	0	0	0	0	1	6.2	1	6.2
	3	1	5.3	0	0	1	6.2	0	0
	4	1	5.3	0	0	2	12.5	0	0
	6	8	42.1	1	5.3	0	0	0	0
	9	6	31.6	1	5.3	8	50	4	25

AT, after treatment; BT, before treatment; H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor.

was started after which the parents were contacted again.

Informed consent for participation in this study was obtained from the parents of all patients, and the experimental design was approved by the Independent Ethics Committee of University of Naples 'Federico II'. Given the fact that patients were symptomatic, the Ethical Committee refused the inclusion of a placebo group. All data were statistically analyzed with the SPSS version 8.0 program (SPSS, Inc., Chicago, IL, USA). Statistical tests used were the χ^2 test and Fisher's exact test, depending on the number of observations.

RESULTS

Forty-one of the 78 children (52.6%) had a pathologic MII/pH. Thirty-five (mean age ± SD: 40.6 ± 36.4 months; range: 1–181 months) out of 41 (85.4%) presented with both esophageal and extraesophageal symptoms of GERD. Of these 35 children, 19 (54.3%) were treated with PPIs (1.4 mg/kg/day) and 16 (45.7%) with H_2RAs (15 mg/kg/day) for 12 weeks (Fig. 1, Table 2). At baseline, both groups were comparable for demographic data and severity of symptom scores. Furthermore, the MII/pH parameters were comparable in the two groups (Table 3). SAP index was positive in eight (42.1%) patients in the group treated with PPIs and in five (31.3%) patients in the group treated with H_2RA ($P = 0.38$). Also, the SI was not statistically different.

Eleven children of the 19 (57.9%) treated with the first cycle of PPI therapy had a complete resolution of the symptoms, while in only five of the 16 children (31.2%) treated with H_2RA during the first cycle, symptoms disappeared (odds ratio [OR] = 3.025; $P = 0.21$). Regarding the first 3 months of treatment (first cycle of treatment), PPI induce an absolute risk reduction of 0.26 in comparison with H_2RAs, meaning that the outcome in the PPI group was 26% better than in the H_2RA group. The relative risk reduction is 38.2%. The 'number needed to treat' is 3.8, meaning that for every 3.8 patients treated with

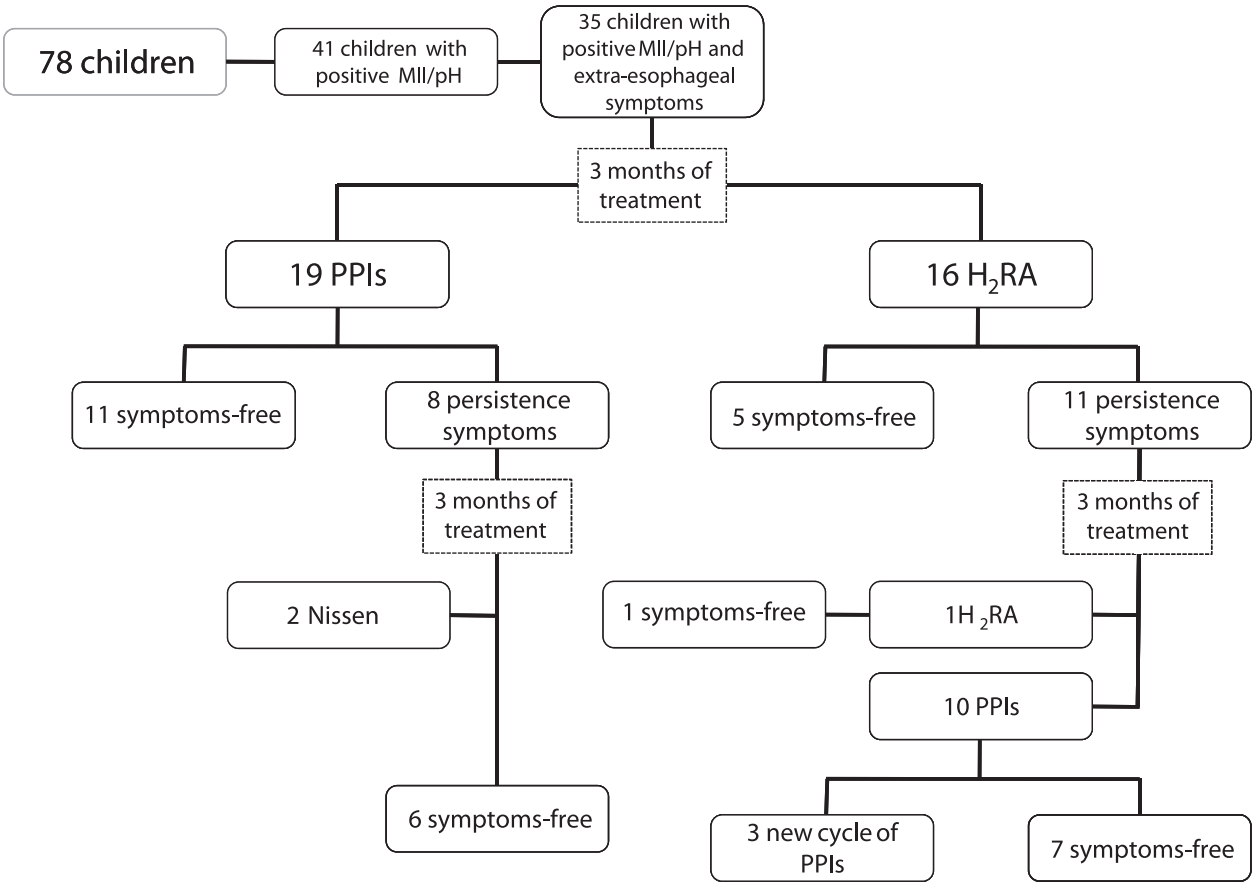

Fig. 1 Diagram of the included patients.

PPIs, there is one more symptom-free compared with the H_2RA group. The symptom score after the first 3 months of treatment was significantly lower ($P < 0.001$) in the children treated with PPIs compared with those treated with H_2RA (Table 4).

Six of the 8 children (31.6%) who showed an improvement but not a resolution of symptoms after 3 months of PPI treatment had another cycle of 3 months during which the same therapy was administered. They became all symptom-free after the second treatment period of 3 months. A Nissen fundoplication was performed in both patients in whom symptoms persisted despite 6 months PPI therapy (10.5%); endoscopy did not reveal hiatal hernia in these patients.

Ten of the 11 patients (90.9%) in whom symptoms persisted after treatment with H_2RAs were switched to PPIs during 3 months. In three of these 10 children (30%), a partial resolution of symptoms was obtained. The remaining seven children became symptom-free. One patient of this group, who had an improvement but not a resolution of symptoms, had another cycle of H_2RA therapy with a complete resolution.

Overall, 35 PPI 3-month treatments were prescribed in 29 patients. In 24/29 (83%) patients, this was related to a complete resolution of symptoms. Of the 17 H_2RA treatments, only six (35.3%) had a complete resolution of symptoms (OR 8.8; $P = 0.03$). No adverse events of the treatment were reported.

Table 2 Clinical characteristics of the study population at inclusion

	PPI group	H_2RA group
N (patients)	19	16
Age (mean ± 1 SD)	46.4 ± 42.5	34.5 ± 28.8months
Vomiting	14	9
Chest pain	5	1
Irritability	5	3
Dysphagia	3	3
Cough	17	16
Respiratory symptoms		
Apnea	6	4
Bronchospasm	1	0
Asthma	5	3
Laryngospasm	5	5
Pneumonia	5	1
Hoarseness	1	1

None of the parameters was statistically significant. H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor; SD, standard deviation.

DISCUSSION

The efficacy of antisecretory treatment in children with extraesophageal symptoms was evaluated in this

Table 3 Multichannel intraluminal impedance and pH monitoring values in both groups with percentage of abnormal results (at inclusion)

	PPI group		H_2RA group		*P*
	Mean ± SD	% abnormal	Mean ± SD	% abnormal	
Total n° reflux	56.5 ± 38.9		45.8 ± 41.3		0.23
Time pH < 4.0	75.1 ± 125.8		69 ± 115.7		0.44
Reflux index	9.9 ± 9.9	42.1	6.1 ± 9.3	37.5	0.47
BEI	49.6 ± 39.9	52.6	30.2 ± 25.2	68.7	0.06
Acid reflux	52.9 ± 40.6		44.6 ± 40.9		0.28
Weakly acid reflux	14.2 ± 9.1		10.3 ± 8.2		0.11
Non acid reflux	18.9 ± 20.9		9.3 ± 9.4		0.06
Symptom index	46.5 ± 24.81	47.3	45.3 ± 34.9	50	0.45
SAP	72.7 ± 33.5	36.8	64.3 ± 42.1	43.7	0.26

% abnormal is the % of patients in whom this parameter was abnormal. BEI, bolus exposure index; H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor; SAP, symptom association probability; SD, standard deviation.

study, and PPIs were shown to be more effective than H_2RAs. Three months of treatment was too short in some of these patients, because resolution was only achieved after 6 months in a subgroup. PPIs are known to be better than H_2RAs in the treatment of esophageal symptoms and esophagitis;[14] our results suggest that PPI are more effective in the treatment of extraesophageal symptoms caused by GER.

It is well known that a variety of extraesophageal symptoms, such as respiratory, and ENT symptoms and disorders, may be manifestations of GERD.[15,16] Symptoms may result from macroaspiration and microaspiration of refluxed gastroduodenal contents causing a direct deleterious effect of gastric juice on the mucosa of the tracheobronchial tree, the laryngopharynx – including vocal cords – the middle ear, and the nasosinusal complex.[15,16] The common vagal nerve innervation of the esophagus and the pulmonary tree may result in reflex-mediated reaction triggering extraesophageal symptoms via neuronal esophageal-pulmonary tree reflex.[9,17]

Compared with the H_2RAs, PPIs have been reported to have a greater inhibitory effect on gastric acid production. A meta-analysis comparing rates of healing of esophagitis demonstrated that omeprazole had a therapeutic advantage of 35–40% over H_2RAs.[5] The duration of PPI treatment needed to result in healing of esophagitis has been suggested to range between 8 and 12 weeks.[18] In adults, it has been demonstrated that effectiveness is directly related to the degree and duration of acid inhibition, and the healing rates for reflux esophagitis appear to be similar for all PPIs.[19] Although PPI therapy provides rapid symptomatic relief and healing of esophagitis, extraesophageal symptoms improve slowly and may require higher doses of PPIs.[20]

On the other hand, the effect of PPIs on extraesophageal or atypical manifestations of GERD remains unclear. Several studies evaluated the efficacy of antisecretory treatment on atypical symptoms of GERD and showed conflicting results.[2,21,22] In adults, several studies evaluating the efficacy of PPI therapy on chronic cough had negative results. A review of different studies comparing PPI treatment with placebo in patients with respiratory symptoms did not find significant differences.[2] These results are confirmed in a large randomized controlled trial conducted in patients with laryngeal reflux and ENT manifestations, which failed to show any benefit of 40-mg esomeprazole during 16 weeks compared with placebo 22. Weakly acid reflux episodes have been demonstrated in adults to be more frequently associated with extraesophageal reflux symptoms such as cough.[21] A limited number of studies in children have evaluated the effect of treatment on atypical reflux symptoms. Khoshoo and Haydel enrolled 46 children

Table 4 Symptom score (mean ± 1 SD) before and after the first cycle of therapy

	PPI (n = 19)		H_2RA (n = 16)		*P*
	BT	AT	BT	AT	
Vomiting	2.26 ± 1.24	0.21 ± 3.9	2.75 ± 3.86	1.75 ± 3.61	0.0003
Chest pain	0.68 ± 2.06	0.05 ± 0.23	0.56 ± 2.25	0.56 ± 2.25	0.01
Irritability	0.84 ± 2.19	0.16 ± 0.69	0.81 ± 1.77	0.25 ± 1	0.6
Difficulty swallowing	0.16 ± 0.37	0 ± 0	1 ± 2.61	0.94 ± 2.62	0.2
Cough	2 ± 2.73	0.26 ± 0.81	2.81 ± 0.98	1.69 ± 1.78	0.0001
Respiratory symptoms	5.84 ± 2.91	0.79 ± 2.42	5.5 ± 3.76	2.5 ± 3.92	0.000001

The *P* value indicates the difference between PPI and H_2RA group after therapy. AT, after therapy; BT, before therapy; H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor.

with nonatopic persistent asthma despite bronchodilators, inhaled corticosteroids, and leukotriene antagonists. A pH-metry was abnormal in 27/46 (59%). Anti-GER treatment (PPI and metoclopramide) in patients with 'GERD and asthma' resulted in a significant reduction in asthma medication. In a subgroup of eight patients with a normal pH-metry, the same treatment resulted in a reduction of asthma medication in two of the eight (25%), while there was no reduction in control patients.[21] Stordal *et al*. performed the first and so far only methodologically sound, randomized, double-blind, placebo-controlled clinical trial analyzing the efficacy of a PPI (omeprazole) in pediatric patients with asthma and GERD. Omeprazole treatment did not improve asthma symptoms in children with asthma and GERD.[19]

A more recent study in adults showed that extra-esophageal symptoms are frequent in patients with classic GERD and that PPI therapy is likely to improve or resolve the symptoms.[23] In our study, treatment with PPI showed a higher efficacy than H_2RA, although the difference did not reach a statistical significant difference. But, after the second cycle, PPIs showed a significant higher efficacy than that of H_2RAs. Differently from experience in adults, according to our data, we can hypothesize that acid reflux and not only weakly acid reflux may cause atypical GERD. This could explain the high efficacy of PPIs on atypical symptoms in children. In addition, our population shows a higher percentage of acid reflux in the impedance analysis compared with other studies in literature. This may be influenced by the use of the Strobel formula for placing of the probe. Other studies in literature show a larger percentage of weakly acid and alkaline reflux. In these studies, the location of the probe was determined with a radiographic control.[24,25]

Wunderlich and Murray first used SAP analysis to determine the temporal relationship between cough and acid reflux events, and found that 35% of patients had a positive SAP.[26,27] In our population, SAP was positive in 37% of the children in both treatment groups, while SI was positive in 50% of patients. This result is comparable with those found in literature.[28]

During treatment, no side effects were reported by the parents. The limits of our study include the open comparative design, the lack of a placebo-controlled group, as well as the lack of a repeated MII/pH during follow-up. However, response to treatment is clinically more relevant than improvement of MII/pH parameters. Moreover, parents of children who were asymptomatic would most likely not have permitted a second MII/PH to be performed.

In conclusion, the improvement of extraesophageal symptoms in children with GERD in response to PPI therapy suggests a possible cause–effect relation. The efficacy of PPIs in the treatment of extraesophageal reflux symptoms suggests the possibility of using these drugs as a better option than H_2RAs, as already approved for erosive esophagitis and relief of GERD typical symptoms. However, because the number of children in our study is small, more data are needed before firm recommendations can be made. Interesting, only two children (5.7 %) underwent a Nissen fundoplication. Larger randomized controlled trials with a structured long-term follow-up are needed to confirm our results.

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