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# Acid and weakly acid gastroesophageal refluxes and type of respiratory symptoms in children

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**KEYWORDS**
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Respiratory manifestations

**Summary**
*Objectives:* To evaluate the association between the frequency of acid reflux (AR) and weakly acid reflux (WAR) and specific respiratory symptoms (RS) in childhood.
*Study design:* We retrospectively reviewed medical records of children with difficult-to-treat RS, not under acid suppressive therapy, and with a positive multiple intraluminal esophageal impedance (pH/MII) monitoring. To discriminate children with prevalent AR and WAR events, a ROC curve was designed and the distribution of the different RS in children with prevalent AR or WAR events was analyzed.
*Results:* A higher number of AR over WAR events was detected ($p < 0.0001$) but the WAR-to-AR events ratio progressively decreased with the age of the subjects ($p < 0.01$). Similar total number of reflux events was found in the three age group and in children with a more prevalent WAR or AR. The most prevalent RS, equally distributed among the three age groups, were persistent and/or nocturnal cough, wheezy bronchitis/asthma, and recurrent lower respiratory tract infections (RLRTI). Apnoea was most frequent in infants ($p = 0.036$). A higher frequency of RLRTI, but not of nocturnal cough or wheezy bronchitis/asthma, was shown in WAR as compared with AR patients ($p = 0.040$), and specifically those in the school-aged group ($p = 0.013$). Age and WAR were respectively identified as independent predictors of apnoea and RLRTI ($p < 0.05$).

*Abbreviations:* WAR, weakly acid reflux; AR, acid reflux; RS, respiratory symptoms; GER, gastroesophageal reflux; pH/MII, multichannel intraluminal impedance associated with pH-metry; SD, standard deviations; ROC, receiver operator characteristic; ORs, odds ratios; 95% CI, 95% confidence intervals; LCR, laryngeal chemoreflexes; LLM, lipid laden macrophages; BAL, bronchoalveolar lavage.

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*Conclusion:* WAR events are common in children with gastroesophageal reflux and difficult-to-treat RS and often associated with RLRTI. These findings support the role of pH/MII monitoring in the evaluation of these patients and may explain the disappointing clinical results often observed with anti-acid treatments.


## Introduction

The pathogenesis of gastroesophageal reflux (GER)-related respiratory symptoms is multifactorial, related to the frequency and duration of the reflux events but possibly also to the acidity of the refluxate which may be aspirated.[1,2] Because respiratory disorders and GER are both common in childhood and often co-exist, the causal relationship between these two conditions may be difficult-to prove also with the aid of supporting tests.[3] With the advent of multichannel intraluminal impedance associated with pH-metry (pH/MII), it has become possible to detect all GER episodes accompanied with a bolus movement and classify GER episodes according to their content (liquid, gas and mixed), pH value and proximal extension.[4] The possibility to measure not only acid, but also weakly acid refluxes and alkaline refluxes, has expanded the diagnostic power of pH detection alone and has expanded our knowledge on this medical condition, common in the pediatric population.[5,6]

In infants with GER and respiratory symptoms it was found that the majority of postprandial reflux episodes were not accompanied by a drop in oesophageal pH and that, because of the frequent feeding and subsequent buffering of gastric contents.[7–9] In contrast, in older symptomatic children, acid and weakly acid refluxes were reported to occur approximately at the same rate.[6,10–12]

Evaluating the possible connection between refluxes and respiratory symptoms, a frequent temporal association was detected in very pre-term infants between GER episodes (acid and weakly acid refluxes) and irregular breathing, with apnoea and/or oxygen desaturation.[9] In addition, it was demonstrated that cough-reflux association seems to be higher in infants than in older children[8] and that both acid and weakly acid reflux events may precede respiratory symptom in term infants and in children with unexplained cough.[13]

More challenging is the assessment of the causal association between acid and weakly acid reflux events and symptoms, when evaluating patients who may complain more than one respiratory complain. Indeed, a question that has not been previously addressed is whether a higher frequency of wheezy bronchitis, asthma, respiratory infections, laryngospasm and apnoea, in addition to cough, may be more often associated with acid versus weakly acid reflux events in children of different ages.

A retrospective study was therefore performed in infants, preschool-aged and school-aged children with GER and difficult-to-treat respiratory symptoms evaluated by oesophageal pH/MII monitoring. The number of acid and weakly acid reflux events was detected and, through a ROC curve analysis, children with more prevalent acid versus weakly acid reflux events were discriminated. The distribution of the different respiratory symptoms in children with more prevalent acid or weakly acid reflux events was then evaluated.

## Methods

### Patients

In this 2-yr retrospective study, we evaluated the clinical records of children admitted between January 2007 and December 2008 because of chronic or recurrent, difficult-to-treat, respiratory symptoms, found to have a 24 h oesophageal pH/MII monitoring positive, according to the criteria previously described.[11,14] Respiratory symptoms included: persistent and/or nocturnal cough, wheezy bronchitis/asthma, recurrent lower respiratory tract infections, laryngospasm and apnoea.[14] We excluded from the study patients with: i) prematurity; ii) neurological abnormalities; iii) swallowing disorders; iv) structural gastrointestinal abnormalities, such as pyloric stenosis, malrotation and annular pancreas; v) motility upper gastrointestinal tract disorders, such as achalasia and delayed gastric emptying; vi) airway or great vessel structural abnormalities; vii) recent (less than four weeks) or current respiratory tract infections. To avoid interference of anti-acid treatment on the frequency of acid versus GER events, children treated ever or in the previous eight weeks with acid suppressor ($H_2$-blockers or proton pump inhibitors) or in the previous week with antiacids or alginates, were not included in the study. The study population was subsequently divided into three age groups: (i) infants, $<$2 yrs old; (ii) preschool-aged children, 2—5 yrs old; (iii) school-aged children, $>$5 yrs old.

Access to health records complied with the Italian legislation and the study was approved by the Ethics Committee of the Gaslini Institute, Genoa, Italy.

### Clinical assessment

Clinical data were collected uniformly in all children, according to the Gaslini Institute clinical protocols.[16,18] Specific tests were also performed to identify conditions such as ciliary dyskinesia, cystic fibrosis and immunodeficiencies. Clinical suspicion of GER warranting investigation was determined based upon: (i) presence of typical features or (ii) severe symptoms possibly related to GER. Indication for 24 h oesophageal pH/MII monitoring was discussed with the child's parents or tutors. When clinically indicated, multidetector computed tomography, fiberoptic bronchoscopy and/or oesophago-gastroduodeno endoscopy, were performed, as previously described.[14] All these investigations were carried out with full-informed, written parental consent.

### Oesophageal pH/MII monitoring procedure

24 h combined esophageal pH/MII monitoring was performed in all patients to detect acid (pH $\leq$4.0), weakly acid (pH >4.0—<7.0) or weakly alkaline (pH $\geq$7.0) refluxes.[11] Briefly, two different types of age appropriate catheters were used: infant (<75 cm of height) and pediatric (>75 cm of height). The impedance—pH catheters were connected an amplifier (Sleuth, Sandhill Scientific, Inc., Highlands Ranch, CO), delivering ultra-low current in a range of 1—2 kHz with resulting current flow variations in response to intraluminal impedance changes. The impedance and pH signals were digitized at 50 Hz, stored with a Sandhill Scientific stationary hard-disk recorder (Sandhill Scientific Inc., Highlands Ranch, CO, USA).[11] Before the start of the recording, the pH electrodes were calibrated using pH 4.0 and 7.0 buffer solutions. The study was performed after an overnight fast. The catheters were passed transnasally and positioned so that the esophageal pH sensor was at the second vertebral body above the diaphragm. The patients were encouraged to maintain normal activities, sleep schedule, and eat their usual meals at their normal times. Event markers on the data logger recorded meal times and posture changes. Between meals, patients were asked to abstain from snacks and acid (pH <5) beverages.

### Data analysis

The impedance—pH recordings were evaluated only if the duration was at least 20 h. All records were analyzed using the Sandhill Technologies software and displayed on a single screen for computer-assisted manual analysis.[11] Recordings was considered "positive" when: (i) the reflux index was >5% in patients older than 12 months and >10% in patients younger than 12 months; (ii) the number of reflux events was >50 in patients older than 12 months and >100 in patients younger than 12 months; (iii) a positive symptom association was demonstrated.[11] The symptom correlation was considered "positive" when >50% of symptoms were preceded by acid or weakly acid refluxes, with latency shorter than 5 min. The correlation between reflux events and symptoms was considered significant only if >6 respiratory symptom occurred during the 24-h monitoring.[11,14]

### Statistical analysis

Descriptive statistics were performed and reported in terms of absolute frequencies or percentages for qualitative data, in terms of means with standard deviations (SD) or medians with first and third quartiles (1q-3q) for quantitative data. Difference between median values of continuous variables was assessed by the Mann—Whitney *U* test. Comparison of frequency distributions was made by means of the Chi—Square test or the Fisher's Exact test in case of expected frequencies less than 5. Comparison of quantitative variables among the 3 age groups was performed using Kruskal—Wallis test. Bonferroni's correction was applied for multiple comparisons.

The best cut off-point able to discriminate between weakly acid and acid reflux patients was estimated on the basis of the receiver operator characteristic (ROC) curve analysis. Patients with a reflux index >5% were considered as "disease positive" patients (patients with gastroesophageal reflux due to acid reflux), whereas patients with a reflux index $\leq$ 5% were considered "disease negative" patients. In order to evaluate the role of different independent explanatory variables in the relationship with apnoea or with recurrent lower respiratory tract infections, two multiple logistic regression models were evaluated. A backward strategy was applied and the Likelihood Ratio test was used to evaluate statistical significance of the variables; Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) were calculated and reported. All tests were two-tailed and *p* values less than 0.05 have been considered as statistically significant. "Statistica release 8" (StatSoft Corp., Tulsa, OK, U.S.A.) for bivariate analyses and "Stata release 11" (Stata Corporation, College Station, TX, U.S.A.) for multivariate analyses were used.

## Results

### Patients

Case notes of 112 children were evaluated. There were 62 males and 50 females (2.5 mo—13.8 yrs old), 26 < 2 yrs of age (infants), 33 preschool-aged 2—5 yrs of age (preschool-aged) and 53 > 5 yrs of age (school-aged). The most prevalent respiratory symptoms were: (i) persistent and/or nocturnal cough (89 patients), (ii) wheezy bronchitis and asthma (75 patients), (iii) recurrent lower respiratory tract infections (59 patients), (iv) apnoea (13 patients), (v) laryngospasm (7 patients) (Table 1). The different respiratory symptoms were equally distributed into the three age groups with the exception of apneas that, as expected, showed a higher prevalence in infants ($p = 0.036$) (Table 1). More than one third of the patient (35.7%), similarly distributed in the three age groups (46.15%, 42.42% and 43.40%,respectively), had gastroenterological symptoms suggesting GER.

### pH/MII monitoring data

The mean total record time was 22.08 (0.22) hours and the median number of reflux events per patient was 52.0 (37.5—76.0). No differences were detected in the median number of reflux events per patient among the three age groups [47.0 (33.5—80.0), 50.0 (37.0—69.0) and 62.0 (44.5—83.5), respectively; $p = 0.096$] (not shown). In the whole study population, the median number of acid reflux events per patient was higher than that of weakly acid reflux events [39.0 (25.0—58.5) and 10.5 (4.5—22.0); ($p < 0.001$)] (Fig. 1A). However, when children were divided in the three age groups, a progressive decrease in the weakly acid reflux-to-acid reflux event ratio was detected with the increasing children age, being 0.72 (0.40—1.77) in infants, 0.29 (0.17—0.55) in preschool-aged children and 0.12 (0.06—0.43) in school-aged children ($p < 0.0001$). (Fig. 1B). No weakly alkaline reflux events were recorded.

**Table 1** Respiratory symptoms in the whole population and in each of the three age groups ($N = 112$).

| | Whole population (No. 112), No. (%) | Infants (No. 26), No. (%) | Preschool-aged children (No. 33), No. (%) | School-aged children. (No. 53), No. (%) |
|---|---|---|---|---|
| Cough | 89 (79.46) | 18 (69.23) | 27 (81.82) | 44 (83.02) |
| Wheezy bronchitis and asthma | 75 (66.96) | 17 (65.38) | 21 (63.64) | 37 (69.81) |
| Recurrent lower respiratory tract infections | 59 (52.68) | 16 (61.54) | 16 (48.48) | 27 (50.94) |
| Apnoea/ALTE | 13 (11.61) | 7 (26.92) | 3 (9.09) | 3 (5.66)[a] |
| Laryngospasm | 7 (6.25) | 1 (3.85) | 2 (6.06) | 4 (7.55) |

ALTE: apparent life-threatening event.
[a] $p = 0.036$ comparison between infants and school-aged children.

## Number and type of reflux events in weakly acid reflux and acid reflux patients

According to the ROC curve analysis, designed on the oesophageal pH/MII monitoring results, the optimal cut off value obtained for the percentage of acid reflux events was 70.37% (Fig. 2). Therefore, 45 children (40.18%) with $\leq$70.37% of acid reflux events were defined as "weakly acid reflux (WAR) patients" and 67 children (59.82%) with $>$70.37% of acid reflux events, were defined as "acid reflux (AR) patients".

As expected, WAR patients were more frequently detected among the infant group (44.4%) than among the preschool-aged group (24.4%) or the school-aged group (31.1%). No difference in the total number of reflux events per patient was detected between WAR and AR children, also when the three age groups were evaluated separately (Table 2). Similarly, no differences in the percentage of children not complaining gastroenterological symptoms suggesting GER were found between WAR and AR children (31.34% and 42.22%, respectively; $p = 0.23$), proportions similar to those observed in the whole study population (35.7%) (not shown).

## Prevalence of respiratory symptoms in weakly acid reflux and acid reflux patients

With the exception of recurrent respiratory infections, that were more frequent in WAR children ($p = 0.040$) (Fig. 3) and remarkably in the school-aged children group ($p = 0.013$) (not shown), the prevalence of the different types of respiratory symptoms was similar in the WAR and AR groups (Fig. 3). Performing multiple logistic regression analysis, as expected we detected an increased risk to develop recurrent respiratory infections for WAR patients, as compared with AR patients ($p = 0.018$), but also an increased risk to develop apneas for infants, as compared with school-aged children, irrespectively of the prevalence of WAR vs AR events ($p = 0.031$) (Table 3).

## Discussion

In this a 2-yr retrospective study we showed: i) a higher prevalence of weakly acid reflux over acid reflux events in infants, progressively decreasing from infancy to late childhood; ii) an increased risk to develop recurrent respiratory

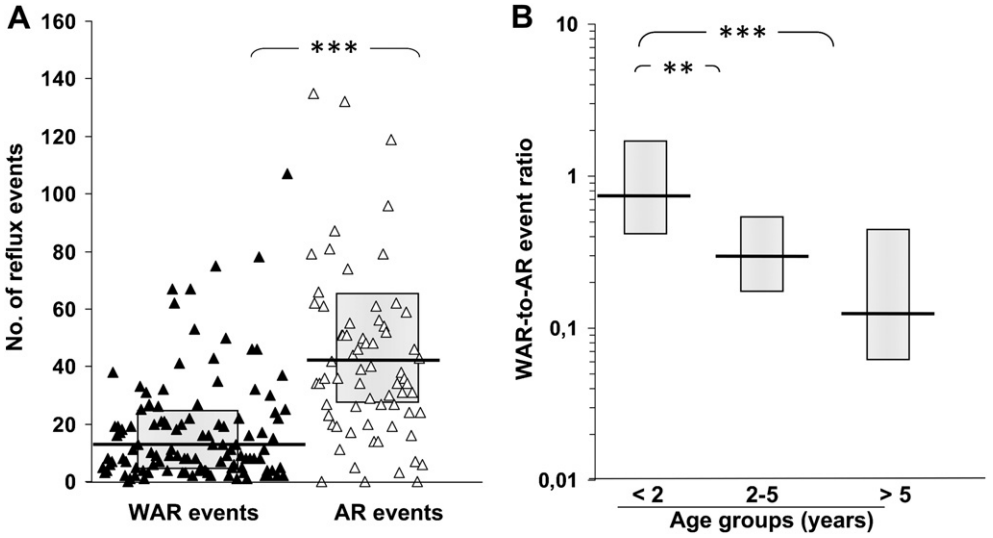


**Figure 1** Number of reflux events in the whole population (panel A) and weakly acid reflux (WAR)-to-acid reflux (AR) event ratio in the three age groups (panel B). Panel A. The number of WAR and AR reflux events are expressed as median (horizontal line) with lower and upper quartiles (grey box) and reported on the ordinate; panel B: WAR-to-AR event ratio are reported on the ordinate whereas the three age groups (infants, preschool-aged childen and school-aged children) are reported on the abscissa. *** = $p < 0.001$; ** = $p < 0.01$.

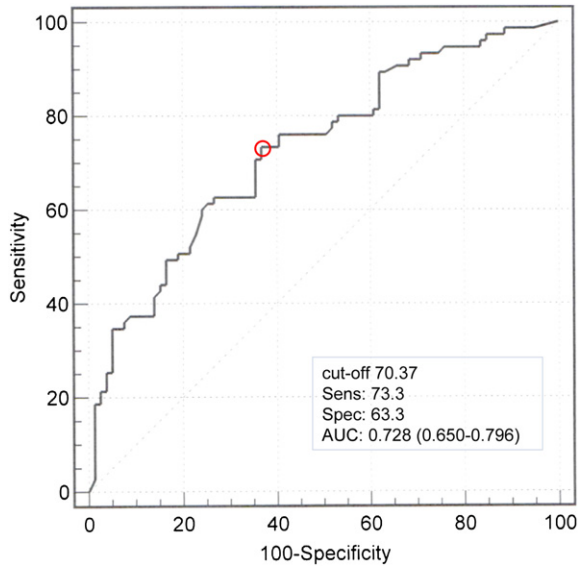


**Figure 2** Receiver operator characteristic (ROC) curve analysis used to estimate the best cut off-point able to discriminate between patients with prevalent weakly acid and acid reflux.

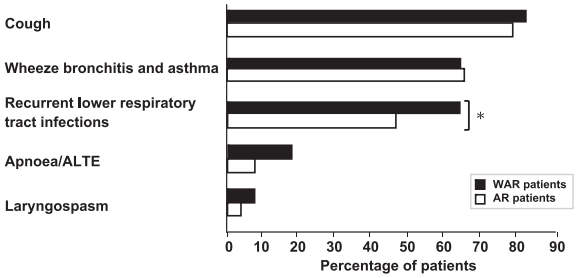


**Figure 3** Distribution of respiratory symptoms at the diagnosis in weakly acid reflux (WAR) patients and in acid reflux (AR) patients analyzed as whole population. Respiratory symptoms are reported on the ordinate whereas the percentage of patients are shown on the abscissa. $* = p < 0.05$.

infections for children with a higher prevalence of weakly acid reflux, and to develop apneas for infants, irrespectively of the prevalence of WAR vs AR events ($p = 0.031$) (Table 2).

With the advent of combined esophageal pH/MII monitoring it has been feasible to demonstrate that in children, and chiefly in the youngest, many reflux episodes are weakly acid.[5–9] Indeed, when performed in infants with GER, pH/MII monitoring showed that more than 70% of all GER events occur during the first 2 h after feeding and are weakly acid.[5,6,8,9] This was expected because during postprandial periods, neutralization of gastric contents occurs for a length of time related to several factors, including the frequency, the composition and the volume of the feeding.[6,15,16] In infants, this phenomenon lasts from 1 to 2 h after each formula feeding, thus for a period of time representing about half of the total measuring time.[17]

In older symptomatic children, as in adults, the general assumption is that acid and weakly acid GER events occur approximately at the same rate.[5,8,11,12,14] However, a remarkable prevalence of acid reflux (94.9%) was detected by Thilmany C. and co-workers, but the study was performed in children with severe chronic respiratory disorders (the vast majority ≥2 yrs old), which also included a small group of patients with cystic fibrosis[18] and similar results were reported by Blondeau K. and co-workers in a cystic fibrosis group.[19] In the present report, that did not include cystic fibrosis patients, we have shown that the higher prevalence of acid reflux events in children with GER and mild-to moderate respiratory symptoms is mainly due to the results obtained in children older than 2 years of age.

An emerged concept is also that reflux-associated supraesophageal symptoms in infants and children can be induced by both acid and weakly acid GER.[6,8,9,13] Consistent with previous studies, showing that in pre-term and term infants GER may trigger apneas,[5,6,9,17,20] we also observed a higher prevalence of apnoea episodes in the youngest, a group where more often weakly acid GER occurred. The induction of apneas by weakly acid GER may be explained by the demonstration that in humans, stimulation of laryngeal chemoreflexes (LCR) by infusion of weakly acid or non-acid solutions can cause laryngeal closure, apnoea episodes and cough through activation of sensory afferents in the superior laryngeal nerve.[21] Studies in animals indicate that with maturation, apnoea component of the LCR decreases while cough becomes prominent.[22] The possibility that weakly acid GER may also induce more frequently than acid GER cough in young infants has been also recently reported.[8] The

**Table 2** Number of total reflux events in WAR and AR patients analyzed as a whole and by age groups.

| | Whole population (No. 112) | Infants (No. 26) | Preschool-aged children (No. 33) | School-aged children (No. 53) |
|---|---|---|---|---|
| WAR patients | | | | |
| No. of total reflux events in WAR patients | 50.00 (34.00—81.50) | — | — | — |
| No. of total reflux events in WAR patients by age groups | — | 46.50 (28.50—73.50) | 50.00 (35.50—79.00) | 69.50 (41.00—106.50) |
| AR patients | | | | |
| No. of total reflux events in AR patients | 53.00 (40.50—72.00) | — | — | — |
| No. of total reflux events in AR patients by age groups | — | 39.00 (30.00—80.00) | 44.00 (37.50—66.50) | 63.00 (44.50—89.50) |

**Table 3** Best fitting logistic regression models for independent predictors of different respiratory symptoms ($N = 112$).

| Outcome | Explanatory variables | | OR | 95% CI | P value[a] |
|---|---|---|---|---|---|
| Apnoea/ALTE | Age (reference category: >5 yrs) | 2–5 yrs | 1.67 | 0.32–8.79 | 0.031 |
| | | <2 yrs | 6.14 | 1.44–26.23 | |
| Recurrent lower respiratory tract infections | Type of reflux (reference category: acid reflux) | Weakly acid reflux | 2.52 | 1.16–5.47 | 0.018 |

OR: odds ratios in the regression model (see materials and methods section).
95% CI: 95% Confidence Interval.
yrs: years.
[a] Likelihood Ratio test.

demonstration that also weakly acid GER can induce apneas and other respiratory disorders in children may be a clinically relevant observation since it can explain the frequently observed failure of acid suppressor in treating respiratory symptoms in this patient population.[23,24]

Acid suppression induced by GER treatment with $H_2$-blockers or proton pump inhibitors has been linked to an increased risk of community-acquired pneumonia, both in adults[25] and in otherwise healthy children.[26] Many factors may support the hypothesis that suppression of gastric acidity may represent a major risk factor for infections. Proton pump inhibitors and $H_2$-blockers may exert a direct inhibitory effect of on leukocyte functions[27,28] and induce significant qualitative and quantitative modifications of the gastrointestinal microflora.[29] However, there is also the possibility that reduction in the refluxate acidity may delay and/or make cough and swallowing reflexes less efficient, thus favoring more frequent and deeper inhalations. This latter supposition may explain the higher frequency of recurrent respiratory infections here reported in children with a high prevalence of weakly acid refluxes and evaluated off acid suppression. A small subgroup of WAR patients[19] underwent fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) for clinical indications. Despite the negativity of microbiological studies on BAL fluid, 11 had elevated BAL neutrophil numbers and 16 an increased proportion of lipid-laden macrophages (LLM), thought to be indirect signs of aspiration.[30] In support of this hypothesis, is the recent observation by Borrelli and co-workers, of positive correlations between non-acid reflux events and, respectively, LLM content and BAL neutrophil percentage in children with GER and respiratory symptoms.[31]

In conclusion we showed that in otherwise healthy pediatric population with GER and respiratory symptoms the prevalence of weakly acid reflux over acid reflux events tend decrease from infancy to school-aged age and that chronological age and acidity of reflux events may predispose to the development of specific respiratory manifestations. These preliminary indications, which need to be confirmed by prospective studies, on larger groups of well characterized children, support the clinical relevance of 24 h oesophageal pH/MII monitoring in the evaluation and treatment of children with GER.

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## Conflict of interest

The authors have no declared conflict of interests.

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