

Weakly Acidic Gastroesophageal Refluxes Are Frequently Triggers in Young Children With Chronic Cough

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Summary. Objective: To evaluate whether the proportion of acid and weakly acidic refluxes preceding cough bursts could be different in infants, preschool- and school-aged children with chronic, unexplained cough. Patients and Methods: One hundred six children with unexplained chronic cough, not receiving acid suppressive therapy, underwent impedance–pH monitoring. They were divided into Group A: <2 years (21 pts), Group B: ≥2 to ≤6 years (41 pts), and Group C: >6 years (44 pts). Reflux was defined as acid (pH <4), weakly acidic (WA; pH 4–7), and weakly alkaline (pH >7). Cough episodes were considered temporally associated with gastroesophageal reflux (GER) when occurring within 2 min after a GER episode. Results: Impedance–pH detected 55.50 (39.00–76.00) reflux episodes/patient with an acid-to-WA reflux event ratio of 3.31 (1.55–8.33). This parameter was significantly lower in Group A (1.33 [0.41–3.40]) than in Group B (3.06 [2.00–6.50]; $P < 0.05$) and Group C (5.09 [2.34–12.43; $P < 0.001$]). No cough episode was preceded by weakly alkaline refluxes in any patient. During impedance–pH recording, 93 patients (87.7%) had at least one cough episode that had been preceded by impedance refluxes in 83 patients. In this latter group (83 pts), the median number of cough episodes was 12.0 (5.0–25.5), of which 48.15% (30.15–71.43%) were preceded by refluxes; GER-preceded cough episodes were similar in the three groups. The majority of children had cough episodes preceded by acid refluxes in the total population (78.3%), in Group B (80.5%) and in Group C (93.7%), but not in Group A (40.0%; $P < 0.001$). Conclusions: In addition to acid, also a significant proportion of WA GER may precede cough episodes in young children with persistent cough, possibly explaining the inconstant effects of anti-acid treatment on respiratory symptoms. *Pediatr Pulmonol.* 2013; 48:295–302. © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Chronic or recurrent cough is a common presenting problem to pediatricians since it affects up to 10% of school-aged children, and is reported by up to 20% of parents of preschool-aged children.¹ Gastroesophageal reflux (GER) has a leading position among the various etiologic factors because of the variety of mechanisms through which GER is able to induce cough. These include laryngeal soiling, pulmonary aspiration, and vagal reflexes.²

However, since also GER is frequently present in childhood, but usually self-limiting and not associated with symptoms, it is often difficult to prove a causal connection between these two conditions, that is, to establish a temporal relationship between cough and reflux episodes. Although the presence of symptoms suggestive of GER disease, such as frequent regurgitation, heartburn, vomiting, abdominal pain, and dysphagia,

are often a reliable indication, their absence cannot exclude GER as an underlying cause of the chronic cough.^{2,3} In addition, because of the variety of triggers

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that can induce cough in children, it is often difficult to demonstrate a clinical improvement of the respiratory manifestations as a result of GER treatment with anti-acid medication or proton pump inhibitors (PPI).^{4,5} Indeed, a recent Cochrane Systematic Review concluded that PPI is not efficacious for cough associated with GER disease symptoms in very young children (including infants).⁵

Since there are no gold-standard diagnostic tests, the relationship between GER and respiratory symptoms is made clinically with some supporting diagnostic evaluations, including pH recording and detection of lipid laden macrophages in the bronchoalveolar lavage fluid.^{6,7} More recently, with the introduction of multichannel intraluminal impedance associated with pH-metry, by measuring changes in electrical impedance at multiple levels of the esophagus, it has become possible to detect both anterograde and retrograde passage of acid, nonacidic and gaseous material and classify GER episodes according to their content (liquid, gas, and mixed), pH value and proximal extension.⁸ The possibility to detect not only acid, but also weakly acidic refluxes and alkaline refluxes, has expanded the diagnostic power of pH detection alone and increased our knowledge of this phenomenon, so common in the pediatric populations.⁹ With impedance-pH recording, it was found that in infants the majority of post-prandial reflux episodes were not accompanied by a drop in esophageal pH because of the frequent feeding and subsequent buffering of gastric contents.¹⁰ In contrast, in older symptomatic children, acid and weakly acidic refluxes were reported to occur approximately at the same rate.¹⁰⁻¹² In addition, it was shown that not only acid but also nonacidic reflux might be associated with respiratory symptoms such as cough.⁹⁻¹³

Indeed, Blondeau et al.¹⁴ observed by esophageal impedance-pH recording, that both acid and nonacidic GER may precede cough in a group of 26 patients (between 1.0 and 10.5 years of age) with chronic unexplained cough. Out of 140 cough bursts, 58 were preceded by impedance acid refluxes, 77 by weakly acidic refluxes and 5 by weakly alkaline refluxes. Significant correlations were detected between age and esophageal acid exposure and number of acid reflux events. However, probably because of the small number of children evaluated, no data were reported of the possible difference between the association of acid versus weakly acidic refluxes and cough in children of different ages.¹⁴ This information may be clinically relevant and explain the often disappointing results of GER treatment with anti-acid medication such as PPI in this patient populations.^{4,5}

The aim of the study was to evaluate whether the proportion of acid and weakly acidic refluxes preceding cough bursts could be different in infants, preschool-

and school-aged children with chronic, unexplained cough.

METHODS

Patients

We retrospectively identified children who had been evaluated at the Gaslini Children's Hospital of Genoa, from January 2007 to December 2010, because of daily cough of unclear etiology for at least 8 weeks² and who had been undergone 24-hr esophageal impedance-pH monitoring, as part of the diagnostic program. Out of the initial 135 children who fulfilled the inclusion criteria, 29 were not included in the study because of the defective flawed or incomplete (<20 hr duration) registration of the esophageal impedance-pH (Fig. 1). The study population, comprising 106 patients (63 boys), was divided into three age groups whose demographic and clinical characteristics are reported in Table 1. Children with prematurity, neurological abnormalities, swallowing disorders, airway or great vessel structural abnormalities, underlying ENT problems or upper airway cough syndrome, suspected asthma responding to treatment, bronchiectasis, cardiac disease, and chromosomal or humoral immunological deficiency were excluded from the study. None of the children had received acid suppressing therapy or prokinetics in the 2 months before the 24-hr esophageal impedance-pH monitoring. The study was approved by the local ethical committee.

Clinical Assessment

Clinical data were collected uniformly in all children. Each patient underwent standard testing, including lung function testing, radiological and immunological evaluations to exclude other underlying disorders. In

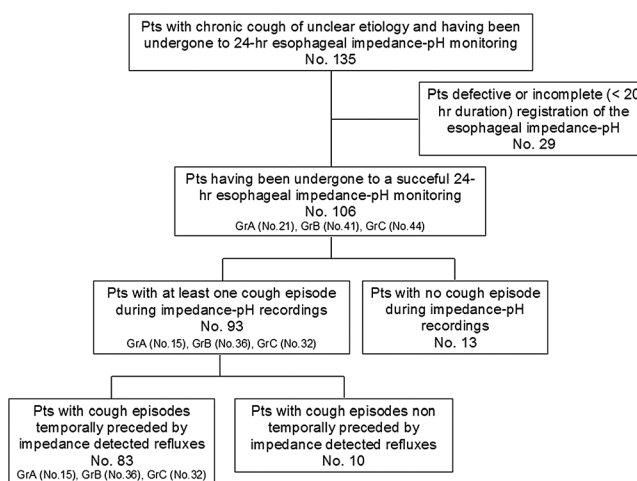


Fig. 1. Flow chart displaying the different subgroups of patients identified by the study.

TABLE 1—Demographic and Clinical Characteristics of 106 Children With Persistent Cough at Diagnosis

	Whole population (No. 106)	Group A infants <2 years (No. 21)	Group B preschool-aged children ≥2 to ≤6 years (No. 41)	Group C school-aged children >6 years (No. 44)
Age	4.84 (2.76–8.16)	1.36 (0.90–1.58)	3.77 (3.04–4.81)	8.71 (7.20–10.45)
Frequency of male gender (No. [%])	63 (59.43)	27 (61.36)	23 (56.10)	13 (61.90)
Frequency of concomitant disorders at diagnosis				
Asthma and/or wheezing (No. [%])	71 (66.98)	30 (68.18)	24 (58.54)	17 (80.95)
Recurrent infections (No. [%])	39 (36.79)	18 (40.91)	9 (21.95)	12 (57.14)
No. of reflux events	55.50 (39.00–76.00)	44.00 (31.00–64.00)	54.00 (41.00–72.00)	67.00 (42.00–85.00)
No. of cough bursts	9.00 (2.00–23.00)	9.00 (3.00–15.00)	10.00 (4.00–23.00)	5.00 (1.00–24.00)

All data are reported as median with lower and upper quartiles in parentheses unless specified.

addition, multidetector computed tomography, fiberoptic bronchoscopy, esophago-gastro-duodeno-scopy were performed when clinically indicated to identify conditions leading to chronic cough.¹⁴ These include asthma, ENT disorders, upper airway cough syndrome, pertussis, ciliary dyskinesia, cystic fibrosis, foreign body inhalation, tuberculosis, cardiac disease, and chromosomal or humoral immunological deficiencies.¹⁴ Indication for 24-hr esophageal pH multichannel intraluminal impedance monitoring was discussed with the child's parents or tutors. All investigations were carried out with full-informed parental consent.

Esophageal Impedance–pH Monitoring Procedure

Combined esophageal impedance–pH was recorded with a 2.1-mm diameter catheter that comprised six electrode pairs to measure intraluminal impedance and two antimony pH sensors. 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 to an amplifier, 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).¹⁰ 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 the esophageal pH sensor was positioned at the second vertebral body above the diaphragm. The patients were encouraged to maintain normal activities, sleep schedule, to eat their usual meals at their normal times and to abstain from snacks and acid (pH < 5) beverages. Before the study, parents were instructed to keep a careful diary, and trained to use a dedicated event marker in the data logger, to record cough episodes and other events such as vomiting, regurgitation, or pyrosis.

Impedance–pH Recording Analysis

The impedance–pH recordings, evaluated only when lasting ≥20 hr, were displayed on a single screen for computer-assisted manual analysis using the Sandhill Technologies software,¹⁰ according to the criteria described by Sifrim D. and coworkers,¹⁵ GER was defined as a sequential orally progressing drop in impedance to <50% of the baseline values starting at the most distal channel and propagating retrograde to at least the next more proximal measuring segment. According to the corresponding pH change, impedance-detected reflux was classified as: (a) acid if pH fell below 4 for at least 4 sec, if pH was already <4, as a decrease of at least 1-pH unit sustained for >4 sec; (b) weakly acidic if pH dropped at least 1-pH unit for >4 sec with the basal pH remaining between 7 and 4; and (c) weakly alkaline when an impedance evidence of reflux was present but the pH did not drop <7.

Association Between Reflux and Cough

As previously reported in other studies,^{16,17} a 2 min period following the onset of a reflux episode was arbitrarily chosen to delineate the time window for association between cough and reflux. Cough as being “associated to reflux” was defined if it occurred within 2 min of a reflux episode, that is, any episode of cough occurring outside the 2-min time window around a reflux episode was considered to have occurred “independent” of reflux.

A reflux event was considered “induced by” cough if cough occurred in the 30 sec preceding reflux.¹⁴ The symptom index, that is, the percentage of cough episodes associated with reflux events, was calculated.

Statistical Analysis

The sample size calculation was based on the fact that the nature of the primary outcome was dichotomic (i.e., proportion of weakly acidic or of acid refluxes that preceded a cough episode); the expected proportion

of weakly acidic refluxes in children with respiratory symptoms, based on literature data,¹⁴ was around 0.45 with an estimate distance from proportion to limit (ω) around 0.20. Assuming an α -error of 0.05 and a two-sided interval, the needed sample required for the analysis, was 24 subjects, according to Dixon and Massey¹⁸ formulation. Considering the fact that we needed to evaluate the data in the three different age categories, we decided to analyze a minimum of 72 patients. The software used for the calculation was NQuery Advisor 7.0, by JD Elashoff.

The secondary outcomes were the possible differences in the proportion of weakly acidic refluxes in infants, preschool- and school-aged children, the acid-to-weakly acidic reflux event ratio and the proportion of cough associated with reflux or not associated in the whole population and in each age group. Descriptive statistics were performed and reported in terms of absolute frequencies or percentages for qualitative data and in terms of medians with first and third quartiles (1q–3q) for quantitative data. Comparison of frequency distributions was made by means of the chi-square test or the Fisher's exact test in case of expected frequencies <5 . Comparison of quantitative variables among the three age groups was performed using Kruskal–Wallis test followed by Bonferroni's correction for multiple comparisons. Correlations were determined using Spearman's correlation coefficient. All tests were two-tailed and P -values <0.05 have been considered as statistically significant. "Statistica release 8" (StatSoft Corp., Tulsa, OK) was used for all analysis.

RESULTS

Patients

One hundred six patients (63 boys) were evaluated. The study population was divided into three age groups whose demographic and clinical characteristics are reported in Table 1. The most prevalent respiratory symptoms associated with chronic cough were wheeze and dyspnoea, not responding to the standard treatment. These symptoms and the frequency of concomitant disorders (such as asthma, wheezing bronchitis, and recurrent respiratory infections) were equally distributed into the three age groups (Table 1).

Gastroesophageal Reflux

More than two thirds of the patient (70.75%) in the whole study population had gastroenterological symptoms suggesting GER (heartburn and/or regurgitation, abdominal pain and frequent vomiting), without any difference among the three age groups (61.90% in infants, 80.49% in preschool-aged and 65.91% in school-aged children, respectively). Impedance recordings detected 6,623 reflux events in the whole study

population, 73.10% acid, and 26.90% weakly acidic. Evaluating the acid-to-weakly acidic reflux event ratio in each patients, a 3.3 (1.5–8.3) median value was detected (Fig. 2A). This ratio was significantly lower in Group A (1.3 [0.4–3.4]), as compared with Group B (3.1 [2.0–6.5]) and Group C (5.1 [2.3–12.4]; Fig. 2B). No weakly alkaline reflux event was recorded in any patient. A weak but significant correlation between age and the acid-to-weakly acidic reflux event ratio was present in the whole population ($r = 0.372$, $P < 0.0001$; data not shown).

Cough

Analysis of dedicated cough marker in the data logger showed that 93 out of the 106 patients (87.7%) had at least one cough episode during impedance–pH recordings, with a median number of 10 (4–24) cough episodes without differences in three age groups ($P = 0.48$). In the 93 patients who had cough episodes detected during impedance–pH recordings, no correlation was demonstrated between age and the number of coughs indicated by the event marker ($r = -0.035$, $P = 0.74$; data not shown).

Gastroesophageal Reflux and Cough

Cough episodes temporally preceded by impedance detected refluxes were found in 83 patients (78.3%). In each of these patient, the median number of cough episodes was 12 (5–25.5), 48.1% (30.1–71.4%) temporally preceded by impedance refluxes (Fig. 3A). No differences in the proportion of cough episodes preceded by impedance refluxes were detected in the three age groups: 50.0% (27.6–75.6%), 42.9% (30.5–60.0%), and 50.0% (31.1–77.7%; $P = 0.54$; Fig. 3B).

In these 83 patients, the percentage of cough episodes preceded by acid refluxes were 75.0% (55.4–100.0%) and, respectively, 45.5% (18.8–93.8%), 75.0% (57.3–100.0%), and 89.5% (66.7–100.0%) in the three age groups, A, B, and C. A significant difference was found between Group A and C, with a high proportion (54.55% [22.9–93.8%]) of cough preceded by weakly acidic refluxes detected in infants (Fig. 3C,D).

Cough preceded by acid refluxes was found in 65 out of the 83 children (78.3%) and with a frequency significantly increasing with the age of the children ($P = 0.0002$) being only 40.0% in Group A, reaching 80.6% in Group B, and 93.8% in Group C; $P = 0.023$ and $P = 0.0003$, respectively, as compared with Group A; Fig. 4A–D). Therefore, a high proportion of infants (60%) had cough preceded by weakly acidic refluxes. No child had cough episodes preceded by both acid and weakly acidic refluxes during impedance recordings. Only 2.4% of total coughs appeared to precipitate reflux events.

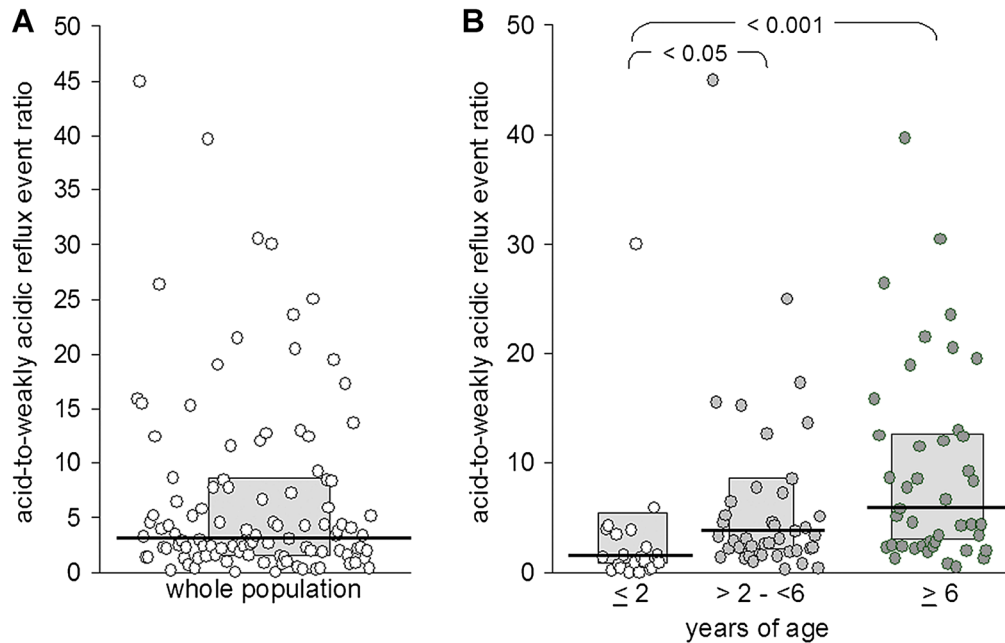


Fig. 2. Acid-to-weakly acidic reflux event ratio in the whole study population (No. 106; panel A) and in the three age groups (panel B): <2 years (No. 21), >2 and <6 years (No. 41), and ≥6 years (No. 44). Acid-to-weakly acidic reflux event ratio is reported on the ordinate whereas the three age groups are reported on the abscissa. Box and horizontal line represent lower and upper quartiles and median value, respectively.

DISCUSSION

Evaluating by impedance–pH recording a large group of children of different ages with chronic unexplained cough, we showed the following points: (a) a clinically significant association between cough and refluxes in the vast majority of the children (>78%); (b) a higher proportion of acid over weakly acidic refluxes in pre-school- and school-aged children but not in infants; and (c) a sizeable percent of cough episodes (>48%) were temporally preceded by refluxes, mostly acid in pre-school- and school-aged children but not in infants. Indeed, in this latter population, more than 50% of cough episodes were preceded by weakly acidic refluxes.

Acid GER has been implicated in the pathogenesis of a wide variety of respiratory symptoms and diseases including chronic unexplained cough, both in adults and in children.^{19,20} Indeed, increased acid exposure has been demonstrated by 24-hr esophageal pH-recording in children with respiratory symptoms, including cough.^{3,21} More recently, with the advent of combined esophageal impedance–pH monitoring it has been feasible to demonstrate that in children, and especially in the younger child, many reflux episodes are weakly acidic.^{9–12,17,22–24}

In children, as in adults, the general assumption is that acid and weakly acidic GER events may occur approximately at the same rate.^{9–13,25,26} However, a

remarkable prevalence of acid reflux (>94%) was detected by some authors regarding children with coexisting severe chronic respiratory disorders including cystic fibrosis. They also found that more than one third of all desaturation episodes were preceded by a reflux event of which the majority (>90%) were acid.^{13,20}

Chang et al.,²⁷ evaluating with a specifically built pHmetry-cough logger 20 ambulatory children, 3 months to 14 years of age, with current chronic cough and suspected GER, did not detect any temporal relationship between acid reflux events and cough.

Rosen and Nurko¹⁷ also studied the time association between reflux and a variety of respiratory symptoms in 28 hospitalized children, 3 months to 18 years of age, some with chronic cough, using combined impedance–pH recording, a patient diary for cough registration, and a 2-min time window for reflux–cough association. Twenty-three of these children were on PPI and 5 on histamine 2 (H2) blockers. They found that overall, 37.6% of the cough events recorded were associated with reflux, and a significant association between reflux and cough was recorded in 33.3% of patients, percentages lower as compared to those detected in our study.¹⁷ Sample size and patient characteristics, including, chronological age, type and severity of respiratory symptom, setting, recording methodologies and treatment, may explain the differences. Indeed, they found that 45% of refluxes were nonacidic and that symptoms

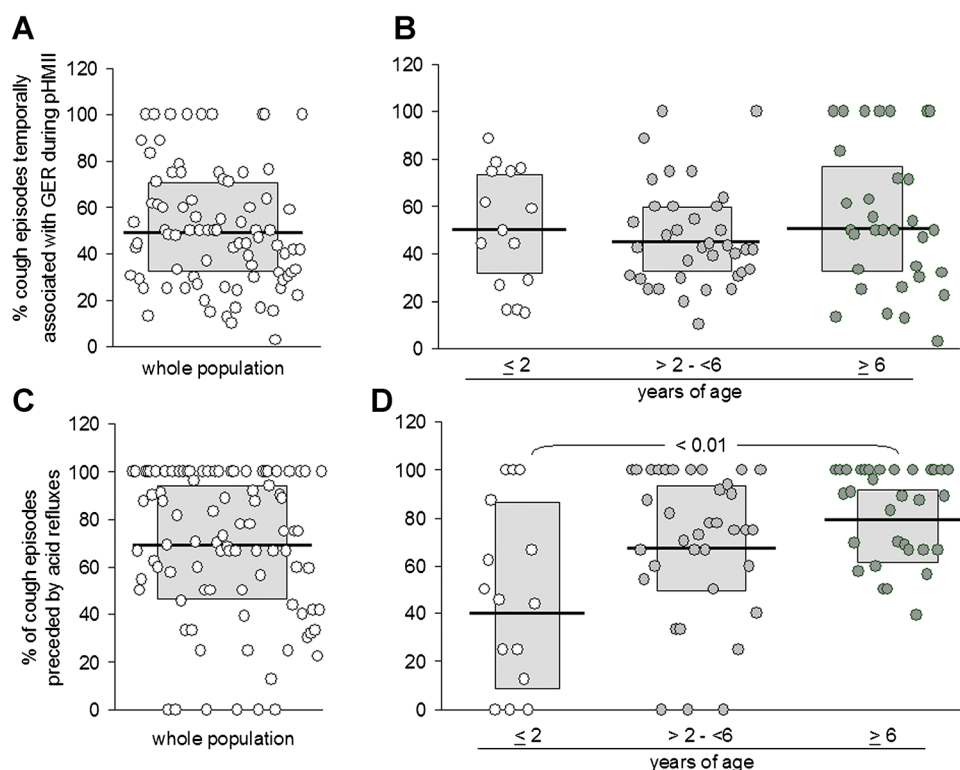


Fig. 3. Proportion of cough episodes temporally associated with GER (panels A and B) with during impedance recording or preceded by acid refluxes (panels C and D) in 83 patients analyzed as a whole (panels A and C) or as three age groups (panels B and D): ≤ 2 years (No. 15), > 2 and < 6 years (No. 36), and ≥ 6 years (No. 32). Proportion of cough episodes temporally associated with GER during impedance recording or preceded by acid refluxes are reported on the ordinate whereas the three age groups are reported on the abscissa. Box and horizontal line represent lower and upper quartiles and median value, respectively.

occurred more frequently when the reflux was nonacidic. A significant association between reflux and cough was also recently detected in a small group of children, “off” PPI or H₂ blockers, with chronic unexplained cough.¹⁴ Interestingly, for unclear reasons, using the event marker, most of these children had an association between acid reflux and cough, whereas, with manometry, the vast majority of them had cough, associated with weakly acidic reflux either alone or in combination with acid.¹⁴ A possible explanation is that acid refluxes may be more clearly perceived by the child and may lead to symptoms more detectable by the parents.

Using event markers in children “off” anti-acid treatment a high percentage of cough episodes temporally preceded by acid refluxes was observed in preschool- and school-aged children but not in infants. The previous data was somehow expected, since during post-prandial 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.^{9,25} In infants and young children, neutralization of gastric contents lasts for hours after each feeding, thus for a period of time representing a

significant proportion of the total measuring time.¹⁶ In agreement with others,¹⁴ weakly alkaline refluxes were extremely rare and never preceded a cough event.

We found that in infants nonacid reflux may be an important predictor of respiratory symptoms and this may explain the inconstant effects of PPI and H₂ blockers on respiratory symptoms in this age population and why lifestyle modifications, including feeding and postural adjustments appear to be more beneficial.^{5,28}

The different frequency of acid and weakly acidic refluxes in infants, preschool- and school-aged children, shown here and in a previous study,²⁹ should be considered when selecting the size and the characteristics of any study on the association between GER and respiratory symptoms and on the effects of anti-acid treatment. This may have even a higher relevance since the prevalence of specific respiratory disorders or the risk of developing them may be different in children with a higher prevalence of weakly acidic versus acid reflux events.²⁹

One possible weakness of the present study is that symptom registration was performed by the parents, using an event marker for cough registration with the

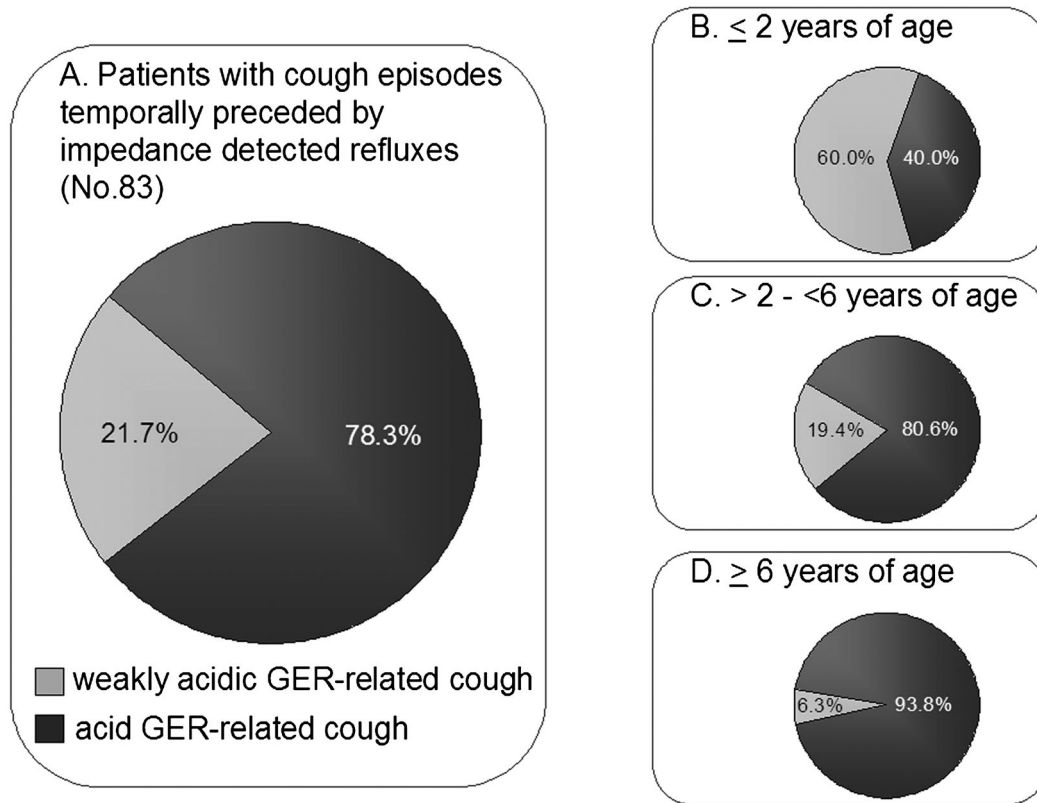


Fig. 4. Relative proportion of children with cough preceded by acid or weakly acidic refluxes in the whole study population (panel A; No. 83) and in the three age groups (panels B–D): ≤2 years (No. 15), >2 and <6 years (No. 36), and ≥6 years (No. 32).

risk of inaccuracy and misinterpretation of the reflux-cough relationship.^{14,16,17} The use of objective techniques for cough detection, such as manometry that detects when cough bursts quickly, briefly, and rising simultaneous intraesophageal pressure,^{14,17} and cough loggers, consisting of electromyographic electrodes and a microphone,³⁰ significantly increase the number of coughs recorded, as compared to the use of an event marker.^{16,17} However, in a recent study reporting the relationship between GER and cough in children with chronic unexplained cough, an acceptable correlation was demonstrated between the number of coughs recorded by manometry and event markers.¹⁴ In addition, cough episodes identified by parents may be more severe and/or long-lasting and therefore probably clinically more relevant than those detected by more objective but more sensitive techniques. Other approaches for objective cough assessments, such as cough meters consisting of electromyographic electrodes and microphone, are fascinating prospective to be validated clinically in this pediatric population.²⁷

Furthermore, this study was slightly underpowered only in the youngest group since we analyzed 21 infants instead of 24. However, the target of 72 patients as statistically planned for the sample size was reached.

Furthermore, visual inspection of the data does not suggest that the study was really underpowered or that larger numbers (24 instead of 21 infants in the youngest group) would have resulted in further significant differences among the three age groups being detected.

CONCLUSION

We showed that in an otherwise healthy pediatric population with unexplained chronic cough a significant proportion of cough episodes may be temporally preceded by refluxes. Most, but not all, of these refluxes are acid in older children but not in infants, supporting the concept that nonacid reflux may be an important predictor of respiratory symptoms in childhood and possibly partially explain the inconstant effects of PPI and on H₂ blockers on respiratory symptoms in this age population.

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