

# The relationship between gastroesophageal reflux disease and recurrent wheezing in children

Vasile Valeriu Lupu, MD, PhD<sup>a</sup>, Ingrith Crenguta Miron, MD, PhD<sup>a</sup>, Ancuta Lupu, MD, PhD<sup>a</sup>, Mihaela Moscalu, PhD<sup>a,\*</sup>, Elena Cristina Mitrofan, MD, PhD<sup>b</sup>, Dragos Munteanu, MD, PhD<sup>a</sup>, Alina Costina Luca, MD, PhD<sup>a</sup>

## Abstract

Gastroesophageal reflux disease occurs when gastric contents flow back into the esophagus and produce symptoms. Recurrent wheezing affects the quality of life for the patient and family. The association of gastroesophageal reflux with recurrent wheezing is suggested by different studies. The purpose of this study was to explore this relationship and to evaluate the outcome after appropriate treatment.

A retrospective study on 85 children with recurrent wheezing, admitted in a pediatric gastroenterology regional center in Romania was performed. 24-hour continuous esophageal pH monitoring was used to evaluate the presence of gastroesophageal reflux and the results were interpreted using the Boix Ochoa score. All patients with positive score received treatment with proton pump inhibitors and they were evaluated again after 2 months.

Gastroesophageal reflux was present in 71 children (83.5%), while 14 (16.5%) had a negative score, with a statistic significance ( $\chi^2=6.88$ ,  $P=.0086$ , 95% confidence interval). After 2 months treatment with proton pump inhibitors, the Boix Ochoa score was still positive in 15 patients (21.13%).

Recurrent wheezing is a solid reason for evaluating the presence of gastroesophageal reflux by 24-hour continuous esophageal pH-metry. Adequate treatment of gastroesophageal reflux solves also the recurrent wheezing in the majority of patients.

**Abbreviations:** GER = gastroesophageal reflux, GERD = gastroesophageal reflux disease, PPI = proton pump inhibitors.

**Keywords:** 24-hour continuous pH-metry, children, gastroesophageal reflux disease, proton pump inhibitors, recurrent wheezing

## 1. Introduction

Gastroesophageal reflux disease (GERD) is defined by American College of Gastroenterology (ACG) as symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung.<sup>[1]</sup> It has a polymorph symptomatology which associates esophageal manifestation (regurgitations, anorexia, reflux esophagitis, esophageal stenosis) and extra-esophageal manifestations

(neurological, oral cavity, nutritional, among which the respiratory ones are the most frequent).<sup>[2]</sup>

Recurrent wheezing is defined as more than 1 episode of wheezing within the last 12 months.<sup>[3]</sup> Wheezing represents a common disorder characterized by a continuous high-pitched expiratory sound produced by an air flux that becomes turbulent flowing thorough the reduced airway caliber.<sup>[4]</sup> It is estimated that about one third of school-age children manifest the recurrent wheezing during the first 5 years of life.<sup>[5]</sup> The most frequent cause of recurrent wheezing in children is asthma, but other causes should be considered in the differential diagnosis. Recurrent wheezing attacks impair the quality of life for the patient and his/her family and represent one of the most common causes of emergency department visits and hospitalizations.<sup>[6]</sup> The rate of presentation to emergency departments and hospitalization was reported to be 16% and 12%.<sup>[7]</sup> The most common causes of recurrent wheezing are: asthma, gastroesophageal reflux disease, foreign body aspiration, bronchopulmonary dysplasia, bronchiolitis obliterans, an immunodeficiency, primary ciliary dyskinesia, vocal cord dysfunction, cardiac etiologies and structural abnormalities.<sup>[8]</sup>

The authors of a study concluded anemia and gastroesophageal reflux (GER) are risk factors for recurrent hospitalizations for wheezing and should be treated.<sup>[6]</sup> Another study concluded that silent GER is common in infants with daily wheezing, and controlling GER improves morbidity and decreases the need for daily asthma medications.<sup>[9]</sup>

Esophageal pH-monitoring was considered the gold standard for the diagnosis of GERD and this test can directly correlate acid reflux episodes with recurrent wheezing. PH-metry in patients

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<sup>a</sup> "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania, <sup>b</sup> Clinic of Pulmonary Disease, Iasi, Romania.

\* Correspondence: Mihaela Moscalu, str. Universitatii, nr. 16, Iasi, 700115, Romania (e-mail: mmoscalu@yahoo.com).

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with suspected GERD-related wheezing may represent a more accurate approach.<sup>[10]</sup>

The aim of this study is to explore this relationship and to evaluate the outcome after appropriate treatment.

## 2. Methods

We performed a retrospective study on a group of 85 children, 1 month – 18 years old, with 2 or more recurrent hospitalizations resulting from wheezing within the last 12 months, admitted in a pediatric gastroenterology regional center in “St. Mary” Children Emergency Clinical Hospital, Iasi, Romania. They were evaluated for the presence of gastroesophageal reflux by 24-hour continuous esophageal pH monitoring and the results were interpreted using the Boix Ochoa score.

Exclusion criteria were: foreign body aspiration, a previous diagnosis of sleep apnea, bronchopulmonary dysplasia, cystic fibrosis, bronchiolitis obliterans, an immunodeficiency, primary ciliary dyskinesia, vocal cord dysfunction, proven food sensitivity, cardiac etiologies and structural abnormalities. Also, children with an acute respiratory tract infection within 1 month of being screened for the study were excluded.

Inclusion criteria	Exclusion criteria
1 month – 18 yr old	foreign body aspiration
two or more recurrent hospitalizations resulting from wheezing within the last 12 months	a previous diagnosis of sleep apnea
	bronchopulmonary dysplasia
	cystic fibrosis
	bronchiolitis obliterans
	an immunodeficiency
	primary ciliary dyskinesia
	vocal cord dysfunction
	proven food sensitivity
	cardiac etiologies and structural abnormalities
	acute respiratory tract infection within 1 mo of being screened for the study

The diagnosis was based on the anamnesis, clinical and paraclinical examination. Previously requested investigations and current hospitalization records were investigated.

We used Boix-Ochoa score ( $N < 11.99$ ) to evaluate gastroesophageal reflux in these children. The test is considered positive if the total percentage of time the pH is below 4 is the most useful single discriminator between physiologic and pathologic reflux.<sup>[11–14]</sup> For the interpretation of results, we used following parameters: the total number of reflux episodes (normal – under 2 episodes an hour on an average); the number of reflux episodes that last for more than 5 minutes (normal – under 8 episodes); the duration of the longest reflux episode (in minutes); the reflux index (RI) = the ratio between the total number of reflux episodes and their duration (normal – under 4); the Euler score =  $x + 4y$ , in which:  $x$  – number of reflux episodes with pH < 4 longer than 1 minute and  $y$  – the number of episodes with pH < 4 longer than 5 minutes.

Medtronic Digitrapper pH 100, SN 37660, with Polygram Net TM pH Testing Application and Zinetics 24 and ComforTec by Sandhill multi-use catheters were used to measure the pH. Esophageal pH monitoring is based on the principle that the passage of the acid gastric content into the esophagus during reflux generates a decrease in the intraesophageal pH. The method consists in measuring the pH in the lower esophagus for 24 hours by means of an electrode placed 5 cm above the cardia

and connected to a portable pH-meter on batteries. The pH can be printed on paper or transferred to a computer, which analyzes different required parameters, depending on which the intraesophageal pH curves are graphically represented.<sup>[15]</sup>

The device was calibrated in 2 solutions with pH 1 and 7 before each use. Before the procedure no food or drink allowed at least 6 hours for children over 1-year-old, at least 3 hours for infants.<sup>[16]</sup> Antacid therapy should be discontinued or at least 6 hours before, the anti H<sub>2</sub> receptor 3 days before, the proton pump inhibitor 7 days before and the prokinetics 48 hours before.<sup>[17]</sup>

The child was placed in the left lateral decubitus (for infants and young children), the examiner on the right side of the patient, and in a seated position for children over 5 to 6 years old. The lubricated electrode was inserted, nasal up to 5 cm above the cardia. The electrode was connected to the pH meter, the caregiver was explained about the function and operation of the device and then, the recording is started. Each patient or caregiver was trained to record in a table any symptoms occurred, the time and body position (supine, standing) and, at the same time, using the button provided on the device.<sup>[12–14]</sup>

All patients with positive score received treatment with proton pump inhibitors and they were evaluated again after 2 months. Statistical Package for Social Sciences software 20 was used for the statistical data processing. For the correlation analysis, the Pearson parametric correlation was used and the correlation coefficients were calculated for a confidence interval of 95%. The logistic regression offers a useful means for the modeling of the dependence of a dichotomous response variable on 1 or several explanatory variables called “predictors,” which can be categorical or continuous. The risk is mathematically modelled in the form of an equation as a predictor variable.

Informed consent was obtained from all patients or from their family, and the “St. Mary” Children Emergency Hospital Ethics Committee’s approval was obtained for publishing this study.

## 3. Results

From 85 children (52 males, 33 females) with recurrent wheezing (Table 1), 71 (83.5%) had gastroesophageal reflux proven by a positive Boix Ochoa score, while 14 (16.5%) had a negative score (Table 2).

All the 71 children with recurrent wheezing and gastroesophageal reflux disease were submitted to postural therapy and to specific diet for their age. The treatment administrated consisted

**Table 1**  
Patients characteristics.

Age	No. cases	%	Sex distribution	
0–6 mo	7	8.23%	Female	2
			Male	5
6 mo–1 yr	9	10.59%	Female	3
			Male	6
1–3 yr	51	60.00%	Female	20
			Male	31
4–7 yr	9	10.59%	Female	5
			Male	4
7–12 yr	8	9.41%	Female	3
			Male	5
12–18 yr	1	1.18%	Female	0
			Male	1
Total	85			

**Table 2****Association of GERD with recurrent wheezing.**

		Recurrent wheezing	
		No. cases	%
Study group (GERD)	+	71	83.5%
	-	14	16.5%
Total		85	

in proton pump inhibitors (PPI)—Omeprazole or Esomeprazole. The usual doses were used with daily administration for 2 months.

After 2 months of treatment with PPI, the pH was measured again. The Boix Ochoa score remained positive for 15 patients (21.13%). For those patients we recommended another 2 months of treatment with PPI.

Correlational analysis showed the presence of a significant correlation between GERD and recurrent wheezing ( $\chi^2=6.88$ ,  $P=.0086$ , 95% confidence interval) (Table 3).

The correlational analysis and the parameters estimation of chance and risk in the occurrence of GERD versus wheezing (Table 4) makes wheezing a reason for searching and objectification of GERD.

#### 4. Discussion

Task Force proposed to use the terms episodic wheezing to describe children who are wheezing intermittently and are well between episodes, but there is poor agreement on definitions of preschool wheezing disorders.<sup>[18]</sup>

Wheezing is the most common symptom associated with asthma in children, but this is also common in non-asthmatic children.<sup>[19]</sup> A study concluded that only 30% of preschoolers with recurrent wheezing are eventually diagnosed with asthma at the age of 6 years.<sup>[20]</sup>

It has been reported that the frequency of GER in 85 infants with recurrent wheezing was 48.2% (41 children had positive pH monitoring results).<sup>[21]</sup>

Two studies reported that about 1/2 to 1/3 of infants and children with early-childhood wheezing developed persistent asthma later.<sup>[22,23]</sup> It is important to make an early and correct diagnosis and provide the proper treatment to infants with wheezing for the prevention of airway remodeling.<sup>[21]</sup>

Wheezing in early childhood is often observed in association with a viral respiratory disease.<sup>[24,25]</sup> Sometimes unnecessary investigations are conducted, inadequate treatment is provided and the child may need hospitalizations resulting in considerable healthcare costs. Misdiagnosis has also led to therapy with inhaled corticosteroids, resulting in some children developing significant steroidal side effects.

**Table 3****Estimate parameters in the association GERD - recurrent wheezing.**

	Chi-Squared $\chi^2$	P 95% confidence interval
Pearson's Chi-Squared test- $\chi^2$	6.888757	0.00868
Coefficient of correlation (Spearman Rank R)	0.4135213	0.00854

**Table 4****Parameters estimation of chance and risk in the occurrence of GERD versus wheezing.**

	Estimated value	95% confidence interval	
		Minimum	Maximum
PARAMETERS of chance			
Odds Ratio (OR)	2.41	1.18	4.98
PARAMETERS of risk			
Relative Risk (RR)	1.23	1.07	1.43

Several studies have reported that boys have an increased risk of early persistent wheezing.<sup>[26]</sup> A recent study reported the presence of recurrent wheezing in 64% of the boys.<sup>[6]</sup> In our study we found similar results, 61.2% of the patients with recurrent wheezing were boys.

There are some studies which confirmed the association between silent GER and food sensitization in infants with recurrent wheezing without food allergy. The presence of silent GER might contribute to early food sensitization and then to the development of atopic asthma in childhood. Weinberger and Abu-Hasan showed that in the silent GER group, 12.2% of patients had food sensitization and in the non-GER group, 20.5% had food sensitization, without significant difference between the 2 study groups. There was no difference between GER parameters of patients who had positive specific IgE to food and those who were negative.<sup>[19]</sup>

There are studies that suggest that most patients with an association between cough and gastroesophageal reflux have predominantly biliary reflux, while wheezing is most often preceded by acid reflux.<sup>[27-29]</sup>

The presence of fluids in the airways can cause bronchospasm. Most commonly unrecognized, macro-aspiration can cause the respiratory tract to close, which can be associated with lesions such as hemorrhagic pneumonitis and non-cardiac pulmonary edema.<sup>[30]</sup> On the other hand, micro-aspiration (reflux theory) can induce bronchospasm directly by stimulating the larynx through the tracheal receptors.<sup>[31]</sup> It is also known that the esophagus and trachea have common embryonic origins, hence the theory that acidification of the distal esophagus causes vagal stimulation resulting in bronchoconstriction, unrelated to micro-aspiration.<sup>[32]</sup>

Regarding the correlation between GER and wheezing, there is not necessarily an etiological link between the 2 conditions. Thus, recent studies have proposed biomarkers to identify GER-associated respiratory infections, parameters from the bronchoalveolar lavage: the lipid-laden alveolar macrophages and the rate of neutrophilic inflammation. It has also been shown that these parameters correlate with GER severity, but their specificity remains debatable.<sup>[33,34]</sup>

There are different methods used to diagnose GERD: 24 hours esophageal pH-monitoring, esophageal manometry, impedance-pH-metry, ultrasonography, including the intraluminal 1, and upper gastrointestinal endoscopy.<sup>[35]</sup> These methods have different specificity and sensitivity. The 24 hours esophageal pH-monitoring is the most used method to diagnose the acid reflux. The sensitivity of the esophageal - pH-monitoring is higher than 85% and its specificity is 95%.<sup>[36]</sup>

Limitations of the study are first the possible bias caused by the retrospective study design, and second, that the esophageal pH-monitoring cannot detect weak acid and nonacid reflux

episodes, also that the data reflect the experience of a single clinical center.

## 5. Conclusions

Recurrent wheezing is a solid reason for evaluating the presence of a gastroesophageal reflux by 24-hour continuous esophageal pH-metry. The bronchial spasm triggered and maintained by the aspiration of the acid refluente remains the most plausible explanation of this relationship and association. Adequate treatment of gastroesophageal reflux resolves also the recurrent wheezing.

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## Author contributions

**Conceptualization:** Vasile Valeriu Lupu, Ingrith Crenguta Miron, Ancuta Lupu, Elena Cristina Mitrofan, Dragos Munteanu, Alina Costina Luca.

**Data curation:** Mihaela Moscalu.

**Formal analysis:** Vasile Valeriu Lupu, Ingrith Crenguta Miron, Ancuta Lupu, Mihaela Moscalu, Elena Cristina Mitrofan, Dragos Munteanu, Alina Costina Luca.

**Investigation:** Vasile Valeriu Lupu, Ingrith Crenguta Miron, Ancuta Lupu, Mihaela Moscalu, Elena Cristina Mitrofan, Dragos Munteanu, Alina Costina Luca.

**Writing – original draft:** Vasile Valeriu Lupu, Ingrith Crenguta Miron, Ancuta Lupu, Mihaela Moscalu, Elena Cristina Mitrofan, Dragos Munteanu, Alina Costina Luca.

**Writing – review & editing:** Vasile Valeriu Lupu, Ingrith Crenguta Miron, Ancuta Lupu, Mihaela Moscalu, Elena Cristina Mitrofan, Dragos Munteanu, Alina Costina Luca.

## References

- [1] Katz PO, Gerson LB, Vela MF. Diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–28.
- [2] Ignat A, Burlea M, Lupu VV, Paduraru G. Oral manifestations of gastroesophageal reflux disease in children. *Romanian J Oral Rehabil* 2017;9:40–3.
- [3] Hermann C, Westergaard T, Pedersen BV, et al. A comparison of risk factors for wheeze and recurrent cough in preschool children. *Am J Epidemiol* 2005;162:345–50.
- [4] Brand PLP, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32:1096–110.
- [5] Mallol J, García-Marcos L, Solé D, et al. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. *Thorax* 2010;65:1004–9.
- [6] Ozdogan S, Tabakci B, Demirel AS, et al. The evaluation of risk factors for recurrent hospitalizations resulting from wheezing attacks in preschool children. *Ital J Pediatr* 2015;41:91. doi: 10.1186/s13052-015-0201-z.
- [7] Bisgaard H, Szefer S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol* 2007;42:723–8.
- [8] Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. *Lancet* 2014;383:1593–604.
- [9] Sheikh S, Stephen T, Howel L, Eid N. Gastroesophageal reflux in infants with wheezing. *Pediatr Pulmonol* 1999;28:181–6.
- [10] Ahmed T, Vaezi MF. The role of pH monitoring in extraesophageal gastro-esophageal reflux disease. *Gastrointest Endosc Clin N Am* 2005;15:319–31.
- [11] Pandolfino JE, Vela MF. Esophageal-reflux monitoring. *Gastrointest Endosc* 2009;69:917–30.
- [12] Lupu VV, Ignat A, Paduraru G, et al. Correlation between the different pH-metry scores in gastroesophageal reflux disease in children. *Medicine (Baltimore)* 2016;95:e3804. doi: 10.1097/MD.0000000000003804.
- [13] Lupu VV, Ignat A, Ciubotariu G, et al. Helicobacter pylori infection and gastroesophageal reflux in children. *Dis Esophagus* 2016;29:1007–12.
- [14] Lupu VV, Burlea M, Nistor N, et al. Correlation between esophageal pH-metry and esophagitis in gastroesophageal reflux disease in children. *Medicine (Baltimore)* 2018;97:e12042. doi: 10.1097/MD.00000000000012042.
- [15] Christopher G, Streets MRCS, Tom R, DeMeester. Ambulatory 24-hour esophageal pH monitoring - why, when, and what to do. *J Clin Gastroenterol* 2003;37:14–22.
- [16] Jamieson JR, Stein CM, De Meester TR, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992;87:171–5.
- [17] Kleiman RE, Goulet OJ, Mieli-Vergani G, et al. Walker's pediatric gastrointestinal disease. 5-th edition, BC Decker Inc 2008;2:1393–400.
- [18] Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS task force on standards for infant respiratory function testing. *European Respiratory Society/American Thoracic Society. Eur Respir J* 2001;17:302–12.
- [19] Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics* 2007;120:855–64.
- [20] Taussig LM, Wright AL, Holberg CJ, et al. Tucson children's respiratory study:1980 to present. *J Allergy Clin Immunol* 2003;111:661–75.
- [21] Sung Kil Kang, Ja Kyoung Kim, So Hyun Ahn, et al. Relationship between silent gastroesophageal reflux and food sensitization in infants and young children with recurrent wheezing. *J Korean Med Sci* 2010;25:425–8.
- [22] Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–8.
- [23] Wennergren G, Amark M, Amark K, Oskarsdóttir S, Sten G, Redfors S. Wheezing bronchitis reinvestigated at the age of 10 years. *Acta Paediatr* 1997;86:351–5.
- [24] Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178:667–72.
- [25] Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005;24(11 Suppl):S217–22.
- [26] Garcia-Marcos L, Mallol J, Solé D, Brand PL. EISL Study Group International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. *Pediatr Allergy Immunol* 2010;21:878–88.
- [27] Kunsch S, Gross V, Neesse A, et al. Combined lung-sound and reflux-monitoring: a pilot study of a novel approach to detect nocturnal respiratory symptoms in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2011;33:592–600.
- [28] Blondeau K, Sifrim D, Dupont L, Tack J. Reflux Cough. *Curr Gastroenterol Rep* 2008;10:235–9.
- [29] Ford AC, Forman D, Moayyedi P, Morice AH. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax* 2006;61:975–9.
- [30] Marik PE. Aspiration syndromes: aspiration pneumonia and pneumonitis. *Hosp Pract* 2010;38:35–42.
- [31] Allen GB, Leclair TR. Acid aspiration-induced airways hyperresponsiveness in mice. *Appl Physiol* 2009;107:1763–70.
- [32] Mathew JL, Singh M, Mittal K. Gastro-esophageal reflux and bronchial asthma: current status and future directions. *Postgrad Med J* 2004;80:701–5.
- [33] Sacco O, Silvestri M. IL-8 and airway neutrophilia in children with gastroesophageal reflux and asthma-like symptoms. *Respir Med* 2006;100:307–15.
- [34] De Baets F, Aarts C. Milk protein and Oil-Red-O staining of alveolar macrophages in chronic respiratory disease of infancy. *Pediatr Pulmonol* 2010;45:1213–9.
- [35] Sifrim D, Blondeau K. New techniques to evaluate esophageal function. *Dig Dis* 2006;2:243–51.
- [36] Simpson WG. Gastroesophageal reflux disease and asthma. Diagnosis and management. *Arc Internal Med* 1995;155:798–803.