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# Usefulness and safety of double endoscopy in children with gastroesophageal reflux and respiratory symptoms

**Nicola Ullmann [a], Oliviero Sacco [a], Paolo Gandullia [b], Michela Silvestri [a], Angela Pistorio [c], Arrigo Barabino [b], Nicola M. Disma [d], Giovanni A. Rossi [a,*]**

[a] *Pulmonary Unit, G. Gaslini Institute, Largo G. Gaslini 5, 16147 Genoa, Italy*
[b] *Gastroenterology Unit, G. Gaslini Institute, Genoa, Italy*
[c] *Clinical Epidemiology and Biostatistics Unit, G. Gaslini Institute, Genoa, Italy*
[d] *Anaesthesiology Unit, G. Gaslini Institute, Genoa, Italy*

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**KEYWORDS**
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**Summary**
*Background:* Management of children with gastroesophageal reflux disease (GORD) and difficult-to-treat (D-T-T) respiratory symptoms may include double fiberoptic, airway and oesophago-gastro-duodenoscopies (DE). A study was performed to evaluate the usefulness and safety of DE in children with severe GORD and D-T-T respiratory symptoms.
*Methods:* A 3-year retrospective review of records of children who underwent DE under general anaesthesia was performed: the relevant clinical information obtained and the occurrence of complications in the 72 h following the DE.
*Results:* Inflammatory changes of the airways were found at bronchoscopy in 40 out of the 60 children: bronchoalveolar lavage (BAL) demonstrated positive lipid-laden alveolar macrophages (LLAM), neutrophilic inflammation or both, respectively in 9, 12 and 16 patients. BAL bacterial cultures were positive in 2 patients with elevated airway neutrophilia. Structural airway abnormalities, explaining not GOR-related D-T-T respiratory symptoms were identified in 11 patients. Oesophagoscopic findings supporting GORD were detected in 32/60 children and confirmed by consistent histological changes in oesophageal mucosal biopsies (OEB) in 27.

The frequency of complications, all minor, was low during the procedure and in the following 72 h. They included mild desaturation, stridor or bronchospasm, vomiting, dysphagia

*Abbreviations:* GORD, gastroesophageal reflux disease; D-T-T, difficult-to-treat; DE, double fiberoptic, airway and oesophago-gastro-duodenoscopies; BAL, bronchoalveolar lavage; LLAM, lipid-laden alveolar macrophages; OEB, oesophageal mucosal biopsies; GOR, gastro-esophageal reflux; PEF, expiratory peak flow; OGD, oesophago-gastroduodeno; CT, computed tomography; EMLA, eutectic mixture of local anesthetics; SD, standard deviations; 1*q*–3*q*, first and third quartiles; LRTI, lower respiratory tract infections; ALTE, apparent life-threatening events.

* Corresponding author. Tel.: +39 010 5636547; fax: +39 010 383953.
*E-mail address:* giovannirossi@ospedale-gaslini.ge.it (G.A. Rossi).

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and hyperthermia requiring antibiotic treatment in 1 patient. No ''new onset'' complication was observed after 48 h following DE. The time-dependent hazard of complications was significantly higher for patients with a history of onset of respiratory symptoms early in life ($\leq$2 years of age) ($p = 0.038$).
*Conclusion:* DE can be useful in the clinical evaluation of children with D-T-T respiratory symptoms and GORD and is associated with low frequency of mild complications when performed by appropriately trained and experienced personnel.


## Introduction

One difficult task in managing children with respiratory symptoms and gastroesophageal reflux (GOR) is to determine to what extent GOR is physiologic or constitutes a pathological condition i.e. a GOR disease (GORD).[1–3] Disorders like asthma, airway infections, wheezy bronchitis and laryngospasm are frequent in children and often related to a variety of constitutional and/or environmental factor, rather than to GORD. Moreover, aspirations of gastric refluxate may occur periodically also in normal subjects, without inducing clinically relevant respiratory symptoms.[3,4] The presence of GOR is easy to demonstrate clinically, but a causal relationship with respiratory symptoms is often difficult to determine since there are no gold-standard diagnostic tests to prove the causal relationship.[4] In addition, because of the complexity of the interaction involved and/or difficulties in obtaining satisfactorily adherence to therapy for a sufficient length of time, lifestyle modifications and pharmacologic treatments of GORD are not always followed by significant improvement in respiratory symptoms, raising doubt on the link between the two conditions.[4,5]

There is a general agreement that surgical options should be considered in these patients only after failure of maximal conservative management.[6–9] Lack of response to treatment may require additional investigations, which include double endoscopy (DE) to detect the presence, type and the severity of inflammatory changes at the oesophageal and airway levels, but also to exclude anatomic malformations or malfunctions.[10,11–13] Ideally, DE should be performed as a unique procedure, i.e. under the same general anaesthesia, but data on the clinical value and feasibility of this procedure in children are scant.[10,14]

To evaluate the usefulness and safety of DE, a 3-year retrospective review of records related to children with severe, difficult-to-treat (D-T-T) respiratory symptoms and GORD was performed. The clinical information obtained and the occurrence of complications during the procedure and in the following 72 h was analyzed.

## Methods

### Patients

The clinical records of children with chronic or recurrent D-T-T respiratory symptoms, with a positive 24-h oesophago-gastric pHmetry, and not responding to standard ''respiratory'' therapy (bronchodilators, inhaled and systemic steroids, leukotriene modifiers and antibiotics) and ''anti-reflux'' treatment (lifestyle modifications and pharmacologic treatment) were evaluated. We excluded from the study patients with: (i) neurological abnormalities and/or dysphagia; (ii) known structural gastrointestinal abnormalities, such as pyloric stenosis, malrotation and annular pancreas; (iii) known motility upper gastrointestinal disorders, such as achalasia and delayed gastric emptying; (iv) clinical history of primary aspiration and known underlying heart disease; (v) recent (less than four weeks) or current respiratory tract infections.

### Clinical assessment

Clinical data were collected uniformly in all children and included age at onset, type, severity, recurrence and/or persistency of respiratory symptoms and presence of co-morbidities. Evaluation of the respiratory impairment degree was performed by spirometry or expiratory peak flow (PEF) monitoring, when cooperation of the children made it possible. Sensitization to the most common classes of allergens was evaluated by skin prick test (Bayropharm, Milan, Italy) and specific IgE against the different allergens tested were determined by solid-phase, chemiluminescent immunometric assays (Immulite, Medical System; Genoa, Italy). Specific tests were also performed to identify conditions such as ciliary dyskinesia, cystic fibrosis and immunodeficiencies. Suspicion of clinical GORD warranting investigation by oesophago-gastroduodenoscopy was determined by the consultant paediatric gastroenterologists (P.G. or A.B.) based upon: (i) presence of typical features, (ii) a positive pHmetry and/or barium contrast fluoroscopy, (iii) severe life-threatening symptoms possibly related to GOR and/or lack of response to anti-reflux therapy. The primary indication(s) for DE was recorded by both the gastroenterologist and the pulmonologist (O.S. or G.A.R.) performing the procedure and discussed with the child's parents, who were informed of the possibility that new investigation might not lead to a new or a definitive diagnosis. When clinically indicated, before or after DE, multidetector computed tomography (CT) was performed with a 64 slices CT scanner (Siemens Somatom Sensation 64, Siemens, Erlangen, Germany) with intravenous contrast agent (Iomeron 300, Bracco, Milano, Italy) to exclude or to confirm the presence of obliterative bronchiolitis, bronchiectasis, airway or pulmonary congenital malformations, tracheal compression by congenital vascular anomalies. Written information giving full details about DE, bronchoalveolar lavage (BAL) and oesophageal mucosal biopsies (OEB) were given to the parents or tutors. All investigations were carried out with full-informed written parental

consent. Access to health records complied with the Italian legislation.

### Double endoscopy

Airways and oesophago-gastroduodeno structures were examined for anatomic and functional abnormalities, while BAL and OEB were performed, when clinically indicated and feasible, to obtain information on the degree and the characteristics of the inflammatory changes. BAL fluid was also used for microbiological assays and to evaluate the lipid-laden alveolar macrophages (LLAM) index, as previously described,[15,16] while OEB to detect the presence of *Helicobacter pylori*.[17,18]

*Anaesthesia*: DE was performed in theatre, under general anaesthesia. Salbutamol (5 mg via nebuliser) was given to patients with reversible airway obstruction, 30 min before induction of anaesthesia. All patients received a standard premedication with rectal midazolam (0.5 mg/kg), and eutectic mixture of local anesthetics (EMLA) cream was placed in the sites of possible venipuncture. Anaesthesia was intravenously induced with propofol (4 mg/kg) and fentanil (3 mcg/kg), and maintained with sevofluorane (1.5–2 MAC) in pure oxygen or oxygen/air mixture. Monitoring included continuous ECG, oxygen saturation, end-tidal $CO_2$ and non-invasive blood pressure. Topic anaesthesia on larynx and vocal cords was performed using plain 1% lidocaine (maximum dose 1 mg/kg), 2 min before the beginning of the procedure.

*Airway endoscopy*: Bronchoscopy was performed in spontaneously breathing anesthetized patients and ventilation was assisted manually, when necessary. 3.8 mm or 4.0 mm external diameter videobronchoscopes (Olympus BF-3C160 or BF-MP160F, Olympus Corp., New Hyde Park, NY) were introduced into a nostril through a face mask, as previously described.[16] BAL was performed, with evaluation of total and differential cell count and of the LLAM index, and quantitative microbiologic tests for bacteria and viruses identification undertaken.[15,16]

*Oesophago-gastroduodeno endoscopy (OGD)*: OGD endoscopy was performed with Olympus endoscopes (GIF-P 140, GIF-P 160 and XP 160, Olympus Corp., New Hyde Park, NY) and OEB taken at least 2 cm above the gastroesophageal junction.[17] A histological diagnosis of oesophagitis on OEB was made if at least 2 of the following 3 features were present: basal cell hyperplasia, increased papillary height, and epithelial inflammation with eosinophils, neutrophils, or lymphocytes.[17] *H. pylori* status was detected by histology of gastric biopsies.[18]

### Postoperative care

Vital signs, recovery patterns and complications during and in the 72 h following DE were prospectively recorded on data sheets. Patients were firstly observed in the theatre recovery area for 20 min, with oxygen given by face mask until fully awake and then observed on the ward for at least 4 h. Oxygen saturation, body temperature, heart rate, respiratory rate and the presence of any problem were recorded every 15 min for the first hour, every 30 min for the next hour and hourly subsequently. Chest radiography was not routinely performed. Any later complication was identified from the nursing observation charts and from the medical notes. Before discharge children were examined by a clinician and the subsequent management discussed at outpatient follow-up, on the basis of the whole clinical evaluation.

### 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. Comparison of frequency distribution was made by means of the Chi-Square test or the Fisher's Exact test in case of expected frequencies less than 5. Bonferroni's correction was applied for multiple comparisons. A survival analysis with the onset of complication as event of interest and time to complication (in hours) as time variable and onset age of symptoms ($\leq$2 years/$>$2 years) as independent indicator of risk was performed; the survival curve was drawn with the Kaplan Meier method and the Log-Rank test was used to compare the curves. $p$ Values less than 0.05 have been considered as statistically significant. The software ''Statistica'' has been used for all the analyses.

## Results

### Patient demographic and clinical characteristics

Case notes of 60 children (38 males and 22 females, 8.5 months to 17.5 years old) were evaluated. The study population, whose demographic characteristics are summarized in Table 1, was divided into three age groups: (i) group A = infants, $<$2 years old (8 patients); (ii) group B = preschool children, 2 to $<$6 years old (33 patients); (iii) group C = school children, $\geq$6 years old (19 patients). As expected, the frequency of atopy and of symptoms duration $>$1 year increased with the patient age ($p = 0.004$), while the occurrence of ''early onset respiratory symptoms'' was highest in group A ($p = 0.0144$).

The most prevalent respiratory conditions present in the clinical records were: (i) recurrent lower respiratory tract infections (19 patients), (ii) persistent and/or nocturnal cough (18 patients), (iii) chronic/recurrent wheeze (13 patients), (iv) 'difficult-to-treat' asthma (11 patients), (v) other symptoms including hoarseness (4 patients), recurrent/spasmodic croup (3 patients), apnoea/ALTE (2 patients), recurrent aspiration pneumonia (2 patients) (Table 2).

### Endoscopic, BAL and OEB findings and their clinical relevance

BAL and OEB were performed respectively in 100% and in 83.3%. The most frequent airway abnormalities detected were non-specific inflammatory changes, generalized to the whole respiratory tract (19 patients), or localized to the larynx and trachea (21 patients). Inflammatory changes, often associated with the presence of viscous,

**Table 1** Demographic and clinical characteristics.

| | Whole population *(No. 60)* No. (%) | Infants (<2 yrs) *(No. 8)* No. (%) | Preschool children (≥2 to <6 yrs) *(No. 33)* No. (%) | Schoolchildren (≥6 yrs) *(No. 19)* No. (%) |
|---|---|---|---|---|
| *Demographic characteristics* | | | | |
| Male gender | 38 (63.3) | 3 (37.5) | 21 (63.6) | 14 (73.7) |
| Prematurity (GA < 37 wks) | 14 (23.3) | 3 (37.5) | 5 (15.2) | 6 (31.6) |
| Atopy | 20 (33.3) | 0 | 8 (24.24)[a] | 12 (66.7)[b,c] |
| Early onset of respiratory symptoms (≤2 yrs) | 25 (43.9) | 8 (100.0) | 21 (63.6) | 6 (31.6)[b] |
| Symptoms duration | | | | |
| ≤1 yrs | 9 (15.8) | 4 (80.0) | 4 (12.1) | 1 (5.3) |
| >1 yrs | 48 (84.2) | 1 (20.0) | 29 (87.9)[a] | 18 (94.7)[b] |

[a] $p < 0.05$, as compared to infants.
[b] $p < 0.01$, as compared to infants.
[c] $p < 0.01$, as compared to preschool children; GA: gestational age; wks: weeks; yrs:years.

purulent bronchial secretions, were equally distributed in the 3 age groups, and included mucosal cobble stoning, erythema, and oedema. Airway abnormalities, not GOR-related but explaining lack of response to treatment, were detected in 11 patients and included: (i) vascular compression of the trachea (in 4 patients, 2 in group A, 1 in group B and 1 in group C); (ii) vascular compression of the main left bronchus (in 1 patient in group B); (iii) tracheoesophageal fistula (2 patients, 1 in group B and 1 in group C); (iv) palsy vocal cord (in 1 group A patient); (v) laryngomalacia (3 group A patients). BAL analysis demonstrated: (i) both neutrophilic inflammation (neutrophil proportion ≥10% of BAL cells) and positive LLAM index (≥20) in 16 patients; (ii) isolated neutrophilia in 12 patients and (iii) positive LLAM without neutrophilia in 9 patients. These changes were equally distributed in the 3 age groups. Positive BAL cultures for *Haemophilus influenzae* and *Moraxella catarrhalis* occurred in 2 patients with elevated airway neutrophilia (>20% BAL neutrophils), 1 in group A and 1 in group B. Viral studies were negative in all the BAL samples, while BAL eosinophilia (≥3% BAL cells) was observed in 4 out of the 20 atopic children, 2 in group B and 2 in group C.

Evidence of reflux on OGD was present in 39 children (4 in group A, 24 in group B and 11 in group C). Oesophagoscopic findings suggesting GOR-related abnormalities were detected in 32/60 patients, equally distributed in the 3 age groups, and included mucosal erythema, oedema, friability, nodularity, vertical banding, patulous appearance of the oesophageal lumen, and presence of gross reflux. These findings were confirmed histologically by OEB analysis in 27 children. OGD endoscopy demonstrated hiatal hernia in 3 group C patients and oesophageal stricture in 2 patients (1 in group B and 1 in group C). Two patients in group C had respectively a diagnosis of eosinophilic oesophagitis and of Barrett's oesophagus. *H. pylori* was detected histologically in 2 patients (1 in group B and 1 in group C).

## Prevalence, type and severity of complications

Patient characteristics and occurrence of complications are shown in Fig. 1. There were no major complications. During the procedure or in the following 4 h, minor complications included transient mild desaturation in 3 patients, and transient stridor and bronchospasm in 2 patients (Fig. 1a). Neither severe or persistent hypoxemia, requiring mechanical ventilation, nor apnoea with or without bradicardia was observed. In the following 24 and 48 h, self-resolving vomiting and dysphagia were recorded respectively in 2 and 1 patient (Fig. 1b and c). Body temperature above 38.5 °C was detected in 6

**Table 2** Indications for double endoscopy in the whole population and in each of the three age groups.

| | Whole population *(No. 60)* No. (%) | Infants (<2 yrs) *(No. 8)* No. (%) | Preschool children (≥2 to <6 yrs) *(No. 33)* No. (%) | Schoolchildren (≥6 yrs) *(No. 19)* No. (%) |
|---|---|---|---|---|
| Recurrent LRTI infections | 19 (31.7) | 4 (50.0%) | 10 (30.3%) | 5 (26.3%) |
| Persistent cough | 18 (30.0) | 4 (50.0%) | 8 (24.2%) | 6 (31.6%) |
| Chronic wheeze | 13 (21.7) | 3 (37.5%) | 8 (24.2%) | 2 (10.5%) |
| ''Difficult-to-treat'' asthma | 11 (18.3) | 1 (12.5%) | 6 (18.2%) | 4 (21.1%) |
| Hoarseness | 4 (6.7) | 2 (25.0%) | 1 (3.0%) | 1 (5.3%) |
| Recurrent/spasmodic croup | 3 (5.0) | 1 (12.5%) | 2 (6.1%) | 0 (—) |
| Apnoea/ALTE | 2 (3.3) | 1 (12.5%) | 1 (3.0%) | 0 (—) |
| Recurrent aspiration pneumonia | 2 (3.3) | 1 (12.5%) | 1 (3.0%) | 0 (—) |

LRTI = Lower respiratory tract infections; ALTE = apparent life-threatening events.

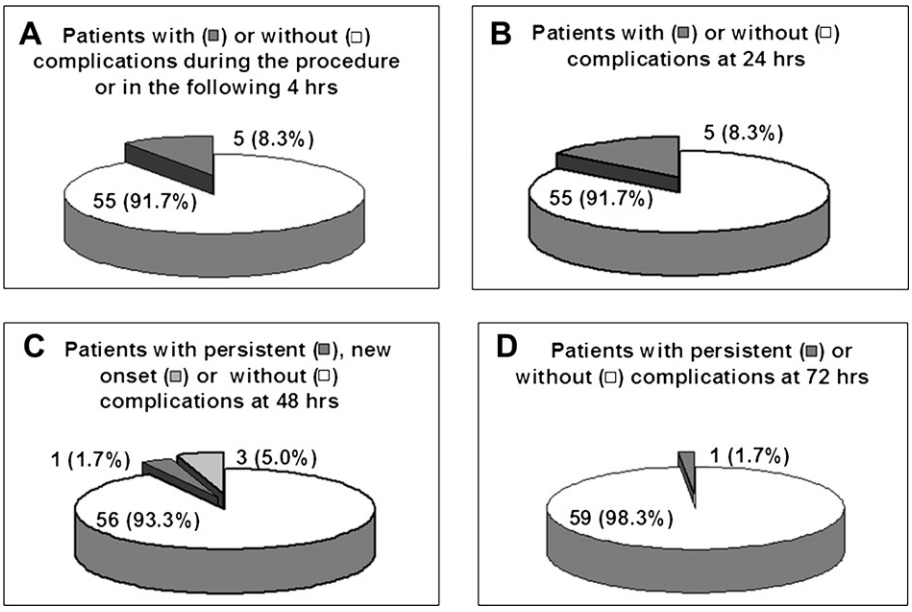


**Figure 1** Frequency of 'still present' and 'new onset' complications at each time point: at endoscopy time or in the following 4 h (A) and 24 h (B), 48 h (C) and 72 h (D) after DE procedure. Only for patients with complications, name initials, age in years (in parenthesis), and symptoms are reported as follows in each panel: Panel A: CS (7.32) arterial oxygen desaturation; RA (10.66) bronchospasm; FF (3.15) arterial oxygen desaturation; SA (2.78) stridor; PG (2.66) arterial oxygen desaturation; Panel B: AA (3.15) fever; FG (7.05) fever; FL (5.09) fever; RA (2.04) fever; TA (6.44) vomiting; Panel C: FG (7.05) fever; BN (6.74) fever, V; CG (5.29) fever; GM (1.64) dysphagia; Panel D: FG (7.05) fever.

patients, all without clinical or roentgenographic evidence of lower respiratory tract infection (Fig. 1b and c). At 72 h, only 1 out of the 6 patients (FG, 7 years old) still had hyperthermia associated with clinical signs of upper respiratory tract infection and was successfully treated with amoxicillin (Fig. 1d). This patient had a history of prematurity (<37 weeks) and apnoea in infancy, was sensitized to house dust mites, was affected by severe GORD, by recurrent respiratory tract infection and D-T-T asthma. No differences in gender, gestational and chronological age, familiar or personal history of atopy, type of gastroesophageal and respiratory symptoms, gastroesophageal and respiratory disease duration were detected between patients with or without complications related to DE. However, as compared with patients without complications, those who developed complications during the follow-up period were more likely to have a personal history of ''early onset'' ($\leq$2 years of age) respiratory symptoms (44.7% and 76.9% of the patients, respectively; $p = 0.039$). Indeed, performing a survival analysis, with the onset of complication (as event of interest), time to complication in hours (as time variable) and age at onset of symptoms, i.e. $\leq$2 years/>2 years (as independent indicator of risk), we found that early onset versus a later onset of respiratory symptoms was associated with a significantly higher rate of complications (Fig. 2) (Log-rank test, $p = 0.038$). Indeed, Fig. 2 showed that only 3 infants (grey circles) among 29 patients with later onset of respiratory symptoms (10.3%) had complications during the follow-up whereas, among 31 patients with early onset of respiratory symptoms, 10 (32.3%) (black circles) had complications during the follow-up. Moreover, this figure clearly demonstrated the statistically significant difference between the 2 curves i.e. patients with later onset of respiratory symptoms (grey circles) and patients with early onset of respiratory symptoms (black circles).

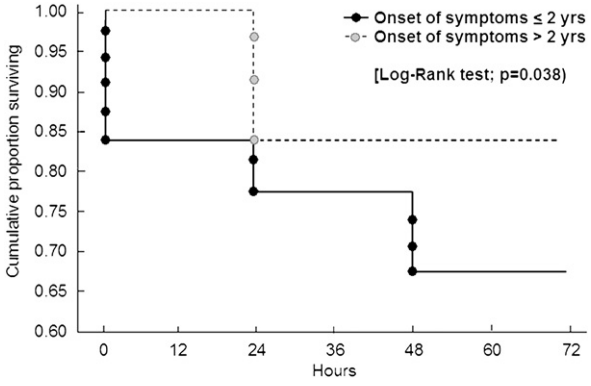


**Figure 2** Survival curve of the rate of complications stratified by onset age of symptoms. The follow-up time expressed in hours is reported on the abscissa whereas the cumulative proportion surviving is reported on the ordinate. Each 'new' onset complication is represented by a grey (patients with later onset of respiratory symptoms) or black (patients with early onset of respiratory symptoms) circle.

## Discussion

The present study shows that in infants and children with D-T-T respiratory symptoms and GORD, a relatively invasive

investigation such as DE may be helpful in establishing a diagnosis and can be safely performed together by well-trained teams. Indeed, a significant proportion of the children evaluated had abnormalities at the airway or at the GO level, explaining lack of response to anti-GOR treatment. In addition, DE was associated with a low prevalence of mild, spontaneously resolving (with one exception), short-lived complications.

In recent years, the association between GORD and respiratory disorders has become the focus of intense study.[1–3,10,13–19] However, there is no general consensus on the most practicable and accurate technique for detecting a causal relationship between GOR and respiratory symptoms and the diagnosis is usually made clinically, sometimes with the support of a pH study, and finally confirmed by a response of airway symptoms to treatment.[20] When no response to standard anti-reflux therapy is observed, additional investigations, such as DE, should be performed to further support or to exclude the diagnosis of GORD-related respiratory symptoms.[16,21] Since the DE is relatively invasive procedure and involves administration of a general anaesthetic, it is important to demonstrate its clinical usefulness and safety.

In the present study DE was helpful in patient management and in guiding surgical decisions. In almost 1 out of 5 children structural and functional anomalies of the airways not GORD-related were detected explaining, at least in part, some of the D-T-T respiratory symptoms. In agreement with a previous report,[22] the not GORD-related airway abnormalities included tracheal and bronchial vascular compression, tracheoesophageal fistula, palsy vocal cord and laryngomalacia. In contrast, in over 60% of our patient population, an abnormal LLAM index and/or a neutrophilic inflammation were detected, associated with inflammatory changes of the airways. Although not specific enough to be diagnostic for GOR-related airway disease, these two BAL parameters have been previously demonstrated to correlate with severity indices of GOR.[15,16] However, neutrophilic airway inflammation is a very common finding in a variety of respiratory disorders and the validation of the presence of lipid-laden macrophages as a diagnostic tool for aspiration has been extremely difficult.[16] In addition, bacterial growth associated with BAL neutrophilia was found in 2 patients, providing information for appropriately guided initiation of antibiotic treatment, while BAL eosinophilia, showing the coexistence of an allergic inflammatory reaction, was detected in 4 out the 20 atopic patients, suggesting the need for additional anti-inflammatory treatment. Due to the relatively low number of patients with the different conditions and the ''complexity'' of their disorders, we could not find any definitive association between the final diagnosis and localized v.s. generalized inflammatory changes in the airway at endoscopy or the predominant respiratory symptoms. As an example, hoarseness or recurrent croup were present in children with laryngomalacia but also with tracheal compression and GOR.

Abnormal oesophagoscopic findings and a histological diagnosis of oesophagitis on OEB were reported only in less than 50% of patients. This is consistent with previous reports[14] and possibly due to high prevalence of weakly acid refluxes observed in children with respiratory symptoms.[23]

Finally, as already shown in studies on the safety of fiberoptic bronchoscopy in children with severe bronchial obstruction, including those with GOR,[12,24] all endoscopies were performed without major complications.

In conclusion, we have shown that DE under general anaesthesia is clinical useful in children with GORD and D-T-T respiratory symptoms and can be performed safely. However, the findings here presented must not be taken as being applicable to all children with GORD and respiratory symptoms, because of some limitations of the study. Firstly, this was a retrospective analysis on a small, highly selected group of children who underwent investigation as part of their clinical assessment rather than according to a strict research protocol. Secondly, these procedures were performed in a centre with appropriately trained and experienced personnel. Finally, we have to recognize that there is always the potential for morbidity, although limited, when performing these procedures due to the complexity of the conditions that may be involved in the pathogenesis of respiratory symptoms in this group of children.

## Conflict of interest

The authors have declared no conflict of interest.

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