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Romanian Guidelines for the Diagnosis and Treatment of GERD-induced Respiratory Manifestations

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ABSTRACT

Background & Aims: Gastroesophageal reflux disease (GERD) is a common condition present in daily practice with a wide range of clinical phenotypes. In this line, respiratory conditions may be associated with GERD. The Romanian Societies of Gastroenterology and Neurogastroenterology, in association with the Romanian Society of Pneumology, aimed to create a guideline regarding the epidemiology, diagnosis and treatment of respiratory conditions associated with GERD.
Methods: Delphi methodology was used and eleven common working groups of experts were created. The experts reviewed the literature according to GRADE criteria and formulated 34 statements and recommendations. Consensus (>80% agreement) was reached for some of the statements after all participants voted.
Results: All the statements and the literature review are presented in the paper, together with their correspondent grade of evidence and the voting results. Based on >80% voting agreement, a number of 22 recommendations were postulated regarding the diagnosis and treatment of GERD-induced respiratory symptoms. The experts considered that GERD may cause bronchial asthma and chronic cough in an important number of patients through micro-aspiration and vagal-mediated tracheobronchial reflex. GERD should be suspected in patients with asthma with suboptimal controlled or after exclusion of other causes, also in nocturnal refractory cough which needs gastroenterological investigations to confirm the diagnosis. Therapeutic test with double dose proton pump inhibitors (PPI) for 3 months is also useful. GERD induced respiratory conditions are difficult to treat; however,proton pump inhibitors and laparoscopic Nissen fundoplication are endorsed for therapy.
Conclusions: This guideline could be useful for the multidisciplinary management of GERD with respiratory symptoms in current practice.

Key words: gastroesophageal reflux disease – GERD – extradigestive manifestations – respiratory manifestations – chronic cough – bronchial asthma – guidelines.

Abbreviations: AET: acid exposure time; CC: chronic cough; CD: crural diaphragm; COPD: chronic obstructive pulmonary disease; DCI: distal contractile integral; EGJ: eso-gastric junction; GERD: gastroesophageal reflux disease; GI: gastrointestinal; HMII: hypopharyngeal multichannel intraluminal impedance; HRM: high-resolution manometry; HRQOL: Health-Related Quality of Life; IPF: idiopathic pulmonary fibrosis; LES: lower esophageal sphincter; LNF: laparoscopic Nissen fundoplication; MII: multichannel intraluminal impedance; MNBI: mean nocturnal baseline impedance; OSAHS: obstructive sleep apnea hypopnea syndrome; PPI: proton pump inhibitor; PSWSI: post-reflux swallow-induced peristaltic wave index; QoL: quality of life; RCT: randomized controlled trial; SAP: symptom association probability; SI: symptom index.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common clinical condition, with a global pooled prevalence of 13.98% and significant regional variation [1]. In Romania, epidemiological data reported a prevalence of GERD varying between 17% [2] and 31% [3].

Gastroesophageal reflux disease with respiratory symptoms is a recognized form of extradigestive GERD according to the Montreal Consensus [4]. Despite the large number of publications available on this topic, there are still many debated aspects regarding the epidemiology, diagnosis, and treatment. Also, to our knowledge there is no common guideline on the

management of GERD with respiratory manifestations, that includes gastroenterologists and pneumologists.

The largest study analyzing the prevalence of extradigestive manifestations in GERD patients over a 5-year period identified an overall prevalence of 30.8%, including a prevalence of 4.8% for bronchial asthma and of 13% for chronic cough (CC) [5]. In Romania, there are few available data [6]; Angelescu et al. [7] identifying CC in GERD patients with a prevalence of 44.5%.

The present guidelines are developed together by the Romanian Societies of Gastroenterology, Neurogastroenterology and the Romanian Society of Pneumology. It provides recommendations for diagnosis and management based on a comprehensive review of the available evidence related to GERD with respiratory manifestations.

METHODS

These clinical guidelines were developed according to the methodology recommended by the United European Gastroenterology using the Delphi method [8]. The Romanian Society of Neurogastroenterology created eleven working groups of experts including gastroenterologists and pneumologists based on their ability to contribute to the work process and their personal experience in the field.

The statements were developed by the main authors and were circulated to all the experts for adjustments. A comprehensive literature research was done by the members of groups for each individual topic. The strength of statements revealed by the literature review was assessed using the GRADE system and the level of evidence was considered high, moderate, low or very low (Table I).

Table I. Grading of the degree of evidence

Degree of evidence	Identification	Meaning
High	A	Several high-quality studies available; very trustful
Moderate	B	Several studies with some limitation available, at least one of high quality; trustful
Low	C	One or more studies with severe limitations; not very trustful
Very low	D	One or more studies with very severe limitations; no evidence available, only expert opinion; use with caution

The statements degree of agreement was obtained using a 6-point Likert scale: strong agreement (A+), agreement (A), weak agreement (A-), weak disagreement (D-), disagreement (D), strong disagreement (D+) (Table II).

Table II. Likert scale

A+	Agree strongly
A	Agree with minor reservation
A-	Agree with major reservation
D-	Disagree with minor reservation
D	Disagree with major reservation
D+	Disagree strongly

The statements were further submitted for the vote to all the participants. A threshold of 80% of participants with A+ and A votes had to be fulfilled in order to allow a given statement to be endorsed in the guideline. After first voting, adjustments of two statements and re-voting was done. Afterwards, the final draft of the manuscript circulated for final approval by all participants.

RESULTS

The statements together with the experts voting results and a short literature review evaluated according to the GRADE system are presented below.

Statement 1. Gastroesophageal reflux disease (GERD) may cause bronchial asthma. ***(STATEMENT ENDORSED; overall agreement 82.05% A+ 28.21% A 53.85% A- 12.82% D- 2.56% D 2.56% D+ 0%; level of evidence: moderate.)***

Incidence and prevalence of concomitant asthma and GERD are highly variable among studies, due to the heterogeneity of study designs and variable definitions of GERD. An association between GERD and respiratory disorders was first described in 1966, implying GERD in the pathophysiology of bronchial asthma [9]. There are many pathophysiological mechanisms proposed to explain a possible GERD – bronchial asthma relationship, including microaspiration of gastric reflux and vagal nerve stimulation leading to bronchoconstriction [10].

Looking at the prevalence of bronchial asthma in GERD populations, many studies have found a modest or even no correlation. In a population-based study in Olmsted County, Minnesota, a self-report questionnaire was mailed to a random sample of 2,200 residents aged 25-74 years. Heartburn and acid regurgitation were not associated with bronchial asthma and no association between typical GERD symptoms and asthma was found [11]. Ruigómez, in a large longitudinal study using data from the UK General practice research database, showed that patients with GERD had no significant increased risk of developing asthma: RR=1.2 (95% confidence interval [CI]: 0.9-1.6) [12]. In another large prospective, multicenter, open cohort study (ProGERD) with 6,215 patients followed for 5 years after initial treatment with esomeprazole for GERD, bronchial asthma was found in 4.8% patients [5]. The prevalence of asthma was significantly related to female gender or a GERD duration of more than 1 year, but no relationship to the type of GERD (erosive or not) was found. Barrett's esophagus patients seem to be more likely to have a diagnosis of asthma than controls (OR=2.15, 95%CI: 1.15–4.03) [13]. In a systematic review published in 2007, Havemann et al [14] found a 4.6% prevalence of bronchial asthma in GERD patients (compared with 3.9% in controls), with a 2.3 overall ratio (95%CI: 1.8-2.8).

Many studies described a relationship between GERD and bronchial asthma exacerbation. In the baseline data from National Heart, Lung, and Blood Institute's Severe Asthma Research Program analysis, the bronchial asthma exacerbations frequency was associated with GERD with a relative risk of 1.6 [15]. This association was recently demonstrated in a meta-analysis of 32 studies, including a total of 1,612,361 patients of all ages. Overall, GERD showed an association with asthma exacerbation

(OR=1.27; 95%CI: 1.18-1.35) and with exacerbations needing oral corticosteroid therapy (OR=1.24; 95%CI: 1.09-1.41) [16]. Even studies based on deep learning and artificial intelligence confirmed the link between GERD and bronchial asthma exacerbations [17].

Even if the evidence shows an increased prevalence of BA in patients with GERD, the causal relationship is difficult to prove. Moreover, although there is a clearly proven link between GERD and exacerbation of bronchial asthma, the results of anti-reflux therapy on pulmonary outcome are inconsistent. Probably GERD should be viewed as a possible contributing factor in some BA patients.

Statement 2. Bronchial asthma may cause GERD. ***(STATEMENT NOT ENDORSED; overall agreement 33.33%: A+ 15.38% A 17.95% A- 30.77% D- 23.08% D 5.13% D+ 7.69%; level of evidence: low.)***

A significant association between asthma and GERD has been shown in epidemiological studies: up to 50% of patients with asthma have associated GERD (46.54%, based on symptoms alone and 52.7% based on pH-monitoring and endoscopy), compared to 23.59% in control groups [18]. In Havemann et al. [14] systematic review, the prevalence of asthma in GERD was 59.2%, with an overall ratio of 5.5 (95%CI: 1.9-15.8) compared to controls. A large longitudinal study using data from the UK General practice research database showed that the relative risk of an incident GERD diagnosis among patients with a new diagnosis of asthma was 1.5 (95%CI: 1.2-1.8), mainly during the first year following diagnosis [12]. In a large European multicenter prospective cohort study (U-BIOPRED) which has included asthmatic patients, GERD was more common in severe asthma (46% in non-smokers, 63% in smokers or ex-smokers, p=0.004) than in mild/moderate asthma (21%) and healthy controls (11%) [19].

There is a great variability of GERD prevalence in bronchial asthma patients, related to the heterogeneity of studies, the definition of GERD (clinical, endoscopic, pH-monitoring) and the diagnosis of asthma. The lack of 24-hour pH-monitoring may underestimate the prevalence of GERD, since "silent" reflux (without symptoms) is not taken into account. In a study that included patients with difficult to control asthma, 70% of patients associated GERD (diagnosed by esophageal manometry and 24-hour esophageal pH monitoring), although 28.5% had no reflux symptoms [20]. In another study, the prevalence of abnormal 24-h esophageal pH monitoring in BA patients without reflux symptoms was 62% [21]. Likewise, in Kiljander et al. [22] study silent reflux was present in 35% of asthma patients. Night reflux is also highly prevalent in asthma patients possible due to the lack of anti-reflux protective mechanisms during sleep [23].

Despite the proven epidemiological link between asthma and GERD, the causal relationship is not fully understood and demonstrated.

Statement 3: GERD may cause chronic cough. ***(STATEMENT ENDORSED, overall agreement 82.05%: A+ 71.79% A 10.26% A- 17.95% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

Chronic cough is defined as a cough lasting 8 weeks or longer [24], a symptom which usually affects women almost twice as frequently as men and which has a significant impact on the quality of life (QoL) of these patients [25]. The reason behind this gender-related prevalence is still unclear, but it is possible that respiratory tract anatomy, hormonal differences and increased sensitivity to cough reflex in women might play a role [25, 26].

There is a generally recognised association between GERD and CC [4], with a metanalysis of 90 studies having observed the occurrence of CC in up to 9.6% of patients suffering from GERD [27]. However, determining causality is a much more challenging task than simply exploring the co-occurrence of the two clinical entities.

In the European ProGERD study, Jaspersen et al. [5] found that GERD might constitute the cause of CC in about 13% of patients; however, the strength of this association remained controversial. In Japan, GERD represented an isolated potential cause of CC in only 6.9% of cases, with an increasing trend of establishing GERD as the etiology of persistent cough [26].

Despite the significant body of epidemiological data that shows an association between GERD and chronic cough, we are still missing a causal link between the two clinical entities. Even if the sensitized vagal esophageal-bronchial reflex plays a major part in this association, the role as a sole trigger of the gastroesophageal reflux remains to be determined, given the fact that most patients suffering from CC report onset of coughing episodes as a response to a rather wide range of triggers (such as environmental factors, excessive use of the larynx by singing, laughing, excessive talking) [28].

Statement 4. Chronic cough may cause GERD. ***(STATEMENT NOT ENDORSED; overall agreement 38.46%: A+ 17.95% A 20.51% A- 15.38% D- 28.21% D 10.26% D+ 7.69%; level of evidence: low.)***

Gastroesophageal reflux disease may trigger CC and may also increase the intra-abdominal pressure during cough episodes. This may cause reflux by exceeding the basal lower esophageal sphincter (LES) pressure and creating a self-perpetuating circle. Therefore, three situations are possible: cough precedes reflux, reflux precedes cough, or cough-reflux-cough cycle [29].

It is very difficult to prove the association between CC and GERD; they may often coexist and the association does not imply a causative relationship in all the cases. In the largest epidemiological study conducted in Europe, the ProGERD study, the association of CC with GERD was found in 13% patients [5]. Other studies showed a prevalence of this association varying between 10-56% [10].

Statement 5. GERD may cause other respiratory disease [idiopathic pulmonary fibrosis (IPF), obstructive sleep apnea hypopnea syndrome (OSAHS), chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, aspiration pneumonia]. ***(STATEMENT NOT ENDORSED; overall agreement 43.59%: A+ 23.08% A 20.51% A- 41.03% D- 5.13% D 7.69% D+ 2.56%; level of evidence: moderate.)***

A study published in 2015 demonstrates that GERD prevalence in idiopathic pulmonary fibrosis (IPF) was higher and IPF patients had decreased LES and upper esophageal sphincter pressure, impaired esophageal peristalsis and bolus

clearance function with more proximal reflux events [30]. In contrast, a meta-analysis including 18 case-control studies with 3,206 patients with IPF and 9,368 controls showed that GERD and IPF may be related. However, the association may also be confounded due to smoking [31].

Another recent meta-analysis evaluated the relationship between OSAHS and GERD and found a significant correlation between these two disorders, but the exact causative relationship remained contradictory [32]. This meta-analysis showed clear evidence that GERD was implicated in OSAHS pathogenesis. OSAHS was significantly associated with increased risk of GERD (OR=1.75, 95%CI: 1.18-2.59, p<0.05). Also, the conclusion of this study was that in treatment of OSAHS, GERD should be considered.

In a retrospective study, Rodríguez et al. [33] including GERD (n=4,391) and COPD patients (n=1,628), during a 5-year follow-up, the relative risk of an incident COPD diagnosis in patients with GERD was 1.17 (95%CI: 0.91-1.49), while the relative risk of an incident GERD diagnosis among patients with COPD was 1.46 (95%CI: 1.19-1.78). The authors concluded that patients with a diagnosis of COPD were at a significantly increased risk of a diagnosis of GERD compared to individuals without COPD diagnosis [33]. Furthermore, two meta-analyses investigated the relationship between GERD and COPD exacerbation and reported a significant correlation between GERD and COPD exacerbation [34, 35]. However, the pathology of GERD in COPD is complex and obscure and the mechanism by which GERD symptoms affect COPD exacerbation remains to be elucidated [34, 35].

Gastroesophageal reflux disease has also been associated with both cystic fibrosis and non-cystic fibrosis bronchiectasis [36–38]. Gastroesophageal reflux disease is highly prevalent (up to 90%) among both children and adults diagnosed with cystic fibrosis, as pepsin and bile acids were found in bronchoalveolar lavage fluid and sputum [36]. The precise nature of the relationship between GERD and bronchiectasis remains elusive. The potential implications of GERD in the pathology of bronchiectasis were investigated by some studies. The study of Lee et al. [39] analyzed 58 patients diagnosed with bronchiectasis found that 26% of them had GERD, of which 73% presented clinically silent reflux. Shoemark et al. [40] identified that aspiration was the cause in 1% of patients diagnosed with bronchiectasis. While these studies suggested a degree of causality between these two disorders, further studies are needed.

Regarding the association between GERD and pneumonia, a large population-based cohort study including 15,715 GERD cases and 15,715 non-GERD matched controls showed that cumulative incidence of pneumonia was significantly higher in GERD patients than that in the non-GERD matched controls, with an adjusted OR of 1.48 (95%CI: 1.31–1.67; p<0.001) within 6-year of follow-up. Gastroesophageal reflux disease was significantly associated with long-term risk of pneumonia, especially in young GERD patients and proton pump inhibitors (PPIs) use longer than 4 months [41].

Statement 6. Other respiratory diseases (IPF, COPD and chronic bronchitis, pulmonary aspiration complications like lung abscess, bronchiectasis, aspiration pneumonitis and OSAHS) may cause GERD. ***(STATEMENT NOT ENDORSED; overall agreement 23.08%: A+ 10.26% A 12.82% A- 20.51% D- 38.46% D 12.82% D+ 5.13%; Level of evidence: moderate.)***

Gastroesophageal reflux disease is well known to determine or exacerbate lung disease. In spite of the fact that is supposed to be a mutual mechanism, most of the studies in the literature are focusing on GERD inducing pulmonary disease and not on the inverse relationship [42, 43].

The most important respiratory mechanisms that could determine GERD are changes in the lung volume affecting the gastro-esophageal junction, the reduce lung compliance, the cough and the breathlessness. The altered respiratory movements and the low lung compliance can enhance trans-diaphragmatic pressure gradient during respiration. These can determine the eso-gastric junction (EGJ) dysfunction, GERD, micro-aspiration and can develop a vicious circle [42, 44].

In IPF the lower pulmonary elasticity can increase the negative intrathoracic pressure. In this event the pressure of the upper esophageal sphincter is decreased, and GERD is determined. Gastroesophageal reflux disease could again predispose to IPF inducing multiple episodes of micro-aspiration. The reduced pulmonary compliance also, could favor the changeset in the position of the mediastinal structures and traction on the esophagus. This can affect the pressure the of LES inducing GERD [45]. The values of inspiratory thoracic pressures inversely correlate with the number of proximal refluxes in esophagus [46]. Hiatal hernia is also found frequently and could be induced by the low pulmonary volumes [47], as IPF is characterized by a stiffer parenchyma and greater negative inspiratory pressures.

In an interesting study performed by Savarino et al. [48], that enrolled 40 patients with IPF, 40 patients with interstitial lung disease other than IPF (non-IPF patients) and 50 healthy volunteers, concluded that IPF patients had significantly higher (p<0.01) esophageal acid exposure and found good correlations between the pulmonary fibrosis high-resolution computed tomography scores and reflux episodes in both the distal and proximal esophagus. However, no difference between the low esophageal sphincter and abnormal motility was found between the IPF and non-IPF patients, concluding that the esophageal motor disturbances is not inducing IPF [48].

The pathophysiology of GERD in COPD could be determined by the increased transdiaphragmatic pressure gradient that is specific to COPD. Patients with COPD have frequent cough, a flattened diaphragm and increased respiratory effort [49]. Gastroesophageal reflux disease is also a predictor factor for COPD gravity [50].

In regard to OSAHS, one recent meta-analysis including with a total sample size of 2,699 included one case–control study and six cross-sectional studies, revealed a significant relationship between OSAHS and GERD, with a pooled OR of 1.75 (95%CI: 1.18-2.59, p<0.05) [32].

In a prospective, cross-sectional study, by Basoglu et al. [51], that included 1,104 patients, the prevalence of GERD was

similar in OSAHS (38.9%) and non-OSAHS (primary snoring) (32%) groups (p=0.064) and concluded that the prevalence of GERD was significantly increased in patients with OSAHS and non-OSAHS compared with general population, but the severity of OSAHS did not influence GERD prevalence [51].

There are not data yet about lung abscess, bronchiectasis and aspiration pneumonitis inducing GERD.

Statement 7. GERD may cause respiratory symptoms in an important number of patients. ***(STATEMENT ENDORSED; overall agreement 89.74%: A+ 66.67% A 23.07% A- 10.26% D- 0% D 0% D+ 0%; level of evidence: high.)***

Between a third and a half of CC patients are reported in a large series as having GERD, but the definition of GERD was unclear [52]. In 1990, Irwin et al [53]., in a cohort study, suggested that GERD may be the cause of chronic nonspecific cough in 21–41% patients [53].

In European or American countries, GERD is the most common cause of CC along with allergic disorders such as asthma and rhinosinusitis [54]. In Asian countries, on the contrary, GERD-related cough has been considered rare, with a prevalence of 0-12% [55].

In a large prospective European study, the ProGERD study, CC could be attributed to GERD in 13% of patients [5].

In a recent systematic review, Irwin et al. [56] identified GERD as the cause of 85% of CC worldwide, especially in Western countries. It has been reported that 69% of the patients presenting with GERD- related cough had comorbid conditions such as asthma or postnasal drip [57]. Gastroesophageal reflux disease can be considered as a potential co-factor in patients with asthma, CC or laryngitis so careful evaluation for non-GERD causes should be undertaken in all of these patients [4, 58].

Using ambulatory pH-impedance monitoring, Sifrim et al. [29] reported that the majority (69.4%) of cough events in subjects with CC, were considered independent of reflux, whereas 30.6% occurred within two minutes of a reflux episode.

Patients who present with classic GERD symptoms and cough tend to have GERD-related cough. Nighttime coughs or coughing after meals are signs associated with reflux-induced cough. When patients deny having GERD, regurgitation, belching or any other symptoms, the likelihood of them actually having acid reflux as a primary cause of their cough is small [59].

When GERD causes cough, gastrointestinal (GI) symptoms can be absent up to 75% of the time, making the diagnosis more challenging [60]. Furthermore, cough and GERD are common diseases and often co-exist, but the association does not imply a causative relationship in all cases. Eastburn et al. [61] showed an occurrence by chance in 25% of cases. Temporal association between reflux episodes and cough could help address correctly CC to reflux, although a diagnostic gold standard is lacking [61].

In non-smoking patients with normal chest X-rays who are not taking angiotensin converting inhibitors, CC is determined in 86% of cases by asthma, postnasal drip syndrome and GERD, although often multiple causes co-exist in a single patient [62].

Gastroesophageal reflux disease has been proposed as a trigger for asthma, a significant association between asthma and GERD has been shown in epidemiological studies: up to 50% of patients with asthma have associated GERD. However, the prevalence of asthma in patients with GERD is still uncertain: 30-90%, compared to an average of 24% in controls [10]. The PROGERD study showed that 4.8% of GERD patients may have asthma, while a higher prevalence (24–29%) of silent GERD can be found in difficult-to-control asthmatic cases [5].

The prevalence of GERD in patients with OSAHS was 12.9%. The prevalence of GERD did not correlate with OSAHS severity. Daytime sleepiness and depression seem to be associated with GERD in patients with OSAHS, while nocturnal reflux symptoms seem to be related to obesity in OSAHS [63].

Statement 8. GERD may cause respiratory symptoms due to micro-aspiration of refluxed gastric content in the respiratory tract. ***(STATEMENT ENDORSED; overall agreement 84.62%: A+ 53.85% A 30.77% A- 15.38% D- 0% D 0% D+ 0%; level of evidence: low.)***

There are few physiological studies that explain how the protective and defense mechanisms of the esophagus and airways respond to micro-aspiration. Healthy patients exposed to air and fluid into the lower esophagus, had different reactions of the upper esophageal sphincter: it relaxed when the air was blown and contracted when water was introduced [10, 46, 64, 65]. These defense reactions reduced their intensity in sleep or supine position and the airways became more vulnerable [66].

Another study, which introduced water into the hypopharynx, showed that the defense reflexes were much more pronounced, at lower volumes of water, than if the water had flowed into the larynx [67]. However, if 0.1N HCl solution is introduced in healthy patients, surprisingly, the pharyngo-laryngeal reflexes are lower in intensity than when water is introduced; this process is thought to occur in the case of esophageal reflux with acid content. This may explain the CC in patients with GERD, in which the defense reflexes and mechanosensitivity are reduced due to the pH of the refluxed content [68]. In patients with GERD without coughing, receiving puffs of air a lower laryngeal adductor reflex was observed compared with patients without GERD [69].

Patients with COPD had a lower sensitivity to puffs of air administered into the pharynx, showing a lower mechanosensitivity of the pharynx and larynx and a higher risk for micro-aspiration [70].

Methods of testing for pulmonary aspirate include determination of bile acids and pepsin in the lower respiratory tract by tracheal aspiration, bronchoalveolar lavage and not sputum testing; these determinations raise issues, including methodology: contamination of sputum products, quantification of pepsin and bile salts, interference with inflammatory factors in the lungs, so these tests are not fully validated [71]. In this context, some studies determined the composition of the micro-aspirate in patients with lung disease or even sputum and reported elevated values of pepsin and bile in bronchopulmonary lavage in patients with IPF [72-74], or in the sputum of patients with COPD and asthma [75, 76]; these studies did not link these high values of pepsin and bile acids with the lung function (a function that was altered anyway).

Equally, the values of pepsin in exhaled condensed breath and esophageal reflux were determined in patients with COPD, without a clear pathogenic correlation [75].

Statement 9. GERD may cause respiratory symptoms due to vagal-mediated tracheobronchial reflex. ***(STATEMENT ENDORSED; overall agreement 82.06%: A+ 28.21% A*** **53.85% A- 15.38% D- 0% D 2.56% D+ 0%; ;evel of evidence: low.)**

The esophagus and bronchial tree develop from the foregut and share a common neural innervation via the vagus nerve. Both esophageal mucosa and submucosa but also respiratory airways have vagal unmyelinated nerve C-fibers. Thermal, mechanical and chemical stimuli may act on their different ion channel type receptors forming action potentials. Two particular receptors are the transient receptor potential vanilloid 1 activated by capsaicin and the transient receptor potential ankyrin 1. In addition, in the esophagus, several acid-sensitive ion channels are also expressed [77]. Signals are conducted to the vagal jugular (neural crest derived) ganglion and then to paratrigeminal nucleus and to the vagal nodose (placode derived) ganglion and then to the nucleus of tractus solitarius. C-fibers from esophageal mucosa and larger respiratory airways conduct predominantly to the vagal jugular ganglion, fibers from esophageal submucosa and smaller intrapulmonary airways conduct mostly to the vagal nodose ganglion [78]. At the central nervous system, signals from the esophagus may result in warning sensations (non-cardiac chest pain and heartburn) and clearance of the esophageal mucosa – increased submucosal secretion and smooth muscle contraction promoting peristalsis (vagal efferent fibers). Signals from the respiratory airways may increase mucus secretion and their clearance by cough and bronchoconstriction (vagal and somatic efferent fibers) [79].

Persistent injury and inflammation may lead to increase excitability of ion channels - a stimulus that was previously subliminal now leads to action potential discharge, with increased frequency and duration (peripheral sensitization). In time, central sensitization may also occur [79].

To note that pressure gradient changes between the abdominal and thoracic cavities during the act of coughing can cause a vicious circle of cough and reflux.

Experimental studies have been performed based on the hypothesis that stimulation of distal esophageal receptors using acid or saline perfusion mimicking acid reflux will result in cough or bronchoconstriction. Inconsistent results on a small number of patients have been obtained [80–87].

Statement 10. GERD should be suspected as a causative factor in non-allergic asthma with adult onset after exclusion of other potential causes. ***(STATEMENT ENDORSED; overall agreement 84.61%: A+ 64.10% A 20.51% A- 7.69% D- 5.13% D 2.56% D+ 0%; level of evidence: low.)***

The frequency of GERD (based on symptoms or pH tests) in asthma patients was reported to be between 15 to 82% compared with 24% in controls [14, 88, 89]. A meta-analysis including 1,612,361 patients of all ages showed that in all populations, GERD had a weak association with bronchial asthma (OR=1.27), lower in adults than in children. The same meta-analysis showed that GERD was associated with frequent asthma exacerbations (OR=1.59) and also with oral corticosteroid dependent exacerbations (OR=1.24) [16]. However, a prospective study found that GERD did not represent an independent factor for more frequent exacerbation [90].

In severe asthma, the frequency of GERD was 42-46% [91, 92], 3 to 10 times higher compared with mild/moderate asthmatics or healthy individuals [89].

A causal link between GERD and asthma is lacking. Gastroesophageal reflux disease was associated with hypo salivation and oropharyngeal problems in patients with asthma [93]. Another theory is that GERD may induce changes in the mucosal immune system that may favor the development of food allergy and allergic sensitization to aeroallergens. The association of GERD with asthma is lower than with allergic rhinitis, even they may share a common pathway [94]. Reflux may produce a subtle perturbation of proteins detectable in the airways lining fluid [95].

It is still unclear whether the severe asthmatics with GERD may represent a distinct phenotype of asthma [95]. The present guidelines for bronchial asthma recommend that patients with poorly controlled asthma should be treated with anti-reflux medication only if they have also symptomatic reflux, recognizing in this way GERD as a trigger for asthma [96].

Gastroesophageal reflux disease should be suspected in asthma patients with symptoms worsening after meals and in patients who do not respond to traditional asthma medications. Patients with heartburn and regurgitation before the onset of asthma symptoms may also be considered of having reflux-induced asthma [62].

Statement 11. GERD should be suspected in patients with suboptimal controlled bronchial asthma. ***(STATEMENT ENDORSED; overall agreement 82.05%: A+ 30.77% A 51.28% A- 15.38% D- 2.56% D 0% D+ 0%; level of evidence: moderate.)***

It has long been observed that GERD has a high prevalence among asthma patients [14, 19, 20, 97-101] (between 30 and 90% based on definition of GERD and variables measured) and it was also associated with poor asthma control [19, 92, 100] and with a high frequency of asthma exacerbations [101, 102]. In addition, symptoms of the two are often very similar, making the distinction between GERD and asthma quite difficult to assess. The most similar symptom is nighttime cough.

Moreover, several studies have evaluated the effect of GERD treatment on asthma non-responders, with conflicting results [14, 20, 98, 99, 101, 103-108]. Some of the most recent studies have concluded that PPIs treatment may have a beneficial effect, especially on symptomatic GERD patients [14, 20, 99, 103, 104, 107]. One study demonstrated that PPIs treatment might improve forced expiratory volume and asthma-related QoL in patients with moderate-to-severe asthma and symptomatic GERD [107]. PPIs are not helpful for those with asymptomatic GERD regarding asthma control [108].

Statement 12. Nocturnal asthma may be suggestive for GERD. ***(STATEMENT NOT ENDORSED; overall agreement 64.11%: A+ 23.08% A 41.03% A- 30.77% D- 5.13% D 0% D+ 0%; level of evidence: low.)***

There are few studies, with a limited number of patients included, on the relationship between nocturnal asthma, a unique physiologic and inflammatory asthma phenotype [109, 110] and GERD. The topic showed conflicting results over the years, both in adults [23, 111-113] and pediatric population [114-116]. The possible explanations may be the different design and methodologies used, especially in terms of functional measures performed during night, regarding both the airway resistance and the intraesophageal pH [111, 115, 116] or the GERD self-reported symptoms [23]. The pro [23, 113, 115, 116] – con [111, 112, 114] balance results of the existing studies favor the role played by the GERD in the clinical picture of nocturnal asthma. Nevertheless, GERD is only one of the causative and precipitating factors of nocturnal asthma, alongside others such as obesity [113], allergic rhinitis [117], obstructive sleep apnea or race-ethnicity [118].

Statement 13. Nocturnal refractory cough is suggestive for GERD. ***(STATEMENT ENDORSED; overall agreement 89.74%: A+ 38.46% A 51.28% A- 7.69% D- 2.56% D 0% D+ 0%; level of evidence: high.)***

There is a lack of studies on refractory CC and on the relationship between nocturnal refractory cough and GERD.

A particular attention to GERD as a potential etiology of nocturnal refractory cough should be given in non-smokers: for example, in a study including 131 such patients, GERD prevalence was found to be 62% [119].

Another survey-based cross sectional study evaluating risk factors for acute, subacute and CC in employed people in Finland included 3,697 subjects and found that 24.3% of those having CC also had GERD. Interestingly, GERD was also reported by subjects with acute, subacute or chronic intermittent cough patterns [120].

In another survey based study with similar design performed in UK and including responders irrespective of their employment status, CC prevalence was found to be 12%, severe form 7% and regurgitation was identified as a strong predictor of CC (OR=1.71) [121].

The existing guidelines advice to evaluate the potential common causes of GERD related refractory cough such as: 1) asthma, cough variant asthma, non-asthmatic eosinophilic bronchitis; 2) upper airways cough syndrome; 3) angiotensin-converting enzyme inhibitors therapy newly initiated.

If GERD is excluded than diagnosis should focus on non-asthmatic pulmonary diseases, OSAHS, cardiac arrhythmias, somatic cough syndrome [122, 123].

More recently GERD-related refractory cough (GERDC) was defined based on existing evidence as a subtype of CC with GERD demonstrated via multi-channel impedance pH monitoring which is resistant to a 8 week course of standard GERD therapy, but responsive to a subsequent intensified regimen [124].

Statement 14. GERD-induced CC should be suspected in patients presenting unexplained cough after standard thoracic imaging investigations (chest x-ray, pulmonary computed tomography) that do not identify a pulmonary cause for this symptom. ***(STATEMENT ENDORSED; overall agreement 92.31%: A+ 64.10% A 28.21% A- 7.69% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

There are no studies focusing on the effectiveness of GERD diagnostic work up in patients with CC and normal results of the thoracic imaging studies (chest X-ray, computed tomography). Therefore, CC related to GERD should be suspected first of all in the presence of concomitant suggestive digestive symptoms of (an undiagnosed) GERD or when there is an already diagnosed GERD and all other more common etiologies of CC were excluded [123].

The supportive evidence comes from studies suspecting GERD per primam in patients with CC and confirming it with pH monitoring studies. One such study enrolled 204 patients with suspected GERD-related CC defined as cough episodes produced about 2 minutes after perceived acid reflux. These patients underwent 24-hour esophageal pH monitoring studies and in 66% of them GERD was diagnosed. In the subset of GERD patients with CC diagnosis was also done based on DeMeester score in 87% of cases [125].

Another retrospective study reviewed the prevalence of cough and throat clearing and their association with reflux episodes in patients who were referred for pH monitoring for suspected GERD. Prevalence of cough and throat clearing on study day was 42%; 28%, only reported cough and 30% reported only throat clearing. Among those with both respiratory symptoms, only 8% had a positive symptom index for GERD, compared to 26% in those with cough only and 22% in those with throat clearing only. Prevalence of excessive cough (more than 23 episodes in 24 hours was 17% in the whole analyzed cohort [126].

In another study who evaluated the prevalence of GERD in patients with asthma or CC referred for pH monitoring, it was found that among 358 patients, 134 (37%) patients had also CC. Interestingly in 50% of patients with CC and GERD, respiratory or reflux symptoms were absent at the time of pH study [124]. GERD should be suspected in patients with CC and normal chest x-ray in whom cough has suggestive characteristics (supine cough associated with heartburn or cough after meals [60, 127].

Statement 15. The presence of typical GERD symptoms in a patient with respiratory manifestations may suggest GERD as the etiology but does not establish a causal relationship. ***(STATEMENT ENDORSED; overall agreement 97.43%: A+ 46.15% A 51.28% A- 2.56% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

Many epidemiologic studies have underlined an association between GERD and extraesophageal manifestations. However, establishing causality is a difficult task.

Respiratory symptoms may occur alone or coexist with typical GERD manifestations, such as heartburn and regurgitation. The prevalence of extraesophageal disorders in patients without typical GERD symptomatology is even more challenging [10].

It was observed that in cases of asthma with GERD diagnosed by esophageal multichannel intraluminal impedance (MII) monitoring combined with pH-metry, up to 40-60% of patients may not exhibit typical reflux symptomatology [128].

Several studies have observed that in the case of patients with moderate to severe reflux objectively identified by esophagogastroduodenoscopy and/or pH monitoring with concomitant typical symptoms, reflux is more likely to be the cause of their extraesophageal symptoms [62]. However, even if respiratory manifestations coexist with typical reflux symptomatology, this may only suggest GERD as the potential etiology, but does not certify a causal relationship between the two clinical entities.

Statement 16. Typical GERD symptomatology is lacking in the majority of patients presenting with respiratory manifestations. ***(STATEMENT ENDORSED; overall agreement 89.75%: A+ 35.90% A 53.85% A- 7.69% D- 0% D 2.56% D+ 0%; level of evidence: high.)***

Gastroesophageal reflux disease may not be the first suspected disease in patients presenting with respiratory symptoms; it is also not usually associated with pulmonary illness [129]. Multiple pathogenic mechanisms can be associated with GERD respiratory symptoms; however, the causal link may be difficult to prove without specific tests, in the absence of typical GERD symptoms [130]. Recent studies showed the absence of typical GERD symptoms in respiratory patients and specific investigations for GERD may be needed for diagnosis [131].

A study on 109 patients with CC showed that GERD was not suspected in any of them based on specific symptoms; however, after 24-hour esophageal pH or MII-pH monitoring, 18 patients were found with GERD, which was subsequently identified as an underlying condition for the chronic coughing [132].

Patients with cystic fibrosis often associate GERD, which seems to play a role in the pathogenesis of the respiratory disease [133]. However, symptoms of these two conditions may overlap, thus clear distinction may be difficult [134].

The GERD symptomatology is frequently encountered in patients with COPD, especially in those with the severe form of COPD. Moreover, GERD is often associated with an increased risk of admission to intensive care units and the use of mechanical ventilation for COPD patients who have developed GERD [135]. In a recent meta-analysis, Huang et al. [34] found that patients with GERD have a risk of more 5-fold higher of developing the exacerbation of COPD. Due to this fact, GERD is considered to be an important factor for the outcomes of COPD. However, despite this risk, it is difficult to demonstrate a causal relationship between GERD and COPD also because medication used in COPD may induce GERD [34].

Statement 17. No single testing methodology exists to definitively identify GERD as the etiology for the suspected extra-esophageal symptoms. ***(STATEMENT ENDORSED; overall agreement 89.75%: A+ 66.67% A 23.08% A- 5.13% D- 2.56% D 0% D+ 2.56%; level of evidence: moderate.)***

In patients with suspected GERD and extra-esophageal symptoms, the first exams performed are laryngoscopy and upper GI endoscopy. Laryngoscopy may show signs of significant laryngeal inflammation (erythema, vocal fold or laryngeal edema, granulation) possibly related to GERD, although these findings show a poor inter/intra-observer agreement [136, 137]. The validity of Reflux Finding Score is questionable since these findings were also present in 86% of asymptomatic patients [138]. Upper GI endoscopy provides conclusive evidence for reflux when Los Angeles grade C or D esophagitis, long-segment Barrett's mucosa or benign strictures is present [139]. However, these changes do not prove a causal relationship between GERD and extra-esophageal symptoms, nor predict the response to PPIs. Also, they have an overall low predictive value in confirming GERD as the etiology for the extra-esophageal symptoms [140]. Esophagitis may be present in 40% of patients with asthma and in 20% of patients with extra-esophageal symptoms [141, 142]. However, esophagitis may be found in 20% of asymptomatic patients and only a minority of patients with esophagitis may have extra-esophageal symptoms [143].

When endoscopy is not conclusive for reflux, ambulatory pH or MII-pH monitoring are recommended. The aim of pH-monitoring is to establish the presence or absence of pathological reflux and evaluate a possible association between symptoms and reflux episodes. This would be an indirect proof that the respiratory symptoms may be caused by reflux. The main parameter of pH-monitoring is acid exposure time (AET). An AET >6% is abnormal (whatever the type of reflux monitoring). When AET is borderline (4-6%) the number of reflux episodes (>80/24h) is an adjunctive metric to be used [139]. Catheter based distal pH monitoring can detect a subgroup of patients with reflux related CC or asthma, as a high AET was observed in 30-50% of them, even if there was no proven benefit of PPIs treatment in these patients [144, 145]. Regarding reflux symptom association for laryngopharyngeal symptoms, pH monitoring is a low reliable tool, as these symptoms have a late onset [146]. Proximal and pharyngeal pH monitoring added little benefit due to several technical limitations (probe positioning, swallowing artifacts, drops in pH value unrelated to reflux, lack of a standardization for normal values) [147]. Wireless pH-monitoring using Bravo capsule has better tolerability and sensitivity due to extended monitoring period (48h). However, the system is very expensive [148].

Combined MII-pH monitoring allows the characterization of reflux events regarding the composition, acidity, duration, and extent above the LES. It has a higher sensitivity for GERD diagnosis, because identifies also weakly acidic or non-acidic refluxes, which represent approximately 20% of total refluxes [149]. In addition, MII-pH monitoring can identify a temporal association between symptoms and refluxes based on Symptom Index (SI >50%) and Symptom Association Probability (SAP >95%). SI and SAP are more reliable when at least three symptom events occur during the test [139]. These parameters can be used only for brief symptoms (such as cough or heartburn), and they are less useful in asthma. SAP "looks" for symptoms 2 minutes before and 2 minutes after the reflux, so identifies both reflux-symptom episodes and symptom-reflux episodes [29]. In patients with extra-esophageal symptoms, MII-pH monitoring showed abnormal

findings in less than 40% of cases, with only 10% having a positive symptom correlation with acid reflux, 30-40% with nonacid reflux and 50-60% had no symptom-reflux correlation at all [150]. The usefulness of the method has been proved in patients with a chronic cough, identifying a high proximal extent of the refluxate, a higher volume clearance and a higher acidic burden in the 15-30 min preceding the cough [151]. Abnormal reflux was found in 69% of these patients (45% acid, 24% nonacid) [152]. However, reflux seems to be a small contributor to cough, as half of the patients have cough-reflux sequence, meaning that the reflux was initiated by the cough and not vice-versa. It is supposed that airway hypersensitivity and a more sensitive cough reflex is the main cause of symptoms in these patients [153].

Despite not having a perfect instrument to diagnose GERD, studies showed that in patients with GERD documented by pH-impedance, surgical treatment is effective in most cases [154]. In addition, AET and the correlation between symptoms and reflux events are predictors of response to anti-reflux therapy [155] at least in patients with typical GERD symptoms. Novel pH-impedance parameters [a low post-reflux swallow-induced peristaltic wave index (PSWSI) or a low mean nocturnal baseline impedance (MNBI)] represent supportive evidence for the presence of GERD [139]. PSWSI and MNBI increase the sensitivity and specificity of pH-impedance monitoring and have a predictive value for response to PPIs [128].

Statement 18. Patients with suspected GERD-induced bronchial asthma should receive a therapeutic test with double-dose proton pump inhibitors for at least 3 months. ***(STATEMENT ENDORSED; overall agreement 97.43%: A+ 58.97% A 38.46% A- 2.56% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

In patients with poor asthma control under conventional treatment and frequent asthma exacerbations, empirical trials with PPI were used for 4-12 weeks with conflicting results. Moreover, a trial of PPI therapy is increasingly being considered as a first-line diagnostic test in those with suspected reflux-related extra-esophageal symptoms [105, 107, 156, 157]. These controversial results are due to different study protocols and populations, due to different end points and also due to the lack of placebo control groups [10].

The outcome in most of the studies was symptomatic improvement at different rates. With double-dose PPIs for 12 weeks, two thirds of the asthmatics reduced their asthma symptoms by nearly 60% [107, 158, 159]. A meta-analysis which included studies comparing asthmatic patients with and without GERD found a greater improvement in peak expiratory flow in asthmatic patients with GERD after empirical PPIs, but did not identify a clinical improvement in these patients [160].

A double-blind trial including 412 asthma patients with poor symptoms control with inhaled corticosteroids and with minimal or no symptoms of typical GERD did not show any improvement in asthma symptoms after empiric double-dose PPIs [98].

The guidelines for the diagnosis and treatment of GERD recommend the therapeutic test with double-dose PPIs for a period of at least 3 months when extra-digestive reflux is suspected in patients who also experience typical GERD manifestations [58, 161].

Statement 19. Patients suspected of GERD-induced CC should receive a therapeutic test with double-dose proton pump inhibitors for at least 3 months. ***(STATEMENT ENDORSED; overall agreement 89.74%: A+ 64.10% A 25.64% A- 10.26% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

Historically, a trial of acid suppressive medication was recommended in the case of patients suffering from suspected GERD-induced CC. However, these recommendations were based mostly on expert opinion and were not supported by substantial scientific evidence [162]. Overall, in these patients, acid suppression using PPIs was proven to aid in healing esophagitis and improving typical symptoms. Unfortunately, the resolution of extraesophageal manifestations is much less predictable [58, 62].

Park et al. [162] published a randomized, placebo-controlled pilot study which included 27 patients with unexplained chronic cough, after excluding subjects with postnasal drip syndrome. They concluded that the empirical use of a standard dose of PPIs for 8 weeks was safe and effective for unexplained chronic cough, irrespective of the presence of gastroesophageal reflux. However, these results should be interpreted keeping in mind the small number of enrolled subjects, which is one of the most important limitations of this study [162].

On the other hand, while accepting the fact that acid suppressive treatment may positively impact patients with GERD-induced chronic cough, the benefits seem to be modest. Herregods et al. [151] showed that a larger volume of refluxate and a longer period of esophageal exposure to reflux were the main factors in inducing cough, while refluxate pH was less relevant. This observation could be the key to understanding the limited efficacy of acid suppressive drugs in placebo-controlled trials [151].

A systematic review published by Kahrilas et al. [163] that included 9 placebo-controlled, randomized clinical trials (RCTs) suggested that the therapeutic benefit of acid-suppressive medication should not be overlooked. However, rigorous patient selection in order to identify potentially responsive populations is of the utmost importance. In order to improve response rates to acid suppressing treatment, they suggest using the methodology of Smith et al. [153] to select only patients with a significant symptom association pattern for cough preceded by acid reflux [163].

In contrast to these findings, a randomised, double-blind, placebo-controlled clinical trial conducted by Shaheen et al. [164] concluded that in patients suffering from CC and minimal or no heartburn, double-dose PPIs administration for 12 weeks did not improve symptoms or health-related QoL.

Statement 20. Patients with suspected respiratory symptoms due to GERD should be referred to a gastroenterologist. ***(STATEMENT ENDORSED; overall agreement 87.18%: A+ 69.23% A 17.95% A- 10.26% D- 2.56% D 0% D+ 0%; level of evidence: low.)***

Extraesophageal manifestations of GERD may lead to significant diagnostic and therapeutic challenge, its management

often requiring a multidisciplinary approach that may include a gastroenterology referral. However, before considering GERD, the work-up of these clinical entities should rule out allergies, malignancy, cardiac and pulmonary causes, as well as possible structural alterations of the pharynx and larynx [165].

There are no solid data regarding the gastroenterology referral. As an advice for best practice, in the case of patients suffering from suspected GERD-induced respiratory symptoms, Vaezi et al. [166] recommend that the initial evaluation should be carried out by the otolaryngology specialist, pulmonologist and/or allergologist, as more often the etiology is not esophageal. Afterwards, the patient could be referred to a gastroenterologist for further investigations in order to assess for gastroesophageal causes of the presenting symptoms.

This algorithm is also supported by Durazzo et al. [10], who note that patients with laryngeal or pulmonary manifestations of GERD are usually seen for the first time by pulmonology and otolaryngology specialists, with a subsequent evaluation in the gastroenterology department.

Patients with suspected GERD-induced respiratory symptoms associated with typical GERD symptoms, due to economic reasons, may start a double-dose PPIs therapeutic trial for 3 months, with the monitoring of pulmonary symptoms and, if possible, of peak expiratory flow rate [58]; however evidence is lacking.

Statement 21. Patients with suspected respiratory symptoms due to GERD should be referred to a gastroenterologist if the therapeutic test with PPIs is inconclusive. ***(STATEMENT ENDORSED; overall agreement 84.61%: A+ 76.92% A 7.69% A- 12.82% D- 2.56% D 0% D+ 0%; level of evidence: low.)***

Solid evidence for referral only after a therapeutic test of patients with suspected respiratory symptoms due to reflux is lacking. If the respiratory manifestations do not improve after a double-dose of PPIs therapeutic trial for 3 months in patients with typical GERD, supplementary evaluation is needed and patients should be referred to a gastroenterologist service in order to confirm the diagnosis [167]. Patients who do not respond to PPIs should be careful evaluated for other causes than GERD and esophageal pH-impedance should be performed to confirm GERD [58].

In the absence of typical GERD manifestations there is no evidence recommending a therapeutic PPIs test before a comprehensive diagnostic work-up, so these patients need a gastroenterologist referral [10, 58, 160].

Statement 22. Patients with respiratory symptoms suspected to be caused by GERD should be evaluated by upper GI endoscopy. ***(STATEMENT ENDORSED; overall agreement 82.05%: A+ 33.33% A 48.72% A- 12.82% D- 2.56% D 0% D+ 2.56%; level of evidence: low.)***

Patients with atypical GERD symptoms usually have a low prevalence of endoscopic esophagitis [168, 169]. A normal upper GI endoscopy is a common finding in patients with GERD-induced respiratory symptoms; only a few have esophagitis or Barrett's epithelium [10]. Moreover, a normal upper GI endoscopy does not rule out the presence of GERD or its involvement in pulmonary abnormalities. Furthermore, the diagnosis of esophagitis does not confirm the relationship between GERD and potential respiratory manifestations.

Therefore, upper GI endoscopy plays a marginal role, and it is not required for the diagnosis of GERD. However, it is mostly performed for evaluation of GERD associated complications and alternative diagnoses [128, 168, 170-172].

Statement 23. Patients with respiratory symptoms suspected to be caused by GERD should be evaluated by upper GI endoscopy only if PPI test is inconclusive. (*STATEMENT NOT ENDORSED; overall agreement 71.80%: A+ 23.08% A 48.72% A- 15.38% D- 10.26% D 2.56% D+ 0%; level of evidence: low.)*

In patients suspected of having GERD-related respiratory symptoms, due to the poor sensitivity of endoscopy and pH monitoring, empiric therapy with PPI is now considered the initial diagnostic step. For those who improve with PPIs, GERD is the presumed etiology, but for those who are unresponsive to such therapy, other diagnostic testing such as MII-pH monitoring may could help to define whether the symptoms are GERD-related or not [128, 170-174].

If an endoscopy is performed, it is recognized that a normal result is a common finding in patients with GERD-induced respiratory symptoms; only a few have esophagitis or Barrett's epithelium. Hence, a normal EGD does not rule out the presence of GERD or its involvement in pulmonary abnormalities. Therefore, upper GI endoscopy is not routinely recommended to be performed in patients who have a failed PPIs test, but may be indicated in patients with symptoms suggestive of complicated GERD or alarm symptoms [10].

Statement 24. The presence of erosive esophagitis (Los Angeles C, D) or Barrett's esophagus in patients with suspected GERD-induced respiratory manifestations does not imply a causal relationship. ***(STATEMENT ENDORSED; overall agreement 89.75%: A+ 61.54% A 28.21% A- 7.69% D- 2.56% D 0% D+ 0%; level of evidence: low.)***

The limited role of upper digestive endoscopy in the diagnosis of suspected GERD-induced respiratory symptoms is due to the fact that while a normal upper GI endoscopy does not rule out GERD or its involvement in the extraesophageal manifestations the presence of esophageal lesions may only suggest not certify GERD as etiology [10, 62, 175, 176]. In addition to this, upper endoscopy can objectively identify GERD only in cases with erosive esophagitis or Barrett's esophagus, but these findings are present in just one third of patients describing reflux symptoms. Moreover, these endoscopic abnormalities are even less common after administering acid-suppressing treatments [58].

Therefore, evidence suggests that pathologic findings at endoscopy have poor predictive value for establishing GERD as the etiology of respiratory symptoms [166] and causal relationship between GERD and respiratory manifestations cannot be demonstrated solely by endoscopic findings of erosive esophagitis or Barrett's esophagus [175].

Statement 25. The absence of esophageal lesions does not exclude GERD in patients with suspected GERD-induced respiratory manifestations. ***(STATEMENT ENDORSED; overall agreement 94.87%: A+ 79.49% A 15.38% A- 5.13% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

The diagnosis of GERD is easily established in the presence of typical symptoms and Los Angeles grade B-D esophagitis at endoscopy, but a normal endoscopy does not exclude GERD [177]. The endoscopy's diagnostic yield is demonstrated to be low, as less than 50% of GERD-induced respiratory symptoms patients have esophagitis [178, 179]. This exam is not capable to demonstrate the causal relationship between pathological acid reflux and respiratory symptoms [175]. GERD-related asthma or CC should not be based solely on upper GI endoscopy [10, 168].

Most patients with CC will have normal endoscopy findings [180]. Baldi et al. [181] considered that upper GI endoscopy should not be included in the diagnostic armamentarium, as he found a very low sensitivity for upper GI endoscopy in patients with reflux cough and he suggested that reflux-induced cough does not correlate well with esophagitis. A Korean study revealed a prevalence of 30% for reflux esophagitis in patients with COPD [182]..

Statement 26. Patients with suspected respiratory symptoms due to GERD should be referred to pH-impedance measurements. ***(STATEMENT NOT ENDORSED, overall agreement 69.23%: A+ 33.33% A 35.90% A- 25.64% D- 5.13% D 0% D+ 0%; level of evidence: moderate.)***

Patients with respiratory symptoms presumed to be determined by GERD often follow a PPIs trial, based on the clinician's symptom assessment. When the diagnosis is uncertain, or treatment fails to improve symptoms, patients should be referred to ambulatory reflux monitoring. Esophageal pH testing is used to confirm pathological gastroesophageal reflux in patients with normal upper GI endoscopy and provides evidence of clinically relevant association between reflux episodes and symptoms. PH-impedance is currently considered the gold standard for GERD diagnosis and should be performed "off" PPIs in unproven GERD, to demonstrate baseline AET [139].

Unexplained CC is one of the most studied extra-esophageal symptoms possibly related with GERD, but reflux seems to be the cause of CC in only one quarter of cases [149]. A high number of patients with presumed reflux-related-CC does not have typical reflux symptoms [149, 183] and in these cases, pH-impedance may be used to identify GERD and to look for the association between reflux episodes and cough. Several studies used 24-hour pH-impedance-pressure monitoring [29, 149, 152] in which pH-impedance and 24-hour manometry recordings were performed simultaneously to identify cough episodes. One study reported that 30% of refluxes were associated with cough bursts and half of those were reflux-cough episodes [29]. Similar results were reported by another study [152]. Twenty [149] to 30% [29] of refluxes that induced cough were weakly acidic or alkaline and would have been missed by pH-monitoring alone. The concomitant use of manometry showed that 40% of cough episodes were not recorded by patients in the diary or on the data logger and in these cases SAP could have been falsely negative [149]. This technique is not routinely used; therefore, patients should be instructed to carefully mark all symptoms in the day of monitoring. A positive SAP for a reflux-induced cough is an independent predictor of response to treatment [184]. Both acid and weakly acid refluxes were associated with cough episodes and the predominance of the latter in some cases could explain the poor response of cough to PPIs therapy.

The role of proximal refluxes in GERD with respiratory symptoms generated numerous discussions. Some studies reported increased number of proximal refluxes and more reflux episodes [185, 186] in patients with GERD with respiratory symptoms compared to GERD without respiratory symptoms, but some studies did not [152]. Also, more pathological distal AET was reported in patients with respiratory symptoms [149]. The abnormal proximal esophageal exposure to reflux in patients with respiratory symptoms (asthma or IPF) was reported by several studies that used hypopharyngeal MII (HMII). HMII uses catheters with impedance electrodes in hypopharynx, at 2 and 4 cm distal to the upper esophageal sphincter and at 3 and 5 cm above the LES and 2 pH probes (in hypopharynx and distal esophagus). Abnormal proximal exposure was reported in 70% of patients with adult-onset-asthma and 1/3rd of events had pH>4 [186]. Proximal reflux [laryngopharyngeal reflux (LPR) or high esophageal reflux] is rare in healthy subjects (≥1 LPR/day or ≥ 5 high esophageal refluxes/day are pathologic) [187, 188].

Komatsu et al. [186] suggested using HMII to select patients with asthma candidates for antireflux surgery. Also, other authors suggested that patients with poorly controlled asthma, frequent episodes of nocturnal respiratory symptoms should be evaluated for acid reflux [189]. Patients with IPF, have high prevalence of GERD (up to 70%) [190-192] and proximal refluxes (54% of cases using HMII) [192]. These findings support the hypothesis of micro- or macro-aspiration of refluxate [29]. Therefore, it is important to identify proximal refluxes and to include them in the final report.

In patients with end stage lung disease, awaiting lung transplantation, pH-impedance should be performed, to identify both acid and weakly acid reflux, because there are studies showing that GERD alters the allograft function and is a risk factor for graft rejection [193].

Statement 27. Esophageal high-resolution manometry (HRM) is useful in the diagnosis of GERD-induced respiratory symptoms. ***(STATEMENT NOT ENDORSED; overall agreement 56.41%: A+ 38.46% A 17.95% A- 20.51% D- 15.38% D 2,.6% D+ 5.13%; level of evidence: moderate.)***

In patients with GERD symptoms, esophageal HRM is performed to establish the precise location of the lower esophageal sphincter for the accurate placement of the pH-(impedance) catheter and for evaluation of the esophageal motor function prior to antireflux surgery. It has only an indirect role in the diagnosis of GERD.

By performing esophageal HRM, the morphology and the vigor of the EGJ, and the integrity and vigor of the contraction of the esophageal body are assessed. In most instances of

symptomatic or documented GERD, the esophageal motor function is normal [194].

In the pathophysiology of GERD, both the EGJ and the esophageal body may be involved. The barrier role of the EGJ is diminished either in the context of a hypotensive LES, or in the situation of the displacement of the LES relative to the crural diaphragm (CD). Type 2 EGJ (separation of < 3 cm between the LES and CD) and type 3 EGJ (separation of > 3 cm between the LES and CD) are indicative of hiatal hernia and EGJ barrier incompetence, with type 3 being correlated with increased reflux severity [195]. A hypotensive LES is also indicative of an insufficient EGJ barrier. A newly described metric which assesses the EGJ efficiency is discussed, the EGJ contractile integral, which more consistently assesses the effectiveness of the EGJ barrier [196]. A combination of low LES basal pressure and hiatal hernia has been correlated with a higher reflux burden [197].

The HRM metric that evaluates the vigor of the contraction of the esophageal body is the distal contractile integral (DCI). In patients with GERD, the HRM evaluation of the esophageal body may elicit intact peristalsis (normal DCI), fragmented peristalsis (peristaltic breaks of ≥ 5 cm in the 20 mm isobaric contour line), ineffective esophageal motility (≥50% of swallows with a low DCI) or absent contractility (all swallows with no distinguishable contraction) [198]. The motor abnormalities of the esophageal body impact the antireflux mechanisms (clearance of the refluxate by the peristaltic wave) and correlate with the severity of GERD [199].

If the esophageal body motor function is abnormal, provocative tests are recommended to evaluate the contraction reserve of the esophagus. The multiple rapid swallow test is such a provocative test, consisting of 5 liquid swallows administered less than 4 seconds apart. A normal response consists of a complete LES relaxation and a post-swallow peristatic contraction that is more vigorous than the mean of previous individual swallows. A low contraction reserve is not necessarily irreversible but has to be taken into consideration if antireflux surgery is planned.

Motor and structural abnormalities of the EGJ as well as motor abnormalities of the esophageal body are both a cause and a consequence of GERD. HRM is the gold standard procedure for the diagnosis of esophageal motor abnormalities, completing the evaluation of GERD patients, with impact on further treatment of GERD, but does not establish a link between GERD and esophageal and extraesophageal symptoms.

Statement 28. PPIs therapy is efficient in treating GERD – induced respiratory symptoms. ***(STATEMENT NOT ENDORSED; overall agreement 56.42%: A+ 28.21% A 28.21% A- 38.46% D- 2.56% D 0% D+ 2.56%; level of evidence: moderate.)***

Statement 28-bis. PPIs therapy could be efficient in treating GERD-induced respiratory symptoms. ***(STATEMENT ENDORSED; overall agreement 100%: A+ 76.92%, A 23.08% A- 0% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

The discovery and introduction into clinical practice of PPIs have changed completely the treatment of GERD and peptic ulcer. However, up to 40% of patients with GERD find only partial or no symptom relief with first-line therapies [200].

There is no consensus about the standard therapy of extra-esophageal manifestations of GERD. Proton pump inhibitors are the most used medication in the suspect of GERD-induced chronic cough. Patients with suspected GERD-related cough should be evaluated first to exclude another cause of CC, prior to starting a trial of PPIs [201]. There are differences between observational studies and data from recent RCTs. Although old studies showed that 70% of patients responded to therapy, data from RCTs suggest that PPIs for patients with CC are not as effective. A recent review from the Cochrane group found that only approximately one third of patients will respond to PPIs [201]. Chan et al. [160], in a meta-analysis of RCTs comparing PPI drugs vs. placebo, evidenced that the efficacy of treatment in patients with GERD-associated cough was present only in a subgroup analysis. Gastroesophageal reflux disease symptoms may be alleviated within 4 to 8 weeks, but the improvement in the cough may take up to 3 months [123].

Proton pump inhibitors treatment of GERD-induced asthma showed an improvement in morning peak expiratory flow rate, but no overall improvement in lung function and asthma symptom scores. Increasing the dose of PPIs or increasing the duration of treatment was not associated with changes in morning peak expiratory flow [10].

There are some rules about PPIs administration. All PPIs should be taken 30 to 60 minutes before a meal except dexlansoprazole, which employs dual delayed-release technology; it can therefore be taken at any time of day [200]. When the standard dose of PPIs is not effective, modification of the lifestyle with PPIs therapy, switching to another PPI, as well as double-dose PPIs, may be effective [201]. Different PPIs formulations (assuming dose equivalent) provide similar rates of symptom relief and healing [202]. The causes of PPI-refractory GERD include adherence, persistent acid, functional disorders, nonacid reflux, and PPIs bioavailability [203]. If respiratory symptoms disappear or improve, PPI therapy should be continued in doses appropriate to control symptoms [204]. Empirical double-dose PPIs therapy is suggested by most guidelines, followed by a MII-pH study in patients who do not respond to PPI [128].

Proton pump inhibitors therapy in extra-esophageal-GERD usually has poor efficacy, especially in the absence of typical symptoms [128].

Statement 29. Baclofen is efficient in treating GERD and GERD induced respiratory symptoms. ***(STATEMENT NOT ENDORSED; overall agreement 56.41%: A+ 12.82% A 43.59% A- 33.33% D- 5.13% D 5.13% D+ 0%; level of evidence: moderate.)***

Baclofen is a g-aminobutyric acid agonist (GABA-b agonist) that reduces the number of reflux episodes by reducing the number of transient LES relaxations. Baclofen was demonstrated to significantly improve GERD-related symptoms [205].

Several studies demonstrated that the neuromodulator Baclofen, as an add-on therapy to the standard anti-reflux therapy, successfully relieved cough in 53–56% of patients with

refractory GERD [206] and showed that 10–20 mg of baclofen three to four times daily for up to four weeks reduced the 24 h esophageal acid and bilirubin reflux [207]. The cough symptom score was reduced at week 2, obviously decreased at week 6 and reached a minimum at week 8 in a small study [208].

It has become the medication of choice for rumination [209]. Compared with placebo, baclofen did not increase the number of severe adverse events in patients with GERD [210].

Baclofen may be a viable option for GERD induced cough unresponsive to PPIs therapy and may be an appropriate therapeutic strategy for the management of refractory GERD but the evidence is from small studies of low and moderate quality [211, 212].

Statement 30. Prokinetic agents are efficient in treating GERD-induced respiratory symptoms. ***(STATEMENT NOT ENDORSED; overall agreement 38.46%: A+ 15.38% A 23.08% A- 33.33% D- 20.51% D 5.13% D+ 2.56%; level of evidence: low.)***

Although data supporting the use of prokinetic agents are scarce, these drugs may play a role in treating GERD-induced respiratory symptoms. They improve the gastric emptying and increase the LES pressure [213, 214].

The role of non-acid reflux in asthmatics who do not respond to PPIs (including bile acids, bile salts and pancreatic enzymes) is also a subject of discussion. Therefore, there is one more benefit from adding a prokinetic drug in the treatment regimen to cover the patients with non-acid reflux [215].

Fifty-eight papers on the topic including prokinetic drugs such as metoclopramide, domperidone, erythromycin, cisapride, mosapride, tegaserod, prucalopride, naronapride were evaluated. However, after eliminating the duplicates and studies available only in abstract, 4 studies were included for full analysis [213-216]. All of them examined the relationship between GERD and asthma. None of them investigated solely the effect of prokinetic agents, but the combination between a prokinetic drug and a PPI. The overall quality of evidence of the gathered data is low (one study with a good design that included a low number of participants and a few with various limitations: participants were aware of their assigned intervention, the intervention included a PPI and the number of participants was too low).

All of the studies had positive results, highlighting that treatment of GERD may reduce the asthma symptoms and the need for rescue medication, along with improvement of pulmonary function tests. Only Bediwy et al. [216] managed to show that adding a prokinetic agent to the standard asthma treatment and PPI can be efficient for GERD-induced respiratory symptoms and besides that, reduction in blood eosinophils and sputum substance P. His study was based on the pediatric population, with a modest number of participants; the effects on the adult patient cannot be extrapolated [216].

Corroborating those mentioned above, we conclude that prokinetic agents may be effective in treating GERD-induced respiratory symptoms.

Statement 31. H2 blockers are inefficient in treating GERD-induced respiratory symptoms. ***(STATEMENT NOT ENDORSED; overall agreement 64.11%: A+ 28.21% A 35.90% A- 30.77% D- 5.13% D 0% D+ 0%; level of evidence: low.)***

We reviewed 13 eligible papers. A recent Cochrane systematic review [103] on 12 RCTs studies the efficacy of GERD treatment in patients with moderate-severe asthma and gastroesophageal reflux. In five trials histamine antagonists proved no significant improvement on forced expiratory volume in the first second, peak expiratory flow, airway hyper-responsiveness, while respiratory symptoms slightly decreased in 2 studies [217, 218]. Nocturnal asthma symptoms tended to insignificantly ameliorate after treatment with H2 blockers [217, 219, 220]. In a double-blind, cross-over trial on 37 children, a modest reduction (30%) of nocturnal asthma symptoms after ranitidine was reported [219]. A slight positive effect on daily usage of bronchodilators was showed as well [217]. Two studies reported a reduction of wheezing [218].

In pediatric population with asthma and GERD, research suggested the lack of benefit from treating children over 1 year old for asthma symptoms with H2 antagonist [221]. The findings are consistent with another result from a prospective study in children with moderate-persistent asthmatic symptoms; 14/44 children that switched from esomeprazole to ranitidine required more re-hospitalizations for asthma exacerbation and experienced more exacerbations per patient (2.2) over half a year ($p<0.05$) than the group who continued the PPIs medication (0.33) and the control group (0.77) [214]. Similarly, another study comparing the PPIs with H2 blockers showed that ranitidine, in contrast to PPIs, did not significantly improve peak expiratory flow and asthma control questionnaire scores ($p<0.05$) [159].

A long term prospective RCT on 62 patients, of whom 22 received ranitidine 150 mg t.i.d indicates that after 24 months, improvement in the asthma status occurred in almost 10% of the H2 blockers group, but adversely, the symptoms worsened in almost one-third [222].

There is a scarcity of controlled studies in the assessment of H2 blockers effect on GERD's CC. Ing et al. attributed fewer than 25% of therapeutic gain to ranitidine (150 mg daily, 8 weeks) in cough change, which is subjectively recorded in patients' diaries [223].

A large, multicenter, COPD gene study established that in patients receiving H2 antagonists for GERD treatment (6,5%) decline of pulmonary function was faster than placebo patients. Both diseases coexist without a correlation between GERD symptoms and COPD [224]. Similar to this trial, an interventional pharmacological study emphasized a statistically non-significant decrease in pulmonary tests in H2 antagonist treated COPD patients [225].

Regarding IPF, data from 3 RCTs indicate a smaller decrease in FVC in patients who are taking H2 blockers than in the control group. However, the analysis is limited by the small number of participants taking H2 antagonist (11/480) [226].

Summarizing, there is not sufficient evidence to infer the benefit of H2 blockers in treating GERD - induced respiratory symptoms.

Statement 32. GERD endoscopic antireflux technics are efficient in treating GERD – induced respiratory symptoms. ***(STATEMENT NOT ENDORSED; overall agreement 25.64%: A+ 15.38% A 10.26% A- 64.10% D- 5.13% D 5.13% D+ 0%; level of evidence: moderate.)***

In an attempt to by-pass the invasiveness, higher costs and inherent risks of anti-reflux surgery, a series of endoscopic techniques were developed in order to treat GERD and its secondary respiratory symptoms in a selected group of patients [227]. Possible contraindications for the minimally invasive approach are considered to be: Los Angeles esophagitis grade of C or higher, the presence of any severe anatomic distortion (large hiatal hernias, severe esophageal dysmotility), effectiveness of PPIs treatment [228].

Among these, the delivery of radiofrequency energy to the muscle layer of the LES and the cardia by means of the Stretta device (Mederi Therapeutics, Norwalk, CT, USA) is believed to cause hypertrophy of the muscularis propria and to reduce transient LES relaxations. This technique is associated with long-term follow-up data and evidence of durable response when analyzing parameters such as the GERD health-related quality of life (GERD-HRQoL) score, the reduction in PPIs use and regression of Barrett's metaplasia [225, 226]. Two prospective observational studies performed on patients with GERD related respiratory symptoms who underwent radiofrequency ablation revealed a significant clinical improvement and a reduction in PPIs usage [227, 228]. However, when comparing Stretta to laparoscopic Toupet fundoplication, a more significant effect in the control of GERD respiratory symptoms and a lower recurrence rate was observed in the latter group of patients [185].

Transoral incisionless fundoplication is a minimally invasive procedure that uses the EsophyX device (EndoGastric Solutions, Redmond, WA) and builds on the basics of surgical fundoplication: through direct visualization of the gastric cardia and gastroesophageal junction and the use of non-absorbable polypropylene fasteners, the stomach is wrapped around the lower esophagus, resulting in a 200°–300° partial fundoplication with a valve in length of 3-5 cm [228]. A retrospective study evaluating the persistence of laryngopharyngeal reflux induced symptoms following the transoral incisionless fundoplication procedure, reported a clinically significant improvement and a reduction in PPIs administration [230].

Other minimally invasive techniques, such as the Medigus ultrasonic surgical endostapler, the endoscopic full thickness plication and the anti-reflux mucosectomy, have been developed. However, at the moment, the literature lacks sufficient data on the devices' effect on GERD induced respiratory symptoms. Further studies need to be conducted in order to fully support their efficiency [227].

Statement 33. Laparoscopic Nissen fundoplication (LNF) is efficient in treating GERD-induced respiratory symptoms. ***(STATEMENT NOT ENDORSED; overall agreement 46.15%: A+ 15.38% A 30.77% A- 25.64% D- 25.64% D 0% D+ 2.56%; level of evidence: moderate.)***

Statement 33-bis. Laparoscopic Nissen fundoplication could be efficient in treating GERD-induced respiratory symptoms. ***(STATEMENT ENDORSED; overall agreement 92.3%: A+ 76.92% A 15.38% A- 7.69% D- 0% D 0% D+ 0%; level of evidence: moderate.)***

After careful evaluation of papers and exclusion of the articles available only in abstract, only 5 papers were eligible for critical review- one of which was a systematic review.

The studies showed an overall amelioration of respiratory symptoms after LNF in patients who had persistent GERD despite anti-secretory medical treatment. Most patients had a significant improvement in cough, followed by hoarseness and asthma symptom score [222, 231, 232]. There was a study that did not prove the benefit of LNF; however, given the small group of patients and the lack of randomization, we cannot extrapolate [233].

Based on the correlation GERD-respiratory symptoms, Sontang et al. [222] conducted a RCT in a small group of patients with asthma and GERD, demonstrating a significant improvement in asthma symptoms in the LNF group compared to medical and placebo groups.

A systematic review and meta-analysis including 3,869 patients published by Tustumi et al. [234] analysed the effect of different techniques of anti-reflux surgery on GERD- induced respiratory symptoms (44% studies included for meta-analysis used LNF). Overall, 88.4% of patients reported complete resolution or the improvement of the cough; also hoarseness and wheezing as well as the corticosteroid dependence was improved [234].

In conclusion, in selected patients with persistent GERD and respiratory symptoms, in absence of other causes, LNF may improve not only the typical symptoms as is already known, but also the "atypical" symptoms such as the cough.

Statement 34. GERD-induced respiratory symptoms patients have a low quality of life. ***(STATEMENT ENDORSED; overall agreement 97.44%: A+ 84.62% A 12.82% A- 2.56% D- 0% D 0% D+ 0%; level of evidence: high.)***

Quality of Life is a complex and broad concept. Recently a more specific and appropriate term, HRQoL is used related to QoL. It can be defined as the patients' subjective perception of the impact of their disease in daily life, psychological, physical, and social functioning and well-being [234, 235].

The relationship between GERD and respiratory symptoms is frequently difficult to establish and sometimes, the typical digestive syndrome could be absent ("silent GERD") [129, 234, 235].

The medical literature search on the QoL of patients with GERD-related respiratory symptoms did not reveal any articles and no HRQoL instruments capture the disease-respiratory specific symptoms of GERD. Only a few articles searched specific asthma and GERD, or CC QoL, COPD, bronchiectasis, sleep apnea or IPF. The severity of these reflux-related disorders (cough, asthma, laryngitis) is well correlated with a significant negative impact on normal daily activity [129, 236-238]. Chronic cough is a common condition that has a significant impact on HRQoL [238, 239].

Gastroesophageal reflux disease frequently accompanies poorly controlled asthma and was associated with significantly worse asthma QoL; 24-62% of patients with asthma have clinically silent GERD and several studies suggested that treatment with PPIs improved asthma QoL questionnaire scores and decreased asthma exacerbations [103, 240].

Numerous studies have reported associations with reflux disease and COPD severity, particularly in relation to increased exacerbations and hospitalisations and reduced QoL in comparison with those with COPD alone [128, 241].

Several studies have shown that PPIs can be of help in improving lung function, reducing the decline of pulmonary functional tests, diminishing the rate of exacerbation of the IPF and improving the disease prognosis [242, 243].

For the evaluation of HRQoL of patients with respiratory simptoms relatead GERD there is a need for a new tool for the assessment, that should should be internationally valid, reliable and responsive. Future studies are required to determine an effective therapy to alleviate these debilitating symptom and to improve overall quality of life for patients suffering from GERD.

RECOMMENDATIONS

The experts' recommendations based on the statements endorsed after voting are presented in Table III.

Pathophysiology (statements 1-5)

The consensus recognized that GERD may be a cause for bronchial asthma and CC. Multiple studies showed that the presence of GERD is associated with higher risk for bronchial asthma and CC. Also, experimental studies showed that cough and bronchoconstriction may be induced by distal esophageal perfusion of acid or saline. However, these experimental studies include small numbers of patients.

Table III. The endorsed statements with grade the of evidence

Statement	Grade of evidence
Pathophysiology	
1. GERD may cause bronchial asthma.	B
2. GERD may cause CC.	B
3. GERD may cause respiratory symptoms in an important number of patients.	A
4. GERD may cause respiratory symptoms due to micro-aspiration of refluxed gastric content in the respiratory tract.	C
5. GERD may cause respiratory symptoms due to vagal-mediated tracheobronchial reflex.	C
Diagnosis	
6. GERD should be suspected as a causative factor in non-allergic asthma with adult onset after exclusion of other potential causes.	C
7. GERD should be suspected in patients with suboptimal controlled bronchial asthma.	B
8. Nocturnal refractory cough is suggestive for GERD.	A
9. GERD-induced CC should be suspected in patients presenting with unexplained cough after standard thoracic imaging investigations (chest x-ray, pulmonary computed tomography) that do not identify a pulmonary cause.	B
10. The presence of typical GERD symptoms in a patient with respiratory manifestations may suggest GERD as the etiology but does not establish a causal relationship.	B
11. Typical GERD symptomatology is lacking in the majority of patients presenting with respiratory manifestations.	A
12. No single testing methodology exists to definitively identify GERD as the etiology for the suspected extra-esophageal symptoms.	B
13. Patients with suspected GERD-induced bronchial asthma should receive a therapeutic test with double-dose PPIs for at least 3 months.	B
14. Patients suspected of GERD-induced chronic cough should receive a therapeutic test with double-dose PPIs for at least 3 months.	B
15. Patients with suspected respiratory symptoms due to GERD should be referred to a gastroenterologist.	C
16. Patients with suspected respiratory symptoms due to GERD should be referred to a gastroenterologist if the therapeutic test with PPIs is inconclusive.	C
17. Patients with suspected respiratory symptoms due to GERD should be evaluated by upper digestive endoscopy.	C
18. The presence of erosive esophagitis (Los Angeles C, D) or Barrett's esophagus in patients with suspected GERD-induced respiratory manifestations does not imply a causal relationship.	C
19. The absence of esophageal lesions does not exclude GERD in patients with suspected GERD-induced respiratory manifestations.	B
Treatment	
20. PPIs therapy could be efficient in treating GERD-induced respiratory symptoms.	C
21. Laparoscopic Nissen fundoplication could be efficient in treating GERD-induced respiratory symptoms.	C
Quality of life	
22. GERD-induced respiratory symptoms patients have a low QoL	A

CC: chronic cough; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; QoL: quality of life.

There is some moderate evidence that GERD may also cause IPF, OSAHS, COPD, cystic fibrosis, bronchiectasis and aspiration pneumonia. The experts did not find enough evidence for the endorsement of a clear causal relationship between GERD and these respiratory diseases. Also, there is evidence that several respiratory conditions may vice-versa cause GERD. The experts did not endorse these statements, noting that this area needs further research.

Several studies revealing the presence of bile and pepsin in bronchopulmonary lavage and sputum suggested that one of the mechanisms involved in pathogenesis of GERD-related respiratory symptoms is micro-aspiration. Despite the low to moderate level of evidence, experts endorsed the statement linking micro-aspiration to respiratory symptoms. In addition to this, there is evidence supporting another mechanism that may explain the occurrence of respiratory symptoms in GERD patients. Recent data showed that the vagal-mediated tracheobronchial reflex may also explain the respiratory symptomatology and this statement was also agreed upon by the expert panel.

Diagnosis (statements 6-19)

Diagnosis of respiratory conditions secondary to GERD is recognized to be difficult. A presumed GERD is diagnosed and treated based only on the presence of heartburn and/or regurgitation. Several guidelines accept GERD management only on a presumed GERD diagnosis in the absence of alarm symptoms. The final GERD diagnosis should be based on digestive investigations. This includes GI endoscopy evidencing esophagitis Los Angeles C or D, or Barrett esophagus and/or esophageal pH/impedance measurements. However, to establish a clear causal relationship between GERD and concomitant respiratory conditions is a difficult task in daily practice. Our expert's opinion highlights this condition.

Patients with respiratory complaints are frequently uncounted in daily practice. It is recognized that all patients with respiratory conditions such as bronchial asthma, CC pulmonary fibrosis, OSAHS, COPD, cystic fibrosis, bronchiectasis and aspiration pneumonia should be investigated to evidence the cause of the disease. This process is not always straightforward.

According to our consensus, in non-allergic adult patients after exclusion of other potential causes and also in patients with suboptimal control or nocturnal symptoms, GERD should be considered as a potential cause. Furthermore, GERD should be considered in patients with a nocturnal refractory cough. It was not the intention of our consensus to investigate in detail the experts' opinion on other multiple respiratory conditions that may occur in daily practice or to give recommendations on these.

We recognize that the management of respiratory diseases in patients with presumed GERD is far more complex and is not limited to conditions included in our paper.

Our consensus highlights those respiratory diseases that should be investigated by the pneumologist as extensively as possible before considering GERD as a possible cause. The reasons behind this statement are: a) presence of GERD symptoms does not mean that GERD is the cause for the respiratory condition; b) many patients with GERD-induced respiratory conditions do not have any GERD symptoms and also c) there is no single investigation that may clearly identify GERD as a cause for the respiratory conditions.

Another diagnostic tool to investigate GERD as the cause for respiratory conditions is the therapeutic test with double dose PPIs. This therapeutic trial is recommended by our experts. However, this test is not perfect, as it works retrospectively and needs a period of 90 days to have the results.

PH-impedance measurements is recognized as the gold standard for diagnosis GERD. Even majority of experts considered pH–impedance useful in patients with respiratory induced symptoms, they did not endorse the compulsory pH-impedance testing. One may speculate that a reason may be the lack of local availability.

Treatment (statements 20-21)

As mentioned before, diagnosis of GERD-induced respiratory diseases is difficult. The therapy of these respiratory conditions is also challenging. The experts' opinion on treatment is clearly highlighting this condition. The statement referring if PPIs is efficient in treating GERD-induced respiratory symptoms did not reach the endorsement agreement and had to be re-voted in a different format. Our guideline recommends using PPIs therapy but the endorsement recognized a limited efficacy.

The therapy with H2 blockers, a less efficient medication than PPI is not endorsed for these patients.

Baclofen may be a viable option in GERD-induced cough unresponsive to PPIs and was also used with some success as add-on therapy to PPIs. However, local experience with Baclofen is limited. The experts did not endorse Baclofen therapy.

Treatment with prokinetics was also not endorsed by the experts. The medical literature review evidenced that this medication may be effective in some patients who do not respond to PPIs. The local availability of this medication is limited to Metoclopramide and Domperidone, also limiting the experts' personal experience.

Surgical procedures such as LNF are currently used for refractory GERD. Many papers including systematic reviews show that the LNF may improve not only typical GERD symptoms, but also atypical symptoms such as cough and bronchial asthma. Our recommendations also highlight that this surgical procedure may be efficient in some patients.

Quality of life (statement 22)

The panel recognized that respiratory symptoms due to GERD affect an important number of patients and this may have an impact on their quality of life. Several papers and systematic reviews from different geographical areas highlight that chronic cough and bronchial asthma due to GERD are present in an important number of patients and also is decreasing their quality of life.

Conflicts of interest: None to declare.

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Authors' contribution: V.L.D, S.A. and D.L.D suggested the guidelines, designed the structure and methodology, identified co-authors and revised the text. O.B.B and D. I. checked all the references, finalized the voting process and revised the text. All authors contributed to the writing of the manuscript, to the elaboration of statements and recommendations, voted them and approved the final version of the text.

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