

## Gastroesophageal reflux disease: diagnosis

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### AUTHORS

Federação Brasileira de Gastroenterologia, Sociedade Brasileira de Endoscopia Digestiva, Colégio Brasileiro de Cirurgia Digestiva, Sociedade Brasileira de Pneumologia e Tisiologia.

### PARTICIPANTS

Aloisio Carvalhaes, Angelo Paulo Ferrari Júnior, Antonio Frederico Magalhães, Ary Nasy, Celso Mirra Paula e Silva, Cláudio L. Hashimoto, Décio Chinzon, Edson Pedro da Silva, Eduardo G. H. Moura, Eponina Maria Oliveira Lemme, Farid Butros Iunan Nader, Fauze Maluf Filho, Gerson R. de Souza Domingues, Igelmair Barreto, Isac Jorge Filho, Ismael Maguilnik, Ivan Ceconello, Jaime Natan Eisig, Joaquim Prado P. de Moraes-Filho, Joffre Rezende Filho, José Carlos Del Grande, José Luiz Pimenta Modena, José Roberto Almeida, Lillian R. O. Aprile, Luciana Camacho-Lobato, Luciana Dias Moretzohn, Marcelo de Souza Cury, Marcio Matheus Tolentino, Marco Aurelio Santo, Marcos Kleiner, Marcus Túlio Haddad, Maria do Carmo Friche Passos, Olavo Mion, Osvaldo Malafaia, Paulo Roberto Savassi Rocha, Rafael Stelmach, Ricardo Aires Correa, Ricardo Correa Barbuti, Richard Gursky, Rimon Sobhi Azzam, Roberto El Ibrahim, Rubéns Antonio Aissar Sallum, Roberto Oliveira Dantas, Schiloma Zaterka, Sérgio Gabriel Silva de Barros, Tomas Navarro Rodriguez, Ulysses G. Meneghelli, Wilson Modesto Polara, Grupo de Esôfago e Motilidade da Disciplina de Gastroenterologia Clínica do Departamento de Gastroenterologia da FMUSP, Sociedade Brasileira de Motilidade Digestiva

### FINAL VERSION

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### CONFLICT OF INTEREST

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### DESCRIPTION OF THE EVIDENCE COLLECTION METHOD

A search was performed in the databases EMBASE, SciELO/LILACS, PubMed/MEDLINE, and Cochrane Library using the following words: signs, symptoms, endoscopy, gastroesophageal reflux, GERD, heartburn, NERD, GERD, esophagus, hydrogen-ion concentration, esophageal pH monitoring, ion-selective electrodes, bravo, capsules, capsule endoscopy, electric impedance, extra-esophageal, asthma, atypical symptoms, chest pain, cough, globus sensations, hoarseness, otorhinolaryngologic diseases, pain, respiratory tract diseases, laryngitis, vomiting, biopsy, histology, dilatation\*, DIS, intercellular, space\*, endosonographies, echo, echo endoscopies, endoscopies, ultrasonic endoscopy, echo-endoscopy, echo endoscopy, echo-endoscopies, ultrasonic, ultrasonic endoscopies, ultrasonography, endoscopic, endoscopic ultrasonography, endoscopic ultrasonographies, ultrasonographies, endoscopic, endosonography, sonography, pulmonary fibrosis, sleep disorders. About 12,000 publications were retrieved using the filters: humans, sensitivity\*, sensitivity and specificity, diagnosis\*, diagnosis, diagnostic, diagnosis, differential, randomized controlled trial, randomized AND controlled AND trial, clinical AND trial, clinical trials, random\*, random allocation, therapeutic use, epidemiologic methods, relative AND risk\*, relative risk, risks, cohort studies, cohort AND study\*, prognosis\*, first AND episode, cohort. Fifty-one studies were selected to support this Guideline, which conferred the degree of recommendation A or B. These recommendations were adapted to our scenario. Experts representing major Brazilian universities including clinical gastroenterologists, digestive surgeons, pathologists, endoscopists, otolaryngologists and pulmonologists attended the meetings to discuss and set these guidelines.

### DEGREE OF RECOMMENDATION AND STRENGTH OF THE EVIDENCE

- A:** Experimental or observational studies of higher consistency.
- B:** Experimental or observational studies of lower consistency.
- C:** Case reports (non-controlled trials).
- D:** Opinion without critical evaluation, based on consensus, physiological studies, or animal models.

## OBJECTIVES

Due to the high prevalence of gastroesophageal reflux disease (GERD), differences in the form of clinical presentation, economic impact, consequences of impaired quality of life, and cost of clinical and laboratory research, international consensus meetings have been encouraged.

On the other hand, the diagnostic and therapeutic management of GERD has varied from center to center, which is an important factor in the search for scientific evidence on the subject and served as motivation for the development of this Guideline, which seeks to answer 14 questions relevant to the clinical diagnosis of GERD.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common disorders in medical practice. Under the same designation, the disease presents distinct clinical conditions such as occasional heartburn, chronic cough, and refractory asthma. As for diagnosis, the endoscopic conditions are very diverse, ranging from the absence of injury to the presence of major complications such as Barrett's esophagus.

GERD is a chronic condition resulting from the retrograde flow from part of gastroduodenal contents into the esophagus and/or organs adjacent to it, resulting in a variable spectrum of esophageal/extra-esophageal signs and/or symptoms, with or without tissue damage.

### 1. SHOULD ADULT PATIENTS WITH GERD MANIFESTATIONS (HEARTBURN AND/OR REGURGITATION), WITHOUT SYMPTOMS OR WARNING SIGNS (WEIGHT LOSS, BLEEDING, SORE THROAT, DYSPHAGIA ETC.) BE SUBMITTED TO UPPER DIGESTIVE ENDOSCOPY (UDE) BEFORE TREATMENT?

In patients with a mean age of 45 years, the presence of heartburn and heartburn symptoms increases the risk for diagnosis of GERD, odds ratio (OR): 1.9 (1.3 to 2.7) and 1.6 (1.0 to 2.4), respectively. And the presence of abdominal pain, chest pain, and nausea symptoms reduces the risk for diagnosis of GERD, OR: 0.6 (0.4 to 0.9); 0.5 (0.3 to 0.8); and 0.7 (0.4 to 0.9), respectively (A)<sup>1</sup>.

In patients with a mean age of 54 years, the presence of pyrosis (or heartburn) symptom has a sensitivity of 67%, specificity 77%, and positive likelihood ratio of 2.83 in the diagnosis of GERD. And the absence of pyrosis (or heartburn) symptom has a sensitivity of 33%, specificity of 24%, and negative likelihood ratio of 0.44 to exclude the diagnosis of GERD (A)<sup>2</sup>.

The use of the reflux disease questionnaire (RDQ) in patients with a mean age of 41 years, with symptoms of GERD, provides a sensitivity of 87.5% and specificity of 75.7%: positive likelihood ratio of 3.6 for diagnosis of GERD and negative ratio of 0.16 to exclude the diagnosis (A)<sup>3</sup>.

In patients with a mean age of 42 years and symptoms of GERD, the use of scale with seven symptoms, compared to EGD, provides sensitivity, specificity, likelihood ratio of 74.3%, 71.6%, 2.61, and 0.36, respectively (A)<sup>4</sup>.

Symptomatic response after four weeks of empirical treatment with esomeprazole 40 mg (86.4%) in patients with GERD is equivalent to the treatment preceded by UDE (87.5%). Similarly, after maintenance treatment with esomeprazole 20 mg (24 weeks), a similar proportion of patients remained responsive (71.8% versus 68.3%), respectively (A)<sup>5</sup>.

## RECOMMENDATION

In populations with GERD prevalence of 12% to 25%, the presence of heartburn and regurgitation symptoms increases the diagnostic confirmation to about 40%. The upper digestive endoscopy does not alter the clinical course when compared to empirical treatment.

### 2. PATIENTS WITH TYPICAL SYMPTOMS AND FREQUENCY GREATER THAN TWICE A WEEK FOR A PERIOD OF NOT LESS THAN FOUR WEEKS WITH NORMAL UPPER DIGESTIVE ENDOSCOPY TEST; IS IT GERD?

In patients (mean age 47 years) with symptoms of GERD and negative UDE, the score of symptoms classified as moderate and severe does not identify GERD patients; sensitivity of 82%, specificity of 22%, positive likelihood ratio of 1.05, and negative ratio of 0.81. And the test with lansoprazole 60 mg daily for seven days in the diagnosis of GERD gives a sensitivity of 97%, specificity of 6%, positive likelihood ratio of 1.03, and negative ratio of 0.03 (A)<sup>6</sup>.

The use of RDQ in patients with a mean age of 41 years with symptoms of GERD provides a sensitivity of 87.5%, specificity of 75.7%, with positive likelihood ratio of 3.6 for diagnosis of GERD and negative ratio of 0.16 to exclude the diagnosis (A)<sup>3</sup>.

## RECOMMENDATION

In patients with non-erosive GERD, with 20% prevalence, the use of symptom score (severe or moderate) increases the diagnostic certainty by up to 40%.

### 3. SHOULD PATIENTS WITH HEARTBURN AND UPPER DIGESTIVE ENDOSCOPY SHOWING NO EROSIONS BE SUBMITTED TO ESOPHAGEAL pH MONITORING TO CONFIRM THE DIAGNOSIS?

In patients with upper gastrointestinal endoscopy without esophageal erosions, with typical symptoms of reflux, mean age 34.4 years, the esophageal pH-metry using a cut-off value of 4.5% of total time with pH < 4 during a 24-hour period has a specificity of 90.4% and sensitivity of 93.3%, with positive likelihood ratio of 9.7 for diagnosis of GERD and negative ratio of 0.07 to rule out the diagnosis (A)<sup>7</sup>.

## RECOMMENDATION

In patients with GERD symptoms and UDE without esophageal erosions, therefore, with pretest probability of about 50%, an abnormal esophageal pH-metry defines the diagnosis of GERD with 90% certainty, and if normal, it rules out the diagnosis with certainty of about 95%.

#### 4. IS THE WIRELESS CAPSULE FOR ESOPHAGEAL pH REGISTRATION BETTER THAN CONVENTIONAL ESOPHAGEAL pH MONITORING FOR THE DIAGNOSIS OF GERD?

Patients in the study of wireless capsule for esophageal pH registration had less discomfort than those who underwent conventional esophageal pH-metry, with 73% and 97%, respectively, reporting some discomfort by the end of monitoring; absolute risk reduction (ARR): 24% – the number needed to treat (NNT): 4%, 23%, and 45%, respectively, reporting a lot of discomfort (ARR = 22% – NNT = 5). Patients monitored by wireless capsule for esophageal pH registration had less interference in daily activities, sleep, and work than the conventional pH-metry, with 14% and 82%, respectively, showing an impact on work (ARR: 68% – NNT: 1) (B)<sup>8</sup>.

On average, the adverse effects were significantly lower in patients of wireless capsule for esophageal pH monitoring than in conventional pH-metry, as well as in physical activities and daily work. The mean number of reflux episodes with less than 5 minutes recorded by conventional pH-metry (n = 129) was two times higher than the wireless capsule for esophageal pH monitoring (n = 53). The abnormal test rates were considered similar: wireless capsule for esophageal pH monitoring (68%) and conventional pH-metry (71%) (B)<sup>9</sup>.

In the study of conventional pH-metry and wireless capsule for esophageal pH monitoring to diagnose GERD using cut-off value for esophageal acid exposure of 2.9%, the estimated number of patients with GERD was similar, 42.4% and 39.3% in 24 hours and 60.0% in 48 hours, respectively. In the first 24 hours, the number of recorded events was significantly higher in the conventional pH-metry (n = 40) than in the wireless capsule (n = 23) (B)<sup>10</sup>.

## RECOMMENDATION

In GERD patients, the use of wireless capsule for pH monitoring, when compared to conventional pH-metry, has the following benefits: less discomfort (NNT 4), less interference with work activities (NNT 1), daily activities, and sleep activities. However, the conventional pH-metry accounts for about two times more reflux episodes in 24 hours. The rates of abnormal tests considered are similar. However, in our area, this diagnostic method is not widely available.

#### 5. SHOULD ALL PATIENTS WITH ATYPICAL MANIFESTATION BE REFERRED TO PERFORM ESOPHAGEAL pH-METRY?

The sensitivity and specificity of esophageal pH-metry to

diagnose GERD in patients with a mean age of 55 years, with history of retrosternal discomfort, non-cardiac, and without heartburn or regurgitation are 33.0% and 24.0%, respectively. The positive likelihood ratio for GERD diagnosis in these patients is 0.43 and the negative is 2.79 (A)<sup>2</sup>.

The prevalence GERD (diagnosed by UDE, esophageal pH-metry, and impedance) in patients with atypical symptoms (hoarseness, chronic cough, and globus) is 63.4%, and the diagnosis in these patients using pH-metry is 46.3%; impedance 48.8%, and the association of the two methods is 61.0% (B)<sup>11</sup>.

Analysis of patients with chronic cough, mean age 56 years, using impedance/pH-metry and pH-metry revealed that most episodes (69.4%) occur regardless of reflux. Of the 30.6% episodes associated with reflux, only 15.0% (the cough) are preceded by GERD, which is 65.0% acid, 29% weakly acid, and 6.0% alkaline. Moreover, analysis of patients showed that sensitivity and specificity of pH-metry and/or diagnostic symptoms of GERD, compared with the calculation of symptom association probability (SAP), is 71.0% and 37.0%, respectively, with positive likelihood ratio of 1.1 and negative of 0.78 (B)<sup>12</sup>.

In patients with atypical symptoms (chronic cough) and esophageal pH-metry altered for acid reflux (56.2%), the treatment with omeprazole 40 mg daily for eight weeks resulted in partial response rate of 40.8% and non-response of 55.1%. Among patients diagnosed with GERD and receiving no treatment, 54.5% had complete resolution of cough at the long-term follow-up (30 months). There was no significant difference in the association of reflux with cough in patients who responded and who did not respond to treatment (B)<sup>13</sup>.

Suspected GERD in patients (40 years old) with otorhinolaryngological symptoms (globus sensation, chronic cough, dysphonia, or sore throat) may be investigated with two-channel pH-metry system and compared with patients with typical symptoms. In patients with atypical symptoms, the analysis by proximal sensor showed a significant difference, with a higher number of refluxes and percentage of time with pH < 4, while the distal sensor analysis showed no difference in rates of reflux. In proximal sensor analysis, the proportion of patients with GERD with or without atypical symptoms is 61% and 22%, respectively (B)<sup>14</sup>.

In distribution of typical and atypical symptoms of 27% and 73%, respectively, patients with typical symptoms have higher rates of symptoms (48%) in pH-metry associated with impedance than patients with atypical symptoms (25%) (B)<sup>15</sup>.

In the investigation of patients with symptoms of GERD diagnosed by pH-metry and impedance, the acid reflux is more associated with patients with typical symptoms and non-acid reflux is more associated with patients with atypical symptoms (B)<sup>16</sup>.

The esophageal pH-metry diagnostic test sensitivity (91%) and specificity (82%) can be increased in conditions in which the selected population of patients with GERD is responsive to treatment compared to nonresponsive. However, it is known that the correlation between response and positive pH-metry is high (true + high) and that many patients with atypical symptoms and negative pH-metry would be positive to the impedance (false - high) (B)<sup>17</sup>.

Whereas:

1. Most atypical episodes occur regardless of reflux. In 15.0% of cases, the cough is preceded by reflux;
2. The use of conventional esophageal pH-metry in patients with chest pain of noncardiac origin has no value in GERD diagnosis;
3. Patients with chronic cough with normal or altered pH-metry may have the same therapeutic result;
4. The presence of non-acid or weakly acid reflux diagnosed by impedance/pH-metry is high and more prevalent in patients (adults = 35%) with atypical symptoms (globus sensation, chronic cough, dysphonia, or sore throat) than in patients with typical symptoms.

#### RECOMMENDATION

Conventional pH-metry in patients with atypical symptoms does not contribute to the diagnosis of GERD, despite increasing the number of diagnoses when used with dual channel.

#### 6. IN PATIENTS WITH ATYPICAL SYMPTOMS, WHAT IS THE CONTRIBUTION OF ESOPHAGEAL IMPEDANCE/pH-METRY?

In the investigation of patients with GERD symptoms using pH-metry and impedance, the acid reflux is more associated with patients with typical symptoms and non-acid reflux with patients with atypical symptoms (B)<sup>16</sup>.

In the detection of acid reflux, the pH-metry compared with the impedance/pH-metry association (gold standard) has 68% specificity on the criterion pH < 4, and 67% when the criterion is the index of symptoms. The percentage of pH < 4 was significantly higher in pH-metry than in the impedance/pH-metry association. In the detection of weakly acid reflux, the pH-metry has a sensibility of 28% when compared with the association of methods, with an 83% rate of false-positive results (A)<sup>18</sup>.

The prevalence of GERD (diagnosed by UDE, pH-metry, and impedance) in patients with atypical symptoms (hoarseness, chronic cough and globus) is 63.4%, and the diagnosis in these patients by pH-metry is 46.3%, impedance 48.8%, and the two associated methods 61.0% (B)<sup>11</sup>.

Analysis of patients with chronic cough, mean age 56 years, using impedance/pH-metry revealed that most episodes (69.4%) occur regardless of reflux. Of the 30.6% episodes associated with reflux, only 15.0% (the cough) are preceded by GERD, which is 65.0% acid, 29% weakly acid,

and 6.0% alkaline. Moreover, analysis of patients showed that sensitivity and specificity of pH-metry and/or diagnostic symptoms of GERD, compared with the calculation of symptom association probability (SAP), is 71.0% and 37.0%, respectively, with positive likelihood ratio of 1.1 and negative of 0.78 (B)<sup>12</sup>.

Whereas:

1. The non-acid or weakly acid reflux is more associated with atypical symptoms;
2. The prevalence of non-acid reflux or weakly acid is 35%;
3. The use of pH monitoring does not diagnose non-acid reflux.

#### RECOMMENDATION

In patients with atypical symptoms, the impedance/pH-metry can contribute to the diagnosis of GERD.

#### 7. SHOULD PATIENTS WITH REFRACTORY GERD BE SUBMITTED TO ESOPHAGEAL BIOPSY?

The one-year follow-up of patients with erosive GERD undergoing treatment with proton-pump inhibitor (PPI) (eight weeks of treatment with lansoprazole 30 mg/day, followed by long-term treatment with lansoprazole 15 to 30 mg/day or omeprazole 20 mg/day) revealed through esophageal biopsy that there is a decrease of 51% to 2% in high-grade hyperplasia of basal lamina, and an increase of 8% to 63% in the number of normal epithelium (B)<sup>19</sup>.

In patients with GERD submitted to UDE during follow-up treatment with PPI for 90 days, presenting incomplete epithelial recovery correlated with sporadic symptoms, the treatment with PPI may be extended, increasing the response, also correlated with recovery of the esophageal dilatation of the intercellular space (B)<sup>20</sup>.

Despite treatment with PPI, 25% of patients with non-erosive GERD progress to erosive in two years, grades A and B, according to the classification of Los Angeles (LA), 0.6% for C and D and 0.5% for Barrett's esophagus. Of the patients who initially had LA grade C/D and A/B, 5.8% and 1.4% of cases, respectively, progress to Barrett's esophagus (B)<sup>21</sup>.

In patients with GERD, the thickness of the lamina propria pretreatment is associated with the severity of esophagitis. After treatment with esomeprazole, the thickness of the basal lamina reduces significantly in patients with erosive and non-erosive GERD (particularly in Los Angeles classification grades C and D) (B)<sup>22</sup>.

The use of histological change scores (hyperplasia of the basal lamina, dilatation of intercellular space, eosinophilia, neutrophilia, erosion/necrosis, papillary elongation), using cut-off > 2, differentiates patients with non-erosive GERD from healthy patients, with sensitivity and specificity of 76% and 85% (positive likelihood ratio of 5 and negative of 0.28). It also differentiates patients with

GERD from healthy patients with sensitivity and specificity of 84% and 85% (positive likelihood ratio of 5.6, negative of 0.18). Note: two biopsies were performed at squamocolumnar junction, two at 2 cm, and two at 4 cm above the junction (B)<sup>23</sup>.

In patients undergoing treatment for two years, the scores of histological changes not taking into account the expansion of the intercellular space (basal lamina hyperplasia, vascular dilation, eosinophils, neutrophils, papillary elongation) and using a cut off value > 2, differentiate GERD patients comparing symptoms and esophageal pH-metry, with sensitivity and specificity of 54% and 73% (positive likelihood ratio of 2 and negative of 0.63) (A)<sup>24</sup>.

Whereas:

In patients on long-term (1-year) PPI therapy:

1. Histological changes may remain, regardless of the presence of symptoms and/or signs;
2. Histological changes may become worse;
3. The severity of esophagitis accompanies the degree of histological change.

#### RECOMMENDATION

The follow-up of patients on PPI therapy with persistent symptoms can best be established with the use of UDE and esophageal biopsy to identify histological signs (intercellular dilation, basal lamina thickening etc.), with a positive and negative likelihood ratios six-fold higher for GERD diagnosis, which allows to establish if clinical treatment should be maintained or not.

### 8. WHAT IS THE ROLE OF THE INTERCELLULAR SPACE DILATION ON ESOPHAGEAL MUCOSA EXAMINATION IN THE DIAGNOSIS OF GERD?

The assessment of histological changes in GERD diagnosis showed that dilation of intercellular space alone has sensitivity and specificity of 86% and 70%, respectively, with positive likelihood ratio of 2.86 and negative of 0.2 (B)<sup>23</sup>.

The presence of intercellular spaces dilation in patients with GERD symptoms who underwent esophageal pH-metry assessment can identify patients with non-erosive and erosive esophageal GERD, with a sensitivity of 68.2% and 90.1%, respectively, and specificity of 91.7%. The positive likelihood ratio increases the diagnostic probability 8.2 to 10.8-fold, respectively, and decreases the negative likelihood ratio 3 to 10-fold, respectively (B)<sup>25</sup>.

After three months of treatment with omeprazole 40 mg, 92% of patients presented recovery of intercellular space, as well as resolution of symptoms (B)<sup>20</sup>.

The intercellular space diameter in distal and proximal esophagus of patients with erosive and non-erosive GERD is 3 to 2-fold higher, respectively, than in healthy patients. These variations in diameter accompany the acid exposure time obtained during pH-metry (B)<sup>26</sup>.

The mean diameter of intercellular spaces in patients with erosive and non-erosive GERD is about 4-fold higher than in patients without reflux (B)<sup>27</sup>.

In patients with symptoms of reflux and chronic laryngitis, the intercellular space diameter is about 3-fold higher than in patients without symptoms (B)<sup>28</sup>.

The intercellular space dilation in patients with GERD is correlated with the score of esophageal symptom and histological signs of esophagitis (B)<sup>29</sup>.

#### RECOMMENDATION

The assessment of intercellular space diameter in esophageal biopsies of patients with suspected GERD increases the probability of diagnostic certainty (positive likelihood ratio 3 and negative 0.2). Moreover, the diameter allows the assessment of treatment response.

### 9. WHAT IS THE ROLE OF THE BASAL PROLIFERATION OF THE LAMINA PROPRIA IN THE DIAGNOSIS OF GERD?

The one-year follow-up of patients with erosive GERD undergoing treatment with PPI (eight weeks of treatment with lansoprazole 30 mg/day, followed by long-term treatment with lansoprazole 15 to 30 mg/day or omeprazole 20 mg/day), revealed through esophageal biopsy that there is a decrease of 51% to 2% in high-grade hyperplasia of basal lamina, and an increase of 8% to 63% in the number of normal epithelium (B)<sup>19</sup>.

There is an increased risk in the presence of minimal change esophagitis, such as basal cell hyperplasia in patients with non-erosive GERD (43.5%), compared to those without acid reflux (symptoms and endoscopy) (10.2%) — an increased risk of 33.3%. After treatment with PPI (esomeprazole 20 mg for 4 weeks), there was no difference in the prevalence of hyperplasia in both groups (B)<sup>30</sup>.

Analyzing the role of basal cell hyperplasia using measurements of sensitivity and specificity of 35% and 71%, respectively, we find that there is little impact on the diagnosis of GERD (positive likelihood ratio of 1.2 and negative 0.91) (B)<sup>31</sup>.

During the endoscopic examination, when the biopsy is performed 2 cm above the Z line, there are signs of histologic response in measurement of lamina propria thickness with the use of PPI. There is no difference between patients with erosive and non-erosive GERD. And there is no correlation between the histological response and clinical improvement (B)<sup>22</sup>.

The assessment of histological changes in GERD diagnosis showed that basal cell hyperplasia alone has sensitivity and specificity of 98% and 45%, respectively, with positive likelihood ratio of 1.78 and negative of 0.04, therefore, basal cell hyperplasia alone is more important to exclude the diagnosis or active disease when it is absent (B)<sup>23</sup>.

## RECOMMENDATION

The assessment of basal cell proliferation (BCP) in esophageal biopsies of patients with suspected GERD allows, in the absence of BCP, to exclude the diagnosis or disease activity (negative likelihood ratio: 0.04). However, the presence alone of BCP has little impact on diagnosis (positive likelihood ratio: 1.78). Although basal cell thickness allows the analysis of therapeutic response (in the absence), it is not correlated with clinical signs.

### 10. WHAT IS THE ROLE OF ENDOSCOPIC ULTRASOUND IN THE DIAGNOSIS OF GERD?

There are significant differences in esophageal wall thickness between patients with erosive and non-erosive GERD evaluated by endoscopic ultrasound, with involvement of the distal wall of the lesions. There is no correlation between duration of symptoms and degree of thickening (B)<sup>32</sup>.

In patients with erosive GERD, there is correlation between structural changes in the wall of the lower esophagus identified by endoscopic ultrasound and functional impairment of the esophagus (pressure) (B)<sup>33</sup>.

## RECOMMENDATION

There is limited scientific information and with little consistency evaluating the use of endoscopic ultrasound in esophageal wall structural changes in patients with erosive GERD, with no clinical application at present.

### 11. SHOULD PATIENTS WITH ASTHMA BE INVESTIGATED FOR GERD?

Frequent regurgitation (greater than once per week) or excessive acid reflux in proximal esophagus (greater than 1.1% of the total time of dual channel esophageal pH-metry) can predict 20% improvement in asthma symptoms, with daily omeprazole 20, 40, or 60 mg for three months, with 100% sensitivity and specificity of 44%, reflecting the certainty of response with a positive likelihood ratio of 1.78, and negative of 0 (zero) (B)<sup>34</sup>.

Therapy with pantoprazole 40 mg daily for 12 weeks showed improvement of symptoms and quality of life with no impact on respiratory function tests in patients with asthma and respiratory symptoms related to gastroesophageal reflux (A)<sup>35</sup>.

Omeprazole 20 mg twice daily and domperidone 10 mg three times daily for 16 weeks reduces the score of morning symptom by 8.5% (17.4% vs 8.9%), nighttime symptoms by 14.2% (19.6% vs 5.4%), and reflux symptoms by 7.1% (8.7% vs 1.6%) (A)<sup>36</sup>.

The use of lansoprazole 30 mg twice daily for 24 weeks in patients with asthma and gastroesophageal reflux reduces the risk of asthma exacerbation in 12.3% — NNT = 8 (A)<sup>37</sup>.

In asthmatic patients, the prevalence of gastroesophageal reflux symptoms can be up to 82%. Symptoms of reflux have 92% sensitivity and specificity of 35% in the diagnosis of GERD in asthmatic patients with and without esophageal pH changes (positive and negative likelihood ratios of 1.41 and 0.22, respectively) (A)<sup>38</sup>.

In patients with and without reflux symptoms and abnormal pH, the presence of wheezing has a sensitivity and specificity of 65% and 58% (positive and negative likelihood ratios of 1.54 and 0.60, respectively) and the presence of cough has a sensitivity and specificity of 98% and 72% (positive and negative likelihood ratios of 3.5 and 0.02, respectively) (A)<sup>38</sup>.

## RECOMMENDATION

The presence of reflux symptoms in some patients with asthma slightly increases the likelihood of diagnostic certainty. In patients with GERD, PPI therapy has NNT of 8 for reducing exacerbation of asthma symptoms. In asthmatic patients with reflux symptoms, normal pH monitoring predicts the lack of therapeutic response.

### 12. SHOULD PATIENTS WITH INTERSTITIAL LUNG DISEASE (PULMONARY FIBROSIS) BE INVESTIGATED FOR GERD?

In patients with idiopathic pulmonary fibrosis, 67% have gastroesophageal reflux. Typical symptoms of reflux have a sensitivity of 65% and specificity of 71% for diagnosing GERD. The positive and negative likelihood ratios are 2.24 and 0.49, respectively (A)<sup>39</sup>.

Prevalence of GERD in patients with idiopathic pulmonary fibrosis can be up to 87%, but only 47% of these patients had symptoms of reflux (A)<sup>40</sup>.

The prevalence of GERD in asthma patients may be lower (68%); and patients with pulmonary fibrosis may have more gastroesophageal reflux at the distal region of the esophagus than patients with asthma (76% vs 57%) (A)<sup>40</sup>.

The risk of GERD in patients with pulmonary fibrosis may be up to 94.1%, compared with patients without fibrosis in which the risk is 50%. Only 25% of patients have typical reflux symptoms (B)<sup>41</sup>.

## RECOMMENDATION

The association of pulmonary fibrosis in GERD is high. Typical symptoms of reflux in these patients slightly increase the likelihood of diagnostic certainty.

### 13. SHOULD PATIENTS WITH APNEA AND/OR SLEEP DISORDERS BE INVESTIGATED FOR GERD?

Patients with sleep apnea have more events of GERD in 8 hours than patients without sleep apnea and a longer time of pH < 4.0 during esophageal pH-metry examination. In patients with sleep apnea, 53.4% of reflux episodes are related to apnea and hypopnea, and 46.8% of all apneas are related to reflux episodes (B)<sup>42</sup>.

In patients being evaluated for sleep disorders, the evaluation by RDQ identified 12.8% of patients with GERD. Excessive sleepiness is associated with severity of GERD symptoms. Patients with GERD had more daytime sleepiness (B)<sup>43</sup>.

Using the GERD Symptom Assessment Score (GSAS) and the questionnaire Sleep Heart Health Study (SHHS) for assessing sleep habits, there was a positive association between sleep disorders and severity of index symptoms. A greater number of awakenings during sleep is also associated with higher rates of GERD symptoms. It was also observed that the poor quality of sleep is related to a greater number of reflux events in the pH-metry (B)<sup>44</sup>.

Heartburn or regurgitation is not related to apnea severity in patients with sleep apnea (B)<sup>45</sup>.

In patients with sleep apnea, about 81% of all acid events are associated with respiratory events (apnea or hypopnea), although there is no correlation between the magnitude of the events and apnea-hypopnea index (B)<sup>46</sup>.

#### RECOMMENDATION

There is association between GERD and apnea and/or sleep disorders. There is direct correlation between the intensity of GERD symptoms and sleep disorders. There is no direct correlation between the intensity of GERD symptoms and sleep apnea. However, there is direct correlation between acid reflux events, sleep disorders, and apnea.

#### 14. SHOULD PATIENTS WITH SIGNS SUGGESTIVE OF POSTERIOR LARYNGITIS BE INVESTIGATED FOR GERD?

The symptoms (hawk, cough, globus, sore throat, or hoarseness) of patients with chronic posterior laryngitis does not improve with the use of esomeprazole 40 mg daily for 16 weeks compared with placebo (A)<sup>47</sup>.

After three months of treatment with lansoprazole 30 mg, there was no difference in the number of patients with chronic laryngitis achieving partial or total resolution of symptoms (cough, globus, sore throat, or hoarseness) compared with placebo (A)<sup>48</sup>.

In patients with symptoms of chronic laryngitis, compared to those with symptoms of heartburn and/or regurgitation, there is a discrepancy between symptoms and reflux parameters (on esophageal pH-metry test). Thirty-three percent of patients with laryngitis have significant reflux, but with no typical symptoms of reflux. Laryngo-

pharyngeal reflux episodes occurred with no difference between patients with symptoms of laryngitis and typical symptoms of reflux. Gastroesophageal reflux episodes in distal esophagus on esophageal pH-metry also occurred with no difference between the two groups (B)<sup>49</sup>.

There is no correlation between chronic laryngitis symptoms and laryngeal reflux grade. Heartburn was worse in the group with laryngeal reflux than in patients without reflux. In addition, the patients with laryngeal reflux had more distal reflux (number of episodes and percentage of time with pH < 4 on esophageal pH-metry) than patients without laryngeal reflux (B)<sup>50</sup>.

The symptoms of chronic laryngitis when compared to the pH-metry alone in the diagnosis of GERD provide likelihood ratio insufficient to increase the diagnostic certainty (Table 1) (B)<sup>51</sup>.

The positive likelihood ratio < 1 and the negative > 1 define signs and symptoms that hinder the diagnosis of GERD (B)<sup>51</sup>.

#### RECOMMENDATION

The response to PPI therapeutic test in patients with chronic laryngitis symptoms (cough, globus, sore throat or hoarseness) does not increase the likelihood alone of GERD diagnosis. The occurrence of symptoms of chronic laryngitis and typical of gastroesophageal reflux is not associated with the frequency and intensity of acid reflux (Figure 1).

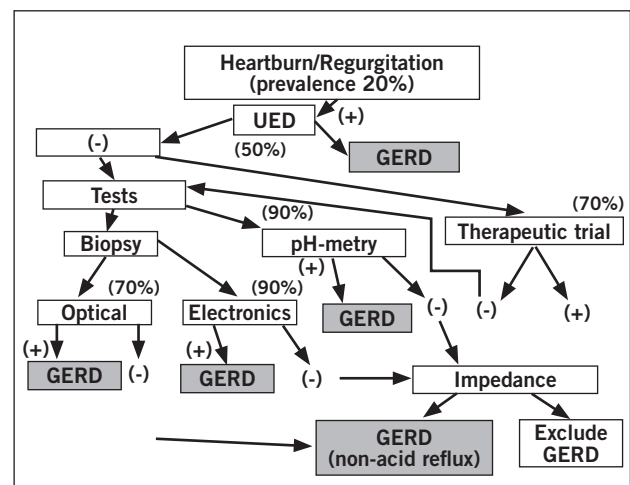


Figure 1 – Diagnostic flowchart of gastroesophageal reflux disease

Table 1 – GERD-associated symptoms

Symptoms	Sensitivity (%)	Specificity (%)	Positive ratio	Negative ratio
Cough	31	53	0.65	1.30
Globus	3	91	0.33	1.06
Hoarseness	44	67	1.35	0.82
Sore throat	10	88	0.83	1.02

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