

## Review

# An Evidence-Based Approach to the Treatment of Gastroesophageal Reflux Disease

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**IMPORTANCE** Gastroesophageal reflux disease (GERD) is prevalent worldwide, particularly in developed countries. It is estimated that the prevalence of GERD in the United States is approximately 20% and that it is increasing because of the epidemic of obesity.

**OBJECTIVE** To review the pathophysiology, clinical presentation, diagnostic evaluation, and treatment of GERD.

**EVIDENCE REVIEW** A search of PubMed was conducted for the years spanning 1985 to 2015 and included the following terms: *heartburn, regurgitation, dysphagia, gastroesophageal reflux disease, cough, aspiration, laryngitis, GERD, GORD, endoscopy, manometry, pH monitoring, proton pump inhibitors, open fundoplication, and laparoscopic fundoplication*. Only articles in English were included.

**FINDINGS** Lifestyle modifications, proton pump inhibitors, and laparoscopic fundoplication are proven treatment modalities for GERD. Endoscopic procedures have not been proven as effective. A Roux-en-Y gastric bypass is the procedure of choice when GERD and morbid obesity coexist.

**CONCLUSIONS AND RELEVANCE** Gastroesophageal reflux disease is a highly prevalent disease. Once the diagnosis has been established, the best results are obtained by a multidisciplinary team with the goal of individualizing treatment for patients.

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The Montreal consensus conference defined gastroesophageal reflux disease (GERD) as “a condition which develops when the reflux of gastric contents causes troublesome symptoms and/or complications.”<sup>1(p1903)</sup>

## Epidemiology and Relevance for Society and the Health Care System

Gastroesophageal reflux disease is prevalent worldwide, particularly in developed countries. It is estimated that the prevalence of GERD in the United States (defined as heartburn and/or regurgitation at least once a week) is approximately 20% and that it is increasing because of the epidemic of obesity.<sup>2</sup> However, the true prevalence of GERD might be higher owing to the fact that many individuals use over-the-counter acid-reducing medications.

The economic impact of GERD is very high, and it is due to direct and indirect costs. The direct health care costs (inpatient and outpatient visits, diagnostic procedures, and medications) are estimated to be around \$9 to \$10 billion per year, with proton pump inhibitors (PPIs) being responsible for a large part of these expenses.<sup>3,4</sup> In addition, there are indirect costs, such as a decrease in productivity at work, workplace absence, and disability.<sup>5</sup>

My objective was to review the pathophysiology, clinical presentation, diagnostic evaluation, and treatment of GERD.

## Methods

A search of PubMed was conducted for the years spanning 1985 to 2015 and included the following terms: *heartburn, regurgitation, dysphagia, gastroesophageal reflux disease, cough, aspiration, laryngitis, GERD, GORD, endoscopy, manometry, pH monitoring, proton pump inhibitors, open fundoplication, and laparoscopic fundoplication*. Only articles in English were included.

## Pathophysiology

Understanding the multifactorial pathophysiology of GERD is crucial for the proper treatment of this disease.

### Lower Esophageal Sphincter

The lower esophageal sphincter (LES) is a 3- to 4-cm-long segment of tonically contracted smooth muscle located in the lower end of the esophagus.<sup>6</sup> The LES is mechanically incompetent (short length

and/or low pressure) in about 60% of patients with GERD.<sup>7</sup> In the remaining 40% of patients, the length and pressure of the LES are normal, but reflux is due to transient LES relaxations, defined as periodic relaxations of the sphincter that are not triggered by swallowing but probably secondary to gastric distension.<sup>6</sup>

### Esophageal Peristalsis

About 30% of patients with GERD have a severe defect of peristalsis due to low-amplitude waves and/or simultaneous contractions, known as ineffective esophageal motility.<sup>8</sup> Defective peristalsis results in slower clearance of the gastric refluxate, with more severe symptoms and worse mucosal damage.<sup>8</sup>

### Diaphragm

The esophageal crus of the diaphragm functions as an extrinsic sphincter, reinforcing the LES through its pinchcock action. This synergist action is lost when a hiatal hernia is present because then the crus presses over the herniated stomach rather than the LES.<sup>9</sup>

### Hiatal Hernia

Gastroesophageal reflux disease and hiatal hernia can exist independently. However, it has been shown that the presence and size of a hiatal hernia are often associated with an incompetent LES, more frequent transient LES relaxations, defective peristalsis, increased esophageal acid exposure, and more severe mucosal damage.<sup>9,10</sup>

### Gastric Refluxate

Both gastric (hydrochloric acid and pepsin) and duodenal contents (bile salts and pancreatic enzymes) reflux from the stomach into the esophagus. Studies with intraluminal impedance technology of patients receiving and then not receiving PPIs, a mainstay of medical therapy, have shown that these medications only alter the pH of the refluxate from acidic to weakly acidic or alkaline but do not change the occurrence or the number of reflux episodes.<sup>11,12</sup> Unfortunately, the current technology allows only for the assessment of the number of reflux episodes and their duration but does not measure the volume of the gastric refluxate, which has important implication for treatment.

### Transdiaphragmatic Pressure Gradient

A transdiaphragmatic pressure gradient is present at the level of the gastroesophageal junction because most of the esophagus is located in the chest under negative pressure while the stomach is exposed to the positive pressure of the abdomen. To avoid reflux, this gradient must be counterbalanced by the LES.

Several studies have shown that the abdominal pressure is increased in obese patients and that there is a direct correlation between pressure, body mass index (calculated as weight in kilograms divided by height in meters squared), and waist circumference.<sup>13,14</sup> In addition, obstructive sleep apnea, which is common in the bariatric population, leads to collapse of the upper airway and the development of a more negative intrathoracic pressure.<sup>15</sup> As a consequence, the transdiaphragmatic pressure gradient is higher in obese patients and thus determines the prolonged periods of nocturnal acid exposure.<sup>16</sup> Herbella et al<sup>17</sup> showed that, in morbidly obese patients, for every 5-point increase in the body mass index, there was a 3-point increase in the reflux score.

Based on these data, it is clear that the pathophysiology of GERD is different in obese patients compared with nonobese patients. These findings must be taken into consideration, particularly when surgical therapy is considered.

Gastroesophageal reflux disease is experienced by 30% to 50% of women during pregnancy, and it is more common in women who were already symptomatic before the pregnancy.<sup>18</sup> Weight gain with an increase in body mass index clearly plays a role, along with a decrease in LES pressure caused by female sex hormones, especially progesterone.<sup>18,19</sup>

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## Clinical Presentation

Heartburn and regurgitation are usually classified as "typical" symptoms, and they are considered by most physicians tantamount to GERD.<sup>20</sup> Some patients also experience dysphagia, which, in the absence of an esophageal stricture and achalasia, is usually due to defective peristalsis and slow bolus transit.<sup>8,21</sup> Others can present with noncardiac chest pain.<sup>22</sup> Atypical symptoms include respiratory symptoms such as chronic cough, aspiration pneumonia, pulmonary fibrosis, hoarseness, globus, and dental erosions.<sup>23-26</sup> These are considered extraesophageal manifestations of the disease.<sup>27</sup>

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## Diagnostic Evaluation

Most physicians believe that a diagnosis of GERD can be firmly established by a careful symptomatic evaluation. Therefore, when patients complain of heartburn, acid-reducing medications are usually prescribed, and a good response is considered indicative of the presence of the disease. This is usually referred to as a "PPI trial."<sup>28</sup> Endoscopy is usually performed for severe or persistent symptoms.<sup>29</sup>

However, many studies have shown that a diagnosis of GERD based on symptoms is wrong in a large percentage of patients. For instance, we performed manometry and pH monitoring for 822 patients who had been referred to the Swallowing Center of the University of California, San Francisco, after receiving a diagnosis of GERD based on symptom evaluation and results of endoscopy (patients with biopsy-proven Barrett esophagus were excluded from the study).<sup>30</sup> Overall, 247 patients (30%) had a normal reflux score (GERD-negative group). When the 2 groups (GERD-negative group and GERD-positive group) were compared, the following was evident: (1) symptoms were unreliable to diagnose GERD because the incidence of heartburn and regurgitation was in fact similar in the 2 groups, (2) the use of acid-reducing medications was similar in the 2 groups, (3) endoscopic evidence of grade I and grade II esophagitis was diagnostically nonspecific because it was detected in 25% of GERD-negative patients, and (4) only pH monitoring identified patients with GERD and stratified them according to the severity of the disease. Particularly in patients who do not respond well to PPI, in patients with extraesophageal symptoms, and before antireflux surgery, the presence of abnormal reflux must be documented objectively by pH monitoring.<sup>31</sup>

### PPI Trial

Proton pump inhibitors are initially prescribed to patients suspected of having GERD with the intent of confirming the clinical di-

agnosis if symptoms are ameliorated, the so-called PPI trial.<sup>28</sup> Although this is a practical approach, considering the very high prevalence of the disease, it is important to underline the limitations of this strategy. For instance, Numans et al<sup>32</sup> performed a meta-analysis (12 studies) to assess the value of the PPI trial compared with 24-hour pH monitoring and found that the PPI trial had a sensitivity of 78% but a specificity of only 54%. Therefore, this is not an accurate test for the diagnosis of GERD, and more objective evidence is needed from a large percentage of patients.<sup>28,32-34</sup>

### Endoscopy

Endoscopy is usually the first test that is performed to confirm a clinical diagnosis of GERD. However, about 50% to 60% of patients with abnormal reflux confirmed by pH monitoring do not have any evidence of mucosal damage.<sup>28,29</sup> In addition, erythema of the distal esophagus predicts reflux disease in only 53% of patients.<sup>35</sup> Upper endoscopy is valuable for excluding other pathologies such as eosinophilic esophagitis, gastritis, peptic ulcers, and Barrett esophagus, a benign stricture and cancer.

### Esophageal Manometry

Esophageal manometry is of limited value in the diagnosis of GERD. The main indications for its use are the proper placement of a probe for pH monitoring (5 cm above the upper border of the LES) and to exclude a primary motility disorder such as achalasia.<sup>36,37</sup> The conventional method of manometry (with water-perfused catheters) that was used for more than 40 years has been recently replaced by high-resolution manometry with solid-state catheters. This new technology allows for a better characterization not only of the esophagogastric junction (the LES and the crural diaphragm) but also of esophageal peristalsis.<sup>21</sup> In addition, by evaluating bolus transit, it may help us to identify patients who are at risk for dysphagia after fundoplication, or it may help us to assess patients who experience dysphagia after a fundoplication, allowing us to identify those who benefit from endoscopic dilatation.<sup>38</sup>

### Ambulatory pH Monitoring

Ambulatory pH monitoring is considered the gold standard for the diagnosis of GERD because it allows for the quantification of the acid exposure and the correlation between symptoms and episodes of reflux. The test should be performed while the patient is not receiving medications, discontinuing H<sub>2</sub> blocking agents for 3 days and PPIs for 7 days before the test.<sup>39</sup> The pH monitoring can be performed by either transnasally placing a catheter 5 cm above the manometrically determined LES or endoscopically placing a capsule 5 cm above the squamocolumnar junction.<sup>39</sup> The temporal correlation between symptoms and episodes of reflux can be established by either the symptom index<sup>40</sup> or the symptom association probability.<sup>41</sup> A negative correlation usually indicates that the symptoms experienced by the patient are not due to reflux.<sup>40,41</sup> Esophageal pH testing can be combined with impedance to detect any type of reflux independent from the pH (acidic, weakly acidic, or nonacidic).<sup>42</sup> This test has the potential of elucidating the nature of symptoms in patients who do not respond to PPI therapy,<sup>42</sup> but additional studies are still needed to determine its role in the diagnostic algorithm of patients suspected of having GERD.<sup>12</sup>

### Barium Swallow

This test is not useful for diagnosing GERD, but it provides important information about the anatomy, such as the presence of an esophageal stricture and the presence, size, and type of a hiatal hernia.

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## Treatment

The goal of treatment is to ameliorate symptoms and esophageal mucosal damage. Four different treatment modalities are available: (1) lifestyle modifications, (2) medications, (3) endoscopic intervention, and (4) surgery.

### Lifestyle Modifications

Patients are asked to elevate the head of the bed and avoid late-night meals, particularly if symptoms are worse at night. In addition, it is recommended that patients avoid alcohol, tobacco, and foods such as chocolate, coffee, and carbonated beverages. Weight loss is considered very important because it has been shown that it can decrease the frequency and severity of GERD symptoms.<sup>43</sup>

### Medications

Histamine-receptor antagonists and PPIs have been the mainstay of therapy for the last 20 years, achieving the therapeutic goal in about 60% of patients.<sup>44</sup> Today, PPIs are preferred because they are more effective than histamine-receptor antagonists in alleviating symptoms and healing esophagitis.<sup>44,45</sup> At the present time, there are 7 different PPIs available with a broad spectrum of costs. Interestingly, a recent meta-analysis of randomized clinical trials has shown that there is no major difference in symptom relief among the available PPIs.<sup>46</sup> Heartburn is usually relieved in the majority of patients, but because PPIs only alter the pH of the gastric refluxate without decreasing the actual number of reflux episodes, regurgitation is not controlled as well in a large percentage of patients.<sup>47</sup> Proton pump inhibitor therapy has been shown to increase the risk for *Clostridium difficile* infection, community-acquired pneumonia, hip fracture, vitamin B<sub>12</sub> deficiency, and hypomagnesemia.<sup>48</sup> In addition, PPI use has been associated with severe cardiac events, such as myocardial infarction, in the general population, because of a potential effect on vascular function,<sup>49</sup> and in patients taking clopidogrel bisulfate after an acute coronary event, because of a decreased inhibition of platelet aggregation.<sup>50</sup>

Patients who receive prokinetic agents such as metoclopramide hydrochloride can have severe adverse effects, and therefore these agents do not have a role to play in the treatment of GERD, except when gastroparesis is present.<sup>51</sup> Treatment during pregnancy is based on the severity of symptoms. Most patients do well with lifestyle modifications and antacids, but for more severe symptoms, H<sub>2</sub> blocking agents should be added to the treatment regimen. Proton pump inhibitors should be used for patients with symptoms that are not responsive. Most PPIs are classified by the US Food and Drug Administration as category B drugs (they can be used during pregnancy). Omeprazole is still considered a type C drug (with no definitive animal or human studies available regarding its safety).<sup>18</sup>

## Endoscopic Therapy

Over the last 20 years, many different types of endoscopic devices have been used to treat GERD, but most of them have been removed from the market because of a lack of safety or because they were not effective. At the present time, only the radiofrequency ablation of the LES and the endoscopic suturing of the LES (transoral incisionless fundoplication) are used. Both procedures require a careful patient selection, excluding patients with a hiatal hernia of more than 2 cm, esophageal dysmotility, Barrett esophagus, Los Angeles grade C or D esophagitis, esophageal stricture, and a body mass index of greater than 35.

Radiofrequency ablation of the LES causes hypertrophy and fibrosis of the LES, which potentially can decrease reflux episodes by increasing LES pressure and decreasing LES relaxations. Even though the procedure is simple and safe, there is no convincing evidence supporting its role in the treatment of GERD. In a prospective, randomized trial of radiofrequency ablation vs placebo, Corley et al<sup>52</sup> showed that, at the 6-month follow-up, there was no difference in daily medication use or in esophageal acid exposure times. In a recent meta-analysis of 4 trials (153 patients), Lipka et al<sup>53</sup> showed that radiofrequency ablation was not better than PPIs with respect to LES pressure, percentage of time pH was below 4, or quality of life.

Transoral incisionless fundoplication creates an endoscopic fundoplication by using T-fasteners between the esophagus and the gastric fundus.<sup>54,55</sup> In a recent multicenter randomized controlled trial, Hunter et al studied patients with "persistent and troublesome regurgitation despite treatment with PPI."<sup>54(p325)</sup> Patients were randomized either to transoral incisionless fundoplication and placebo or to sham transoral incisionless fundoplication and PPIs. At 6-month follow-up, resolution of regurgitation occurred in 65% of patients who underwent transoral incisionless fundoplication and 45% of patients who received PPIs. However, there was no difference in the improvement of heartburn or pH scores; pH scores were decreased but not normalized.<sup>54</sup> There are no long-term results with this technique, and it has been suggested that a progressive deterioration of the new valve occurs over time, with resumption of medications in almost two-thirds of patients.<sup>55</sup> Interestingly, the Society of American Gastrointestinal and Endoscopic Surgeons supports the use of these techniques,<sup>56</sup> whereas the American College of Gastroenterology clearly stated in its recent guidelines that current endoscopic therapy should not be considered as an alternative to medical or surgical therapy.<sup>57</sup> At the present, it appears that an effective endoscopic treatment is not available and that the choice of treatment is still between PPIs and surgery.<sup>58</sup>

## Surgery

While the majority of patients with GERD do well with lifestyle modifications and PPI therapy, a small percentage of the following patients need surgical intervention: patients whose symptoms (regurgitation, cough or asthma due to aspiration, or dental erosions) are not controlled by medications because of the persistent reflux of weakly acidic or alkaline gastric contents through an incompetent LES; patients who experience complications with PPI therapy; young patients who do not want to take medications for the rest of their lives; patients in whom GERD is associated with a large hiatal hernia; and morbidly obese patients who have GERD but cannot lose weight with lifestyle modifications only.

Patient selection is critical to achieve a good outcome. Campos and colleagues<sup>59</sup> showed that the best predictors of a successful fundoplication are the presence of typical symptoms such as heartburn, a positive pH test result, and a good response to PPI therapy. In 2013, a panel of expert gastroenterologists and surgeons reviewed the diagnostic algorithm necessary before surgery.<sup>12</sup> The consensus was that no single test can provide the entire clinical picture and that barium esophagography, endoscopy, manometry, and pH monitoring should be performed for any patient considered for surgery.<sup>12</sup>

Textbooks traditionally list a number of procedures that are named after surgeons who devised effective antireflux operations at a time when little was known about the pathophysiology of GERD (Nissen in 1956, Toupet in 1963, Dor in 1964, Belsey in 1966, Lind in 1966, Rossetti in 1967, Hill in 1967, and Guarner in 1975). However, it is time to go beyond the eponyms and to recognize the technical elements<sup>60</sup> that are important in performing an operation that controls reflux, lasts over time, and is associated with minimal adverse effects: (1) Extensive mediastinal dissection is performed, in particular, when a hiatal hernia is present, in order to have about 3 cm of esophagus without any tension below the diaphragm. (2) Transection of the short gastric vessels is performed in order to have a tension-free fundoplication. (3) An approximation of the right and left pillar of the crus using nonabsorbable sutures is made in order to restore the synergistic action of the diaphragm with the LES and to avoid recurrent herniation of the stomach. For patients with GERD and a sliding hiatal hernia, the reduction of the hernia and the approximation of the crura can usually be accomplished without using mesh. Similarly, gastropexy is rarely performed. Placement of mesh and gastropexy can be very important for patients with large paraesophageal hernias. (4) A bougie is used to avoid a fundoplication that is too tight and postoperative dysphagia. (5) There are 2 types of fundoplication, total or partial (anterior or posterior). In the United States, mostly based on retrospective reviews, a total fundoplication is the procedure of choice because it is thought to provide better reflux control than a partial fundoplication.<sup>61,62</sup> However, many prospective randomized trials and meta-analyses have shown that a total fundoplication and either a partial posterior or a partial anterior fundoplication result in similar control of the abnormal reflux, irrespective of the quality of peristalsis. These results have been confirmed by long-term follow-up.<sup>63-66</sup> Based on these data, the choice of the type of wrap should be left to the individual surgeon, mostly based on his or her own training and experience. Ten-year follow-up studies have shown that the procedure controls symptoms in about 90% of patients.<sup>67</sup> Postoperatively, some patients use PPIs because of recurrent symptoms, but only one-third have recurrent reflux when tested by pH monitoring.<sup>68</sup> Overall, the failure of a fundoplication to resolve symptoms is secondary to 1 or more of the following: wrong indication for the operation, wrong preoperative workup, or failure to execute the proper technical steps.<sup>69</sup>

However, even though they are dissatisfied with the PPI therapy, some patients are reluctant to undergo a laparoscopic fundoplication for fear of adverse effects such as dysphagia, difficulty in vomiting, and gas bloat. Recently, a new device has been proposed as an alternative to laparoscopic fundoplication to fill this "therapeutic gap."<sup>70</sup> Patients with a large hiatal hernia and those with abnormal peristalsis are not candidates for this procedure. This device is composed of a ring of titanium beads that is placed

laparoscopically around the gastroesophageal junction; this ring expands during the passage of a food bolus and then returns to a contracted state, providing augmentation of the LES. The placement of the ring is simple, and the technique is easily reproducible, therefore eliminating some of the variability often present during the performance of a fundoplication. Ganz and colleagues<sup>71</sup> prospectively evaluated this device in 100 patients with GERD. The primary outcome (normalization of esophageal acid exposure or a  $\geq 50\%$  reduction in exposure at 1 year) was achieved for 64% of patients only. Nineteen percent of patients experienced postoperative dysphagia, usually responding to dilatation, and 2 patients required removal of the device. There were no documented cases of erosion of the device into the esophagus or stomach. A larger number of patients and a longer follow-up are needed to confirm the role of this device in the treatment algorithm of GERD.

A challenging dilemma exists when GERD is present in a morbidly obese patient who has failed to lose weight using conservative measures. As already discussed, the pathophysiology of GERD is different in these patients, and an increased gradient between the stomach and the esophagus plays a major role in this difference. For this patient population, most experts agree that a laparo-

scopic fundoplication is associated with a high failure rate and that Roux-en-Y gastric bypass is the procedure of choice for the following reasons: (1) it can be performed laparoscopically, (2) it is a good antireflux operation because the small gastric pouch has few parietal cells and the Roux limb avoids bile reflux, and (3) it results in an excellent weight loss.<sup>72,73</sup>

## Conclusions

Gastroesophageal reflux disease is a highly prevalent disease. The diagnosis must be properly established by use of appropriate tests, in addition to a symptomatic evaluation, before therapy is initiated. The best results are obtained by a multidisciplinary team with the goal of individualizing treatment for patients. Lifestyle modifications and pharmacological therapy control symptoms and mucosal injury for most patients, but approximately 30% to 40% of patients might need surgical intervention. A laparoscopic fundoplication is the mainstay of surgical therapy, with the Roux-en-Y gastric bypass reserved for morbidly obese patients with GERD.

### ARTICLE INFORMATION

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