Non-acid reflux: Clinical manifestations, diagnosis, and management

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INTRODUCTION

Patients with suspected gastroesophageal reflux disease (GERD) who have been treated with a proton pump inhibitor (PPI) can have persistent symptoms due to a variety of causes. A subset of these patients have symptoms related to continued reflux of non-acidic material [1]. This topic review will review the clinical manifestations, diagnosis, and management of non-acid reflux. A general approach to patients with suspected GERD who have persistent symptoms despite PPI therapy is presented separately. (See "Approach to refractory gastroesophageal reflux disease in adults".)

TERMINOLOGY

- Acid reflux is defined as the reflux of gastric contents with a pH <4.0
- Non-acid reflux is defined as reflux of gastric contents with a pH >4.0 (ie, above the threshold used by conventional pH monitoring to identify acid reflux)

Some experts define gastroesophageal reflux (GER) episodes with a pH of 4.0 to 7.0 as weakly acidic reflux, and GER with a pH above 7.0 weakly alkaline [2]. However, given the low prevalence of weakly alkaline reflux episodes, we separate GER episodes into acid and non-acid using a cutoff value of 4.0, thereby grouping weakly acidic and weakly alkaline reflux into "non-acid" reflux.

EPIDEMIOLOGY

There are limited data on the prevalence of non-acid reflux episodes in patients with gastroesophageal reflux disease (GERD) whose symptoms are controlled with proton pump inhibitors (PPIs) (ie, the prevalence of asymptomatic non-acid reflux).

It is estimated that approximately 40 percent of GERD patients have persistent symptoms despite PPIs, and with objective testing, up to 40 percent of these patients have symptomatic non-acid reflux (figure 1) [3-7]. In a multicenter study that included 168 GERD patients with persistent symptoms on a PPI twice daily who underwent combined multichannel intraluminal impedance and pH (MII-pH) monitoring. Among 144 patients who recorded symptoms during the study period, 53 (37 percent) had a positive symptoms index with non-acid reflux, while only 16 (11 percent) had a positive symptom index for continued acid reflux [3]. (See 'Impedance pH testing' below and "Esophageal multichannel intraluminal impedance testing", section on 'Combined multichannel intraluminal impedance and pH'.)

PATHOGENESIS

Non-acid reflux episodes primarily occur in the postprandial period as transient lower esophageal sphincter relaxation occurs more frequently following meal-induced distension of the gastric fundus (figure 2). In patients on proton pump inhibitors (PPIs), treatment changes the acidity of the refluxate but does not decrease the volume of reflux or affect structural and motility abnormalities at the gastroesophageal junction responsible for GERD (ie, hiatal hernias, decreased lower esophageal sphincter pressure, transient lower esophageal relaxations). In patients not taking acid suppressive medications (ie, off PPI therapy), non-acid reflux results when gastric acid is buffered by the ingested food in the postprandial period [8,9].

The exact mechanism by which non-acid reflux episodes produce symptoms remains uncertain. It is hypothesized that abrupt distension of the lower esophagus stimulates mechanoreceptors in the esophagus. In addition, the composition (mixed liquid-gas) and proximal extent of refluxate (episodes reaching the proximal esophagus) are important determinants of whether reflux episodes are symptomatic [10-12].

CLINICAL FEATURES

The majority of non-acid reflux episodes do not cause symptoms. Patients with symptomatic non-acid reflux usually present with heartburn (pyrosis) and regurgitation despite acid

suppressive therapy [4]. Whether extra-esophageal symptoms can truly be attributed to non-acid reflux is unclear [13,14]. In one study in which 50 patients with chronic cough underwent combined MII-pH monitoring while on acid suppressive therapy, there was an association between cough and non-acid reflux in only 13 patients (26 percent) [14].

DIAGNOSTIC EVALUATION

Clinical suspicion and diagnosis — Non-acid reflux should be suspected in patients with gastroesophageal reflux disease (GERD) that is refractory to maximal acid suppression therapy (eg, twice daily proton pump inhibitor [PPI]). Patients with suspected non-acid reflux require an upper endoscopy with biopsies to exclude alternative diagnoses (eg, eosinophilic esophagitis). We perform combined multichannel intraluminal impedance and pH (MII-pH) testing to establish the diagnosis of non-acid reflux. A refluxate with pH >4 in a patient in whom at least one-half of the symptoms are associated with reflux is diagnostic of non-acid reflux. (See "Approach to refractory gastroesophageal reflux disease in adults", section on 'Diagnostic testing'.)

Impedance pH testing — MII-pH has a high sensitivity for detecting reflux episodes. In patients with refractory GERD symptoms in whom non-acid reflux is suspected, we perform testing on acid-suppressive therapy (ie, a PPI twice daily before meals) for at least one week before combined MII-pH testing. MII-pH testing while on PPI therapy can clarify the effectiveness of acid suppression by evaluating distal esophageal acid exposure and evaluate whether episodes of non-acid reflux are associated with symptoms. (See "Esophageal multichannel intraluminal impedance testing".)

Impedance pH testing uses inherent conductive or resistive properties of the intraluminal bolus (liquid, gas, or mixed) to examine the presence and transit of the bolus in the esophageal lumen. Impedance-detected reflux episodes associated with a decline in pH from above to below 4.0 are considered acid, whereas impedance-detected reflux episodes during which the pH remains above 4.0 are considered to be non-acid (figure 3). In addition, combined MII-pH monitoring also provides information on the number of acid and non-acid reflux episodes, and their relationship with symptoms. A detailed description of MII-pH is presented separately. (See "Esophageal multichannel intraluminal impedance testing".)

Esophageal manometry in selected patients — We perform esophageal manometry in patients with refractory symptoms who are being considered for surgery. In addition, we perform esophageal manometry in patients with concurrent dysphagia and/or chest pain to

rule out achalasia and other esophageal motility disorders, if not previously performed. (See "Overview of gastrointestinal motility testing".)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of non-acid reflux includes persistent reflux of gastric acid into the esophagus, a reflux-sensitive esophagus, and functional heartburn. Non-acid reflux can be distinguished from these conditions by impedance pH testing. Patients with reflux-sensitive esophagus have normal acid exposure but a positive symptom association with acid or weakly acid reflux. Patients with functional heartburn have normal acid exposure and a negative symptom reflux association. (See "Approach to refractory gastroesophageal reflux disease in adults", section on 'Functional heartburn' and "Esophageal multichannel intraluminal impedance testing", section on 'Symptom correlation measures'.)

In patients with concurrent chest pain and dysphagia, the differential diagnosis includes an esophageal motility disorder and eosinophilic esophagitis. Non-acid reflux can be distinguished from these conditions by impedance pH testing, esophageal manometry, and upper endoscopy with biopsies of the esophagus. Evaluation of patients with refractory GERD symptoms is discussed in detail separately. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Histology' and "Approach to refractory gastroesophageal reflux disease in adults", section on 'Functional heartburn'.)

MANAGEMENT

There have been few studies of specific therapy in the treatment of non-acid reflux, and treatment approaches are evolving [15]. While recommendations were largely based on observational studies and clinical experience, data from randomized trials seem to confirm the initial recommendations.

Initial management

Reinforce lifestyle modification and PPI therapy adherence — Lifestyle and dietary modification, and compliance with PPI therapy should be reinforced. Patients should be instructed to take a PPI 30 minutes before a meal. Lifestyle interventions that have been demonstrated to improve esophageal pH and/or symptoms in patients with GERD include weight loss for patients who are overweight or have had recent weight gain, elevation of the head of the bed, refraining from assuming a supine position after meals, and avoidance of

meals two to three hours before bedtime [16]. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Lifestyle and dietary modification'.)

Reflux inhibitors — For patients who remain symptomatic despite compliance with lifestyle interventions and PPI therapy, we suggest additional treatment with baclofen. We initiate therapy with a low dose of baclofen (5 to 10 mg twice a day before meals). In patients who fail to respond, we make incremental changes and increase the dose by 5 mg every four days to 20 mg three times a day while carefully monitoring for side effects. Because baclofen crosses the blood-brain barrier, a variety of central nervous system-related side effects may occur. These include somnolence, confusion, dizziness, lightheadedness, drowsiness, weakness, and trembling. We usually continue baclofen for four to eight weeks before stopping, if it is ineffective.

Data to support the use of baclofen in patients with non-acid reflux are limited. Baclofen reduces the rate of transient lower esophageal sphincter relaxations, and in physiologic studies, has been associated with a reduction in both acid and non-acid postprandial reflux [17-19]. In a meta-analysis of nine randomized trials that included 283 patients with GERD and healthy volunteers who were assigned to baclofen or placebo, baclofen resulted in a reduction in the number of reflux episodes per patient, the average length of reflux episodes, and the incidence of transient lower esophageal sphincter relaxation [20]. However, the meta-analysis included patients with functional heartburn and reflux-sensitive esophagus. In one trial that included add-on therapy with baclofen, treatment significantly reduced the total number of non-acid reflux episodes regardless of the presence of a hiatal hernia [21].

Subsequent management — The subsequent approach to management depends upon the symptomatic response to treatment.

Patients who respond to reflux inhibitors — In patients with a symptomatic response to reflux inhibitor therapy (eg, baclofen), we attempt to decrease the PPI dose, and if possible discontinue PPI therapy, over a four to eight-week interval. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Discontinuing PPIs'.)

Patients with refractory symptoms — We reserve fundoplication for patients with symptoms refractory to medical therapy in whom we can document ongoing (non)acid reflux being associated with symptoms. Fundoplication has the potential to reduce non-acid reflux by strengthening anatomic antireflux mechanisms [22-24]. In one study of 15 patients off PPI therapy before and seven months after laparoscopic Nissen-Rossetti fundoplication found that laparoscopic fundoplication improved acid reflux parameters (percent time pH <4 and

DeMeester score) and the total number of impedance-detected episodes of both acid and non-acid reflux (figure 4) [22]. In a randomized trial that included 366 patients with persistent reflux symptoms on PPI therapy [25], 78 patients with documented reflux-related heartburn were randomized to undergo antireflux surgery (laparoscopic Nissen fundoplication) or receive active treatment (twice daily PPI plus baclofen with desipramine based on the symptoms) or control treatment (twice daily PPI). Treatment success in the surgery group was significantly higher as compared with active medical treatment and control groups (67, 28, and 12 percent, respectively), suggesting that a highly selected group of patients with documented reflux-related heartburn refractory to PPI therapy, benefits from laparoscopic Nissen fundoplication. However, patients must also be counseled on the existing data supporting laparoscopic Nissen fundoplication, which show that response rates are not as high as those published in surgery versus PPI trials [26,27]. In addition, predicting which patients will respond to fundoplication is also challenging. A retrospective review of 34 pediatric patients having fundoplication concluded that none of the reflux parameters detected on preoperative MII-pH testing predicted the outcome of antireflux surgery [28]. (See "Surgical treatment of gastroesophageal reflux in adults", section on 'Complete fundoplications' and "Approach to refractory gastroesophageal reflux disease in adults".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Esophageal manometry and pH testing".)

SUMMARY AND RECOMMENDATIONS

- Non-acid reflux is the reflux of gastric contents with a pH >4.0. (See 'Terminology' above.)
- It is estimated that approximately 40 percent of GERD patients have persistent symptoms despite PPIs, and with objective testing, approximately 40 percent of these patients have symptomatic non-acid reflux. (See 'Epidemiology' above.)
- Non-acid reflux episodes primarily occur in the postprandial period as transient lower esophageal sphincter relaxation occurs more frequently following meal-induced distension of the gastric fundus. The composition and proximal extent of refluxate are important determinants of whether episodes are symptomatic. (See 'Pathogenesis' above.)

- The majority of non-acid reflux episodes do not cause symptoms. Patients with symptomatic non-acid reflux usually present with heartburn and/or regurgitation despite acid suppressive therapy. (See 'Clinical features' above.)

- Non-acid reflux should be suspected in patients with GERD that is refractory to maximal acid suppression therapy (eg, twice daily PPI). Patients with suspected non-acid reflux require an upper endoscopy with biopsies to exclude alternative diagnoses (eg, eosinophilic esophagitis). Combined multichannel intraluminal impedance and pH (MII-pH) testing is required to establish the diagnosis of non-acid reflux. A refluxate with pH >4 in a patient in whom at least one-half of the symptoms are associated with reflux is diagnostic of non-acid reflux. (See 'Diagnostic evaluation' above.)

- We perform esophageal manometry in patients with dysphagia and/or chest pain to rule out achalasia and other esophageal motility disorders, and in patients with refractory symptoms who are being considered for surgery. (See 'Esophageal manometry in selected patients' above.)

- Lifestyle and dietary modification, and compliance with PPI therapy should be reinforced in all patients with non-acid reflux. In patients who fail to respond to lifestyle interventions and PPI therapy, we suggest reflux inhibitor therapy (**Grade 2C**). We use additive therapy with a low dose of baclofen (5 to 10 mg twice a day before meals). In patients who fail to respond, we incrementally increase the dose while monitoring for side effects. (See 'Reflux inhibitors' above and 'Reinforce lifestyle modification and PPI therapy adherence' above.)

- The subsequent approach to management depends upon the symptomatic response to treatment. In patients with a symptomatic response to reflux inhibitor therapy, we attempt to decrease the PPI dose, and if possible discontinue PPI therapy, over a four to eight-week interval. (See 'Subsequent management' above.)

- In patients with refractory symptoms of non-acid despite medical therapy in whom the diagnosis is confirmed by MII-pH monitoring with positive symptom association, we suggest laparoscopic Nissen fundoplication (**Grade 2C**). Patients must be counseled on the limited data supporting laparoscopic Nissen fundoplication and difficulty in predicting which patients will respond to fundoplication. (See 'Patients with refractory symptoms' above and "Surgical treatment of gastroesophageal reflux in adults", section on 'Operative techniques'.)

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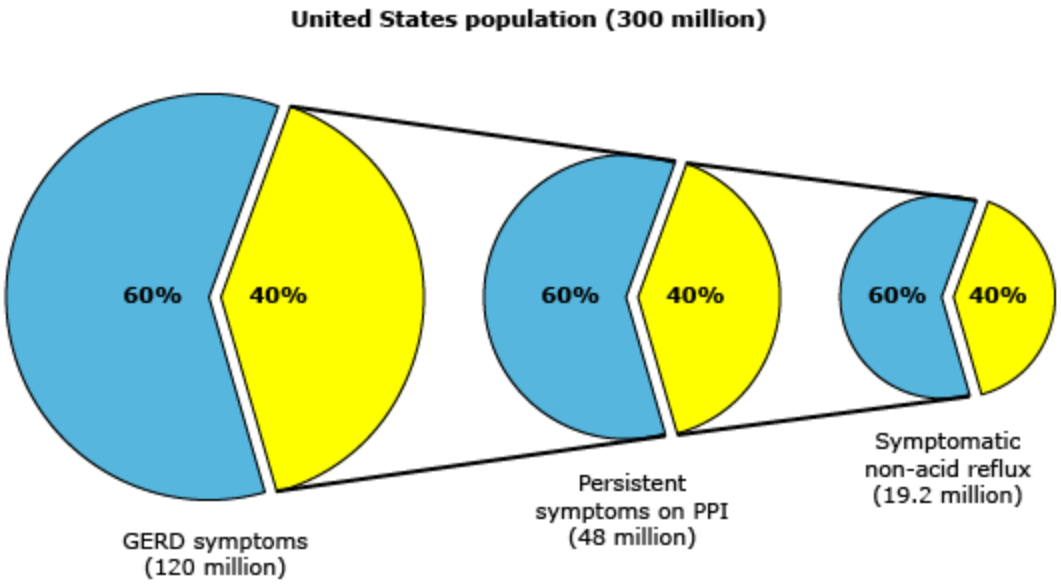
Topic 2244 Version 19.0

GRAPHICS

Estimated prevalence of non-acid reflux

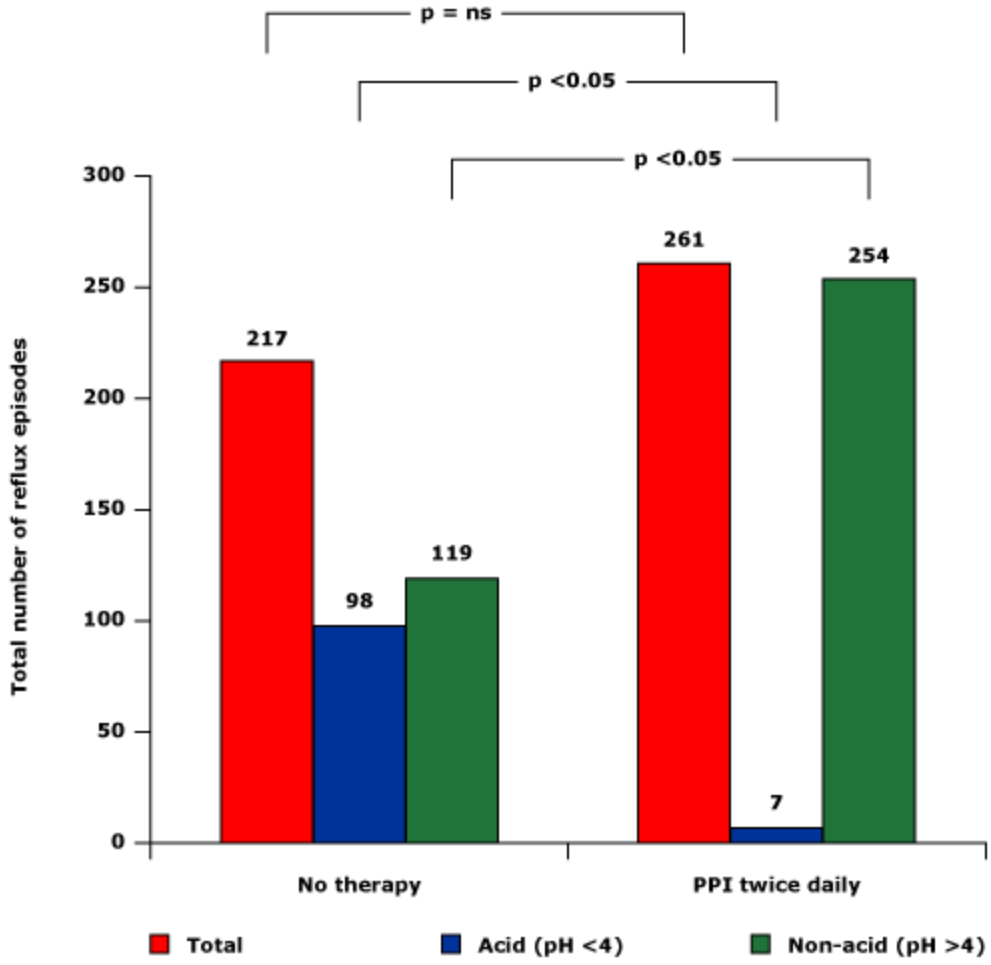


Estimated prevalence of GERD symptoms, persistent symptoms on PPI, and symptomatic non-acid reflux in the United States population (60-40 rule). Epidemiologic studies estimate that approximately 40 percent of the adult population in the United States experiences reflux symptoms at least once a week. Large clinical trials evaluating the efficacy of acid suppressive therapy in the treatment of GERD indicate that approximately 40 percent of GERD patients treated with PPI have persistent symptoms on therapy. Clinical investigations evaluating the association between persistent symptoms on PPI therapy with reflux episodes indicate that approximately 40 percent of patients have symptoms preceded by non-acid reflux. Based on this proportion, we estimate that roughly 19 million adults in the United States have symptomatic non-acid reflux.

%: percent; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor.

Graphic 57581 Version 2.0

Gastroesophageal reflux in the postprandial period off and on acid suppressive therapy

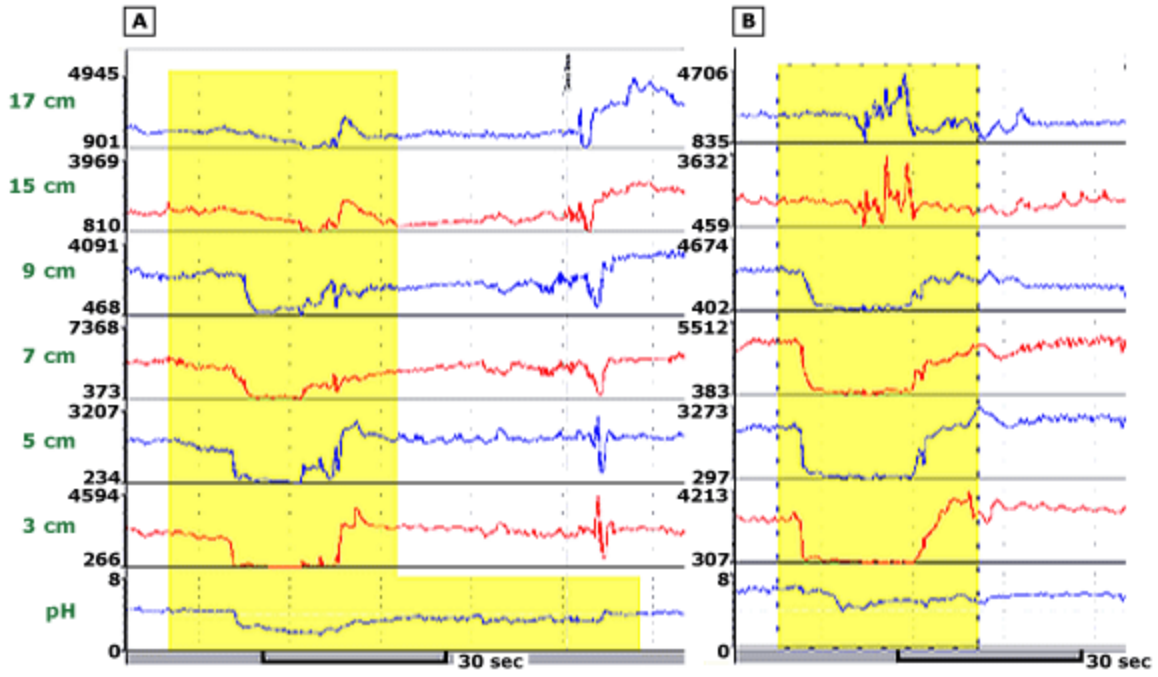


The total number of reflux episodes remains unchanged while the number of acid reflux episodes decreases and the number of non-acid reflux episodes increases on therapy. This indicates that proton pump inhibitor (PPI) therapy only changes the composition of the postprandial refluxate without affecting the total number of reflux episodes.

Data from: Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophagel impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology 2001; 120:1599.

Graphic 76249 Version 3.0

Reflux episodes identified by combined impedance-pH monitoring

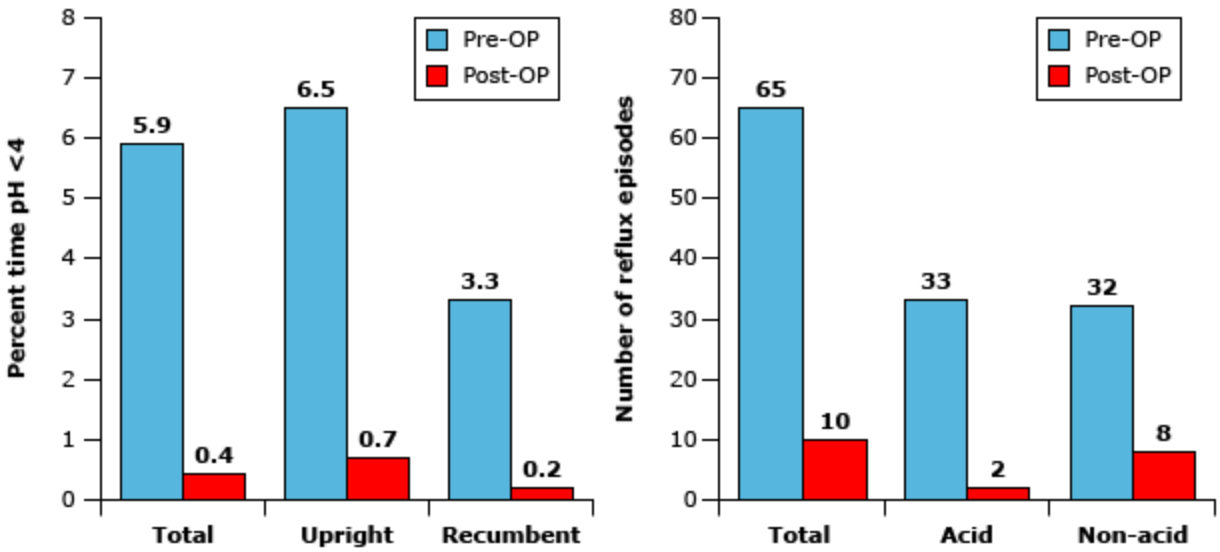


Impedance-measuring segments are located 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter (LES), the esophageal pH sensor 5 cm above the LES (bottom channel). Reflux episodes are detected by the rapid decline in impedance starting in the distal esophagus and over time advancing proximally (ie, retrograde bolus movement). The example on the left (A) is an acid reflux episode as esophageal pH declines from above to below 4.0. Note that the esophageal pH remains below 4.0 longer than the refluxate presence in the esophagus and is later cleared by a swallow. The example on the right (B) is a non-acid reflux episode as the esophageal pH remains above 4.0. Note that this reflux episode would have been missed by conventional pH monitoring alone.

Courtesy of Radu Tutuian, MD, and Donald O. Castell, MD.

Graphic 80772 Version 2.0

Impedance-pH monitoring before and after laparoscopic Nissen fundoplication



Pre-OP: pre-operation; Post-OP: post-operation.

Data from: del Genio G, Tolone S, del Genio F, et al. Total fundoplication controls acid and nonacid reflux: Evaluation by pre- and postoperative 24-h pH-multichannel intraluminal impedance. Surg Endosc 2008; 22:2518.

Graphic 60423 Version 1.0

Contributor Disclosures

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