Title:
GASTRO-ESOPHAGEAL REFLUX DISEASE: LIMITS OF MEDICAL TREATMENT AND SURGICAL INDICATIONS

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Gastro-esophageal reflux disease: limits of medical treatment and surgical indications

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ABSTRACT
Proton-pump inhibitors (PPI) have long been considered as the ideal treatment for gastroesophageal reflux disease (GERD), and their limitations and side effects have revealed a need for new therapeutic approaches. At present, the therapeutic gains achieved are relatively small or limited to groups of patients with specific characteristics. This article updates the contributions, indications, and limitations of pharmacological, endoscopic, and surgical treatment.

Keywords: Gastroesophageal reflux. Pharmacological. Endoscopic. Surgical treatment.

INTRODUCTION
There is a wide variety of therapeutic options to treat the different forms of presentation of gastroesophageal reflux disease (GERD) (Table 1). The purpose of this
Lifestyle modifications are part of the usual initial measures (Table 2). They are especially useful in patients with mild and intermittent symptoms. The limited scientific evidence in this area indicates that only elevation of the head of the bed and weight loss are associated with improvement in symptoms in case-control studies (1,2).

PHARMACOLOGICAL TREATMENT

Antacids and alginate
Antacids are fast-acting, short-lived compounds that neutralize acid and reduce pepsin activity. They provide rapid short-term relief but are not effective in healing erosive esophagitis (EE) (3). They may interfere with the absorption of other drugs (tetracycline, digoxin, etc.). Absorbable antacids have more systemic side effects (alkalosis), so they should be used for short periods. Non-absorbable antacids, depending on their composition, may cause diarrhea, constipation, or depletion of phosphates among other unwanted effects, and should be used with caution in patients with renal insufficiency (3,4). Alginate interacts with acid forming a pH-neutral barrier “raft” floating on top of the ingested chyme that co-localizes in the region of the acid pocket. Combined with an antacid, it rapidly reduces the symptoms and damage caused by acidic and non-acid reflux components such as pepsin and bile acids (5). Its benefits are scarce in GERD. It is considered as an alternative treatment for non-erosive gastroesophageal reflux disease (NERD), and complementary in patients with GERD refractory to PPIs (6).

Mucosal protective agents
These compounds generate a protective layer of esophageal mucosa and/or strengthen its defense mechanisms. Sucralfate (sucrose sulfate and aluminum hydroxide) binds to proteins selectively in erosive lesions, facilitating their healing (7). It is effective in the improvement of
symptoms in patients with reflux esophagitis (8). Sucralfate’s role in NERD is not well determined. It is generally considered as a complementary therapy.

It is not recommended in patients aged < 14 years, nor in patients with severely altered renal function. Experimental animal studies do not suggest harmful effects on pregnancy (9). It can decrease the absorption of a wide group of drugs.

The association of hyaluronic acid, chondroitin sulfate, and poloxamer 407 has a mechanism of action similar to that described for sucralfate. It is more effective than placebo, even in patients with persistent symptoms despite PPI treatment (10), although without proven scientific evidence.

Experience with drugs directly aimed at increasing mucosal barrier resistance such as irsogladine or rebapimide is scarce, with wide variability and generally limited to symptomatic improvement (11,12).

**Transient lower esophageal sphincter relaxation (TLESR) inhibitors**

TLESR is the main cause of reflux in normal subjects and in patients with mild GERD. It plays an important role in the development of GERD. TLESR inhibitors are indicated in patients with persistent regurgitation despite appropriate antisecretory treatment (13). Of the different groups of drugs investigated, only \( \gamma \)-aminobutyric acid B (GABA B) receptor agonists and metabotropic glutamate receptors subtype 5 (mGluR5) antagonists have reached the stage of clinical use (14).

Baclofen is the most emblematic representative of GABA B receptor agonists; its neurological side effects limited its use and promoted the development of other molecules such as lesogaberan and arbaclofen placarbil, with little therapeutic gain (13). This, along with side effects, has stopped its development.

mGluR5 act at a peripheral and central level decreasing vagovagal reflex. The most studied drugs are mGluR5 ADX 10059 and AZD2066. Available data from clinical trials are limited. The effectiveness in controlling TLESR of ADX 10059 is overshadowed by the presence of side effects, and the efficacy and safety of AZD2066 need further assessment (4).

**Promotility agents**
One of the most attractive therapeutic targets is that aimed at correcting or improving some of the most important factors related to GERD: LES hypotension, poor esophageal clearance, and delayed gastric emptying. Multiple drugs have been investigated, including: selective dopamine receptor antagonists, selective 5-HT4 receptor agonists, muscarinic agonists, and even an antibiotic of the macrolide group, erythromycin. Its effectiveness in the esophagus is low and its clinical use is conditioned by the side effects that have led to the withdrawal of some drugs such as cisapride. Its use is relegated to patients with symptoms related to regurgitations and delayed gastric emptying (15).

Inhibitors of acid secretion

The two most important groups of gastric acid secretion inhibitors are histamine H2 receptor antagonists (H2RAs), and proton-pump inhibitors (PPIs).

H2RAs (cimetidine, ranitidine, famotidine, nizatidine, and roxatidine) decrease gastric acid secretion by reversibly binding to histamine H2 receptors located on gastric parietal cells. They are more effective than placebo at relieving GERD symptoms (16) but are ineffective in healing esophagitis (18). They are indicated in patients with mild GERD and PPI intolerance. The addition of bedtime H2RAs as complementary therapy to PPIs is clinically effective in controlling nocturnal acid breakthrough and GERD symptoms, but patients develop tolerance after weeks or months. Side effects are rare (approximately 4 %) (17). Standard dose increase has shown no benefit (16).

PPIs block acid production by irreversibly inhibiting the H+/K+/ATPase pump (proton pump) on the surface of gastric parietal cells. Because of their high power of acid secretion inhibition, they are recommended as first-line treatment in patients with GERD and other acid-related diseases.

The United States Food and Drug Administration (FDA) has approved six subtypes of PPIs: omeprazole, lansoprazole, pantoprazole, rabeprazole, and the stereoisomeric compounds esomeprazole and dexlansoprazole. Although their basic structure is similar, in a small number of patients metabolic pathways and genetic variation in CYP2C19 cause differences in inhibitory activity (18). In most cases these differences have minimal effects on clinical response and healing of lesions.
They should be taken 30 minutes before the first meal of the day and, if necessary, a second dose will be taken before dinner (19). PPIs are well tolerated, with few adverse events and no significant differences between them. However, despite their excellent safety profile, there is growing concern about their overuse and the numerous adverse events that have been reported. Most of these relate to prolonged inhibition of acid secretion, pharmacological interactions, or idiosyncrasy or hypersensitivity reactions, and are based on observational and retrospective studies with low evidence and few consistent data demonstrating a causal link. They are sometimes contradictory, and many of these alterations have not been confirmed with prospective clinical trials (20,21) (Table 3).

Medical treatment of GERD in different situations

Erosive GERD (EE)/Non-erosive GERD (NERD)

Healing of esophagitis is directly related to length of exposure to pH > 4, and treatment duration. Healing rates with PPIs range from 87.7 % to 95.4 % (22). Although patients with EE or Barrett’s esophagus have a longer acidic and weakly acidic exposure of the distal esophagus than that of NERD patients (23), both symptom severity and treatment response are similar (24), and therefore no differences in initial treatment have been established.

Barrett’s esophagus (BE)

The use of PPIs for BE is recommended in all clinical guidelines (25). Recommendations are made on the need to maintain treatment on a chronic basis, and to provide for different situations in relation to the presence or absence of different degrees of dysplasia or esophageal adenocarcinoma (EAC). It is recommended to increase the dose if necessary, repeating endoscopy after 3-6 months and, depending on the results, to perform endoscopic ablation or surgery. Monitoring reflux, both before and after endoscopic ablation (26), is advisable since a greater response to radiofrequency ablation has been described when effective pHmetric control is achieved (27). In some cases, it may be helpful to add bile salt chelators and prokinetics.
Although a lower risk of dysplasia/EAC has been observed with the use of aspirin, NSAIDs, and statins in association with double doses of PPIs (28), their routine use (25) is not recommended given the low risk of progression of non-dysplastic BE, and the possible side effects of these drugs.

**Extraesophageal manifestations of GERD (EGERD)**

EGERD manifestations with an accepted relationship with GERD include cough, laryngopharyngeal reflux, asthma, and chest pain. They always require an investigation of other causes. A better response to anti-reflux treatment is obtained in patients who present with typical symptoms, a pathological acid/weakly acidic exposure in the esophagus, or when there is a positive symptomatic association (29). Treatment with double doses of PPIs and lifestyle modifications is recommended for 3-6 months, as EGERD symptoms take longer to improve than typical GERD manifestations. If symptoms persist despite treatment, it is advisable to perform a 24-hour impedance-pHmetry on-treatment. If the result remains positive for reflux or there is a positive symptomatic association, anti-reflux surgery should be considered.

**Maintenance therapy**

Given the high frequency of clinical recurrence in both EE (about 100 %) and NERD (≈ 75 %) (30,31), and the likelihood of progression from NERD to EE (32), maintenance therapy is recommended with the minimum dose of PPI able to control symptoms and avoid lesions (33).

**Refractory GERD**

A patient is considered to be refractory to PPI treatment when symptoms or lesions persist after 12 weeks on double dose of PPIs. In patients with persistence of symptoms with a single dose of a PPI, doubling the dose is recommended (33,34). If improvement is not achieved, it is advisable to rethink the diagnosis by assessing other diagnostic possibilities: therapeutic noncompliance, hypersensitive esophagus, large hiatal hernias, or hypersecretion states (Zollinger-Ellison syndrome), and to check for reflux (pHmetry-impedance on- or off-treatment, depending on the case). If refractory
reflux is confirmed, then endoscopic or surgical treatment should be considered.

**ENDOSCOPIC TREATMENT OF GERD**

In the last 20 years, various endoscopic techniques have been developed for the treatment of GERD (Table 4). Techniques based on the submucosal injection of different substances into the esophago-gastric junction (EGJ) and some sutures such as EndoCinch™ or NDO Plicator have been abandoned due to complications and/or poor efficacy. Other techniques are in the early stages of development. At present, the possibilities of endoscopic treatment are:

1. **Induction of fibrosis at the EGJ.** The main representative is the Stretta® device, approved by the FDA in 2000. This catheter is inserted over a guide, fixing the distal end in the EGJ, previously located by endoscopy. The inflation of the balloon at its tip causes the deployment of small needles that are inserted into the muscle layer and, by means of a pedal, energy is released that causes increases in temperature of 65-85 °C. The procedure begins 1 cm above the EGJ and extends to the entire LES and the gastric cardia. The objective is to increase resistance by decreasing compliance and increasing the thickness of the LES (35).

   As in most publications on endoscopic procedures, results are highly variable. Some meta-analyses show significant improvement in terms of both acid exposure and PPI discontinuation, while other studies do not find any such improvements (36,37). Follow-up reports covering eight and ten years indicate the maintenance of a statistically significant improvement in quality of life, and up to 41% of patients free of PPIs (38). Complications and adverse events are mild, although some serious events have also been reported (38).

2. **Endoscopic plication systems.** The most developed techniques are TIF (transoral incisionless fundoplication) with the EsophyX™ system, and the MUSE™ device (Medigus, TelAviv, Israel).

   The TIF technique was approved by the FDA in 2007. The EsophyX™ TIF 2.0 procedure is currently used. It consists in performing a fundoplication that resembles the laparoscopic one. It is performed under direct vision, using
polypropylene plates for suturing. There are several studies with this system: a) RESPECT, comparing EsophyX™ 2.0 and placebo against a sham maneuver and PPIs, and showing a significant improvement of symptoms in the fundoplication group (39,42); b) TEMPO, which randomly compares patients treated with TIF and others treated with high doses of PPIs (40), concluding that TIF is more effective at six months than PPIs at maximum doses to eliminate symptoms of regurgitation and extraesophageal involvement. In the 5-year results of 44 patients (41), 86% had no regurgitation, 80% improved their atypical symptoms, and 66% abandoned their daily use of PPIs. A meta-analysis (42) comparing the efficacy of TIF or laparoscopic fundoplication (LF) versus placebo or the use of IBPs in patients with GERD includes seven studies with a total of 1,128 patients. The authors conclude that LF is the technique that further improves LES pressure and decreases the proportion of time with pH < 4, while TIF achieves the largest increase in quality of life. TIF is considered as a relatively safe technique with few serious complications (42).

The MUSE™ plication was approved by the FDA in 2014. It consists in the creation of a previous partial fundoplication using a modified endoscope with ultrasound and a stapler, which allows the placement of two or three plates, each with five titanium staples. Results have been published at six months and then annually over four years, evaluating efficacy and safety in 37 patients (43). The proportion of patients who remained without PPIs was 83.8% at six months, and 69.4% at four years. The comparison between TIF and MUSE™ shows similar results at six to 12 months in complication rates, subsequent requirement for anti-reflux surgery, and reduction or discontinuation of PPIs (44).

3. Mucosectomy/anti-reflux ablation systems. They are known by the acronyms ARMS (anti-reflux mucosectomy) or ARMA (anti-reflux mucosal ablation). Both procedures have been described by H. Inoue. In 2014, the results obtained with ARMS in the gastric side of the cardia in ten patients with refractory GERD using the cap system after submucosal injection were published (45). An improvement in symptoms was described with a significant reduction of the
proportion of time at pH < 4. All patients discontinued their PPIs; two patients needed endoscopic dilation for stenosis. The same group has recently published their experience in 12 patients with refractory GERD (46), in whom they performed a gastric mucosal ablation by subcardial retrovision and using spray coagulation with a catheter. At nine months, they refer a significant improvement in symptoms and DeMeester’s score. They had no complications and the authors point out that this technique applies to patients who require PPIs following other techniques such as ARMS.

SURGICAL TREATMENT
Surgical treatment is, in selected groups of patients, a good alternative to medical treatment. Its effectiveness is similar and in some cases superior to short- and long-term drug treatment (47). The most common indications for surgical treatment are shown in table 5.

Laparoscopic fundoplication, with its different variants (the 360° fundoplication or Nissen technique, the 270° partial posterior fundoplication or Toupet technique, and the 180° anterior fundoplication or Dor technique) are the most commonly used procedures. The objectives of these techniques are to achieve at least 3 cm of intra-abdominal esophagus, repair the diaphragmatic hiatus, and create a valve mechanism. The Dor fundoplication, due to its lower anti-reflux power, is reserved for the treatment of motor disorders after esophageal myotomy.

The Nissen fundoplication is the reference anti-reflux technique. It achieves reflux control in approximately 90% of patients. Its most frequent side effects are temporary dysphagia and air trapping.

In the Toupet technique, the plication with the gastric fundus only surrounds the posterior 3/4 parts of the abdominal esophagus. The results are similar to those of the Nissen technique, and since the closure of the plication is not complete, the symptoms caused by air trapping are reduced. Although most surgeons consider the Nissen technique to be the most effective, no randomized study has been able to show that it is superior to the Toupet procedure (48).
In the long term, fundoplication failure rates are estimated between 5% and 20%. Most common complications include plication herniation, which generally results in dysphagia, chest pain, and recurrence of reflux. Reoperation for previous failure is more difficult than the first surgery, postoperative complications are more frequent, and the efficacy in controlling reflux is lower.

Reoperation is only recommended in patients with recurrent erosive esophagitis and/or who are highly symptomatic, with marked deterioration in their quality of life due to severe reflux or distal obstruction to the passage of the bolus. The surgeon performing the reoperation must be experienced in anti-reflux surgery, reoperations, and gastric and esophageal resections. Although the recommended approach is laparoscopic, conversion to open surgery is possible.

Reinterventions may require procedures such as mesh hiatalplasty to reinforce the closure of the diaphragmatic crura, relaxation incisions in the diaphragm, and esophageal elongation by tubulizing the proximal stomach to make a “new abdominal esophagus” (Collis gastroplasty). In multioperated patients with refractory reflux or severe esophageal motility disorders, duodenal diversion or, currently, gastric bypass may be the definitive solution.

**New alternatives**

Two systems have been presented in recent years as an alternative to traditional laparoscopic fundoplication. The objective of both is to maintain the anatomy of the gastroesophageal junction, and to try exclusively to increase LES pressure.

The LINX system is based on the placement around the gastroesophageal junction of a flexible ring of beads with a magnetic core, linked by a titanium thread. The magnets help keep the LES closed. During food intake, the force of the peristaltic waves and the relaxation of the LES cause the magnets to separate, facilitating the passage of the bolus. It was approved by the FDA in 2012. The technique is performed laparoscopically. In patients with a hiatal hernia > 3 cm, closure of the diaphragmatic pillars is associated, so the difference with fundoplication is the absence of fundic mobilization. It has a good safety profile and has been shown to be effective in controlling symptoms and esophageal pH in selected patients (typical symptoms, with
response to PPIs, hiatal hernia < 3 cm, absence of severe esophagitis). Good results have been reported at six and 12 years, with a reduction of 50% or more in the average daily dose of PPIs in 89.5% of patients (49). In approximately 5.5% of cases, it is necessary to remove the implanted devices. The mean time elapsed between the placement of the LINX and its removal was 863 days (50). MRI compatibility is dependent on the LINX model implanted. In the absence of more randomized studies with a sufficient number of patients and follow-up, it is presented as a good alternative to fundoplication in selected patients.

The EndoStim™ system is based on electrical stimulation of the LES by inserting two electrodes into the muscle layer of the distal esophagus, connected to a pulse generator implanted in the abdominal wall, which is controlled by an external programmer. The goal is to increase sphincter pressure without compromising sphincter relaxation or esophageal peristalsis. Most of the studies at six and 12 months report good results in terms of improved quality of life and reduction or discontinuation of PPI treatment. It has a good safety profile with little or no dysphagia.

CONCLUSIONS

PPIs have long been considered as the ideal treatment for GERD. Limitations discovered in recent years regarding this group of drugs have revealed the need for new pharmacological, endoscopic, and surgical therapeutic approaches. Currently, the therapeutic gains achieved are relatively small or restricted to groups of patients with special characteristics.

REFERENCES


22. Zheng RN. Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. World J


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<td>2. Pharmacological treatment</td>
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<td>– Antacids/alginate</td>
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<td>– Mucosal protectors</td>
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<td>– Transient LES relaxation (TLESR) inhibitors</td>
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<tr>
<td>– Prokinetic agents</td>
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<tr>
<td>– Inhibitors of acid secretion</td>
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<tr>
<td>– Pain modulators</td>
</tr>
<tr>
<td>3. Endoscopic treatment</td>
</tr>
<tr>
<td>– Injection/implants</td>
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<tr>
<td>– Fibrosis by thermal energy</td>
</tr>
<tr>
<td>– Suture/staple</td>
</tr>
<tr>
<td>– Mucosectomy/ablation</td>
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<tr>
<td>4. Surgical treatment</td>
</tr>
<tr>
<td>– Fundoplication</td>
</tr>
<tr>
<td>• Total (Nissen)</td>
</tr>
<tr>
<td>• Partial (Toupet, Dor)</td>
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<tr>
<td>– New therapeutics</td>
</tr>
<tr>
<td>• Linx™</td>
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<td>• EndoStim™</td>
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</table>
Table 2. Lifestyle modifications for GERD

- Avoid large meals
- Avoid problematic foods (high fat, citrus, coffee, carbonated beverages, alcoholic beverages, spicy foods, chocolate, onions, carminatives)
- Reduce fluids during meals
- Avoid bending over or lying down after meals (within 2-3 hours)
- Avoid eating before exercise
- Raise the head of the bed (nocturnal symptoms)*
- Weight loss (overweight)*
- Quit smoking
- Avoid tight clothing
- Avoid as much as possible drugs that can promote reflux (nitrates, anticholinergics, theophylline, calcium channel blockers, bisphosphonates, etc.)

*Measures associated with improvement of GERD symptoms in case-control studies.
Table 3. Potential safety issues associated with PPI use

<table>
<thead>
<tr>
<th>Safety problem</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>Malabsorption of acid-dependent nutrients</strong></td>
<td>Uncertain clinical significance</td>
</tr>
<tr>
<td>Iron</td>
<td></td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Possible, not confirmed</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>Increased hip fractures</td>
<td>Controversial relationship. Assess prophylaxis in patients with osteoporosis</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Magnesium/potassium</td>
<td></td>
</tr>
<tr>
<td>Instability</td>
<td>Uncommon. Control in patients at risk</td>
</tr>
<tr>
<td>Paresthesia</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dementia</td>
<td>Inconsistent evidence</td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>Control in patients at risk</td>
</tr>
<tr>
<td><strong>Increased risk of infections</strong></td>
<td>Proven relationship with little clinical relevance</td>
</tr>
<tr>
<td>Enteric infections</td>
<td>Low clinical relevance except in at-risk patients</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Rare. Important cofactor. Avoid PPIs in patients at risk</td>
</tr>
<tr>
<td><em>Campylobacter, Salmonella</em></td>
<td>Controversial association, very low risk</td>
</tr>
<tr>
<td>Bacterial peritonitis</td>
<td>Controversial association, very low risk</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Variable, not very significant relationship</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>Little significant clinical relevance</td>
</tr>
<tr>
<td>ICU</td>
<td>Not proven</td>
</tr>
<tr>
<td>COVID-19</td>
<td>More studies required</td>
</tr>
<tr>
<td><em>Hypergastrinemia effects</em></td>
<td>Proven relationship with little clinical relevance</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ECL cell hyperplasia</td>
<td>Little relevance. Assess in cases with marked hypergastrinemia</td>
</tr>
<tr>
<td>Gastric tumors</td>
<td>Possible increased risk in <em>H. pylori</em> patients. Probable confounders</td>
</tr>
<tr>
<td>Acid rebound hypersecretion</td>
<td>Frequent. Adjust to the lowest effective dose</td>
</tr>
<tr>
<td>Fundic polyps</td>
<td>Proven relationship with little clinical relevance. Follow-up in exceptional cases</td>
</tr>
</tbody>
</table>

**Pharmacological interactions**
- Confirmed relationship with multiple drugs
- Reducing absorption
- Altering metabolism Potentially important (HIV protease inhibitors, antifungals, etc.)

**Idiosyncratic/hypersensitivity reactions**
- Anaphylaxis Rare, potentially serious. Avoid and/or withdraw PPIs in patients with risk factors
- Interstitial nephritis
- Other

**Other**
- Collagenous colitis Rare. Inconsistent evidence. More studies required
- Cardiac ischemia
- Chronic kidney disease
- Cerebral ischemia
- Other
<table>
<thead>
<tr>
<th>Injection or implantation</th>
<th>Thermal energy fibrosis</th>
<th>Suture or stapling</th>
<th>Mucosectomy or ablation</th>
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<tbody>
<tr>
<td>Enteryx</td>
<td>Stretta®</td>
<td>EndoCinch™</td>
<td>ARMS (anti-reflux mucosectomy)</td>
</tr>
<tr>
<td>Gatekeeper</td>
<td>Plicator</td>
<td>ARMA (anti-reflux mucosal ablation)</td>
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<tr>
<td>Durasphere</td>
<td>EsophyX™</td>
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<tr>
<td>Plexiglas</td>
<td>MUSE™ (Medigus)</td>
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<td></td>
<td>Other</td>
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Table 5. Most common indications for surgical treatment of GERD

- Patients who do not respond to medical treatment
- Patients who respond well but have an early recurrence after stopping medical treatment, and who reject chronic drug treatment
- Patients with disease progression requiring high doses of PPIs
- Complicated GERD (Barrett’s esophagus, esophageal ulcer, stenosis, large hiatal hernia)
- Intolerance to drug treatment
- Extraesophageal symptoms secondary to GERD