



**EDUCATIONAL OBJECTIVE:** Readers will be familiar with the indications for further diagnostic testing and surgery in patients with gastroesophageal reflux disease

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# Antireflux surgery in the proton pump inhibitor era

## ABSTRACT

Although proton pump inhibitors (PPIs) are now the first-line treatment for gastroesophageal reflux disease (GERD), surgery still has several specific indications. We review the current treatment of GERD and discuss how antireflux surgery fits into the overall scheme.

## KEY POINTS

If a PPI in twice-daily doses fails to relieve GERD symptoms, a pH study combined with multichannel intraluminal impedance testing can help in deciding whether to try surgery.

Antireflux surgery can be considered for erosive esophagitis that does not resolve with drug therapy, for volume regurgitation (particularly if it occurs at night or if there is a risk of aspiration), and for patients who need lifelong treatment for reflux but have had a serious adverse event related to PPI therapy.

Studies are needed to directly compare medical and surgical therapy in patients with extraesophageal manifestations of GERD and refractory symptoms, a difficult group of patients.

Drugs that inhibit transient relaxation of the lower esophageal sphincter are under investigation, as are minimally invasive procedures to manipulate the physical barrier to reflux.

FOR MOST PATIENTS WITH gastroesophageal reflux disease (GERD), a proton pump inhibitor (PPI) is the first choice for treatment.<sup>1</sup> But some patients have symptoms that persist despite PPI therapy, some desire surgery despite successful PPI therapy, and some have persistent extraesophageal symptoms or other complications of reflux. For these patients, surgery is an option.<sup>2</sup>

In this article, we review the management of GERD and clarify the indications for antireflux surgery based on evidence of safety and efficacy.

## GERD DEFINED: SYMPTOMS OR COMPLICATIONS

Defining the role of antireflux surgery is difficult, given the variety of presentations and the absence of a gold standard for diagnosing GERD. Most adults experience several episodes of physiologic reflux daily without symptoms.<sup>3</sup> But a broad array of symptoms have been attributed to GERD, including chest pain, cough, and sore throat, and some conditions caused by acid reflux (eg, Barrett esophagus) can be asymptomatic.<sup>4,5</sup>

Given these challenges, in 2006 the Montreal Consensus Group defined GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms or complications.”<sup>4</sup> Critical to the Montreal definition is the distinction between “troublesome symptoms” and “complications” or bodily injury (TABLE 1).

## HEARTBURN ISN'T ALWAYS GERD

Typical GERD presents with the classic symptoms of pyrosis (heartburn) or acid regurgitation, or both.

Dr. Madanick has disclosed teaching and speaking for AstraZeneca corporation, makers of Nexium.

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**Alarm features of stomach or esophageal cancer: weight loss, dysphagia, vomiting, GI bleeding, anemia, chest pain, epigastric mass**

**TABLE 1**

**The Montreal Consensus Group definition of syndromes associated with gastroesophageal reflux disease**

**Esophageal syndromes**

Symptomatic syndromes  
 Typical reflux syndrome  
 Reflux chest pain syndrome

**Esophageal injury syndromes**

Reflux esophagitis  
 Reflux stricture  
 Barrett esophagus  
 Esophageal adenocarcinoma

**Extraesophageal syndromes**

**Established associations**

Reflux cough  
 Reflux laryngitis  
 Reflux asthma  
 Reflux dental erosions

**Proposed associations**

Sinusitis  
 Pulmonary fibrosis  
 Pharyngitis  
 Recurrent otitis media

BASED ON VAKIL N, VAN ZANTEN SV, KAHRILAS P, DENT J, JONES R, AND THE GLOBAL CONSENSUS GROUP. THE MONTREAL DEFINITION AND CLASSIFICATION OF GASTROESOPHAGEAL REFLUX DISEASE: A GLOBAL EVIDENCE-BASED CONSENSUS. AM J GASTROENTEROL 2006; 101:1900-1920, WITH PERMISSION FROM MACMILLAN PUBLISHERS LTD.

Although these symptoms are often thought to be specific for GERD, other causes of esophageal injury—eg, eosinophilic esophagitis, infection (*Candida*, cytomegalovirus, herpes simplex virus), pill-induced esophagitis, or radiation therapy—can produce similar symptoms. Other causes, including coronary artery disease, biliary colic, foregut malignancy, or peptic ulcer disease, should also be considered in patients with supposedly typical GERD. Life-threatening mimics of GERD, such as unstable angina, should be excluded if they are likely, before proceeding with evaluating for possible GERD. Therefore, the initial history and examination should focus on appropriate diagnosis, with careful delineation of symptom quality.

Alarm features for advanced pathology<sup>6-8</sup> include involuntary weight loss, dysphagia,

vomiting, evidence of gastrointestinal blood loss, anemia, chest pain, and an epigastric mass.<sup>7</sup> Admittedly, these features are only mediocre for detecting or excluding gastric or esophageal cancer, with a sensitivity of 67% and a specificity 66%.<sup>9</sup> Nevertheless, they should prompt an endoscopic examination. In patients who have alarm features but have not yet been treated for GERD, upper endoscopy can identify an abnormality in about 60% of patients.<sup>10-12</sup>

**■ PPIs HAVE REPLACED ANTACIDS AND HISTAMINE-2 RECEPTOR ANTAGONISTS**

When the symptoms suggest GERD and no alarm features are present, an initial trial of the following lifestyle changes is reasonable:

- Avoiding acidic or refluxogenic foods (coffee, alcohol, chocolate, peppermint, fatty foods, citrus foods)
- Avoiding certain medications (anticholinergics, estrogens, calcium-channel blockers, nitroglycerine, benzodiazepines)
- Losing weight
- Quitting smoking
- Raising the head of the bed
- Staying upright for 2 to 3 hours after meals.

For someone with mild symptoms, these changes pose minimal risk. Unfortunately, they are unlikely to provide adequate symptom control for most patients.<sup>13-17</sup>

Before PPIs were invented, drug therapy for GERD symptoms that did not resolve with lifestyle changes consisted of antacids and, later, histamine-2 receptor antagonists. When maximal therapy failed to control symptoms, fundoplication surgery was considered an appropriate next step.

PPIs substantially changed the management of GERD, suppressing acid secretion much better than histamine-2 receptor antagonists. Taken 30 minutes before breakfast, a single daily dose of a PPI normalizes esophageal acid exposure in 67% of patients.<sup>18</sup> Adding a second dose 30 minutes before dinner raises the number to more than 90%.<sup>19</sup>

PPIs have consistently outperformed histamine-2 blockers in the healing of esophagitis and in improving heartburn symptoms and are now the first-line medical therapy for uncomplicated GERD.<sup>6,8,20-25</sup>

## ■ WHEN PPIs WORK, SURGERY OFFERS NO ADVANTAGE

Patients may not want to take a PPI for the rest of their life, for a number of reasons: cost, the need to take one or more pills daily, and potential adverse effects.<sup>26</sup> In these cases, the physician can counsel the patient on the relative merits of long-term medical therapy vs surgery (TABLE 2).<sup>2,26</sup>

The LOTUS trial (Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic GERD) compared long-term drug therapy with surgery to maintain remission of symptoms in GERD.<sup>27</sup> In this trial, 554 patients whose symptoms initially responded to the PPI esomeprazole (Nexium) were randomized to continue to receive esomeprazole (n = 266) or to undergo laparoscopic antireflux surgery (288 were randomly assigned, and 248 had the operation). Dose adjustment of the esomeprazole was allowed (20–40 mg/day). A total of 372 patients completed 5 years of follow-up (192 esomeprazole, 180 surgery).

Symptoms stayed in remission in 92% of the esomeprazole group and 85% of the surgery group ( $P = .048$ ). However, the difference was no longer statistically significant after modeling the effects of study dropout. The rate of severe adverse events was similar in both groups: 24.1% with esomeprazole and 28.6% with surgery.

These findings indicate that if symptoms fully abate with medical therapy, surgery offers no advantage. In addition, patients who desire surgery in the hope of avoiding lifelong drug therapy should be made aware that drug therapy and reoperation are often necessary after surgery.<sup>28</sup> In most cases, antireflux surgery is unnecessary for patients whose GERD fully responds to PPI therapy.

## ■ IF PPIs FAIL, FURTHER TESTING NEEDED

But many patients who take PPIs still have symptoms, even though these drugs suppress acid secretion and heal esophagitis. In fact, symptoms completely resolve in only about one-half of patients with erosive disease and one-third of those without erosive disease.<sup>21</sup>

Reasons for an incomplete symptomatic response to PPIs are various. Acid reflux

TABLE 2

### Complications and adverse events related to medical and surgical therapy for gastroesophageal reflux disease

#### Proton pump inhibitor therapy<sup>26</sup>

*Clostridium difficile* infection

Bacterial overgrowth in the small intestine, and other enteric infections

Pneumonia

Loss of bone density

Acute interstitial nephritis

Vitamin B<sub>12</sub> and iron deficiencies

#### Antireflux surgery (perioperative)<sup>2</sup>

Conversion from laparoscopic to open procedure (0%–24%)

Perforation (0%–4%)

Pneumothorax (0%–1.5%)

Wound infection (0.2%–3.1%)

Herniation at site of laparoscopic port (0.2%–9%)

Death (0.07%)

#### Antireflux surgery (postoperative)<sup>2</sup>

Dysphagia (0%–25%)

Gas bloating (5%–34%)

Need for antisecretory drugs (6%–62%)

Reoperation (0%–15%)

can persist, but this accounts for only 10% of cases.<sup>29</sup> About one-third of patients have persistent reflux that is weakly acidic, with a pH higher than 4.29. However, most patients with persistent typical GERD symptoms do not have significant, persistent reflux, or their symptoms are not related to reflux events. In these cases, an alternative cause of the refractory symptoms should be sought.

Further diagnostic testing is indicated when symptoms persist despite PPI therapy. Upper endoscopy will reveal an abnormality such as persistent erosive esophagitis, eosinophilic esophagitis, esophageal stricture, Barrett esophagus, or esophageal cancer in roughly 10% of patients in whom empiric therapy fails.<sup>10</sup>

Although patients with persistent symptoms have not been enrolled in many randomized controlled trials, a multivariate analysis showed that failure of medical therapy heralds a poor response to surgery.<sup>30</sup> Data such as these have led most experts to discourage fundoplication for such patients now, unlike in the pre-PPI era.

**pH and intraluminal impedance testing**

However, this recommendation against surgery is not a hard-and-fast rule.

When symptoms of GERD do not respond to twice-daily PPI therapy and the results of upper endoscopy are negative, then an esophageal pH study combined with multichannel intraluminal impedance (MII-pH) testing may help identify patients who will respond to an intensification of medical therapy or to surgery, particularly if symptoms correlate with documented reflux events<sup>31-33</sup> (FIGURE 1). Most experts believe that esophageal MII-pH testing should be performed while the patient is taking a PPI to best identify patients whose refractory symptoms are most likely to be related to ongoing reflux.

**In patients with esophageal regurgitation,** most will not achieve adequate relief of symptoms with PPI therapy alone.<sup>34</sup> The therapeutic gain of PPI therapy vs placebo averaged just 17% in seven randomized, controlled trials, more than 20% less than the response rate for heartburn.<sup>34</sup> This is likely because of structural abnormalities such as reduced lower esophageal sphincter pressure, hiatal hernia, or delayed gastric emptying. Antireflux surgery can correct these structural abnormalities or prevent them from causing so much trouble; however, the presence of true regurgitation should first be confirmed by MII testing. If regurgitation is confirmed, antireflux surgery is warranted, particularly in patients with nocturnal symptoms who may be at high risk of aspiration. With careful patient selection, regurgitation symptoms improve in about 90% after surgery.<sup>2</sup>

**In patients with heartburn,** if esophageal acid exposure continues to be abnormal on MII-pH testing, then an escalation of therapy may improve symptoms, particularly if symptoms occur during reflux or if they partially responded to PPI therapy. Options in this sce-

nario include alteration or intensification of acid-suppressive therapy, treatment with baclofen (Lioresal), and antireflux surgery.<sup>18,35,36</sup> In randomized controlled trials of patients whose symptoms partially responded to PPIs, antireflux surgery has performed similarly to PPIs in terms of improving typical GERD symptoms, particularly regurgitation.<sup>27,37-41</sup> Although this scenario is a reasonable indication for antireflux surgery, recommendations should be made with appropriate restraint since it is not easily reversible, some patients experience complications, and up to one-third will have no therapeutic benefit.<sup>30</sup>

**Nonacid reflux.** In some cases, MII-pH testing during PPI therapy will reveal reflux of weakly acidic (pH > 4) or alkaline stomach contents, often called “nonacid reflux.”<sup>29</sup> Nonacid reflux is often present in patients with esophagitis that persists despite PPI therapy, indicating that even weakly acidic stomach contents can injure the mucosa.<sup>42</sup> Since intensifying the acid-suppressive therapy is unlikely to improve these symptoms, antireflux surgery may have a role.

In one study,<sup>43</sup> nonacid reflux was well controlled by laparoscopic Nissen fundoplication, although 15 (48%) of 31 patients had persistent symptoms of GERD after surgery. No patient had a strong symptom correlation with postoperative reflux events, suggesting an alternative cause of the persistent symptoms. Therefore, antireflux surgery for nonacid reflux should be limited exclusively to patients with strong symptom correlation, and even then it should be considered with restraint, given the limited evidence for benefit and the potential for harm.

**If testing is negative.** In studies investigating the diagnostic yield of MII-pH testing, more than 50% of patients who had refractory symptoms had a negative MII-pH test.<sup>29</sup> In such situations, when the symptoms are strongly correlated with reflux events, the patient is said to have “esophageal hypersensitivity.” A few small studies have suggested that such patients may benefit from surgery, but these data have not been replicated in randomized controlled trials.<sup>32</sup>

When the testing is negative and there is no correlation between the patient’s symptoms and reflux events, the patient is unlikely

**Lifestyle modifications for mild symptoms pose minimal risk but are unlikely to provide adequate relief for most patients**

## A test to distinguish acid from nonacid reflux

In many patients with gastroesophageal reflux disease, proton pump inhibitor (PPI) therapy fails to relieve the symptoms. Combined multichannel intraluminal impedance testing and esophageal pH testing (MII-pH testing) can help determine if symptoms correlate with acid or with nonacid reflux material.

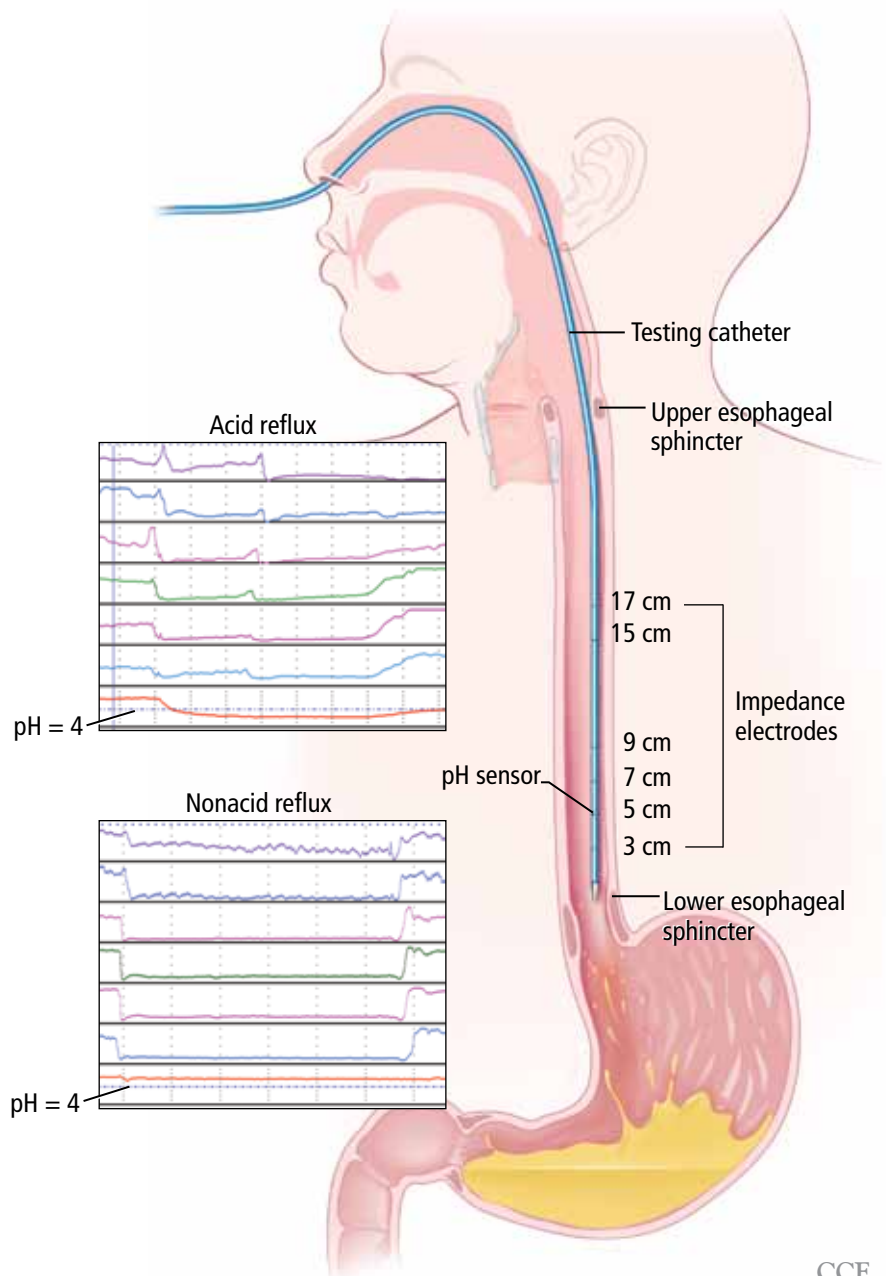
MII-pH testing can help determine if an intensification of acid-suppressive drug therapy is worth trying or, in the case of nonacid reflux, if the patient might benefit from antireflux surgery.



The ambulatory 24-hour test is performed while the patient is taking a PPI to see if refractory symptoms correlate with reflux events.

The patient keeps a diary of events, including the time and type of food intake, when PPI pills are taken, and the time symptoms occur. This information is later correlated with the data on the recording monitor.

Along the catheter, MII electrodes detect reflux events over time at specific points above the lower esophageal sphincter, ie, at 3, 5, 7, 9, 15, and 17 cm. A pH sensor 5 cm above the lower sphincter can detect weakly acidic ( $\text{pH} > 4$ ) or alkaline stomach contents (nonacid reflux), a possible cause of symptoms that persist despite PPI therapy.



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FIGURE 1

to benefit from antireflux surgery. Care of these patients is beyond the scope of this review.

### ■ SURGERY RARELY IMPROVES COUGH, ASTHMA, OR LARYNGITIS

GERD has been implicated as a cause of chronic cough, asthma, and laryngitis, although each of these has many potential causes.<sup>44-46</sup> Despite these associations, the evidence for therapeutic benefit from antireflux therapy is weak.

PPI therapy shows no benefit over placebo for chronic cough of uncertain etiology, but some benefit if GERD is objectively demonstrated.<sup>47</sup> Laryngitis resolved in just 15% of patients on esomeprazole vs 16% of patients on placebo after excluding patients with moderate to severe heartburn.<sup>48</sup>

In a large randomized controlled trial in patients with asthma, there was no overall improvement in peak flow for the PPI group vs the placebo group, although significant improvement occurred in patients with heartburn and nocturnal respiratory symptoms.<sup>46</sup>

Potent antisecretory therapy seems to improve extraesophageal symptoms when typical GERD symptoms are also present, but it otherwise has shown little evidence of benefit.

The evidence for a benefit from antireflux surgery in patients with extraesophageal GERD syndromes is even more limited. Although one systematic review<sup>49</sup> found that cough and other laryngeal symptoms improved in 60% to 100% of patients with objective evidence of GERD who underwent fundoplication, virtually all of the studies were uncontrolled case series.<sup>49</sup>

The lone randomized controlled trial in the systematic review compared Nissen fundoplication with ranitidine (Zantac) or antacids only for patients with asthma and GERD, and found no significant difference in peak expiratory flow among the three groups after 2 years. However, asthma symptom scores improved in 75% of the surgical group, 9% of the medical group, and 4% of the control group.<sup>50</sup>

In a study that was not included in the prior systematic review, patients with laryngopharyngeal reflux unresponsive to aggressive acid suppression who subsequently underwent fundoplication fared no better than those who did not.<sup>51</sup>

Thus, based on the available data, antireflux surgery is only rarely indicated for extraesophageal symptoms, especially in patients who have no typical GERD symptoms or in patients whose symptoms are refractory to medical therapy.

### ■ SURGERY FOR EROSIVE ESOPHAGITIS OR BARRETT ESOPHAGUS IF PPI FAILS

Lifelong antireflux therapy is indicated for patients with severe erosive esophagitis or Barrett esophagus. Erosive esophagitis recurs in more than 80% within 12 months of discontinuing antisecretory therapy.<sup>52</sup> Both Barrett esophagus and esophageal adenocarcinoma are strongly associated with GERD, and nearly 10% of patients with chronic reflux have Barrett esophagus.<sup>53,54</sup> It is suspected that suppressing reflux reduces the rate of progression of Barrett esophagus to esophageal adenocarcinoma, but this remains to be proven.

Perhaps the strongest indication for surgery in the PPI era is for patients who have persistent symptoms and severe erosive esophagitis (Los Angeles grade C or D) despite high-dose PPI therapy. If other causes of persistent esophagitis have been ruled out, fundoplication can induce healing and improve symptoms.<sup>55,56</sup> In these cases, surgery is done to induce remission of the disease when maximal medical therapy has been truly unsuccessful.

Randomized controlled trials suggest that medical and surgical therapies are equally effective for preventing the recurrence of erosive esophagitis or the progression of Barrett esophagus. In a study of 225 patients, at 7 years of follow-up, esophagitis had recurred in 10.4% of patients on omeprazole vs 11.8% of those who had undergone antireflux surgery.<sup>40</sup> Similarly, open Nissen fundoplication was no different from drug therapy (histamine-2 receptor antagonist or PPI) for progression of Barrett esophagus over a median of 5 years.<sup>57</sup> A meta-analysis with nearly 5,000 person-years each in the medical and surgical groups also found no significant difference in rates of cancer progression.<sup>58</sup>

Notably, symptoms such as dysphagia, flatulence, and the inability to burp occurred significantly more often in the surgical groups in these studies.

**In the vast majority of patients, anti-reflux surgery is unnecessary if GERD is fully responsive to PPI therapy**

In view of these data, antireflux surgery has no significant advantage over medical therapy for maintaining healing of erosive esophagitis or preventing progression of Barrett esophagus. Thus, it should be reserved for patients who do not desire lifelong drug therapy, provided they understand that there is no therapeutic advantage for their esophagitis or for Barrett esophagus.

### ■ SPECIFIC INDICATIONS FOR ANTIREFLUX SURGERY

Now that we have PPIs, several situations remain in which surgery for GERD is either indicated or worth considering.

Antireflux surgery is clearly indicated for:

- Patients with erosive esophagitis that does not heal with maximal drug therapy
- Patients with volume regurgitation, particularly if it occurs at night or if there is evidence of aspiration
- Patients who require lifelong treatment for reflux but who have had a serious adverse event related to PPI therapy, such as refractory *Clostridium difficile* infection.

Antireflux surgery is also worth considering in patients who for personal reasons wish to avoid long-term or lifelong drug therapy.

Patients should be informed, however, that antireflux surgery has not been shown to be better than medical therapy for maintaining remission of symptoms, for preventing progression of Barrett esophagus, or for maintaining healing of erosive esophagitis. Medical therapy is still the first option for these patients.

Surgery may also be considered in patients with persistent symptoms who have a partial response to medical therapy, who show persistent acidic or weakly acidic reflux on MII-pH testing, and whose symptoms have been correlated with reflux events. Although surgery is not sure to improve their symptoms, benefit is more likely in this patient population compared with those without these characteristics.

### Extrasophageal GERD

In patients suspected of having extrasophageal GERD, surgery should be considered if typical GERD symptoms are present and improve with PPI therapy, if the extrasophageal syndrome partially responds to PPI therapy,

and if MII-pH testing demonstrates a correlation between symptoms and reflux. Surgery may have a stronger indication in this setting if the patient has nocturnal reflux or extraesophageal symptoms.

### When is surgery not an option?

In general, surgery should not be considered in patients who do not have a partial response to PPI therapy or who do not have a strong symptom-reflux correlation on MII-pH testing. In all cases of failed medical therapy without persistent severe erosive disease, the threshold for opting for surgery should be high, given the uncertain response of these patients to surgery.

Peristaltic dysfunction is a relative but not an absolute contraindication to surgery.<sup>59</sup>

### ■ RISKS, BENEFITS OF SURGERY FOR GERD

The patient's preference for surgery over drug therapy should always be balanced against the risks of surgery, including both short-term and long-term adverse events, to allow the patient to make an adequately informed decision (TABLE 2).<sup>2,26</sup>

Adverse events associated with PPI therapy are rare and in many cases the association is debatable.<sup>26</sup> Nonetheless, long-term PPI therapy has been most strongly associated with an increased risk of *C difficile* infection and other enteric infections, although the absolute risk of these events remains low.

Complication rates after antireflux surgery depend on the surgeon's experience and technique. Death is exceedingly rare. In most high-volume centers, the need to convert from laparoscopic to open fundoplication occurs in fewer than 2.4% of patients.<sup>2</sup>

Potential perioperative complications include perforation (4%), wound infection (3%), and pneumothorax (2%).<sup>2</sup>

Antireflux surgery is also associated with a significant risk of dysphagia, bloating, an inability to burp, and excessive flatulence, all of which can markedly impair the quality of life.

A major consideration is that fundoplication is generally irreversible. Reoperation rates have been reported to range from 0% to 15%.<sup>2</sup> Furthermore, up to 50% of patients still need medical therapy after surgery.<sup>60,61</sup> Of note, only about 25% of patients on medical therapy after surgery will actually have an abnormal pH study.<sup>61</sup>

**With careful patient selection, reflux symptoms improve in about 90% after surgery**

## MORE STUDY NEEDED

Future studies directly comparing medical and surgical therapy for carefully selected patients with extraesophageal manifestations of GERD and refractory symptoms should help further de-

lineate outcome in this difficult group of patients.

Under development are new drugs that may inhibit transient relaxation of the lower esophageal sphincter, as well as minimally invasive procedures, which may alter the indications for surgery in coming years.<sup>36</sup>

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