Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

Antireflux surgery – choosing the right candidate

André J. Smout[a,b], Marlies P. Schijven[b,c,d] and Albert J. Bredenoord[a,b]

[a]Department of Gastroenterology & Hepatology, Amsterdam University Medical Center, Amsterdam, The Netherlands; [b]Amsterdam Gastroenterology and Metabolism, Amsterdam, The Netherlands; [c]Department of Surgery, Amsterdam University Medical Center, Amsterdam, The Netherlands; [d]Amsterdam Public Health, Digital Health, Amsterdam, The Netherlands

ABSTRACT

Introduction: Surgical gastric fundoplication is an effective treatment option for gastroesophageal reflux disease. In contrast to acid suppression, fundoplication nearly abolishes all types of reflux, acid and nonacid. However, in some cases, lasting side effects of the procedure may overshadow its positive effects. It has remained difficult to determine which patients are the most suitable candidates for fundoplication.

Areas covered: This review aims to evaluate the available data on preoperative factors that are associated with the outcome of fundoplication and to determine which combination of patient characteristics and preoperative test results provides optimal selection. In addition, we assess the need for tailoring the procedure on the basis of the preoperative quality of esophageal peristalsis,

Expert opinion: Surgical treatment of gastroesophageal reflux disease is underutilized as it may provide an excellent option for a subset of GERD patients. It is not sensible to restrict surgical treatment to patients who do not respond to acid suppression. However, meticulous patient selection is key. Most importantly, surgical treatment should not be considered in patients in whom there is no convincing evidence that the symptoms are caused by reflux. Impaired esophageal peristalsis should not be regarded as a contraindication against fundoplication.

1. Introduction

Gastroesophageal reflux disease (GERD) is defined as the presence of bothersome reflux symptoms (heartburn, regurgitation, or other) and/or distal esophageal mucosal lesions (esophagitis, intestinal metaplasia) that are brought about by the reflux of gastric contents [1]. This definition encompasses a broad spectrum of GERD phenotypes which can be distinguished by endoscopy and pH-impedance monitoring. Studies using these techniques have made clear that erosive and non-erosive forms of the disease cannot be distinguished on the basis of symptoms, that the reflux does not need to be excessive and that the refluxate needs not to be acidic to cause typical reflux symptoms [2]. Analysis of the temporal association between symptom episodes and reflux events, using indices such as the Symptom Index (SI) and the Symptom Association Probability (SAP), makes it possible to identify patients with functional heartburn, whose reflux-like symptoms are not caused by reflux [3].

GERD is a very common disease: a systemic review concluded that the global prevalence of GERD can be estimated at 14% [4]. Many GERD sufferers in the community never consult a doctor for their symptoms, others consult a general practitioner and only a small percentage is seen by a medical specialist. This has been called the GERD iceberg [5].

For at least 30 years now, reduction of gastric acid secretion by a proton pump inhibitor (PPI) is the cornerstone of GERD treatment. This therapy suffices in the majority of cases. However, whereas PPI-resistant esophagitis is very rare,

insufficient response of typical reflux symptoms occurs in a third to a half of patients on PPIs [6,7]. PPI-refractory GERD is often defined as persistence of heartburn and/or regurgitation after 2–3 months of treatment with a PPI taken in double dose [8,9]. Referral centers that use not only endoscopy but also esophageal manometry and pH-impedance monitoring to evaluate patients with PPI-refractory symptoms report that at least one-third of these patients do not have GERD [10,11]. In the majority of these, a diagnosis of functional heartburn, defined as reflux-like symptoms but absence of signs of GERD at endoscopy and pH-impedance monitoring, is arrived at [12].

GERD therapy by surgical fundoplication was first described by the Swiss surgeon Rudolph Nissen as an open procedure, in which a 360° fundic wrap was constructed around the esophagogastric junction. Nowadays, the procedure is almost always carried out laparoscopically. In most centers, partial fundoplication (Toupet, Dor) has become the preferred option because it has been shown that this provides reflux control that is similar to that of a complete wrap and leads to less dysphagia [13]. The mechanisms through which fundoplication works include an increase in lower esophageal sphincter (LES) pressure, a decrease in the frequency of transient LES relaxations and strengthening of the so-called flap valve formed by the angle of His [14].

In contrast to acid-suppressant therapy, which only renders the refluxate less acidic, fundoplication strongly reduces reflux of all types, whether acid or nonacid, with or without duodenogastric component [15,16].

Article highlights

- Fundoplication should only be carried out when there is incontrovertible evidence that the patient has GERD.
- If the symptom response to acid suppression is unsatisfactory, there is a high probability that the diagnosis of GERD is not correct.
- Meticulous pre-fundoplication work-up including upper endoscopy, esophageal manometry, and ambulatory reflux monitoring is mandatory.
- Ineffective esophageal motility is not a contraindication against fundoplication, but tailoring of the procedure (partial rather than 360° wrap) is recommended.
- The safety of fundoplication in patients with esophageal aperistalsis is still questionable.

Recurrence of reflux after initially successful fundoplication does occur, but the magnitude of this phenomenon is limited. In a nation-wide Swedish study that involved 2655 patients who underwent laparoscopic antireflux surgery, 82.3% of the participants were still free from reflux recurrence after 5 years [17].

Fundoplication may be effective, but very few GERD patients undergo fundoplication and interest in fundoplication may even be declining. Data from nationwide databases indicate that the number of surgical fundoplications performed in the US is decreasing and that only 0.05% of patients with GERD are treated with fundoplication [18]. This is not very surprising given that PPIs are recommended as the first-line therapy for GERD in most guidelines. Moreover, long-term PPI use is safe. Fundoplication can fail to relieve reflux symptoms or can bring about bothersome new symptoms, in particular dysphagia. However, persistent dysphagia is rare and in randomized trials that compared laparoscopic fundoplication with medical treatment, no difference in the rate of long-term dysphagia between the two treatment arms was found [19–21].

In recent years, several guidelines and expert recommendations regarding the indications for fundoplication have been published [8,22–28]. However, as shown in Table 1, there are marked differences between the proposed indications and most are not sufficiently detailed.

For this review, we have searched the literature, using PubMed, for original clinical studies that yielded information on relationships between preoperative patient factors and outcome of surgical fundoplication as treatment of GERD. Review papers and articles that expressed an opinion without providing new facts were not included.

The overarching aim of this exercise was to arrive at science-based recommendations on how to identify GERD patients who are likely to benefit from fundoplication. In our review, we confined ourselves to laparoscopic fundoplication, which is usually combined with diaphragmatic cruroplasty. In this review, other surgical procedures such as anterior gastropexy and implantation of antireflux devices were not taken into account nor were peroral endoscopic procedures.

2. Preoperative factors affecting outcome

Selecting the right candidates for fundoplication is likely to be benefited by having a proper insight into and understanding of the preoperative factors that determine the outcome of

Table 1. Indications for fundoplication as worded in guidelines, consensus papers, and expert panel recommendations.

Asia-Pacific consensus (2016) [23]

- 'refractory GORD symptoms failing medical therapy'
- 'only recommended with objectively documented reflux'

Management options Expert Panel (2018) [8]

- 'abnormal acid exposure on double-dose PPI'
- 'Reflux sensitivity to regurgitation with large hiatal hernia'

ICARUS guidelines (2019) [24]

- Typical symptoms of heartburn, with good response to PPI
- GERD symptoms and hiatal hernia, Barrett's esophagus or esophagitis LA B or higher
- GERD symptoms and paraesophageal hernia

SAGES guidelines for the surgical treatment of gastroesophageal reflux (2021) [25]

- 'confirmed chronic or chronic refractory GERD' (not specified)

2020 Seoul Consensus (2021) [26]

- 'proven GERD' (not specified)
- 'other esophageal motility disorders should be excluded'

ESNM/ANMS consensus paper (2021) [22]

- 'Proper preoperative evaluation and appropriate patient selection'
- 'Ambulatory reflux monitoring is important as part of this evaluation'

American College of Gastroenterology (2022) [27]

- Esophagitis LA grade C or D, large hiatal hernia, and/or persistent troublesome symptoms with objective evidence of GERD

Multi-society consensus conference and guideline (2023) [28]

- Typical symptoms, endoscopy, manometry, and pH-testing
- Additional testing may be required for patients with atypical symptoms
- Severe comorbid disease or BMI > 50: Roux-en-Y gastric bypass

antireflux surgery. Many studies have provided pieces of information on the predictive values of preoperative patient characteristics. In this section of the review, these will be summarized and discussed.

2.1. Esophageal symptoms

The two most typical symptoms of GERD are heartburn, defined as a relatively short-lived retrosternal burning sensation, and regurgitation, defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx [1]. In most GERD patients, the incidence of regurgitation episodes is lower than the incidence of heartburn episodes [29]. It is important to note that PPIs reduce the symptom regurgitation much less effectively than the symptom heartburn [30]. In placebo-controlled trials, the response of regurgitation to PPI was only 17% greater than the response to placebo, whereas the gain for heartburn was approximately 41% [31]. It is likely therefore that persisting regurgitation is an important determinant of PPI refractoriness.

In contrast, when GERD is treated by means of fundoplication, the symptom regurgitation appears to respond as profoundly as the symptom heartburn. In a 2014 systematic review on the effectiveness of fundoplication, Lundell and colleagues found that, on average, the procedure reduced the proportion of patients with heartburn from 93.1% before operation to 3.8% 1 year after operation and the proportion of patients with regurgitation from 78.4% to 1.9% [32].

In randomized controlled trials in which fundoplication was compared with PPI maintenance treatment, the prevalence of both heartburn and regurgitation after fundoplication was found to be lower than during continued PPI use [33–35].

Chest pain, which in the context of GERD is episodic and retrosternally located, can be regarded as a third typical reflux symptom. It is much less common than heartburn but its association with reflux events can be assessed with pH-impedance monitoring [36].

2.2. Extraesophageal symptoms

The list of extraesophageal or supraesophageal reflux symptoms, also referred to as atypical symptoms, is long and subject to much debate. The problem is that, for most of these symptoms, it is virtually impossible to prove with diagnostic testing that they are caused by reflux, in particular in an individual patient. In most of the studies in which the effects of fundoplication on extraesophageal symptoms were assessed, the primary focus was on typical reflux symptoms and the indication for the operation was not based on the concurrent extraesophageal symptoms.

In a prospective US study in 113 GERD patients, laparoscopic fundoplication was found to lead to improvement of heartburn and regurgitation scores in 87.8% and 87.4%, respectively. Improvement of cough, hoarseness, and wheeze, when present preoperatively, was reported by 50.5%, 46.0%, and 48.1% of the patients, respectively [37]. In another US study, fundoplication was less successful in the subgroup of 123 patients who had atypical symptoms preoperatively than in the 29 patients with typical symptoms (success rates 41% vs 85%, respectively) [38]. In an Australian study, candidates for antireflux surgery were divided into three groups: those with typical symptoms during the 24-hour pH study, those who reported atypical symptoms, and those who were symptom-free during the 24-hour test. One year after the operation, there were no differences in heartburn scores between the three groups. However, postoperative satisfaction score was significantly higher in the group who had typical symptoms [39].

The 'reflux cough syndrome' lends itself to attempts toward objective diagnosis with ambulatory pH-impedance monitoring and analysis of the temporal association between cough events and reflux episodes [40]. However, this technique cannot be regarded as the gold standard for diagnosis of reflux-related cough. In all published case series in which the effect of fundoplication on cough was evaluated, the majority of the patients (between 64% and 91%) reported improvement of their cough [41–47].

2.3. Response to PPI

Whereas patients whose reflux symptoms respond insufficiently to PPI treatment may be more likely to opt for surgical intervention, the question is whether they are the best candidates for it. Since poor PPI responders are less likely to have GERD, it was to be expected that they respond less favorably to antireflux surgery. Over the years, several studies have provided evidence that supports this assumption.

In one of these, multivariate analysis was performed on data from 199 patients undergoing Nissen fundoplication in a US center. A clinical response to acid suppressive therapy was one of the factors that predicted a successful outcome (odds ratio 3.3) [48]. Another US study, in 100 patients, concluded that complete resolution of symptoms with acid suppression therapy was a predictor of postoperative success [49]. In a Canadian prospective study in 719 patients, follow-up quality-of-life scores were higher in the PPI-responder subgroup than in the PPI non-responders, although esophageal acid exposure responded equally well to fundoplication in the two subgroups [50]. In a study from the UK, in which 324 patients underwent fundoplication, the difference in success rate between PPI-responders and non-responders was slightly less convincing (94% vs 87%, $p = 0.08$) [51]. In 2007, it was reported from the U.S.A. that in 166 patients who had undergone Nissen fundoplication, successful outcome of fundoplication was observed less often in those who had not responded to acid suppression preoperatively than in the subgroup with complete or partial response (56% and 77%, respectively) [38]. In 2014, an Egyptian study in 370 patients also reported that symptom relief after fundoplication was achieved less frequently in the subgroup who had a poor response to PPI treatment, but in the same year a possibly underpowered French study (35 patients) failed to confirm the trend [52,53].

2.4. Reflux exposure, reflux-symptom association, and 'GERD phenotypes'

In patients with (suspected) GERD, ambulatory pH-impedance monitoring is often used since this test provides information on reflux episodes (acid as well as nonacid) and on associations between symptom episodes and reflux events. When reflux is in the physiological range but episodes of heartburn or regurgitation occur in temporal relation with reflux events, the phenotype reflux hypersensitivity is diagnosed [12]. Patients whose symptom episodes appear not to be related to reflux events are diagnosed with functional heartburn, a condition that is defined as 'retrosternal burning discomfort or pain refractory to optimal antisecretory therapy in the absence of GERD, histopathologic mucosal abnormalities, major motor disorders, or structural explanations' [12]. Functional heartburn is a disorder of gut–brain interaction rather than GERD.

The studies that explored the predictive value of preoperatively measured reflux variables for the outcome of fundoplication have yielded mixed results. In three studies, the outcome of fundoplication was found not to correlate with preoperative esophageal acid exposure, total number of impedance-detected reflux episodes and SAP [38,54,55]. In three other studies, better fundoplication outcomes were observed in patients with high acid exposure and/or a positive SAP [56–58]. To our knowledge, there is only one study in which abnormal preoperative pH findings were found to predict worse outcome of fundoplication [59].

Several studies have shown that also patients with reflux hypersensitivity are good candidates for fundoplication [60–62]. Only one study indicates that the results in reflux hypersensitivity may be not as good as with other GERD phenotypes [63].

Patients with functional heartburn do not have GERD. At least half of the patients referred to tertiary centers because of PPI-refractory 'reflux' symptoms, are diagnosed with functional heartburn [10]. These patients are poor candidates for surgery [64].

2.5. Esophagitis

Whereas for many decades GERD equated to reflux esophagitis, we now know that in the majority of untreated patients with GERD the distal esophageal mucosa does not show macroscopic signs of inflammation, such as erosions or ulcers. Patients with so-called non-erosive reflux disease (NERD) cannot be distinguished from those with esophagitis (ERD) on the basis of their symptoms. An Australian study that analyzed data from 262 patients who had undergone fundoplication found no association between preoperative esophagitis and long-term outcome of the procedure [56]. A Dutch study compared the 5-year outcomes of Nissen fundoplication in 96 patients with NERD and 117 patients with ERD. It was found that symptom relief, reduction in PPI use, improvement in quality-of-life, and reduction in esophageal acid exposure were similar in the two groups [65].

It is important to note that even in patients who undergo endoscopy as part of the diagnostic work-up, the distinction between NERD and ERD is often not really made, because the endoscopy is often done while the patient is on PPI treatment.

2.6. Hiatal hernia

In patients with a sliding hiatal hernia, reflux mechanisms other than transient relaxation of the LES, such as low basal sphincter pressure and straining-related pressure gradients, play a more prominent role in the pathophysiology. These lead to more excessive reflux [66]. In line with this, hiatus hernia size is a significant predictor of reflux esophagitis [67,68]. However, asymptomatic hiatus hernia is also prevalent and this is not regarded as indication for surgery [69].

The question to be addressed here is whether presence or size of a hiatus hernia affects the outcome of surgical fundoplication.

In a US study of 290 fundoplications, failure of the procedure occurred in 13% of patients with a hiatal hernia >3 cm, versus in 4% of patients with no or a small hernia [70]. Also in a study from Ireland in 131 patients after fundoplication, a hiatus hernia >3 cm was found to be one of the statistically significant predictors of fundoplication failure [59]. In contrast, in another study, preoperatively measured size of hiatus hernia was not significantly different in the group with successful outcome of Nissen fundoplication from that in the group with treatment failure (2.7 vs 2.9 cm $p = 0.56$) [38]. According to some surgeons, it is important to assess the extent of esophageal shortening in patients with a hiatus hernia preoperatively, because in their opinion this information is helpful during the conduct of the surgical procedure [71–73].

In the case of a paraesophageal hernia, part of the contents of the peritoneal cavity (stomach, colon, or other) has become positioned in the thoracic cavity, alongside the distal esophagus. The gastroesophageal junction may still be positioned at the level of the diaphragm. A paraesophageal hernia may cause retrosternal pain, dysphagia, and/or upper GI bleeding, but heartburn and regurgitation can also occur. Whereas the risk of incarceration of the hernia, with life-threatening consequences, is nowadays deemed to be low, there seems to be consensus that symptomatic paraesophageal hernia deserves surgical correction. The question is whether correction of a paraesophageal hernia should always be combined with a fundoplication. In the ICARUS guidelines on the selection of patients for antireflux surgery, there was an overall agreement of 97.1% for the addition of fundoplication to paraesophageal hernia repair [24].

2.7. Barrett's metaplasia

In the pathogenesis of Barrett's metaplasia in the distal esophagus, a recognized precancerous condition, excessive gastroesophageal reflux plays an important role. The question to be addressed in this review is whether the presence of Barrett's esophagus makes a GERD patient a better or worse candidate for antireflux surgery. Theoretically, it can be argued that even asymptomatic patients with Barrett should be offered fundoplication because the procedure reduces reflux, whether acid or nonacid, more effectively than a PPI. However, there is no evidence that fundoplication reduces the chance of progression from metaplasia to adenocarcinoma [74]. Several studies have shown that fundoplication reduces symptoms as effectively in patients with Barrett's esophagus as in other patients with GERD [75–77].

2.8. Impaired esophageal motility

During the first weeks after fundoplication transient dysphagia is common, but persistent postoperative dysphagia is a dreaded complication of antireflux surgery in a small subset of patients. Intuitively, it seems likely that the chance of worsening or development of dysphagia after fundoplication is increased when primary and/or secondary peristalsis is weak preoperatively. Several studies published in the past three decades have provided information on the predictive value of impaired esophageal motility for the development of postoperative dysphagia [37,38,54,68,78–87]. These studies, summarized in Table 2, either compared subgroups of patients with normal and abnormal preoperative esophageal motility or used correlation analysis techniques. As shown in Table 2, in none of these studies impaired esophageal motility, as measured preoperatively with a standard manometric technique, was identified as predictive factor for postoperative dysphagia.

However, it has been reported that the esophageal response to a series of rapid swallows (known as multiple rapid swallows, MRS), as assessed with high-resolution manometry, can predict post-fundoplication dysphagia [83,84]. Low

Table 2. Studies in which the predictive value of preoperative esophageal manometry for development of dysphagia after surgical fundoplication was assessed.

First author (year)	Ref	Country	Nr of patients in study	Manometric technique	Esophageal motility			Pre-op manometry predictive of post-op dysphagia?	
					Normal	Ineffective	Aperistalsis	standard manometry	multiple rapid swallows
Bremner (1994)	[78]	USA	100	Conv. (5-Ch)	56	44	0	no	x
Rydberg (1999)	[79]	Sweden	106	Conv. (3-Ch)	39	60	7	no	x
Fibbe (2001)	[80]	Germany	200	Conv. (8-Ch)	100	92	8	no	x
Munitiz (2004)	[68]	Spain	93	NR	52	41	0	no	x
Morgenthal (2007)	[38]	USA	166	NR	NR	NR	NR	no	x
Del Genio (2008)	[54]	Italy	62	Conv. (8-Ch)	40	22	NR	no	x
Strate (2008)	[81]	Germany	200	Conv. (8-Ch)	100	100	NR	no	x
Booth (2008)	[82]	UK	127	Conv. (3-Ch)	75	52	NR	no	x
Brown (2011)	[37]	USA	113	HRM	66	47	0	no	x
Shaker (2013)	[83]	USA	63	HRM with MRS	60	3	0	no	yes
Hasak (2019)	[84]	USA	157	HRM with MRS	132	23	2	no	yes
Nikolic (2020)	[85]	Austria	144	HRM	72	72	NR	no	x
Tran (2021)	[88]	Australia	748	HRM/Conv.	708	0	40	no	x
Hodges (2023)	[87]	USA	220	HRM with MRS	NR	NR	0	no	no

Conv, conventional. NR, not reported. Ch, channel. HRM, high-resolution manometry. MRS, multiple rapid swallows. x, not done.

strength of the first esophageal contraction that follows the deglutitive inhibition is considered to be the most relevant parameter. However, in a recently published study by another research group, this could not be confirmed [87]. Clearly, the results of additional, prospective studies on this potential predictive factor should be awaited.

It should be noted that in the studies listed in Table 2 few patients with complete esophageal aperistalsis were included. The only exception is the retrospective study by Tran and colleagues that analyzed data from 40 GERD patients who underwent fundoplication despite a complete absence of esophageal contractions at preoperative manometry [86]. Postoperatively, the dysphagia scores in patients with absent contractility were not statistically different from the dysphagia scores reported by patients in the control group, who all had normal motility. Seven of the forty patients with absent contractility had systemic sclerosis and their postoperative outcome did not differ from the outcome in the other 33 patients [86].

Several earlier studies had also arrived at the conclusion that fundoplication is safe in patients with complete aperistalsis, such as seen in systemic sclerosis, but these were case series that lacked comparison with a control group with normal or less severely disturbed esophageal motility [88–91]. Most experts continue to be reluctant to perform a fundoplication in patients with an aperistaltic esophagus. They fear esophageal decompensation with massive stasis and widening.

2.9. Hypercontractile esophageal motility

Apart from esophageal hypoperistalsis, also hypercontractile activity has been considered as a predictive factor for poor outcome of fundoplication.

In a study conducted in Sao Paulo, Brazil, patients with GERD who also had manometrically confirmed diffuse esophageal spasm, nutcracker esophagus, or hypertensive LES were found to have symptomatic outcomes after fundoplication that were comparable to those of patients with normal esophageal motility [92].

In a report that describes 38 patients, it is concluded that preoperatively identified hypercontractile motility disorders (nutcracker esophagus, distal esophageal spasm, and

hypertensive LES) often improve after fundoplication [93]. In all patients, fundoplication led to normalization of esophageal acid exposure [93]. In a study of 643 patients who had antireflux surgery for GERD, 15 had hypercontractile esophagus and 4 had hypertensive LES. After fundoplication, heartburn improved in 78% of the patients and resolved in 57%. Chest pain improved in 80% of those who had this symptom and developed in 23% who did not have it preoperatively [94].

2.10. Gastric emptying

Delayed gastric emptying is a recognized factor in the pathophysiology of GERD and, clinically, esophagitis is often found in patients with severe gastric retention. It is also known that gastric retention can be induced by fundoplication when the vagus nerve is damaged inadvertently. In some studies, gastric emptying was found to be faster after fundoplication than preoperatively [95,96]. In a study in 106 patients undergoing Toupet fundoplication, there was no overall change in gastric emptying, but acceleration was found in 18% and delay in 12% of patients [97]. However, the question is whether that preoperatively delayed gastric emptying is a predictor of less optimal results after fundoplication. In one of the early studies, preoperatively delayed gastric emptying of solids was found to be associated with symptoms of bloating after fundoplication, but interpretation is hampered by the fact that 50 of the 81 patients underwent additional procedures, such as highly selective vagotomy [98]. In yet another study, preoperatively delayed gastric emptying was documented in 31% of patients, but there was no correlation with outcome after fundoplication [99].

2.11. Obesity

It may be more difficult for the surgeon to perform fundoplication in a patient with (morbid) obesity, but the question is whether obesity reduces the success rate of the procedure.

At least four studies concluded that obesity was not associated with a poorer outcome after fundoplication [100–103]. Only one of these studies focussed on patients with morbid obesity, defined as BMI >35 kg/m^2. In a series of 224 patients

of whom 187 underwent laparoscopic Nissen fundoplication and 37 a Belsey Mark IV procedure, the recurrence rate was significantly higher in the obese subgroup (BMI >30) than in those with normal BMI (31% vs 8%, respectively) [104]. It should be noted that the overall recurrence rate was higher in the Belsey Mark IV than in the Nissen group (27% vs 8.6%) [104]. One study reported that preoperative morbid obesity (BMI >35 kg/m^2) was associated with failure of Nissen fundoplication, while obesity (BMI 30–34.9 kg/m^2) was not [38].

Recent reports suggest that, in patients with morbid obesity, reflux symptoms respond as well to bariatric surgery (Roux-en-Y gastric bypass) as to fundoplication [105,106].

2.12. Other comorbidities

Eosinophilic esophagitis (EoE) is an immune-based disease entity characterized histologically by infiltration of eosinophils into the esophageal mucosa and clinically by dysphagia for solids and liquids and occasional food impaction. Reflux plays a role in the pathophysiology of the disease in a proportion of EoE patients. Most guidelines recommend to exclude EoE before considering antireflux surgery. It has been reported that in five out of five EoE patients who underwent fundoplication the symptoms persisted [107].

It is not certain whether comorbid functional dyspepsia (FD) or irritable bowel syndrome (IBS) diminishes the chance of a favorable outcome of fundoplication because relevant studies are scarce. One study concluded that comorbid IBS did not affect the outcome of fundoplication, and that IBS symptoms had improved after the operation in 25 of the 31 patients [108]. Another study reported that patients with preoperative symptoms of functional bowel disorders were more likely to have a poor outcome [109].

In a Swedish nationwide population-based cohort study, comorbidity, assessed by the Charlson comorbidity index [110], was found to be a risk factor (HR 1.36) for reflux recurrence after antireflux surgery [17].

2.13. Psychiatric illness and chronic pain

There is limited information about the effect that psychosocial factors may have on the outcome of fundoplication. In a study of 166 patients who had undergone Nissen fundoplication, a trend toward poorer outcome ($p = 0.06$) in patients with a history of psychiatric illness was reported [38]. Two small studies by one and the same author in a US center indicate that patients with a DSM-IV psychiatric diagnosis or chronic pain syndrome are much more often dissatisfied with the result of fundoplication [111,112]. In an Austrian study involving 38 patients with major depression and 38 patients without, dysphagia and chest pain were much more prominent after floppy Nissen fundoplication in the former group [113].

2.14. Combinations of preoperative characteristics

In their recent retrospective analysis of 690 GERD patients of whom 88% underwent surgical fundoplication and 12% other procedures, Zimmermann and colleagues distinguished 12 subgroups, on the basis of combinations of various preoperative factors. The subgroup with the highest postoperative GERD-HRQL scores at 1 year, present in 4% of the patients, was defined by obesity, ineffective esophageal motility, and paraesophageal hernia, while the subgroup with the lowest scores, present in 6%, was defined by obesity, hypotensive LES, and paraesophageal hernia. However, at the 2- and 5-year timepoints, there were no differences in patient-reported outcomes between the subgroups [114].

3. Implications for patient management

How should the accumulated information on correlations between preoperative patient factors and the outcome of fundoplication be used to optimize care for patients with GERD? The response to this question can be broken down into 1) patient selection and 2) tailoring of the surgical procedure.

3.1. Patient selection

As summarized in Table 1, guidelines on surgical treatment of GERD issued by professional societies and expert panels do not go into detail as it comes to selection criteria for fundoplication. In our review, we have used the scientific literature on outcome-predicting preoperative factors as the basis for our recommendations regarding patient selection. In this process, we have focussed on the scenario in which bothersome reflux symptoms are the primary motivation for considering surgical treatment.

Whereas many different preoperative patient-based factors have been found to predict outcome of fundoplication, some of these cannot be taken too seriously, either because the study results are conflicting, or the power of the prediction is low, or because it is not practical to take the factor into account. For instance, the fact that in one study overall satisfaction with outcome was higher among male patients and the chance of reflux recurrence higher in females in another [17,56] would not led us to disadvise the operation to potential female candidates. The less so because female gender was not found to be a predictor in dozens of other studies. Differences in inclusion criteria and outcome measures used in the published series add to the complexity of weighing the study results. However, we believe the following factors to be the most important predictors of success of fundoplication as treatment for GERD:

- Predominance of typical reflux symptoms (heartburn, acid regurgitation)
- Positive response of the patient's symptoms to PPI treatment
- Positive symptom-reflux association as assessed with ambulatory monitoring
- Absence of esophageal aperistalsis or severely impaired peristalsis
- Absence of morbid obesity (BMI >35)
- Absence of significant psychiatric, somatic, and functional comorbidities

The most pivotal criterion that has to be met before considering fundoplication is that the patient must have a proven diagnosis of GERD. Whereas a PPI might be used as a diagnostic test, surgical fundoplication (or other invasive treatment with risk of irreversible side-effects) should never be used as such.

In candidates in whom the proof of GERD consists of PPI-refractory reflux esophagitis and/or significant Barrett's metaplasia, it is still important to analyze the origin of the patient's symptoms because unrealistic expectations about the effect of fundoplication must be avoided.

3.2. Procedure tailoring

When preoperative manometry has shown that esophageal peristalsis is weak, most surgeons would be reluctant to do a total, 360° wrap, and choose for a partial fundoplication instead. In case of absent peristalsis, many surgeons would refrain from doing any type of fundoplication.

The concept of tailoring because of impaired esophageal motility was challenged by several studies. A study from San Francisco compared outcome data of a tailored procedure (235 patients) with data of total fundoplication (122 patients). The type of operation was not determined by manometric findings. The incidence of postoperative dysphagia was found to be similar in the two groups [115]. In a randomized clinical study from Germany, 100 patients with normal esophageal motility and 100 patients with esophageal dysmotility were randomized to either Nissen or Toupet fundoplication. Four months after the operation, dysphagia was reported by 44% of Nissen recipients and 17% of Toupet recipients ($p < 0.0001$) [80]. However, because there were also many cases of new-onset dysphagia after Nissen fundoplication in the normal motility group, the authors concluded that tailoring is irrational. Seven years later, 2-year outcome data of the same study were published. Dysphagia was still found to be more frequent following a Nissen than after a Toupet procedure (19% vs 8%, $p < 0.05$). However, since the difference in dysphagia did not correlate with preoperative motility, the authors again concluded that tailoring of surgical management is not useful [81].

In a clinical trial conducted in the UK, 127 GERD patients were randomized to Nissen or Toupet fundoplication. One year after operation, dysphagia and chest pain on eating were more prevalent in the Nissen group (27% vs 9% and 22% vs 5%, respectively) [82]. However, postoperative symptoms in patients who had ineffective esophageal motility preoperatively did not differ from those with normal preoperative motility. The authors concluded that tailoring of antireflux procedures on the basis of preoperative manometric results should be abandoned [82].

It is surprising that the authors of the above mentioned publications dismissed the option of tailoring because they found no statistically significant correlations between preoperative manometric findings and postoperative dysphagia scores. We would rather conclude that because the dysphagia rates were significantly higher after Nissen than after Toupet fundoplication a tailored approach is warranted in cases with impaired esophageal motility. However, many surgeons already perform a partial (Toupet) fundoplication as their standard procedure, for good reasons. They could choose for a Dor procedure when peristalsis is very poor.

In our opinion, there is insufficient data to support the view that a tailored fundoplication is safe in cases of total absence of esophageal peristalsis.

4. Conclusions

Usually, fundoplication as treatment for GERD is only considered when the effects of PPI treatment are not satisfactory, or when PPI side-effects are experienced or anticipated. In the process of determining whether a patient is a suitable candidate for fundoplication, all preoperative factors that are known to predict the outcome of the procedure should be weighed. However, drawing conclusions from the scientific literature on these factors is hampered by wide variations in study design, diagnostic work-up, patient selection, fundoplication techniques, and outcome measures.

The most important requirement for antireflux surgery is an incontrovertible diagnosis of GERD, as evidenced by typical reflux symptoms (heartburn and/or regurgitation), shown to be temporally associated with reflux events (positive SI and/or SAP), or reflux-induced mucosal lesions (reflux esophagitis grade B or higher or significant intestinal metaplasia). Fundoplication for atypical symptoms is not supported by the results of well-designed studies. When the indication for fundoplication is based on mucosal lesions, it is still important to analyze the patient's symptoms, in order to manage expectations about the outcome of surgery.

The impact of weak preoperative esophageal peristalsis on the outcome of fundoplication appears to be limited, but in these cases partial rather than full fundoplication is recommended. Partial fundoplication also has advantages in patients with normal esophageal motility and can be used as the standard procedure. In case of total aperistalsis, fundoplication is best avoided.

5. Expert opinion

PPI treatment of GERD is effective and safe. Once a PPI has been started, however, it is often continued for the remainder of the patient's life, leading to high cumulative costs and possibly to side-effects. This prolonged use is somewhat surprising because more than half of all GERD patients are not satisfied with the response of their symptoms to PPIs [6,7]. Furthermore, the diagnosis of GERD is often not correct, since at the bottom of the GERD iceberg it is based on symptoms and the response to PPI and the performance of the so-called PPI test is poor [116,117]. To complicate matters further, stopping PPI treatment leads to rebound hypersecretion of gastric acid, with induction of acid-related symptoms, even in those who did not have these symptoms at the start [118]. At the top of the iceberg, in tertiary referral centers, where patients with alleged PPI-refractory GERD abound, at least half of the potential candidates for antireflux surgery do not to have GERD [10,11]. Most of these patients have functional heartburn and it can be challenging to explain to them why surgical treatment is not indicated. In the subset of tertiary setting

patients in whom GERD has been proven beyond doubt, the adjective 'PPI-refractory' is often not accurate. Most of these patients report that acid inhibition did reduce their symptoms, but that the remaining symptoms are still bothersome. Even when the refluxate is no longer acidic, regurgitation can be bothersome enough to consider surgical treatment. In cases like these, the algorithm in Figure 1 can be consulted and the factors that might affect the outcome of surgical treatment should be weighed. In our institution, the standard procedure is laparoscopic Toupet fundoplication (270°). When severe esophageal hypomotility is present, a Dor fundoplication is chosen for. Until now, we have refrained from performing fundoplication in patients with complete esophageal aperistalsis, such as in systemic sclerosis. Despite some reassuring reports in the literature, we are reluctant to change this strategy and prefer to await the results of new, prospective studies.

When symptoms other than typical heartburn and regurgitation are involved, it is important to differentiate the
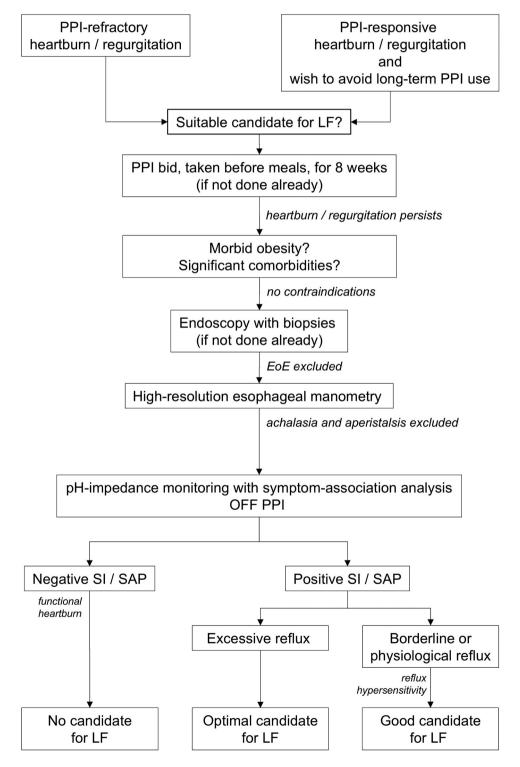
Figure 1. Algorithm for selection of patients with heartburn and/or regurgitation for laparoscopic fundoplication.

LF, laparoscopic fundoplication.

expectations regarding the effects of fundoplication. For instance, if the patient also has dyspeptic symptoms, it should be made clear that it is very unlikely that these will respond sufficiently to fundoplication. On the contrary, these might become worse.

Whereas this review focussed on patient selection, it goes without saying that for optimal results of antireflux surgery, a skilled surgeon is essential. We believe that care of fundoplication candidates should be provided by a team of dedicated surgeons, gastroenterologists, motility lab technicians, and nurses. It is also essential that all relevant arguments pro and contra surgical treatment of GERD, as compared with medical treatment, and perhaps other treatment modalities, are shared and discussed with the patient and that the decision to proceed to surgery is taken conjointly.

One could argue that the care for patients presenting with reflux symptoms is affected negatively by the GERD iceberg that prevails in most health-care systems. It is likely that among the patients who reach the top of the iceberg there are relatively few good candidates for antireflux surgery, and that many potential candidates lower down the iceberg miss out on optimal treatment. Lowering the threshold for access to reflux testing could help to reshape the iceberg. The available evidence indicates that, when testing is done, it is best performed off PPI treatment, and using pH-impedance monitoring.

In our opinion, fundoplication should not be carried out with the aim to treat extraesophageal symptoms, because in most cases it is impossible to ascertain that the patient's symptoms are reflux-related. However, unexplained cough may be an exception to this rule, since reflux-related cough can be identified by specialized monitoring techniques [119]. Fundoplication could be offered to patients with extraesophageal symptoms who also have proven GERD and bothersome typical esophageal symptoms, with the proviso that they should have realistic expectations about an effect on their extraesophageal symptoms.

In this Expert Opinion we have confined our assessment to laparoscopic fundoplication, because this is by far the most frequently used and best studied surgical procedure for the treatment of GERD. Some of the other surgical and endoscopic options for treatment of GERD hold promise, but with none of these the experience is as extensive as with laparoscopic fundoplication.

It is clear that our understanding of who are good candidates for antireflux surgery and who are not has increased considerably in the past two decades. We know now that many cases of failure of fundoplication are in fact failures of patient selection. But many questions still await a well-informed response.

Further advance in the field requires more well-designed, large-scale, multi-center prospective studies on the efficacy of fundoplication, rather than retrospective cohort descriptions. To make this possible, collaborating fundoplication research groups should be formed and preoperative work-up techniques and outcome measures should be standardized.

Funding

Declaration of interest

Reviewer disclosure

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900–1920. doi: 10.1111/j.1572-0241.2006.00630.x
• This classical landmark paper defined gastroesophageal reflux disease, based on consensus by 44 experts from 18 countries.
2. Sifrim D, Holloway R, Silny J, et al. Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. Gastroenterology. 2001;120(7):1588–1598. doi: 10.1053/gast.2001.24841
3. Kamal AN, Clarke JO, Oors JM, et al. The role of symptom association analysis in gastroesophageal reflux testing. Am J Gastroenterol. 2020;115(12):1950–1959. doi: 10.14309/ajg.0000000000000754
• In this paper the techniques for symptom association analysis and their role as tool for diagnosis of GERD were assessed.
4. Nirwan JS, Hasan SS, Babar ZU, et al. Global prevalence and risk factors of gastro-oesophageal reflux disease (GORD): systematic review with meta-analysis. Sci Rep. 2020;10(1):5814. doi: 10.1038/s41598-020-62795-1
5. Earnest D, Robinson M, Rodriguez-Stanley S, et al. Managing heartburn at the 'base' of the GERD 'iceberg': effervescent ranitidine 150 mg b.D. provides faster and better heartburn relief than antacids. Aliment Pharmacol Ther. 2000;14(7):911–918. doi: 10.1046/j.1365-2036.2000.00785.x
6. El-Serag H, Becher A, Jones R. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. Aliment Pharmacol Ther. 2010;32(6):720–737. doi: 10.1111/j.1365-2036.2010.04406.x
7. Delshad SD, Almario CV, Chey WD, et al. Prevalence of gastroesophageal reflux disease and proton pump inhibitor-refractory symptoms. Gastroenterology. 2020;158(5):1250–61.e2. doi: 10.1053/j.gastro.2019.12.014
8. Yadlapati R, Vaezi MF, Vela MF, et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: recommendations from an expert panel. Am J Gastroenterol. 2018;113(7):980–986. doi: 10.1038/s41395-018-0045-4
9. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut. 2012;61(9):1340–1354. doi: 10.1136/gutjnl-2011-301897
10. Herregods TV, Troelstra M, Weijenborg PW, et al. Patients with refractory reflux symptoms often do not have GERD. Neurogastroenterol Motil. 2015;27(9):1267–1273. doi: 10.1111/nmo.12620
11. Roman S, Keefer L, Imam H, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. Neurogastroenterol Motil. 2015;27(11):1667–1674. doi: 10.1111/nmo.12666

12. Aziz Q, Fass R, Gyawali CP, et al. Esophageal disorders. Gastroenterology. 2016;150(6):1368–1379. doi: 10.1053/j.gastro.2016.02.012

13. Broeders JA, Mauritz FA, Ahmed Ali U, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg. 2010;97(9):1318–1330. doi: 10.1002/bjs.7174

14. Ireland AC, Holloway RH, Toouli J, et al. Mechanisms underlying the antireflux action of fundoplication. Gut. 1993;34(3):303–308. doi: 10.1136/gut.34.3.303

15. Frazzoni M, Conigliaro R, Melotti G. Reflux parameters as modified by laparoscopic fundoplication in 40 patients with heartburn/regurgitation persisting despite PPI therapy: a study using impedance-pH monitoring. Dig Dis Sci. 2011;56(4):1099–1106. doi: 10.1007/s10620-010-1381-4

16. Bredenoord AJ, Draaisma WA, Weusten BL, et al. Mechanisms of acid, weakly acidic and gas reflux after anti-reflux surgery. Gut. 2008;57(2):161–166. doi: 10.1136/gut.2007.133298

17. Maret-Ouda J, Wahlin K, El-Serag HB, et al. Association between laparoscopic antireflux surgery and recurrence of gastroesophageal reflux. JAMA. 2017;318(10):939–946. doi: 10.1001/jama.2017.10981

18. Khan F, Maradey-Romero C, Ganocy S, et al. Utilisation of surgical fundoplication for patients with gastro-oesophageal reflux disease in the USA has declined rapidly between 2009 and 2013. Aliment Pharmacol Ther. 2016;43(11):1124–1131. doi: 10.1111/apt.13611

19. Garg SK, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2015;2015(11):Cd003243. doi: 10.1002/14651858.CD003243.pub3

20. McKinley SK, Dirks RC, Walsh D, et al. Surgical treatment of GERD: systematic review and meta-analysis. Surg Endosc. 2021;35(8):4095–4123. doi: 10.1007/s00464-021-08358-5

21. Tristão LS, Tustumi F, Tavares G, et al. Fundoplication versus oral proton pump inhibitors for gastroesophageal reflux disease: a systematic review and meta-analysis of randomized clinical trials. Esophagus. 2021;18(2):173–180. doi: 10.1007/s10388-020-00806-w

22. Zerbib F, Bredenoord AJ, Fass R, et al. ESNM/ANMS consensus paper: diagnosis and management of refractory gastro-esophageal reflux disease. Neurogastroenterol Motil. 2021;33(4):e14075. doi: 10.1111/nmo.14075

23. Fock KM, Talley N, Goh KL, et al. Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus. Gut. 2016;65(9):1402–1415. doi: 10.1136/gutjnl-2016-311715

24. Pauwels A, Boecxstaens V, Andrews CN, et al. How to select patients for antireflux surgery? The ICARUS guidelines (international consensus regarding preoperative examinations and clinical characteristics assessment to select adult patients for antireflux surgery). Gut. 2019;68(11):1928–1941. doi: 10.1136/gutjnl-2019-318260
•• Results of the work of a consensus group, consisting of 35 GERD management experts from 15 countries, with votes on 37 statements on the selection of patients for antireflux surgery.

25. Slater BJ, Dirks RC, McKinley SK, et al. SAGES guidelines for the surgical treatment of gastroesophageal reflux (GERD). Surg Endosc. 2021;35(9):4903–4917. doi: 10.1007/s00464-021-08625-5

26. Jung HK, Tae CH, Song KH, et al. 2020 Seoul consensus on the diagnosis and management of gastroesophageal reflux disease. J Neurogastroenterol Motil. 2021;27(4):453–481. doi: 10.5056/jnm21077

27. Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2022;117(1):27–56. doi: 10.14309/ajg.0000000000001538

28. Slater BJ, Collings A, Dirks R, et al. Multi-society consensus conference and guideline on the treatment of gastroesophageal reflux disease (GERD). Surg Endosc. 2023;37(2):781–806. doi: 10.1007/s00464-022-09817-3

29. Klauser AG, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet. 1990;335(8683):205–208. doi: 10.1016/0140-6736(90)90287-F

30. Kahrilas PJ, Jonsson A, Denison H, et al. Regurgitation is less responsive to acid suppression than heartburn in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2012;10(6):612–619. doi: 10.1016/j.cgh.2012.01.022

31. Kahrilas PJ, Howden CW, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. Am J Gastroenterol. 2011;106(8):1419–1425. quiz 26. doi: 10.1038/ajg.2011.146

32. Lundell L, Bell M, Ruth M. Systematic review: laparoscopic fundoplication for gastroesophageal reflux disease in partial responders to proton pump inhibitors. World J Gastroenterol. 2014;20(3):804–813. doi: 10.3748/wjg.v20.i3.804

33. Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. Gut. 2008;57(9):1207–1213. doi: 10.1136/gut.2008.148833

34. Lundell L, Miettinen P, Myrvold HE, et al. Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. Clin Gastroenterol Hepatol. 2009;7(12):1292–1298. quiz 60. doi: 10.1016/j.cgh.2009.05.021

35. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA. 2011;305(19):1969–1977. doi: 10.1001/jama.2011.626

36. Herregods TVK, Bredenoord AJ, Oors JM, et al. Determinants of the association between non-cardiac chest pain and Reflux. Am J Gastroenterol. 2017;112(11):1671–1677. doi: 10.1038/ajg.2017.288

37. Brown SR, Gyawali CP, Melman L, et al. Clinical outcomes of atypical extra-esophageal reflux symptoms following laparoscopic anti-reflux surgery. Surg Endosc. 2011;25(12):3852–3858. doi: 10.1007/s00464-011-1806-y

38. Morgenthal CB, Lin E, Shane MD, et al. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. Surg Endosc. 2007;21(11):1978–1984. doi: 10.1007/s00464-007-9490-7

39. Chin KF, Myers JC, Jamieson GG, et al. Symptoms experienced during 24-h pH monitoring and their relationship to outcome after laparoscopic total fundoplication. Dis Esophagus. 2008;21(5):445–451. doi: 10.1111/j.1442-2050.2007.00798.x

40. Bogte A, Bredenoord AJ, Smout AJ. Diagnostic yield of oesophageal pH monitoring in patients with chronic unexplained cough. Scand J Gastroenterol. 2008;43(1):13–19. doi: 10.1080/00365520701580421

41. Ekström T, Johansson KE. Effects of anti-reflux surgery on chronic cough and asthma in patients with gastro-oesophageal reflux disease. Respir Med. 2000;94(12):1166–1170. doi: 10.1053/rmed.2000.0944

42. Novitsky YW, Zawacki JK, Irwin RS, et al. Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. Surg Endosc. 2002;16(4):567–571. doi: 10.1007/s00464-001-8328-y

43. Allen CJ, Anvari M. Preoperative symptom evaluation and esophageal acid infusion predict response to laparoscopic Nissen fundoplication in gastroesophageal reflux patients who present with cough. Surg Endosc. 2002;16(7):1037–1041. doi: 10.1007/s00464-001-8330-4

44. Thoman DS, Hui TT, Spyrou M, et al. Laparoscopic antireflux surgery and its effect on cough in patients with gastroesophageal reflux disease. J Gastrointest Surg. 2002;6(1):17–21. doi: 10.1016/S1091-255X(01)00013-0

45. Allen CJ, Anvari M. Does laparoscopic fundoplication provide long-term control of gastroesophageal reflux related cough? Surg Endosc. 2004;18(4):633–637. doi: 10.1007/s00464-003-8821-6

46. Faruqi S, Sedman P, Jackson W, et al. Fundoplication in chronic intractable cough. Cough. 2012;8(1):3. doi: 10.1186/1745-9974-8-3

47. Hoppo T, Komatsu Y, Jobe BA. Antireflux surgery in patients with chronic cough and abnormal proximal exposure as measured by

hypopharyngeal multichannel intraluminal impedance. JAMA Surg. 2013;148(7):608–615. doi: 10.1001/jamasurg.2013.1376

48. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg. 1999;3(3):292–300. doi: 10.1016/S1091-255X(99)80071-7

49. Jackson PG, Gleiber MA, Askari R, et al. Predictors of outcome in 100 consecutive laparoscopic antireflux procedures. Am J Surg. 2001;181(3):231–235. doi: 10.1016/S0002-9610(01)00553-0

50. Anvari M, Allen C. Surgical outcome in gastro-esophageal reflux disease patients with inadequate response to proton pump inhibitors. Surg Endosc. 2003;17(7):1029–1035. doi: 10.1007/s00464-002-8571-x

51. Wilkerson PM, Stratford J, Jones L, et al. A poor response to proton pump inhibition is not a contraindication for laparoscopic antireflux surgery for gastro esophageal reflux disease. Surg Endosc. 2005;19(9):1272–1277. doi: 10.1007/s00464-004-2238-8

52. Hamdy E, El Nakeeb A, Hamed H, et al. Outcome of laparoscopic Nissen fundoplication for gastroesophageal reflux disease in non-responders to proton pump inhibitors. J Gastrointest Surg. 2014;18(9):1557–1562. doi: 10.1007/s11605-014-2584-3

53. Borie F, Zarzavadjian le Bian A, Millat B. Long-term quality of life in gastroesophageal reflux disease after NISSEN fundoplication: does it depend on preoperative responsiveness to proton pump inhibitors? Surg Laparosc Endosc Percutan Tech. 2014;24(4):332–336. doi: 10.1097/SLE.0000000000000027

54. Del Genio G, Tolone S, Del Genio F, et al. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. J Gastrointest Surg. 2008;12(9):1491–1496. doi: 10.1007/s11605-008-0583-y

55. Broeders JA, Draaisma WA, Bredenoord AJ, et al. Impact of symptom-reflux association analysis on long-term outcome after Nissen fundoplication. Br J Surg. 2011;98(2):247–254.

56. O'Boyle CJ, Watson DI, DeBeaux AC, et al. Preoperative prediction of long-term outcome following laparoscopic fundoplication. ANZ J Surg. 2002;72(7):471–475. doi: 10.1046/j.1445-2197.2002.02455.x

57. Khajanchee YS, Hong D, Hansen PD, et al. Outcomes of antireflux surgery in patients with normal preoperative 24-hour pH test results. Am J Surg. 2004;187(5):599–603. doi: 10.1016/j.amjsurg.2004.01.010

58. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2015;13(5):884–891. doi: 10.1016/j.cgh.2014.08.029
   • **This prospective study analyzed treatment results in 187 GERD patients who underwent pH-impedance testing. Factors that predicted the response to antireflux therapy (PPI treatment or fundoplication) were identified.**

59. Power C, Maguire D, McAnena O. Factors contributing to failure of laparoscopic Nissen fundoplication and the predictive value of preoperative assessment. Am J Surg. 2004;187(4):457–463. doi: 10.1016/j.amjsurg.2003.12.034

60. Bell RC, Hanna P, Brubaker S. Laparoscopic fundoplication for symptomatic but physiologic gastroesophageal reflux. J Gastrointest Surg. 2001;5(5):462–467. doi: 10.1016/S1091-255X(01)80083-4

61. Broeders JA, Draaisma WA, Bredenoord AJ, et al. Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication. Br J Surg. 2009;96(9):1023–1030. doi: 10.1002/bjs.6684

62. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. N Engl J Med. 2019;381(16):1513–1523. doi: 10.1056/NEJMoa1811424
   •• **In this well-designed randomized controlled trial in patients with PPI-refractory heartburn, laparoscopic Nissen fundoplication was found to be superior to medical treatment.**

63. Patel A, Sayuk GS, Gyawali CP. Prevalence, characteristics, and treatment outcomes of reflux hypersensitivity detected on pH-impedance monitoring. Neurogastroenterol Motil. 2016;28(9):1382–1390. doi: 10.1111/nmo.12838

64. Thompson SK, Cai W, Jamieson GG, et al. Recurrent symptoms after fundoplication with a negative pH study—recurrent reflux or

functional heartburn? J Gastrointest Surg. 2009;13(1):54–60. doi: 10.1007/s11605-008-0653-1

65. Broeders JA, Draaisma WA, Bredenoord AJ, et al. Long-term outcome of Nissen fundoplication in non-erosive and erosive gastro-oesophageal reflux disease. Br J Surg. 2010;97(6):845–852. doi: 10.1002/bjs.7023

66. van Herwaarden MA, Samsom M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. Gastroenterology. 2000;119(6):1439–1446. doi: 10.1053/gast.2000.20191

67. Jones MP, Sloan SS, Rabine JC, et al. Hiatal hernia size is the dominant determinant of esophagitis presence and severity in gastroesophageal reflux disease. Am J Gastroenterol. 2001;96(6):1711–1717. doi: 10.1111/j.1572-0241.2001.03926.x

68. Munitiz V, Ortiz A, Martinez de Haro LF, et al. Ineffective oesophageal motility does not affect the clinical outcome of open Nissen fundoplication. Br J Surg. 2004;91(8):1010–1014. doi: 10.1002/bjs.4597

69. Kohn GP, Price RR, DeMeester SR, et al. Guidelines for the management of hiatal hernia. Surg Endosc. 2013;27(12):4409–4428. doi: 10.1007/s00464-013-3173-3

70. Soper NJ, Dunnegan D. Anatomic fundoplication failure after laparoscopic antireflux surgery. Ann Surg. 1999;229(5):669–676. discussion 76–7. doi: 10.1097/00000658-199905000-00009

71. Gastal OL, Hagen JA, Peters JH, et al. Short esophagus: analysis of predictors and clinical implications. Arch Surg. 1999;134(6):633–636. discussion 7–8. doi: 10.1001/archsurg.134.6.633

72. Mattioli S, Lugaresi ML, Di Simone MP, et al. The surgical treatment of the intrathoracic migration of the gastro-oesophageal junction and of short oesophagus in gastro-oesophageal reflux disease. Eur J Cardiothorac Surg. 2004;25(6):1079–1088. doi: 10.1016/j.ejcts.2004.02.009

73. Horvath KD, Swanstrom LL, Jobe BA. The short esophagus: pathophysiology, incidence, presentation, and treatment in the era of laparoscopic antireflux surgery. Ann Surg. 2000;232(5):630–640. doi: 10.1097/00000658-200011000-00003

74. Corey KE, Schmitz SM, Shaheen NJ. Does a surgical antireflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. Am J Gastroenterol. 2003;98(11):2390–2394. doi: 10.1111/j.1572-0241.2003.08702.x

75. Ozmen V, Oran ES, Gorgun E, et al. Histologic and clinical outcome after laparoscopic Nissen fundoplication for gastroesophageal reflux disease and Barrett's esophagus. Surg Endosc. 2006;20(2):226–229. doi: 10.1007/s00464-005-0434-9

76. Cowgill SM, Al-Saadi S, Villadolid D, et al. Does Barrett's esophagus impact outcome after laparoscopic Nissen fundoplication? Am J Surg. 2006;192(5):622–626. doi: 10.1016/j.amjsurg.2006.08.010

77. Parrilla P, Martínez de Haro LF, Ortiz A, et al. Barrett's esophagus without esophageal stricture does not increase the rate of failure of Nissen fundoplication. Ann Surg. 2003;237(4):488–493. doi: 10.1097/01.SLA.0000059971.05281.D2

78. Bremner RM, DeMeester TR, Crookes PF, et al. The effect of symptoms and nonspecific motility abnormalities on outcomes of surgical therapy for gastroesophageal reflux disease. J Thorac Cardiovasc Surg. 1994;107(5):1244–1249. discussion 9–50. doi: 10.1016/S0022-5223(94)70044-3

79. Rydberg L, Ruth M, Abrahamsson H, et al. Tailoring antireflux surgery: a randomized clinical trial. World J Surg. 1999;23(6):612–618. doi: 10.1007/PL00012356

80. Fibbe C, Layer P, Keller J, et al. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology. 2001;121(1):5–14. doi: 10.1053/gast.2001.25486

81. Strate U, Emmermann A, Fibbe C, et al. Laparoscopic fundoplication: Nissen versus toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility. Surg Endosc. 2008;22(1):21–30. doi: 10.1007/s00464-007-9546-8

82. Booth MI, Stratford J, Jones L, et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (toupet)

fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg. 2008;95 (1):57–63. doi: 10.1002/bjs.6047

83. Shaker A, Stoikes N, Drapekin J, et al. Multiple rapid swallow responses during esophageal high-resolution manometry reflect esophageal body peristaltic reserve. Am J Gastroenterol. 2013;108 (11):1706–1712. doi: 10.1038/ajg.2013.289

84. Hasak S, Brunt LM, Wang D, et al. Clinical characteristics and outcomes of patients with postfundoplication dysphagia. Clin Gastroenterol Hepatol. 2019;17(10):1982–1990. doi: 10.1016/j.cgh.2018.10.020

85. Nikolic M, Schwameis K, Kristo I, et al. Ineffective esophageal motility in patients with GERD is no contraindication for Nissen Fundoplication. World J Surg. 2020;44(1):186–193. doi: 10.1007/s00268-019-05229-y

86. Tran S, Gray R, Kholmurodova F, et al. Laparoscopic fundoplication is effective treatment for patients with gastroesophageal reflux and absent esophageal contractility. J Gastrointest Surg. 2021;25 (9):2192–2200.

• **Largest reported series of patients with absent esohageal peristalsis who underwent fundoplication.**

87. Hodges MM, DeSouza ML, Reavis KM, et al. Abnormal response after multiple rapid swallow provocation is not predictive of post-operative dysphagia following a tailored fundoplication approach. Surg Endosc. 2023;37(5):3982–3993. doi: 10.1007/s00464-022-09507-0

88. Poirier NC, Taillefer R, Topart P, et al. Antireflux operations in patients with scleroderma. Ann Thorac Surg. 1994;58(1):66–72; discussion–3. doi: 10.1016/0003-4975(94)91073-1

89. Watson DI, Jamieson GG, Bessell JR, et al. Laparoscopic fundoplication in patients with an aperistaltic esophagus and gastroesophageal reflux. Dis Esophagus. 2006;19(2):94–98. doi: 10.1111/j.1442-2050.2006.00547.x

90. Goldberg MB, Abbas AE, Smith MS, et al. Minimally invasive fundoplication is safe and effective in patients with severe esophageal hypomotility. Innovations (Phila). 2016;11(6):396–399. doi: 10.1097/imi.0000000000000318

91. Armijo PR, Hennings D, Leon M, et al. Surgical management of gastroesophageal reflux disease in patients with severe esophageal dysmotility. J Gastrointest Surg. 2019;23(1):36–42. doi: 10.1007/s11605-018-3968-6

92. Dell'acqua-Cassão B, Mardiros-Herbella FA, Farah JF, et al. Outcomes of laparoscopic Nissen fundoplication in patients with manometric patterns of esophageal motility disorders. Am Surgeon™. 2013;79(4):361–365. doi: 10.1177/000313481307900423

93. Crespin OM, Tatum RP, Yates RB, et al. Esophageal hypermotility: cause or effect? Dis Esophagus. 2016;29(5):497–502. doi: 10.1111/dote.12367

94. Barreca M, Oelschlager BK, Pellegrini CA. Outcomes of laparoscopic Nissen fundoplication in patients with the "hypercontractile esophagus". Arch Surg. 2002;137(6):724–728. discussion 9. doi: 10.1001/archsurg.137.6.724

95. Maddern GJ, Jamieson GG. Fundoplication enhances gastric emptying. Ann Surg. 1985;201(3):296–299. doi: 10.1097/00000658-198503000-00006

96. Viljakka M, Saali K, Koskinen M, et al. Antireflux surgery enhances gastric emptying. Arch Surg. 1999;134(1):18–21. doi: 10.1001/archsurg.134.1.18

97. Schuchert MJ, Pettiford BL, Abbas G, et al. The use of esophageal transit and gastric emptying studies in the evaluation of patients undergoing laparoscopic fundoplication. Surg Endosc. 2010;24 (12):3119–3126. doi: 10.1007/s00464-010-1099-6

98. Lundell LR, Myers JC, Jamieson GG. Delayed gastric emptying and its relationship to symptoms of "gas float" after antireflux surgery. Eur J Surg. 1994;160(3):161–166.

99. Wayman J, Myers JC, Jamieson GG. Preoperative gastric emptying and patterns of reflux as predictors of outcome after laparoscopic fundoplication. Br J Surg. 2007;94(5):592–598. doi: 10.1002/bjs.5465

100. Fraser J, Watson DI, O'Boyle CJ, et al. Obesity and its effect on outcome of laparoscopic Nissen fundoplication. Dis Esophagus. 2001;14(1):50–53. doi: 10.1111/j.1442-2050.2001.00157.x

101. Winslow ER, Frisella MM, Soper NJ, et al. Obesity does not adversely affect the outcome of laparoscopic antireflux surgery (LARS). Surg Endosc. 2003;17(12):2003–2011. doi: 10.1007/s00464-003-8118-9

102. Anvari M, Bamehriz F. Outcome of laparoscopic Nissen fundoplication in patients with body mass index ≥35. Surg Endosc. 2006;20 (2):230–234. doi: 10.1007/s00464-005-0031-y

103. Chisholm JA, Jamieson GG, Lally CJ, et al. The effect of obesity on the outcome of laparoscopic antireflux surgery. J Gastrointest Surg. 2009;13(6):1064–1070. doi: 10.1007/s11605-009-0837-3

104. Perez AR, Moncure AC, Rattner DW. Obesity adversely affects the outcome of antireflux operations. Surg Endosc. 2001;15(9):986–989. doi: 10.1007/s004640000392

105. Joseph S, Vandruff VN, Amundson JR, et al. Roux-en-Y gastric bypass versus fundoplication for gastroesophageal reflux disease in patients with obesity results in comparable outcomes. Surgery. 2024;175(3):587–591. doi: 10.1016/j.surg.2023.10.031

106. Colvin JS, Jalilvand AD, Um P, et al. Mid-term outcomes of nissen fundoplication versus roux-en-y gastric bypass for primary management of gastroesophageal reflux disease in patients with obesity. Surg Laparosc Endosc Percutan Tech. 2023;33(6):627–631. doi: 10.1097/SLE.0000000000001215

107. Dellon ES, Farrell TM, Bozymski EM, et al. Diagnosis of eosinophilic esophagitis after fundoplication for 'refractory reflux': implications for preoperative evaluation. Dis Esophagus. 2010;23(3):191–195. doi: 10.1111/j.1442-2050.2009.01019.x

108. Raftopoulos Y, Papasavas P, Landreneau R, et al. Clinical outcome of laparoscopic antireflux surgery for patients with irritable bowel syndrome. Surg Endosc. 2004;18(4):655–659. doi: 10.1007/s00464-003-8162-5

109. Axelrod DA, Divi V, Ajluni MM, et al. Influence of functional bowel disease on outcome of surgical antireflux procedures. J Gastrointest Surg. 2002;6(4):632–637. doi: 10.1016/S1091-255X(01)00050-6

110. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383. doi: 10.1016/0021-9681(87)90171-8

111. Velanovich V, Karmy-Jones R. Psychiatric disorders affect outcomes of antireflux operations for gastroesophageal reflux disease. Surg Endosc. 2001;15(2):171–175. doi: 10.1007/s004640000318

112. Velanovich V. The effect of chronic pain syndromes and psychoemotional disorders on symptomatic and quality-of-life outcomes of antireflux surgery. J Gastrointest Surg. 2003;7(1):53–58. doi: 10.1016/S1091-255X(02)00136-1

113. Kamolz T, Granderath FA, Pointner R. Does major depression in patients with gastroesophageal reflux disease affect the outcome of laparoscopic antireflux surgery? Surg Endosc. 2003;17(1):55–60. doi: 10.1007/s00464-002-8504-8

114. Zimmermann CJ, Kuchta K, Amundson JR, et al. Personalized anti-reflux surgery: connecting GERD phenotypes in 690 patients to outcomes. Surg Endosc. 2024;38(6):3273–3278. doi: 10.1007/s00464-024-10756-4

115. Patti MG, Robinson T, Galvani C, et al. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg. 2004;198(6):863–869. discussion 9–70. doi: 10.1016/j.jamcollsurg.2004.01.029

116. Johnsson F, Hatlebakk JG, Klintenberg AC, et al. One-week esomeprazole treatment: an effective confirmatory test in patients with suspected gastroesophageal reflux disease. Scand J Gastroenterol. 2003;38(4):354–359. doi: 10.1080/0036552031002139

117. Bytzer P, Jones R, Vakil N, et al. Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2012;10(12):1360–1366. doi: 10.1016/j.cgh.2012.06.030

118. Reimer C, Søndergaard B, Hilsted L, et al. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. Gastroenterology. 2009;137(1):80–7, 7.e1. doi: 10.1053/j.gastro.2009.03.058

119. Herregods TVK, Pauwels A, Jafari J, et al. Ambulatory pH-impedance-pressure monitoring as a diagnostic tool for the reflux-cough syndrome. Dis Esophagus. 2018;31(1):1–7.