

How to select patients for anti-reflux surgery? The ICARUS guidelines (International Consensus regarding preoperative examinations and clinical characteristics assessment to select adult patients for AntiReflUx Surgery)

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Abbreviations

DES	Distal esophageal spasm
EGJ	Esophago-gastric junction
EoE	Eosinophilic esophagitis
ERD	Erosive reflux disease
FD	Functional dyspepsia
GER	Gastro-esophageal reflux
GERD	Gastro-esophageal reflux disease
HH	Hiatal hernia
IBS	Irritable bowel syndrome
ISDE	International diseases of the esophagus
LES	Lower esophageal sphincter
MRS	Multiple rapid swallow
NCCP	Non-cardiac chest pain
NERD	Non-erosive reflux disease
PEH	Para-esophageal hernia
PPI	Proton pump inhibitor

Abstract

Objective: Anti-reflux surgery can be proposed in patients with gastro-esophageal reflux disease, especially when proton pump inhibitor use leads to incomplete symptom improvement. However, to date, international consensus guidelines on the clinical criteria and additional technical examinations used in patient selection for anti-reflux surgery are lacking. We aimed at generating key recommendations in the selection of patients for anti-reflux surgery.

Design: We included 35 international experts (gastroenterologists, surgeons and physiologists) in a Delphi process and developed 37 statements that were revised by the Consensus Group, to start the Delphi process. Three voting rounds followed where each statement was presented with the evidence summary. The panel indicated the degree of agreement for the statement. When 80% of the Consensus Group agreed (A+/A) with a statement, this was defined as consensus. All votes were mutually anonymous.

Results: Patients with heartburn with a satisfactory response to PPIs, patients with a hiatal hernia (HH), patients with esophagitis LA grade B or higher and patients with Barrett's esophagus are good candidates for anti-reflux surgery. An endoscopy prior to anti-reflux surgery is mandatory and a barium swallow should be performed in patients with suspicion of a HH or short esophagus. Esophageal manometry is mandatory to rule out major motility disorders. Finally, esophageal pH (+/- impedance) monitoring off PPI is mandatory to select patients for anti-reflux surgery, if endoscopy is negative for unequivocal reflux esophagitis.

Conclusion: With the ICARUS guidelines, we generated key recommendations for selection of patients for anti-reflux surgery.

Keywords: anti-reflux surgery, patient selection, Delphi process

Introduction

Gastro-esophageal reflux disease (GERD) occurs when the reflux of (duodeno)-gastric contents into the esophagus causes troublesome symptoms and/or tissue damage (esophagitis, stricture, Barrett's esophagus).¹ GERD is a very common condition with a prevalence of 20% in the Western population. It may present with a broad spectrum of symptoms, subdivided into typical, esophageal manifestations (heartburn and regurgitation) and a variety of atypical, extra-esophageal symptoms, such as chronic cough, wheezing and hoarseness. Typical and atypical symptoms can co-exist in the same patient.²⁻⁴

Proton pump inhibitors (PPIs) are the first line medical treatment for patients with GERD, and PPI therapy has proven to be highly effective in healing esophagitis.^{5,6} However, efficacy rates for symptom relief are significantly lower, with between 10 and 40% of GERD patients failing to respond symptomatically, either partially or completely.⁶ Underlying mechanisms behind symptom generation in refractory GERD are the presence of weakly acidic and bile reflux, residual acid reflux, esophageal hypersensitivity and psychological co-morbidities.⁶

When lifestyle modifications, dietary changes and especially when medical treatment (antacids, histamine 2 (H₂-) receptor antagonist and PPIs) for GERD fails, anti-reflux surgery can be proposed. Anti-reflux surgery can also be recommended in case of intolerance to PPIs or as an alternative in anticipated long-term medical therapy in young GERD patients. While medical treatment is focused on reducing the acidity of the refluxate, classic anti-reflux surgery generates a mechanical and functional barrier preventing reflux from gastric contents into the esophagus.

Several long term follow-up studies looking at recurrence rates of reflux symptoms have been published over the last years. A recent Swedish study followed 2655 patients who

underwent primary laparoscopic anti-reflux surgery for a mean of 5.1 years and demonstrated recurrence of reflux in 470 (17.7%) of patients. Risk factors for recurrence of reflux were female gender, older age and co-morbidity.⁷ A 5-year follow up study, the LOTUS trial, demonstrated that a standardized laparoscopic Nissen fundoplication performed in expert centers and treatment with esomeprazole had similar outcome results concerning treatment failure rate, albeit that relief of heartburn was somewhat superior after surgery. The vast majority of patients achieved and remained in remission after 5 years, both in the surgical group as well as in the medical treatment group.⁸ However, the LOTUS study only enrolled patients with complete symptom control on esomeprazole and the results are not necessarily applicable to the group of patients with insufficient symptom control on PPIs, which constitutes a risk factor for a poor outcome.⁹

Selection of patients for anti-reflux surgery is traditionally based on the symptom pattern (preferably typical GERD symptoms), on the response to PPIs (at least partial response) and on the result of esophageal pH or pH-impedance monitoring (pathological acid exposure in the absence of acid suppressive therapy).^{9,10} In 2013, a US-based consensus concerning pre-operative diagnostic workup before anti-reflux surgery was published, however, this was a national consensus (the expert panel consisted of only American experts), achieved through informal voting¹¹.

The literature reports that outcome of anti-reflux surgery is influenced by anatomical and technical aspects as assessed by endoscopy, radiology, manometry and reflux monitoring, but also by demographic and co-morbidity factors such as the presence of irritable bowel syndrome (IBS), functional dyspepsia (FD), anxiety and depression. However, it is unclear to which extent these aspects should influence decisions to perform anti-reflux surgery, and to

date global consensus guidelines on the clinical criteria and additional technical examinations used in patient selection for anti-reflux surgery are lacking.

Therefore, the aim of this project was to develop a global and multidisciplinary consensus on patient characteristics and preoperative examinations that could offer the clinician guidance in selecting adult GERD patients for classic anti-reflux surgery and possibly in adapting the technical aspects of the intervention in order to optimize clinical outcome.

Methods

A Delphi process was started, with support from the International Society for Diseases of the Esophagus (ISDE), to develop consensus statements for preoperative investigations and their results in the selection of adult patients for anti-reflux surgery. This approach combines the principles of evidence-based medicine, supported by systematic literature reviews and the use of a voting process. This method is an increasingly used in health care as a rigorous means of determining consensus for complex problems in medicine for which evidence from controlled trials is lacking.^{1,12-15}

The principal steps in the process were: 1) selection of an international Consensus Group consisting of several experts in GERD management with different clinical and scientific background to contribute to this expert panel; 2) development of draft statements by a Working Group composed of 5 Consensus Group experts with varied backgrounds; 3) systematic literature reviews to identify evidence to support each statement; 4) three rounds of repeated voting of the statements and voting discussion until a stable level of consensus voting was reached; and 5) grading of the strength using accepted criteria.¹⁶

For the Consensus Group, which comprised the Working Group, 42 international experts with demonstrated knowledge/expertise were invited, and 35 from 15 countries (Australia, Belgium, Brazil, Canada, Denmark, France, Italy, Japan, Netherlands, Norway, Sweden, Switzerland, Turkey, UK and USA) agreed to participate. The group, consisting of gastroenterologists, surgeons and physiologists combined a diversity of views and expertise related to GERD diagnosis and management.

We conducted a systematic literature search using a number of relevant keywords (MeSH: anti-reflux surgery and manometry / endoscopy / pH-metry / gastric emptying / comorbidities / barium X-ray). A core panel of 5 members reviewed the list of publications and identified the ones relevant to the process. These were stored in PDF format on a central server to which Delphi panel members had access. The references cited in this chapter are only a selection of the articles reviewed in each area and were selected to clarify the discussion.

The Working Group developed an initial 27 statements and prepared and reviewed the evidence to support the statements that were presented to the Consensus Group. The Consensus Group subsequently revised, expanded and consolidated the statements, ultimately providing 37 statements to start the Delphi process. The experts were then allocated to groups of 4 and each member also functioned as lead expert for one statement. Each lead expert prepared a short summary of the available evidence (using the papers on the central server as literature source) for this statement, which was later further updated based on input from other members. Statements were revised by the Working Group based on the feedback from the Consensus Group before the start of the first voting round and based on additional literature reviews, but also after each voting round.

Three voting rounds followed where each statement was presented with the evidence summary, and then the entire panel indicated the degree of agreement for the statement using a 6-point Likert scale (Table 1). When 80% of the Consensus Group agreed (A+ or A) with a statement, this was defined as consensus. All votes were mutually anonymous. The strength of evidence for each statement was scored using the GRADE system (Table 2).¹⁷ All statements with grading and references are found in table 3.

The following statements, on relevant aspects to consider adult patients for anti-reflux surgery, were composed by the Working Group and reviewed and adjusted as needed by the Consensus Group. All statements label patients with certain characteristics as “good candidates for anti-reflux surgery”. This does not imply that surgery must be pursued in these patients, but it identifies them as potentially suitable for referral for surgery. Moreover, it is essential to understand that a decision for anti-reflux surgery based on a single characteristic (captured in a single statement) is also not appropriate. Referring a patient for anti-reflux surgery has to be an informed decision process, based on both positive and negative supporting findings.

Results

Clinical presentation and co-morbidities

1. Patients with heartburn as the main symptom who respond satisfactorily to PPIs are good candidates for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 94.1%: A+ 67.6%, A 26.5%, A- 5.9%, D- 0.0%, D 0.0%, D+ 0.0%. GRADE A

The vast majority of pre- and post-surgery studies in the literature enroll patients with 'typical' GERD symptoms which include both heartburn and regurgitation, as well as GERD patients who have typical symptoms refractory to acid suppression therapy. Several peer-reviewed studies investigating patients who reported a complete or partial response to PPI therapy prior to anti-reflux surgery, showed a benefit of anti-reflux surgery.¹⁸⁻²¹ Moreover, the response to PPI therapy, good compliance and objective preoperative evidence of acid reflux all predict a favorable outcome.²² However, specific data on heartburn as the main symptom pre-operatively and the response of heartburn symptoms to anti-reflux surgery were (often) not provided.

There is also the issue of the terminology "satisfactorily", which is very subjective. It has indeed been shown that responses to satisfactorily relief could possibly be influenced by baseline severity.^{23,24} However, this terminology is easy to understand by patients and it fits within the practice of medicine in the office setting. Furthermore, in IBS therapy trials, the usefulness of "satisfactorily relief" as an outcome parameter was linked to its ability to integrate various symptoms and the impact of therapy on various symptoms.²⁵

2. Patients with regurgitation as the main symptom are good candidates for anti-reflux surgery, regardless of the response pattern to PPI therapy.

STATEMENT *NOT* ENDORSED, overall agreement 79.4%: A+ 14.7%, A 64.7%, A- 11.8%, D- 5.9%, D 2.9%, D+ 0.0%.

GRADE B

The ability for PPIs to adequately improve regurgitation appears to be much less than their ability to improve heartburn.^{26,27} In the literature there is a lack of solid evidence to support the statement above. However, in a systematic analysis, surgery does appear to be superior to PPIs in alleviating symptomatic regurgitation, although dysphagia, rectal flatulence and the inability to belch or vomit were significantly more common in patients treated surgically.^{8,28,29} Important to notice is that symptoms of regurgitation due to primary esophageal motility disorders (e.g. achalasia, rumination syndrome) have to be ruled out by means of esophageal motility testing (preferably using high-resolution manometry (HRM)) before referring a patient for anti-reflux surgery.

3. Patients with reflux-hypersensitive esophagus (normal acid exposure but positive symptom association with reflux events) are good candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 55.9%: A+ 5.9%, A 50.0%, A- 26.5%, D- 11.8%, D 2.9%, D+ 2.9%.

GRADE C

Reflux hypersensitivity is categorized as a functional disorder in the latest Rome IV criteria and defined as “patients with esophageal symptoms who lack evidence of reflux on endoscopy or abnormal acid burden on reflux monitoring, but show triggering of symptoms by physiologic reflux”.³ Symptoms in patients with reflux hypersensitivity are caused by reflux events (main difference with functional heartburn), therefore anti-reflux surgery can theoretically improve symptoms as it minimizes esophageal reflux. The majority of studies suggest that patients with a hypersensitive esophagus are possibly good candidates for anti-reflux surgery^{4,30-34}, while a few reports suggest the opposite.³⁵ More specifically, outcome

in patients with hypersensitive esophagus where reflux has been documented in the past (either by the presence of esophagitis or a pathological acid exposure time) is similar as to patients with documented reflux without being hypersensitive.^{31,32} However, a recent study by Patel et al. showed that pure acid sensitivity was a negative predictor for symptom improvement with anti-reflux therapy, including surgical management.³⁵ Moreover, patients with reflux hypersensitivity often display a high level of anxiety. Blondeau et al. demonstrated that psychosocial factors and somatization might contribute to symptom perception in patients with reflux hypersensitivity.³⁶ This confounding factor has to be taken into consideration before referring these patients for anti-reflux surgery.

4. Patients with functional heartburn (Rome III/IV criteria, who have no association of symptoms with documented episodes of reflux events) are poor candidates for surgery.

STATEMENT ENDORSED, overall agreement 100%: A+ 91.2%, A 8.8%, A- 0.0%, D- 0.0%, D 0.0%, D+ 0.0%.

GRADE B

Functional heartburn is defined according to the Rome IV criteria as “a burning retrosternal discomfort or pain refractory to optimal anti-secretory therapy in the absence of gastro-esophageal acid reflux, histopathologic mucosal abnormalities, major motor disorders, or structural explanations”.³ In other words, in functional heartburn, symptoms manifest themselves without association to reflux events. From the mechanistic point of view, it is therefore unlikely that functional heartburn would be improved by anti-reflux surgery. The few available studies do not support the efficacy of surgery.^{34,37}

5a. Patients with non-cardiac chest pain are good candidates for anti-reflux surgery only if symptoms can be attributed to reflux.

STATEMENT *NOT* ENDORSED, overall agreement 79.4%: A+ 14.7%, A 64.7%, A- 14.7%, D- 2.9%, D 2.9%, D+ 0.0%.

GRADE C

Non cardiac chest pain (NCCP) is a common condition, with a prevalence of up to 25% in the US adult population.³⁸ After excluding a cardiac cause, reflux is the most common underlying mechanism for this disorder. Patients with NCCP might be referred to anti-reflux surgery after ruling out esophageal motility disorders such as hypercontractile esophagus and functional chest pain.³⁹ Although literature on GERD-related NCCP as the sole indication for surgical treatment is non-existent, fundoplication has been performed in this patient group. Improvement after surgical treatment is better in patients with a clear correlation between reflux events and symptoms, in patients who also display typical reflux symptoms such as heartburn and thirdly when there is a satisfactory response to PPIs prior to the surgery.⁴⁰⁻⁴⁶

5b. Patients with extra-esophageal syndromes (asthma, chronic cough or laryngitis) are good candidates for anti-reflux surgery only if symptoms can be attributed to reflux

STATEMENT *NOT* ENDORSED, overall agreement 44.1%: A+ 8.8%, A 35.3%, A- 44.1%, D- 8.8%, D 2.9%, D+ 0.0%.

GRADE C

The vast majority of data is reported in patients with typical GERD symptoms and co-existing extra-esophageal symptoms that seem to respond to surgery. Varying degrees of symptom

improvement has been shown mainly in case series in respiratory symptoms, asthma, cough and laryngopharyngeal symptoms.⁴⁷⁻⁷¹ Few data are available on the outcome of anti-reflux surgery for isolated atypical symptoms. Moreover, patient selection remains uncertain as there is no well-established method for demonstrating that these symptoms can be attributed to reflux. The use of symptom markers is valid for typical reflux symptoms, however in case of extra-esophageal symptoms it has been subject of debate for a long time. An objective monitoring for chronic cough can be added through ambulatory manometry or acoustic monitoring.⁷²⁻⁷⁵ Outcomes of Nissen fundoplication in patients with chronic cough attributable to reflux were good albeit in uncontrolled and often retrospective studies, but these were selected patients who also displayed a positive pH-monitoring.^{50-60,62-70} It has to be stressed out that none of the studies were placebo/sham controlled, which is pivotal in studying the exact effect of anti-reflux surgery in chronic cough patients.

6. Patients with eosinophilic esophagitis (EoE) on esophageal biopsies are poor candidates for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 88.2%: A+ 61.8%, A 26.5%, A- 8.8%, D- 2.9%, D 0.0%, D+ 0.0%. GRADE C

There is evidence in the literature that eosinophilic esophagitis in children and adults does not respond to anti-reflux surgery.⁷⁶⁻⁷⁹ Obtaining esophageal biopsies in all patients evaluated for Nissen fundoplication is debatable, as reports suggest a low prevalence of eosinophilic esophagitis in adults with refractory heartburn.⁸⁰

7. Patients with scleroderma (and/or other severe smooth muscle disease) are poor candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 64.7%: A+ 11.8%, A 52.9%, A- 26.5%, D- 5.9%, D 2.9%, D+ 0.0%.

GRADE C

Data on the outcome of anti-reflux surgery in scleroderma patients (systemic sclerosis) is contradictory: there are a few non-randomized studies reporting (partial or full) resolution of reflux symptoms ~~positive results of anti-reflux surgery~~, while other studies suggest that surgery is of limited success in these patients.⁸¹⁻⁸⁶ Although the severity of reflux symptoms improved after Nissen fundoplication, post-operative dysphagia was present in 38-71% of scleroderma patients.^{81,83,87} A retrospective study suggested laparoscopic Roux-en-Y gastric bypass might be a better option in patients with systemic sclerosis-associated reflux: less dysphagia and improved reflux control was seen after Roux-en-Y gastric bypass compared to fundoplication.^{83,88} Although the esophagus is not always affected in patients with systemic sclerosis, the majority of patients with esophageal involvement is found to have aperistalsis, which is a risk factor for postoperative dysphagia also in non-scleroderma patients.⁸⁹⁻⁹¹

8. Patients with concomitant functional disorders such as dyspepsia and IBS are good candidates for anti-reflux surgery, only if symptoms can be attributed to reflux.

STATEMENT *NOT* ENDORSED, overall agreement 64.7%: A+ 23.5%, A 41.2%, A- 26.5%, D- 8.8%, D 0.0%, D+ 0.0%.

GRADE B

According to Rome IV criteria, functional dyspepsia (FD) is defined as “a medical condition that significantly impacts on the usual activities of a patient and is characterized by one of the following symptoms: postprandial fullness, early satiation, epigastric pain or epigastric burning that are unexplained after a routine clinical evaluation”.⁹² Within patients with FD, a distinction between postprandial distress syndrome (PDS), with predominant postprandial fullness and early satiation and epigastric pain syndrome (EPS) characterized by epigastric pain or epigastric burning is made. There are currently no data about the influence of Rome III/IV FD comorbidity on the outcome of anti-reflux surgery, but it may parallel the inferior response to PPIs.⁹³ Studies suggest that anti-reflux surgery is not contraindicated in patients with dyspepsia comorbidity since these symptoms also tend to improve, but they do point out that the expected outcome is worse in patients with dyspepsia comorbidity.⁹⁴

IBS is defined in the Rome IV criteria as “recurrent abdominal pain associated with defecation or a change in bowel habits”. Disordered bowel habits are typically present (i.e. constipation, diarrhea, or a mix of constipation and diarrhea), as are symptoms of abdominal bloating/distention. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months.⁹⁵ A study by Raftopoulos et al. demonstrated that preoperative IBS is not a contraindication of anti-reflux surgery.⁹⁶ Although Axelrod et al. do not state that IBS is a contraindication of anti-reflux surgery, they showed that patients with a diagnosis of functional bowel disease or with preoperative symptoms of functional bowel disease were more likely to have a poor outcome compared to patients without the diagnosis or symptoms of functional bowel disease.⁹⁷ The reported data - although scarce and variable in quality - indicate that neither FD nor IBS comorbidity is a contraindication for anti-reflux surgery because of a similar improvement of typical reflux

symptoms. However extensive counselling about the possibility of persistent functional GI symptoms and increased risk of gas-bloat syndrome postoperatively is warranted.

9. Patients with a BMI > 35 kg/m² are poor candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 23.5%: A+ 2.9%, A 20.6%, A- 17.6%, D- 14.7%, D 38.2%, D+ 5.9%.

GRADE B

Obesity has been implicated as a major and independent risk factor for GERD by several mechanisms (increase of the intra-gastric pressure and of the abdominal-thoracic pressure gradient, increased gastric peptic secretion, abnormal gastric emptying).^{98,99} Losing weight should be the first pillar in GERD treatment for obese patients. Although Perez et al. demonstrated that there was a 31% occurrence rate of GERD after anti-reflux surgery in 48 obese patients, other more recent studies have shown that preoperative obesity was not associated with a poorer outcome following laparoscopic Nissen fundoplication.¹⁰⁰⁻¹⁰⁴

10. Patients with psychiatric illness (major depression or anxiety disorder) are good candidates for anti-reflux surgery only if symptoms can be attributed to reflux.

STATEMENT *NOT* ENDORSED, overall agreement 32.4%: A+ 2.9%, A 29.4%, A- 29.4%, D- 20.6%, D 14.7%, D+ 2.9%.

GRADE C

Only few studies investigated the influence of psychiatric comorbidity on the outcome of anti-reflux surgery in GERD patients. It has been demonstrated that patients with GERD and

concomitant psychiatric disorders (major depression or anxiety as defined by the DSM-IV) have more severe symptoms and lower quality of life at baseline. Even if a 24h pH-monitoring is normal after surgery, these patients report less symptom relief and less quality of life improvement compared to patients without psychiatric comorbidity.^{105–108}

11. Patients known with substance abuse (such as alcohol abuse and drug abuse) are poor candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 26.5%: A+ 8.8%, A 17.6%, A- 50.0%, D- 5.9%, D 17.6%, D+ 0.0%.

GRADE D

Alcohol and smoking may induce GER by decreasing lower esophageal sphincter (LES) pressure and disturbance of esophageal motility, although there is no evidence that lifestyle and dietary changes e.g. stopping smoking, will improve symptoms.^{99,109–112} Impaired swallow-induced LES relaxation and esophageal body dysmotility were observed both in healthy volunteers and in symptomatic patients with dysphagia receiving opioids.^{113,114} Additionally, there is no evidence in the literature that all these factors may have an impact on the results of anti-reflux surgery.^{115,116}

12. Patients with dental erosions related to documented reflux are good candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 44.1%: A+ 0.0%, A 44.1%, A- 29.4%, D- 8.8%, D 5.9%, D+ 11.8%.

GRADE D

The literature on dental erosions related to GERD is limited. Most studies indicate an increased prevalence of dental erosions in patients with GERD.¹¹⁷ On average, 17 to 68% with GERD have dental erosions.¹¹⁸⁻¹²⁴ A study by Wilder-Smith et al. showed that esomeprazole 20mg b.i.d. significantly reduced the decrease in enamel thickness compared to placebo, suggesting that treatment of GERD may reduce the development of dental erosions.¹²¹ In a 1-year follow-up study, the same group described no further progression in erosive tooth wear in 74% of the patients.¹²⁵ However, to date there are no studies available evaluating the effect of anti-reflux surgery on dental erosions.

Esophagogastroduodenoscopy

13. Endoscopy is mandatory and has to be carried out in the last year prior to anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 94.1%: A+ 82.4%, A 11.8%, A- 5.9%, D- 0.0%, D 0.0%, D+ 0.0%. GRADE B

The literature on the use of and diagnostic output from endoscopy in the preoperative work-up of GERD patients before anti-reflux surgery is very extensive. Although there is no solid evidence that endoscopy is mandatory prior to anti-reflux surgery, there seems to be a general consensus that endoscopy shall be performed before anti-reflux surgery. The proper timing for endoscopy has not been studied so far and is therefore not well-defined and the voting outcome reflects the opinion and clinical experience of the experts of the panel.

14. There is no need to wean the patient off PPI for an endoscopy in the preoperative work-up for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 88.2%: A+ 41.2%, A 47.1%, A- 2.9%, D- 5.9%, D 0.0%, D+ 2.9%. GRADE C

The literature to support a decision on whether there is greater value of maintaining or for stopping PPI therapy before making a decision regarding selection of a patient for anti-reflux surgery is scarce. Standard current practice seems to either perform endoscopy on PPI or not to specify.^{28,126,127} The information gained by pre-operative endoscopy relates to the need to assess and grade dysplasia in Barrett's esophagus, identify the possibility of a short esophagus and assess the size and configuration of hiatal hernia (HH).^{128,129} As interrupting PPI therapy for these assessments is unnecessary and unhelpful, patients can therefore continue their PPI treatment regimen for endoscopic assessment of reflux prior to a decision regarding the potential value of anti-reflux surgery.

15. Patients with GERD symptoms and an endoscopic diagnosis of a HH are good candidates for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 82.4%: A+ 20.6%, A 61.8%, A- 14.7%, D- 2.9%, D 0.0%, D+ 0.0%. GRADE B

A HH disrupts the anatomy and physiology of the normal anti-reflux mechanism (reducing the LES-length and LES-pressure, impairing augmentation of the LES by the right crus, impairing esophageal peristalsis, increasing cross-sectional area of the esophago-gastric junction (EGJ)). The herniated stomach acts as a reservoir allowing reflux into the lower

esophagus during swallowing. The presence of a HH is associated with increased symptoms of reflux, increased prevalence and severity of reflux esophagitis, Barrett's esophagus, esophageal adenocarcinoma and reduced efficacy of PPI.^{130,131} The severity of esophagitis is best predicted by size of HH, followed by LES pressure, in that order.¹³² Although patients with a large HH are more prone to have pathological reflux and more symptoms, not all patients with a HH have GERD.¹³³

Up to date, there are no prospective studies reporting the influence of HH in recommending anti-reflux surgery. The Canadian Consensus Conference on the management of GERD in adults did suggest that a significant HH, because of its likely contribution to reflux in an individual patient, may tip the balance towards surgery.¹³⁴ Most series looking for independent predictors of success for anti-reflux surgery did not find presence of HH to be significant in multivariate analysis.^{10,135}

16a. Patients with GERD symptoms and unequivocal presence of reflux esophagitis LA grade A or higher off PPI are good candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 50.0%: A+ 17.6%, A 32.4%, A- 47.1%, D- 2.9%, D 0.0%, D+ 0.0%.

GRADE B

16b. Patients with GERD symptoms and unequivocal presence of reflux esophagitis LA grade B or higher off PPI are good candidates for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 91.2%: A+ 47.1%, A 44.1%, A- 8.8%, D- 0.0%, D 0.0%, D+ 0.0%.

GRADE B

GERD patients can be subdivided into those with erosive reflux disease (ERD, presence of mucosal breaks) and those with non-erosive reflux disease (NERD, absence of mucosal breaks) based on upper gastrointestinal endoscopy findings.¹³⁶ It has been demonstrated that progression from NERD to erosive esophagitis occurs while regression from ERD to NERD is rare.^{137,138} The diminished response to medical treatment in NERD patients would support a greater role for surgery in NERD than in ERD. It has been demonstrated that subjective and objective long-term outcomes of Nissen fundoplication were similar in ERD and NERD, and results were sustained for up to 5 years after surgery.¹³⁹ Moreover, in terms of symptoms and signs of erosive esophagitis a long-term study reported that surgery was superior to conservative management with modified lifestyle and medication.¹³⁸

Historically, reflux esophagitis off PPI was considered a good selection criterion, usually in combination with abnormal pH-metry, for patient selection for an anti-reflux surgery. Active esophagitis is a definite sign of ongoing pathological reflux and may help to select patients for surgery. More than 85% of the patients with documented esophagitis were satisfied with the results of surgery (laparoscopic or open).¹⁴⁰ However, previous studies demonstrated that up till 15 % of the general population have esophagitis LA grade A or higher. Almost half of these patients, in particular those with LA grade A are asymptomatic.^{2,141}

Patient selection though remains mostly based on symptoms, as indicated by the recent LOTUS trial.^{8,142}

17. Patients with GERD symptoms without reflux esophagitis during endoscopy performed off PPIs are poor candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 2.9%: A+ 0.0%, A 2.9%, A- 2.9%, D- 23.5%, D 44.1%, D+ 26.5%.

The diagnosis of NERD is based on upper gastrointestinal endoscopy findings and a positive pH or pH-impedance study.^{3,136} Impairment of quality of life however and severity of symptoms are similar as for ERD.^{143,144} In theory, the diminished response to medical treatment in NERD patients could support a greater role for surgery in NERD than in ERD. When comparing long-term outcome results of anti-reflux surgery in PPI-refractory NERD and ERD patients, it was demonstrated that both subjective and objective long-term outcomes were similar in ERD and NERD, and results were sustained for up to 5 years after surgery.^{32,145}

18. Patients with GERD symptoms and Barrett's esophagus (non-dysplastic specialized intestinal metaplasia) on biopsies of the distal esophagus are good candidates for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 82.4%: A+ 17.6%, A 64.7%, A- 14.7%, D- 2.9%, D 0.0%, D+ 0.0%. GRADE B

The presence of Barrett's esophagus can be considered proof of the presence of GERD. Many studies confirm that anti-reflux procedures in patients with Barrett's esophagus effectively reduce reflux-related symptoms and that uncomplicated Barrett's esophagus does not influence outcome of anti-reflux surgery.^{22,146-155} A meta-analysis found no evidence that anti-reflux surgery prevents the progression to carcinoma of the esophagus, therefore post-operative endoscopic follow-up should be maintained.¹⁵⁶ In patients with refractory GERD eligible for anti-reflux surgery the presence of Barrett's esophagus should not be a contra-indication. On the other hand, anti-reflux surgery should not be suggested to

asymptomatic patients with Barrett's esophagus or to patients with short segment Barrett's esophagus to prevent evolution to dysplasia or adenocarcinoma.

19. In patients considered for anti-reflux surgery, biopsies of the esophageal body should be obtained during endoscopy.

STATEMENT *NOT* ENDORSED, overall agreement 73.5%: A+ 58.8%, A 14.7%, A- 11.8%, D- 2.9%, D 2.9%, D+ 8.8%.

GRADE C

EoE and GERD are distinct clinical entities, theoretically with different pathophysiology and treatment. However, their differentiation may sometimes be problematic and disease previously thought to be associated with GERD may really be manifestations of EoE.^{157,158} Additionally, there may be a benefit of treatment of GERD in EoE, particularly in pediatric patients.^{159,160} Further confounding this issue of distinction is that patients not suspected of having EoE (those not undergoing preoperative biopsy) who receive anti-reflux surgery, have been reported to have poor outcomes.^{77,79} The finding of eosinophils on biopsy does not necessarily confirm the diagnosis of EoE or exclude other esophageal diseases, therefore rendering the need for mandatory biopsies questionable.^{161,162} It has been shown that cost-benefit is only present when the prevalence of abnormal findings is expected to be 8% or more.¹⁶³

Barium swallow

20. In patients with suspicion of HH or short esophagus a barium swallow is mandatory in the preoperative work-up for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 88.2%: A+ 44.1%, A 44.1%, A- 5.9%, D- 2.9%, D 2.9%, D+ 0.0%. GRADE B

It is commonly accepted that 2.5 cm of intra-abdominal esophagus is necessary to perform an effective anti-reflux procedure. Today, most anti-reflux operations are performed laparoscopically. The pneumoperitoneum necessary to perform laparoscopy elevates the diaphragm into the mediastinum and appears to “lengthen” the esophagus. Failure to recognize that the esophagus is shortened may result in an inadequate length of intra-abdominal esophagus at surgery. If a HH repair is constructed under tension on a short esophagus, the hernia is reduced below the diaphragm at surgery and then retracts into the chest over time. The fundoplication may or may not remain subdiaphragmatically or it may disrupt or “slip” onto the stomach. Slipped Nissen fundoplications may therefore result from the failure to recognize a shortened esophagus before surgery. The occurrence of the true short esophagus is indeed thought to be responsible for 20% to 33% of the surgical failures after open or laparoscopic fundoplication.¹⁶⁴ A study by Mattioli et al. demonstrated that short esophagus is present in about 20% of patients undergoing routine anti-reflux surgery, highlighting the importance of performing adequate testing.¹⁶⁵

If the hernia is identified in the upright position, it is assumed that there is esophageal shortening. In addition, the esophagus is probably shortened when the HH length is 5 cm or greater alone or in combination with a stricture or a long-segment (> 3 cm) Barrett’s esophagus.^{164,166} Other radiological findings that suggest a short esophagus include severe extensive ulcerative esophagitis, straightening or loss of the angle of His, the presence of a stricture alone, and type III mixed or complex para-esophageal hernias.¹⁶⁷

In summary, if endoscopy reveals the presence of a large hernia and/or the presence of severe esophagitis or long segment Barrett's esophagus, a barium swallow performed by a dedicated upper GI radiologist is strongly recommended before surgical intervention. This will allow to better plan the technical details of the surgery in order to eventually reduce the risk of anatomical and/or symptomatic recurrence.^{168,169}

21. Patients with GERD symptoms and a small or medium size sliding HH on barium swallow are good candidates for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 82.4%: A+ 20.6%, A 61.8%, A- 8.8%, D- 8.8%, D 0.0%, D+ 0.0%. GRADE B

Very few studies have examined the effect of a HH on the outcome of anti-reflux surgery. A study by Power et al. defined a hiatal hernia size >3 cm at time of the surgery as a predictor of failure.¹³⁵ However, the presence and the size of a HH had no relationship with outcome according to several other studies.¹⁷⁰⁻¹⁷³

22. Patients with GERD symptoms and a large sliding HH on barium swallow are good candidates for anti-reflux surgery in the absence of short esophagus.

STATEMENT ENDORSED, overall agreement 85.3%: A+ 50%, A 35.3%, A- 8.8%, D- 2.9%, D 0.0%, D+ 2.9%.

GRADE B

Upper endoscopy and barium swallow are commonly used to diagnose short sliding HH. It has been demonstrated, that in morbidly obese patients, barium swallow is superior to

endoscopy in diagnosing sliding HH.¹⁷⁴ Preoperative barium swallow can reveal more details on the sliding hiatal hernia and contribute to better tailoring the anti-reflux surgery.¹⁶⁸ Although there is currently no consensus on the definition for small, medium and large HH, often the cutoff of >3cm or hernias belonging to category II till IV have been used to define a large hiatal hernia.^{94,175,176} As 2.5 cm of intra-abdominal esophagus is mandatory to offer effective anti-reflux surgery, in large sliding HHs (larger intra-thoracic component), a more comprehensive dissection is needed.¹⁶⁴

23. Symptomatic patients with a para-esophageal hernia on barium swallow are good candidates for anti-reflux surgery in addition to para-esophageal hernia repair.

STATEMENT ENDORSED, overall agreement 97.1%: A+ 44.1%, A 52.9%, A- 2.9%, D- 0.0%, D 0.0%, D+ 0.0%. GRADE C

Para-esophageal hernias (PEH) are subtypes of HH, defined as a herniation of the peritoneal cavity into the chest through the diaphragmatic hiatus.

Given the difficulty of distinguishing if reflux symptoms are from PEH alone or independent of the PEH, most surgeons routinely add an anti-reflux procedure (fundoplication) after PEH repair in elective situations.¹⁷⁷ A recent pilot trial by Muller-Stich et al, showed a lesser degree of reflux and a less esophagitis in patients where a fundoplication was added to the PEH repair compared to those with a PEH repair only.¹⁷⁸

Some authors advocate a selective approach to anti-reflux procedures, with pre-operative testing (including manometry, pH-metry, or endoscopy) and patient symptoms determining whether or not to add a fundoplication.¹⁷⁹ Others suggest always performing an anti-reflux procedure, but tailoring the type of fundoplication (e.g. full or partial) depending on the

patient.¹⁸⁰ A minority suggest that fundoplication should be avoided due to the increased risk of dysphagia with anti-reflux procedures after PEH repair.¹⁸¹ None of these approaches however have been proven superior to others in a prospective trial.

24. Patients with GERD symptoms and a short esophagus on barium swallow are poor candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 17.6%: A+ 2.9%, A 14.7%, A- 23.5%, D- 41.2%, D 11.8%, D+ 5.9%.

GRADE C

In the absence of adequate comparative studies, the question of the short esophagus remains controversial, and there is insufficient evidence to preclude patients with radiological suspicion of a short esophagus from anti-reflux surgery. If patients progress to surgery, there is also insufficient evidence to define the best surgical procedure in this scenario. Well-designed case-control or randomized clinical trials are needed to provide an evidence base to address this question.

Esophageal manometry

25. Esophageal manometry is mandatory to select patients for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 94.1%: A+ 82.4%, A 11.8%, A- 5.9%, D- 0.0%, D 0.0%, D+ 0.0%.

GRADE D

Esophageal manometry should be performed prior to anti-reflux surgery to rule out a major motor disorder, such as achalasia, EGJ outflow obstruction or absent contractility.^{182,183}

There is no data to support that the manometric finding of distal esophageal spasm (DES), Jackhammer esophagus or minor disorders of peristalsis, such as fragmented peristalsis predicts post-operative dysphagia. Incorporating HRM and impedance into pressure flow parameters might be helpful in predicting outcome since the dysphagia risk index appeared to be helpful in identifying patients at risk for post-fundoplication dysphagia.¹⁸⁴

26. Patients with GERD symptoms and a hypercontractile esophagus (Jackhammer and the previously described Nutcracker) esophagus on manometry are good candidates for anti-reflux surgery if symptoms can be attributed to reflux.

STATEMENT *NOT* ENDORSED, overall agreement 64.7%: A+ 11.8%, A 52.9%, A- 29.4%, D- 2.9%, D 2.9%, D+ 0.0%.

GRADE D

Data on outcome of anti-reflux surgery of patients with a hypercontractile esophagus is scarce: there are no randomized, controlled trials available in literature. However, retrospective data on outcome of patients with nutcracker esophagus (although no longer defined in the Chicago classification v3.0) undergoing anti-reflux surgery show no difference compared to patients with a normal esophageal motility pattern.¹⁸⁵ Manometric abnormalities after a Nissen fundoplication were even improved in 2 patients with a Jackhammer esophagus.¹⁸⁶ Hypertensive esophageal contraction patterns are not a contraindication for anti-reflux surgery however, patients and clinicians should be aware of the risk of developing chest pain after the surgery.¹⁸⁷

27. Patients with GERD symptoms and distal esophageal spasm on manometry are poor candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 64.7%: A+ 26.5%, A 38.2%, A- 20.6%, D- 11.8%, D 0.0%, D+ 0.0%. GRADE D

Patients with DES are poor candidates for anti-reflux surgery, provided that the motor disorder has been well characterized, preferably using HRM. Therapeutic approaches indicated for patients with DES include medicines such as sildenafil, as well as endoscopic injection of botulin toxin and surgical myotomy.^{188–190} Although some patients may benefit from acid suppressive therapy, anti-reflux surgery as the unique treatment should be avoided in patients with DES.

28. In patients with GERD symptoms and hypocontractility of the esophageal body on manometry, anti-reflux surgery should be tailored.

STATEMENT *NOT* ENDORSED, overall agreement 47.1%: A+ 5.9%, A 41.2%, A- 41.2%, D- 0.0%, D 5.9%, D+ 5.9%.

GRADE D

There are no good data to suggest tailoring of anti-reflux surgery to esophageal body hypomotility or hypocontractility.^{191,192} Provocative manoeuvres during manometry could in the future identify patients where peristaltic performance following fundoplication can modify the risk for postoperative dysphagia. Multiple rapid swallows (MRS) are often added to the manometric protocol as a marker for esophageal body peristaltic reserve. It has been

shown that MRS testing before laparoscopic anti-reflux surgery is able to help predict late postoperative dysphagia.^{193,194}

29. Patients with GERD symptoms and severe hypocontractility or failed peristalsis on manometry are poor candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 64.7%: A+ 8.8%, A 55.9%, A- 23.5%, D- 2.9%, D 8.8%, D+ 0.0%.

GRADE D

Hypocontractility is not a contraindication for anti-reflux surgery, since surgery more often than not improved these manometric abnormalities.¹⁹¹ Further research is warranted since very little data exists on outcome of patients with the most severe hypocontractility or aperistalsis. Similar as described above (statement 28) is the importance of adding MRS during a manometric protocol, which is a marker of contractile reserve of the esophagus.^{193,194} In addition, anti-reflux surgery can be tailored to each individual patient.

It has to be repeated that the main indication for manometry in GERD patients considered for anti-reflux surgery is to identify patients with aperistalsis due to achalasia, who are candidates for fundoplication only when combined with myotomy of the LES.

Reflux monitoring

30. Esophageal pH (+/- impedance) monitoring off therapy is mandatory to select NERD patients for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 97.1%: A+ 91.2%, A 5.9%, A- 0.0%, D- 2.9%, D 0.0%, D+ 0.0%.

GRADE B

In the absence of esophagitis (i.e. presence of mucosal breaks), pathological GER and/or positive reflux symptom association "off" therapy should be documented before embarking to anti-reflux surgery.^{22,33,195-198} In the preoperative setting, the added value of impedance in patients "off" therapy remains to be determined.

Data on preoperative assessment "on" PPIs are scarce. Few uncontrolled and short studies suggest that good postoperative outcomes can be achieved in patients who are refractory to PPIs in whom pH-impedance monitoring demonstrated either an abnormal number of reflux episodes or positive symptom association analysis.^{33,199}

31. Esophageal pH (+/- impedance) monitoring off therapy should be performed for selection for anti-reflux surgery of patients who have short Barrett's esophagus in the absence of erosive esophagitis.

STATEMENT ENDORSED, overall agreement 88.2%: A+ 41.2%, A 47.1%, A- 5.9%, D- 0.0%, D 5.9%, D+ 0.0%. GRADE B

Esophageal (impedance-) pH-monitoring off therapy should be performed in patients with short segment Barrett's esophagus as it provides an objective quantification of patient's GER.¹⁹⁵ This evaluation off PPI therapy would provide a baseline comparator in assessing the efficacy of acid suppressive and/or reflux reducing therapies.

32. Patients with GERD symptoms and normal reflux exposure on pH (+/- impedance) monitoring off PPI therapy are poor candidates for anti-reflux surgery.

STATEMENT ENDORSED, overall agreement 82.4%: A+ 17.6%, A 64.7%, A- 17.6%, D- 0.0%, D 0.0%, D+ 0.0%. GRADE B

There is very limited data examining the outcomes of surgery in patients with normal reflux monitoring. This is in large part due to the fact that most of the studies evaluating outcomes of anti-reflux surgery require abnormal reflux monitoring as a criteria to be eligible for surgery.⁵⁷ Based upon the available evidence, it would appear that patients with normal reflux exposure on pH (+/- impedance) monitoring off therapy are indeed poor candidates for anti-reflux surgery.

33a. Patients with GERD symptoms, a normal reflux exposure on pH (+/- impedance) monitoring off therapy and a positive symptom association are good candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 58.8%: A+ 14.7%, A 44.1%, A- 23.5%, D- 17.6%, D 0.0%, D+ 0.0%.

33b. Patients with GERD symptoms, a normal reflux exposure on pH (+/- impedance) monitoring off therapy and a positive reflux symptom association are good candidates for anti-reflux surgery, only if symptoms respond to PPI therapy.

STATEMENT *NOT* ENDORSED, overall agreement 73.5%: A+ 11.8%, A 61.8%, A- 14.7%, D- 5.9%, D 5.9%, D+ 0.0%.

There is very limited data examining the outcomes of surgery in patients with normal reflux monitoring. This is in large part due to the fact that most of the studies evaluating outcomes

of anti-reflux surgery require abnormal reflux monitoring as a criteria to be eligible for surgery.⁵⁷ Some studies do suggest that reflux-hypersensitive patients with typical symptoms and an unsatisfactory response to PPIs may benefit from anti-reflux surgery with an outcome similar to the one of patients with pathological reflux.^{31,200} However, as mentioned above (statement 3) a recent study by Patel et al. showed that pure acid sensitivity was a negative predictor for symptom improvement with anti-reflux therapy, including surgical management.³⁵ Results should therefore be interpreted with caution.

34a. Patients with GERD symptoms and pathologic reflux exposure on pH (+/- impedance) monitoring off therapy and a negative reflux symptom association are eligible for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 58.8%: A+ 5.9%, A 52.9%, A- 29.4%, D- 8.8%, D 2.9%, D+ 0.0%.

34b. Patients with GERD symptoms and pathologic reflux exposure on pH (+/- impedance) monitoring off therapy and a negative reflux symptom association are eligible for anti-reflux surgery, only if symptoms respond to PPI therapy.

STATEMENT *NOT* ENDORSED, overall agreement 66.7%: A+ 6.1%, A 60.6%, A- 9.1%, D- 6.1%, D 18.2%, D+ 0.0%.

The literature available suggests that patients with proven pathological acid exposure who do not experience symptoms during pH (+/- impedance) monitoring or presenting a negative symptom-reflux association may still obtain good results from anti-reflux surgery.^{33,197}

Moreover, there is a subgroup of patients that is truly refractory to PPIs, with ongoing acid secretion.¹⁹⁸

35. Patients with pathologic reflux exposure on pH (+/- impedance) monitoring on PPI who respond to baclofen therapy are good candidates for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 20.6%: A+ 5.9%, A 14.7%, A- 61.8%, D- 2.9%, D 11.8%, D+ 2.9%.

Baclofen, a GABA B-agonist, is known to reduce the number of transient LES relaxations and subsequently, it reduces all types of reflux, including weakly acidic reflux.²⁰¹ To date, there are no studies comparing baclofen with anti-reflux surgery, therefore it would be too speculative to say that patients responding to baclofen are good candidates for anti-reflux surgery. In the very recently published pediatric GER clinical guidelines, the use of baclofen prior to anti-reflux surgery can be considered in children in whom other pharmacological treatments have failed (weak recommendation).²⁰²

Gastric emptying

36. A gastric emptying test for solid food is necessary to select GERD patients with concomitant dyspeptic symptoms for anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 5.9%: A+ 2.9%, A 2.9%, A- 8.8%, D- 5.9%, D 67.6%, D+ 11.8%.

Studies performed to assess the role of a preoperative gastric emptying test in anti-reflux surgery have generated controversial results: some studies have shown that this evaluation

is useful to select the best type of surgery and to avoid surgical failures, while others have denied the validity of such an approach.^{203–205} However, so far no study has been performed to establish whether the assessment of gastric emptying is relevant or not to favor success of surgery in GERD patients with concomitant dyspepsia symptoms.

37. If the gastric emptying test is abnormal for solid food, patients should not undergo an anti-reflux surgery.

STATEMENT *NOT* ENDORSED, overall agreement 2.9%: A+ 0.0%, A 2.9%, A- 0.0%, D- 20.6%, D 67.6%, D+ 8.8%.

Literature shows that there is no evidence to suggest that preoperative slow gastric emptying for solids is associated with a poor outcome after surgery with regard to reflux parameters.^{206,207} A study by Lundell et al. suggests that a slow preoperative gastric emptying for solids is weakly associated with symptoms of bloating.²⁰⁷ However, two other studies investigating the relationship between gastric emptying rates before and outcome after anti-reflux surgery could not confirm this.^{203,204} There is insufficient evidence to support the statement.

Recommendations

Based on the statements that generated consensus a number of recommendations can be made for selecting patients for anti-reflux surgery. These are summarized in Table 4.

The Delphi process also identified several areas of uncertainty, requiring further research. It is unclear whether patients with regurgitation as a main symptom, patients with non-cardiac

chest pain, patients with extra-esophageal manifestations of reflux and patients with dental erosions are good candidates for anti-reflux surgery (statements 2,5,12). There is a lack of prospective controlled trials to support these statements. Patients with reflux hypersensitivity, patients with concomitant FD and IBS, and patients with major psychiatric co-morbidity are not considered good candidates for anti-reflux surgery (statements 3,8,10). There is a need for additional markers of beneficial outcome of anti-reflux surgery in these patients, given the frequent overlap of GERD with FD and IBS symptoms. There is no consensus that patients with scleroderma are poor candidates for anti-reflux surgery (statement 7). It is unclear to which extent patients with Jackhammer (or Nutcracker) esophagus or spasm on manometry are eligible for anti-reflux surgery (statements 26,27). The impact of esophageal hypocontractility on the eligibility or type of anti-reflux surgery is unclear (statements 28,29). It is unclear whether patients with reflux hypersensitivity are eligible for anti-reflux surgery (statement 33). Finally, it is unclear whether patients with pathological reflux monitoring but negative symptom association are good candidates for anti-reflux surgery (statement 34).

It is important to stress that the decision of referring a patient for anti-reflux surgery has to take into account all positive as well as all negative support findings. Selecting patients suitable for anti-reflux surgery cannot be captured by one single statement and remains subject to guided clinical judgement and patient preference.

Conclusion

GERD, often accompanied by the typical reflux symptoms heartburn and regurgitation or by atypical reflux symptoms such as chronic cough and wheezing, is very common in the Western World.^{1,2} The first line treatment for GERD is acid suppressive therapy, most often

by PPI intake. PPIs have shown to be very effective in healing esophagitis, however up to 40% of GERD patients remain symptomatic while on an adequate dose of PPIs.^{5,6} Anti-reflux surgery is often recommended for patients with insufficient relief of symptoms during PPI intake, in case of intolerance to or anticipated long-term use of PPIs. However, to date, consensus guidelines defining clinical criteria and additional technical examinations that need to be performed for patient selection for anti-reflux surgery are lacking. Therefore, we aimed to develop the ICARUS guidelines using a Delphi process.

The Consensus Group defined several statements that may guide clinicians and surgeons in their decision to select patients for anti-reflux surgery. All patients require endoscopy, pH-monitoring off PPI and esophageal manometry. The consensus process also identified areas of uncertainty and some patient groups in whom referral for surgery should be avoided, such as functional heartburn.

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Tables and Figures

Table 1: 6-point Likert scale.

point	description
A+	agree strongly
A	agree with minor reservation
A-	agree with major reservation
D-	disagree with major reservation
D	disagree with minor reservation
D+	disagree strongly

Table 2: Grading of recommendations assessment, development and evaluation system ¹⁶

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect <ul style="list-style-type: none">• Several high-quality studies with consistent results• In special cases: one large, high-quality multicenter trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <ul style="list-style-type: none">• One high-quality study• Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <ul style="list-style-type: none">• One or more studies with severe limitations
D	Very low	Any estimate of effect is very uncertain. <ul style="list-style-type: none">• Expert opinion• No direct research evidence• One or more studies with very severe limitations

Table 3: All statements with grading and references.

Statement	Grade of Evidence	References
1. Patients with heartburn as the main symptom who respond satisfactorily to PPIs are good candidates for anti-reflux surgery.	A	18-25
2. Patients with regurgitation as the main symptom are good candidates for anti-reflux surgery, regardless of the response pattern to PPI therapy.	B	8,26-29
3. Patients with reflux-hypersensitive esophagus (normal acid exposure but positive symptom association with reflux events) are good candidates for anti-reflux surgery.	C	3,4,30-36
4. Patients with functional heartburn (Rome III/IV criteria, who have no association of symptoms with documented episodes of reflux events) are poor candidates for surgery.	B	3,34,37
5a. Patients with non-cardiac chest pain are good candidates for anti-reflux surgery only if symptoms can be attributed to reflux.	C	38-46
5b. Patients with extra-esophageal syndromes (asthma, chronic cough or laryngitis) are good candidates for anti-reflux surgery only if symptoms can be attributed to reflux.	C	47-75
6. Patients with eosinophilic esophagitis (EoE) on esophageal biopsies are poor candidates for anti-reflux surgery.	C	76-80
7. Patients with scleroderma (and/or other severe smooth muscle disease) are poor candidates for anti-reflux surgery.	C	81-91
8. Patients with concomitant functional disorders such as dyspepsia and IBS are good candidates for anti-reflux surgery, only if symptoms can be attributed to reflux.	B	92-97
9. Patients with a BMI>35 kg/m ² are poor candidates for anti-reflux surgery.	B	98-104
10. Patients with psychiatric illness (major depression or anxiety disorder) are good candidates for anti-reflux surgery only if symptoms can be attributed to reflux.	C	105-108
11. Patients known with substance abuse (such as alcohol abuse and drug abuse) are poor candidates for anti-reflux surgery.	D	99,109-116
12. Patients with dental erosions related to documented reflux are	D	117-125

good candidates for anti-reflux surgery.		
13. Endoscopy is mandatory and has to be carried out in the last year prior to anti-reflux surgery.	B	8,28,127
14. There is no need to wean the patient off PPI for an endoscopy in the preoperative work-up for anti-reflux surgery.	C	28,126-129
15. Patients with GERD symptoms and an endoscopic diagnosis of a hiatal hernia (HH) are good candidates for anti-reflux surgery.	B	10,130-135
16a. Patients with GERD symptoms and unequivocal presence of reflux esophagitis LA grade A or higher off PPI are good candidates for anti-reflux surgery.	B	2,8,136-141
16b. Patients with GERD symptoms and unequivocal presence of reflux esophagitis LA grade B or higher off PPI are good candidates for anti-reflux surgery.	B	
17. Patients with GERD symptoms without reflux esophagitis during endoscopy performed off PPIs are poor candidates for anti-reflux surgery.	B	3,32,136,143-145
18. Patients with GERD symptoms and Barrett's esophagus (non-dysplastic specialized intestinal metaplasia) on biopsies of the distal esophagus are good candidates for anti-reflux surgery.	B	22,146-156
19. In patients considered for anti-reflux surgery, biopsies of the esophageal body should be obtained during endoscopy.	C	77,79,157-163
20. In patients with suspicion of HH or short esophagus a barium swallow is mandatory in the preoperative work-up for anti-reflux surgery.	B	164-169
21. Patients with GERD symptoms and a small or medium size sliding HH on barium swallow are good candidates for anti-reflux surgery.	B	135,170-173
22. Patients with GERD symptoms and a large sliding HH on barium swallow are good candidates for anti-reflux surgery in the absence of short esophagus.	B	94,164,168,174-176
23. Symptomatic patients with a para-esophageal hernia on barium swallow are good candidates for anti-reflux surgery in addition to para-esophageal hernia repair.	C	177-181
24. Patients with GERD symptoms and a short esophagus on barium swallow are poor candidates for anti-reflux surgery.	C	164,166,167

25. Esophageal manometry is mandatory to select patients for anti-reflux surgery.	D	182-184
26. Patients with GERD symptoms and a hypercontractile esophagus (Jackhammer and the previously described Nutcracker) esophagus on manometry are good candidates for anti-reflux surgery if symptoms can be attributed to reflux.	D	185-187
27. Patients with GERD symptoms and distal esophageal spasm on manometry are poor candidates for anti-reflux surgery.	D	188-190
28. In patients with GERD symptoms and hypocontractility of the esophageal body on manometry, anti-reflux surgery should be tailored.	D	191-194
29. Patients with GERD symptoms and severe hypocontractility or failed peristalsis on manometry are poor candidates for anti-reflux surgery.	D	191,193,194
30. Esophageal pH (+/- impedance) monitoring off therapy is mandatory to select GERD patients for anti-reflux surgery.	B	22,33,195-199
31. Esophageal pH (+/- impedance) monitoring off therapy should be performed for selection for anti-reflux surgery of patients who have short Barrett's esophagus in the absence of erosive esophagitis.	B	195
32. Patients with GERD symptoms and normal reflux exposure on pH (+/- impedance) monitoring off PPI therapy are poor candidates for anti-reflux surgery.	B	57
33a. Patients with GERD symptoms, a normal reflux exposure on pH (+/- impedance) monitoring off therapy and a positive symptom association are good candidates for anti-reflux surgery.	C	31,35,57,200
33b. Patients with GERD symptoms, a normal reflux exposure on pH (+/- impedance) monitoring off therapy and a positive reflux symptom association are good candidates for anti-reflux surgery, only if symptoms respond to PPI therapy.	B	
34a. Patients with GERD symptoms and pathologic reflux exposure on pH (+/- impedance) monitoring off therapy and a negative reflux symptom association are eligible for anti-reflux surgery.	C	33,197,199
34b. Patients with GERD symptoms and pathologic reflux exposure on pH (+/- impedance) monitoring off therapy and a negative reflux	C	

symptom association are eligible for anti-reflux surgery, only if symptoms respond to PPI therapy.		
35. Patients with pathologic reflux exposure on pH (+/- impedance) monitoring on PPI who respond to baclofen therapy are good candidates for anti-reflux surgery.	D	201,202
36. A gastric emptying test for solid food is necessary to select GERD patients with concomitant dyspeptic symptoms for anti-reflux surgery.	C	203-205
37. If the gastric emptying test is abnormal for solid food, patients should not undergo an anti-reflux surgery.	C	203,204,206,207

Table 4: Summary of the ICARUS guidelines.

Recommendations	Based on statement(s)
Anti-reflux surgery can be considered for patients with typical symptoms of heartburn, with a good response to PPIs.	1
Patients with functional heartburn and patients with eosinophilic esophagitis are poor candidates for anti-reflux surgery.	4,6
Patients with morbid obesity and patients with substance abuse are not excluded from anti-reflux surgery.	9,11
Endoscopy (during the last year) is mandatory prior to referral for anti-reflux surgery. There is no need to wean the patient off PPI for endoscopy.	13,14
Patients with GERD symptoms and a hiatal hernia, Barrett's esophagus, or erosive esophagitis grade B or higher at endoscopy are good candidates for anti-reflux surgery.	15,16b,18
Patients without erosive esophagitis are not excluded from anti-reflux surgery.	17
There is no need to obtain routine biopsies of the distal esophagus in patients considered for anti-reflux surgery.	19
A barium X-ray should be obtained in patients with suspicion of a hiatal hernia or short esophagus when considered for anti-reflux surgery.	20
Patients with GERD symptoms and a hiatal hernia on X-ray are good candidates for anti-reflux surgery.	21,22
Patients with GERD symptoms and a para-esophageal hernia on X-ray are good candidates for anti-reflux surgery in addition to para-esophageal hernia repair.	23

A short esophagus on barium X-ray does not exclude the patient from anti-reflux surgery.	24
Esophageal manometry and esophageal pH-monitoring (+/- impedance) are mandatory prior to referral for anti-reflux surgery. The latter is preferentially done off PPI and in NERD patients.	25,30,31
Patients with normal pH-monitoring off PPI are poor candidates for anti-reflux surgery.	32
Response to baclofen does not enhance patient eligibility for anti-reflux surgery.	35
There is no need to assess gastric emptying rate in patients considered for anti-reflux surgery.	36,37